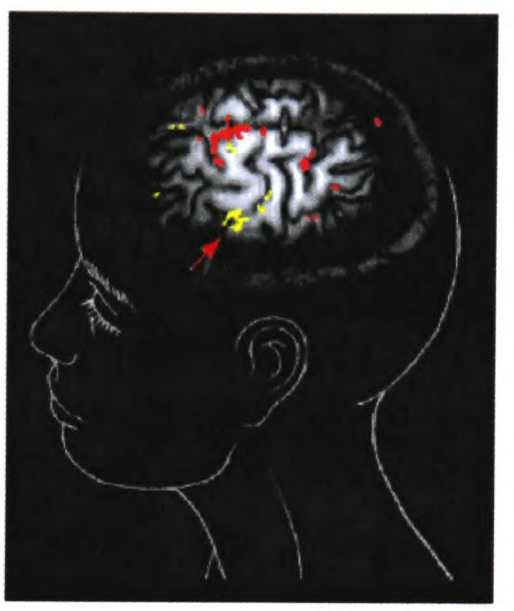
# Impulsivity, the Orbitofrontal Cortex, and Borderline Personality Disorder



Heather Berlin
Magdalen College, Oxford

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Department of Experimental Psychology, University of Oxford

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# Impulsivity, the Orbitofrontal Cortex, and Borderline Personality Disorder

Heather Berlin, Magdalen College
D.Phil. Thesis, Trinity Term 2003
Department of Experimental Psychology, University of Oxford

## Abstract

Damage to the orbitofrontal cortex (OFC) has been associated with disinhibited or socially inappropriate behaviour and emotional irregularities in both humans and monkeys. Prominent characteristics of several personality disorder syndromes, in particular Borderline Personality Disorder (BPD), are impulsivity and affective instability.

This investigation aimed to determine if certain aspects of the Borderline Personality syndrome, in particular impulsivity, are associated with OFC dysfunction. Basic questionnaires of personality, emotion, and impulsivity together with tasks sensitive to frontal lobe dysfunction that assess possible factors related to impulsivity, including time perception, sensitivity to reinforcers, and spatial working memory (SWM), were administered to OFC lesion, BPD, non-OFC prefrontal cortex lesion control, and normal control participants.

OFC and BPD patients performed similarly, in that they were more impulsive, reported more inappropriate behaviours, BPD traits, anger, and less happiness than both control groups. They were also less open to experience and had a faster perception of time (in terms of time production) than normal controls. They performed differently on other tasks: BPD patients were less extraverted and conscientious and more neurotic and emotional than all other groups. OFC patients had more severe deficits in reversing stimulus-reinforcer associations compared to all other groups and had a faster perception of time (in terms of time estimation) than normal controls.

Both OFC and non-OFC lesion patients had mixed lesions that included dorsolateral prefrontal cortex (DLFC) damage. Accordingly, they both had SWM deficits, a task used to control for DLFC damage, compared to normal and BPD participants. Since BPD participants were not impaired on this task and non-OFC patients did not perform poorly on the same tests that OFC patients did, the neuropsychological deficits of BPD and OFC patients could not be attributed to SWM deficits or DLFC dysfunction.

The findings suggest that some of the cognitive/behavioural deficits commonly found in BPD patients are related to OFC dysfunction while others are unrelated and are perhaps related to other brain systems. The possibility of amygdala dysfunction is discussed. The similarities and dissociations found between BPD and OFC patients on certain tasks may lead to a better understanding of the aetiology of BPD and the functions of the OFC. Theoretical and therapeutic implications of the findings are discussed.

## Long Abstract

Damage to the orbitofrontal cortex (OFC) has been associated with disinhibited or socially inappropriate behaviour and emotional irregularities in both humans and monkeys (see Section 1.7). Studies suggest that prefrontal regions, particularly the OFC, play an important role in the regulation of impulsivity in non-human primates, a role that may be primarily inhibitory on subcortical areas facilitating impulsivity (see Section 1.7.6). Most human studies suggest that the OFC exerts an inhibitory influence on impulsivity and, when damaged, can lead to impulsive behaviour (see Section 1.7.6). Prominent characteristics of several personality disorder syndromes, in particular Borderline Personality Disorder (BPD), are impulsivity and affective instability. Despite the abundance of evidence linking impulsivity to frontal lobe dysfunction, there is only some evidence that there are underlying frontal lobe deficits in personality disorder patients with a history of impulsivity (Bazanis et al., 2002) and even less evidence involving BPD specifically. Therefore, further investigation is needed.

This study aimed to determine if certain aspects of the Borderline Personality syndrome, in particular impulsivity, are associated with prefrontal cortex (PFC), specifically OFC, dysfunction. Thus, the aim was to answer the question: To what extent do BPD patients with impulsive symptoms, who often are characterised by executive dysfunction (see Section 1.12.9.1), in the absence of overt neurological disorders and psychosis, also display evidence of prefrontal brain dysfunction, and if so, exactly which areas of the PFC are associated with which aspects of the BPD syndrome? This issue was explored by using selected basic questionnaires of personality, emotion, and impulsivity together with a number of computer based tasks sensitive to frontal lobe dysfunction that assess possible underlying factors related to impulsivity, including time perception and sensitivity to reinforcers (a visual object-reversal task[1]). These tests were administered to OFC lesion (n=23), non-OFC PFC lesion control (n=20), BPD (n=19), and normal control (n=39) participants. All BPD patients were self-harmers (see Sections 1.12.3 & 1.12.4); cutting and burning being the most common forms of self-harm exhibited. This objective measure of impulsive behaviour was important in obtaining a homogenous patient group as Diagnostic and Statistical Manual of Mental Disorders (DSM) classification of BPD can be subjective (Nurnberg et al., 1991; Follett, 1996; Follette & Houts, 1996).

In accordance with the main hypothesis of this investigation that BPD is associated with OFC dysfunction, BPD patients had some neuropsychological deficits similar to those of OFC patients. However, OFC and BPD patients performed differently on other tasks (described below). These findings suggest that some of the cognitive/behavioural deficits commonly found in BPD patients are related to OFC dysfunction, while others are unrelated and are perhaps related to other brain systems. The possibility of amygdala dysfunction is discussed (see Sections 1.12.7, 4.3.3,

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[1] This test is composed of two tasks: an "acquisition" task where participants learn to touch one of two patterns on the computer screen and to avoid touching the other; and a "reversal" task where they then learn to reverse or extinguish that response based on monetary rewards and punishers (see Section 2.3.2.1).

4.4.2, & below). The similarities and dissociations found between BPD and OFC patients on certain tasks may lead to a better understanding of both the aetiology of BPD and the functions of the OFC. Theoretical and therapeutic implications of the findings are discussed (see Sections 4.1.9, 4.1.10, & 4.6).

In support of the main hypothesis, OFC and BPD participants behaved in the same way on certain tasks in that they were both significantly different, in the same direction, from normal participants and on some tests also from non-OFC participants. Both BPD and OFC patients were more impulsive in terms of self-report impulsivity (including non-planning, motor, and cognitive subscales), reported more inappropriate/"frontal" behaviours, BPD characteristics, subjective anger, and less subjective happiness than normal and non-OFC participants. BPD participants were significantly more impaired than OFC participants on all of these measures. Further, both OFC and BPD participants were more behaviourally impulsive (in terms of errors/second, total number of errors, and mean time latency on the Matching Familiar Figures Test[2]), had a faster perception of time in terms of time production (producing more time in total and specifically at 60 and 90 seconds), and were less open to experience than normal participants with OFC participants being more impaired than BPD participants on the behavioural impulsivity "errors/sec" and "total number of errors" variables.

BPD and OFC patients behaved differently in that BPD participants were significantly less extraverted and conscientious and more neurotic and emotional (in terms of total subjective emotionality and a higher frequency of sadness, fear, and disgust) than all other groups. Further, BPD participants had a bigger change in fear, sadness, and anger than non-OFC participants (and OFC patients in the case of fear)[3]. OFC participants performed worse on the reversal task (made less money, fewer reversals, and were more insensitive to punishment) compared to all other groups. In addition, OFC participants had a significantly faster perception of time in terms of total time estimation than normal controls while BPD participants were not significantly different from normal controls. Finally, both lesion patient groups, OFC and non-OFC, had a deficit in spatial working memory (SWM; made more errors and used a poorer strategy) compared to normal and BPD participants. The SWM task was used to control for dorsolateral prefrontal cortex (DLFC) damage (see Section 1.10.2), as both lesion groups contained patients with mixed lesions that included DLFC damage. Since BPD participants were not impaired on this task and non-OFC patients did not perform poorly on the same tests that OFC patients did, the neuropsychological deficits of BPD and OFC patients could not be attributed to SWM deficits or DLFC dysfunction.

The finding that BPD patients reported significantly more BPD traits, were more emotional and impulsive, and had impaired personality traits compared to normal controls, coincides with the

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[2] A cognitive behavioural measure of impulsivity where participants are asked to choose the target picture out of eight highly similar pictures. Latency to first response and accuracy of choice or total errors are measured. A high number of errors/second indicates impulsiveness (see Section 2.3.2.2).

[3] Normal participants did not complete the Emotional Change Questionnaire, as it measured emotional changes after brain injury or onset of psychiatric illness.

definition of the borderline syndrome (see Appendix 6). However, it is interesting that BPD patients reported significantly more "frontal" behaviours compared to controls and had similar deficits to OFC patients in terms of impulsivity, time production, emotion (anger and happiness), personality (openness to experience), "frontal" behaviours, and BPD traits. This supports the theory that some BPD patients, in particular self-harmers, have similar deficits to OFC patients and accordingly perhaps some type of OFC dysfunction. This OFC dysfunction may be neuroanatomical (BPD patients may have decreased grey matter in their OFC), neurophysiological (BPD patients may have hyper- or hypoarousal of their OFC), or neurochemical (BPD may have a lack of serotonin or in their OFC; see Section 1.12.9.1.4). More research is needed to discover the exact nature of this dysfunction.

It may be that OFC dysfunction causes the same cognitive and behavioural abnormalities in OFC lesion and BPD patients, but does so in two different ways. For example, OFC patients may be less sensitive to reinforcers, as demonstrated by their poor reversal performance, while BPD patients may be more sensitive to reward and punishment, as they were unimpaired on the reversal task (see Sections 4.4.1.1 & 4.4.3), and thus more emotional[4] and introverted (possibly caused by overactivity of the amygdala; discussed below). Impulsivity may be a result of both types of dysfunction (hyper- and hypo- sensitivity to reinforcers). Further, impulsivity interacting with introversion and high emotionality may cause BPD patients to harm themselves while OFC patients, who are impulsive but not introverted or extremely emotional, do not. OFC patients were not abnormally extraverted either, which combined with impulsivity could lead patients to harm others, in line with Paris' (1997) theory (see Footnote 37).

Some of the differences in performance between OFC and BPD patients may be explained by abnormal amygdala function in addition to OFC dysfunction in BPD patients. For example, evidence of hyper-responsivity of the amygdala has been found in BPD patients (Herpertz et al., 2001; see also Sections 1.12.7, 1.12.8, & 4.4.2). This hyper-responsivity might represent an oversensitisation to aversive emotional stimuli (Herpertz et al., 2001). So, perhaps BPD patients' emotional and personality abnormalities are related to amygdala dysfunction, while their impulsivity, inappropriate behaviours, and time production deficits are related to OFC dysfunction or a combination of both. BPD patients' OFC dysfunctions (demonstrated by their similar performance to OFC patients on certain tasks) may also be exacerbated by amygdala dysfunction, thus explaining the worse performance of BPD compared to OFC patients on impulsivity, frontal behaviour, BPD, emotion, and personality questionnaires[5]. Therefore, it is plausible that a dysfunction of the limbic-orbitofrontal axis is involved in BPD, at least in a subgroup of patients

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[4] According to Weiskrantz (1968), Gray (1975), and Rolls (1999), emotions are simply states elicited by rewards and punishments.

[5] BPD patients scored worse than OFC patients on all questionnaires, even when they both scored worse than normals. Yet, on the behavioural tasks, when both BPD and OFC patients did worse than normals, BPD patients were never worse than OFC patients and OFC patients were often worse than BPD patients. This could indicate that OFC patients' performance on the questionnaires was affected by a slight lack of insight.

(Van Reekum, 1993). The "lesions" that contribute to BPD may include increased limbic discharge and decreased OFC function.

The frontal lobes have been proposed to play an important role in regulating impulsivity, as was demonstrated in this study, although it is unclear as to exactly how this occurs. None of the biological knowledge to date has led to reliable pharmacotherapy for excessive impulsivity. Further, there is little understanding to date of the mechanisms by which those drugs that have been found empirically to have some efficacy (e.g. the psychomotor stimulants in attention deficit hyperactivity disorder) exert their therapeutic effect. By bringing together knowledge from different areas of research it is hoped that a cross fertilisation will be achieved that will lead to a sharpening of concepts, an improvement in methodology, the stimulation of biological studies, and effective treatments of impulsivity (Evenden, 1999c) in both psychiatric and neurological populations.

There were some limitations to this study. For example, self-report questionnaire measures rely on patients' insight into their own condition, and patients may be slightly unaware of some of their own abnormalities due to their condition. However, OFC and BPD patients still reported being significantly worse than controls on almost all self-report measures and self-report measures correlated with behavioral measures of impulsivity. Also, most BPD patients were medicated, which could have affected the results. However, even though they were on medication aimed at improving many of the behaviours that were being tested, BPD patients still showed significant deficits on almost all variables.

This study is unique in comparing the clinical population of BPD patients to PFC brain lesion patients and perhaps will start a trend in that direction. Comparing psychiatric to brain damaged/neurological patients can be an excellent way to increase understanding of the biological aetiology of certain psychiatric disorders as well as the functions of the brain. Patients with psychiatric disorders may not have overt anatomical deficits. Their neurological dysfunctions may be more subtle and therefore best measured by comparing their performance to that of patients with known areas of brain damage on the same neuropsychological tests. This can help establish exact anatomical correlates related to psychiatric disorders. It is hoped that this study has contributed to our understanding of the association between frontal dysfunction and impulsive behaviour, the behavioural changes exhibited by patients with PFC damage, and the cognitive and biological processes that are impaired in impulsive people in the context of BPD. Ideally, this research will lead to future studies that discover and further delineate brain-behaviour relationships, contribute to the prevention and treatment of neurological and psychological disorders, and expand our knowledge of the complex interactions of the human brain and mind.

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# Chapter 1: INTRODUCTION

> "I do anatomise and cut up these poor beasts (he said to Hippocrates) to see the cause of these distempers, vanities, and follies, which are the burden of all creatures."
> - Democritus (c. 460 - 370 BC)

## 1.1 Aims of this Investigation

Impulsive behaviour is considered to be a prominent characteristic of several personality disorder syndromes. However, understanding its neural basis has been hampered by the absence of satisfactory definitions and by its association with a diverse range of behavioural manifestations. The study of Phineas Gage (Harlow, 1848) is thought of as the foundation for the idea that various areas of the brain determine both emotional states and mental processing. Phineas Gage was the foreman of a railway construction team working on the Rutland and Burlington Rail Road. While tamping down the blasting powder for a dynamite charge, Gage inadvertently sparked an explosion. The inch-thick iron tamping rod rocketed through his left orbitomedial frontal lobe (illustrated in Figure 1.1) causing him to become more impulsive and aggressive. Since the publication of the case of Phineas Gage it has been known that frontal lobe injury can alter not only the cognitive aspects of personality, but its affective and emotional aspects as well. Yet, to date, that knowledge has remained by and large either ignored or overshadowed by speculation. One reason for the neglect is the difficulty in defining and objectifying abnormalities of personality, affect, and emotion; another is dissociating those abnormalities from cognitive disorders to which they may be secondary. The vagaries of some of the published attempts at cerebral localisation of certain functions confuse this issue further. Therefore, more research is needed to either correlate personality abnormalities to cognitive and anatomical deficits or to disentangle them.

**Figure 1.1**: a) Computer generated image of the passage of the bar through the skull of Phineas Gage (Damasio et al., 1994). Damasio et al. (1994) discovered that most of the damage was done to the ventromedial region of the frontal lobes on both sides. Since the part of the frontal lobes responsible for speech and motor functions was apparently spared and Damasio et al. (1994) observed the same sort of change in other patients with similar lesions, causing a defect in rational decision making and the processing of emotion, they concluded that the changes in social behaviour observed in Phineas Gage were probably due to this lesion. b) A photograph of the actual skull of Phineas Gage preserved in the Warren Medical Museum of Harvard University (Walsh, 2000).

Since alterations of personality have been associated with frontal lobe damage, it is appropriate to presume that disorders of personality may involve underlying frontal lobe impairments, whether they are anatomical in nature or involving altered neuromodulation or both. The lack of cognitive control and disinhibition (a distinctive symptom of orbitofrontal cortex damage) associated with impulsivity in certain personality disorders, which leads to hedonistic action, is strikingly similar to behaviour reported after frontal lobe damage (e.g. Phineas Gage (Harlow, 1848), postleukotomy). The possibility that sociopathic behaviour could be related to frontal malfunction has been recognised previously (Pontius, 1972; Bazanis et al., 2002). Several aetiologies can be considered: actual structural damage to the frontal cortex and/or its pathways in adulthood, during development or genetically mediated, a lagging in the laying down of myelin, or altered neuromodulation. If impulsive personality disorders are found to be related to frontal lobe dysfunction, then further investigation is needed to determine which aetiological theory is plausible or if there are varying causes. Frontal lobe damage has been associated with an inability to exert an inhibitory influence on cognitive and motor processes and may explain the impulsive behaviours found in people diagnosed with Antisocial or Borderline Personality Disorder (BPD). However, more evidence is needed to demonstrate frontal lobe abnormality as the cause of the impulsive behaviours exhibited in the context of these personality disorders.

Concerning Antisocial Personality Disorder, a number of authors posited a role for frontal lobe dysfunction in psychopathic behaviour (Flor-Henry, 1973; Gorestien, 1982; Mitchell et al., 2002). Although initial studies provided supporting data, some studies found no relationship between psychopathy and frontal lobe dysfunction (e.g. Hare, 1984). It is possible that the different conclusions in these studies are due to the heterogeneity of subjects in terms of diagnostic subtype or intelligence (Devonshire et al., 1988). There are, however, fewer neuropsychological studies of BPD than of Antisocial Personality Disorder. I have therefore chosen to investigate BPD patients to increase our understanding of such a complex and, to date, scarcely investigated disorder. Still, despite the low number of studies investigating BPD and brain dysfunction, some recent studies have concluded that some patients with BPD have evidence of frontal system dysfunction (see Section 1.12.9.1). Nevertheless, the causal role of neuropsychological impairments related to BPD symptoms remains controversial and further evidence is needed to make definite brain-behaviour correlations.

Studies suggest that prefrontal regions, particularly orbitofrontal cortex (OFC), play an important role in the regulation of impulsivity in non-human primates, a role that may be primarily inhibitory on subcortical areas facilitating impulsivity (see Section 1.7.6). In the human brain, the OFC has also been associated with the control of impulsive behaviour. Most human studies suggest that the OFC exerts an inhibitory influence on impulsivity and, when damaged, can lead to impulsive behaviour. Despite the abundance of evidence linking impulsivity to frontal lobe dysfunction (see Section 1.7.6), there is only some evidence that there are underlying frontal lobe

deficits in personality disorder patients with a history of impulsivity (Bazanis et al., 2002) and even less evidence involving BPD specifically, thus further investigation is needed.

Hence, the aim of this investigation is to determine if the BPD syndrome is associated with prefrontal cortex dysfunction and to answer the question: To what extent do BPD patients with impulsive symptoms, who often are characterised by executive dysfunction (see Section 1.12.9.1), in the absence of overt neurological disorders and psychosis, also display evidence of prefrontal brain dysfunction, and if so, exactly which areas of the prefrontal cortex are associated with which aspects of the BPD syndrome?

This issue is explored by administering selected, basic, personality and emotion questionnaires, together with a number of computer based tasks sensitive to frontal lobe dysfunction and that assess possible underlying factors related to impulsivity, including sensitivity to reinforcers, to OFC lesion patients, control patients with prefrontal cortex damage outside of the OFC (mostly patients with dorsolateral prefrontal cortex damage), BPD patients, and normal controls. If deficits that are normally found in prefrontal lesion patients are also found in impulsive BPD patients, then it would link certain symptoms of BPD to underlying neurocognitive problems particularly frontal lobe problems and lead to effective treatments. In addition, by comparing impulsive BPD patients to non-clinical (normal) participants on these same neuropsychological traits, perhaps it can be determined if the intense impulsivity, among other abnormalities, exhibited by clinical BPD patients is at the high end of a continuum with the normal (non-clinical) population. Further, this investigation aims to determine which specific areas of the frontal lobe are involved in which aspects of personality, emotion and impulsive behaviour i.e. orbitofrontal cortex (OFC) versus dorsolateral prefrontal cortex (DLFC). For example, although some early animal studies have found abnormal voracity and aggressiveness with large frontal lobe lesions (Fulton et al., 1932; Kennard, 1945), lesions of the DLFC or large lobotomies that spare the posterior orbital area, not orbital lesions, increase the aggressiveness of the monkey (Singh, 1976). Conversely, impaired decision-making when punishers and rewards are involved has been associated with ventromedial and OFC, but not DLFC deficits, while worked memory deficits had the opposite relationship (Bechara et al., 1998). Although there is evidence that frontal lobe patients show classical impulsive behaviour (see Section 1.7.6), very few rigorous studies have been carried out to investigate which parts of this complex area of the brain are specifically involved in impulsivity (behavioural or cognitive). Further investigation is therefore needed in determining exactly which parts of the frontal lobe contribute to which aspects of impulsivity.

More specifically, one aim of this research is to determine if patients with BPD have deficits indicative of OFC dysfunction like in the reversing of previously learned stimulus-reinforcement associations (see Section 1.7) and/or have deficits indicative of DLFC dysfunction like in spatial working memory (see Section 1.10.2). Experimental data suggest that the OFC plays a role in the *reversing* of associations between stimuli and reinforcers (Rolls et al., 1994; Hornak et al., 2003a, in press). A fundamental deficit shown by non-human primates and humans with OFC

lesions is a difficulty in reversing behavioural responses to changed reinforcement contingencies (Butter, 1969; Dias et al., 1996; Iversen & Mishkin, 1970; Jones & Mishkin, 1972; Passingham, 1972; Rosenkilde, 1979; Rolls et al., (1994); Hornak et al, 2003a, in press). Rolls et al. (1994) and Hornak et al. (2003a, in press) have shown that patients with OFC damage have alterations in their responses to changes in rewards and losses of rewards. These problems in responding to changing reinforcers may contribute to their everyday behavioural difficulties. This is consistent with the hypothesis that the OFC plays a role in the process by which stimuli are associated with reinforcers. Other studies have found that impulsive people are less sensitive to punishment and more sensitive to reward than non-impulsive people (Gray, 1973; Pickering & Gray, 1999; see Section 1.7.6). Therefore, sensitivity to reward and punishment may be an important factor in determining personality.

Thus, it is certainly useful to apply tests of cognitive-affective reversal involving rewards and punishments, which has been found to be impaired in patients with OFC lesions, to studies of impulsive BPD patients in order to learn more about the association between frontal dysfunction and impulsive behaviour. Further, in order to increase our understanding of the behavioural changes seen in patients with prefrontal cortex (PFC) damage, which is potentially important in their rehabilitation, the impulsivity of PFC lesion patients was measured. Specifically, patients with OFC damage, and control patients with non-OFC PFC damage were assessed with measures of impulsivity as well as tasks involving sensitivity to reward and punishment, spatial working memory, time perception, personality, and emotion (the reasons these specific tasks were administered are described in the sections to follow). By administering these same tests to impulsive BPD patients, this research aims to assess to what extent OFC dysfunction and sensitivity to stimulus-reinforcer associations, among other functions, may be related to their impulsivity. In sum, this study aims to increase our understanding of the association between frontal dysfunction and impulsive behaviour, the behavioural changes seen in patients with PFC damage, and the cognitive and biological processes that are impaired in impulsive people, particularly in the context of BPD, which can have direct preventative and therapeutic implications.

## 1.2 History of the Psychobiology of Personality

One of the major precepts of the Greek physician Hippocrates (c. 460-344 BC), the traditionally held "Father of Medicine", was the rule of harmony; the theory that all body systems are in balance and that disease results from an imbalance. He thought disease was caused by *insonomia*, the preponderance of one of the four bodily fluids or "humours": yellow bile, black bile, phlegm, or blood. Galen (c. 130-201 AD) extended Hippocrates' theory of the humours to personality. Galen, the physician to Marcus Aurelius and intellectual heir to Hippocrates, was one of the most influential physicians of all times. Like Hippocrates, he taught the importance of maintaining balance between the four bodily humours. He proposed further that each fluid was associated with a specific personality characteristic or temperament. Blood was associated with a sanguine

personality i.e., laughter, music, and a passionate disposition. Someone with a phlegmatic personality was sluggish and dull, while yellow bile represented an individual quick to anger or choleric (cholera meaning yellow as in yellow fever). Lastly, black bile represented a melancholic (melan meaning black) or depressed personality (for a historical review, see Hergenhahn, 1992).

From the time of Galen's famous theory of humours, people have speculated about links between personality or mind and biology or body. For example, Freud (1923) anchored his theory of the mind or personality in biology, and Murray (1938) defined needs as "physio-chemical" forces in the brain. In the mid 20th century, Eysenck began a sustained effort to link the trait factors of personality, extraversion, neuroticism, and psychoticism, to individual differences in nervous system structures and functioning. Early on (Eysenck, 1957; 1967), he used Pavlovian concepts of excitation and inhibition; later (Eysenck & Eysenck 1985; Eysenck, 1990), he turned to arousal and such brain structures as the reticular formation[1] and the limbic system (described in Footnote 52). Gray (1981; 1987a) proposed an alternative factor structure of traits and a correspondingly different conception of their biological basis (described in more detail in Section 1.3). Cloninger (1991; 1998) proceeded in the opposite direction, using individual differences in chemically defined neural pathways to define scales of personality traits. Heritability studies flourished as a way to estimate genetic contributions to trait differences. Though, for all of the progress and excitement, at the beginning of the 21st century, almost 2,500 years since Hippocrates, definitive and replicable results linking biology and personality still remain somewhat elusive. However, modern versions of the theories of the past, which attempted to understand personality and its psychobiological substrates via the usual methods of natural science, are now being given fresh impetus by our abilities to carry out advanced functional imaging studies of the brain and to interpret these findings in relation to neurally inspired computational models of the relevant brain systems and/or processing operations.

In recent times, Hans Eysenck's and Jeffrey Gray's theories have been most influential on studies concerning the psychobiology of personality. They have been among the foremost proponents of the hypothesis that personality traits provide a window on individual differences in brain functioning. Gray (1973) revolutionised thinking about the nature of personality traits, arguing that they reflect motivational systems that evolved to increase adaptation to classes of stimuli associated with positive and negative reinforcement. Individual differences in personality thereby reflect variation in the sensitivity to such stimuli, and overall personality represents the relative strength of sensitivities to various stimulus classes. For example, impulsive people have been described as more sensitive to reward than to punishment, approaching reward situations even when punishers make restraint more appropriate (see Gray, 1973; Pickering & Gray, 1999; Section

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[1] The reticular formation contains a number of neuron groups and fiber tracts that run the full length of the lower brain stem (medulla, pons, and midbrain). The ascending fibers carry information to the cerebellum, hypothalamus, thalamus, limbic system, and cerebral cortex. These connections allow the reticular formation to modulate the activity of neurons diffusely throughout the central nervous system, and thereby regulate both the sleep-wake cycle and levels of arousal and activity while awake (Crossman & Neary, 2000).

1.7.6). Sensitivity ultimately means reactivity of the neurobiology associated with a motivational system. Gray (1973; 1992) accordingly outlined neurobehavioural models of several traits and others have extended Gray's work (Cloninger et al., 1993; Netter et al., 1996; Zuckerman 1991). Nevertheless, a comprehensive neurobehavioural model of personality traits has yet to be proposed. Such a model must specify the behavioural and emotional characteristics of each trait, the brain structures that underlie each trait, and the neurobiological variables that account for individual differences in the expression of each trait. The aim of this research is to help clarify these issues for the personality trait of impulsivity. Impulsiveness (or impulsivity), in its narrow sense, is usually defined as a tendency to act rapidly without deliberation or consideration (discussed further in Section 1.4.1).

### 1.3 Why Focus on Impulsivity and not Extraversion?

Impulsiveness has been considered basic to the concept of extraversion (E) (Eysenck 1981), and Eysenck's E scale was sometimes used as a measure of impulsivity. However, impulsivity has developed from being thought of as a facet of E to being considered a trait in its own right, which is highly correlated with E. For example, E has been shown to correlate positively with the Barratt Impulsivity Scale (a self-report measure of impulsivity) (Barratt & Patton, 1983).

One reason I have chosen to investigate impulsivity rather than extraversion is that Gray's model of personality, which emphasises impulsivity as a main trait with a biological underpinning, has a better founding based on experimental evidence (discussed in detail below) than Eysenck's model, which emphasises extraversion as a main trait related to biological systems. In comparing the two theories I am mainly concerned with studies of extraversion (E) and neuroticism (N) on the one hand (Eysenck's theory) and anxiety (Anx) and impulsivity (Imp) on the other (Gray's theory), because the two theories have a similar view of psychoticism (P). Studies show that Imp and Anx are more strongly and coherently related to dependent measures (Gray, 1981). Validation of Gray's theory is also provided by experiments showing that personality effects are primarily moderated by reinforcement signals (as Gray predicts) rather than level of stimulation or arousal (as Eysenck predicts) (see Corr et al., 1997; Pickering et al., 1997). Also, overall, mood data fit with Gray's theory quite well (Matthews & Gilliland, 1999).

Gray's personality theory began as a modification to the Eysenck theory, but now is usually seen as an alternative theory (Gray, 1981). Eysenck (Eysenck 1967; Eysenck & Eysenck, 1985), in his revised 1967 "Arousal" model proposed that there is a biological foundation for extraversion and neuroticism, or lack of that trait. He identified two principal brain systems as the key components of his conceptual nervous system: reticulo-cortical (controlling the cortical arousal generated by incoming stimuli) and reticulo-limbic (controlling responses to emotional stimuli) circuits. He believed that E relates to arousability of the reticulo-cortical circuit, so that extraverts are typically more aroused than introverts. However, people actively seek a moderate level of arousal, so that relationships between personality and arousal may also reflect individual

differences in strategies for seeking or avoiding stimulation. In addition, under high levels of stimulation, a protective "transmigrational inhibition" may lead to paradoxically reduced arousal. For example, introverts may have higher levels of activity in the reticular part of the brain, and thus be chronically more aroused, than extraverts (Eysenck, 1994). Eysenck associates N with arousibilty of the limbic circuit, such that neurotics become more aroused than stable individuals as a consequence of emotion-inducing stimulation. So, neuroticism is founded on a separate biological system related to the visceral brain that produces autonomic arousal. Eysenck separates the arousal produced by reticular activity, the basis for extraversion, which he calls "arousal", from the autonomic arousal, the basis for neuroticism, which he calls "activation". The neuropsychology of Eysenck's third dimension of P has not been worked out in detail. Eysenck (1992) suggests that P is inversely related to serotonergic function, but more recently (Eysenck, 1997), that P is linked to dopamine. A criticism of Eysenck's personality theory is that the testing is based entirely on self-reports and is therefore likely to be heavily influenced by the respondent's mood at the time.

Gray, on the other hand, agreed with Eysenck's former 1957 (Eysenck, 1957) model, which had *anxiety* and *impulsivity* as sub-levels of extraversion, but then decided to form his own theory based on those traits rather than Eysenck's 1967 arousal/activation theory (Eysenck, 1967). Gray disagreed with Eysenck's elimination of Impulsivity from his 1967 model, and therefore changed Eysenck's theory by modifying both the psychometric alignment of the personality dimensions and, to some extent, their biological bases. Gray (1970) modified Eysenck's theory by proposing two new dimensions of anxiety (Anx) and impulsivity (Imp) oriented at 30 degrees from Eysenck's orthogonal E and N dimensions (see Figure 1.2 for Eysenck's model with Gray's new dimensions superimposed). Gray's model is often assumed to posit a 45 degree rotation, but Gray points out that this is a misconception derived from the way in which the model was presented graphically (e.g. Gray 1981). The 30 degree rotation model aligns Anx most closely with N and Imp most closely with E. Anx also correlates to some degree with introversion and with low psychoticism (Gray 1987b). The Imp dimension correlates most highly with E, but also correlates to some extent with P and N.

Gray's conceptual nervous system (Gray 1987a) is shown in Figure 1.3 (Pickering & Gray, 1999). Anxiety is associated with sensitivity of the "behavioural inhibition system", which is activated by fear, novelty stimuli, and signals of punishment or non-reward. As anxiety levels increase, sensitivity to punishment, non-reward, and novelty signals also increase. The core of the system is a septo-hippocampal comparator that detects mismatch between the actual and the predicted state of the world. Mismatch detection results in inhibition of ongoing behaviour and increased arousal and attention. The comparator works in conjunction with other brain structures, such as the PFC, permitting some cognitive control over anxiety in humans and various ascending afferents from more primitive levels of the brain. Gray (1987a) discusses the neural system supporting Imp, the "behavioural activation system", more briefly. It is sensitive to signals of reward and non-punishment and influences probability of approach behaviour. So, as impulsivity

levels increase, sensitivity to reward and non-punishment signals also increase. Gray (1987a, 1991) sees the "behavioural activation system" as associated with mesolimbic dopaminergic pathways ascending nucleus A10 of the ventral tegmentum of the brainstem (Gray et al., 1991). Gray agrees with Eysenck that a third major dimension of personality is required, aligned at least approximately with P, which Gray (1991) relates to the fight/flight system. Gray believes that extraversion-introversion (E-I) and neuroticism (N) result from the interactions of anxiety and impulsivity. In short, the "behavioural activation system" activates approach behaviours in response to cues for reward or non-punishment. It may be linked neurophysiologically with the motor programming system and the neurotransmitter dopamine is said to play an essential moderating role in the functioning of the "behavioural activation system". The cluster of approach traits such as extraversion, impulsivity, novelty searching and positive affectivity have all been discussed in terms of the "behavioural activation system", which is often referred to as the *engine* of behaviour. In contrast, the "behavioural inhibition system" is the braking system to the engine of the "behavioural activation system". It activates inhibitory behaviours in response to signals of punishment, non-reward, novel stimuli, and innate fear stimuli. The "behavioural inhibition system" is affected by the neurotransmitter serotonin. It is important to note that most of Gray's work has been exclusively done on animals, which makes generalizing his results to humans slightly difficult.

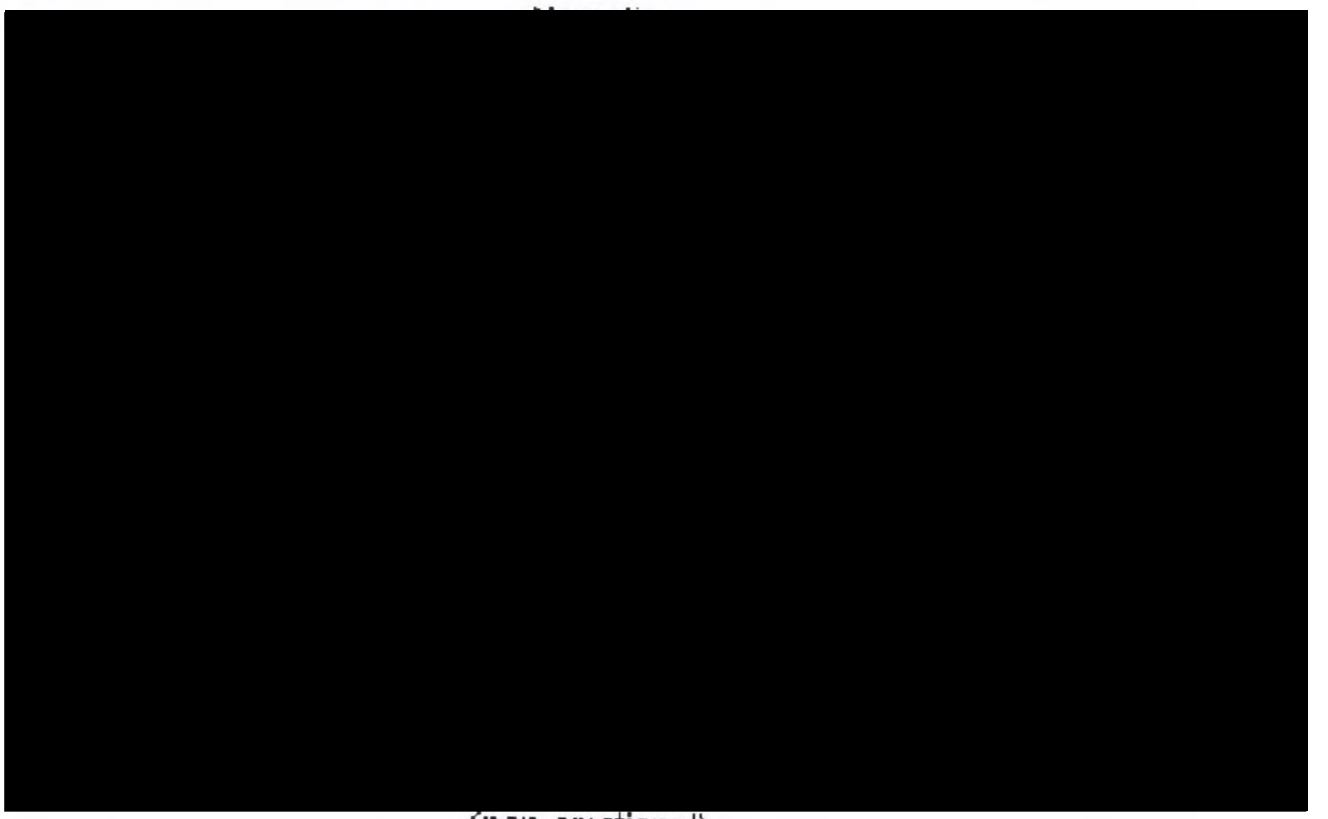


**Figure 1.2**: Pictorial model of Eysenck's theory of personality with Gray's dimensions of Anxiety and Impulsivity superimposed at 30° rotations. Eysenck believes that there are two major dimensions of personality accounting for the many different types of personality we encounter. They are *extraversion-introversion* and *neurotic-normal (emotionally stable)*. Each of these dimensions is made up of several second-order factors. Extraversion breaks down into activity, sociability, risk-taking, impulsiveness, expressiveness, reflectiveness, and responsibility and neuroticism into self-esteem, happiness, anxiety, obsessiveness, autonomy, hypochondriasis, and guilt. When the factors are plotted against one another, we end up placing a person on the scales shown in the diagram. The quarters of the circle roughly correspond, incidentally, to the ancient Greeks' division into phlegmatic, choleric, sanguine, and melancholic (Underwood, 2000).

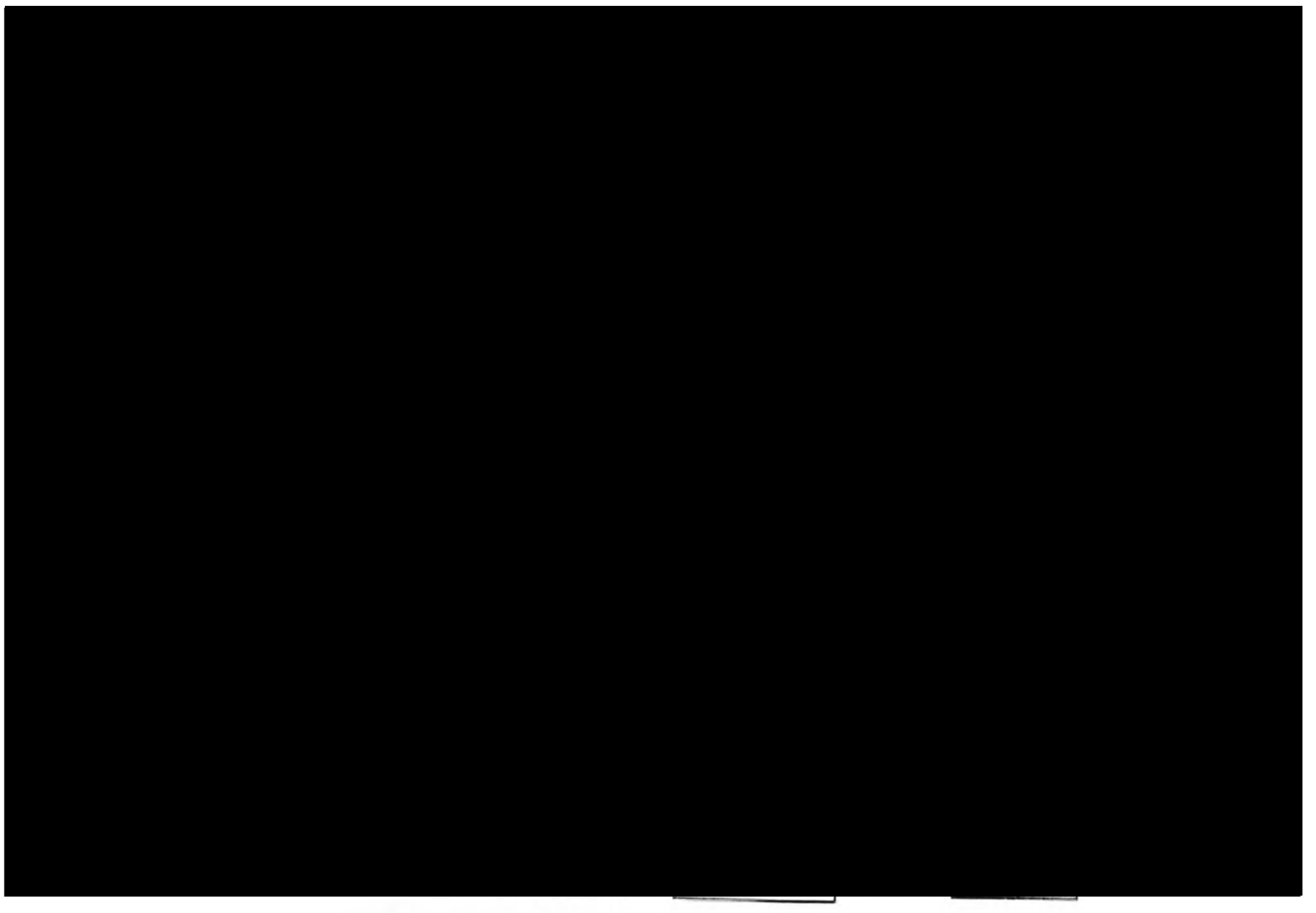

**Figure 1.3**: Jeffrey Gray's schematic conceptual nervous system model with "behavioural activation system" and "behavioural inhibition system" interactions (Pickering & Gray, 1999). The arousal system is depicted as affecting response selection mechanisms but it is likely to have a direct effect on the response systems. Pathways are functionally excitatory except where minus signs indicate functionally inhibitory effects. Learned inputs are denoted by pathways ending in round arrow heads. Gray argues that inhibition of the "behavioural inhibition system" by the "behavioural activation system" may be significant (Pickering & Gray, 1999).

Although there are many studies with conflicting results, physiological studies tend to support Gray's theory. Eysenck predicts that both E and N should relate to central nervous system and autonomic nervous system arousal respectively. In Gray's theory, if both "behavioural activation system" and "behavioural inhibition system" activity feed into greater noradrenergic arousal, impulsives (or neurotic extraverts in Eysenck's theory) are expected to show more arousal in response to reward signals, whereas anxious (or neurotic introverts in Eysenck's theory) individuals should be more responsive to punishment cues. In an Electroencephalogram (EEG)[2] study, Stenberg (1992) manipulated positive and negative imagery in subjects classified by the Eysenck Personality Inventory (Eysenck & Eysenck, 1964; measures E and N) and the Karolinska Scales of Personality[3]. The Eysenck Personality Inventory E and N dimensions were not significantly related to any of the EEG measured brain activity. However, factor analysis of the joint personality scales revealed factors that resembled Gray's Imp and Anx dimensions. More impulsive subjects showed signs of lower EEG arousal than low impulsive subjects and more anxious subjects showed greater right-side frontal theta activity across all conditions, suggesting higher emotionality. Further, high anxious subjects showed higher beta rhythm activation to the negative emotional condition, but the high impulsives did not show a corresponding reaction to the

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[2] The physics of the physiological and brain imaging techniques [i.e. EEG/ERP (p.19), fMRI (p.38), PET(p.55), CT(p.83), and MRI (p.83)] can be found in Toga & Mazziotta (2000).

[3] A 135-item questionnaire measuring relatively stable personality traits that are often classified into four factors associated with neuroticism, psychoticism, non-conformity, and extraversion (see Ortet et al., 2002).

positive emotional condition. These results suggest that the use of Gray's dimensions is preferable. Stenberg also concludes that there is more support for the view that Imp is associated with *low* arousal than with facilitation of positive affect. O'Gorman & Lloyd (1987) also found evidence that Imp may be especially predictive of brain activity, in line with Gray's theory, as opposed to E. Measures of spontaneous EEG activity in the 8-14-Hz band (alpha) obtained while subjects opened and closed their eyes on instruction were related to scores on the Eysenck Personality Questionnaire-E (Eysenck & Eysenck, 1975; measures E and N) scale and scales of narrow and broad impulsiveness. Subjects with high scores on narrow impulsiveness were found to show less alpha activity than subjects with low scores. No significant relationships with alpha activity emerged for the other personality scales. It was concluded that impulsiveness rather than Eysenck Personality Questionnaire-E is the major correlate of differences in EEG-defined arousal.

On balance, findings in conditioning experiments appear to favour Gray (1981). Studies by Gupta (1990; Gupta & Gupta, 1984; Gupta & Shukla, 1989) confirm a primary prediction of the theory, that of enhanced instrumental conditioning to reward signals. Further, results with verbal operant conditioning under reward are more consistent with Gray's than with Eysenck's theory and some studies suggest that Anx and Imp are more reliable predictors of conditioning than E and N (although there are others that fail to support this conclusion). In addition, effects of E on eyelid conditioning were found to be associated with Imp and venturesomeness rather than with sociability and E (Eysenck & Levey, 1972; Frcka & Martin, 1987). Gray (1981) infers that Imp rather than E may be the key causal factor. Additionally, Barratt (1971) found that both Imp and Anx were correlated with stronger conditioning. Gray's dimensions were also more valid predictors of conditioning than E and N in studies that required subjects to learn to respond to "go" cues or reward signals, indicating reward or active avoidance of punishment and to "no-go" cues or punishment signals indicating omission of reward or passive avoidance of punishment (Zinbarg & Revelle, 1989; Corr et al., 1995a). Thus, the conditioning data show effects of Gray's dimensions.

So, consistent with Gray's (1981) position, there are some areas of research where Imp does seem to be somewhat more predictive than either sociability or E, including spontaneous EEG (Stenberg, 1992) and interactive effects of personality and caffeine on verbal ability (Revelle et al., 1980). Further, other paradigms, most notably mood induction and instrumental conditioning, show differential effects of reward and punishment manipulations comparable with Gray's theory. Hence, Gray's theory receives its greatest support from the role of motivational signals as an important factor moderator of personality effects and from the broad association between Imp and "behavioural activation".

Despite the supportive evidence for Gray's theory cited above, the association of impulsivity with extraversion remains an unresolved issue. Impulsivity is made up of a heterogeneous cluster of lower order traits that includes terms such as sensation seeking, risk taking, novelty seeking, boldness, adventuresomeness, boredom susceptibility, and unreliability. On the basis of Jung's concept of extraversion, Eysenck & Eysenck (1975) included impulsivity in

their measure of extraversion, only to remove much of it later because evidence indicated that impulsivity and extraversion were separate traits (Guilford 1975, 1977; Rocklin & Revelle, 1981). Currently, most models of trait personality also separate impulsivity and extraversion into distinct traits (Costa & McCrae, 1985; 1992; Goldberg & Rosolack, 1994; Tellegen, 1985; Tellegen & Waller, 1997; Zuckerman, 1994; Zuckerman et al., 1991). However, several trait psychologists continue to associate impulsivity and extraversion. Gray (1973; 1987a; 1992) proposed that impulsivity represents the interaction of the higher-order traits of extraversion, neuroticism, and psychoticism. Eysenck (Eysenck, 1981; Eysenck & Eysenck, 1985) defines lower-order traits of extraversion that include sensation seeking, venturesomeness, carefreeness, and liveliness, whereas impulsivity itself is included in the higher-order trait psychoticism (Eysenck et al., 1985a). Similarly, Cloninger's personality questionnaire replaces extraversion with a higher-order trait of novelty seeking, which, according to several lines of evidence, is aligned much more closely with impulsivity and sensation seeking than with extraversion (Cloninger et al., 1991; 1993; Heath et al., 1994; Stallings et al., 1996; Waller et al., 1991; Zuckerman et al., 1991).

This issue is complex because the content of different measures of impulsivity is heterogeneous, ranging from purely motor and cognitive impulsivity to novelty and sensation seeking, boldness, thrill and adventure seeking, and risk taking. Not all of these measures are highly interrelated nor are they consistent in their correlation with extraversion (Depue & Collins, 1999). Depue & Collins (1999) plotted the loadings of personality traits from 11 studies in which more than one multidimensional personality questionnaire was jointly factor analysed as a means of deriving general traits of personality. All of these studies defined a general non-affective impulsivity trait, referred to as constraint, which was separated from the general extraversion trait. Extraversion and non-affective constraint dimensions were generally identified and found to be orthogonal and impulsivity/sensation seeking (ISS) traits associated with strong positive affect (e.g. novelty seeking, sensation seeking, venturesomeness, boldness, and risk-taking) arose as a joint function of the interaction of extraversion and constraint.

Cloninger (1986; 1987; Cloninger et al., 1991) and Zuckerman (1991) have argued that a major line of neurobiological influence lies with the cluster of impulsivity and sensation seeking (ISS) traits rather than along the extraversion dimension. Similarly, Gray (1973, 1987c, & 1992) proposed that impulsivity rather than extraversion is associated with a line of causal influence. Depue & Collins (1999), at odds with Gray, Zuckerman, and Cloninger, align the causal neurobiological axis of personality with extraversion rather than the cluster of ISS personality traits which lie rotated approximately 45 degrees from extraversion in the direction of low constraint. Depue & Collins (1999) expect that dopamine correlates of ISS traits would tend to be weak and inconsistent, whereas more consistent correlations should be found with extraversion. However, even Depue & Collins (1999) concede that the data are indecisive and scanning measures of dopaminergic function appear to align more closely with ISS traits than extraversion. Therefore, based on the above evidence, the fact that impulsivity rather than extraversion is used as a

descriptive personality trait and/or behavioural characteristic in clinical populations, and the fact that impulsivity can be operationalised more definitively than E to be measured in non-human animal as well as human studies, I am focusing my investigation on impulsivity.

I am however measuring E in the context of a 5 trait personality self-report questionnaire. The Big Five Inventory (John et al., 1991), a personality questionnaire in standard use, measures five major personality traits (openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism) and was administered to examine the relationship between impulsivity and other personality traits, in particular extraversion.

## 1.4 Impulsivity

### 1.4.1 Definition of Impulsivity

The concept of impulsivity covers a wide range of "actions that are poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation and that often result in undesirable outcomes" (Evenden, 1999a, p.1). Thus, impulsivity plays an important role in normal as well as pathological behaviour as expressed in many forms of mental illness such as personality disorders, mania, ADHD, and substance abuse disorders. Impulsiveness can be defined in a broad sense as a character trait that relates to the control of thoughts and behaviour. It interacts with other personality traits to impact everyday behaviours that are classified as normal, pathological, or marginal within the context of the social definition of mental health. This classification can be based on several different procedures including the use of cut-off points on a measurement scale that separates normal from pathological behaviours (see Section 4.2). Thus, impulsivity in combination with other personality traits produces a wide range of profiles that can be related to normal or pathological behaviours (see Section 4.4.1.3).

Impulsivity has also been defined as swift action without forethought or conscious judgment (Hinslie & Shatzky, 1940), behaviour without adequate thought (Smith, 1952), and the tendency to act with less forethought than do most individuals of equal ability and knowledge (Dickman, 1993). Some definitions of impulsivity include a number of subtraits. Eysenck and Eysenck (1977) related impulsivity to risk taking, lack of planning, and making up one's mind quickly. Patton et al. (1995) separated impulsivity into three components: acting on the spur of the moment (motor activation), not focusing on the task at hand (attention), and not planning and thinking carefully (lack of planning). Some authors argue that impulsivity and compulsivity are opposite ends of a spectrum (Stein et al., 1994, 1996). Others contend that event-related cortical potentials can be used to measure impulsivity (Marinkovic et al., 2000) and still others that impulsivity can be measured with laboratory behavioural tasks (Cherek et al., 1997; Dougherty et al., 1999a).

Biological studies examining impulsive aggression (Barratt et al., 1997a; Linnoila, 1983) have found that individuals who planned aggressive acts had larger evoked potential amplitudes and higher cerebral spinal fluid serotonin metabolite levels than those who did not plan similar

aggressive acts. Likewise, individuals with impulsive aggression responded differently to treatment with anticonvulsants than did individuals with planned aggressive acts (Barratt et al., 1997b). Thus, a definition of impulsivity needs to incorporate rapidity of response and lack of planning.

Several behavioural models of impulsivity have been developed on the basis of findings from laboratory tasks used to measure impulsivity. These tasks fall into three broad categories: 1) punishment and/or extinction paradigms, in which impulsivity is defined as the perseverance of a response that is punished or unrewarded (Matthys et al., 1998); 2) reward-choice paradigms, in which impulsivity is defined as preference for a small immediate reward over a larger delayed reward (Ainslie, 1975); and 3) response disinhibition/attentional paradigms, in which impulsivity is defined either as making responses that are premature or as the inability to withhold a response (Dougherty et al., 1999b; Halperin et al., 1991). To incorporate these models into a definition of impulsivity, the definition should include the following elements: 1) decreased sensitivity to *negative* consequences of behaviour; 2) lack of regard for long-term consequences; and 2) rapid, unplanned reactions to stimuli before complete processing of information.

Socially, impulsivity has been thought of as a learned behaviour, coming from a family environment in which the child learns to react immediately to obtain what is desired for gratification (L'Abate, 1993). In this framework, impulsive individuals do not have the capacity to weigh the consequences of actions, either for themselves or for others. Thus, a definition that includes the social aspects of impulsivity needs to incorporate the fact that impulsivity often has an impact, not only on the impulsive individual, but also on others.

Moeller et al. (2001) proposed a definition of impulsivity that could be used to bridge the gap between clinical work and research. They defined impulsivity as:

> "a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or to others" (p. 1784).

Several key features of this definition should be highlighted. First, impulsivity is defined as a *predisposition,* part of a pattern of behaviour rather than a single act. This distinction is important clinically because research on treatment of impulsive aggression shows that individuals with a pattern of impulsive aggression respond differently to medication than those with a pattern of primarily premeditated aggression (Barratt et al., 1997b). Second, impulsivity involves *rapid unplanned* action that occurs before the opportunity to consciously weigh the consequences of an act. This feature separates impulsivity from impaired judgment or compulsive behaviours, in which planning occurs before the behaviour. Again, this distinction is important for research and treatment. Incarcerated individuals with premeditated aggression (arguably poor judgment) exhibited different patterns of brain activity than incarcerated individuals with impulsive aggression (Barratt et al., 1997a). Last, impulsivity implies action *without regard to the consequences* of these actions. Impulsivity often involves risks, but it is not the result of the types of risk often related to sensation seeking. The aspects of impulsivity described in Moeller et al.'s (2001) definition are

important because they can be related to the underlying biological substrates of impulsive behaviour and hence to treatment for impulsivity.

### 1.4.2 Measurement of Impulsivity

There is confusion about exactly how to conceptualise and measure impulsivity which has been an imprecise construct in the literature. Dozens of scales, subscales, and behavioural measures have been created to measure impulsivity, which are only modestly inter-correlated (Barratt & Patton, 1983; White et al., 1994; Parker & Bagby, 1997), suggesting different underlying conceptions of the construct. The literature reveals considerable diversity in theory, definition, and approach to the measurement of impulsivity (Luengo et al., 1994), with little agreement on how to conceptualise the construct (Parker & Bagby, 1997). Different schemes to characterise the multidimensional nature of impulsivity have been proposed (Gerbing et al., 1987; White et al., 1992) but have had little impact on the research and theory concerning the mechanisms underlying impulsivity. However, recent studies have identified a range of important potential mechanisms underlying impulsive behaviour.

The term impulsiveness has been applied to many different aspects of the operant behaviour of humans and animals, for example the emission of premature responses in schedules in which reinforcement is made contingent upon pausing (Gordon, 1979; Van den Broek et al., 1987a; Sagvolden & Berger, 1996), emitting short latency incorrect responses in conditional discrimination tasks (Kagan, 1966; Van den Broek et al., 1987b; Harrison et al., 1997a; Evenden, 1999b), failure of responding to decline in extinction schedules (Berger & Sagvolden, 1998; Sagvolden et al., 1998), premature termination of sequences of response (Evenden, 1998a), impaired temporal differentiation of responding (Walker, 1982; Van den Broek et al., 1992), and choice of small earlier reinforcers in preference to delayed larger reinforcers (Ainslie, 1975; Mazur, 1987; Logue, 1988). It seems unlikely that such disparate behaviours reflect a unitary underlying behavioural process, however deficits in behavioural inhibition (Soubrie, 1986), waiting capacity (Thiebot et al., 1985), timing (Siegman, 1961; Barratt, 1981), behavioural switching (Ho et al., 1998), and tolerance of delay of gratification (Mischel, 1966; Logue, 1988) have been proposed to encompass many of these behavioural phenomena (for a review see Ho et al., 1999). Further, given the diversity of behaviours most often characterised by impulsivity (e.g. violence, gambling, spending sprees, substance abuse, promiscuous sexual behaviour, and self-injurious behaviour), it seems it can not be best understood as a product of a single appetitive or particular consumed substance. Instead impulsive behaviour must be related to the pattern of rewards available for certain behaviours.

Impulsiveness may arise from properties that generally reward behaviour (Mazur et al., 1987; Shizgal & Conover, 1996). In fact, some argue that measurement of impulsivity is implicitly or explicitly equated with the effect delay has on the value of reward (Monterosso & Ainslie, 1999). They believe that impulsivity in animal models, which typically use one of three models:

delay of reward, differential reinforcement of low rate responding (DRL), or autoshaping, can be measured in this way. The steepness by which delay diminishes value (the temporal discount function) is treated as an index of impulsivity, since it has long been observed that the basic machinery of motivation favours more immediate reward. An organism, be it a person or pigeon, will engage more readily in a behaviour that immediately brings a positive outcome than one in which the same outcome occurs after a period of delay. The function relating the length of delay to the diminution in the motivating force of the reward is the temporal discount factor.

Deficient inhibition of prepotent behaviour, assessed using "stop-signal" tasks has been associated with attention deficit hyperactivity disorder (ADHD) and trait impulsivity (Schachar et al., 1993; Logan et al., 1997). Impulsivity in drug users has been linked to increased discounting of delayed large rewards in favour of immediate small rewards (Kirby et al., 1999). Impulsive aggressive behaviours have also been associated with executive cognitive processes (Lau et al., 1995). Further, considerable research suggests that impulsive behaviour is associated with increased reward responsiveness or reduced responsiveness to punishment (Newman 1987; Lykken, 1995). Although these studies have contributed to our knowledge of the mechanisms of impulsivity and behavioural regulation, their major limitation is that they present only single mechanism models of impulsivity. Evidence from studies of human personality suggests that impulsivity may be made up of several independent factors (Evenden, 1999c). There seems to be not just one unitary "impulsivity" or only one type of impulsive behaviour, instead there seems to be several related phenomena that are usually classified together as impulsivity and that lead to different forms of impulsive behaviour which may be influenced by different biological mechanisms. Thus, perhaps different facets of impulsivity relate to different areas of the brain (specifically, within the PFC). Accordingly, the construct of impulsivity was tested in this study using different measures that perhaps assess slightly different functions, which collectively may give an approximate measure of the multivariate construct of impulsivity. Due to time constraints, I did not attempt to measure all of the diverse behaviours that have traditionally been labelled as impulsive but rather, I measured a few specific aspects of impulsivity. The reasons I have chosen to examine those particular aspects of impulsivity are discussed below.

Although a wide variety of measures are correlated with impulsivity and many have been used as "measures" of impulsivity, there are primarily three main classes of instruments that appear to measure key aspects of impulsivity: self-report measures, behavioural/laboratory measures (including temporal measures, although discussed in a separate section), and event-related potentials.

#### 1.4.2.1 Self-report Measures of Impulsivity

Traditionally, human personality is studied methodologically by applying factor analysis to the responses made to self-report questionnaires, to examine whether the variability in the answers can be accounted for by one or more statistical factors. As questionnaires are revised over a long period

of research, the factors emerging from the analysis may change but this does not mean that human personality has changed but rather the questionnaire may not capture the complexity of what is being studied. Questionnaires purported to measure impulsivity provide evidence that the construct of impulsivity is multifaceted and can be described in a variety of different ways (see Evenden, 1999a). Personality theorists have devised a number of measures of impulsiveness and self-control, mostly, but not exclusively, based on self-report questionnaires (Barratt, 1981, 1983; Barratt & Patton, 1983; Eysenck et al., 1985b). These measures have helped reveal impulsiveness as a behavioural feature that can vary between individuals and that may correlate with biological variables (Barratt, 1983; Eysenck & Eysenck, 1977).

Since a single definition of impulsivity is not readily agreed upon, it can be operationally defined and the measures of impulsivity used should be chosen accordingly. I have thus chosen specific questionnaires and behavioural measurements of impulsivity with this in mind. I elected to administer the Barratt Impulsivity Scale (BIS-11) (Barratt 1959; Patton et al., 1995) as it is the first impulsivity scale developed specifically to measure impulsiveness that was not part of an omnibus test battery like the Thurstone Temperament Scale (Thurstone, 1953). As discussed above, there are many measures and definitions of impulsiveness based on a wide range of models including psychosocial development (L'Abate, 1993), arousal (Eysenck & Eysenck, 1985), information processing (Dickman, 1993), learning theory (Wallace & Newman, 1990), and biological substrates (Gray, 1987a,c; Stein et al., 1993). The Barratt and Patton (1983) approach assumes that there is some truth in all these theories of impulsiveness because data consistent with the construct defined by each theory have been explained. The BIS, which has gone through several versions, was initially developed to separate impulsiveness from anxiety. Barratt and his colleagues are aware of the shortcomings of self-report scales, like the impulsive patients' questionable ability to assess their own cognitive function, but they offer little in the way of alternatives. Analysis of the BIS-10 (Patton et al., 1995) lead to three second order factors: attentional, motor, and non-planning impulsiveness. Barratt (1994) suggests that the BIS-11 is made up of three subtraits: "ideomotor" impulsiveness involving acting without thinking, a "careful planning" subtrait involving attention to details, and a future oriented "coping stability" subtrait that seems to differentiate most between normal controls and patients with psychopathy (Barratt, 1994).

H. J. Eysenck has been influential via his theory that E, and by extension, impulsivity, are caused by low cortical arousal (Eysenck, 1967). Even though this theory is controversial, as it does not explain all of the data, it has inspired many studies. Eysenck is best known for identifying three dimensions of personality, extraversion (E), neuroticism (N), and psychoticism (P) (Eysenck & Eysenck, 1985), based upon self-report questionnaires. He found that items which intuitively reflected impulsivity are often associated with different personality factors on the Eysenck Personality Questionnaire-R (Eysenck & Eysenck, 1992; measures E, N, and P), namely P and E. He notes that there is a difference between postulating the existence of a trait and demonstrating it psychometrically. Eysenck's impulsiveness scale, the I-5 (Eysenck & Eysenck, 1977), and later,

the revised I-7 (Eysenck et al., 1985b), identifies two factors; impulsivity described as unconscious risk taking, and venturesomeness or conscious sensation seeking. Empathy was used as a buffer category (Eysenck, 1993). I have not chosen to use Eysenck et al.'s (1985b) Impulsiveness scale (I-7), a standard self-report measures of impulsivity, for it has been shown to correlate significantly with the BIS-10 (Luengo et al., 1991) and to use both measures would be redundant. Further, it has some overlapping questions with the BIS-11 and it tests other factors in addition to impulsivity (i.e. ventursomeness and empathy) which are not of prime concern to this investigation.

Self-report measures, such as the Barratt Impulsiveness Scale (Patton et al., 1995) and the Eysenck Impulsiveness Scale (I-7) (Eysenck et al., 1985b), have the advantage of allowing the researcher to gather information on a variety of types of acts and on whether these acts constitute long-term patterns of behaviour. Examples of items used in self-report measures include: "I act on impulse" and "I plan tasks carefully". The drawbacks of self-report measures include the need to rely on the veracity of the individual completing the questionnaire. In addition, these measures are unsuitable for repeated use, thus limiting their usefulness in treatment studies.

### 1.4.2.2 Behavioural Measures of Impulsivity

In addition to measuring impulsivity based largely on introspection and self-report there are a number of behavioural approaches that assess impulsiveness (Barratt & Patton, 1983; Wallace and Newman, 1990). These have advantages in that they can be used to study the behaviour of both animals and humans. Three broad categories of behavioural laboratory paradigms have been used to measure impulsivity: 1) punishment and/or extinction paradigms (Matthys et al., 1998), 2) reward-choice paradigms (Ainslie, 1975), and 3) response disinhibition/attentional paradigms (Dougherty et al., 1999a; Halperin et al., 1991). However, as stated above, the construct of impulsivity is multifaceted and can be described in a variety of different ways

Some tests measure impulsivity in terms of behavioural inhibition or the ability to suppress behaviour when faced with punishment, novelty, or non-reward. This is typically measured by a Go/No-Go task in which behavioural inhibition is needed or an overt conflict emerges between making ("Go") and refraining ("No-Go") response based on reward, punishment, or non-reward. Another behavioural measure of impulsivity is delay of reinforcement. Logue (1995) states "People often do things that result in some immediate gratification, but which in the long run are not very beneficial. Engaging in such behaviours can be termed impulsiveness." This approach taken by Logue and others like Trevor Robbins and his group of researchers (e.g. Cardinal et al., 2001) considers self-control (the inverse of impulsivity) as a function of factors controlling the choice of delayed reinforcers (Logue, 1988; Rachlin, 1995). In other words, impulsivity is considered a problem with the ability to delay gratification. In this approach impulsivity is usually measured as preference for a small immediate reward over a delayed larger reward. The advantages of this approach are practical, it is easily defined in the laboratory, in can be examined in both humans and other species, and it encompasses quite a lot of human behaviour (Logue, 1988). Yet,

the implication is that impulsivity is a unitary behaviour, which, as discussed above, is more evidently a multifaceted construct that cannot be measured by a single behavioural test.

Buss and Plomin (1975) conclude that impulsivity consists of more than one dimension of control and consider inhibitory control to be the core of impulsivity, but consider decision time, persistence, and boredom or sensation seeking to be other important aspects of impulsivity. Dickman (1990) has distinguished two different types of impulsivity which appear to be unrelated; dysfunctional impulsivity, the tendency to act with less forethought than most people do which leads the person into difficulties, and functional impulsivity, the tendency to act with little forethought when the situation is optimal as not all impulsive behaviour is disadvantageous. Dickman (1993) has also reviewed evidence for the involvement of cognitive processes in impulsivity and proposed that individual differences in impulsivity may be related to differences which allocate attention. Even though impulsive individuals claim to act with less foresight, they often respond more slowly in experimental tasks than non-impulsive individuals (e.g. Dickman, 1985). Dickman suggests that perhaps highly impulsive people spend less of that preparation time focusing on the task in hand. Low impulsives are superior on tasks which require fixation of attention; whereas Dickman suggests that high impulsives could potentially perform better on tasks where attention needs to be switched rapidly. However, Dickman (1993) also identified two aspects of impulsivity which he explicitly omitted from his analysis: reflection-impulsivity and disinhibition. Reflection-impulsivity is measured by the Matching Familiar Figures Test (MFFT) (Kagan, 1966) which Dickman suggests is a separate dimension since results on the MFFT do not correlate with either self-report or other behavioural measures of impulsivity. On the other hand, syndromes of disinhibition are evidenced for example, by an increased number of correct "go" responses in a "go/no-go" discrimination test (Newman et al., 1985). Thus, within functional impulsivity, Dickman identifies at least three separate dimensions: attentional, reflection-impulsivity, and disinhibition.

In addition to administering a self-report measure of impulsivity (the BIS-11), I administered a behavioural measure of impulsivity, the Matching Familiar Figures Test (MFFT). This is a cognitive behavioural measure of reflection-impulsivity and is a standard, internally consistent, stable, reliable, and well validated (Glow et al., 1981) measure of impulsivity. Reflection-impulsivity has been conceptualised as an individual variable describing the cognitive processes involved in reflecting on the accuracy of available hypotheses (Kagan & Messer 1975). Operationally, the variable has been defined as a composite of two dimensions: latency to first response and accuracy of choice or total errors. These two dimensions are combined in the MFFT (Kagan et al., 1964), regarded as the primary (and often the only used) index of reflection-impulsivity.

So, although informative, self-report measures are primarily descriptive of behavioural tendencies in complex social situations, and are therefore unlikely to reveal more fundamental behavioural processes that may be entailed in impulsivity in animals. Barratt (Barratt et al., 1995)

has indicated that restricting the measurement of impulsiveness to self-report, rating scale, or structured interview techniques is an incomplete approach to impulsiveness. "The use of biological measures as well as environmental (primarily social stimuli) or milieu measures of impulsiveness will add significantly to the predictive value of self-report measures" (Barratt et al., 1995). Barratt (1994; Barratt et al., 1995) has suggested, biological and behavioural measures that do not correlate with self-report measures could be used as predictive measures of impulsiveness.

The advantages of laboratory measures of impulsivity include their suitability for repeated use, with consequent suitability for treatment studies, and their potential for use in laboratory animals, thus allowing for comparative studies of the basic biochemistry of these behaviours. For example, animal studies using paradigms that are based on reward-choice models and response disinhibition/attentional models have found evidence for a negative correlation between impulsivity and serotonin function (Evenden, 1999b; Puumala & Sirviö, 1998). The primary disadvantages of these measures are that they do not incorporate the social aspects of impulsivity and do not measure long-term patterns of behaviour.

#### 1.4.2.3 Physiological Measures of Impulsivity

Electrical brain activity or event-related potentials (ERPs) recorded while people perform various tasks have targeted specific waveforms as potential measures of biological predispositions to impulsiveness. Action-oriented personality traits such as impulsivity have been related to a pronounced amplitude increase of auditory evoked ERPs with increasing stimulus intensity (Hegerl et al., 1995). Further, a positive waveform (P300) recorded in response to target stimuli during the performance of a wide range of tasks has been related to impulsivity and impulse control disorders (Sunohara et al., 1999; Harmon-Jones et al., 1997). The advantage of this type of measure is that it is directly related to brain function. One disadvantage is that, like behavioural laboratory measures, ERPs do not incorporate the social aspects of impulsivity. Another disadvantage is that ERPs have been reported to be related to a variety of neurological and psychiatric conditions (Korpelainen et al., 2000; Iwanami et al., 2000) and thus are not a specific measure of impulsivity. Although event-related potentials are not unique markers, combined with other measures of impulsivity, they are valuable predictors. However, ERP tests were not used in this study in consideration of the large number of tests in the battery and the lack of equipment availability.

#### 1.4.2.4 Temporal Measures of Impulsivity

Barratt's research suggests that psychomotor and cognitive processing of time duration as well as "cognitive tempo" are related to impulsiveness (see Section 1.11.3). Stanford & Barratt (1996) analysed data from 150 male adolescents that included verbal, motor, and impulsiveness measures and found that three first order factors (verbal skills, cognitive tempo, and finger tapping) combined to produce one second order factor of temporal information processing. The BIS had a negative loading on the verbal skills factor, and, along with the Matching Familiar Figures Test

(MFFT) (Kagan, 1966 or Kagan et al., 1964), had a positive loading on a cognitive tempo factor. Thus, impulsivity seems to be negatively related to verbal skills and positively related to poor judgements of time duration. Barratt has also shown that timing and rhythm measures of motor and cognitive tasks are related to impulsiveness (Barratt et al., 1981; Barratt, 1983). In the history of the concept of impulsiveness, both motor and cognitive dimensions of impulsivity were evident. Accordingly, Barratt suggests that temporal information processing underlies these two aspects of impulsivity.

"Timing" is another way to test for impulsiveness behaviourally. Van den Broek et al. (1987a) tested impulsive and non-impulsive subjects (measured by the MFFT) using a procedure in which they were asked to space responses by at least 10s (inter-response time (IRT) >10, a.k.a. differential reinforcement of low rate responding (DRL) 10). The presence of a cue light and instructions were varied in four phases. Impulsive subjects consistently earned fewer reinforcers than non-impulsive subjects in the absence of a cue and explicit instructions due to the emission of a higher proportion of short IRTs, although both groups performed near optimal when explicit instructions about the cue light were provided. In Van den Broek (1992), impulsive and non-impulsive subjects were tested on a time reproduction and time production task. The impulsive subjects produced time intervals that were too short and were poorer at discriminating time intervals. Thus, it appears that impulsive individuals have a problem in evaluating subjective time, since for them subjective time seems to pass more slowly, which may lead to the behavioural deficits identified above. Accordingly, participants were given time production, estimation, and pacing tasks. It is predicted that impulsive participants will overestimate and underproduce time intervals and have a faster cognitive tempo than normal participants (see Section 1.11.3 for detail).

Seeing that differences between impulsive and non-impulsive individuals have been found using Van den Broek et al.'s (1987a) model of the DRL test, it would be interesting to compare results of BPD patients to those of normal controls and frontal lobe patients on this task. In the DRL procedure, an operant response is rewarded only if it occurs after a fixed interval of time has expired since the last response. Premature responses not only go unrewarded, but also reset the expired time to zero, after a brief time-out interval. Impulsivity here is equated to the extent to which an organism behaves prematurely, undermining its own attainment of reward. This procedure has also gone by the name "IRT>t" (inter-response time > set time interval). However, in the DRL procedure, organisation of motor behaviour is of primary importance so influences from drug-induced or individual differences in activation or sedation can affect the rate of responding and thus affect the accurate measurement of impulsivity. In other words, it does not distinguish impulsivity from changes in general levels of activity; either hyperactivity or hypoactivity. Therefore, the paced fixed consecutive number schedule (FCN) was developed which uses a choice procedure to measure impulsivity rather than being based upon the rate of responding. The paced FCN minimises the confound between impulsive performance and general level of motor activity and is a useful way to look at deficits of inhibition of behaviour as a measure of impulsivity. The

paced FCN has only been used in animal studies, thus I developed a version that can be used with humans. Once validated, it can be used in a future study as a behaviour test of impulsivity.

In the non-paced or free operant FCN, in animal studies, a fixed number of responses are required on one lever before a response on a second lever can result in reward. If the reward lever is pressed too soon, then there is a brief pause and a new chain of responses must be started. This minimises the DRL problem in that the task is based on response choice, not response rate. A general increase or decrease in response rate brought about by increased activation or sedation should not necessarily affect response choice. However, alterations in response rate will still affect the amount of time taken to complete the schedule requirement, thus not entirely eliminating the potential influence of timing on choice behaviour. So a better alternative is the paced FCN where the maximum rate of responding is controlled by the experimenter, which minimises further the potential influence of timing on choice behaviour. In the paced FCN there is a minimum time between two consecutive responses but no maximum time. Further, the task can be made more difficult by varying the time required to complete the response chain by changing the allowable time between responses. So the amount of time taken to complete the chain can be varied to some extent independently of the number of responses required.

Evenden (1998b) found no advantage of the FCN 32 over the FCN 8 schedule in rats. So I propose using an FCN 8 schedule in humans with button presses spaced out alternatively by 2 seconds (the fast condition) and by 5 seconds (the slow condition). Evenden (1998b) found that in rats, the average chain length in the slow component was consistently shorter than that in the fast component. So, the longer interval responses led to a shorter mean chain length. In the future, I wish to compare the size of decrease in performance between the two conditions in BPD patients, high trait impulsive normals, frontal lobe patients, and normal controls.

Although both are described as measures of impulsivity in the broad sense, the key factors controlling performance on the paced FCN and tests of delay of reinforcement are slightly different. In FCN procedures, organisation of behaviour is of primary importance and in delay of reinforcement procedures, the ability to assess subtle differences in the outcome of behaviour is most important. Yet, the FCN is still measuring the ability to delay a response in order to gain a reward. Thus, the paced FCN test is a viable behavioural test of impulsivity. However, an important feature of impulsivity is not adequately measured by both delay of reinforcement and paced FCN procedures, that of "reflection-impulsivity" (Kagan, 1966) or the need to collect information and reflect upon it before making a decision. Kagan's (1966) MFFT adequately captures this aspect of impulsivity, thus this behavioural test of impulsivity was administered.

Timing is therefore a crucial aspect of impulsivity as it has been shown to affect performance on many different procedures that measure impulsivity such as delay of reinforcement, DRL, and FCN tasks. Such tasks are dependent on the animal's value of temporal intervals. However, based on their investigations, Ho et al. (1998) propose that "behavioural

switching" (or rate of switching between two response alternatives) is the main determinant of performance in at least some of the behavioural tasks relevant to the impulsiveness construct.

#### 1.4.2.5 Summary of the Measurement of Impulsivity

In all, it seems that a satisfactory explanation of impulsivity demands examining several independent, interacting factors. Different suggestions as to what these factors may be, together with some attempt at a brief definition of each, can be found in Evenden (1999a). Although most researchers agree that impulsivity is multi-factorial, there is little agreement as to what these factors are, which could be related to the fact that different researchers use different theoretical approaches as their starting point. Therefore, due to the multi-definitional nature of impulsivity, I have chosen to measure impulsivity by both cognitive/behavioural and self-report methods in order to gain an overall sense of this illusive construct. Also, to investigate the relationship between impulsiveness and temporal processing, time estimation, production, and pacing tasks were administered (discussed in Sections 1.11.3 & 1.11.4). As, based on the evidence described above, it seems that a convergence of data among a wide range of measurements (e.g. cognitive/behavioural, self-report, and temporal) should be used to define impulsivity, a construct with a multitude of definitions.

## 1.5 Emotion

### 1.5.1 Definition of Emotion

Hundreds of philosophers and researchers have tried to create an exact definition of emotion. Unfortunately, the only common ground is the conclusion that emotion is not easy to define (Richins, 1997). The human understanding of what emotions are is a long and complex story. I will present only an outline of this history (for more detail, see Candland et al., 1977; Strongman, 1978; & Leventhal et al., 1986).

The thinkers of the last two thousand years were inspired first by Aristotle and much later by Descartes. In the fourth century BC, Aristotle (c. 384-322 BC) considered emotion an experiencing and evaluating of stimuli that weights experiences, taking into account the potential for gain or pleasure. This definition represents the first signs of dualism, the belief that mind and body are two completely different entities. The consequence of this belief is that mind and body were studied like two isolated and even irreconcilable subjects. For two thousand years the emotion concept did not change measurably. In the seventeenth century, Descartes (1649) thought that emotion mediated between a stimulus and a response, causing the response to be less rational than it would have been. Another important change that this philosopher was involved with was the transformation of the duality of mind-body to a soul-body relation (Strongman, 1978). Aristotle and Descartes have in common that they both used the functioning of the body as a major explanatory principle of emotion. Another commonality is the relevance granted to the mind or, as Descartes named it, the soul. Also, both authors suggested that the mind and the body are two completely different and autonomous elements of a human being. This dualistic approach asserts

that emotion is a mediator between an environmental stimulus and a response, deviating behaviour from a purely rational reaction (Strongman, 1978).

Dictionaries in the 17th and 18th centuries described emotion in a direct meaning from the Latin derivation *emovere* (to move away from): "1695: a moving out, a migration; 1735: causing a movement; 1822: a physical moving, stirring or agitation". Parallel to these developments, a definition related to mental states was also formed: "1660: a vehement or excited mental state; 1735: tending or able to excite emotion; 1808: a mental feeling or affection; 1847: connected with the feelings or passions" (Candland et al., 1977 p. 4).

Since the advent of the scientific method the research of emotion has branched into distinct fields such as psychology, phenomenology, behaviourism, and neurology (Strongman, 1978). The indiscriminate use of concepts like emotion, motivation, affect, and mood by researchers in different areas has created confusion. So as a first approach, I will explain the differences between emotion and these other conceptions (see Holbrook & O´Shaughnessy, 1984). To separate the concepts of emotion and motivation some authors suggest that emotions are externally triggered, that is they are environmental, whereas motivations are internally fired up. Another difference is the active-passive factor. Motivations are action oriented and emotions are a series of reactions to surrounding situations. The discrimination between emotion and affect is even less clear. One possible way to differentiate them is by the strength of an affective state. If the intensity is mild it is considered an affect, if it is intense then it is an emotion (Fell, 1977). Mood and emotion are two terms easily mixed up, but Fell (1977) explains that the former has a longer span and is a general stimulus, in other words it is difficult to determine the source of the mood. Meanwhile, emotion has a short-term effect and it is relatively easy to pinpoint the source of the affective state. Therefore, emotions are responses to environmental stimuli that create an intense but short-term affective state. It is important to realise that this definition is one of many possibilities. Some conceptualisations are broader and even present opposite elements.

One broad and better definition is given by Kleinginna and Kleinginna (1981). They gathered, analysed, and classified 92 definitions and 9 skeptical statements about the concept of emotion concluding that there is little consistency among definitions and many are too vague. Therefore, the researchers suggested a comprehensive definition:

> "Emotion is a complex set of interactions among subjective and objective factors, mediated by neural/hormonal systems, which can: (a) give rise to affective experiences such as feelings of arousal, pleasure/displeasure; (b) generate cognitive processes such as emotionally relevant perceptual effects, appraisals, labeling processes; (c) activate widespread physiological adjustments to the arousing conditions; and (d) lead to behaviour that is often, but not always, expressive, goal directed, and adaptive" (p. 355).

The definition of emotion will change considering the disciplines of the researchers and their objectives. However, no matter how far the study of emotion goes, it is difficult to find one correct and unique definition.

### 1.5.2 Theories of Emotion

In the last century, theories of emotion have developed rapidly in different areas of human knowledge. Biological, behavioural, and cognitive approaches are the most commonly mentioned disciplines in the study of emotion. Every one of these fields works at a different pace and with distinct methodologies creating a wide array of concepts, interpretations, and theories. I will focus on the biological/cognitive approach as I am most interested in the neurological correlates of emotion. The biological approach spans from the study of bodily expression to the new research of the neuronal system. The most relevant theories were created by W. James, C. Lange, W. Cannon, D. Bindra, A. Damasio, and E. Rolls.

One of the most famous theories of emotion was the James-Lange theory created by William James and Carl Lange (1884). According to this theory, arousal and action lead to emotion, as emotion is how we label certain kinds of arousal and action. Thus, when I notice I am running away, I decide I must be afraid. More specifically, James believed that "bodily changes follow directly the perception of the exciting fact, and that our feeling of the same changes as they occur is the emotion" (James, 1890 p. 449). The basic implication of this theory is that the feeling aspect of emotion, provoked by the activity of the cerebral cortex is a response to a change of the body's organs and muscles. This feeling is the emotion itself (Candland 1977).

Critics of the James-Lange theory were Walter Cannon (1927) and Philip Bard (1934). The Cannon-Bard theory argues that emotions and automatic changes occur simultaneously but independently. They proposed that an environmental stimulus activates receptors, which send impulses to the cortex. The cortex stimulates thalamic processes and finally, these processes act in specific patterns that correspond to particular emotional expressions manifested by the excitement of certain muscles and viscera (Strongman 1978). Simply put, the feeling of emotion arises when the thalamus is aroused by an element of the environment.

Bindra (1969) suggested a model that integrates emotional and motivational feelings. This approach is called central motive state (CMS). The CMS is the outcome of the joint perception of environmental and physiological action on a common set of neurons. The firing of the neurons, mediated by the CMS creates autonomic discharge, postural adjustments and environmentally organised motor output (Strongman 1978). The CMS is not a drive state that is autonomous of external conditions, thus it is alterable by experience, but also contains inherited components (Candland et al., 1977). This is an important aspect of Bindra's model because it means that the CMS can be classically conditioned. In other words, an organism can be trained to react in a certain manner to a stimulus via the conditioning of the central motive state.

Recently, Antonio Damasio (1994) reformed the James-Lange theory creating his somatic marker[4] hypothesis. According to his theory, feedback from the peripheral nervous system controls the "decision" about the correct behavioural response rather than the "emotional feelings" as proposed by the James-Lange theory (Kringelbach, 2002).

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[4] A change in body state including musculoskeletal and visceral alterations associated with emotional states.

An alternative approach to these bodily theories of emotion has been proposed by Weiskrantz (1968), Gray (1975), and Rolls (1999). These theorists regard emotions as states elicited by rewards and punishers where emotional stimuli are mediated and evaluated by specific brain structures, which consequently give rise to changes in bodily responses and subjective "feelings" or emotions (Kringelbach, 2002). In other words, emotions are states produced by instrumental reinforcing stimuli. So, sensitivity to reward and punishment, which was tested with the reversal task in this study, should be important in determining emotion. Some stimuli are "primary" or unlearned reinforcers (e.g. the taste of food when an animal is hungry) while others, "secondary" reinforcers, may become reinforcing by learning because they are associated with primary reinforcers (e.g. money or an approaching predator) (Rolls, 1999). Rolls (1986a,b) presents the OFC as a structure involved in the adjustment of previously formed (presumably in the amygdala) stimulus-reinforcement associations, which are the basis of the characterisation of various emotional sates. Rolls (1999) believes that emotions are states elicited by rewards and punishers, including changes in rewards and punishments. A reward is anything for which an animal will work for and a punisher is anything that an animal will work to escape or avoid. Accordingly, many approaches to or theories of emotion have in common that part of the process involves "appraisal" (Frijda 1986; Oatley & Johnson-Laird 1987; Lazarus 1991; Izard 1993; Stein et al., 1994). In addition, this theory takes us full circle back to Aristotle's theory that emotion is experiencing and evaluating stimuli that takes into consideration the potential for gain or pleasure.

Weiskrantz (1968), Gray (1975), and Rolls' (1999) approach to emotion was taken in this thesis as their theory offers several advantages over the other theories of emotion. One main advantage is that this framework offers an operational definition of emotion, namely reward, anything an animal will work for, and punishment, anything an animal will work to avoid. The theory also emphasises the OFC, the area under investigation in this thesis, as a main brain area involved in emotion. In accordance, recent studies have found that the reward value of primary reinforcers such as taste, smell, and visual stimuli can be found in the OFC (Rolls et al., 2000b). Further, although strong reciprocal connections are found between the OFC and the amygdala and scientific evidence suggests a similar role for the two brain areas (LeDoux, 1996; Rolls 1999), the OFC appears to be more important for emotion in humans and higher primates (Rolls, 1999) (discussed further in Section 4.7; see also Footnote 13).

### 1.5.3 Measurement of Emotion

Ventral prefrontal lesion patients[5] have been found to be impaired on an oral subjective emotional change questionnaire compared to non-ventral prefrontal lesion patients (Hornak et al., 1996), the former having significantly more emotional change than the latter. In addition, performance on the subjective emotional change questionnaire was significantly positively correlated with a behaviour

[5] The description "ventral" is given to indicate that there was pathology in the orbitofrontal or related parts of the frontal lobe, and not in the more dorsolateral parts of the frontal lobe.

questionnaire (Rolls et al., 1994; Hornak et al., 1996) designed to reflect the types of behaviour problems that have been found to result from frontal cortex damage (Levin et al., 1991) (the behaviour questionnaire was modified and also used in the current study; see Section 1.8 for details). So, the more "frontal" behaviour exhibited by patients, the more they reported considerable changes in emotion since their injury. In order to extend these findings to determine the relationship of emotion to discrete brain areas within the ventral PFC, a modified version of this subjective emotional change questionnaire, in the form of a written self-report questionnaire, was administered in the current study, which contained patients with more discrete prefrontal lesions. The Emotional Change Questionnaire used in this study measures *change* in capacity to feel each of the following five positive and negative emotions since brain injury: sadness, anger, fear, happiness, and disgust. The questionnaire also assesses the direction of that change, either increased or decreased. However, this questionnaire does not assess the frequency of emotions. Therefore, a Subjective Emotion Questionnaire, based on the Emotional Change Questionnaire, but that assesses *how often* the subjects experience each of the five emotions, was also administered. These questionnaires, measuring both change in capacity to feel as well as frequency of each emotion, were administered to gain a better understanding of the relationship between the PFC, specifically the OFC, and emotion. Further, these questionnaires were given to help determine which specific emotions, if any, are impaired after OFC damage and in the context of BPD and what similarities and differences emerge between these two patient populations' emotional impairments. Finally, comparing information gathered from other tests administered in this battery to the information attained from the emotion questionnaires can help clarify the relationship between emotion, personality, impulsivity, "frontal" behaviours, and reward and punishment insensitivity.

The five emotions chosen for both of the emotion questionnaires were based on Ekman's (Ekman & Friesman, 1975) cross-cultural studies of human expressions, which have strongly suggested an innate, biological basis for emotional experience. His research was based on universally recognised facial emotions and analyses of emotion terms in all the world's major languages (Kringelbach, 2002). Based on this research six "fundamental" emotions emerged, which can act as basic building blocks to our entire emotional repertoire: anger, sadness, happiness, disgust, fear, and surprise. Surprise was not incorporated into the questionnaire used here since it was extended from a previously developed questionnaire (Rolls et al., 1994; Hornak et al., 1996) that did not test surprise because it was considered to be a reaction to novelty versus frequency rather than an emotion. Further, the emotions tested in the original emotion questionnaire corresponded to the main emotions tested in facial and vocal expression identification tasks in which patients also took part, which did not include surprise.

There are some flaws of measuring emotion by this self-report method. For example, patients may lack insight into their emotions, however, when available, answers to the questionnaires were collaborated with staff presiding over the patients or spouses. Methods that use

written or oral descriptions given by a subject make the basic assumption that emotional experiences can be described and communicated verbally. This assumption is an influence of psycholinguistics, which asserts that any emotional experience is extensively language-dependent (Kroeber-Riel, 1986). However, a possible flaw is that verbal measures tap the evaluative content of cognitive evaluation but they may do little to measure accompanying physiological changes (Holbrook & O'Shaughnessy 1984). A likert-type[6] scale was used to measure frequency of emotion with answer choices as follows: Almost always = 1, Often = 2, Occasionally = 3, and Rarely/ Never = 4. This type of verbal rating scales is most widely used because it is simple to construct, administer, and code (Assael, 1995). However, by offering a specific number of response categories, the respondent has a limit to the range of his emotional response.

An alternative would be to use non-verbal or psychophysiological techniques to measure emotion such the Galvanic Skin Response (GSR) or to use a combination of techniques like heart rate and electromyography. However, while these techniques enjoy some success, they are difficult to administer and are not able to identify specific emotions (Aaker et al., 1986). Also, these measures fail to reflect the valence of emotional reactions and psychophysiological reactions may represent a number of processes. That is, the data are analysed as inputs and outputs without considering the cognitive processes at work inside the subject (Wiles & Cornwell, 1990). Additionally, in the GSR test, the skin's electrical resistance is affected by the activity of the sweat glands that are controlled by the sympathetic nervous system (Wiles & Cornwell, 1990) and the measure of that activity can be seen as an expression of intensity of the emotional behaviour (Kroeber-Riel, 1986). So, this method is limited to measure the intensity of emotions. On the other hand, verbal self-report techniques are more able to recognise specificity and cognitive differences in emotion (Hunt, 1989). Thus, after comparing the advantages and disadvantages of both the verbal and non-verbal methods, it was concluded that the verbal self-report questionnaire is the most practical way to test emotion in relation to the current study. In sum, as the historical review has showed, emotion is not an easy concept to study and the scientific measurement of this phenomenon remains a considerable challenge.

## 1.6 The Prefrontal Cortex

The anatomy and connections of the OFC, medial PFC, and DLFC will be discussed. The functions of the OFC (the area currently under investigation) and the DLFC (the main site of damage in the control lesion patients) are then discussed in further detail in Sections 1.7 and 1.10 respectively.

### 1.6.1 Neuroanatomy of the Prefrontal Cortex

The prefrontal cortex has extensive connections with many other brain areas and can be divided into three regions: orbitofrontal, medial, and dorsolateral based on Brodmann's areas or on the

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[6] Likert-type scaling involves having subjects rank their responses to a set of items on a range of numbers, such as 0-4. The term is derived from the industrial psychologist Rensis Likert (1932) who first used such scales.

projections it receives from the mediodorsal nucleus of the thalamus (Fuster, 1997). Brodmann's (1909) brain map, based on cytoarchitectonics (the study of differences in cell types), is the most commonly used delineation of cortical areas. Brodmann's areas in monkeys (Cercopithecus) and humans are not necessarily homologous so the numbers "missing" in the sequence only exist in his maps of the monkey cortex (Dubin, 2002). The prefrontal cortex is situated in front of the motor and premotor cortices, Brodmann's areas (BA) 4 and 6, in the frontal lobe and the OFC is usually defined as BA 10, 11, 12, 13 & 47[7], the medial region as areas 8, 9, and 10, and the dorsolateral region as areas 9 and 46. Figure 1.4 illustrates Brodmann's original cytoarchitectonic map of the human cerebral cortex. Since the attributions of function have been developed since Brodmann's anatomic descriptions, Figure 1.5a is a clearer version of the cytoarchitecture of Brodmann's areas and their relation to function in the human brain (Dubin, 2002). As mentioned above, Brodmann's nomenclature from the human was not consistent with that of his primate brain. By investigating the frontal cortex of the monkey to try to resolve the inconsistencies, Walker (1940) found that the monkey (species Macaca fascicularis, a.k.a. crab-eating macaque) OFC was less homogeneous than Brodmann had originally proposed. Thus, he further subdivided the monkey OFC (originally BA 10, 11 &12) to include areas 13, and 14 (see Figure 1.5b). More recently, Petrides & Pandya (1994) reconciled the remaining inconsistencies between the human and monkey (species Macaca mulatta, a.k.a. Rhesus) brain maps (e.g. the missing area 47 on the monkey) by reanalysing the architechtonic features of both. They modified and further subdivided Brodmann's human brain areas by, among other things, labelling lateral parts of the orbitofrontal gyri as 47/12. Petrides & Pandya's (1994) cytoarchitechtonic map is illustrated in Figure 1.6 and areas 10, 11, 12/47, 13, & 14 correspond to the OFC, areas 8B, 9 & 10 to the medial PFC, and areas 9, 9/46d, 9/46v, & 46 to the DLFC.

The prefrontal cortex can also be divided into the same three main regions based on the divisions of the mediodorsal nucleus (Fuster, 1997). First, the magnocellular, medial, part of the mediodorsal nucleus projects to the orbital (ventral) surface of the PFC (which includes BA 12 & 13) called the orbitofrontal cortex, which also receives input from among other areas, the visual, gustatory, olfactory, and somatosensory cortices. Second, the pars paralamellaris (most lateral) part of the mediodorsal nucleus projects to the frontal eye fields (BA 8) in the anterior bank of the arcuate sulcus and is referred to as the medial PFC (Rolls, 2001). Finally, the parvocellular, lateral, part of the mediodorsal nucleus projects to the dorsolateral PFC, which receives inputs from the parietal cortex, and is involved in tasks such as spatial short-term memory tasks (Fuster, 1997; see Rolls & Treves, 1998 and Section 1.10.2).

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[7] BA 25 was included and BA 47 was excluded when classifying OFC lesion patients in this study as this corresponded with the neurosurgeon's classification system (see also Section 2.2.2).

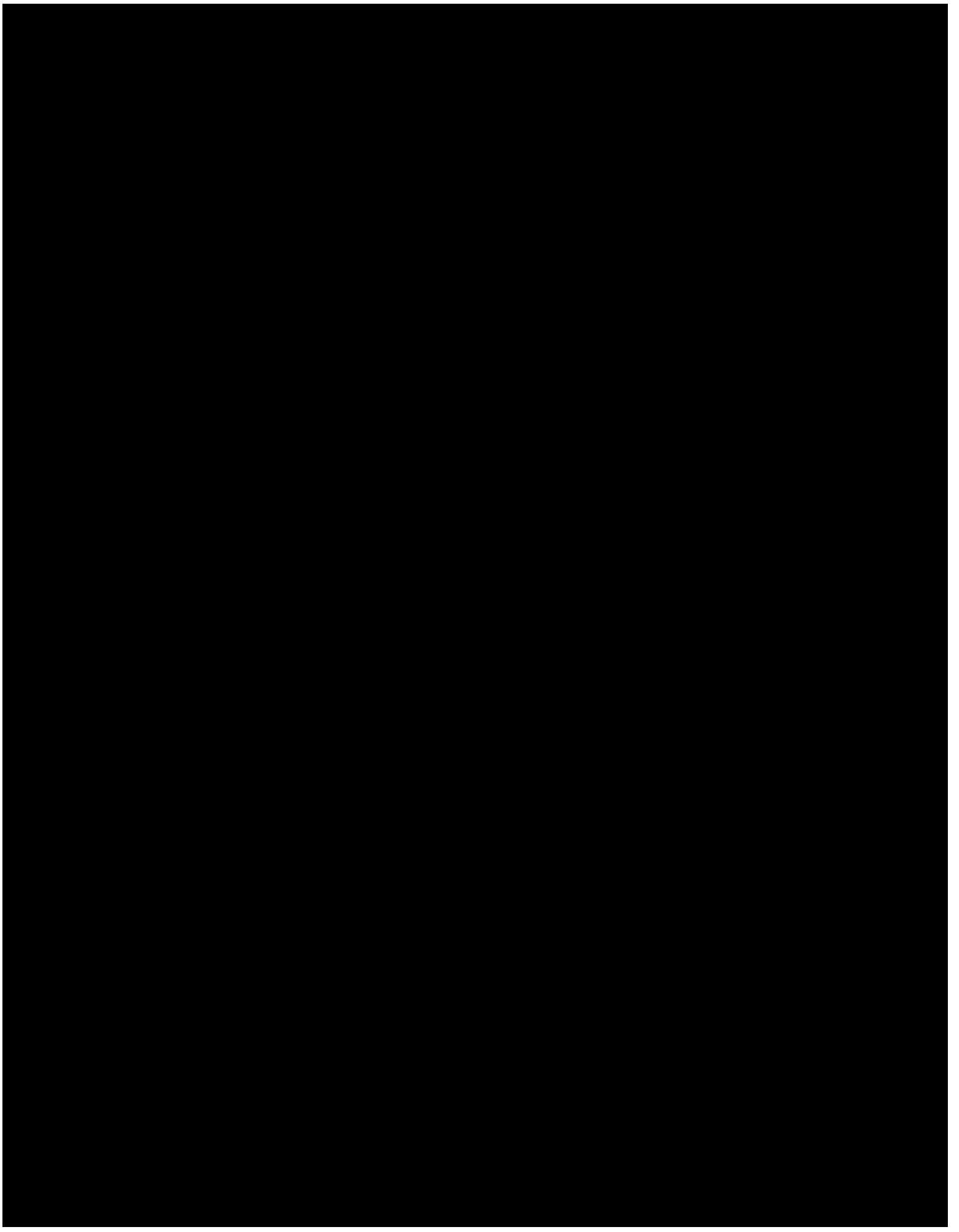

**Figure 1.4:** Original cytoarchitectonic map of the human cerebral cortex by Brodmann (1909). The top picture is the lateral surface and the bottom picture is the medial surface.

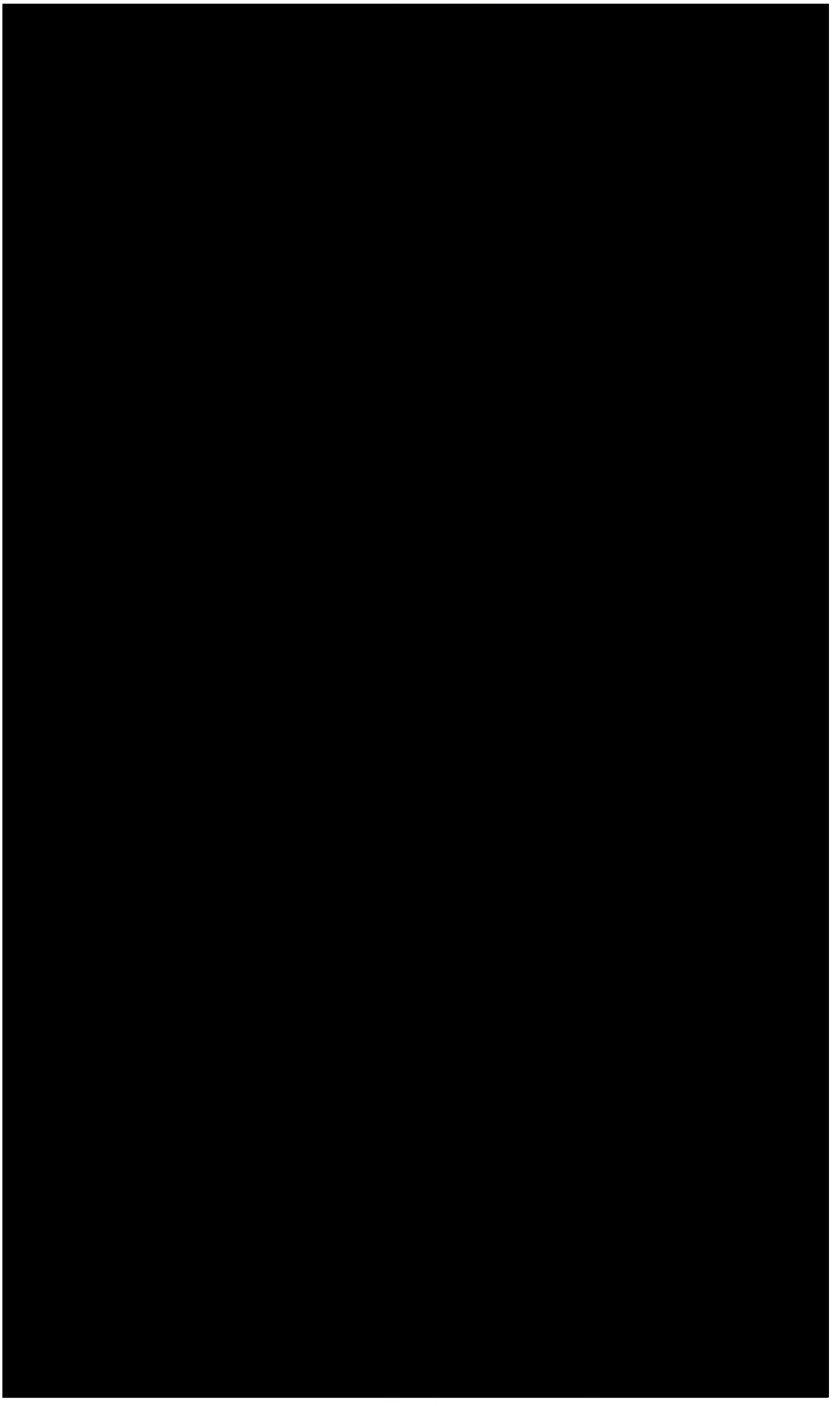

**Figure 1.5a:** A clearer version of the cytoarchitecture of Brodmann's areas and their relation to function in the human brain (Dubin, 2002). The top picture is the lateral surface and the bottom picture is the medial surface.

**Figure 1.5b:** Cytoarchitechtonic map of the frontal lobe of the monkey (Macaca fascicularis) brain by Walker (1940).

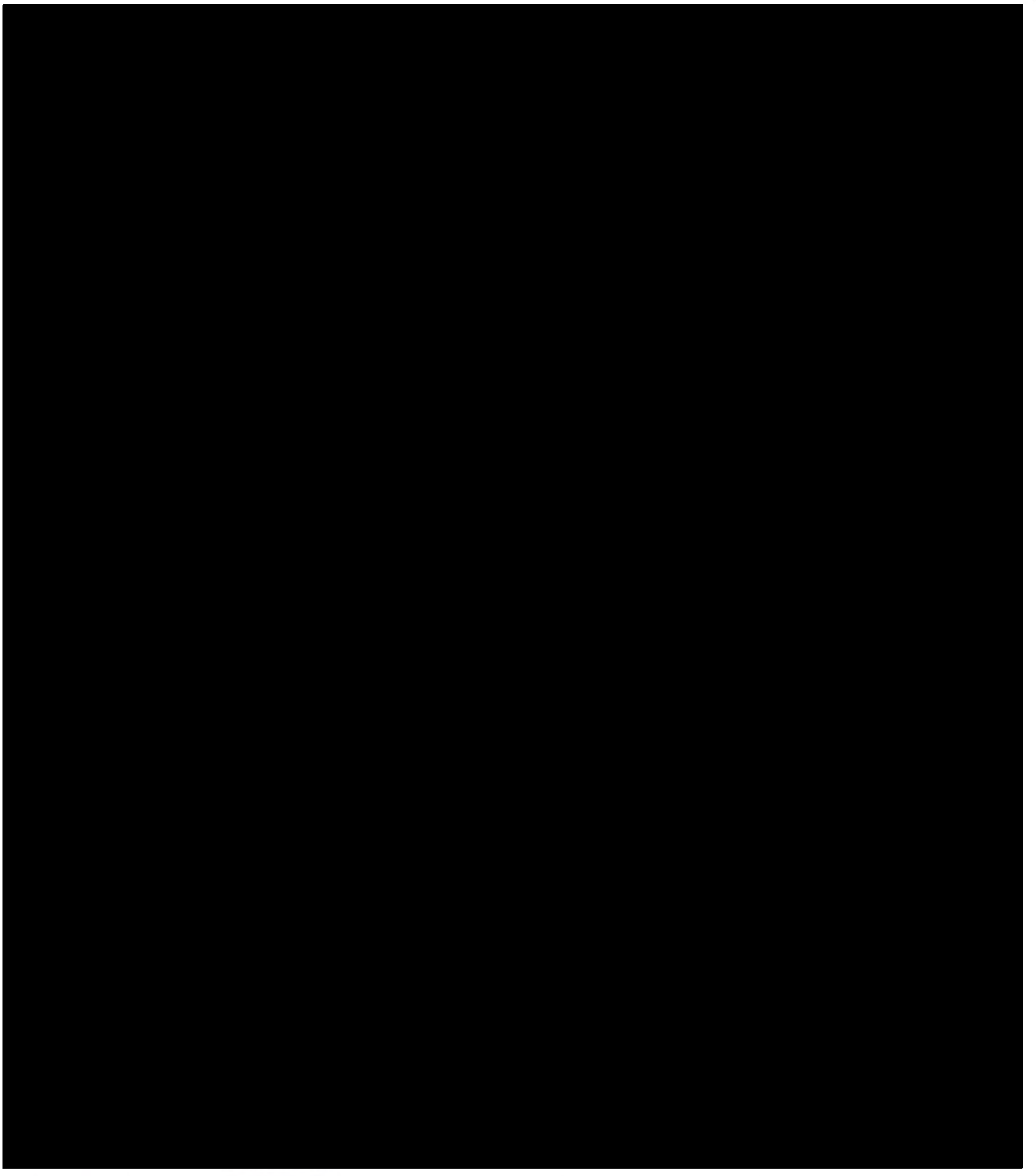

**Figure 1.6:** Schematic diagrams of lateral (A), medial (B) and inferior/ventral (C) surfaces of the human frontal lobe illustrating Petrides & Pandya's (1994) modified cytoarchitechtonic map based on Brodmann's areas and reanalysis of the cytoarchitechtonic features of both the human and monkey PFC so that the classification of areas in the monkey and human brain correspond more efficiently.

### 1.6.2 Connections of the Prefrontal Cortex

#### 1.6.2.1 Orbitofrontal Cortex Connections

The OFC has connections with and receives information from the auditory, somatosensory, and ventral or object processing visual cortices, the olfactory region of the pyriform cortex, and the gustoratory cortex in the insula (Kolb & Whishaw, 1996). Rolls et al. (1990) discovered a taste area in the lateral part of the OFC, and showed that this was the secondary taste cortex in that it receives a major projection from the primary taste cortex (Baylis et al., 1995). More medially, there is an olfactory area (Rolls & Baylis, 1994). Anatomically, there are direct connections from the primary

olfactory and pyriform cortex to area 13a of the posterior OFC, which in turn has onward projections to a middle part of the orbitofrontal cortex (area 11) (Price et al., 1991; Morecraft et al., 1992; Barbas, 1993; Carmichael et al., 1994). Visual inputs reach the OFC directly from the inferior temporal cortex, the cortex in the superior temporal sulcus, and the temporal pole (see Seltzer & Pandya, 1989; Barbas, 1988, 1993, 1995; Barbas & Pandya, 1989; Morecraft et al., 1992; Carmichael & Price, 1995). There are corresponding auditory inputs (Barbas, 1988, 1993), and somatosensory inputs from somatosensory cortical areas 1, 2 and SII in the frontal and pericentral operculum, and from the insula (Barbas, 1988; Carmichael & Price, 1995).

A circuit is formed by subcortical projections beginning in the OFC on the interior surface of the frontal lobe anterior to the premotor cortex, which includes the ventral portion of the caudate nucleus, the globus pallidus and substantia nigra of the basal ganglia, and the ventral anterior and dorsal medial nuclei of the thalamus (Bramham, 2001). The caudal OFC receives strong inputs from the amygdala (e.g. Price et al., 1991). The OFC also receives inputs via the mediodorsal nucleus of the thalamus, pars magnocellularis, which itself receives afferents from temporal lobe structures such as the prepyriform (olfactory) cortex, the amygdala and the inferior temporal cortex (see Price, 2001). The OFC projects back to temporal lobe areas such as the inferior temporal cortex, and, in addition, to the entorhinal cortex (or "gateway to the hippocampus") and cingulate cortex (Insausti et al., 1987). The OFC also projects to the preoptic region and lateral hypothalamus, to the ventral tegmental area (Nauta, 1964; Johnson et al., 1968), and to the head of the caudate nucleus (Kemp & Powell, 1970). Reviews of the cytoarchitecture and connections of the OFC are provided by Petrides & Pandya (1994), Pandya & Yeterian (1996), Carmichael & Price (1994, 1995), Barbas (1995), and Price (2001). See Figure 1.7 from Rolls (1999) for a schematic diagram showing of some of the connections of the OFC.

### 1.6.2.2 Medial Prefrontal Cortex Connections

The medial prefrontal cortex is connected from the anterior cingulated cortex to the ventromedial striatum, globus pallidus and substantia nigra, and medial dorsal nucleus of the thalamus (Cummings, 1992). Ongur & Price (2000) review the architectonic subdivisions and connections of the orbital and medial prefrontal cortex (OMPFC) in rats, monkeys and humans and show that cortico-cortical connections provide the basis for recognition of "medial" and "orbital" networks within the OMPFC. These networks also have distinct connections with structures in other parts of the brain. The orbital network receives sensory inputs from several modalities, including olfaction, taste, visceral afferents, somatic sensation and vision, which appear to be especially related to food or eating. In contrast, the medial network provides the major cortical output to visceromotor structures in the hypothalamus and brainstem and thus appears to function as a visceromotor system (An et al., 1998; Ongur et al., 1998). The two networks have distinct connections with areas of the striatum and mediodorsal thalamus. In particular, projections to the nucleus accumbens and the adjacent ventromedial caudate and putamen arise predominantly from the medial network. Both

networks also have extensive connections with limbic structures. Based on these and other observations, the OMPFC appears to function as a sensory-visceromotor link, especially for eating. This linkage appears to be critical for the guidance of reward-related behaviour and for setting of mood (Ongur & Price, 2000).

### 1.6.2.3 Dorsolateral Prefrontal Cortex Connections

The DLFC projects to all of the premotor areas of the frontal lobes and has reciprocal connections with posterior parietal areas and the superior temporal sulcus (Fuster, 1997). It also has extensive connections to regions to which the posterior parietal cortex also project, including the cingulated cortex, basal ganglia, and superior colliculus (Kolb & Whishaw, 1996). A DLFC-subcortical circuit originates in the lateral convexity of the frontal lobe anterior to the premotor area and involves the dorsolateral area of the caudate nucleus, areas of the globus pallidus and substantia nigra, and ventral anterior and dorsal nuclei of the thalamus (Cummings, 1995).

Petrides & Pandya (1999) re-examined the connections of the dorsolateral prefrontal cortical areas in the monkey (macaca mulatta) using fluorescent tracers placed in selected areas of the DLFC. The study of the connections of the three mid-dorsolateral prefrontal areas 9, 9/46 and 46[8] provided further support for the architectonic segmentation proposed by Petrides & Pandya (1994). Although there was a considerable degree of similarity in the connection patterns of these related areas, there were also certain key differences. They found that all three areas receive input from the multimodal superior temporal sulcal cortex, the rostral superior temporal gyrus, the anterior and posterior cingulate cortex and the retrosplenial cortex. Thus, these areas maintain preferential connections with multimodal temporal areas, on the one hand, and paralimbic cortical areas, such as the cingulate, the retrosplenial and the rostral temporal cortex, on the other hand. The major difference in connectivity between area 9 and areas 9/46d and 46 is the lack of input from lateral and medial parietal cortex in the case of area 9. So, area 9 has the same basic pattern of connections as areas 46 and 9/46, but, unlike the latter areas, it does not receive input from the lateral and medial parietal cortex. Finally, Petrides & Pandya (1999) found that caudal to area 9, on the dorsomedial portion of the frontal cortex, there is a distinct strip of cortex, area 8B, which unlike area 9, receives significant input from the prestriate cortex and the medial parietal cortex, but it is considered by Petrides & Pandya (1994) to be part of the medial PFC. The functions of the DLFC are discussed in Section 1.10.

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[8] For the rest of this section, all brain areas referred to are Petrides & Pandya's (1994) areas from their modified cytoarchitechtonic map based on Brodmann's areas (see Figure 1.4).

**Figure 1.7:** Schematic diagram showing of some of the connections of the OFC. V1=primary visual (striate) cortex; V2 & V4 = further cortical vision areas; VPL= ventro-postero-lateral nucleus of the thalamus which conveys somatosensory information to the primary somatosensory cortex (areas 1, 2, & 3) (Rolls, 1999).

## 1.7 Functions of the Orbitofrontal Cortex

Much of what is known about the function of the OFC has been discovered via lesion, neuroimaging, and neuronal recording studies. The majority of the studies concerning OFC function were performed with macaques or with humans since the OFC brain region is well developed in primates but relatively poorly developed in rodents.

### 1.7.1 The Orbitofrontal Cortex and Object Working Memory

Meunier et al. (1997) found that object memory processes, evaluated by delayed nonmatching-to-sample with trial-unique stimuli and object reversal learning, were more severely impaired by OFC than by anterior cingulate lesions in rhesus monkeys. Spatial memory processes, assessed by spatial delayed response and spatial reversal learning, showed a weak trend in the opposite direction, though on these tasks neither lesion produced a serious loss. Comparison of these results with those

of earlier studies on the effects of various limbic system lesions suggests that object memory processes, including object recognition and object-reinforcement association, are served by a circuit consisting mainly of the rhinal cortex (in the temporal lobe), OFC, and the magnocellular division of the medial dorsal thalamic nucleus (Rolls, 2001). Although both rhinal and OFC components of this circuit appear to participate in both functions, evidence from Meunier et al. (1997) and earlier studies (see Rolls, 2001) suggests that the OFC component is more important for stimulus-reinforcement associative memory, i.e. the formation across trials of associations between particular objects or classes of objects and reward, whereas the rhinal component is more critical for recognition memory, i.e. the storage and retrieval within trials of the representations of particular objects. Thus, the results on object reversal learning suggest that the associative-memory deficits after OFC lesion are related to the formation of stimulus-reinforcement associations. Meunier et al.'s (1997) evidence points to deficits in rhesus monkeys after OFC damage of memory across trials for object class (i.e. old vs. new) and for specific objects. However, deficits in reversal or perseverative errors after OFC lesions seem to arise from difficulty in suppressing or unlearning the previous stimulus-reward association, a difficulty seen in both monkeys with ventral frontal ablations (Iversen & Mishkin, 1970; Jones & Mishkin, 1972) and, more recently, in humans with damage to ventral (OFC) as compared with non-ventral frontal cortex (DLFC) (Rolls et al., 1994; Hornak et al., 2003a, in press).

Rolls (2001) has shown that the OFC remembers the recent reward association of stimuli by synaptic plasticity, so that no ongoing neuronal firing is needed to implement stimulus-reinforcer association memory. In contrast, he believes that the inferior convexity PFC (Walkers area's 12 & 45; just lateral of the OFC) and the DLFC implement a short-term memory[9] for stimuli that is maintained by the active continuing firing of neurons that hold the representation active during the delay period (Rosenkilde et al., 1981; Wilson et al., 1993; Rao et al., 1997b). Accordingly, more lateral lesions in the Macaque, in the inferior convexity, can affect short-term object memory, like delayed matching to sample and to non-sample tasks (Passingham, 1975; Mishkin & Manning, 1978; Kowalska et al., 1991). However, the inferior convexity's specific involvement in short-term object memory as opposed to short-term spatial memory is not yet clear (Rao et al., 1997b) and the medial frontal cortex may also contribute to this function (Kowalska et al., 1991). Note that the short-term object memory system, which receives inputs from temporal lobe visual cortical areas concerned with object representation, is different from the short-term spatial memory system associated with the DLFC, which receives inputs from the parietal cortex (see Rolls & Treves, 1998 and Section 1.10.2).

### 1.7.2 Effects of Macaque Orbitofrontal Cortex Lesions

The primate OFC is thought to be involved in stimulus-reinforcement association learning as it receives inputs from the inferior temporal visual cortex and OFC neurons reverse visual stimulus-

[9] In this thesis, short-term memory is interchangeable with the term working memory.

reinforcer associations in as little as one trial (Thorpe et al 1983; Rolls et al 1996a). This coincides with the impaired performance seen in macaques after OFC damage at tasks involving altering behaviour when reinforcement contingencies change. On these tasks, OFC lesioned macaques make inappropriate responses like continuing to behaviourally respond to previously rewarded stimuli or to a non-rewarded stimulus. So, OFC lesioned monkeys go on the "No-Go" trials in the "Go/No-Go" task (Iversen & Mishkin, 1970), respond to the object that was formerly rewarded with food on the object reversal task, and continue to respond to an object which is no longer rewarded in the extinction task (Butter, 1969; Jones & Mishkin, 1972). The OFC not only contains neurons that evaluate whether a reward is expected and generate a mismatch if reward is not obtained when expected, but also contains neurons that only respond on non-reward trials (Thorpe et al., 1983). Further, damage to the caudal OFC in the monkey produces emotional changes like decreased aggression to humans and to stimuli such as a snake and a doll and a reduced tendency to reject foods such as meat (Butter, et al., 1969; Butter, et al., 1970; Butter & Snyder, 1972) or to display the normal preference ranking for different foods (Baylis & Gaffan, 1991). Therefore, it seems that the OFC is involved in the rapid updating by relearning, or reversing, of stimulus-reinforcer associations and in emotional responses that involve correcting previously learned reinforcement contingencies in situations involving frustration.

### 1.7.3 Effects of Human Orbitofrontal Cortex lesions

Patients with OFC damage have exhibited major changes in personality, behaviour, and social conduct often displaying a lack of affect, social inappropriateness, and irresponsibility (Damasio, 1994; Rolls, 1999). Additional support for the role of the OFC in personality and behaviour is demonstrated in frontotemporal dementia, a progressive neurodegenerative disease attacking the frontal lobes which produces major behavioural changes in personality and social conduct similar to those changes seen in OFC lesion patients like social disinhibition and withdrawal, inability to appreciate irony or other subtle aspects of language, impaired planning skills, and difficulties with working memory (Rahman et al., 1999). This behaviour may be explained by the fact that humans with ventral frontal lobe damage (including the OFC) have shown impairments in tasks which require an alteration in behaviour in response to change in environmental reinforcement contingencies (Rolls et al., 1994; Damasio 1994; Rolls, 2001; Hornak et al., 2003a, in press; see also Goodglass & Kaplan, 1979; Jouandet & Gazzaniga, 1979; Kolb & Whishaw, 1996). For example, Bechara and colleagues (1994, 1996, & 1997) found that patients with frontal damage were more likely to choose cards from a deck which although giving significant rewards, also led to large penalties and the net gains of which were lower than from other decks. Thus, patients were not affected by the negative consequences of their actions as they did not switch from the deck of cards that was providing significant rewards even when large punishments were incurred. Using the Wisconsin Card Sorting Task (WCST; where cards are to be sorted according to colour, shape, or number of items on each card depending on whether the examiner says "right" or "wrong" to each

placement), Milner (1963) showed that frontal patients either had difficulty in determining the first sorting principle, or in shifting to a second principle when required[10]. In stylus mazes[11], frontal patients have difficulty in changing direction when a sound indicates that the correct path has been left (Milner, 1982).

Further, patients with ventral frontal lobe lesions made more errors and completed fewer reversals on a visual reversal (and a similar extinction) task involving alteration of reinforcement contingencies than control patients with damage elsewhere in the frontal lobes or to other brain regions (Rolls et al., 1994). The impairment correlated highly with the socially inappropriate or disinhibited behaviour of the patients (assessed in a Behaviour Questionnaire) and with their subjective evaluation of the emotional changes since the brain damage (Rolls et al., 1994). Since the location of the stimuli constantly switched and a response was required and made on each trial, the continued choice of the no longer rewarded stimulus in the reversal task can be interpreted as a failure to reverse stimulus-reinforcer associations, and not as motor response perseveration, which may follow much more dorsal PFC damage. Also, Hornak et al. (1996) found that patients with ventral frontal lobe lesions who displayed socially inappropriate behaviour were also impaired on social signals including for example face and voice expression identification. There was also a strong positive correlation between the degree of altered emotional experience and the severity of the behavioural problems (e.g. disinhibition) found in these patients. The control patients, with brain damage outside the ventral frontal lobe, did not have these behavioural problems, were unimpaired on face expression identification, were significantly less impaired at vocal expression identification, and reported little subjective emotional change (Hornak et al., 1996).

It is interesting to note that in the reversal and extinction tasks, the WCST, and the stylus maze, frontal patients could often verbalise the correct response or rules, yet were unable to correct their behaviour or strategies appropriately (Milner, 1963, 1982; Rolls et al., 1994). This is consistent with the idea that the OFC is involved in executing behaviours that are performed by evaluating environmental stimuli-reinforcement associations (Rolls, 1999). So, some of the personality changes that can follow frontal lobe damage in humans, particularly OFC damage (Rolls et al., 1994; Hornak et al., 1996) like euphoria, irresponsibility, lack of affect, and lack of concern for the present or future (see Kolb & Whishaw, 1996; Damasio, 1994; Rolls, 1999) may be related to a dysfunction in correctly assessing and altering behaviour appropriately in response to changes in reinforcement contingencies. As mentioned above, frontal patients rated high on a Behaviour Questionnaire that included: disinhibited or socially inappropriate behaviour; misinterpretation of other people's moods; impulsiveness; unconcern or underestimation of the seriousness of their condition; and lack of initiative (Rolls et al., 1994), and these behaviours correlated with reversal and extinction learning impairments (Rolls et al., 1994). So, perhaps the

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[10] Milner's patients had damage to BA 9, so this dysfunction was related to DLFC damage and thus most likely to a deficit in shifting attention between sets as discussed in Section 1.10.1.

[11] The task is to learn the way through a labyrinth consisting of points in a point matrix.

insensitivity to reinforcement changes in the learning task may be at least part of what produces the behavioural changes found in these ventral frontal patients. Thus, the OFC may be involved in the ability to respond rapidly and appropriately to social reinforcers which is an important aspect of primate (including human) social behaviour.

One aim of the current research is to build on the previous work (Rolls et al., 1994; Hornak et al., 1996) that found patients with ventral frontal lobe lesions to be impaired at emotion-related reversal and measures of behavioural and emotional change. This is being followed up by using modified versions of the behaviour and emotion questionnaires as well as the visual discrimination reversal test to study patients with more circumscribed lesions within the frontal lobe. In this way, I hope to gain a better understanding of the contribution of orbitofrontal, medial, and dorsolateral regions of the frontal lobe to the behavioural changes found in the earlier studies and to determine if double dissociations exist between OFC and non-OFC prefrontal lesion patients on measures of personality traits, prefrontal functions, and different aspects of impulsivity. Accordingly, BPD patients, characterised by impulsivity and inappropriate behaviour in social situations, were also tested with the visual reversal task and modified behaviour and emotion questionnaires as I hypothesise that they will have deficits similar to those of OFC patients.

### 1.7.4 Neuroimaging Studies

Using functional Magnetic Resonance Imaging (fMRI), Francis et al. (1999) found that a weak but very pleasant touch of the hand with velvet produced much stronger activation of the OFC than a more intense but affectively neutral touch of the hand with wood that produced more activation of the primary somatosensory cortex than the pleasant stimuli. This indicates that a primary reinforcer that can produce affectively positive emotional responses is represented in the human OFC and provides a basis for the OFC involvement in stimulus-reinforcement association learning, the possible bases for emotional learning. Recently, Rolls et al. (2003) found that there is also a representation of the affectively negative aspects of touch, including pain, in the human OFC. Also, parts of the human OFC have been shown to be activated by taste stimuli (such as glucose) (Small et al., 1999; O'Doherty et al., 2001a), and by the pleasantness of olfactory stimuli where OFC activation decreases to a food that has been eaten to satiety so that it no longer is rewarding or smells pleasant (O'Doherty et al., 2000). Using fMRI and a probabilistic visual association task, O'Doherty et al. (2001b) showed that the magnitudes of abstract rewards and punishers (monetary gains and loss) are represented in the human OFC. Medial OFC activation correlated with the amount of money received and lateral OFC activation correlated with the amount of money lost.

So, human OFC neuroimaging studies provide evidence that representations of many types of reward and punishers are found in the OFC supporting Rolls' theory of emotion (see Section 1.5.2) (Rolls, 1999). This data also implies that the behavioural and emotional changes seen after OFC damage are related to alterations in the processing and learning of changing stimulus-reinforcement associations.

### 1.7.5 Neurophysiological Studies

In addition to the lesion and neuroimaging evidence, neurophysiological studies also implicate the OFC's involvement in the rapid learning and alteration (when reinforcement contingencies change) of stimulus-reinforcement associations. To implement this, the OFC has the necessary representation of primary reinforcers, including taste and somatosensory stimuli and can receive visual information (Booth & Rolls, 1998; Rolls, 2000a), which it can then associate at the neuronal level with primary reinforcers such as taste, and reverse these associations rapidly, in as little as one trial (Thorpe et al., 1983; Rolls et al., 1996b). Although learning is slower, olfactory stimulus can also be conditioned in this way, and although there is less direct evidence, auditory stimuli most likely can be associated with primary reinforcers in the OFC as well (see Rolls, 2001). The OFC also has neurons that detect non-reward, which are likely to be used in behavioural extinction and reversal (Thorpe et al., 1983) perhaps by helping to reset the reinforcement association of neurons in the OFC and by sending a signal to the striatum[12] (Rolls & Johnstone, 1992; Rolls, 1994b; Williams et al., 1993). In fact, it is most likely via the striatum, which can route signals to produce appropriate behaviours to non-rewards, that the OFC may influence behaviour when it is decoding or altering responses to altering reinforcement contingencies (see Rolls, 1999). Some of the evidence for this is that neurons which receive input from the OFC and reflect OFC neuronal responses are found in the ventral part of the head of the caudate nucleus and the ventral striatum (Rolls et al., 1983; Williams et al., 1993) and lesions of the ventral part of the head of the caudate nucleus impair visual discrimination reversal (Divac et al., 1967).

The impairment in forming stimulus-reinforcement associations when contingencies change produced by OFC damage may be polymodel. Recordings from single cells in monkeys indicate different populations of neurons within the OFC are activated for positively versus negatively affective taste, olfactory, and visual stimuli (Rolls & Scott, 2001). Further, OFC lesions in monkeys lead to an impairment in the learning of a tactual discrimination reversal (Deuel & Mishkin, 1977). A similar deficiency is likely to extend to olfactory reversal learning, since OFC neurons were found to encode the reward value of olfactory stimuli in both monkeys (Rolls et al., 1996a) and rats (Schoenbaum & Eichenbaum, 1995), just as was shown for visual stimuli in monkeys. The OFC receives inputs about potential secondary reinforcers like visual and olfactory stimuli as well as about primary reinforcers (Rolls, 2000b) and seems to be involved in the relation of reward with various stimuli like food and touch. The primary taste cortex represents what the taste is while the secondary taste cortex is located in the OFC and represents the reward value of the taste (Rolls, 2001). The OFC also contains secondary and tertiary taste and olfactory neurons that respond to the reward value of olfactory stimuli and to the odour of food only when the monkey is hungry (Critchley & Rolls, 1996). This corresponds with Rolls' (1997, 1999) finding that the response of neurons in the OFC, but not neurons at earlier stages of processing, decreases

[12] The straitum is part of the basal ganglia, which is involved in the facilitation of movement (Crossman & Neary, 2000)

to food when the reward value of the food decreases by feeding primates to satiety. Further, monkeys work for electrical brain stimulation of the OFC if they are hungry, but not if they are satiated (Mora et al., 1979; Rolls, 1994a) and lesions of the OFC lead to much less discrimination of foods and other items (Baylis & Graffan, 1991). So, the fact that many orbital neurons in monkeys respond differentially to food and liquid reward vs. non-reward, expected vs. unexpected reward, and one type of reward vs. another (Rosenkilde et al., 1981; Thorpe et al., 1983) can be attributed to the olfactory and gustatory properties of neurons located in the secondary or higher-order sensory processing areas of the posterior OFC (Baylis et al., 1995; Rolls et al., 1990; Takagi, 1986; Tanabe et al., 1975a,b; Yarita et al., 1980).

In sum, OFC neurons can encode the reward value of the visual stimuli used in learning and reversal tasks, by quickly changing their visual firing rate to such visual stimuli accordingly (Rolls et al., 1996a; Thorpe et al., 1983). This effect could be related to the convergence of visual, olfactory, and gustatory information onto OFC neuronal clusters and even single neurons (Rolls & Baylis, 1994; Thorpe et al., 1983). Thus, the reversal learning deficits after OFC damage may be due, at least in part, to a loss of neurons that code the reward values of sensory stimuli. Decoding and rapidly readjusting the reinforcement value of visual stimuli is likely to be crucial for emotions, as Rolls describes emotions as responses elicited by reinforcing signals (Rolls, 1986a, b, 1990, 1995, 1999, 2000c), and in social situations where reinforcing stimuli are continually being exchanged and updated[13].

### 1.7.6 The Orbitofrontal Cortex and Impulsivity

Based on previous findings, it is hypothesised in this study that the PFC plays a role in behavioural and cognitive impulsivity and therefore in BPD as impulsivity is a main feature of this disorder. Humans and animals are subject to behavioural control by internal motivational states (impulses) that are either innate or conditioned. These states can be related to the desire to seek food, water, sex, and other primary reinforcers. There appears to be however, an active inhibitory control mechanism in the brain to modulate this type of preponent responding, particularly in higher animals (Diamond, 1988; Damasio, 1996; Robbins, 1996; Dias et al., 1997). This inhibitory control mechanism may provide the substrate by which rapid, conditioned responses and reflexes are suppressed, so that slower cognitive mechanisms can guide behaviour. This form of inhibitory impulse control appears to be a principle function of the PFC as dysfunction of the PFC is thought to produce impulsivity associated with a number of pathological states (Robbins, 1990, 1996;

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[13] Although the amygdala receives similar inputs and is involved in some of the same functions as the OFC, there is evidence that it may function less effectively in the rapid learning and reversal of stimulus-reinforcement associations, as indicated by the greater difficulty in obtaining reversal from amygdala neurons (Rolls, 1992, 2000d), and by the greater effect of OFC lesions in the continuing choice of no longer rewarded stimuli (Jones & Mishkin, 1972). In primates, the need for very rapid stimulus-reinforcement re-evaluation and the development of powerful cortical learning systems may result in the OFC effectively taking over this aspect of amygdala function (see Rolls, 1992, 1999).

Damasio, 1996). In addition, lowered serotonin levels, specifically in the PFC, have been related to impulsive behaviour (see Section 4.1.10).

Impulsivity is one of the core features in patients with frontal lobe dysfunction (Lhermitte, 1986; Miller, 1992; Kraus& Maki, 1997; Fuster, 1997). Damage to frontal cortical regions can lead to marked incidence of cognitive deficits, including impairments in inhibitory control (Iversen & Mishkin, 1970; Goldman et al., 1971; Milner, 1982; Petrides & Milner, 1982; Goldman-Rakic, 1987; Fuster, 1988; Damasio, 1996; Goldman-Rakic et al., 1996; Robbins, 1996). Frontal damage can cause disinhibition, such that behaviour becomes largely guided by previously conditioned or pre-potent responses that are inappropriate in the current situation (Drewe, 1975; Milner, 1982; Robbins, 1996). Specifically, damage within the OFC or prelimbic cortex of humans leads to a tendency to preferentially respond for immediate small rewards over delayed, more efficient rewards[14] (Bechara et al., 2000; Damasio, 1996). Thus, when the PFC is damaged, the behaviour of the organism becomes dominated by pre-potent tendencies, which result from drive states, conditioned associations, or unconscious/reflexive responses. Further, studies of OFC lesions in humans have revealed an autonomic pattern of deficits (Damasio et al., 1990) and subtle executive deficits in real world social contexts (Grattan et al., 1994; Eslinger & Damasio, 1995). In accord, damage to the OFC has been associated with disinhibited or socially inappropriate behaviour, misinterpretation of moods, and impulsivity (Levin, 1991; Rolls et al., 1994; Damasio, 1994).

As discussed above (Sections 1.7.2 & 1.7.3), a fundamental deficit shown by non-human primates and humans with OFC lesions is a difficulty in reversing behavioural responses to changed reinforcement contingencies (Butter, 1969; Dias et al., 1996a; Iversen & Mishkin, 1970; Jones & Mishkin, 1972; Passingham, 1972; Rosenkilde, 1979; Rolls et al., 1994). Humans and monkeys with OFC damage are impaired at reversal and extinction, continuing to make responses that are no longer rewarded (Rolls et al., 1994; Freedman et al., 1998; Iversen & Mishkin 1970; Rolls, 1996; Meunier et al., 1997). Inhibitory control required for discrimination reversal seems to be at the level of stimulus-reward associations. A study in marmosets demonstrated that lateral frontal cortex lesions caused deficits in extra-dimensional attentional shifting, whereas OFC lesions caused deficits in discrimination reversal (Dias et al., 1996a, 1996b; see Section 1.10.1). The role of the OFC in reward is suggested by strong inputs from basal amygdala (Porrino et al., 1981; Potter & Naunta, 1979) and transsynaptically, from ventral striatum (Haber et al, 1995) with its reward related neurons (Nishijio et al., 1988; Schultz et al., 1992). Further, OFC neurons showed smaller activations during the delay periods of spatial and object matching tasks compared with DLFC neurons, but responded to delivery of juice reward at the end of the trial (Niki et al 1972; Rosenkilde et al., 1981). OFC neurons also can discriminate between primary and conditioned appetitive and aversive stimuli and are activated specifically in extinction or reversal trials (Thorpe et al., 1983). Tremblay & Schultz (2000) found that non-human primate OFC neurons respond to stimuli associated with reinforcers, are concerned with the expectation of reward, and detect reward

[14] Based on a gambling task by Bechara et al. (1994) - see Section 1.7.3 for more detail.

delivery at the end of the trial. Neurons in the caudally adjoined OFC taste area showed specific gustatory and olfactory responses that were modified in relation to the animal's satiation (Rolls & Baylis, 1994; Rolls et al., 1989, 1996a). Thus, OFC neurons may respond to rewards in a manner appropriate for reinforcing behavioural reactions and when the OFC is damaged, associations may form between stimuli and rewards but then it may be difficult to re-associate the previously rewarded stimulus with punishment. This type of deficit will result in perseveration of previously rewarded stimuli and thus in the overt, socially inappropriate behaviour demonstrated by OFC patients. Hence, the impulsive, inappropriate behaviour demonstrated by BPD patients could perhaps be the result of an underlying OFC dysfunction.

The specific effects of OFC lesions on discrimination reversal may result from the fact that during reversal subjects have to shift responding away from a previously reinforced stimulus while learning a new response. The originally reinforced stimulus has probably developed conditioned reinforcing properties (as it has been contingently associated with primary reward), and OFC damage most likely produces the inability to inhibit responding towards that pre-potent or conditioned stimulus. So, response inhibition may be an active process for modulating reward-stimulus-response associations, allowing animals to shift between old and new contingencies and inhibit inappropriate responses to conditioned stimuli. Further, using fMRI in humans, Elliot et al. (2000) found responses to both reward level in the context of increasing reward and penalty level in the context of increasing penalty in the ventral prefrontal cortex. In addition, O'Doherty et al. (2001b), using fMRI, found that the OFC is activated by monetary rewards and punishments and the magnitude of the brain activation is related to the magnitude of the rewards and punishments received. Also, medial OFC activation was correlated with the amount of money received and lateral OFC activation was correlated with the amount of money lost. Therefore, it is suggested that the OFC represents the magnitudes of abstract rewards and punishments. So, based on the extensive evidence that the OFC is involved in the processing and learning of reinforcement contingencies and damage causes a difficulty in modifying responses, especially when followed by negative responses, it seems likely to contribute to the inappropriate and impulsive behaviour shown by OFC patients.

Impulsivity has been operationalised by some as a choice of immediate smaller reward over a larger delayed or uncertain reward (Crean et al., 2000; Cardinal et al., 2001). Psychiatric outpatients at high risk for engaging in impulsive behaviours discounted delayed rewards more sharply and scored higher on self-report impulsivity measures relative to low-risk impulsivity outpatients (Crean et al., 2000). Impulsive people have been described as more sensitive (in terms of reactivity of the neurobiology associated with a motivational system) to reward than to punishment, approaching reward situations even when punishers make restraint more appropriate (Gray, 1973). Impulsive people have shown poor passive avoidance (withholding a response to avoid punishment) to aversive conditioned stimuli (Corr et al., 1995). High reward dependence (RD) subjects, measured by Cloninger's Tridimensional Personality Questionnaire (Cloninger et

al., 1991), learned more appetitive conditioned stimulus-unconditioned stimulus (CS-UCS) associations than low RD subjects and high harm avoidance (HA) subjects learned more aversive CS-UCS associations than low HA subjects (Corr et al., 1995). Passive avoidance learning has been shown to occupy a central role in accounts of disinhibited behaviour, ranging from psychopaths' persistent criminality (Hare, 1970) to extraverts' gregariousness (Gray, 1970). Using two successive go/no go discrimination tasks, consistent with previous findings, Patterson et al. (1987) found that extraverts committed more passive avoidance errors than introverts (Newman et al., 1985) and failed to pause following punished errors[15] (Nichols & Newman, 1986). Impulsive people (neurotic extraverts) displayed the same pattern of performance differences. Also, longer pausing following punishment predicted better learning from punishment. These results suggest that, in the presence of salient cues for reward, impulsives' characteristic reaction to punishment interferes with processing punished errors and may contribute to their more general propensity for impulsive, non-reflective action (Patterson et al., 1987). Results from three experiments showed that psychopaths and extraverts exhibited deficits in passive avoidance relative to non-psychopaths and introverts respectively. In addition, the passive avoidance deficit was particularly evident in tasks that required subjects to inhibit a rewarded response in order to avoid punishment. These results emphasise the importance of reward in mediating the passive avoidance deficit of "disinhibited" individuals (Newman et al., 1985). Additionally, high impulsive (neurotic extraverts) subjects exhibited inappropriately rapid tracing speeds when instructed to trace a circle template (i.e. behaved impulsively) to a greater extent than low impulsive (stable introverts) subjects in the presence of reward cues and performance reversed when punishment cues were present (Wallace & Newman, 1990). It is therefore suggested that disinhibited and impulsive behaviours are related to sensitivity to reward and punishment contingencies. More specifically, it is proposed that impulsive people are more sensitive to reward and/or less sensitive to punishment (Pickering & Gray, 1999).

Since OFC lesion patients have been found to have alterations to their sensitivity to reward and punishment and exhibit impulsive behaviours, I aim to determine to what extent impulsivity, which has been shown to be related to alterations in sensitivity to positive and negative reinforcement, in normal and in clinical populations (i.e. BPD patients), is associated with OFC dysfunction. Therefore, a reversal task, based on reward and punishment contingencies, was administered. This may also help clarify the relationship between impulsivity and perseveration. Evidence for an association between perseveration and impulsivity derives partly from clinical observations of the co-existence of the two behavioural features in patients with frontal lobe disease (Fuster, 1997), and partly from studies of psychiatric patients, in particular impulsive psychopaths where results thus far have been mixed. Gorenstein (1982) found that psychopaths were more perseverative than non-psychopaths on the WCST; however, Hare (1984) could not replicate this. Devonshire et al. (1988) suggested that this discrepancy might have been due to differences in methods used to classify subjects. Using Nelson's (1976) modified card sorting task

[15] Measured by response speed on trials immediately following punishment.

(MCST), Devonshire et al. (1988) found no differences between psychopaths and non-psychopaths defined using Hare's (1984) criteria, whereas there were group differences when patients were grouped according to Blackburn's (1974) criteria where "secondary psychopaths"[16] were more perseverative than "primary psychopaths"[17]. Van den Broek & Bradshaw (1993) found that perseverative responding on the MCST was significantly correlated with an impulsivity index derived from the MFFT in a normal sample yet no relationship was found between perseveration and a questionnaire measure of impulsivity (the BIS-8). Thus, by administering a reversal task and both self-report (BIS-11) and behavioural measures (MFFT) of impulsivity to BPD patients, lesion patients and normal participants, I hope to clarify the relationship between impulsivity and perseveration and examine the relationship between impulsivity and the OFC.

### 1.7.7 Theories about Orbitofrontal Cortex Function

There are three main theories that aim to explain the impairments OFC lesions patients have demonstrated on neuropsychological tasks; the motor response inhibition hypothesis, the somatic marker theory, and the stimulus-reinforcement association theory. The theory that the impairments seen in OFC patients are due to a lack of motor response inhibition uses as its main argument the fact that primates (including humans) perseverate during object-reversal learning tasks (Rolls et al., 1994; Dias et al., 1996b). However, neurophysiological recordings of OFC neurons in monkeys show activity to stimuli presented and rewards received but not to motor responses (Rolls, 2001) and OFC lesioned monkeys have shown that errors on reversal learning are not only caused by perseverative responses but can also be caused by a failure to learn to respond to currently rewarded stimuli (Iversen & Mishkin, 1970). Finally, on a reversal task in humans (Hornak et al., 2003a, in press), location of the stimuli constantly switched and a response was required and made on each trial, so the continued choice of the no longer rewarded stimulus can be interpreted as a failure to reverse stimulus-reinforcer associations rather than motor response perseveration.

Bechara and colleagues (1997) suggest that the poor performance on their gambling task demonstrated by OFC lesion patients (discussed in detail in Section 1.7.3) is not due to failure of inhibitory control but to failure to anticipate future outcomes. Damasio extends this idea and interprets OFC dysfunctions in terms of his somatic marker hypothesis, where feedback from the peripheral nervous system controls the "decision" about the correct behavioural response rather than the "emotional feelings". Thus, somatic markers (changes in body state including musculoskeletal and visceral alterations associated with emotional states) link behaviours and situations with contingent affective consequences (Damasio, 1994). This decision-making theory is however flawed in that inactivation of bodily feedback does not inhibit behaviour to emotion-provoking stimuli (e.g. Schacter & Singer, 1962) and Damasio does not adequately explain why some stimuli produce emotional responses while others do not (Rolls, 1990, 1999).

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[16] Characterised by high average scores on trait anxiety, measured psychometrically, and social withdrawal.
[17] Characterised by low average scores on trait anxiety and high scores on sociability.

Alternatively, Rolls (1999, 2001) proposes that the impairments in OFC lesion patients are related to the formation or learning of new stimulus-reinforcement contingencies rather than the inability to inhibit a previously learned response. He believes the OFC is involved in representing the reward value of stimuli and learning and altering stimulus-reinforcer associations between rewards and punishers and previously neutral stimuli. In support of this theory, OFC lesions in monkeys produced altered food preferences (Baylis & Gaffan, 1991) and a unilateral crossed lesion study found that the OFC is important for the alteration of stimulus-reward associations (Baxter et al., 2000; see Section 4.7). Neurophysiological studies show that brain-stimulation reward[18] of the OFC is possible in hungry monkeys but decreases once they are satiated (Mora et al., 1979) and taste and olfactory OFC neurons' decrease in their response to food related taste and odours after satiation of that food (Rolls et al., 1989; Critchley & Rolls, 1996). Further, OFC neurons can reverse odour-taste and visual-taste associations and can reverse their response properties in a visual discrimination task after only one trial (Rolls et al., 1996a,b; Thorpe et al., 1983).

Overall, the evidence seems to strongly support Rolls' view that the OFC is largely involved in representing and altering the reward value of primary and secondary reinforcers. So, behavioural impulsivity, of the kind I have tested with the Matching Familiar Figures Test (MFFT), and impairments in reversal displayed by OFC patients may result from a problem in modulating stimulus-reward associations or in shifting between old and new contingencies, rather than a lack of motor response inhibition, leading to a failure to inhibit inappropriate responses to conditioned stimuli. In sum, the apparent failure to inhibit responses seen in OFC humans and monkeys, which contributes to the observed deficits on neuropsychological tests and the socially inappropriate behaviours exhibited by OFC patients, may be caused by a failure to alter stimulus-reinforcement associations.

### 1.7.8 Summary of Orbitofrontal Cortex Function

Damage to the OFC is associated with disinhibited or socially inappropriate behaviour, misinterpretation of peoples' moods, and impulsivity (Damasio, 1994; Rolls et al., 1994). In addition to being disinhibited and impulsive patients with OFC damage have shown alterations in their responses to changes in rewards and losses of rewards. The evidence that the OFC is involved in the processing and learning about rewards and punishments is extensive (Rolls, 2000e). Non-human primates and humans with OFC lesions perseverate, continuing to make responses that are no longer rewarded (Iversen & Mishkin. 1970; Rolls et al., 1994). Further, in an fMRI study, the OFC was activated by monetary rewards and punishments and the magnitude of the activation was related to the magnitude of the reinforcers (O'Doherty et al., 2001b). This suggests that the OFC represents magnitudes of abstract rewards and punishments. Therefore, a difficulty in modifying responses or in learning about altered stimulus-reinforcement associations (altered reinforcement

[18] Where animals work in order to obtain electrical stimulation of certain brain areas (Rolls, 1999).

sensitivity), as opposed to motor inhibition, may contribute to the everyday disinhibited, impulsive, and inappropriate behaviours expressed by OFC patients.

### 1.8 Measurement of Orbitofrontal Cortex Behaviours

In two previous studies (Rolls et al 1994, Hornak et al., 1996) with frontal lesion patients with rather large lesions, a behaviour questionnaire was administered that reflected the degree of disinhibited and socially inappropriate behaviour exhibited by patients. For this questionnaire, a member of staff involved in each patient's care was asked to complete the questionnaire, which was designed to reflect the types of behaviour problems that have been found to result from frontal cortex damage (Levin et al., 1991). They were asked to rate on a likert scale, from 0 to 1.5, eleven different inappropriate behaviours. Rolls et al. (1994) found that ventral frontal lesion patients scored significantly higher on the behaviour questionnaire (had more inappropriate behaviours) than the non-ventral prefrontal lesion patient group and no patient in the non-ventral prefrontal lesion group was disinhibited or socially inappropriate. Further, the behaviour questionnaire score was highly correlated with poor performance on a reversal task of simple visual discrimination where ventral patients continued to make responses to a previously rewarded stimulus (the more inappropriate behaviours reported, the worse the ability to reverse). Finally, as mentioned in the Section 1.5.3, there was a strong positive correlation between emotional change scores and the behaviour questionnaire, therefore the more inappropriate behaviours reported, the more changes in emotion since their head injury were reported (Rolls et al 1994, Hornak et al., 1996).

A modified version of the behaviour questionnaire was administered in the current study. This version expanded the questionnaire to 20 questions from the old version, which was slightly vague, asking about the exact same behaviours but with more specific and detailed questions. Also, this questionnaire was given directly to participants as Bramham (2001) found that there was no significant discrepancy in answers between spouses and PFC patients when the same questions were asked of them both. The Frontal Behaviour Questionnaire was administered in order to further delineate brain behaviour relationships by testing prefrontal lesion patients with more discrete damage than those in the previous studies so as to determine if in fact OFC lesion patients show more inappropriate "frontal" behaviours than non-OFC (mostly DLFC) patients and to further explore the relationship between disinhibited and inappropriate behaviour, emotion, personality, and reversal of visual stimuli. This test was also used to measure the extent to which BPD patients exhibit inappropriate "frontal" behaviours, thus testing the main hypothesis that BPD patients have some type of underlying PFC deficit.

### 1.9 Differences between the OFC and the Dorsolateral Prefrontal Cortex

Stuss & Benson (1989) categorised the functions of the PFC into two groups. The first group of functions involves cognitive processes like sequencing, forming mental sets, and integrating behaviours and is suggested to be mediated by the DLFC. The second group of functions involves

more primitive processes like drive, motivation, and will, and is thought to be associated with OFC activation.

Clinical observations, group, and neuroimaging studies provide evidence for the dissociation of cognitive functioning and affective/social behaviour related respectively to DLFC and OFC damage. Damasio et al. (1990) found that orbitomedial damage was associated with impaired affective processes and inappropriate social interactions like disinhibited emotional expression, sexual disinhibition, impaired decision-making, and reduced sense of responsibility, while Dubois et al. (1995) describe patients with DLFC damage as having impaired motivation and abstract reasoning. Walker & Blummer (1989) also found that OFC damage can introduce abnormal sexual behaviour, while DLFC lesions may reduce sexual interest. Further, Sarazin et al. (1998) found that impairments on cognitive tasks were correlated with cerebral glucose metabolism in the DLFC and anterior cingulated cortex, while behavioural disturbances were associated with metabolism in the OFC and frontopolar cortex.

This evidence provides support for the argument that despite the fact that the cognitive, behavioural, social, and emotional impairments that arise after prefrontal damage are often grouped together under the term "dysexecutive syndrome" (Braddeley & Wilson, 1988), it may be more appropriate to consider the individual deficits and their related underlying mechanisms separately. So, given the abundance of different presentations with no one fundamental symptom, deficits resulting from PFC damage should be considered as groups of problems rather than one syndrome and be investigated separately as related to discrete lesions within the PFC.

## 1.10 Functions of the Dorsolateral Prefrontal Cortex

I will discuss some of the functions of the DLFC, as it was the main area of damage in the control PFC lesion patient group (17 out of the 20 control lesion patients had DLFC damage). Specifically I will explore the role of the DLFC in impulsivity, spatial working memory, and time perception (time perception and the DLFC are discussed in Section 1.11.2.2).

### 1.10.1 The Dorsolateral Prefrontal Cortex and Impulsivity

Frontal lobe damage can cause disinhibiton or impulsivity such that the behaviour of a subject is guided by previously acquired responses that are inappropriate to the situation (Milner 1963; Mishkin, 1964; Iversen & Mishkin, 1970). Impulsivity or disinhibition can be selective for particular cognitive functions and different regions of the PFC can account for the different cognitive functions that are related to the multifaceted construct of impulsivity. For example, whereas damage to the DLFC (BA 9) in monkeys can cause loss of inhibitory control in attentional selection (Milner, 1963), damage to the OFC in monkeys causes a loss in inhibitory control in affective processing, thereby impairing the ability to alter behaviour in response to fluctuations in the emotional response to stimuli (Dias et al., 1996b). Thus, I propose that different cognitive functions related to impulsivity are distributed within different regions of the prefrontal cortex.

The effects of lesions of the lateral[19] (BA 9) and orbital PFC were compared on the ability of marmoset monkeys to shift t+-heir responding at two different levels of response selection, that of stimulus-reward or affective associations (visual discrimination reversal) and that of attentional selection for specific perceptual dimensions (attentional set shifting) (Dias et al., 1996a). Dias et al. (1996a) devised a procedure for examining, in monkeys, the dissociable forms of inhibitory control of behaviour that operate at these two levels of response selection, namely changes in assignment of affective association of specific visual stimuli and shifts in selective attention from one perceptual dimension of a complex visual stimulus (such as form) to another (Roberts et al., 1988), the former being akin to an emotional reversal task, the later to the Wisconsin Card Sorting Task (WCST; described in Section 1.7.3) in humans. Dias et al. (1996a) found that lesions of the DLFC, but not the OFC, impaired the ability to shift an attentional set from one perceptual dimension to another (e.g. shapes to lines) (a.k.a. extra-dimensional shift). In contrast, lesions of the OFC, but not the DLFC, impaired the ability of marmosets to reverse stimuli-reward associations within a particular perceptual dimension (e.g. shapes) (a.k.a. intra-dimensional shift). Thus, reversing a stimulus-reward association between the same pair of exemplars within a dimension, as distinct from shifting an attentional set between dimensions, was impaired by a lesion to the OFC and not the DLFC.

Thus, the capacity to reverse affective associations for specific visual stimuli seems to be mediated by regions within the OFC, consistent with its close connection with the limbic system (Nauta, 1971; Amaral, 1993). In contrast, regions within the DLFC may be implicated in the higher-order shifting of attention between supra-ordinate features of visual stimuli, such as their perceptual dimensions, like when switching from shape to colour as the relevant sort cue in the WCST. In sum, preliminary findings have demonstrated that although DLFC, but not OFC, is the critical locus in *shifting* an attentional set *between* perceptual dimensions; OFC but not DLFC is the critical locus in *reversing* a stimulus-reward association *within* a particular perceptual dimension (Dias et al., 1996b). This double dissociation between behavioural effects of the DLFC and OFC lesions in marmosets provides insight into the functional organisation of the PFC in primates. Further, these impairments were restricted to the first occasion that such shifts in responding were required and neither lesion disrupted the ability of the marmosets to acquire, develop, or maintain an attentional set toward one particular dimension. This highlights the specificity of the deficit to one of inhibitory control mechanisms.

Dias et al. (1997) extend their original results by demonstrating that mechanisms of inhibitory control and "on-line" processing (involved in working memory) are independent within the PFC and that those PFC areas involved in the suppression of previously established response sets are not involved in the acquisition of such response sets. Traditionally, impairments in inhibitory control shown by patients with PFC damage on tests like the WCST have been

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[19] Dias et al. (1996a,b) refer to this lesion simply as "lateral PFC", but since it is part of the DLFC, defined as BA 9 and 46 (see Section 1.6.1), henceforth I will refer to it as DLFC.

accounted for in terms of deficits in inhibiting an attentional set and by extension to DLFC damage (Milner, 1964; Mishkin, 1964; Cicerone et al., 1983). More recently, Goldman-Rakic (1987) has suggested that impairments in inhibitory control may reflect an underlying deficit in the ability to hold information on-line in working memory. The results of the Dias et al. (1997) study cannot be easily accounted for by this working memory theory of PFC function because all of the discriminations involved short-term memory but only those involving inhibition of a previously required response were impaired. They suggest that the impairments were attributable to a loss of inhibitory control at two different levels of cognitive processing: affective processing (after OFC lesions) and attentional processing (after DLFC lesions). Whether other regions of the PFC are involved more generally in response selection based on emotional or higher order attentional factors is unclear. Certainly lesions involving areas 13, 14, and 32 on the ventromedial and medial surfaces in macaque monkeys impair the ability to associate reward with particular visual stimuli (Iversen & Mishkin, 1970; Gaffen & Murray, 1990; Gaffen et al., 1993), a deficit similar to that seen after damage to the amygdala (Gaffen & Murray, 1990), to which these regions of the PFC are heavily interconnected. Also, Iversen & Mishkin (1970) showed that monkey lesions restricted to areas 13 and 14 on the orbital surface abolished the improvement in performance that is usually seen across a series of visual discrimination reversals; an impairment that could reflect a failure in reassociating previously rewarded stimuli with punishment.

These findings of a double dissociation between DLFC and OFC in the marmoset on discrimination reversal and attentional set shifting suggest that impulsivity or inhibitory control operate across functionally distinct regions within the PFC. Support for this hypothesis comes from ablation (Diamond & Goldman-Rakic, 1989) and electrophysiological recording (Funahashi et al., 1993) studies in rhesus monkeys, which demonstrate that inhibitory control mechanisms operate together with on-line processing within the DLFC to control performance on the spatial delayed response task. Although damage to DLFC causes a loss of inhibitory control in attentional selection, damage to the OFC causes a loss of inhibitory control in affective processing. These findings provide an explanation for the apparent discrepancy between human and non-human primate studies in which disinhibition as measured on the WCST is associated with the DLFC, whereas disinhibition as measured on discrimination reversal is associated with the OFC. Accordingly, the impairment on the WCST that has been associated with damage to the DLFC, but not the OFC, in humans, (Milner 1964; Eslinger & Damasio 1985; Shallice & Burgess 1991) is similar to the impairment in shifting an attentional set described in Dias et al. (1997) that is associated with damage to the DLFC rather than the OFC in the marmoset. I therefore propose that certain aspects of impulsivity are related to DLFC functioning and certain aspects to OFC functioning. In particular, OFC lesion patients are expected to perform poorly on the emotion-related reversal task, which involves reinforcement contingencies, while patients with DLFC should remain unaffected.

Further, Van den Broek & Bradshaw (1993) found that perseverative responding on the Modified Card Sorting Test (MCST) was significantly correlated with an impulsiveness index derived from the Matching Familiar Figures Test (MFFT) but not with a questionnaire of impulsivity. It has been suggested that questionnaire measures relate primarily to individuals' social behaviour, whereas behavioural measures like the MFFT measure cognitive tempo (Barratt & Patton, 1983). So perseveration on the MCST may be correlated with impulsive cognitive tempo, but not with the degree to which people are impulsive in social or interpersonal situations. Since the MCST is widely considered sensitive to dysfunction of the DLFC, impulsive cognitive tempo may be due in part to DLFC dysfunction whereas impulsivity in social situations (disinhibition), which involves processing of reward and punishment cues may be due in part to OFC function. So, perhaps there is a dissociation between different aspects of impulsivity and respectively between OFC and DLFC functions. Accordingly, the PFC is not a homogeneous region of the cortical mantle, but rather a collection of several distinct architectonic areas (Brodmann, 1905, 1908, 1909; Von Economo & Koskinas, 1925; Sarkissov et al., 1955; Sanides, 1962; Barbas & Pandya, 1989; Petrides & Pandya, 1994, 1999). Yet to date, there is only modest evidence in humans to indicate what regional specialisations of function exist in the prefrontal cortex (Duncan & Owen, 2000).

### 1.10.2 The Dorsolateral Prefrontal Cortex and Spatial Working Memory

#### 1.10.2.1 Definition of Working Memory

The frontal cortex helps mediate working memory (WM), a system that is used for the temporary (short-term) storage and "on-line" manipulation of information that is necessary for many higher cognitive functions, such as language, planning and problem solving (Smith & Jonides, 1999). The concept of WM has been described and discussed in various ways; as a cognitive system for both the temporary storage and manipulation of remembered information (Baddeley, 1986), as the type of memory that is active and only relevant for a short period of time (Fuster, 1995; Goldman-Rakic, 1995) and, most specifically, as the process by which a remembered stimulus is held "on-line" to guide behaviour in the absence of external cues (Goldman-Rakic, 1987, 1996). In general, WM can be described as the ability to hold an item of information transiently in the mind in the service of comprehension, thinking, and planning (Baddeley, 1986; Carpenter & Just, 1988). Traditionally WM has been divided into two types of components or processes: short-term storage or active maintenance (on the order of seconds) for maintaining mental representations in an active state (keeping information available "on-line"), associated with more posterior brain regions, and executive control processes that operate on the contents of storage, governing the encoding manipulation and retrieval of information in WM associated with the PFC. The executive component or the capacity for processing or manipulating information held in the WM "buffer" (temporary storage unit), is often referred to as the "central executive" (Baddeley, 1986) or supervisory attentional system (Shallice, 1982). Working memory in its simplest form, like when

holding a phone number in mind long enough to dial it, may decay passively and/or instantaneously. In its most elevated form, WM serves as a workspace for holding items of information in mind as they are recalled manipulated, and/or associated to other ideas and incoming information.

Working memory and conditional associative learning are thought to play important roles in the self-regulation of behaviour (Petrides et al., 1993a,b; Lau et al., 1995) and are likely to contribute to the reflectivity/planning functions underlying behavioural inhibition (Barratt & Patton 1983). Working memory may be involved in the ongoing, moment to moment, regulation of behaviour and serve to modulate activity in behavioural inhibition systems, such as the system described by Gray (1987a). It is widely accepted that the PFC plays a critical role in the neural network subserving WM (Levy & Goldman-Rakic, 2000), which experimental studies in both monkeys and humans have clearly demonstrated (Goldman-Rakic, 1987; Fuster, 1997; Smith & Jonides, 1999). A set of elemental processes, including the maintenance, manipulation, and utilisation of mental representations, has been postulated to constitute an operational WM system, which contributes to the "higher" cognitive functions, such as reasoning and planning, thought to be related to the PFC (Baddeley, 1986; Goldman-Rakic, 1987).

### 1.10.2.2 Evidence for the Role of the DLFC Cortex in Spatial Working Memory

Evidence for the role of the frontal lobes in spatial working memory (SWM) processes has come from both animal and human subjects. Studies in the monkey have indicated that PFC areas differ in major ways in terms of their cortical and subcortical connections (see Pandya & Yeterian, 1985). These differences in the local circuitry of the various prefrontal areas, which is reflected in their specific cytoarchitectonic pattern, coupled with their distinct inputs and outputs, indicate specialised functional contributions. With regard to the issue of whether there is a critical region of the PFC that might underlie the monitoring of information in WM; work with patients indicates that some part of the DLFC might be critical, because this region is consistently involved in the patients who are impaired on self-ordering tasks (Petrides & Milner, 1982). The work with patients, however, could not specify the critical region because the lesions involved multiple areas. Studies with monkeys in which lesions could be restricted with precision within a given region led to the identification of the mid-DLFC (BA 9, 46, & 9/46) as the critical region for the monitoring of information within WM (Petrides, 1991, 1995a). Further, there is considerable evidence from functional neuroimaging in human subjects (for review see Owen, 1997a; D'Esposito et al., 1998; Petrides, 2000a) and studies of monkeys with lesions limited to the mid-DLFC (Petrides, 1991, 1995b) that this region is involved in WM.

The critical role of the DLFC in spatial working memory (SWM) was established by a long line of studies with monkeys, originating in the classic demonstration by Jacobson (1936) that

lesions of the PFC impair performance on delayed-response tasks[20] (e.g., Mishkin, 1957; Gross & Weiskrantz, 1962; Goldman & Rosovold, 1970; Butters et al., 1971; Goldman et al., 1971; Passingham, 1975; Mishkin & Manning, 1978; Funahashi et al., 1993; Petrides, 1991, 1995a,b). Since the 1970s, several studies recording the activity of single neurons in monkeys performing various delayed-response tasks demonstrated that certain neurons in the DLFC continue to discharge during the delay period, appearing to maintain temporarily the processed information (e.g. Fuster & Alexander, 1971; Kubota & Niki, 1971; Fuster, 1973; Niki, 1974a, 1974b; Kojima & Goldman-Rakic, 1982; Miller et al., 1996). This work clearly established the existence of sustained neuronal activity during the delay period within the DLFC and further reinforces the notion that this region of the cortex plays a crucial role in SWM.

In the monkey, lesions of the DLFC, and in particular of the sulcus principalis, give raise to deficits on memory tasks containing a spatial element (Mishkin, 1964; Goldman & Rosvold, 1970; Butters et al., 1971). In man, frontal lobe lesions impair the learning of stylus mazes in both the visual (Milner, 1964) and tactile (Corkin, 1965) modalities and under different motivating conditions (Canavan, 1983), the deficits being more striking after right than after left frontal lobectomy (Milner, 1964, 1975). More specifically, visuospatial processes engaged in humans by activities such as chess playing, following maps, recalling one's location with respect to landmarks, or painting and drawing from memory, and studied in animals by delayed response tasks, have been shown to rely on the dorsolateral prefrontal convexity both in monkeys (Fuster & Alexander, 1971; Kubota & Niki, 1971; Funahashi et al., 1989; MacAvoy et al., 1991; Friedman & Goldman-Rakic, 1994) and in humans (Freedman & Oscar-Berman, 1986; Verin et al., 1993). In contrast, WM for features of objects or faces engages anatomically different prefrontal regions located in an inferior position in the PFC in both humans and monkeys (Cohen et al., 1994; Adcock et al., 1996; Courtney et al., 1996; McCarthy et al., 1996).

In the DLFC and inferior convexity (Walker's areas[21] (WA) 12 & 45; just lateral of the OFC), the firing of the neurons may be related to the memory of spatial responses or objects (Goldman-Rakic, 1996; Wilson, 1993) or both (Rao et al., 1997b). However, the DLFC (BA 46) seems to be specifically involved in remembering the locations of spatial responses in, for instance, spatial delayed-response tasks (Goldman-Rakic, 1996). Single cell recordings made while monkeys engage in spatial-storage tasks have found "spatial memory" cells in the DLFC (BA 9 and 46). These cells selectively fire during a delay period and are position specific. Physiological recordings in the principal sulcus and arcuate regions (both part of the DLFC) of monkeys trained to perform delayed-response tasks demonstrate that neurons in these areas hold representations of spatial stimuli "on-line" for brief periods when such stimuli are no longer present and must be recalled (Funahashi et al., 1989; Fuster, 1973). This activity is considered a neural correlate of WM, a

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[20] In a delayed-response task, the monkey is presented with a stimulus in a certain location and after a delay, asked to move their eyes to where the stimulus was previously located.

[21] See Figure 1.5b for an illustration of Walker's (1940) cytoarchitechtonic map of the frontal lobe of the monkey.

process of updating information on a trial by trial basis. These prefrontal areas are connected with the posterior parietal cortex, from which they presumably access spatial information (Selemon & Goldman-Rakic, 1988; Cavada & Goldman-Rakic, 1989; Petrides & Pandya, 1984). Numerous other studies support the notion that the WM function of the DLFC is specialised for spatial information (see Goldman-Rakic, 1987). Wilson et al. (1993) conducted experiments on monkeys that show that the inferior convexity (WA 12 & 45; just lateral of the OFC) is involved in mnemonic processing of objects and faces, whereas the principal sulcus and arcuate areas of the dorsolateral convexity are dedicated to spatial processing. Recordings made while monkeys engaged in object storage tasks have found delay sensitive "object memory" cells in a more ventral region of the PFC that are object specific (Wilson et al., 1993; see also different findings by Rao et al., 1997b, described in Section 1.10.2.3). Further, clinical studies with patients with inferior frontal cortex damage are impaired in recognising recently seen faces and words and in the classification of visual patterns (McCarthy & Warrington, 1990). Thus, neurons in the PFC that code for information related to stimulus identity are dissociable from those that code information related to stimulus location. The implications of these findings are that spatial and object WM have different neural bases and that at least part of memory is in PFC, with spatial information being represented more dorsally than object information. This indicates that the PFC contains separate processing mechanisms for remembering what and where an object is; the former being related to OFC function and the later to DLFC function (see Section 1.7.1).

Levy & Goldman-Rakic (2000) believe that the DLFC is composed of several subregions, based on the sensory nature of the information being processed in WM, regardless of the level of processing. Further, they believe that the cortex surrounding the principal sulcus (WA 46 in the primate) is specialised for visual spatial processing, whereas cortex on the inferior convexity (WA 12 & 45), below area 46, is involved in visual non-spatial (e.g. face/object) processing within WM. In the visual domain, lesion studies in the non-human primate provide evidence for a model of anatomical and functional segregation of the PFC, based at least in part on sensory processing, in which the DLFC (WA 46 including the principal sulcus) is specialised for spatial cognition involving a WM process, whereas the inferior convexity/ventrolateral PFC (WA 12 & 45) plays a role in object cognition involving WM. DLFC lesions consistently produce a deficit restricted to visio-spatial cognition (Goldman-Rakic, 1987). Rarely, if ever, have monkeys with DLFC lesions exhibited strong or permanent impairments on object-based tasks. For example, Levy & Goldman-Rakic (2000) found that lesions to the monkey DLFC region produced a significant and stable impairment on two spatial WM tasks, but little or no impairment on two non-spatial WM tasks. More specifically, only lesions of dorsolateral areas (WA 46 & 8A) impaired WM processes, whereas lesions of the dorsomedial areas (WA 9 & 8B) were without lasting impairment. Further, the deficit following the DLFC lesion was confined to the spatial domain and did not encompass object WM. The finding of a dissociation of deficits on non-spatial and spatial WM tasks after DLFC lesions, and the marked impairment observed in both simple and complex SWM tasks,

confirm and extend the evidence for a specialisation in DLFC for SWM, regardless of the level of processing within this domain. Finally, the findings revealed that DLFC areas are no less critical for tasks with low WM demand than for more complex sequential processing with higher WM load (Levy & Goldman-Rakic, 2000). These results support an anatomical-functional segregation of the PFC for WM based on the type of information being processed rather than on the nature of the operations performed[22].

So, different areas within the PFC are involved in the process of WM and each area seems to process different types of information. For example, the inferior convexity cortex (WA 12 & 45) lying below and adjacent to the principal sulcus is a likely candidate for processing non-spatial (colour and form) information, in that lesions of this area produce deficits on tasks requiring memory for the colour of patterns of stimuli (e.g. Passingham, 1975; Mishkin & Manning, 1978). Further, the receptive fields of the neurons in the inferior convexity cortex, unlike those in area 46 in the DLFC above, represent the fovea (Mikami et al., 1982; Suzuki & Azuma, 1983), the region of the retina specialised for the analysis of fine detail and colour-stimulus attributes important for the recognition of objects. Several studies indicate that the inferior convexity may be specialised for non-spatial processing (Levy & Goldman-Rakic, 2000). Neurons exhibiting selective neuronal activity for patterned memoranda were almost exclusively found in or around WA 12 on the inferior convexity of the PFC, beneath the principal sulcus, while neurons that responded selectively in the spatial delay response trials were rarely observed in this region, appearing instead in the DLFC regions where spatial processing has been localised in previous studies (Goldman-Rakic, 1996). Thus, the evidence for the dissociation of inferior prefrontal and DLFC lesions vis-à-vis object processing (reviewed by Goldman-Rakic, 1987) establishes that non-spatial attributes of an object or stimulus may be processed separately from those dedicated to the analysis of spatial location and vice-versa. Further, within the inferior PFC, different features appear to be encoded by different neurons (Wilson et al., 1993). So, feature and spatial memory (what and where an object is) are dissociable not only at the location level but at the cellular level as well.

Single neuron recording has been used extensively to dissect the neuronal elements involved in WM processes. It has been found that the same PFC neuron appears always to code the same location and different neurons code different locations (Goldman-Rakic, 1996). Consequently, different neurons capable of holding specific visio-spatial co-ordinates "on-line" appear to be aggregated into a WM system in the DLFC. These and other results provide evidence at a cellular level for the theorised role of PFC neurons in WM i.e. maintenance of representational information in the absence of the stimuli that was initially present. Accordingly, it has been observed that monkeys and humans with PFC lesions have little difficulty in moving their eyes to a visible target or reaching for a desired object; rather their problem is organising and directing the same motor responses to remembered targets and objects. Further, damage to the PFC does not

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[22] See Section 1.10.2.3 for further discussion about the process vs. domain theories of DLFC SWM function.

impair knowledge about the world or long-term memory; it impairs only the ability to bring this knowledge to mind and utilise it to guide behaviour (Goldman-Rakic, 1996).

Neuroimaging evidence also supports a distinction between human spatial and object WM (McCarthy et al., 1994, 1996; Owen et al., 1996a; Faillenot et al., 1997). By adapting tasks derived from delayed-response tasks[23] used in monkeys, functional imaging studies in humans have repeatedly shown significant increases of the activity in the DLFC in SWM tasks (Owen 1997a; Ungerleider et al., 1998; Smith & Jonides, 1999), confirming that this area plays a crucial role in SWM processes in humans. Positron Emission Tomography (PET) studies have demonstrated activation of the DLFC associated with representation of both spatial and non-spatial information (Fuster et al., 1985; Jonides et al., 1993; Baker et al., 1996). SWM tasks predominately activated right DLFC while non-spatial tasks predominately activated left DLFC. This still supports the proposal that neural activity in the DLFC has a specific role in holding information "on-line" in WM (Goldman-Rakic, 1987).

### 1.10.2.3 Theories of Specialisation of Function of Spatial Working Memory within the DLFC

Two divergent positions have emerged that, while focusing on a similar anatomical distinction between dorsolateral and ventrolateral PFC regions, differ fundamentally in terms of the precise functions ascribed to those regions. One view, based on lesion and electrophysiological-recording studies in the monkey (Funahashi et al., 1989; Wilson et al., 1993; Levy & Goldman-Rakic, 1999), is that WM processes are organised according to the type ("domain") of information being processed, with DLFC regions being concerned principally with memory for spatial material and ventrolateral regions being concerned with memory for non-spatial material (Goldman-Rakic, 1987, 1994, 1995; Courtney et al., 1996, 1997, 1998). According to this view, information domain, not process, is thought to be mapped across the PFC. Hence, the PFC is thought to be organised by the modality of the information being stored. So, for example, spatial information is thought to be represented more dorsally than object information (Wilson et al., 1993). In the alternative "process" view, based largely on lesion studies in the monkey, a functional distinction is drawn between the mid-dorsolateral and mid-ventrolateral PFC regions, based on the type or nature of the processes carried out by each region respectively (Petrides, 1994, 1995b; Owen, 1997a,b; Owen et al., 1999). In this view, the mid-ventrolateral PFC (BA 45 & 12/47; see Figure 1.6) is concerned principally with the active organisation of sequences of responses based on conscious, explicit retrieval of information from posterior association systems, while mid-DLFC (BA 9, 46, & 9/46; see Figure 1.6) is used when active manipulation or monitoring of such information is required within WM. Thus, it is believed that the PFC is organised by process, with ventrolateral regions (BA 45 & 47) mediating operations needed to sustain storage and DLFC regions (BA 9 & 46) implementing the active manipulation of information held in storage. According to this view, the mid-DLFC should

[23] Tasks where monkeys are required to maintain a mental representation during a delay period and then use this representation to guide the choice of response at the end of the delay.

be recruited in both spatial and non-spatial tasks but only when active manipulation or monitoring of information is required (Petrides, 1994; see Figures 1.4 & 1.5a for Brodmann's brain maps).

Domain-specific theorists have conducted experiments that show that the DLFC is involved in spatial WM and that the ventral lateral PFC is involved in non-spatial object WM (see Section 1.10.2.2). Conversely, process-specific theorists performed experiments that indicate, in humans and monkeys that both mid-DLFC and mid-ventrolateral PFC can be activated during spatial WM tasks. For example, Owen (1997a), a process-specific theorist, performed a meta-analysis of activation studies that employed both spatial and non-spatial WM tasks and failed to dissociate peaks of activation for these tasks within the DLFC. Owen and colleagues have also reported the engagement of different PFC regions with different levels of executive demand (Owen et al., 1998, 1999). Further, several functional neuroimaging studies have provided evidence to support the process-specific model of WM within the lateral frontal cortex (Owen et al., 1996b, 1998; Owen, 1997a; Petrides et al., 1993a,b, 1995b). Functional neuroimaging data with normal human subjects have shown increases in activity within the human mid-DLFC whenever subjects had to monitor information within WM regardless of the nature of the stimulus information (visual spatial, visual non-spatial, auditory, etc.) (Owen, 1997a; D'Esposito et al., 1998; Petrides, 2000b). Owen et al. (1996b) showed that either, or both, of the two lateral regions can be activated in visual spatial memory tasks, depending on the precise executive process. In another fMRI study, identical regions of the lateral PFC were shown to be involved in both spatial and non-spatial WM tasks when all factors unrelated to the type of stimulus material were appropriately controlled (Owen et al., 1998). Further, Stern et al. (2000) found that when two non-spatial WM tasks were compared, although both mid-DLFC and right ventrolateral frontal cortex were activated in both tasks, the memory task that had the higher monitoring requirement, yielded significantly greater signal intensity changes during an fMRI in BA 9/46 of the right mid-DLFC than the memory task with a lower monitoring requirement. In addition, the process-specific model is supported by electrophysiological data (Rao et al., 1997b) where, in a SWM task, over half (52 percent, or 64/123) of the PFC neurons that showed delay activity, showed delay activity to *both* what and where object information. Further, lesion work in non-human primates (Petrides, 1995a) found that the monitoring requirement, that is, the necessity to consider both the presented and non-presented stimuli for success in a particular trial, was the critical variable, giving rise to an impairment after mid-DLFC impairment.

For each of the findings in the literature supporting the process-specific theory, there are numerous functional imaging studies that support a domain-based segregation of function within the PFC (Smith et al., 1995, 1996; Courtney et al., 1996, 1997, 1998; McCarthy et al., 1996; Belger et al., 1998; Kelly et al., 1998; Kohler et al., 1998; Smith & Jonides, 1999). However, disparities exist between these studies with respect to the exact loci of spatial and non-spatial WM. For example, the inferior frontal region has been related to object WM and a caudal portion of the superior frontal gyrus to spatial WM (Courteny et al., 1996, 1998) and the right PFC has been

predominately activated by SWM and the left PFC by object WM (Smith et al., 1995; McCarthy et al., 1996; D'Esposito et al., 1998). Despite the disparities, these studies still provide support for the domain-specific theory in that tasks equated for WM demand, but formatted for different domains, activated different PFC regions.

Although there is evidence supporting each of the two competing theories concerning the specialisation of function of WM within the DLFC, the evidence in support of the domain-specific theory has more theoretical appeal. One reason for this is that more posterior, extrastriate cortical regions (in the occipital lobe) are organised, at least in part, into anatomically distinct pathways, functionally specialised for identifying spatial locations (the occipital pathway or dorsal stream) or object features (the occipitotemporal pathway or ventral stream) (Ungerleider & Mishkin, 1982). Whilst these posterior association areas project reciprocally to wide-spread frontal lobe regions, a certain degree of topographical order appears to be maintained (Barbas, 1988; Cavada & Goldman-Rakic, 1989; Webster et al., 1994; Carmichael & Price, 1995). In any case, both theories emphasise the role of the DLFC in SWM when it involves monitoring of information. Therefore, I have chosen to use a SWM task, which requires active monitoring of information, to assess DLFC function. Comparing participants' performance on the SWM test, believed to be sensitive to DLFC function, with measures of impulsivity, personality, emotion, and time perception, will lead to a better understanding of the relationship between these functions and the DLFC. Finally, giving this SWM/DLFC function test to BPD patients will help determine if their behavioural and emotional problems are related specifically to OFC deficits or to DLFC dysfunctions as well.

## 1.11 Time Perception

### 1.11.1 Theories of the Neurocognitive Mechanisms of Time Perception

Much remains to be understood about the functional neuroanatomy of temporal information processing. Time is clearly a source of information that shapes ones' behaviour. The sense of time passing is fundamental to the sequential structuring of activities in our daily lives where we are often confronted with a wide range of durations to which we frequently adapt either consciously or unconsciously. Humans are remarkably proficient at perceiving the passage of time and producing precisely timed behaviours; many of which depend on both explicit prospective and implicit or retrospective temporal judgements. For these events, multiple processes seem to determine our subjective perception of current time for intervals lasting on a scale of milliseconds to seconds. As discussed below, our subjective sense of time passing is believed to be either based on memory for previous events that occurred during a particular time interval, or read off of an internal clock-like device in the brain, or both. Most theories of prospective timing embody similar components (Wearden, 1999) including an internal timekeeper, attention, and memory (Gibbon et al., 1984; Matell & Meck, 2000). A clock metaphor is used to describe the timekeeper mechanism, which represents subjective time through the accumulation or readout of pulses, possibly generated by oscillators. Thus, the basic features of most psychophysical or neurobiological models of the

mechanisms of timing capacity involve an "internal clock" and memory and decision-making devices that translate clock readings into behaviour (Church, 1984; Church & Broadbent, 1990; Treisman & Brogan, 1992). A representation of subjective time may then be passed on to WM (Rao et al., 2001), a short-term repository where interval representations may be maintained and manipulated in accord with current goals, like comparing two time intervals. Working memory may therefore alter stored representations of time as well.

In general, temporal duration judgements are thought to be based upon neurocognitive mechanisms (Carson & Feinberg, 1968). There is, however, considerable debate concerning the representational mode in which time is represented in the brain and thus there exists many different theories concerning the mechanisms of timing. Some models suggest neuronal oscillations or interval based mechanisms like "biological clocks" (Wittman, 1999). Some suggest that timing deficits are due to impairments in various non-temporal processes such as motor implementation, attention, and memory (Harrington & Haarland, 1999; Rao et al., 2001). Results from focal lesion research suggest the right middle-frontal and inferior-parietal cortices comprise a pathway that supports attention and WM operations, which are crucial for timing (Harrington & Haarland, 1999). Functional imaging data also provide some converging evidence for this proposal (for a review, see Harrington & Haarland, 1999). In all, it seems clear that information used in the analysis of passing time is derived from various cognitive processes. Based on evidence that frontal lobe damage creates problems in time estimation (e.g. Mimura et al., 2000; see Section 1.11.2), an aim of the current research is to help clarify the precise neuroanatomical correlates of time perception within the frontal lobe and to determine its relationship to impulsivity.

### 1.11.2 The Prefrontal Cortex and Time Perception

Studies have shown that prefrontal brain areas, lesions of which have been shown to impair episodic and WM in amnesiac and frontal syndromes, are also implicated in time estimation (Mimura et al., 2000). Amnesiac patients, who have episodic memory problems, are inaccurate in estimating temporal duration. On verbal time estimation measures, where participants estimate elapsed time in seconds, amnesiacs underestimate time intervals (Kinsbourne & Hicks, 1990; Nichelli et al., 1993; Williams et al., 1989)[24]. This suggests that time estimation depends upon retrieval of events that occurred during the time interval. In addition to memory, processes that mediate duration estimation may include decision mechanisms for which frontal-executive functions play a crucial role (Fuster, 1997). Prefrontal lesions have been shown to interfere with timing in rats (Glickstein et al., 1964; Meck et al., 1984) and humans (Bruyer & Bontemps-Devogel, 1979). Single unit recordings in monkeys reveal firing in frontal brain regions that correlates with task-relevant temporally separated events (Fuster, 1993; Niki & Watanabe, 1979). In the neuropsychological literature, patients have been reported who demonstrate time estimation

[24] While most amnesiacs underestimate time, some are prone to overestimate (for example, case BB in Nichelli et al., 1993). Thus, it is hard to determine whether amnesiacs over- or underestimate time.

problems within the context of damage to frontal systems. For example, an amnesiac patient (case BB in Nichelli et al., 1993), who overestimated time, had severe frontal impairment. Further evidence for the role of frontal systems in time estimation is the finding of a negative correlation between magnitude of time estimation and performance on a test of cognitive estimation thought to assess frontal functions, in Korsakoff amnesiac[25] and alcoholic subjects (Shaw & Aggleton, 1994).

In addition, supporting evidence for the role of the frontal lobe in time estimation was found in a study by Mimura et al. (2000) investigating the time estimation ability of patients with frontal damage and Korsakoff amnesia. They found that frontal patients deviated from clock time more than Korsakoff patients did at short intervals (<1 minute), whereas at longer intervals, Korsakoff patients were less accurate than frontal patients and alcoholics, increasingly underestimating durations as intervals grew longer. Frontal patients, compared to normals, overestimated short intervals (<30 seconds) in inverse proportion to their performance on the WCST (a test shown to be sensitive to frontal lobe function, see Section 1.7.3) and as intervals grew longer, overestimation yielded to underestimation. Conversely, Korsakoff patients were unimpaired at short intervals and increasingly underestimated as intervals grew longer. In addition, Korsakoff patients underproduced longer time intervals while frontal patients had no significant difference in time production compared to normals. Thus, both WM and episodic memory may play a role in temporal cognition. The impaired WM that is typically associated with DLFC dysfunction (Petrides, 2000a,b) may result in quicker turnover of information held in WM, which may generate a sense of more time passing thus inflating subjective duration (Kinsbourne, 2000). Mimura et al. (2000) believe that the timing system, perhaps based on striatum (see Footnote 12), may receive WM information from the PFC and record time passing according to the rate at which turnover occurs thus explaining why frontal patients tend to overestimate short durations to a greater extent than normal controls or Korsakoff patients. On the other hand, temporal duration beyond 30 seconds may require episodic memory[26], thus putting Korsakoff patients at a disadvantage (Mimura et al., 2000). This explains the inaccurate duration judgements in Korsakoff patients at intervals beyond one minute in both time estimation and production. Korsakoff patients' overproduction at longer durations, in excess of 30 seconds, approximates this WM time frame. So subjective time perception is proposed to be related to WM at short intervals and WM has been associated with the PFC (see Sections 1.7.1 & 1.10.2).

Previous studies have indicated that time estimation is dependent on an internal clock that is mediated by frontal brain regions (Church, 1984; Meck, 1983; Meck et al., 1984). Some researchers have reported that frontal patients' internal clocks are driven more quickly than the internal clocks of normal individuals (Hoagland 1933; Carlson & Feinberg 1968). This can be

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[25] When someone drinks excessively they may develop a thiamine deficiency, which can lead to personality alterations and a loss of memory known as Korsakoff amnesia. Limbic structures including the hippocampus are thought to be involved in the syndrome. Korsakoff amnesiacs have trouble acquiring new information (anterograde amnesia) and remembering things that happened before the illness (retrograde amnesia) (Crossman & Neary, 2000).

[26] Episodic memory is memory of personally experienced events.

considered the "cognitive pace theory" so that time estimation problems are related to an exceedingly fast or slow internal cognitive clock. Alternatively, patients' difficulties in time estimation could represent a generic problem in decision-making about abstract types of information as frontal patients often have difficulty on other types of cognitive estimation tasks like estimating how much a familiar product is likely to cost (Smith & Milner, 1984) or inferring familiar facts from experience (e.g. "How tall is the average English women's spine?"; Shallice & Evans, 1978). Mimura et al. (2000) dismiss both of these theories of time estimation. They dismiss the first theory because while frontal patients overestimated time particularly at short intervals in Mimura et al. (2000), the accelerated counting of some frontal patients could only partially explain their propensity towards verbal overestimation. Many of the frontal patients did not demonstrate severe rapid counting and there was no consistency in the magnitude or direction (i.e. over- or underestimation) of their estimations over different time intervals. Thus, problems with an internal clock mechanism do not wholly explain the data. Mimura et al. (2000) dismiss the second theory because they believe that the types of decisions made in cognitive estimations of other types of abstract information are different than the ones made in temporal tasks.

Mimura et al. (2000) believe a better explanation of time perception implies WM as a major component of the system underlying time judgement. The PFC is thought to maintain information in WM (Cohen et al., 1997; Courtney et al., 1997) and frontal lesions interfere with WM (Baddeley, 1986; Shimamura, 1995). As new information enters the WM store, old information must be expelled from it. Rapid turnover of information held in the WM store would generate a sense of more time passing (Kinsbourne, 2000). This should be particularly striking in frontal patients at the short intervals (<30 seconds). At such times rather little loss might be expected from someone with an intact WM. Accordingly, Mimura et al.'s (2000) frontal patients overestimated the shortest time interval (10 seconds) to a greater extent than any other time interval. Thus, WM seems to play a critical role in temporal duration judgement for short intervals. Further, the relationship between performance on the WCST and accuracy of time estimation was significant for brief periods of time (up to 30 seconds) within the time frame of WM (Wickelgren & Berian, 1971; Baddeley, 1986; Washburn & Astor, 1998). For longer intervals, the tendency to overestimate appears to be counteracted and even reversed, depending on the severity of the memory deficit (Miruma et al., 2000). Thus, the internal clock is either inactivated in frontal patients or the hypothetical clock does not exist and the frontal patients' deviations in time estimation reflect memory-related difficulties. More clarification is needed concerning the relationship between WM and time perception. By administering time estimation, perception, and pacing tasks I will examine further the underlying neurocognitive mechanisms of time perception.

Finally, imaging studies show the activation of the PFC in tasks that require estimation of brief durations (Hinton et al., 1996) or timing of movements (Rao et al., 1997a). The implication of the PFC in time perception has also been assessed using electrophysiological methods (Elbert et al., 1991; Bruder et al., 1992; Casini & Macar, 1996). For example, Pouthas et al. (2000) found

that the right frontal cortex plays a significant role in the formation of temporal judgements. Using event-related potentials (ERPs) and PET imaging in humans, they were able to show differences in the time course of activations between duration and intensity processing of visual stimuli, and thus were able to determine the brain areas activated when subjects performed a duration task. They found that processing of duration information specifically involves the right frontal cortex. This is consistent with the neuropsychological data of Harrington et al. (1998), where only patients with right lesions, as opposed to left lesions, showed time perception deficits.

### 1.11.2.1 The Role of the Right Prefrontal Cortex in Time Perception

There have been a few studies concerned specifically with hemispheric specialisation of time perception. However, when studies are investigating discrete timing, a pattern sometimes emerges that is characterised by right hemispheric activity in the prefrontal and parietal cortices. Further, studies with neurological patients and with electrophysiological measures support the proposed right hemispheric lateralisation of cortical involvement in time perception. Specifically, one PET study found a right hemispheric bias for interval and illumination intensity discriminations (Maquet et al., 1996), possibly attributed to the emphasis on sustained attention and WM. However, another PET study did not uncover a hemispheric bias for interval discriminations (Jueptner et al., 1995). Yet, Harrington et al. (1988) found that, in humans, only patients with right hemisphere damage (RHD), as opposed to patients with left hemisphere damage (LHD), showed time perception deficits. 100% of the RHD patients with impaired timing and anterior damage had lesions in premotor and prefrontal cortex (BA 6, 8, 9, and 46) and with posterior damage had lesions in the inferior parietal cortex. All LHD patients with normal timing had damage to these same regions, whereas few, if any, RHD patients with normal timing had similar lesion distributions. These results implicate a right hemisphere prefrontal-inferior parietal network in timing. Harrington et al. (1998) was the first to show directly that the right hemisphere is essential for time keeping as only RHD was associated with a disruption in time discriminations. Their study implicated the right inferior parietal lobe and areas of the right prefrontal cortex in time perception. This corresponds with the reciprocal connections between inferior parietal and prefrontal cortical areas found in monkeys (Selemon & Goldman-Rakic, 1988). Electrophysiological recordings have also shown a right hemisphere bias for temporal processing (Brunia & Damen, 1988), especially in the parietal cortex. One theory is that the right hemisphere possibly regulates timekeeping operations (Harrington et al., 1998). Accordingly, right hemisphere activation of prefrontal and inferior parietal cortex has been found for rhythm discriminations, which have a time dependent component (Roland et al., 1981). Another theory is that judgement in duration may engage attentional operations that are asymmetrically represented in the cerebral cortex (Harrington et al., 1998). Attention may be required to operate a timekeeper or clock, such that the clock is not continually activated when attention is disrupted (Macar et al., 1994). This possibly extends the prevailing

view of the right hemisphere as biased for switching and sustaining spatial attention (Corbetta et al., 1993; Smith et al., 1996) to include the domain of time perception.

In terms of time estimation deficits, Shallice & Evans (1978) suggest that the frontal lobes are involved in cognitive estimation. This notion stemmed from their finding that patients with frontal lobe lesions (both right and left hemispheric) gave a higher number of bizarre answers than did patients with more posterior brain lesions to questions that required reasoning based on general knowledge but for which no immediate obvious strategy was available. Further, supporting Shallice and Evans' theory, Smith & Milner (1984) found that patients with right frontal lobe lesions, compared to patients with left frontal lobe, temporal lobe lesions, and normal controls, were the only group impaired on price estimation (another type of cognitive estimation task). Yet, a correlation was also obtained between error score in price estimation and lesion size for the left frontal lobe group. Smith & Milner (1984) regard the deficit in estimation as a special instance of a difficulty in the formation and utilisation of cognitive plans (Pribram, 1961; Luria, 1966; Guilford, 1967) or strategies for problem solving (Petrides & Milner, 1982; Cicerone et al., 1983). I propose that these deficits in estimation can be expanded to the ability to estimate time intervals. More generally, I predict that frontal lobe damage will produce deficits in time estimation. So, along with exploring the role of the PFC in time perception, I investigated if there were hemispheric differences in time perception by testing lesion patients with both left and right hemispheric PFC damage on time perception tasks.

### 1.11.2.2 The Role of the DLFC and Working Memory in Time Perception

Since the DLFC is known to be involved in WM and WM is purported to be involved in time perception, some propose that underlying DLFC deficits will affect time perception. Many studies sight the DLFC as an integral part of a neural network that contributes to time perception (discussed below). Timing theory suggests that activation in systems integrally involved in encoding and formulating a representation of time (pacemaker and attention operations) should develop at the onset of a to-be-remembered event (Gibbon et al., 1984; Matell & Meck 2000) followed by activation of systems concerned with manipulating information in WM, comparing intervals, and implementing a response (Rao et al., 2001). The cerebellar dentate nucleus[27], which has been implicated in timing, projects to the DLFC and premotor cortex (Middleton & Strick, 1994; Strick et al, 1993). These cortical sites may directly mediate interval timing (Rao et al., 1997a) because of their punitive role in WM and attention (Posner & Dehaene, 1994). Most investigations of frontal cortical mechanisms in timing have been conducted on animals and suggest that the frontal cortex supports WM, which underlies timing (Gibbon et al., 1997). However, although frontal cortex damage disrupts time discrimination in rats, (Olton, 1989; Meck, 1996), the findings in humans are discrepant (Ivry & Keele, 1989; Lacruz et al., 1992; Nichelli et

[27] The cerebellar dentate nucleus is a group of nerve cell bodies deep inside the cerebellum, which plays a role in the control of skilled, rapid movement (Crossman & Neary, 2000).

al., 1995) and have not delineated specific neural networks that could advance explanations of the cognitive processes underlying time perception. Yet, focal lesion investigations of animals and humans have shown that the frontal and parietal lobes are essential for accurate time perception, perhaps due to their purported attention and WM functions. The role of the parietal cortex in attention has been well documented (Posner & Petersen, 1990; Mesulam, 1990; Coull, 1998), and EEG recordings (Miniussi et al., 1999) and lesion work (Harrington et al., 1998) have supported its involvement in time perception. Accordingly, the role of the DLFC in WM is well documented in both monkeys (Petrides, 1994) and humans (Smith & Jonides, 1999), and its involvement in time perception has been supported by lesion work in rats (Meck et al., 1987; Olton et al., 1988) and humans (Villa et al., 1990; Harrington et al, 1998). Right hemisphere activity has been shown in both of these areas during discrete time measurement tasks (discussed in Section 1.11.2.1). Using fMRI in humans, Lewis & Maill (in press) found activity in the DLFC, the ventral lateral PFC, frontal pole, and the insula, but no parietal activity, during a time production task when attentional and motor-preparatory activity were subtracted out. This supports the dissociation between the PFC's involvement in time perception, namely WM, and the parietal cortex's role, namely attention.

As mentioned in Section 1.11.2.1, Harrington et al. (1988) found, in humans, that only patients with right hemisphere lesions in the anterior premotor and prefrontal cortex (BA 6, 8, 9, and 46) and in posterior inferior parietal cortex, as opposed to patients with left hemisphere lesions in the same areas, showed time perception deficits that implicated a right hemisphere prefrontal-inferior parietal network in timing. Time-dependent attention and WM functions may contribute to temporal perception deficits observed after damage to this network. These findings, which associate time perception competency with the PFC, could reflect the roles of one or more of these areas in sustaining on-line representations of a standard interval for comparison with a target interval presented immediately after, a WM function. Accordingly, duration perception deficits have been associated with damage in the middle and superior frontal gyri (BA 9 and 46) within the DLFC, which are critical for WM (Goldman-Rakic, 1987; Harrington et al 1998). In addition, the cerebral areas that are normally activated during time perception tasks share some similarities to the patterns of activation described in visuo-spatial WM tasks (Jonides et al., 1993). The involvement of WM in time measurement, when making comparisons of time intervals, may be used to maintain the current interval in mind while the previous or standard interval is retrieved from long-term memory in order to make a comparison. Or, for time estimation tasks, WM may be used to remember when the time interval started (or the "reading" off of the "internal clock") in order to make a subtraction from when the time interval ended, if of course, we use some sort of marker to denote time intervals prospectively. Finally, as discussed in Section 1.11.2, WM may be involved in keeping track of the previous events that occurred during a particular time interval that may affect subjective sense of time passing (Miruma et al., 2000).

It seems reasonable that the perception of time relies on stored representations of memories in WM (Gibbon et al., 1984) and that, accordingly, the DLFC may be associated with the memory demands in time measurement tasks. The DLFC appears to be important for such functions as primacy or relative recently of events, and self-monitoring (Passingham, 1975; Petrides 1991, 1994). Further, during time production tasks, activation was observed in regions commonly associated with temporary storage functions, including bilateral premotor (BA 6) and right DLFC (BA 9, 10, and 46) (Goldman-Rakic, 1999; Smith & Jonides, 1999; Cohen et al., 1997). Right DLFC activation is also unique to performing time discriminations (e.g. Koch et al., 2002). This corroborates with the findings that damage to these same regions in the right, but not left, hemisphere produces time perception deficits (Harrington et al., 1998).

The premotor cortex and the DLFC may be involved in different WM functions (Cohen et al.,1997; Awh et al., 1995), the former being implicated in a "rehearsal circuit" in tasks involving maintenance of information, like item recognition, the latter in an "executive circuit" in tasks requiring manipulation of stored information, like WM tasks (Rao et al., 2001). So, working memory may manipulate stored representations of time. Accordingly, in a human fMRI study, Rao et al. (2001) found that when time intervals were compared, premotor activation began early, consistent with the need for maintaining the standard interval during the trial, whereas DLFC activation unfolded later in association with comparing two time intervals and selecting a response. This provides evidence for different WM functions underlying time perception and, in particular, for the role of the DLFC in this process.

In sum, subjective time perception has been proposed to be related to WM at short intervals and WM has been associated with DLFC functioning (Kinsbourne, 2000; Mimura et al., 2000). Accordingly, an fMRI study (Rao et al., 2001) found late activation of the DLFC during comparison of time intervals. Further, focal lesion studies of animals and humans have shown that the prefrontal lobes are essential for accurate time perception, perhaps due to their purported WM functions (Casini & Ivry, 1999; Harrington et al., 1998; Meck et al., 1987). However, there is still no clear consensus as to exactly which areas of the PFC are related to which aspects of time perception. Therefore, I will test patients with precise PFC lesions on time perception tasks to examine exactly which areas of the PFC are related to which aspects of time perception. It may be that cognitive pace (Hoagland 1933; Carlson & Feinberg 1968) or decision making about abstract types of information (Shallice & Evans, 1978; Smith & Milner, 1984), which could be related to OFC function, rather than WM and DLFC function, underlie certain aspects of time perception. Further, if BPD patients have deficits in time perception, it can be determined if their deficits correlate with poor performance on the SWM task (a test of DLFC function) or if in fact other dysfunctions (perhaps related to the OFC) could better explain their timing deficits.

### 1.11.3 Time Perception and Impulsivity

Historically, there appears to be a split between the methodology used to investigate impulsivity in children and that used with adults. Studies with children have used behavioural tasks in conjunction with personality inventories while studies with adults relied predominately on personality inventories often excluding behavioural measures (Barratt & Patton, 1983). Although self-report measures are useful for identifying individuals' locations on a hypothesised trait dimension, questionnaires alone are not as beneficial as using them in conjunction with behavioural measures in elucidating the mechanisms of impulsive, disinhibited behaviour (see Section 1.4). Bachorowski & Newman (1985) found that there were no significant time estimation differences between groups divided using self-report personality inventories (including the BIS and Eysenck's E scale), however time estimation scores correlated negatively with motor inhibition scores (a behavioural measure of impulsivity). Low motor inhibition scorers (impulsive subjects) overestimated time despite the inability of self-report inventories to differentiate between under- and overestimaters. Hogan (1978) predicted that extraverts would overestimate time intervals due to their experiencing greater perceptual/cognitive boredom than introverts. However, although Bachorowski & Newman (1985) found no E-I differences in time interval estimation, Hogan's hypothesis fits nicely with the relationship found between time estimation and motor inhibition performance. Subjects unable to demonstrate motor inhibition (perhaps due to an inability or unwillingness to tolerate the boredom associated with the task) were more likely to experience even these brief events as being longer. Accordingly, behavioural measures of impulsivity have proven better than self-report questionnaire measures at differentiating subjects on time perception deficits.

Barratt (1983, 1985) and Barratt & Patton (1983) have suggested that impulsive individuals may be characterised by an impairment in their ability to judge time. They have proposed that time perception is an important variable that can, in part, explain the differences in people in terms of self-control. One corollary of this point is that time perspective is somehow related to the systematic biases in the way that people perceive the passage of time. Such a bias may be augmented by an association between time perception and impulsivity. A number of approaches have been involved in conceptualising the importance of time duration. One approach has been the information-processing paradigm, represented in studies of time elapsed for decision-making (Hicks et al., 1976; Ornstien, 1972; Zackay & Fallach, 1984; Jones & Boltz, 1989). Another is the notion of an internal clock (Ornstein, 1972; Zackay & Fallach, 1984). Davids & Falkoff (1975) suggest that there is a relationship between time perception and delay of gratification. They believe that to the extent that people can assess accurately the passage of time, they can be more effective in their ability to tolerate delay of reward. It may be that the more likely they are to systematically distort time by regarding it as passing more slowly (a likely case for impulsive people), the less likely they will be to delay gratification. Impulsivity can be broadly defined as "a tendency to respond quickly to a given stimulus, without deliberation and evaluation of consequences" (Gerbing et al., 1987 p. 357) and hence is a good indicator of the capacity to delay gratification. As

such, one might expect impulsivity to be related to distorted time perception with impulsive people regarding time as passing more slowly so that increased impulsivity in a person will lead to increased frustration with the passage of time and to a lowered tolerance of delay of reward. Accordingly, Gerbing et al. (1987) claimed that the engine for this sense of frustration is that "the internal clocks of impulsive individuals run faster than the internal clocks of non-impulsive individuals" (p. 362). Further, since high impulsive subjects have been shown to under-reproduce intervals in time judgement tasks (e.g. Van den Broek et al., 1992) it has been suggested that high impulsive subjects have a faster cognitive tempo than low-impulsive subjects so that the rate of information processing of cognitive tempo is related to impulsiveness (Barratt 1983, 1985; Barratt & Patton, 1983). Hence, I hypothesise that certain types of impulsivity in normal, PFC lesion, and BPD individuals will be related to distorted time perception.

A brief review of the literature has found positive, negative, and ambiguous results with regard to the association between time perception and impulsivity (Siegman, 1961; Spivack & Levine, 1964; Geiwitz, 1965; Stein et al., 1968; Davids & Falkoff, 1975; Gorman & Wessman, 1977; Barratt & Patton, 1983; Bachorowski & Newman, 1985; Van den Broek et al., 1992). Some suggest that ability to estimate the passage of time is related to self-control (Siegman, 1961; Stein et al., 1968; Davids & Falkoff, 1975; Barratt & Patton, 1983) with some finding a negative relationship between time perception and impulsivity (Gorman & Wessman, 1977; Vella, 1977). Van den Broek et al., (1992) found that impulsive individuals (measured by the MFFT) tended to under-reproduce the passage of time in a temporal reproduction task. However, the results fell just short of conventional significance levels. Gerbing et al. (1987) found no correlation between time estimation measures and self-report impulsivity scales. Lennings & Burns (1998) also found that impulsivity, measured by a self-report scale (the Schalling Impulsivity Scale; Schalling et al., 1983), was not associated with time estimation abilities. Yet, self-report impulsivity scales may not be assessing the same aspects of impulsivity as behavioural measures (e.g. the MFFT), which have been found to be related to time perception (Barratt, 1985; Van den Broek et al., 1987a, 1992; Van den Broek & Bradshaw, 1993).

Although studies have shown inconsistent and contradictory evidence concerning the relationship between impulsiveness and temporal discrimination, theories of impulsivity have suggested that impulsive individuals differ from non-impulsive individuals in their ability to judge or estimate time (Barratt 1985; Barratt & Patton 1983). In support of this theory, Van den Broek et al. (1992) found that impulsive subjects (measured by the MFFT) tended to under-reproduce time intervals and non-impulsive subjects over-reproduced and Barratt (1985) found the same relationship in terms of time production between delinquents (scoring high on impulsivity based on the MFFT) and normal subjects. In addition, Van den Broek et al. (1987a) found that in an operant temporal differentiation schedule of reinforcement where subjects had to delay responding 10 seconds to obtain a monetary reward (interresponse-time, IRT > 10 seconds), impulsive subjects (measured by the MFFT) were less able to delay responding than were non-impulsive subjects (see

Section 1.4.2.4). The possibility that performance on these schedules is related to impulsivity is further supported by the finding that clinical groups, in whom impulsive behaviour is a defining trait (hyperactive children, Gorden, 1979; delinquent adolescents, Barratt, 1981), also perform poorly on these schedules. However, it is hard to say whether impulsive subjects' poor performance is related to a failure in response inhibition or a failure of temporal discrimination. Seigman (1961) found that compared to normal subjects, delinquents (who are usually highly impulsive) performed worse on a motor inhibition test (circle tracing), had a shorter future time perspective (measured by their expectations of future events), and showed a non-significant tendency to underestimate time intervals. Siegman (1961) thus proposed that delinquents have "relatively more rapid internal clocks". In contrast, Orme (1962a,b, 1964) found that psychopaths consistently overestimated intervals of time and Capepella et al. (1977) found that hyperactive children also overestimated the passage of time, and the longer the period of time that they were required to estimate, the greater the error. However, Senior et al. (1979) were unable to find an association between overestimation and hyperactivity and concluded that time estimation is "unrelated to hyperactivity, impulsivity, or short attention span". On the other hand, Walker (1982) found that on a reproduction task impulsive boys (defined by the MFFT) underestimated, whereas non-impulsive boys overestimated time intervals. Further, Van den Broek et al (1992) found that on a time reproduction task, impulsive subjects (measures by the MFFT) tended to under-reproduce the standard, whereas the non-impulsive subjects over-reproduced the standard. In sum, results seem to favour the theory that impulsivity and time perception are related but the exact nature of this relationship remains unclear.

Barratt (1981) found that conceptual tempo, time perception, and cortical functioning (measured by ERPs) were interrelated and that controls were significantly different from psychiatric patients and delinquents on these measures. Control subjects were more accurate and consistently overproduced time intervals whereas delinquents and psychiatric patients underproduced time intervals, so time seemed to pass more slowly for them than for the controls. The data also suggested immature cortical functioning among the psychiatric patients and delinquents compared to the controls. Further, while there were significant differences between controls and both psychiatric and delinquent individuals on the MFFT, the BIS showed no significant group differences. Van den Broek et al (1992) found the same pattern, where impulsive subjects measured by the MFFT did differ in terms of time reproduction but did not when measured with the BIS or the I7[28]. Thus, the MFFT and the BIS may not be measuring the same aspects of impulsivity (Saunders et al., 1973). These overall results indicate that cognitive tempo, as measured by the MFFT and time perception, which seem to be related to each other, can differentiate between impulsive and non-impulsive individuals.

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[28] Eysenck's (1993) impulsivity questionnaire (I7) identifies two factors; impulsivity described as unconscious risk taking, and venturesomeness or conscious sensation seeking. Empathy is used as a buffer category (see Section 1.4).

Impulsivity has also been linked to both the ability to estimate long periods of time and to preferred time zones (short or long, past or future) (Barratt & Patton, 1983). Highly impulsive responders have been shown to underestimate long periods of time (Barratt & Patton, 1983). So, time appears to pass slowly for them, which may cause them to be inpatient. Consequently, highly impulsive subjects tend to show poor awareness of the passage of time and to have shortened time perspectives, especially future time perspective (Barratt & Patton, 1983; Gorman & Wessman, 1977). Lennings (1991) found that impulsivity had a strong negative relationship with time awareness (the extent to which people are aware of the day-to-day passage of time in their lives) but, contrary to the findings of Barratt & Patton (1983) and Gorman & Wessman (1977), found no relationship between impulsivity and time perspective (the importance people place on reflection of the past and anticipation of the future). However, these studies have assessed time perspective using orientation measures, meaning a person's preference for or awareness of particular time zones, rather than investigating the possible relationship between time perception at discrete intervals and temperament.

### 1.11.4 Summary of Time Perception

Evidently, the studies described above provide inconsistent and contradictory evidence concerning the relationship between temporal discrimination and impulsiveness. Overall, impulsive subjects (usually measured by behavioural rather than self-report measures of impulsivity) have been known to have deficits in time perception. In general, findings suggest that high impulsive subjects have faster cognitive tempos than low impulsive subjects (Barratt, 1983). Barratt (1981, 1985) found significant differences between normal subjects and delinquents on a time production task when impulsivity was measured with the MFFT (a behavioural measure), but not when measured with the BIS (a self-report measure) and, in general, behavioural measures of impulsivity do not correlate with self-report measures of impulsivity (Barratt & Patton, 1983). This suggests that the MFFT and the BIS are assessing different aspects of impulsivity, which may be related to different regions within the prefrontal cortex. Thus, by examining subjects with both behavioural and self-report impulsivity, I aim to determine if OFC lesion patient are in fact impaired on both measures of impulsivity as compared to DLFC patients. If so, future studies may be done with even more discrete lesion patients to determine specifically which parts of the OFC are associated with which aspects of impulsivity. Further, by administering both the MFFT and the BIS along with time estimation, production, and pacing tasks, to normal, PFC lesion, and BPD subjects, I aim to explore the relationship between behavioural and cognitive impulsivity and temporal discrimination.

Based on the evidence above, I propose that cognitive tempo and time perception will be altered in impulsive subjects. Further, a test of SWM known to assess underlying DLFC dysfunction will be given to see if in fact time perception is related to DLFC function and to determine to what extent WM is involved in time perception. Theoretically, if time perception is related to WM then subjects with DLFC lesions and/or with SWM deficits should have deficits on

time perception tasks. However, if time perception is related to an increased cognitive tempo, poor decision making, or lack of inhibitory control due to frustration (e.g. wanting an immediate reward like the end of the task), things which have been related to OFC function (see Section 1.7), than OFC patients should have time perception deficits[29].

## 1.12 Borderline Personality Disorder

### 1.12.1 Definition of Borderline Personality Disorder

Borderline personality disorder (BPD) is a mental illness characterised by impulsivity, pervasive instability in moods, interpersonal relationships, self-image, and behaviour. This instability often disrupts family and work life, long-term planning, and the individual's sense of self-identity. Originally thought to be at the "borderline" between psychosis and neurosis (Stern, 1938), people with BPD suffer from a disorder of impulsivity and emotional dysregulation. The most commonly used criteria for BPD are set in the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV; American Psychiatric Association (APA), 1994) and are described as follows:

> "A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:
> 1. frantic efforts to avoid real or imagined abandonment. Note: Do not include suicidal or self-mutilating behaviour covered in Criterion 5.
> 2. a pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation.
> 3. identity disturbance: markedly and persistently unstable self-image or sense of self.
> 4. impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating). Note: Don't include suicidal or self-mutilating behaviour covered in Criterion 5.
> 5. recurrent suicidal behaviour, gestures, or threats, or self-mutilating behaviour
> 6. affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
> 7. chronic feelings of emptiness
> 8. inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights)
> 9. transient, stress-related paranoid ideation or severe dissociative symptoms" (p. 654)

See Appendix 6 for a more detailed description of BPD from the DSM-IV, including prevalence and course of the disorder. Next, I will describe the measure used in this study to assess BPD traits and discuss in further detail the relationship between BPD and self-harm (as all of the BPD patients tested were self-harmers), impulsivity, emotion, and the neurobiological correlates of the disorder.

### 1.12.2 Measurement of Borderline Personality Disorder Traits

Gordon Claridge and his colleagues (Claridge & Broks, 1984; Rawlings, 1983) developed the Schizotypal Traits Questionnaire (STQ), which is made up of two scales, a Schizotypal Personality Scale (STA) and a Borderline Personality Disorder Scale (STB). The two scales are based on the criteria for Schizotypal and BPD set in the Diagnostic and Statistical Manual-Third edition (DSM-III; APA, 1980) respectively[30]. A study by Shankar (1998) of clinically diagnosed BPD patients has

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[29] As far as I know, there have been no studies to date concerning BPD and time perception of short intervals.
[30] The criteria for Schizotypal and BPD did not change in the DSM-IV (APA, 1994).

supported the construct and discriminant validity of the STB. In a factor analysis study of the STB, Rawlings et al. (2001) found that two factors were produced, Hopelessness, including items associated with dejection and purposelessness and thoughts concerned with suicide and self-harm, and Impulsiveness, including items associated with impulsive behaviours that are ultimately self-destructive (e.g. alcohol abuse and reckless money spending) and destructive behaviours directed against others and their property. Rawlings et al. (2001) also compared the STB to an 80 item BPD questionnaire recently developed by Poreh (unpublished), which is based on the nine criteria for BPD in the DSM-IV. Thus, Poreh used a similar approach to the development of the STB but his questionnaire was much longer. Rawlings found that the two factors produced by Poreh's questionnaire, Identity/Interpersonal and Impulsivity/Affect, showed some overlap with the two STB factors. However, Poreh's "Suicide-Self mutilation" subscale loaded on the Impulsivity/Affect factor, whereas the STB suicidal thoughts and self-harm items were clearly identified with the Hopelessness factor.

The Poreh BPD questionnaire is too long to be practical for the purposes of this study, as a large battery of tests was administered. Furthermore, there is not enough validation data to support using the Poreh BPD questionnaire. I am aware of one other self-report BPD questionnaire, the Borderline Syndrome Index (Conte et al., 1980). This is a 52 item forced choice scale designed to assess borderline psychopathology associated with the concept of BPD. However, again, this scale is too long to be practical in light of the battery of tests given. So, the concise (18-item) STB, which is based on DSM criteria, was administered in this study in order to measure BPD traits. The main reason the STB (BPD Questionnaire)[31] was administered was not only to measure BPD traits in BPD patients but also to measure BPD traits in OFC participants in order to determine if in fact OFC patients report similar behaviours to those exhibited within the BPD syndrome. If OFC patients do report a high number of BPD traits, this would support the main hypothesis that there is a relationship between the BPD syndrome and OFC dysfunction. Further, by administering the BPD Questionnaire to normal controls as well, it can be determined if BPD traits are normally distributed in the population with BPD patients at the extreme end of a continuum. Finally, by administering the BPD Questionnaire along with the other tests in the battery, the relationship between BPD and among other things, "frontal" behaviours, emotion, impulsivity, personality, and sensitivity to reward and punishment can be explored[32].

### 1.12.3 Definition of Self-harm

Self-harm, or intentionally causing harm to ones own body, is a behaviour that has been present since the earliest days of mankind (for a brief history, see Favazza & Simeon, 1995). The oldest record of such activity dates as far back as 440 BC in Book VI of Herodotus' *Histories* concerning Cleomenes, the son of Anaxandridas, king of the Spartans. The graphic account is as follows:

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[31] Future use of the term "BPD Questionnaire" will be referring to Gordon Claridge's STB.
[32] Both the Frontal Behaviour and BPD Questionnaires are described in further detail in Chapter 2 (Methods).

> "So Cleomenes came back; but had no sooner returned than he, who had never been altogether of sound mind, was smitten with downright madness....Cleomenes had no sooner got the knife than, beginning at his legs, he horribly disfigured himself, cutting gashes in his flesh, along his legs, thighs, hips, and loins, until at last he reached his belly, which he likewise began to gash" (section 75).

Self-harm can be defined as the deliberate, direct alteration of body tissue without conscious suicidal intent and can be divided into two categories (Favazza & Simeon, 1995). Culturally sanctioned self-harm includes practices (e.g. ear-piercing and tattoos) as well as rituals (e.g. circumcision and scarification) that reflect society's traditional beliefs and symbols. Deviant self-harm can be categorised by the clinical context in which it mainly occurs (Winchel & Stanley, 1991), primarily within BPD, or based on the degree of tissue destruction and rate and pattern of behaviour (Favazza & Rosenthal, 1990, 1993).

Deliberate self: -injury, -mutilation, -abuse, -wounding, -inflicted violence, -injurious behaviour, -mutilative behaviour, and -destructive behaviour, as well as, para-suicide and non-fatal "act" wrist cutting, are all definitions of self-harm that cover the same actions. These actions include cutting, burning skin by physical means using heat, burning skin by chemical means using caustic liquids, punching hard enough to cause bruises, head banging, hair pulling from head, eyelashes, eyebrows, and armpits (Trichotillomania), poisoning by ingesting small amounts of toxic substances to cause discomfort or damage, insertion of foreign objects, excessive nail biting to the point of bleeding and ripping cuticles, excessive scratching by removing top layer of skin to cause a sore, bone breaking, gnawing at flesh, wound interference to prevent wounds from healing thus prolonging the effect, tying ligatures around the neck, arms, or legs to restrict the flow of blood, medication abuse without intention to die, alcohol abuse, illegal drug use, and smoking (the last three items are deemed socially acceptable) (Favazza & Simeon, 1995). People who smoke and drink alcohol are not consciously harming themselves. They are taking part in a socially accepted lifestyle; it is only once these actions become excessive that problems can occur. Cutting and burning were among the most common forms of self-harm of the BPD patients tested.

### 1.12.4 Borderline Personality Disorder and Self-harm

As mentioned above, all of the BPD patients tested were self-harmers. This objective measure of impulsive behaviour was important in obtaining a homogenous patient group as DSM classification of BPD alone can be subjective (Nurnberg et al., 1991; Follett, 1996; Follette & Houts, 1996).

Self-harm/mutilation occurs in a wide variety of psychiatric disorders, including psychotic illness and mental retardation. However, self-harm is particularly associated with BPD as the DSM-IV criteria for BPD includes the behaviour. Some authors describe tension relief and other positive effects as a result of the self-mutilation (Favazza, 1987). The onset of the behaviour is typically in adolescence and the self-harm often becomes the individual's habitual way of dealing with personal distress. Interspersed with the episodes of self-harm are periods of calm, as well as eating disorders, alcoholism or other substance abuse, or kleptomania. This pattern has been described as "repetitive self-mutilation syndrome" (Favazza, 1992). Someone who displays self-

harming behaviours in lieu of any other BPD symptoms would be classified according to the DSM-IV as having an "impulse-control disorder not otherwise specified". Patients who self-harm are preoccupied with, and repeatedly fail to resist, harming themselves. They experience increased feelings of tension immediately before hurting themselves, followed by feelings of relief or pleasure afterward. Such behaviour is not intended to result in death and is not a response to psychotic experiences (Favazza & Simeon, 1995).

### 1.12.5 Impulsivity and Self-harm

Descriptive and systematic data reveal that repetitive self-mutilation is typically an impulsive act. Bennum (1983) reported that 70% of self-mutilators feel that they have no control over the act. Favazza and Conterio (1989) reported that 78% of individuals in their sample decided to self-harm on the spur of the moment, and another 15% made the decision within an hour of the act. The act was then always (30%) or almost always (51%) carried out. In another sample, less than 15% of self-mutilators reported an inner struggle to resist the behaviour (Gardner & Gardner, 1975). Simeon et al. (1992) found a significant correlation between frequency of self-mutilation and self-report impulsivity.

Further, Herpertz et al. (1997a) found that impulsivity is a major factor in personality disordered inpatients with moderate self-mutilating behaviour (i.e. skin-cutting and burning; 48% were diagnosed with BPD). Self-mutilators exhibited an enduring pattern of impulsivity including various modes of impulsive behaviour, a deficit in future-oriented problem solving, and affective hyper-reactivity[33]. A fast cognitive tempo was not found to be characteristic of self-mutilators, but self-report measures of cognitive tempo (the BIS-10 subscale of cognitive impulsivity) were used that may not be sufficient to assess cognitive tempo (Barratt, 1994) and that may need to be supplemented by more objective measures of cognitive impulsivity. As mentioned in Section 1.4, impulsiveness is a broad personality trait consisting of several subtypes (Barratt, 1985) that may not all be represented in a comprehensive questionnaire.

Psychological and biological studies demonstrate that pathological self-mutilation is characterised by impulsivity, and depending on the type, by aggression or compulsivity (Favazza & Simeon, 1995). Compulsive self-mutilation (e.g. hair pulling, nail biting, skin picking, scratching) contains a mixture of impulsive and compulsive elements, but lacks aggression. Episodic/repetitive self-mutilation (e.g. skin cutting, burning) is especially associated with impulsivity and aggression. Serotonergic dysregulation has been implicated in both compulsive and repetitive self-mutilation (Gardner et al., 1990; Simeon et al., 1992) and although not proven, noradrenergic and opiatergic systems may also play a role (Siever et al., 1992; Coid et al., 1983). Also, negative childhood experiences may influence the development of psychological and biochemical vulnerabilities that may result in adult self-mutilation (Van der Kolk & Soporta, 1991).

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[33] Measured by the State-Trait Anger Expression Inventory (Spielberger, 1988).

### 1.12.6 Borderline Personality Disorder and Impulsivity

Since there is no generally accepted definition of impulsivity, the term is used inconsistently (Herpertz, 1995). The definition of impulsivity spans the range from rapid, poorly planned and monitored responses noted on cognitive testing, through disinhibited affects such as irritability, to more overt behaviours such as reckless driving, and culminating finally at the level of syndrome or disorder as in BPD (see Section 1.4.1).

In the DSM-IV (APA, 1994), disorders of impulse control are characterised by a failure to resist an impulse, drive, or temptation to perform a harmful act to the person or to others; there is increasing tension or arousal before the act, and pleasure, relief, or gratification when the act is performed. The DSM-IV diagnostic criteria for BPD include several impulsivity related items:

> "1) Impulsivity in at least two areas that are self damaging (e.g. spending, sex, substance abuse, reckless driving, binge eating) 2) affective instability due to a marked reactivity of mood (e.g. intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days): and 3) inappropriate, intense anger or difficulty in controlling anger (e.g. frequent displays of temper, constant anger, recurrent physical fights)" (p. 654).

However, this definition, though helpful in clinical settings, lacks the operational quality that would allow its application in non-human, animal behaviour studies. Some biological studies examine impulsivity in terms of motor disinhibition and aggression (Hollander & Stein, 1995). Impulsivity may also be regarded, in terms of personality, as a person's enduring tendency to react quickly to stimuli instead of suppressing responses (Buss & Plonin, 1975). Such a concept includes functioning at a fast cognitive tempo that compromises accuracy (Dickman & Meyer, 1988) and to a "present needs orientation" as opposed to future-oriented problem solving (Barratt, 1994). In the current study, the overt, self-harming behaviour exhibited by the BPD patients can be operationalised as an objective measure of their behavioural impulsivity.

Impulsivity is one of the DSM-IV diagnostic criteria for BPD, as are affective instability and identity disturbance. Yet, in a stepwise multiple regression, Links et al. (1999) found that impulsivity (measured by the "impulse action" subscale score from the Diagnostic Interview for Borderlines-DIB[34]), as opposed to other aspects of BPD, is stable over a 7-year follow-up period, able to predict the persistence versus remittance of BPD over 7 years of follow-up, and is more predictive of the level of borderline psychopathology on the follow-up. The authors conclude that "impulsivity is stable over time and highly predictive of borderline psychopathology over 7 years' follow-up" (p.1) and suggest that treatment of impulsivity may impact the course of BPD.

Thus, the concept of impulsivity is strongly linked to the diagnosis of BPD (Gunderson et al., 1981; APA, 1994). In fact, the DSM-IV defines BPD as "a pervasive pattern of instability of interpersonal relationships, self-image and affects, and marked impulsivity that begins in early adulthood and is present in a variety of contexts". Kruedelbach et al. (1993) believe the concept of

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[34] Gunderson et al. (1981) created the DIB, a semi-structured clinical interview designed to diagnose BPD. Zanarini et al., (1989b) revised the DIB to sharpen its ability to differentiate between BPD and other personality disorders and created the DIB-R. It considers symptoms that fall under four main headings, affect, cognition, impulse action patterns, and interpersonal relationships.

BPD, as defined in DSM-III-R, can be largely explained by the convergence of two broad personality traits. The first of these would be labelled as behavioural disinhibition, which refers to the inability to inhibit behaviour, even when such behaviour is detrimental to the person in the long run. The primary manifestations of behavioural disinhibition are impulsivity and the inability to inhibit aggressive responses. Both of these are criteria for BPD. The second trait would be labelled as negative affectivity, the tendency to experience a wide range of negative emotions, even in the absence of external stressors (Watson & Clark, 1984). The combination of disinhibition and marked depression and helplessness often result in suicidal behaviour, another criterion of DSM-IV BPD (Kruedelbach et al., 1993). The strength of the association between impulsivity and BPD has lead to the hypothesis that BPD is an impulse control disorder (Gunderson & Zanarini, 1989; Gunderson & Phillips, 1991). In fact, BPD has been conceptually included in a cluster of personality disorders characterised by impulsive behaviour, which includes Antisocial Personality Disorder (Zanarini et al., 1989a; Stein et al, 1993). Further, Gunderson & Phillips (1991) reviewed family history studies, response to medication, and biological marker studies and suggest that "impulse dysregulation, as opposed to affective dysregulation, is primary to this disorder".

Experimental evidence supports the role of impulsivity in BPD. A study that used questionnaire and cognitive/behavioural measures of impulsivity found a higher level of impulsivity in patients with BPD than normal controls. BPD patients (n=14) performed impulsively by choosing a smaller, immediate reward more often than a larger but progressively delayed reward (reward-delay avoidance) and had higher BIS-11 total and attentional subscale scores than controls (n=17) (Dougherty et al., 1999a). Van Reekum et al. (1994) found that impulsivity measures [the motor subscale of the BIS-10, the Buss-Durkee Hostility Inventory (BDHI), and the Suicidal Behaviours Questionnaire (SBQ)] correlated highly with Diagnostic Interview for Borderlines-Revised (DIB-R) and social functioning [measured by the Social Adjustment Scale-Self Report (SAS-SR)[35]] scores. This finding extends the earlier conclusions of Gardner et al. (1991), in suggesting that anger, irritability and guilt (BDHI), along with suicidality (SBQ), and inattentiveness/restlessness/acting without anticipation (BIS motor), are all powerfully associated with current DIB-R diagnosis and social functioning (SAS-SR). So, these elements of impulsivity seem to be central to BPD and to the social functioning of people with BPD. Conversely, demographic variables, past history of alcoholism, depression, and Antisocial Personality Disorder were not associated with current DIB-R diagnosis and social functioning (SAS-SR) (Van Reekum et al., 1996a).

Several studies have found a relationship between suicidality and impulsivity in patients with BPD. In a recent study by Soloff et al. (2000a), patients with BPD (some of whom also had major depression) were compared to patients with major depression alone on measures of depressed mood, hopelessness, impulsive aggression, and suicidal behaviour. A higher level of impulsive

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[35] BIS-10 (Barratt, 1985); BDHI (Buss & Durke, 1957); SBQ (Linehan, 1983); DIB-R (Zanarini et al., 1989); SAS-SR (Weismann & Bothwell, 1976).

aggression or hopelessness or a diagnosis of BPD predicted a greater number of suicide attempts. Similarly, in a previous study by Soloff and colleagues (1994), BPD patients with a history of suicide attempts had more impulsive actions, Antisocial Personality Disorder comorbidity, and depression than those without a history of suicide attempts. To determine which factors are most important in predicting suicidality, Mann et al. (1999) examined suicide attempts in patients with mood disorders, psychoses, and other diagnoses. The severity of observer-rated depression or psychosis did not distinguish the patients who had attempted suicide from those who had never attempted suicide. However, rates of lifetime aggression and impulsivity were greater in attempters. Thus, impulsivity appears to be an important factor in suicide attempts in patients with BPD.

Kruedelbach et al. (1993) found that BPD substance abusers were significantly more impulsive than non-BPD substance abusers across many measures of impulsivity. The BPD patients abused more substances, displayed more impulsive gambling behaviours, and scored higher on all psychometric measures of impulsivity. Consistent with their pattern of poor impulse control, compared to non-BPD substance abusers, BPD patients tended to use a variety of escape-avoidance coping strategies, including more drug abuse, more often than problem-solving and positive appraisal when faced with difficult situations. The picture is not one of thrill-seeking impulsivity, but rather the desperate use of impulsive behaviours to cope with internal emotional pressure. Accordingly, BPD patients are at greater risk for substance abuse when they are faced with negative emotional states and social rejection (Kruedelbach et al., 1993).

In sum, studies of patients with BPD have found that impulsivity is a key factor in the diagnosis of BPD. Thus, behavioural and pharmacologic treatments of BPD that target impulsive behaviours may be effective (see Section 4.6).

### 1.12.7 Borderline Personality Disorder and Emotion

Quality and intensity of affective responses to environmental events influence mood and basic features of personality functioning, such as the organisation of social relationships and impulse control. Consequently, rigid and poorly adapted affective responses are seen as a central feature of personality disorders. BPD, in particular, is thought, by some, to arise from affective vulnerability (Linehan, 1993). Clinical observations indicate that BPD patients experience a wide range of emotional dysregulations like intense anger, affective instability, and chronic emptiness (DSM-IV; APA, 1994). The inability to regulate one's affective responses leads to marked, rapidly changing mood states and predisposes patients to various kinds of self-destructive behaviour (Herpertz et al., 1997b). Since affective dysregulation is a key feature in BPD, Linehan & Head (1992) suggest that BPD patients' propensity for self-destructive behaviour could be associated with a failure to adequately process information about experienced emotions or a maladaptive response to intolerable affectivity.

Some studies have investigated the processing of emotional information in BPD. Epidemiological studies report a high degree of comorbidity, ranging from 35 to 51.5% (Pope et

al., 1983; Frances et al., 1984), between BPD and major mood disorders. Yet, the clinical affective liability found in BPD patients is clearly distinct from that found in unipolar major depression and bipolar disorder (New et al., 1995; see also Kutcher et al., 1987 in Section 1.12.9). Some believe that the affective vulnerability found in BPD patients is caused by hyperarousal, including high sensitivity to emotional stimuli and high emotional intensity (Linehan, 1993). Using affective stimuli related to the BPD subjects' characteristic fear of being abandoned, Herpetz et al. (1997b) found that self-ratings indicated more intense emotional experiences and an increased sensitivity to even low-level emotional stimuli in subjects with impulsive self-harming behaviour [most of whom met the diagnostic criteria of BPD (14 out of 25)] compared to other types of personality disorders. Self-mutilators exhibited an enduring pattern of impulsive behaviour, a deficit in future-oriented problem solving, and affective hyper-reactivity. Frank & Hoffman (1986) and Ladisich & Feil (1988) found that BPD patients were significantly more accurate at identifying the emotional content of videotapes than normal controls. Recently, Yen et al. (2002) examined the relationship between specific dimensions of affect regulation [measured by the Affect Intensity Measure (Larson & Diener, 1987) and Affect Control Scale (Williams et al., (1997)] and borderline traits (measured by the Personality Diagnostic Questionnaire-Revised[36]) in 39 BPD patients. Hierarchical regression analyses indicated that the level of affect intensity and affect control were significantly associated with number of BPD traits, even after controlling for level of depression. These results suggest that BPD patients experience emotions more intensely and have greater difficulty in controlling their affective responses.

However, in many studies, psychophysiological evidence for affective hyperarousal could not be found. Herpertz et al. (1999) tested BPD patients' responses to affective stimuli on a variety of physiological indicators of emotion like heart rate, startle response, and skin conductance and found no evidence for affective hyperarousal in BPD patients. In fact, eletrodermal responses of BPD patients were lower than the control group indicating physiological *hypo*arousal. Using a number of self-report items of affective processing, Levine et al. (1997) found significantly lower levels of emotional awareness and more intense negative responses to standardised everyday life events in BPD patients compared to normal controls. In addition, Sprock et al. (2000) compared BPD patients (n=18) to depressed patients (n=18) and to a non-psychiatric control group (n=18) on a series of neuropsychological tasks. They found that the BPD group performance did not differ from the normal group on most tasks of executive functioning or memory, and the introduction of emotional stimuli did not impair performance. The depressed group performed less effectively than the other groups. Thus, there may be considerable heterogeneity in the cognitive functioning of BPD patients, with those exhibiting significant cognitive deficits comprising only a subgroup.

In addition to subcortical pathways of emotional processing, which are thought to act automatically even without awareness of the stimuli (Whalen et al., 1998), prefrontal cortical

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[36] This is a 100 item, self-administered, true/false questionnaire created by Hyler et al. (1988) that yields personality diagnoses consistent with the DSM-IV diagnostic criteria for the axis II disorders.

structures have been shown to be involved in assigning meaning to emotional stimuli (Teasdale et al., 1999), or, more generally, in consciously experiencing emotion (Lane et al., 1997; Reiman et al., 1997). However, so far, few neurological correlates of abnormal emotional processing in BPD patients have been identified. In an fMRI study Herpertz et al. (2001) found that BPD (n=6), but not control, subjects had an elevated blood oxygenation level dependent (BOLD) fMRI signal bilaterally in the amygdala and fusiform gyrus (BA 37), a region implicated in complex visual feature detection and recognition of facial expression (George et al., 1993), in reaction to standardised, visual, aversive, emotional stimuli. A further area of activation was located in the right frontal inferior gyrus (BA 47) and in the left medial frontal gyrus (BA 10) of the BPD subjects. BA 47 was activated in four, and BA 10 in three, out of the six BPD subjects.

Herpertz et al. (2001) suggest that the enhanced amygdala activation in BPD patients reflects the intense and slowly subsiding emotions commonly observed in response to even low-level stressors in BPD patients (Herpetz et al., 1997b). Thus, amygdala activation may be a biological indicator of intense aversive emotions in the sense of a high intensity of affective associations to given stimuli. Further, BPD subjects' perceptual cortex (BA 37) may be modulated through the amygdala leading to increased attention to emotionally relevant environmental stimuli. BA 10 (medial/OFC) has been suggested to be associated with processing affect-related meanings, either accessed by external stimuli or related to memory (Herpertz et al., 2001). Therefore, the medial/OFC PFC appears to mediate subjective emotional responses. The activation pattern found in the OFC or ventrolateral PFC (BA 47) suggests enhanced activation of ventrolateral areas that are thought to exhibit top-down control over limbic pathways (Drevets, 1999). An abnormal elevation of cerebral blood flow in the OFC has also been reported during induced aversive emotional states in patients suffering from anxiety disorders or depression (Drevets, 1999). These parts of the PFC (BA 10 and 47) are directly connected with the basal nucleus of the amygdala, have been regarded as a gateway for distinctive sensorial information, and may modulate or inhibit amygdala-driven emotional responses and thus provide top-down control of the amygdala (Drevets, 1999; Morgan et al., 1994; Rauch et al., 1998). So, the OFC, with its strong inter-connections with subcortical areas implicated in emotional behaviour (see Section 1.6.2.1), may play a role in correcting emotional responses (Drevets, 1998; Rolls et al., 1994; Hornak et al., 1996).

### 1.12.8 Link between Emotion and Impulsivity in Borderline Personality Disorder

Impulsivity has been linked to affective dysregulation resulting in irritability and in marked, rapid shifts of affective states as seen in BPD (Van Reekum et al., 1994). Intense affective instability may be regarded as an impulsive phenomenon (Westen et al., 1992; Torgersen et al., 1994). One argument is that rapid mood shifts in reaction to even low-level stimuli found in BPD patients (Herpetz et al., 1997b) show phenomenological similarities to impulsive behaviour, which has been defined as an enduring tendency to react quickly instead of suppressing response (Buss & Plonin, 1975). The close relationship between impulsivity and affective hyperactivity is supported by the

clinical observation that impulsive behaviours such as self-harm often occur in the context of intense episodic dysphoria (Herpertz, 1995) and are used as a maladaptive mechanism for relieving unbearable negative affect (Linehan, 1987). Herpertz et al. (1997b) found that patients suffering from personality disorders with impulsive self-harming behaviour (14 out of 25 were diagnosed with BPD) reported a higher intensity of affective experience in an affect-stimulation experiment in relation to non-impulsive patients and normal controls. These results suggest that poor affect regulation resulting from affective hyper-reactivity to environmental stimuli (positively or negatively valenced) is a crucial part of impulsivity in patients with self-harming behaviour and more generally in patients with BPD (Herpertz et al., 1997b). Further, processes regulating affective reactivity to stimuli appear to be different from those regulating mood (Cowdry et al., 1991) and are perhaps rather related to processing regulating impulsivity.

### 1.12.9 Neurobiology of Borderline Personality Disorder

Studies have shown an association between BPD and histories of brain pathologies/brain dysfunction (Van Reekum, 1993; Andrulonis et al., 1981). Research has tentatively identified a large subgroup of BPD patients with histories of developmental or acquired brain insults (Van Reekum et al., 1993, 1996b). Van Reekum et al. (1993) found that 81% of patients with BPD and 22% of control psychiatric patients had a history of brain injury; developmental (44%), acquired (58%) or both. Also, the prevalence of traumatic brain injury has been shown to be higher in subjects with BPD than in psychiatric controls (Streeter et al., 1995). Since traumatic brain injury occurred prior to the full expression of the BPD clinical syndrome (subjects were head-injured male veterans), it may be related to the cause, and not the result, of BPD. Analogous evidence for causation is provided by evidence that brain (specifically PFC) dysfunction is involved in Antisocial Personality Disorder (Elliott, 1986); a disorder that frequently overlaps with BPD[37] (Becker et al., 2000). The case for causality of brain dysfunction would be strengthened by studies that document an improvement in brain function coinciding with improved behavioural functioning.

Specific neuropsychiatric abnormalities, such as lateralised neurological soft signs[38] and associated impairment on select neuropsychological tests, have been found in patients with personality disorders characterised with impulsivity. Gardner et al. (1987) found that BPD subjects as a group had significantly more neurological soft signs than normal controls. Stein et al. (1993) found that patients with BPD had significantly more left-sided neurological soft signs than normal

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[37] Since most people with Antisocial Personality Disorder (APD) are men and most people with BPD are women, Paris (1997) argued that APD and BPD are products of the same core (impulsive, reactive) psychopathology interacting with male and female gender traits respectively. In this distinction, APD is characterised by outward-directed aggression and exploitation, whereas BPD is characterised by inward-directed aggression and victimisation.

[38] Neurological soft signs refer to non-localised neurological phenomena that occur in the absence of evidence of gross neurological disease. For example, involuntary movements, motor disorders where voluntary movement is impaired without muscle weakness (apraxias), and difficulties in performing rapid alternating movements and in discerning double simultaneous stimulations (Adams, 1997).

controls. Increased left-sided soft signs were significantly correlated with lower performance or more errors on Trailmaking A and B (Reitan, 1969)[39] and on the MFFT (see Section 2.3.2.2) (tests that assess impulsive response style). Right-sided soft signs were associated with frontal lobe impairment as measured by the WCST. Further, previous work on the neuropsychology of BPD supports the notion that the disorder is associated with impairment in complex information processing. Burgess (1990) found that patients with BPD, compared to normal control subjects, had deficits on tests that require planning, multiple operations, and maintenance of a prolonged response over time. Impairment in tasks of complex information processing, which appear to be associated with increased neurological soft signs, may contribute to difficulties in building and maintaining a coherent and stable sense of self, and in using past experience to organise present behaviour and to predict future consequences. However, despite the correlations, a causal relationship between neurological soft signs and BPD has not been established.

Neurophysiologically, Blackwood et al. (1986) recorded auditory P300 event-related potentials (ERPs) in 39 patients with a variety of character and personality disorders. BPD subjects were distinguished from non-BPD disturbed subjects and from controls by changes in the latency and amplitude of the P300 component of the auditory ERPs. Further, Kutcher et al. (1987) measured P300 and other long-latency auditory ERPs in 22 BPD patients, 32 subjects with other personality disorders, 29 schizophrenics, 22 depressives, and 74 normal controls. BPD patients had a longer P300 latency and smaller P300 amplitude compared to patients with non-BPDs. Long-latency ERPs were similar in the BPD and schizophrenic groups and did not differentiate BPD patients with a concurrent diagnosis of schizotypal personality disorder from those without schizotypal personality disorder. The P300 latency and amplitude changes distinguished the BPD and schizophrenic groups from normal controls, those with major depressive disorder, and those with non-BPDS. These findings suggest that although some BPD patients may have depressive symptomatology, they share with schizophrenics a dysfunction of auditory neurointegration.

Several studies have investigated cognitive functioning of patients with BPD using neuropsychological tests. Neuropsychological disturbances, particularly disturbances in memory, have been posited as contributing to the unstable involvement in interpersonal relationships that patients with BPD frequently demonstrate. Empirical studies have suggested that memory deficits, including the recall of learned material, are present in some patients with BPD. O'Leary et al. (1991) found that patients with BPD were significantly impaired on complex auditory and visual memory tasks [the Rey-Osterreith Complex Figure Task (Rey, 1941; Osterrieth, 1944) and story recall on the Wechsler Memory Scale (Wechsler & Stone, 1974)] and tasks of visual discrimination and filtering. However, cueing seems to bring performance back to normal (O'Leary et al., 1991). Poor performance on tests particularly involving multi-step, multi-element, associative operations

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[39] Targets are displayed on the screen and the patient taps on each target in order as quickly as possible. Two sequences are used, simple numeric (Trails A), and an alternating sequence of letters and numbers "1-A-2-B-3-C..." (Trails B), which is harder. Time taken to complete the task and number of errors made are measured.

(e.g. delayed memory, similarity comparisons, and proverb interpretations) have also been reported (Burgess, 1992). Further, self-injurious behaviour has been observed to correlate with a variety of deficits in memory in patients with BPD (Burgess, 1991). On the other hand, other studies (Cornelius et al., 1989) found no consistent pattern of abnormalities on neuropsychological testing in patients with BPD. However, only a limited number of neuropsychological tests were used and some data were collected in a retrospective manner.

In general, past studies suggest that BPD is associated with information processing, including memory deficits. Such impairments in complex information processing implies the involvement of the frontal lobe which is thought to be involved in mediating complex aspects of goal directed behaviour (Shallice et al., 1989). The dysfunction of such behaviour could lead to impulsive, maladaptive behaviour. Accordingly, I am investigating whether BPD patients have difficulties on specific neuropsychological tests that assess OFC and DLFC functions (like reversal & SWM). While no one would suggest that neuropsychological deficits are the cause of BPD, deficits in perception and retrieval from memory may contribute to some of the cognitive and behavioural difficulties observed in this disorder.

#### 1.12.9.1 Borderline Personality Disorder and Prefrontal Cortex Dysfunction

What is most obvious about BPD patients is their impulsive, often self-mutilative behaviour, their affective disinhibition, and their frequent failure, despite apparent learning, to apply gains made in psychotherapy. This behavioural pattern suggests that they suffer from a dysfunction in limbic and frontal sites. Thus, the possibility of frontal system cognitive dysfunction in BPD has been raised. In fact, although results have been variable, studies suggest that individuals with BPD exhibit cognitive deficits suggestive of frontal lobe dysfunction (Sprock et al., 2000). For example, frontal system cognitive functions have been shown to be inversely correlated to DIB score (Van Reekum, 1996). Further, Van Reekum et al. (1993) found that seven of nine subjects with BPD had evidence of frontal system dysfunction. Deficits most often included impulsiveness, cognitive inflexibility, poor self-monitoring, and perseveration. These deficits were most often in the WCST, the Rey-Osterrieth Complex Figure (copy and recall) and the Trials B (assess impulsive response style) tests. Burgess (1990) found evidence for more frontal lobe system impairment among BPD patients than among normal controls using tests sensitive to information processing (see Section 1.12.9). This "frontal" pattern of cognitive deficits is consistent with the behavioural disturbance that defines BPD.

BPD, as discussed above, is characterised by impulsivity, a behavioural dimension that is thought to have specific neurobiological correlates (Stein et al., 1993). Since impulsivity is considered to be the primary feature of BPD and OFC dysfunctions are suggested to underlie certain aspects of impulsivity (see Section 1.7.6), I hypothesise that patients with BPD may have underlying OFC deficits. Some studies to date suggest underlying frontal lobe deficits in patients with BPD (see Section 1.12.9.1-3 below). Yet, although some evidence has implicated specific

regions within the frontal cortex related to BPD (within certain subpopulations of BPD[40]), there is no definitive evidence, to date, concerning specificity of location of dysfunction. Knowledge of the specific brain abnormalities associated with BPD (in certain subgroups of patients) would be useful for developing effective treatment plans.

#### 1.12.9.1.1 Neuropsychological Evidence

The results of many neuropsychological tests suggest that primary deficits displayed by BPD patients reflect a frontal and possibly primarily orbitofrontal system dysfunction (Van Reekum et al., 1996). Van Reekum et al. (1993, 1996) reported that BPD subjects (n=48 and n=24 respectively) may have cognitive dysfunction in the frontal lobe of the brain. A pilot neuropsychological study showed that seven of nine subjects with BPD had evidence of frontal system dysfunction (Van Reekum et al., 1993; see Section 1.12.9.1). These results help to support the hypothesised existence of an organic BPD subgroup. Further, Van Reekum et al. (1996) found that 13 of 24 subjects with BPD had suffered a brain insult and there were correlations between neurodevelopmental/acquired brain injury score and Diagnostic Interview for Borderlines (DIB) score ($r = 0.47$), and between frontal system cognitive functioning and DIB score ($r = -0.37$). These results support the hypotheses of a possible frontal system cognitive dysfunction in BPD. Further, Swirsky-Sacchetti et al. (1993) reported that BPD patients (n=10) had deficits in front-temporal regions of the brain on various neuropsychological measures compared to non-patient controls (n=10) and Stein et al. (1993) reported that increased neurological soft signs observed in impulsive BPD subjects (n=28) were associated with impairments in frontal lobe executive function (see Section 1.12.9).

Bazanis et al. (2002) found that BPD patients (n=42; 41 had a history of self-harm) had impairments on a planning task and on a decision-making task, where they displayed a pattern of delayed and maladaptive choices when choosing between competing actions and exhibited impulsive, disinhibited responding when gambling on the outcome of their decisions. There was no evidence of impaired visual recognition memory and only limited effects of their current medication and history of substance abuse. These findings suggest that BPD is associated with complex impairments in dissociable cognitive processes mediated by circuitry encompassing the frontal lobes. These impairments may mediate some of the behavioural changes evident in BPD. However, further work is needed to examine the specificity of these findings. This finding is consistent with the cognitive and physiological effects observed in OFC lesioned patients (Cummings, 1985). Cummings' (1985) description of the behavioural consequences of OFC lesions is striking in its similarity to the behaviour of patients with BPD:

> "Lesions in this region appear to divorce frontal monitoring systems from limbic input, resulting in disinhibited behaviour syndrome where impulses are acted on without consideration of consequences, antisocial actions occur, and emotional lability is marked."

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[40] Andrulonis & Vogel (1984) suggest that BPD is composed of several subcategories, one being organic, with different etiological components, and therefore, different treatment components.

It is biologically plausible that a dysfunction of the limbic-orbitofrontal axis is involved in BPD, at least in a subgroup of patients (Van Reekum, 1993). The "lesions" that contribute to BPD therefore seem to include increased limbic discharge (e.g. epilepsy with limbic foci leading to interpersonal distress) and decreased OFC function (e.g. in traumatic brain injury).

#### 1.12.9.1.2 Functional Evidence

Electroencephalogram (EEG) abnormalities have been reported to be more prevalent in BPD patients than in control patients with other psychiatric disorders (Andrulonis et al., 1981; Snyder & Pitts, 1984; Cowdry et al., 1985). The site of the reported abnormalities varies in that slow, fast, and mixed waves have been reported in frontal, frontotemporal, and occipital brain regions (Synder & Pitts, 1984). Increased risk for head injury might exist in patients with BPD because of their impulsivity. This explanation might account for the findings of different locations of EEG abnormalities in the brain (New et al., 1995).

Positron Emission Tomography (PET) studies in subjects with BPD have repeatedly reported functional abnormalities in the frontal lobe of the brain. Using PET, Goyer et al. (1994) reported that there were significant changes in the frontal cortex metabolism, as measured by cerebral metabolic rates of glucose, in subjects with BPD (n=6) compared with normal controls (n=43). There was a significant decrease in frontal cortex metabolism in the BPD group. Similarly, in a PET study, De la Fuente et al. (1997) reported, in a semiquantitative analysis of regional brain glucose metabolic activities, that patients with BPD (n=10), with no current DSM-III-R Axis I diagnoses and free of any psychotropic substances, had bilateral hypometabolism in premotor and prefrontal cortical areas compared to control subjects (n=15). Further, using PET neuroimaging during a pharmacologic challenge with d,l fenfluramine[41], Soloff et al. (2000b) found that impulsive aggression in BPD patients (n=5) was associated with diminished serotonergic regulation in the PFC, including medial and orbital regions (BA 10 & 11). So, BPD patients had reduced activity in areas of the PFC associated with regulation of impulsive behaviour following serotonergic stimulation. Impulsivity, a leading characteristic of patients with BPD, might be related to the hypofrontality found in these studies. Accordingly, as discussed previously, lesions in the PFC of primates are known to produce disinhibition (Fuster, 1997) and frontal brain injury in humans can cause personality changes (Silver et al., 1987; Stuss & Benson, 1986). Some of these changes are remarkably similar to certain BPD symptoms. Moreover, the frontal cortex is the main source of input to midbrain serotonergic neurons of the dorsal raphe nucleus (Mayberg et al., 1990) and serotonin system dysfunction is thought to be involved in the production of impulsiveness in BPD patients (Brown et al., 1982; Coccaro et al., 1989; Hollander et al., 1994; see also Section 1.12.9.1.4). So, the diminished frontal metabolism in BPD patients could cause, act in parallel with,

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[41] A well established index of serotonin (5-HT) activity is the dose dependent release of prolactin (a protein hormone) in response to the 5-HT agonist d,l, fenfluramine (Coccaro et al., 1989), a specific 5-HT releasing agent and reuptake inhibitor. Impulsivity has been associated with reduced prolactin response to d,l, fenfluramine (Coccaro et al., 1989; Lopez-Ibor et al., 1991).

or exacerbate impaired serotonergic function and therefore be related to their impulsivity (De la Fuente, 1997).

Using magnetic resonance (MR) spectroscopy[42], Van Elst et al. (2001) examined the brains of patients with BPD and found a significant (19%) reduction of absolute N-acetylaspartate (NAA)[43] concentrations in the DLFC of BPD patients ($p$ = 0.01) compared with control subjects. As far as I know, to date, there has been only one published fMRI study with BPD patients. In this study, discussed above in Section 1.12.7, using standardised aversive emotional stimuli, Herpertz et al. (2001) found that BPD (n=6), but not control, subjects had an elevated BOLD fMRI signal bilaterally in the amygdala and fusiform gyrus and in the left medial and right ventrolateral PFC in response to aversive emotional stimuli. They suggest that BPD subjects' perceptual cortex may be modulated through the amygdala leading to increased attention to emotionally relevant environmental stimuli and that the medial/ventrolateral PFC may be a gateway for distinctive sensorial information and may modulate or inhibit amygdala-driven emotional responses and thus provide top-down control of the amygdala (see also Drevets, 1999; Morgan et al., 1994; Rauch et al., 1998). Yet, more fMRI studies are needed to help clarify the previous, less differentiated, PET findings of hypofrontality in patients with BPD.

#### 1.12.9.1.3 Structural Evidence

The abnormalities reported in EEG studies of BPD patients suggest that structural brain abnormalities might exist in BPD as well. However, neither gross inspection nor quantitative measures have revealed brain Computed Tomography (CT) abnormalities in BPD patients more frequently than in normal controls. Snyder et al. (1983) reported no gross clinical abnormalities in the CT scans of BPD patients (n=26). Schulz et al. (1983) found there was no difference in the ventricle-brain ratio between BPD patients (n=8) and healthy comparisons (n=18). Lucas et al. (1989) reported that BPD subjects (n=31) had a narrower third ventricle compared to healthy comparisons (n=28) but there were no differences in the ventricle-brain ratio and in a rating of the frontal lobe atrophy between subjects with and without BPD. However, CT technology may not be sensitive enough to detect subtle variations in structural neuroanatomy.

Brain Magnetic Resonance Imaging (MRI) studies have been able to repeatedly demonstrate structural abnormalities of the brain in subjects with psychiatric illnesses (Lyoo et al., 1996, 1997) with better resolution and clear differentiation of grey matter, white matter, and cerebral spinal fluid relative to the CT scanning (Na et al., 1991). As far as I know, only two MRI studies involving BPD patients have been published to date. The first MRI study that evaluated the structural abnormalities of the brain in subjects with the sole diagnosis of BPD was published by

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[42] A technique that measures the nuclear spin and the splitting of energy levels of atoms in a magnetic field. In the human brain, strong proton signals come from N-acetylaspartate (NAA).

[43] An amino acid found in high concentrations in the neurons of the central nervous system. The role of NAA in the brain is not well understood. However, the amount of NAA (as measured by proton MR spectroscopy) is accepted as being a direct marker for viable neurones.

Lyoo et al. (1998). The other study by Driessen et al. (2000) found reduced hippocampus (16% smaller volume, $p < .001$) and perhaps amygdala (8% smaller volume, $p < .05$) volume in 21 female patients with BPD compared to healthy controls. Lyoo et al. (1998) found that BPD patients (n=25) had a smaller frontal lobe volume (6.2% volume decrease) compared to healthy subjects (n=25). Since impulsivity, a defining feature of BPD, has been reported to be closely related to frontal lobe dysfunction in people with impulsive personality disorders (Stein et al., 1993; Goyer et al., 1994), and people with frontal lobe structural damage have shown problems with impulse control (Damasio et al., 1990), the finding of a smaller frontal lobe in BPD patients (Lyoo et al., 1998) may provide a structural basis for understanding this psychopathology in the context of BPD.

It is evident that more MRI studies of BPD patients are needed to better determine if in fact BPD patients have decreased prefrontal lobe volume or any other brain abnormalities. This information could reveal potentially useful biological variables that may allow for sub-typing BPD since the diagnostic validity of BPD has been repeatedly questioned (Nurnberg et al., 1991; Tyrer, 1994). Finding definitive brain abnormalities in a subgroup of patients with BPD would also be helpful in planning useful rehabilitation programs.

#### 1.12.9.1.4 Neurochemical Evidence

Impulsivity in patients with personality disorders has been associated with diminished levels of cerebrospinal fluid 5-hydroxyindoleacetic acid [5-HIAA; a serotonin (5-HT) metabolite], blunted neuroendocrine responses to serotonergic agonists, and decreased glucose utilisation in the PFC (Soloff et al, 2000b). This suggests that reduced serotonin levels in the PFC are related to the impulsive behaviour of the BPD patients. In fact, Soloff et al. (2000b) found that patients with BPD have diminished response to serotonergic stimulation in areas of PFC associated with regulation of impulsive behaviour, particularly in medial and orbital regions of the right PFC (BA 10) (see Section 1.12.9.1.2). Leyton et al. (2001) found that both men (n=5) and women (n=8) with BPD, compared to healthy men (n=6) and women (n=5), had significantly lower alpha-[(11)C]methyl-L-tryptophan (alpha-[(11)C]MTrp) trapping[44] in corticostriatal sites, including bilateral medial frontal gyrus and OFC (BA 8, 10, & 11), and striatum (see Footnote 12). This correlated negatively with impulsivity scores on a "go/no-go" task. So, low 5-HT synthesis capacity in corticostriatal pathways may contribute to the development of impulsive behaviours in people with BPD.

Hansenne et al. (2002) found that 20 BPD inpatients exhibited blunted prolactin response (see Footnote 41) to flesinoxan, a highly potent and selective 5-HT1A (a 5-HT receptor) agonist, as compared to controls (n=20), whereas depressed inpatients (n=20) did not differ from controls. Moreover, prolactin responses to flesinoxan were lower among BPD inpatients than among depressed inpatients and were lower in BPD patients with past history of suicide attempts (n=8) than in those with a negative history. So, these results suggest that BPD is characterised by lower

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[44] Trapping of the 5-HT precursor analog alpha-[(11)C]MTrp was used as an index of 5-HT synthesis capacity.

5-HT1A receptor sensitivity and that 5-HT1A activity is involved in suicidal behaviour. Rinne et al. (2002) found that in 38 non-schizophrenic, non-bipolar female patients with BPD, the selective serotonin reuptake inhibitor (SSRI) fluvoxamine, but not placebo, produced a robust and long-lasting reduction in scores on the rapid mood shifts subscale of the BPD Severity Index (Arntz et al., 2003), but no difference between groups was observed on impulsivity and aggression subscale scores. The latter finding may be due to gender-specific reasons. In general, these studies show a major involvement of serotonergic function in BPD patients and are consistent with previous studies linking lower serotonergic activity with impulsivity (see Section 4.1.10).

Reduced serotonin levels in the frontal lobe may also be related to the self-harming behaviour often exhibited by BPD patients. Accordingly, abnormalities of 5-HT and noradrenergic functioning have been implicated in aggressive impulsivity, self-injurious behaviour (SIB), and suicidal behaviour (Oquendo & Mann, 2000). Most studies suggest that impulsive aggression is related to lower levels of central nervous system 5-HT. Some studies demonstrate that increased norepinephrine (NE) correlates to impulsive aggression, whereas other studies demonstrate an opposite relationship (see Oquendo & Mann, 2000). The role of NE in impulsive aggressive behaviour is still unclear. The role of dopamine (DA) in human studies of these behaviours requires further investigation as well. For example, the presence of lower levels of 5-HT and abnormalities in the DA system have been related to SIB in patients with BPD and depression (Oquendo & Mann, 2000). Suicidal behaviours and the lethality of suicide attempts may also be linked to the abnormalities in neurotransmitter systems similar to those found in patients with impulsive aggression and SIB, namely, lowered 5-HT transmission and enhanced DA and NE functioning (Oquendo & Mann, 2000). Simeon et al. (1992) matched 26 self-mutilators with personality disorders to 26 control subjects with personality disorders. Self-mutilators had significantly more severe character pathology, had greater lifetime aggression, and were more antisocial than the control subjects. The degree of self-mutilation was significantly correlated with impulsivity, chronic anger, and somatic anxiety and both self-mutilation and impulsivity showed significant negative correlations with platelet imipramine[45] binding sites. The results demonstrate the contribution of severe character pathology, aggression, impulsivity, anxiety, and anger to self-mutilation and provide preliminary support for the hypothesis of underlying serotonergic dysfunction facilitating self-mutilation.

### 1.12.9.2 Summary of the Neurobiology of BPD

The aspects of personality disorders that are likely to have biological correlates are those involving regulation of affects, impulse/action patterns, and anxiety/inhibition (Skodol et al., 2002). Key psychobiological domains of BPD include impulsivity, associated with reduced serotonergic activity in the brain (Brown et al., 1982; Coccaro et al., 1989; Hollander et al., 1994), and affective

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[45] Imipramine, a tri-cyclic antidepressant of the dibenzazepine group, blocks the amine reuptake pump for serotonin and noradrenaline, allowing these neurotransmitters longer contact time with the receptor site.

instability, associated with increased responsivity of cholinergic systems (Keller et al., 1987; Steinberg et al., 1997). There may also be a strong genetic component for the development of BPD (Siever et al., 2002), but it seems clear, at least, that there are strong genetic influences on traits that underlie it, such as neuroticism, impulsivity, anxiety, affective lability, and insecure attachment (see Skodol et al., 2002).

Based on existing evidence, Korzekwa et al. (1993) suggest that only certain individual traits found in BPD, such as impulsivity, are defined by biological markers. Several lines of research support the hypothesis that there is a biological basis for the impulsivity seen in BPD. Family studies show a high rate of BPD and/or impulsivity in relatives of BPD patients and preliminary twin studies have provided evidence for a genetic basis for certain traits associated with the diagnosis, including impulsivity (Siever, 2002). Various studies have found decreased central and peripheral serotonergic and noradrenergic functioning in BPD (for a review, see Soloff, 2000). Neuropsychological studies have shown a variety of disturbances in BPD, including deficits in recall of learned material and completion of complex cognitive tasks (Burgess, 1990; O'Leary et al., 1991). EEG studies have demonstrated a variety of abnormalities in BPD patients (see Section 1.12.9.1.2). CT studies have not yielded any specific finding associated with BPD or impulsivity, but more advanced technology MRI studies have found structural abnormalities in BPD compared to healthy controls (see Section 1.12.9.1.3). However, only two MRI studies have been done thus far and more investigations are needed to support or disprove these findings. Finally, functional brain imaging technology (i.e. PET studies) have found some differences in brain activity in BPD patients compared to normal controls but more advanced technology fMRI studies (only one reported to date) may provide more specific information in the future (see Section 1.12.9.1.2). Thus, while a number of lines of research are suggestive of biological disturbances associated, in particular, with the impulsive aspect of BPD, a neuroanatomical/physiological explanation of the aetiology of BPD remains to be clarified.

Since two defining features of BPD are impulsivity and emotional instability (APA, 1994) and OFC patients show the same types of inappropriate behaviours (see Sections 1.7.3 & 1.7.6), I hypothesise that OFC dysfunction could be the common underlying feature for these types of inappropriate behaviours in BPD patients. Thus, self-report and behavioural measures of impulsivity and emotion, and neuropsychological tests sensitive to OFC and DLFC function (a control test), were administered to determine if there are in fact underlying PFC function deficits in patients with BPD. If so, I aim to determine specifically which parts of the PFC (i.e. OFC or DLFC) are related to which aspects of impulsivity and emotion. It is hoped that this investigation will clarify the relationship between BPD and brain dysfunction so as to help clinicians in their understanding of the interplay between brain and cognitive/psychodynamic functioning and guide researchers to study this system more thoroughly in BPD. It must also be kept in mind that brain dysfunction must interact with environmental and psychodynamic factors to produce behaviour change. Prospective studies that incorporate measures of brain dysfunction and measures of

environmental and psychodynamic factors will be needed to determine the way in which this interaction occurs as well as to identify useful treatment programs.

### 1.13 Summary of this Investigation

The OFC is thought to be involved in the reversing of stimulus-reinforcement associations (see Sections 1.7.7 & 1.7.8) and ventral frontal lobe lesions patients have alterations in their responses to changes in rewards and losses of rewards (Rolls et al., 1994), which may contribute to their everyday behavioural difficulties. Other studies have found that impulsive people are less sensitive to punishment and more sensitive to reward than non-impulsive people (Gray, 1973; Pickering & Gray, 1999; see Section 1.7.6). Therefore, sensitivity to reward and punishment may be an important factor in determining personality. Since alterations in personality such as impulsivity have been associated with OFC damage (Damasio, 1994; Rolls, 1999), I am investigating whether BPD patients, with similar characteristics as PFC lesion patients (i.e. impulsivity), have PFC impairments. Specifically, I hypothesise that BPD patients will have neuropsychological deficits similar to those of OFC patients.

This investigation aims to answer the question: To what extent do BPD patients with impulsive symptoms, who often are characterised by executive dysfunction (see Section 1.12.9.1), in the absence of overt neurological disorders and psychosis, also display evidence of PFC dysfunction and if so, exactly which areas of the PFC are associated with which aspects of the BPD syndrome?

This issue was explored by administering basic questionnaires of personality, emotion, and impulsivity together with a number of computer based tasks sensitive to frontal lobe dysfunction and that assess possible underlying factors related to impulsivity, including sensitivity to reward and non-reward, to PFC lesion, BPD, and normal control participants. Specifically, patients with OFC damage, and control patients with PFC damage outside of the OFC (mostly patients with DLFC damage), were assessed with measures of emotion, personality, and impulsivity as well as tasks involving sensitivity to reward and punishment, spatial working memory, and time perception. By administering these same tests to impulsive BPD patients, this research aims to assess the extent to which sensitivity to changing stimulus-reinforcer associations, among other functions, may be related to their impulsivity.

Building on previous work (Rolls et al., 1994; Hornak et al., 1996), which found patients with ventral frontal lobe lesions to be impaired at emotion-related learning and measures of behavioural and emotional change, modified versions of the behaviour and emotion questionnaires as well as the visual discrimination reversal test were used in the current investigation to study patients with more circumscribed lesions within the frontal lobe. In this way, a better understanding of the contribution of orbitofrontal, medial, and dorsolateral regions of the frontal lobe to the behavioural changes found in the earlier studies can be attained. Further, although there is evidence that frontal lobe patients show classical impulsive behaviour, very few rigorous studies have been

carried out to investigate exactly which parts of this complex area of the brain are specifically involved in impulsivity. This study can help determine if double dissociations exist between OFC and non-OFC prefrontal lesion patients on measures of emotion, personality, prefrontal functions, and different aspects of impulsivity. This will help to clarify which specific areas of the PFC are involved in which aspects of personality, emotion, and impulsive behaviour. Accordingly, BPD patients, characterised by impulsivity and inappropriate behaviour in social situations, were given the same measures of impulsivity and PFC function in order to assess possible PFC abnormalities.

Based on evidence described in this review, patients with OFC lesions, as compared to patients with non-OFC PFC lesions (mostly DLFC) and normal controls, are expected to be more emotional and perform poorly on the probabilistic emotion-related reversal task, the self-report and behavioural measures of impulsivity, and the time perception tasks. Conversely, patients with DLFC lesions are expected to perform poorly on the spatial working memory task. If neuropsychological deficits that are found in OFC lesion patients are also found in impulsive BPD patients, it would link BPD to OFC neurocognitive problems and lead to effective treatments. BPD patients are expected to have deficits on the tests associated with OFC functions if OFC dysfunctions are related to the impulsivity (and perhaps emotional instability) that characterises BPD patients. Alternatively, BPD patients should perform poorly on all PFC tests if both OFC and DLFC dysfunctions are related to the impulsivity central to their disorder, or solely on the SWM task if DLFC dysfunction alone is the cause of their cognitive and behavioural abnormalities. In addition, by comparing impulsive BPD patients to non-clinical (normal) participants on the same neuropsychological traits, perhaps it can be determined if the abnormal behaviours, like intense impulsivity, exhibited by clinical BPD patients is at the high end of a continuum with the rest of the population. In sum, this study aims to increase our understanding of the association between frontal dysfunction and impulsive behaviour, the behavioural changes seen in patients with PFC damage, and the cognitive and biological processes that are impaired in impulsive people, particularly in the context of BPD, which can have direct preventative and therapeutic implications.

# Chapter 2: METHODS

## 2.1 Design

A between subjects design was used to compare 101 subjects. Appropriate ethics approval was obtained from the Department of Experimental Psychology (University of Oxford), the Ethical Committee (Research) of the Institute of Psychiatry (King's College London), and the Oxfordshire Psychiatric Research Ethics Committee. Copies of the consent forms and information sheets given to control, lesion, and BPD participants are provided in Appendices 1-4. Consent was obtained before testing began.

## 2.2 Participants

Data were collected from 101 participants in total consisting of 39 normal control participants, 43 PFC lesion patients (20 with PFC lesions outside of the OFC and 23 with OFC lesions) and 19 BPD patients. The number of normal control patients tested was larger than the other groups because they were easier to recruit and having a larger number of normal participants decreased the variability within that group. All participants spoke English as their native language and were willing and able to participate. The education level of the subjects varied. While most had completed A-levels, some completed university, and very few had completed post-graduate studies.

The age of the participants in total ranged from 18 to 71 with a mean age of 41.82 (+/-16.43 SD). There were 34 male and 67 female participants. More females were tested than males because most of the BPD patients were females, corresponding to the higher prevalence of BPD in females in the population [BPD is diagnosed about 75% of the time in females (DSM-IV; APA, 1994)]. So, more females in the normal population were tested to try to correct for any potential differences in gender. 10 (25.6 %) male and 29 (74.4%) female normal control participants were tested ranging in age from 18 to 71 with a mean age of 40.28 (+/-20.51 SD). 8 (40%) male and 12 (60%) female non-OFC participants were tested who ranged in age from 19 to 71 with a mean age of 45.95 (+/-15.11). 15 (65.2%) male and 8 (34.8%) female OFC patients were tested who ranged in age from 30 to 63 with a mean age of 48.65 (+/- 9.99). Finally, 1 (5.3%) male and 18 (94.7%) female BPD patients were tested as BPD is more prevalent, being diagnosed about 75% of the time, in females (DSM-IV; APA, 1994). The BPD patients tested were aged between 19 and 49 with a mean age of 32.37 (+/-8.37). Note that most patients are not diagnosed with BPD until early adulthood as the angst of puberty can mimic some BPD symptoms. However, that trend is beginning to change (Pheil, 2002). Tables 2.1 & 2.2 show the gender frequencies and age descriptives of all, normal, non-OFC, OFC, and BPD participants.

As ANOVAs revealed between groups differences in terms of age [$F(3,97)=4.36$, $p=.006$] and gender [$F(3,97)=7.30$, $p=.000$], ANCOVAs, among other analyses, were performed in order to rule out any confounding effects of age or gender on the results. The results of these analyses revealed no significant age or gender effects (see Section 3.3 for more detail).

**Table 2.1**: Gender frequencies for all, normal, non-OFC, OFC, and BPD participants

| | **Frequency** | **Percent** |
|---|---|---|
| **All Participants** | | |
| Male | 34 | 33.7 |
| Female | 67 | 66.3 |
| Total | 101 | 100.0 |
| **Normal Participants** | | |
| Male | 10 | 25.6 |
| Female | 29 | 74.4 |
| Total | 39 | 100.0 |
| **Non-OFC Participants** | | |
| Male | 8 | 40.0 |
| Female | 12 | 60.0 |
| Total | 20 | 100.0 |
| **OFC Participants** | | |
| Male | 15 | 65.2 |
| Female | 8 | 34.8 |
| Total | 23 | 100.0 |
| **BPD Participants** | | |
| Male | 1 | 5.3 |
| Female | 18 | 94.7 |
| Total | 19 | 100.0 |

**Table 2.2**: Age descriptives of all, normal, non-OFC, OFC, and BPD participants

| **Participant Group** | **Minimum Age** | **Maximum Age** | **Mean Age** | **S.D.** |
|---|---|---|---|---|
| All Participants | 18 | 71 | 41.82 | 16.43 |
| Normal Participants | 18 | 71 | 40.28 | 20.51 |
| Non-OFC Participants | 19 | 71 | 45.95 | 15.11 |
| OFC Participants | 30 | 63 | 48.65 | 9.99 |
| BPD Participants | 18 | 49 | 32.37 | 8.37 |

### 2.2.1 Normal Control Participants

In order to provide normative data, 39 normal controls were recruited through the subject panel at the Department of Experimental Psychology, University of Oxford. The patients were invited to participate via a letter that included information briefly explaining the details about the study (see Appendix 2). If they agreed to take part, participants were asked to sign and return a consent form (see Appendix 1) and arrangements were made via e-mail or phone for them to come to the Oxford University Department of Experimental Psychology for testing. They were paid £3.50 per hour for their participation and were reimbursed for their travel expenses. Participants were excluded if they had disturbed vision (despite corrective devices), had a history of or current neurological illness, a current major psychiatric illness, or current substance or alcohol abuse.

### 2.2.2 Prefrontal Lesion Participants

A total of 43 frontal lesion patients were included in this study. Of those, 19 were recruited from the Department of Neurosurgery, King's College Hospital, London; 16 were recruited from the International Subarachniod Aneurysm Trial (ISAT) at the Radcliffe Infirmary, Oxford; and 8 were recruited from the Rivermead Rehabilitation Centre (Headway House), Oxford. The patients

recruited from King's College Hospital had discrete surgical lesions. Those recruited from the ISAT at the Radcliffe Infirmary had a subarachnoid haemorrhage and a coiling or clipping of a ruptured Anterior Communicating Artery (ACA) or Middle Cerebral Artery (MCA) aneurysm and were left with a focal infarction in the frontal lobe. Participants recruited from the Rivermead Rehabilitation Centre were outpatients with traumatic brain injury[46] and slightly larger areas of damage than the other lesion patients.

Of the 43 frontal lesion patients, 7 received their lesion as a result of a surgical excision of a brain tumour (3 meningioma, 2 oligodendroglioma, 1 astrocytoma, 1 malignant ependymona) and 10 received a surgical excision of the frontal lobes as part of a treatment for severe epilepsy. 18 patients had a subarachnoid haemorrhage and a coiling or clipping of a ruptured ACA or MCA aneurysm (8 ACA, 10 MCA), which resulted in ischemia or infarction in the ventral prefrontal cortex as this is the territory the ACA and MCA feeds, and 8 patients received their lesion as a result of traumatic brain injury. The time since the patients sustained their lesion varies considerably from 6 months to 20 years. The clinical information of each lesion patient is listed in Table 2.3.

The site of the lesion was ascertained by acquiring MRI or CT scans and/or neurosurgeons' reports and brain maps. The size of the lesions also varied across patient groups. Some of the patients who received their lesion as a result of head injury had quite extensive bilateral ventral frontal damage, whereas other patients who received their lesions via neurosurgical excision or stroke had smaller discrete unilateral lesions.

Table 2.4 shows the lesion site information for each patient. In order to ascertain any localisation of function, a method of categorisation (Rowe et al., 2000) was chosen in which the patients' lesions were labelled and patients were categorised into groups and compared according to three prefrontal regions. Patients were classified according to the prefrontal sectors' functional significance into which the lesions encroached. These areas were defined anatomically as orbital (Brodmann areas 10, 11, 12, 13 & 25), medial (Brodmann areas 8, 9, & 10), and dorsolateral (Brodmann areas 9 & 46) PFC. See Figure 1.4 for the cytoarchitecture map of Brodmann's areas. Patients are shown as having a lesion in a given region if their lesion extended to include at least some part of that region. Most patients had mixed lesions. However, some had either OFC, DLFC, or medial PFC damage alone. Figure 2.1 shows illustrations of the neurosurgeons' drawings of the location of lesions (shown in red) of the subset of patients in this study who were referred from King's College Hospital.

Patients who took part formed an unselected group and were entered consecutively into the study as they were referred. Exclusion criteria included damage outside of the PFC (with some minor exceptions, see Table 2.4), disturbed vision (despite corrective devices), current psychiatric

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[46] Traumatic brain injury is a non-degenerative, non-congenital insult to the brain from an external mechanical force, possibly leading to permanent or temporary impairments of cognitive, physical, and psychosocial functions with an associated diminished or altered state of consciousness (Kolb & Wishaw, 1996).

illness, and substance or alcohol abuse. Patients were invited to participate by letter which included an information sheet briefly explaining details about the study and what they would be asked to do (see Appendix 3).

If they agreed to take part, participants were asked to sign and return a consent form (see Appendix 1) and a letter was sent to the patients' general practitioner to inform them of their patients participation in the study and what the study was about (see Appendix 5). Finally, arrangements were made via e-mail or phone for the patients to come to the Oxford University Department of Experimental Psychology or for the researcher to go to the Rivermead Rehabilitation Centre for testing. Travel expenses were reimbursed.

As testing time was limited for the King's College patients, the questionnaires were mailed to them directly and returned via post. They did not come to the Department of Experimental Psychology or the Rivermead Rehabilitation Centre and did not complete the behavioural tests [although, some previously collected reversal data by J. O'Doherty and J. Hornak was obtained for some of these patients (Rolls et al., 1994)]. They were also not given the BPD Questionnaire, at the request of the Institute of Psychiatry (London), due to clinical sensitivity issues.

**Table 2.3: Clinical information of lesion patients**

| Patient | Gender | Age | Years since surgery | Aetiology of Lesion |
|---|---|---|---|---|
| Patients with Orbitofrontal cortex damage | | | | |
| **BK** | F | 60 | 6 | Meningioma |
| **RS** | F | 51 | 7 | ACA aneurysm and subarachnoid haemorrhage |
| **SU** | F | 52 | 4 | Meningioma |
| **RC** | M | 30 | 13 | Epileptic Focus |
| **HR** | M | 55 | 0 | Meningioma |
| **CE** | M | 63 | 1 | Astrocytoma |
| **TM** | M | 32 | 10 | Epileptic Focus |
| **LS** | F | 49 | 11 | Epileptic Focus |
| **GW** | M | 32 | 12 | Epileptic Focus |
| NS | M | 52 | 2 | ACA aneurysm and subarachnoid haemorrhage |
| RSt | M | 54 | 3 | ACA aneurysm and subarachnoid haemorrhage |
| JP | F | 60 | 2 | ACA aneurysm and subarachnoid haemorrhage |
| SS | F | 46 | 2 | ACA aneurysm and subarachnoid haemorrhage |
| VS | F | 60 | 4 | ACA aneurysm and subarachnoid haemorrhage |
| JH | F | 57 | 1 | MCA aneurysm and subarachnoid haemorrhage |
| PQ | M | 46 | 2 | MCA aneurysm and subarachnoid haemorrhage |
| AN | M | 40 | 1 | ACA aneurysm and subarachnoid haemorrhage |
| ST* | M | 41 | 8 | TBI |
| CD* | M | 53 | N/A | TBI |
| PF* | M | 30 | N/A | TBI |
| MB* | M | 50 | N/A | TBI |
| MT* | M | 59 | N/A | TBI |
| CM* | M | 47 | N/A | TBI |
| Patients with Non-Orbitofrontal cortex damage | | | | |
| **PW** | M | 48 | 0 | Contusions: focal head injury |
| **PR** | M | 25 | 2 | Ogliodendroglioma |
| **GP** | M | 42 | 2 | Epileptic Focus |
| **DS** | M | 31 | 14 | Epileptic Focus |
| **DV** | M | 32 | 10 | Epileptic Focus |
| **FH** | F | 25 | 13 | Oligodendroglioma |
| **EH** | F | 45 | 20 | Epileptic Focus |
| **SC** | F | 19 | 4 | Epileptic Focus |
| **SP** | F | 32 | 5 | Epileptic Focus |
| **HB** | F | 34 | 0 | Malignant Ependymona |
| GH | M | 53 | 3 | ACA aneurysm and subarachnoid haemorrhage |
| MG | F | 71 | 3 | MCA aneurysm and subarachnoid haemorrhage |
| MP | F | 57 | 1 | MCA aneurysm and subarachnoid haemorrhage |
| EI | F | 50 | 3 | MCA aneurysm and subarachnoid haemorrhage |
| JW | F | 61 | 2 | MCA aneurysm and subarachnoid haemorrhage |
| MF | F | 48 | 1 | MCA aneurysm and subarachnoid haemorrhage |
| PC | M | 52 | 3 | MCA aneurysm and subarachnoid haemorrhage |
| MB | F | 71 | 3 | MCA aneurysm and subarachnoid haemorrhage |
| PT* | F | 67 | 5 | MCA aneurysm and subarachnoid haemorrhage |
| NJ* | M | 47 | N/A | TBI |

Key to Table 2.3:
M=Male, F=Female, ACA=Anterior Communicating Artery, MCA=Middle Cerebral Artery, TBI=Traumatic brain injury, Patient initials in bold=King's College surgical lesion patients, Patient initials in plain lettering=Radcliffe Infirmary International Subarachnoid Aneurysm Trial patients, *=Rivermead patients, N/A=not available

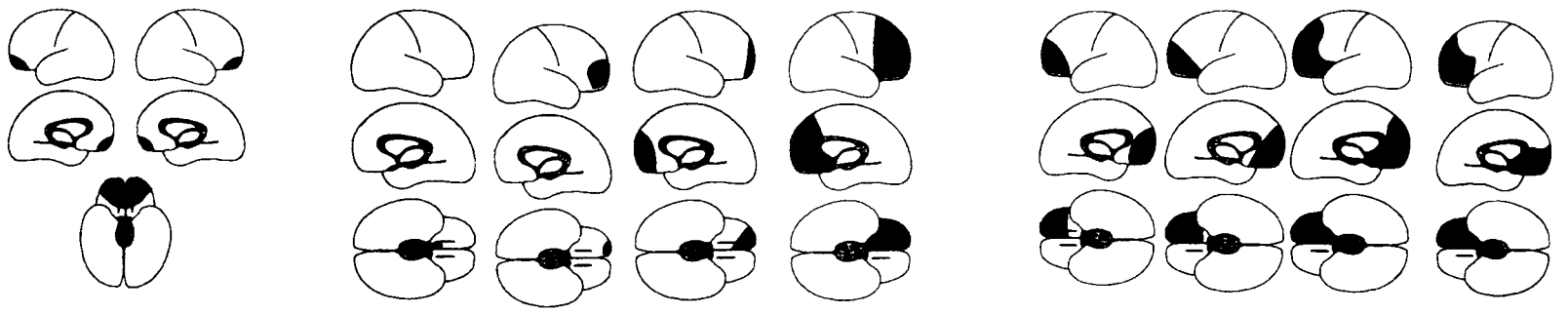
**Table 2.4: Lesion sites - classification according to the 3 main subdivisions of PFC**

| Patient | Side | Orbital | Medial | Dorsolateral |
|---|---|---|---|---|
| | BA: | 10,11,12,25 | 8,9,10 | 9,46 |
| Patients with Orbitofrontal cortex damage | | | | |
| NS | Bilat | ++ | | |
| **BK** | Bilat | ++ | ++ | |
| ST* | Bilat | ++ | +(R) | +(R) |
| CD* | Bilat | ++ | ++ | ++ |
| MB* | Bilat | ++ | ++ | ++ |
| AN | Bilat | ++ | ++ | ++ |
| PF* | Bilat | ++ | ++ | ++ |
| **RS** | Right | + | | |
| **SU** | Right | + | | |
| JP | Right | + | + | |
| **RC** | Right | + | + | |
| SS | Left | + | + | |
| VS | Left | + | ++ | |
| JH | Left | + | + | |
| RSt | Right | + | | + |
| PQ | Right | + | + | + |
| MT* | Right | + | + | + |
| CM* | Right | + | + | + |
| **HR** | Right | + | + | + |
| **CE** | Left | + | + | + |
| **TM** | Left | + | + | + |
| **LS** | Left | + | + | + |
| **GW** | Left | + | + | + |
| Patients with Non-Orbitofrontal cortex damage | | | | |
| **PW** | Bilat | | (++) Fr. pole | |
| **PR** | Left | | + | |
| **GP** | Left | | + | |
| NJ* | Bilat | | ++ | ++(some T) |
| **DV** | Right | | + | + |
| **FH** | Right | | + | + |
| **EH** | Right | | + | + |
| **SC** | Right | | + | + |
| **SP** | Right | | + | + |
| **HB** | Left | | + | + |
| **DS** | Right | | | + |
| GH | Right | | | + |
| PT* | Right | | | + (some BG) |
| EI | Right | | | + (some BG) |
| MG | Right | | | + (someP+T) |
| MP | Right | | | + (someP+T) |
| JW | Right | | | + (someP+T) |
| MF | Right | | | + (some T) |
| PC | Left | | | + (someP+T) |
| MB | Left | | | +(some T) |

Key to Table 2.4:
BA=Brodmann Area, Bilat=Bilateral, BG=Basal Ganglia, P=Parietal, T=Temporal, +=Unilateral lesion, ++=Bilateral lesion, Patient initials in bold=King's College surgical lesion patients, Patient initials in plain lettering=Radcliffe Infirmary International Subarachnoid aneurysm trial patients, *=Rivermead patients

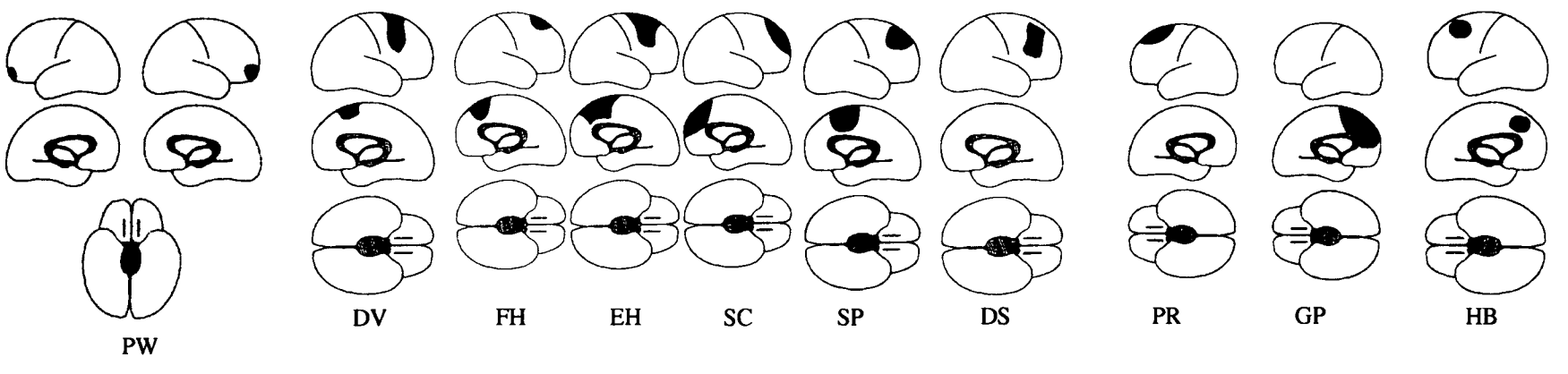
**Figure 2.1: <u>Lesion Sites of King's College Neurosurgical Patients</u>** (lesion sites are shown in red and the patients' initials are below each brain diagram)

<u>OFC lesion patients</u>




Bilateral lesion | Right-sided lesions | Left-sided lesions

<u>Non-OFC lesion patients</u>




Bilateral lesion | Right-sided lesions | Left-sided lesions

### 2.2.2.1 Control Participants with Prefrontal Cortex Damage Outside of the OFC

20 patients were included in a group who fulfilled the criteria of having PFC damage outside of the OFC (non-OFC group) and served as a lesion control group. Dorsolateral prefrontal cortex (DLFC) damage (with or without medial PFC damage) was the main site of damage for inclusion in this group. Three patients, however, had medial PFC damage alone (1 with bilateral medial damage and 2 with left-sided medial PFC damage). Of the remaining patients, regardless of whether or not they had medial damage, 1 had bilateral DLFC damage, 13 had damage to the right DLFC, and 3 had damage to the left DLFC. In total, 3 patients had medial PFC damage alone, 2 had DLFC damage alone, 7 had DLFC and medial damage, 2 had DLFC and some basal ganglia damage, 2 had DLFC and some temporal damage, and 4 had DLFC and some temporal and parietal damage (see Table 2.4). Figure 2.1 contains pictures based on neurosurgeon drawings of the non-OFC lesion sites for the King's College surgical patients only.

### 2.2.2.2 Orbitofrontal Cortex Lesion Participants

23 patients were included in the OFC lesion group. The criterion for inclusion in this group was that the patient had damage including or restricted to the OFC (either bilaterally or unilaterally). Of these patients, regardless of whether or not they had DLFC or medial damage, 7 had bilateral OFC damage, 9 had damage to the right OFC, and 7 had damage to the left OFC. In total, 3 patients had OFC damage alone, 1 had OFC and DLFC damage, 6 had OFC and medial PFC damage, and 13 had OFC, medial PFC, and DLFC damage (see Table 2.4). Figure 2.1 contains pictures based on neurosurgeon drawings of the OFC lesion sites for the King's College surgical patients only.

### 2.2.3 Borderline Personality Participants

19 BPD inpatients were tested at the Bethlem Royal Hospital Crisis recovery Unit, London. Patients in this group met the criteria for BPD set in the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV; APA, 1994). See Appendix 6 for a list of the DSM-IV criteria for BPD. In addition, these patients were all self-harmers (see Sections 1.12.3 & 1.12.4). Cutting and burning were among the most common forms of self-harm in the patients tested. This objective measure of impulsive behaviour was important in obtaining a homogenous patient group as DSM classification of BPD can be subjective (Nurnberg et al., 1991; Follett, 1996; Follette & Houts, 1996). All participants were consecutively admitted inpatients in a six month rehabilitation program where they were taught to seek alternatives to self-harm, to gain a greater understanding of the meaning self-harm has for them, and to tolerate distressing feelings.

The patients were invited to participate by verbal explanation and by a letter that included information briefly explaining details about the study and what they would be asked to do (see Appendix 4). If they agreed to take part, participants were asked to sign and return a consent form (see Appendix 1), their psychiatrist was notified, and arrangements were made via the nursing staff for an appointment to be tested at the Bethlem Royal Hospital Crisis Recovery Unit. Participants

were excluded if they had disturbed vision (despite corrective devices), had a history of or current neurological illness, or current substance or alcohol abuse. Most of the self-harming BPD inpatients were on prescription medications such as mood stablisers, anti-psychotics, and/or anti-depressants. However, medication effects did not seem to be an issue as BPD patients performed poorly almost all tasks despite being on medications aimed at improving some of the negative behaviours and emotions that were being tested (see Section 4.9 for more detail).

## 2.3 Measures and Procedures

Participants were asked to first complete six self-report questionnaires. They were then given four cognitive/behavioural tests. Questionnaire and test order was randomised. Copies of all of the questionnaires and verbatim instruction for all of the tests are included in Appendices 7- 17.

### 2.3.1 Questionnaires and Dependent Variables

The following six short, self-report, paper and pen questionnaires assessing impulsivity, personality, emotion, and inappropriate "frontal" behaviour were administered. Participants were asked to read the instructions on top of each questionnaire and were free to ask questions concerning the instructions if they needed clarification. In instances where participants had some trouble reading, the questionnaires were conducted verbally.

#### 2.3.1.1 Self-report Impulsivity Measure: Barratt Impulsiveness Scale

All participants completed the Barratt Impulsiveness Scale, version 11 (BIS-11) (Patton et al., 1995) (see Appendix 7). This is a 30-item, 4-point likert scale questionnaire that is widely used to measure impulsivity in a variety of populations and has been validated in both impulsive and normal populations (Patton et al., 1995; Coccaro, 1996; Cherek, 1997). The reliability and validity of the BIS-11 has also been repeatedly shown in a variety of languages (Patton et al., 1995; Bayle et al., 2000; Fossati et al., 2001; Someya et al., 2001; Moeller et al., 2002). The BIS-11 is structured to assess long-term patterns of behaviour by asking subjects to answer questions about the way they think and act without relation to any specific time period. Thus, it tends to be used as a trait measure of impulsivity. Some sample items from the BIS-11 are "I act on impulse", "I plan tasks carefully", and "I act without thinking". The BIS-11 is made up of three subscales: non-planning, motor, and cognitive impulsivity. The non-planning impulsivity subscale is made up of 11 of the 30 items and contains questions like "I plan tasks carefully" and "I am more interested in the present than in the future". The motor impulsivity subscale is made up of 11 of the 30 items and contains items like, "I act on the spur of the moment" and "I do things without thinking". Finally, the cognitive impulsivity subscale consists of 8 out of the 30 items and contains questions which inquire about propensity for quick decisions like, "I make up my mind quickly" and "I am a careful thinker". Each of these subscales was measured in addition to the overall impulsivity score.

**Dependent Variables Measured in the Barratt Impulsiveness Scale**

1) Total impulsivity score (0-120)

2) Non-planning impulsivity (0-44)

3) Motor impulsivity (0-44)

4) Cognitive impulsivity (0-32)

### 2.3.1.2 Personality Questionnaire: The Big Five Inventory

The five factor model of personality has grown out of efforts by many researchers (Klages, 1926; Baumgarten, 1933; Allport & Odbert, 1936), beginning over 75 years ago, to reduce the myriad elements of personality to an elemental set. The Big Five Inventory (BFI) (John et al., 1991) (see Appendix 8) is a recent product of this ongoing endeavour, and owes much to Costa and McCrae's work of the past ten years (for a review, see John & Srivastava, 1999). The BFI is a 44-item 5-point likert scale questionnaire designed to measure extraversion, agreeableness, conscientiousness, neuroticism, and openness to experience. The BFI measure was constructed as a compromise between Goldberg's (1992) conception of the basic five traits as broad domains of individual differences found in self-rating measures of personality trait adjectives; and McCrae and Costa's (1996) five factor model of personality, in which the traits are taken more seriously as basic organic structures inherent in all humans. The five scales or broad domains of the five factor model and a set of adjectives that describe the aspects of personality that were measured are below (from Costa & McCrae, 1992).

**Dependent Variables Measured in the Big Five Inventory**

1) Extraversion (E): talkative, energetic, enthusiastic, adventurous, outgoing (vs. introversion: reserved, quiet, shy) (0-40)

2) Agreeableness (A): helpful, trusting, forgiving, considerate, cooperative (vs. antagonism: fault-finding, quarrelsome, rude, cold) (0-45)

3) Conscientiousness (C): thorough, reliable, persevering, efficient, organised (vs. lack of direction: careless, disorderly, lazy, distractible) (0-45)

4) Neuroticism (N): gloomy, tense, worrying, moody, nervous, unstable (vs. emotionally stable: relaxed, stable, confident, calm) (0-40)

5) Openness to experience (O): wide interests, original, curious, artistic, imaginative, inventive, idealistic (vs. closed to experience: unimaginative, conventional) (0-50)

### 2.3.1.3 Borderline Personality Questionnaire

Developed at the University of Oxford by Gordon Claridge and colleagues (Claridge & Broks, 1984), the Borderline Personality Questionnaire (STB) assesses BPD characteristics and was modelled on the DSM-III (APA, 1980) criteria for BPD. The STB is made up of 18 questions with simple "yes" and "no" answers. A study by Shankar (1998) of clinically diagnosed BPD patients

has supported the construct and discriminant validity of the STB (see Appendix 9; see also Section 1.12.2).

**Dependent Variable Measured in the Borderline Personality Questionnaire**

1) Total BPD Questionnaire Score: the total number of questions answered with "yes" (0-18).

### 2.3.1.4 Frontal Behaviour Questionnaire

This self-report 20-item, 5-point likert scale (0, .25, .5, 1.0, & 1.5) questionnaire was designed to measure types of behavioural problems generally believed to result from frontal damage (Levin et al., 1991) such as disinhibition, social inappropriateness, perseveration, and cooperativeness. This questionnaire was developed based on a behavioural test in Rolls et al. (1994) where a member of staff involved in the patients care or rehabilitation was asked to complete the questionnaire. It was designed to provide a measure of the kinds of behavioural problems, especially social, that occurred in patients with frontal lesions (see Appendix 10; see also Section 1.8).

**Dependent Variable Measured in the Frontal Behaviour Questionnaire**

1) Total Frontal Behaviour Score (0-30)

### 2.3.1.5 Subjective Emotion Questionnaire

This questionnaire measures, on a 4-point likert scale (0, 1, 2, 3), *how often* participants experience each of the following emotions in their current daily life: sadness, anger, fear, happiness, and disgust (see Appendix 11). This questionnaire was developed based on a verbal subjective emotion test in Rolls et al., (1994) where participants were questioned about any change they experienced in the intensity or frequency of each of the above mentioned five emotions since their brain injury. The five emotions were chosen because they corresponded to the main emotions that occurred in tests of facial (Ekman & Freisen, 1975) and vocal expression identification in which the patients also took part. The five emotions were based on Ekman's (Ekman & Friesman, 1975) cross-cultural studies of human expressions, which have strongly suggested an innate, biological basis for emotional experience. According to Ekman (1999) there are six "fundamental" emotions that act as basic building blocks to our entire emotional repertoire: anger, sadness, happiness, disgust, fear, and surprise. Surprise was not incorporated into the questionnaire used here since it was extended from a previously developed questionnaire (Rolls et al., 1994; Hornak et al., 1996) that did not test surprise because it was considered to be a reaction to novelty versus frequency rather than an emotion (see also Section 1.5.3).

**Dependent Variable Measured in the Subjective Emotion Questionnaire**

1) Total Subjective Emotion Score (0-15)

2) Subjective Sadness Score (0-3)

3) Subjective Anger Score (0-3)

4) Subjective Fear Score (0-3)

5) Subjective Happiness Score (0-3)

6) Subjective Disgust Score (0-3)

#### 2.3.1.6 Emotional Change Questionnaire

Only lesion and BPD patients completed this questionnaire (Appendix 12) that assesses *change* since brain injury or onset of personality disorder (usual age of onset for BPD is in early adulthood) in capacity to feel each of the following positive and negative emotions: sadness, anger, fear, happiness, and disgust (see Appendix 12). Patients were given 1 point for an increase, -1 point for a decrease and 0 points for no change. This test was developed based on a verbal subjective emotion test in Rolls et al. (1994) and Hornak et al. (1996) (see Sections 1.5.3 & 2.3.1.5).

**Dependent Variables Measured in the Subjective Emotional Change Questionnaire**

1) Total number of emotions changed (regardless of increase or decrease) (0-5)

2) Change in Sadness: raw score on Sadness (-1,0,1)

3) Change in Anger: raw score on Anger (-1,0,1)

4) Change in Fear: raw score on Fear (-1,0,1)

5) Change in Happiness: raw score on Happiness (-1,0,1)

6) Change in Disgust: raw score on Disgust (-1,0,1)

### 2.3.2 Tests and Dependent Variables

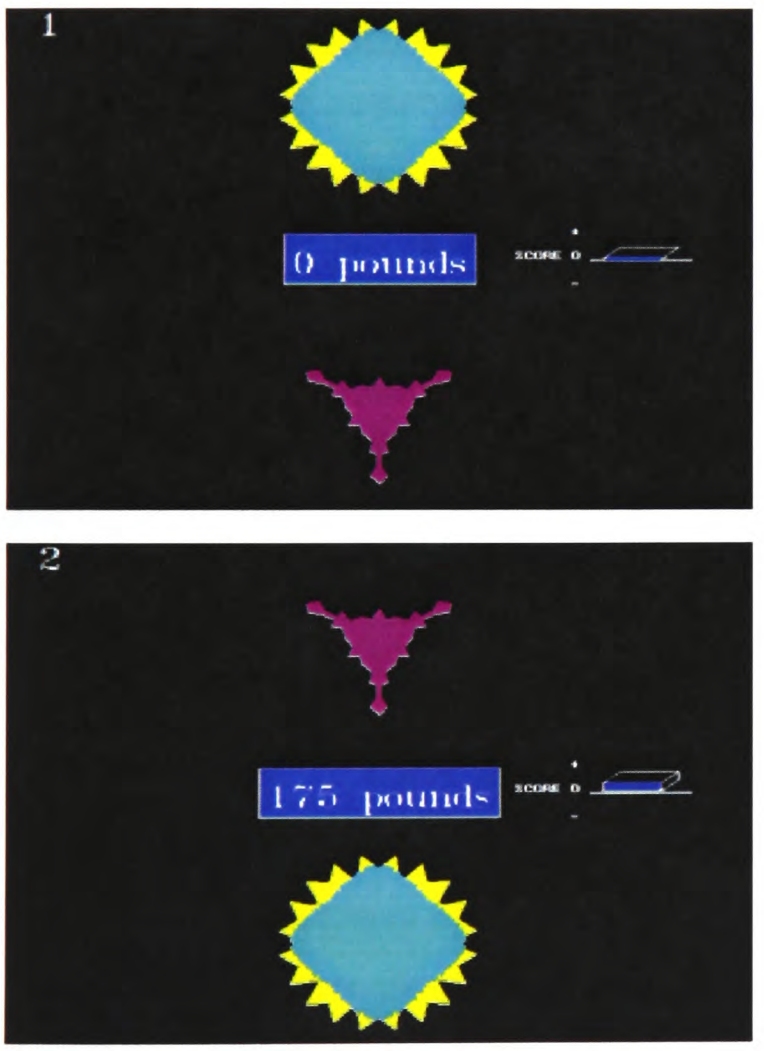
The following four (three computer based and one paper based) neuropsychological tests designed to assess OFC and DLFC activity, impulsivity, and time perception were administered.

#### 2.3.2.1 The Probabilistic Reversal Test

This test was created by O'Doherty et al. (2001b) and was carried out on a computer with a touch screen attached. The test was composed of two tasks: an "acquisition" task where participants learn to touch one of two patterns on the computer screen and to avoid touching the other; and a "reversal" task where they then learn to reverse or extinguish that response. In each task the participants were presented with two highly discriminable shapes (different shape pairs were used for the two tasks). Also displayed on the screen was the total amount of money that the participant won (beginning at £0 at trial one) in a bar chart representation (on the right of the screen) and in numerical form (in the centre between the shapes). On each trial the position of the two shapes was randomly alternated between the top and bottom of the screen, so as to eliminate the possibility of patients using the spatial position of the shapes to solve the task (as one of the aims of the task was to assess object and not spatial learning). A visual representation of the task is shown in Figure 2.2.

A number of steps were taken to ensure that the feedback given to the participants during the task performance was as salient as possible, in order to minimise the possibility of participants not attending to the relevant information when performing the task. The amount won or lost on a stimulus was displayed prominently in flashing colours superimposed on the stimulus for 3 seconds. To indicate a monetary loss, the message displayed was "Sorry! You have lost £...." and a descending auditory sound was heard, while a monetary gain was indicated by the message "Well Done! You have won £...." and an ascending auditory sound. A small amount won or lost resulted in a brief sound (as little as 100 milliseconds) and a large win or loss resulted in a longer duration sound (up to 1.5 seconds). The amount won or lost and the total amount was displayed by colour code, where blue signified a monetary gain and red a monetary loss.

**Figure 2.2**: Probabilistic reversal task using money as a secondary reinforcer




| | S+ | S- |
|---|---|---|
| *Reward:Punish Ratio* | 70:30 | 40:60 |
| *Reward Ranges* | £80-250 | £30-60 |
| *Punishment Ranges* | £10-60 | £250-600 |

**2.3.2.1.1 The Acquisition Task**

Participants were asked to choose between one of two shapes on each trial. The participant could win or lose money on either stimulus but one stimulus was designated the good stimulus (S+) in that the ratio of magnitude of rewards and punishments obtainable on that stimulus was such that consistent selection of that stimulus led to an overall monetary gain. The other stimulus was designated the bad stimulus (S-) and the contingencies were arranged so that consistent selection of that stimulus led to an overall monetary loss. Participants were instructed to determine by trial and error which was the good stimulus and continue to choose that stimulus in order to gain the most

money (see Appendix 13). This task was complete once the subjects learned to consistently select the positive stimulus (to select S+ 16 out of the previous 18 consecutive responses) and there was no reversal. This task enabled participants to familiarise themselves with the task demands and appreciate the probabilistic nature of the reward contingencies. Successful completion of the task indicated that participants understood the task demands and were able to adequately follow the instructions, thus controlling for those explanations for poor performance on the reversal task.

#### 2.3.2.1.2 The Reversal Task

This task followed the same rules as the acquisition task, except that once the subject had attained criterion and were consistently choosing the S+, the reward contingencies were reversed so that the old S+ became the new S- and the old S- became the new S+. The participants were told that once they had worked out which one was the good pattern and had chosen it consistently a certain number of times, the contingencies would change and they would have to alter their behaviour accordingly and switch patterns (see Appendix 14 for the verbatim instructions). The criterion (not made explicit to the participant) for successful acquisition of an S+ in the reversal task was 9 out of the previous 10 consecutive responses. Once the criterion was reached, the reward contingencies were gradually reversed over a period of ten trials by altering the reward contingencies of the two stimuli in incremental steps until a complete reversal had occurred.

#### 2.3.2.1.3 Reward Contingencies

The reward/punishments were decided on the basis of a pseudo-random sequence. In both subtasks, the ratio of rewards to punishments for the S+ was 70:30, whereas that for the S- was 40:60. The magnitude of the rewards also varied, according to a uniformly distributed random sequence. In the acquisition task, the rewards for S+ ranged from £60 to £200 and the losses from £10 to £50. The rewards for the S- ranged from £10 to £100 and the losses form £70 to £300. In the reversal task, the rewards for the S+ ranged from £80 to £250 and the losses form £10 to £60. The rewards for the S- ranged from £30 to £60 and the losses from £250 to £600 (see Figure 2.2). These particular values and ratios were chosen based on preliminary pilot experiments with normal participants to give the task the appropriate level of difficulty as reflected by the fact that normal participants could achieve between 3 and 4 reversals over 100 trials (O'Doherty, 2000, see also Figure 3.27).

#### 2.3.2.1.4 Procedure for the Probabilistic Reversal Task

The participants were read a set of instructions (see Appendix 13) for the first acquisition task and when the experimenter was satisfied that the patient understood the task instructions, they were invited to begin the task. When participants reached criterion on the acquisition task or completed 100 trials (whichever came sooner), they were then asked to stop the task and invited to move onto the reversal task (provided they achieved criterion within 100 trials- if not, they did not go on to the

reversal task). They were then read a further set of instructions (see Appendix 14), were asked to begin, and were asked to stop at the 100th trial.

**Dependent Variables Measured in the Probabilistic Reversal Task**

1) Number of trials to reach criterion on the acquisition task: the number of trials taken to acquire the positive stimulus- the criterion was reached by selecting S+ 16 out of the previous 18 consecutive responses.

2) Total pounds accumulated after 100 trials on the reversal task

3) Number of trials until the first reversal on the reversal task: the number of trials taken to achieve the first reversal was marked by the trial where the participant starting consecutively touching the new positive stimulus (S+).

4) Total number of reversal achieved by 100 trials: a successful reversal was considered choosing the new positive stimulus (S+) 9 out of the previous 10 responses. It was still counted as a reversal in cases where a reversal was started but was cut off in process by the 100th trial. This was true for all but two OFC participants who had chosen the new positive stimulus simply by random chance but never truly reversed.

5) Punishment insensitivity on the reversal task: the total number of consecutive touches to a stimulus after having lost a minimum of £250. This is effectively a measure of the extent to which participants fail to *switch* immediately from a stimulus on the next trial following a large loss (£250 corresponds to the lower bound of the money that can be lost by touching S-).

6) Reward insensitivity on the reversal task: the total number of times a participant touched a stimulus and won a minimum of £80 but did not touch the same stimulus again on the next trial. This effectively measures the extent to participants fail to *stick* to a stimulus following a large gain on that stimulus (£80 corresponds to the lower bound of the amount that can be won on S+).

### 2.3.2.2 Matching Familiar Figures Test

This is an internally consistent, stable, reliable, and well validated (Glow et al., 1981) cognitive behavioural measure of impulsivity in standard use created by Kagan (1966). Reflection-impulsivity has been conceptualised as an individual variable describing the cognitive processes involved in "reflecting on the accuracy of available hypotheses" (Kagan & Messer 1975). Operationally, the variable has been defined as a composite of two dimensions: latency to first response and accuracy of choice or total errors. These two dimensions are combined in the Matching Familiar Figures Test (MFFT) (Kagan et al., 1964), regarded as the primary (and often the only used) index of reflection-impulsivity. Using the standard form of this test, each participant is presented with a picture of a familiar object (the standard) on a piece of paper and a set of 8 highly similar variants on another piece of paper directly below where only one of the set of variants is exactly the same as the standard. See Figure 2.3 for an example of a target figure and its variants that were presented on a single trial. The test was set-up in a notebook that was placed on a

stand so that the both the stimulus and the alternatives were clearly visible to the participant at the same time. The pages were at right angles to each other and were inserted in clear plastic to keep them clean. The task is to select (point to) from the set of variants the one that is exactly the same as the standard. If the response is correct the participant goes on to the next item. If incorrect, the participant is told to choose again with a maximum of 8 errors per item.

Participants were read the instructions (see Appendix 15) and were given 2 practice items (a picture of a boat and a cowboy respectively), which had only 6 variants each to choose from, in order to become familiar with the task. They were then given 12 trials with 8 variants each to choose from, with a different target object for each trial (the standard object pictures were a dog, rose, soldier, graph, baby, lamp, dress, lion, glasses, plane, leaf, and bed).

A stop watch was used to record the time latency of the participants' first response on each trial (participants were aware they were being timed). Total number of errors made before choosing the correct item and the order in which errors were made were also recorded.

**Figure 2.3 Example of a trial on the MFFT**: Participants were presented with a target picture (top) and eight highly similar variants (below; one of which is identical to the standard) and were asked to choose the one that was exactly like the target (the correct answer is rose # 6- the second from the left on the bottom row).

**Dependent Variables Measured in the Matching Familiar Figures Test (MFFT)**

1) Mean time latency: the mean number of seconds until first response across all trials.

2) Total number of errors: (across all trials)

3) Total number of errors per second: the total number of errors divided by the average number of seconds taken to choose the first stimulus across all trials. The higher the number, the more impulsive (i.e. the more errors made and the less time taken to think about the choice before making a selection).

### 2.3.2.3 Spatial Working Memory Task

This task is from the Cambridge Neuropsychological Test Automated Battery (CANTAB; CeNeS Ltd, Cambridge)[47] and was carried out on a computer with a touch screen attached. This is a test of spatial working memory (SWM) and strategy performance. Participant were asked to find a blue token in each of the boxes displayed and use them to fill up an empty column on the right hand side of the screen, whilst not returning to boxes where a blue token had previously been found. See Figure 2.4 for what is displayed on the screen.

The test begins with a number of coloured squares (boxes) being shown on the screen. The number of boxes is gradually increased until it is necessary to search a total of eight boxes. The colour and the position of the boxes used are changed from trial to trial to discourage the use of stereotyped search strategies.

The participant must touch each box in turn until one opens with a blue "token" (smaller blue box inside of the larger coloured box) inside (a search). Returning to an empty box already sampled on this search is an error. When the blue token has been found, the participant has to place it in the right column ("black hole") by touching the right hand side of the screen. The box that contained the blue token will not contain another blue token on this trial. Returning to this box is also an error. The subject must then begin a new search for the next blue token. It may be in any of the boxes that so far have been empty. The order in which the subject searches the boxes is determined by the subject themselves, but the number of empty boxes they must visit (discounting errors) is determined by the computer. At the end of each trial when the column is full, a "COMPLETE" message is displayed followed shortly afterward by the message "NEW SET".

Subjects were read the instructions (see Appendix 16) and were given four practice trials. On the first trial, 3 red boxes are displayed on the screen and on the right side a black area called "home". The experimenter demonstrates the first trial by going through the set of instructions step by step and the subject practices on the next three trials (each of these trials also consist of 3 coloured boxes) in which they must find the blue token hidden in each of the boxes in order to move onto the next trial. After the first set of four trials made up of 3 boxes each is complete and

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[47] "CANTAB" is a neuropsychological testing system offering sensitive and specific cognitive assessment, administered via a touch-screen from a computer running Windows. It is comprised of a battery of 13 tests of cognition, however only the SWM test was used for the purposes of this study.

the participant feels comfortable with the task, the actual test begins. The test trials consist of four trials with 4 boxes, four trials with 6 boxes, and four trials with 8 boxes. After completion of the last trial the computer test automatically stops and the participants are told they are finished. The computer records the number of errors made.

**Dependent Variables Measured in the Spatial Working Memory Task**

1) SWM Between errors: between errors are defined as the number of times the subject revisits a box in which a token has previously been found.

2) SWM Within errors: within errors are defined as the number of errors made within a search, i.e. the number of times a subject revisits a box already found to be empty during the same search.

3) SWM Strategy: Owen et al. (1990) have suggested that an efficient strategy for completing this task is to follow a predetermined sequence by beginning with a specific box and then, once a blue token has been found, to return to that box to start the new search sequence. An estimate of the use of this strategy is obtained by counting the number of times the subject begins a new search with the same box. A high score denotes poor use of this strategy and a low score denotes effective use.

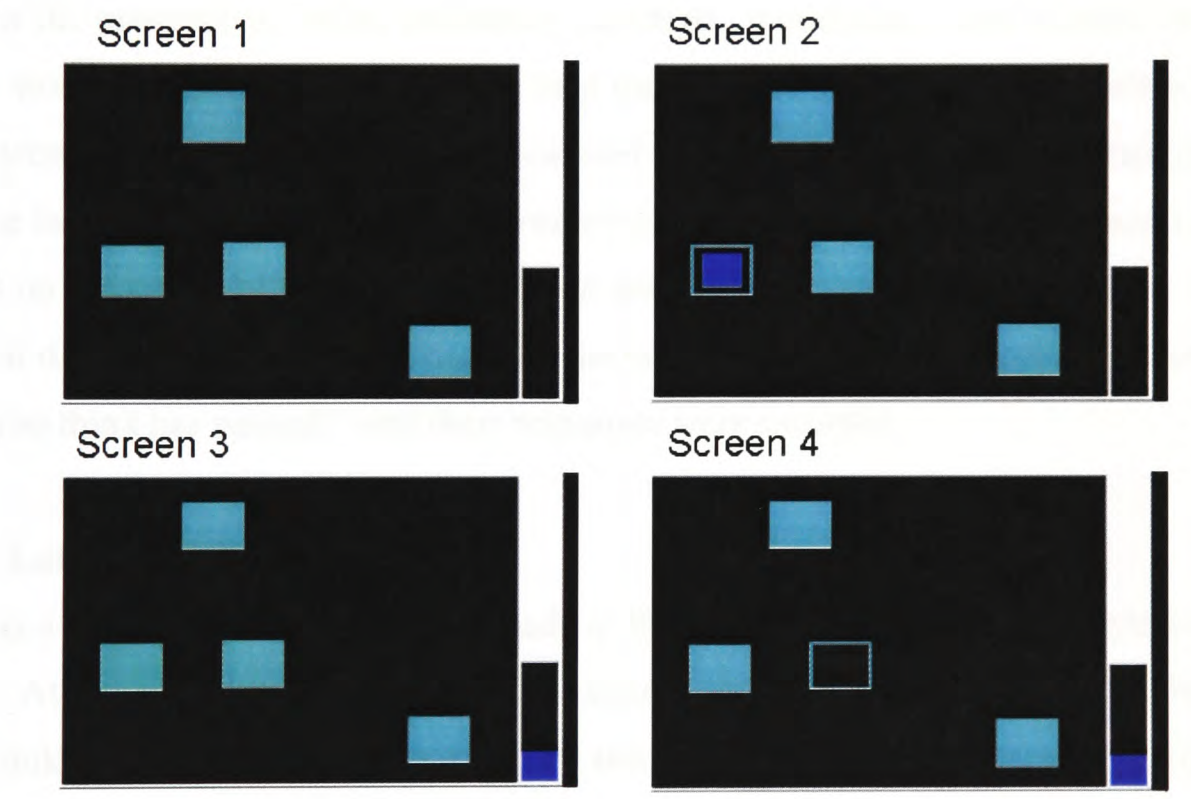


**Figure 2.4 Example of SWM task**: Screen 1 is what the participant sees initially. Screen 2 is what appears when the participants chooses a box containing a blue token and Screen 3 is shown after they place the blue token in "home" on the right of the screen. Screen 4 is shown as they continue to choose. This time there is no blue token in the chosen box so they must try another one and so on until all four tokens are found and "home" is completely full, at which point they go onto the next trial.

### 2.3.2.4 Time Perception Task

Time perception was measured in order to examine the relationship between impulsivity and time perception and to investigate the underlying brain mechanisms involved in short-term time perception (see Sections 1.11.2 & 1.11.3). For all tasks, participants were asked not to look at their watch or a clock. The time perception task was made up of three parts; time estimation, time production, and time pacing. See Appendix 17 for all time perception instructions.

#### 2.3.2.4.1 Time Estimation Task

Participants were asked to estimate time intervals during which they were distracted by reading random numbers off of a computer screen. Participants sat facing the computer monitor and during each trial they were required to read numbers (1-9) aloud in order to prevent subvocal counting. Number stimuli were presented in a random sequence throughout each predetermined interval. The rate of the stimulus presentation was variable, ranging in presentation time from 100 to 2900 milliseconds, and was predetermined regardless of participants' response rate. Stimuli were presented at random times to prevent participants using pacing as a marker for time. Stimulus presentation and timing were controlled by a computer program specifically designed for this task.

There was one retrospective interval and the rest were prospective. In the retrospective case participants were simply asked to read aloud each consecutive number that appeared on the centre of the computer screen and were not told it was a time estimation task. They were then presented with one 10 second interval and asked at the end of the interval how much time they thought had passed from the moment the trial began (a green cross appeared on the centre of the screen) to the moment the trial ended (a red cross appeared on the centre of the screen). Their response was then recorded.

In the prospective verbal estimation paradigm, participants were warned before each trial that they would be asked to estimate how long the trial had lasted. Time intervals were 10, 30, 60, and 90 seconds. Each time interval was presented twice in a random sequence making up 8 trials in all. At the beginning of the task participants were told to read aloud each consecutive number that appeared on the centre of the computer screen and that they would be asked at the end of the trial how much time they thought had passed. At the end of each trial they were then asked "How much time do you think has passed?" and their responses were recorded.

#### 2.3.2.4.2 Long-Term Time Estimation

There was a long-term time estimation made at the end of the entire time experiment (at about 20 minutes). At the end of the time estimation experiment, participants were asked "How much time do you think has passed from the moment we started the time task until now?" Their response was recorded and compared to the actual time that had passed, which was kept track of on a wristwatch.

#### 2.3.2.4.3 Time Production Task

Participants performed the same task as in the time estimation except they were asked to indicate when they thought a predetermined time interval was over. Thus, they were producing rather than estimating time intervals. Time intervals and number of trials were the same as in the time estimation task except there was no retrospective time interval. Participants were asked to read the randomly presented numbers (1-9), that ranged in presentation time from 100 to 2900 milliseconds, off of the computer screen and to say stop when they thought that x number of seconds had passed (they were asked to produced 10, 30, 60 and 90 second intervals two times each in randomised

order). The computer program was set to keep producing numbers for up to 5 minutes. When the participant said stop, the experimenter pressed the "Q" key and the computer program stopped running numbers and recorded how many seconds had passed from the beginning of that particular trial until the "Q" key was pressed. For each time interval, the computer recorded time interval was compared to the actual time interval participants were asked to produce.

**2.3.2.4.4 Time Pacing Task**

Participants were asked to count out loud starting from 1 going upward consecutively at what they felt was a 1/second rate and to stop counting when the experimenter said "stop". No distracter task was used. Time intervals were the same as for the time estimation and production tasks, namely 10, 30, 60, and 90 seconds, but each interval was only presented once in a random sequence. Participants were asked to start counting from 1 at the beginning of each new trial. The actual clock time was kept track of on a stop watch, by the experimenter, out of the participants' view. The experimenter said "stop" when the stop watch reached the time of the particular interval that was being tested. The number the participant arrived at when the experimenter said stop was then recorded and compared to the actual interval time.

**Dependent Variables Measured of Time Perception Task**

1) Retrospective time estimation at 10 seconds: the number of seconds estimated at the 10 second time interval when participants were not told it was a time estimation task.

2) Time estimation at 10 seconds (prospective): the average number of seconds estimated across the two 10 second time intervals when participants were told it was a time estimation task

3) Time estimation at 30 seconds (prospective): same as above but for 30 seconds.

4) Time estimation at 60 seconds (prospective): same as above but for 60 seconds.

5) Time estimation at 90 seconds (prospective): same as above but for 90 seconds.

7) Total time estimation: the sum of the average times estimated at 10, 30, 60, and 90 seconds divided by 190 (190 = the total number of seconds that actually passed).

8) Long-term time estimation: the difference between the actual time and the participants' estimate of the time that passed from the beginning to the end of the entire time perception experiment.

9) Time production at 10 seconds: the average number of seconds produced across the two 10 second time intervals.

10) Time production at 30 seconds: same as above but for 30 seconds.

11) Time production at 60 seconds: same as above but for 60 seconds.

12) Time production at 90 seconds: same as above but for 90 seconds.

13) Total time production: the sum of the average times produced at 10, 30, 60, and 90 seconds divided by 190 (190 = the total number of seconds participants were asked produce)

14) Average concept of a second (Cognitive Pace): the total number of seconds that actually passed across all four time intervals (10+30+60+90=190 seconds) divided by the total number of seconds

counted by the participant across all four time intervals. This number gives the participants' average concept of a second. A number greater than one means they have a slow cognitive pace. In other words, they think a second is longer than it actual is. A number less than one means they have a fast cognitive pace and think a second is less than the actual clock second.

# Chapter 3: RESULTS

This chapter is divided into three major sections. In the first section, various data anomalies are discussed and means and standard deviations for the variables for all participants are reported. In the second section correlations between the most salient variables for the entire sample are reported in order to examine the interactions between the different tests. Finally, in the last section of this chapter, results of one-way Analyses of Variance and Least Significant Difference post-hoc tests are reported, which were used to determine group differences on all of the variables. The data were analysed in SPSS version 11 (SPSS inc.) and an alpha level of .05 was used for all statistical tests unless otherwise stated.

## 3.1 Preliminary Analyses

### 3.1.1 Data Anomalies

SPSS descriptive statistical analyses (boxplots) were used to evaluate possible outliers. These analyses were performed for each measure taken across all subjects. Using standard SPSS procedures as described by Kinnear & Gray (2000; p. 98), univariate extreme outliers were identified when they were 3 or more interquartile ranges outside of the central interquartile range. Individual data points were then removed from the data set to create a new data set with outliers excluded upon which ANOVAs were performed. For each variable, two Analyses of Variance (ANOVA) were performed: one ANOVA with outliers included in the data set and another ANOVA performed on the data with outliers excluded. When results from both ANOVAs were significant, only the ANOVA with outliers included was reported. In the instance that an ANOVA with outliers included was significant, but the same ANOVA done with outliers excluded was not significant, a Kruskal-Wallis non-parametric test was performed as normality of that variable could not be presumed. In the instance that the Kruskal-Wallis test yielded significant results, only the original non-parametric ANOVA test results with outliers included was reported. If the Kruskal-Wallis yielded non-significant results, no results were reported for that variable. This procedure is thus a conservative way to ensure that the statistical results are well justified.

Missing data: Not all participants completed all tests. In some instances, participants were unable to complete certain tasks because they proved too difficult for them, thus accounting for some of the missing data. In addition, due to testing time constraints, the King's College Hospital patients were not given the behavioural tests [i.e. the reversal, MFFT, SWM, and time perception tasks; however, some reversal data previously collected on some of these patients by J. O'Doherty and J. Hornak (Rolls et al., 1994) was used]. King's College patients were also not given the BPD Questionnaire due to sensitivity issues.

### 3.1.2 Means and Standard Deviations

Table 3.1 presents the means and standard deviations for all variables for the entire sample. Tables 3.2 to 3.5 also present the means and standard deviations, but for normal, non-OFC lesion, OFC lesion, and BPD participants respectively.

**Table 3.1: Means and Standard Deviations for All Participants**

| Variable | *M* | *SD* | *N* |
|---|---|---|---|
| **Demographics** | | | |
| Age in years | 41.82 | 16.43 | 101 |
| Gender [1] | .66 | .48 | 101 |
| **Self-report impulsivity (BIS-11)** [2] | | | |
| Non-planning impulsivity | 26.58 | 6.68 | 101 |
| Motor impulsivity | 23.72 | 4.59 | 101 |
| Cognitive impulsivity | 17.38 | 4.16 | 101 |
| Total impulsivity score | 67.63 | 12.89 | 101 |
| **Personality questionnaire (BFI)** [3] | | | |
| Extraversion | 24.58 | 7.11 | 101 |
| Agreeableness | 33.58 | 6.64 | 101 |
| Conscientiousness | 31.68 | 7.43 | 101 |
| Neuroticism | 26.41 | 7.67 | 101 |
| Openness to experience | 34.78 | 7.77 | 101 |
| **Frontal Behaviour Questionnaire** [4] | | | |
| Total frontal behaviour score | 10.39 | 3.15 | 101 |
| **Subjective Emotion Questionnaire** [5] | | | |
| Sadness | 1.38 | .76 | 100 |
| Anger | 1.13 | .90 | 100 |
| Fear | .91 | .94 | 100 |
| Happiness | 1.76 | .79 | 100 |
| Disgust | .89 | .90 | 100 |
| Total subjective emotion score | 6.07 | 2.26 | 100 |
| **Emotional Change Questionnaire** [6] | | | |
| Change in Sadness | .35 | .71 | 52 |
| Change in Anger | .27 | .77 | 52 |
| Change in Fear | .00 | .71 | 52 |
| Change in Happiness | -.019 | .80 | 52 |
| Change in Disgust | .17 | .58 | 52 |
| Total number of emotions changed | 2.77 | 1.77 | 52 |
| **BPD Questionnaire** [7] | | | |
| Total BPD score | 8.07 | 4.86 | 60 |
| **Behavioural impulsivity (MFFT)** [8] | | | |
| Total number of errors on the MFFT | 12.43 | 8.76 | 79 |
| Mean time latency on the MFFT | 44.75 | 27.58 | 79 |
| Total errors per second on the MFFT | .53 | .72 | 79 |
| **Probabilistic reversal test** [9] | | | |
| Number of trials to reach criterion (to acquire S+) | 34.80 | 23.13 | 80 |
| Total pounds accumulated on reversal task | 756.26 | 3638.09 | 93 |
| Number of trials until first reversal | 30.61 | 16.83 | 89 |
| Total number of reversals | 2.956 | 1.38 | 93 |
| Punishment insensitivity | 5.42 | 6.47 | 93 |
| Reward insensitivity | 3.31 | 4.07 | 93 |
| **Spatial working memory task** [10] | | | |
| Between errors on spatial working memory | 35.72 | 28.56 | 81 |
| Within errors on spatial working memory | 3.72 | 9.36 | 81 |

| | | | |
|---|---|---|---|
| Strategy for spatial working memory | 33.38 | 6.32 | 81 |
| **Time perception task** [11] | | | |
| Retrograde time estimation for 10 seconds | 12.41 | 34.40 | 78 |
| Time estimation at 10 seconds | 9.20 | 14.93 | 78 |
| Time estimation at 30 seconds | 29.12 | 35.70 | 78 |
| Time estimation at 60 seconds | 57.35 | 47.95 | 78 |
| Time estimation at 90 seconds | 81.88 | 57.23 | 78 |
| Total time estimation | .93 | .76 | 78 |
| Time production at 10 seconds | 17.75 | 8.21 | 78 |
| Time production at 30 seconds | 44.72 | 20.59 | 78 |
| Time production at 60 seconds | 75.66 | 27.56 | 78 |
| Time production at 90 seconds | 107.06 | 42.62 | 78 |
| Total time production | 1.29 | .47 | 78 |
| Average in years concept of a second | 1.30 | .31 | 78 |
| Long-term time estimation | -4.42 | 12.25 | 77 |

***Note 1.*** *Gender*: men were coded 0, women 1.
***Note 2.*** The higher the mean, the higher the impulsivity.
***Note 3.*** The higher the mean, the more each trait is exhibited.
***Note 4.*** The higher the mean, the greater the number of "frontal" behaviours exhibited.
***Note 5.*** *Sadness, Anger, Fear, Happiness, Disgust*: the higher the mean, the more frequently each emotion is experienced. *Total subjective emotion score*: the higher the mean, the more emotional.
***Note 6.*** *Sadness, Anger, Fear, Happiness,* and *Disgust*: -1 = decrease in emotion, 0 = no change in emotion, and 1 = increase in emotion. *Total number of emotions changed*: the higher the mean, the greater the number of emotions changed.
***Note 7.*** The higher the mean, the greater the number of BPD traits exhibited.
***Note 8.*** *Number of errors on the MFFT* and *errors per second on the MFFT*: the higher the mean, the more impulsive. *Time latency on MFFT*: the higher the mean, the less impulsive.
***Note 9.*** *Acquisition of positive stimulus*: the higher the mean, the greater the number of trials required to acquire the positive stimulus. *Total pounds earned on reversal task*: the higher the mean, the more money earned. *Number of trials until first reversal*: the higher the mean, the greater the number of trials completed until reaching the first reversal. *Total number of reversals*: the higher the mean, the greater the number of reversals achieved. *Punishment insensitivity*, *reward insensitivity*: the higher the mean, the more insensitive.
***Note 10.*** *Between errors on SWM*, *within errors on SWM*: the higher the mean, the greater the number of errors made. *Strategy for spatial working memory*: the higher the mean, the worse the strategy used.
***Note 11.*** *Retrograde time estimation at 10 seconds*, *time estimation at 10, 30, 60, and 90 seconds, and total time estimation*: the higher the mean, the greater the number of seconds estimated. *Time production at 10, 30, 60, and 90 seconds and total time production*: the higher the mean, the greater the number of seconds produced. *Average concept of a second*: the higher the mean, the greater the average concept of a second. *Long-term time estimation*: the higher the mean, the greater the number of minutes estimated.

**Table 3.2: Means and Standard Deviations for Normal Participants**

| Variable | *M* | *SD* | *N* |
|---|---|---|---|
| **Demographics** | | | |
| Age in years | 40.28 | 20.51 | 39 |
| Gender [1] | .74 | .44 | 39 |
| **Self-report impulsivity (BIS-11)** [2] | | | |
| Non-planning impulsivity | 22.38 | 4.60 | 39 |
| Motor impulsivity | 22.05 | 3.53 | 39 |
| Cognitive impulsivity | 15.69 | 3.07 | 39 |
| Total impulsivity score | 60.13 | 9.46 | 39 |
| **Personality questionnaire (BFI)** [3] | | | |
| Extraversion | 25.74 | 6.81 | 39 |
| Agreeableness | 33.69 | 6.55 | 39 |
| Conscientiousness | 33.64 | 6.44 | 39 |
| Neuroticism | 23.38 | 6.83 | 39 |
| Openness to experience | 38.72 | 9.27 | 39 |
| **Frontal Behaviour Questionnaire** [4] | | | |
| Total frontal behaviour score | 9.25 | 1.95 | 39 |
| **Subjective Emotion Questionnaire** [5] | | | |
| Sadness | 1.15 | .63 | 39 |
| Anger | .74 | .55 | 39 |
| Fear | .62 | .67 | 39 |
| Happiness | 2.13 | .52 | 39 |
| Disgust | .62 | .54 | 39 |
| Total subjective emotion | 5.26 | 1.40 | 39 |
| **BPD Questionnaire** [6] | | | |
| Total BPD score | 5.18 | 3.20 | 17 |
| **Behavioural impulsivity (MFFT)** [7] | | | |
| Total number of errors on the MFFT | 8.21 | 6.01 | 39 |
| Mean time latency on the MFFT | 55.62 | 30.68 | 39 |
| Total errors per second on the MFFT | .27 | .47 | 39 |
| **Probabilistic reversal test** [8] | | | |
| Number of trials to reach criterion (to acquire S+) | 27.77 | 19.17 | 39 |
| Total pounds accumulated on reversal task | 2092.77 | 2603.86 | 39 |
| Number of trials until first reversal | 28.46 | 12.56 | 39 |
| Total number of reversals | 3.46 | .99 | 39 |
| Punishment insensitivity | 3.90 | 6.19 | 39 |
| Reward insensitivity | 2.05 | 2.02 | 39 |
| **Spatial working memory task** [9] | | | |
| Between errors on spatial working memory | 23.10 | 18.27 | 39 |
| Within errors on spatial working memory | 2.00 | 3.22 | 39 |
| Strategy for spatial working memory | 31.15 | 6.26 | 39 |
| **Time perception task** [10] | | | |
| Retrograde time estimation for 10 seconds | 6.92 | 3.67 | 39 |
| Time estimation at 10 seconds | 6.35 | 2.62 | 39 |
| Time estimation at 30 seconds | 20.58 | 10.28 | 39 |
| Time estimation at 60 seconds | 45.38 | 24.50 | 39 |
| Time estimation at 90 seconds | 65.00 | 33.40 | 39 |
| Total time estimation | .72 | .35 | 39 |
| Time production at 10 seconds | 17.99 | 5.35 | 39 |
| Time production at 30 seconds | 47.82 | 15.24 | 39 |
| Time production at 60 seconds | 83.91 | 26.18 | 39 |
| Time production at 90 seconds | 124.17 | 39.49 | 39 |
| Total time production | 1.44 | .42 | 39 |
| Average in years concept of a second | 1.36 | .322 | 39 |

| | | | |
|---|---|---|---|
| Long-term time estimation | -5.23 | 10.34 | 39 |

***Note 1.*** *Gender*: men were coded 0, women 1.
***Note 2.*** The higher the mean, the higher the impulsivity.
***Note 3.*** The higher the mean, the more each trait is exhibited.
***Note 4.*** The higher the mean, the greater the number of "frontal" behaviours exhibited.
***Note 5.*** *Sadness, Anger, Fear, Happiness, Disgust*: the higher the mean, the more frequently each emotion is experienced. *Total subjective emotion score*: the higher the mean, the more emotional.
***Note 6.*** The higher the mean, the greater the number of BPD traits exhibited.
***Note 7.*** *Number of errors on the MFFT* and *errors per second on the MFFT*: the higher the mean, the more impulsive. *Time latency on MFFT*: the higher the mean, the less impulsive.
***Note 8.*** *Acquisition of positive stimulus*: the higher the mean, the greater the number of trials required to acquire the positive stimulus. *Total pounds earned on reversal task*: the higher the mean, the more money earned. *Number of trials until first reversal*: the higher the mean, the greater the number of trials completed until reaching the first reversal. *Total number of reversals*: the higher the mean, the greater the number of reversals achieved. *Punishment insensitivity, reward insensitivity*: the higher the mean, the more insensitive.
***Note 9.*** *Between errors on SWM, within errors on SWM*: the higher the mean, the greater the number of errors made. *Strategy for spatial working memory*: the higher the mean, the worse the strategy used.
***Note 10.*** *Retrograde time estimation at 10 seconds, time estimation at 10, 30, 60, and 90 seconds, and total time estimation*: the higher the mean, the greater the number of seconds estimated. *Time production at 10, 30, 60, and 90 seconds and total time production*: the higher the mean, the greater the number of seconds produced. *Average concept of a second*: the higher the mean, the greater the average concept of a second. *Long-term time estimation*: the higher the mean, the greater the number of minutes estimated.

**Table 3.3: Means and Standard Deviations for Non-Orbitofrontal Lesion Participants**

| Variable | *M* | *SD* | *N* |
|---|---|---|---|
| **Demographics** | | | |
| Age in years | 45.95 | 15.12 | 20 |
| Gender [1] | .60 | .503 | 20 |
| **Self-report impulsivity (BIS-11)** [2] | | | |
| Non-planning impulsivity | 25.40 | 5.97 | 20 |
| Motor impulsivity | 21.85 | 5.17 | 20 |
| Cognitive impulsivity | 16.25 | 2.65 | 20 |
| Total impulsivity score | 63.30 | 9.80 | 20 |
| **Personality questionnaire (BFI)** [3] | | | |
| Extraversion | 25.70 | 6.31 | 20 |
| Agreeableness | 35.80 | 5.38 | 20 |
| Conscientiousness | 33.35 | 7.33 | 20 |
| Neuroticism | 23.05 | 5.94 | 20 |
| Openness to experience | 32.45 | 7.77 | 20 |
| **Frontal Behaviour Questionnaire** [4] | | | |
| Total frontal behaviour score | 8.85 | 1.91 | 20 |
| **Subjective Emotion Questionnaire** [5] | | | |
| Sadness | 1.16 | .60 | 19 |
| Anger | .74 | .56 | 19 |
| Fear | .68 | .75 | 19 |
| Happiness | 2.05 | .78 | 19 |
| Disgust | .79 | .92 | 19 |
| Total subjective emotion score | 5.42 | 1.80 | 19 |
| **Emotional Change Questionnaire** [6] | | | |
| Change in Sadness | .05 | .69 | 20 |
| Change in Anger | -.05 | .69 | 20 |
| Change in Fear | -.05 | .69 | 20 |
| Change in Happiness | .00 | .73 | 20 |
| Change in Disgust | .10 | .55 | 20 |
| Total number of emotions changed | 2.15 | 1.84 | 20 |
| **BPD Questionnaire** [7] | | | |
| Total BPD score | 4.10 | 2.33 | 10 |
| **Behavioural impulsivity (MFFT)** [8] | | | |
| Total number of errors on the MFFT | 18.22 | 7.35 | 9 |
| Mean time latency on the MFFT | 42.32 | 20.50 | 9 |
| Total errors per second on the MFFT | .54 | .32 | 9 |
| **Probabilistic reversal test** [9] | | | |
| Number of trials to reach criterion (to acquire S+) | 36.78 | 21.62 | 9 |
| Total pounds accumulated on reversal task | 1066.67 | 2707.81 | 15 |
| Number of trials until first reversal | 23.13 | 18.90 | 15 |
| Total number of reversals | 3.20 | 1.27 | 15 |
| Punishment insensitivity | 5.13 | 4.42 | 15 |
| Reward insensitivity | 3.87 | 5.03 | 15 |
| **Spatial working memory task** [10] | | | |
| Between errors on spatial working memory | 64.22 | 29.03 | 9 |
| Within errors on spatial working memory | 11.44 | 23.44 | 9 |
| Strategy for spatial working memory | 38.67 | 2.29 | 9 |
| **Time perception task** [11] | | | |
| Retrograde time estimation for 10 seconds | 8.63 | 9.05 | 8 |
| Time estimation at 10 seconds | 5.63 | 2.43 | 8 |
| Time estimation at 30 seconds | 23.52 | 14.15 | 8 |
| Time estimation at 60 seconds | 68.44 | 62.05 | 8 |
| Time estimation at 90 seconds | 103.44 | 79.11 | 8 |

| | | | |
|---|---|---|---|
| Total time estimation | 1.06 | .75 | 8 |
| Time production at 10 seconds | 18.59 | 5.06 | 8 |
| Time production at 30 seconds | 39.93 | 16.81 | 8 |
| Time production at 60 seconds | 75.51 | 33.99 | 8 |
| Time production at 90 seconds | 96.31 | 47.27 | 8 |
| Total time production | 1.21 | .52 | 8 |
| Average in years concept of a second | 1.31 | .44 | 7 |
| Long-term time estimation | -5.00 | 8.98 | 7 |

***Note 1.*** *Gender*: men were coded 0, women 1.
***Note 2.*** The higher the mean, the higher the impulsivity.
***Note 3.*** The higher the mean, the more each trait is exhibited.
***Note 4.*** The higher the mean, the greater the number of "frontal" behaviours exhibited.
***Note 5.*** *Sadness, Anger, Fear, Happiness, Disgust*: the higher the mean, the more frequently each emotion is experienced. *Total subjective emotion score*: the higher the mean, the more emotional.
***Note 6.*** *Sadness, Anger, Fear, Happiness,* and *Disgust*: -1 = decrease in emotion, 0 = no change in emotion, and 1 = increase in emotion. *Total number of emotions changed*: the higher the mean, the greater the number of emotions changed.
***Note 7.*** The higher the mean, the greater the number of BPD traits exhibited.
***Note 8.*** *Number of errors on the MFFT* and *errors per second on the MFFT*: the higher the mean, the more impulsive. *Time latency on MFFT*: the higher the mean, the less impulsive.
***Note 9.*** *Acquisition of positive stimulus*: the higher the mean, the greater the number of trials required to acquire the positive stimulus. *Total pounds earned on reversal task*: the higher the mean, the more money earned. *Number of trials until first reversal*: the higher the mean, the greater the number of trials completed until reaching the first reversal. *Total number of reversals*: the higher the mean, the greater the number of reversals achieved. *Punishment insensitivity, reward insensitivity*: the higher the mean, the more insensitive.
***Note 10.*** *Between errors on SWM, within errors on SWM*: the higher the mean, the greater the number of errors made. *Strategy for spatial working memory*: the higher the mean, the worse the strategy used.
***Note 11.*** *Retrograde time estimation at 10 seconds, time estimation at 10, 30, 60, and 90 seconds, and total time estimation*: the higher the mean, the greater the number of seconds estimated. *Time production at 10, 30, 60, and 90 seconds and total time production*: the higher the mean, the greater the number of seconds produced. *Average concept of a second*: the higher the mean, the greater the average concept of a second. *Long-term time estimation*: the higher the mean, the greater the number of minutes estimated.

**Table 3.4: Means and Standard Deviations for Orbitofrontal Participants**

| Variable | *M* | *SD* | *N* |
|---|---|---|---|
| **Demographics** | | | |
| Age in years | 48.65 | 9.98 | 23 |
| Gender [1] | .43 | .59 | 23 |
| **Self-report impulsivity (BIS-11)** [2] | | | |
| Non-planning impulsivity | 29.09 | 6.18 | 23 |
| Motor impulsivity | 24.78 | 3.89 | 23 |
| Cognitive impulsivity | 17.57 | 4.45 | 23 |
| Total impulsivity score | 71.43 | 9.88 | 23 |
| **Personality questionnaire (BFI)** [3] | | | |
| Extraversion | 27.83 | 5.76 | 23 |
| Agreeableness | 34.35 | 5.10 | 23 |
| Conscientiousness | 33.65 | 5.33 | 23 |
| Neuroticism | 26.26 | 6.16 | 23 |
| Openness to experience | 32.83 | 8.51 | 23 |
| **Frontal Behaviour Questionnaire** [4] | | | |
| Total frontal behaviour score | 11.30 | 3.75 | 23 |
| **Subjective Emotion Questionnaire** [5] | | | |
| Sadness | 1.30 | .76 | 23 |
| Anger | 1.39 | .89 | 23 |
| Fear | .57 | .59 | 23 |
| Happiness | 1.65 | .77 | 23 |
| Disgust | .83 | .88 | 23 |
| Total subjective emotion score | 5.74 | 2.17 | 23 |
| **Emotional Change Questionnaire** [6] | | | |
| Change in Sadness | .39 | .722 | 23 |
| Change in Anger | .34 | .83 | 23 |
| Change in Fear | -.17 | .65 | 23 |
| Change in Happiness | .17 | .88 | 23 |
| Change in Disgust | .08 | .59 | 23 |
| Total number of emotions changed | 3.00 | 1.75 | 23 |
| **BPD Questionnaire** [7] | | | |
| Total BPD score | 7.79 | 4.69 | 14 |
| **Behavioural impulsivity (MFFT)** [8] | | | |
| Total number of errors on the MFFT | 21.00 | 9.94 | 12 |
| Mean time latency on the MFFT | 26.92 | 15.82 | 12 |
| Total errors per second on the MFFT | 1.20 | 1.16 | 12 |
| **Probabilistic reversal test** [9] | | | |
| Number of trials to reach criterion (to acquire S+) | 41.00 | 22.29 | 13 |
| Total pounds accumulated on reversal task | -2074.90 | 4885.91 | 20 |
| Number of trials until first reversal | 32.88 | 21.21 | 16 |
| Total number of reversals | 1.95 | 1.61 | 20 |
| Punishment insensitivity | 9.50 | 8.43 | 20 |
| Reward insensitivity | 5.35 | 5.02 | 20 |
| **Spatial working memory task** [10] | | | |
| Between errors on spatial working memory | 65.79 | 29.49 | 14 |
| Within errors on spatial working memory | 6.64 | 11.08 | 14 |
| Strategy for spatial working memory | 37.21 | 4.98 | 14 |
| **Time perception task** [11] | | | |
| Retrograde time estimation for 10 seconds | 38.31 | 81.06 | 13 |
| Time estimation at 10 seconds | 23.88 | 33.36 | 13 |
| Time estimation at 30 seconds | 58.07 | 72.59 | 13 |
| Time estimation at 60 seconds | 85.65 | 86.37 | 13 |
| Time estimation at 90 seconds | 109.19 | 87.77 | 13 |

| | | | |
|---|---|---|---|
| Total time estimation | 1.46 | 1.44 | 13 |
| Time production at 10 seconds | 20.10 | 17.28 | 13 |
| Time production at 30 seconds | 46.43 | 40.04 | 13 |
| Time production at 60 seconds | 66.13 | 34.54 | 13 |
| Time production at 90 seconds | 83.86 | 45.26 | 13 |
| Total time production | 1.14 | .67 | 13 |
| Average in years concept of a second | 1.13 | .23 | 13 |
| Long-term time estimation | -6.69 | 17.78 | 13 |

***Note 1.*** *Gender*: men were coded 0, women 1.
***Note 2.*** The higher the mean, the higher the impulsivity.
***Note 3.*** The higher the mean, the more each trait is exhibited.
***Note 4.*** The higher the mean, the greater the number of "frontal" behaviours exhibited.
***Note 5.*** *Sadness, Anger, Fear, Happiness, Disgust*: the higher the mean, the more frequently each emotion is experienced. *Total subjective emotion score*: the higher the mean, the more emotional.
***Note 6.*** *Sadness, Anger, Fear, Happiness,* and *Disgust*: -1 = decrease in emotion, 0 = no change in emotion, and 1 = increase in emotion. *Total number of emotions changed*: the higher the mean, the greater the number of emotions changed.
***Note 7.*** The higher the mean, the greater the number of BPD traits exhibited.
***Note 8.*** *Number of errors on the MFFT* and *errors per second on the MFFT*: the higher the mean, the more impulsive. *Time latency on MFFT*: the higher the mean, the less impulsive.
***Note 9.*** *Acquisition of positive stimulus*: the higher the mean, the greater the number of trials required to acquire the positive stimulus. *Total pounds earned on reversal task*: the higher the mean, the more money earned. *Number of trials until first reversal*: the higher the mean, the greater the number of trials completed until reaching the first reversal. *Total number of reversals*: the higher the mean, the greater the number of reversals achieved. *Punishment insensitivity, reward insensitivity*: the higher the mean, the more insensitive.
***Note 10.*** *Between errors on SWM, within errors on SWM*: the higher the mean, the greater the number of errors made. *Strategy for spatial working memory*: the higher the mean, the worse the strategy used.
***Note 11.*** *Retrograde time estimation at 10 seconds, time estimation at 10, 30, 60, and 90 seconds, and total time estimation*: the higher the mean, the greater the number of seconds estimated. *Time production at 10, 30, 60, and 90 seconds and total time production*: the higher the mean, the greater the number of seconds produced. *Average concept of a second*: the higher the mean, the greater the average concept of a second. *Long-term time estimation*: the higher the mean, the greater the number of minutes estimated.

**Table 3.5: Means and Standard Deviations for Borderline Personality Disorder Participants**

| Variable | *M* | *SD* | *N* |
|---|---|---|---|
| **Demographics** | | | |
| Age in years | 32.37 | 8.36 | 19 |
| Gender [1] | .95 | .22 | 19 |
| **Self-report impulsivity (BIS-11)** [2] | | | |
| Non-planning impulsivity | 33.42 | 4.65 | 19 |
| Motor impulsivity | 27.84 | 3.79 | 19 |
| Cognitive impulsivity | 21.79 | 4.03 | 19 |
| Total impulsivity score | 83.00 | 10.13 | 19 |
| **Personality questionnaire (BFI)** [3] | | | |
| Extraversion | 17.11 | 4.86 | 19 |
| Agreeableness | 30.11 | 8.54 | 19 |
| Conscientiousness | 23.53 | 6.39 | 19 |
| Neuroticism | 36.32 | 2.98 | 19 |
| Openness to experience | 31.53 | 6.67 | 19 |
| **Frontal Behaviour Questionnaire** [4] | | | |
| Total frontal behaviour score | 13.27 | 3.28 | 19 |
| **Subjective Emotion Questionnaire** [5] | | | |
| Sadness | 2.16 | .68 | 19 |
| Anger | 2.00 | 1.05 | 19 |
| Fear | 2.16 | .95 | 19 |
| Happiness | .84 | .50 | 19 |
| Disgust | 1.63 | 1.11 | 19 |
| Total subjective emotion score | 8.79 | 2.25 | 19 |
| **Emotional Change Questionnaire** [6] | | | |
| Change in Sadness | .88 | .33 | 9 |
| Change in Anger | .77 | .44 | 9 |
| Change in Fear | .55 | .72 | 9 |
| Change in Happiness | -.55 | .52 | 9 |
| Change in Disgust | .55 | .52 | 9 |
| Total number of emotions changed | 3.55 | 1.23 | 9 |
| **BPD Questionnaire** [7] | | | |
| Total BPD score | 12.95 | 2.77 | 19 |
| **Behavioural impulsivity (MFFT)** [8] | | | |
| Total number of errors on the MFFT | 12.95 | 8.17 | 19 |
| Mean time latency on the MFFT | 34.84 | 19.86 | 19 |
| Total errors per second on the MFFT | .63 | .64 | 19 |
| **Probabilistic reversal test** [9] | | | |
| Number of trials to reach criterion (to acquire S+) | 44.05 | 28.41 | 19 |
| Total pounds accumulated on reversal task | 748.00 | 2984.91 | 19 |
| Number of trials until first reversal | 37.42 | 17.63 | 19 |
| Total number of reversals | 2.79 | 1.36 | 19 |
| Punishment insensitivity | 4.47 | 4.42 | 19 |
| Reward insensitivity | 3.32 | 4.63 | 19 |
| **Spatial working memory task** [10] | | | |
| Between errors on spatial working memory | 25.95 | 19.06 | 19 |
| Within errors on spatial working memory | 1.42 | 2.52 | 19 |
| Strategy for spatial working memory | 32.63 | 6.15 | 19 |
| **Time perception task** [11] | | | |
| Retrograde time estimation for 10 seconds | 7.28 | 6.34 | 18 |
| Time estimation at 10 seconds | 6.31 | 2.63 | 18 |
| Time estimation at 30 seconds | 29.19 | 30.17 | 18 |
| Time estimation at 60 seconds | 57.88 | 34.95 | 18 |
| Time estimation at 90 seconds | 89.15 | 53.18 | 18 |

| | | | |
|---|---|---|---|
| Total time estimation | .96 | .56 | 18 |
| Time production at 10 seconds | 15.12 | 2.85 | 18 |
| Time production at 30 seconds | 38.86 | 9.00 | 18 |
| Time production at 60 seconds | 64.71 | 15.36 | 18 |
| Time production at 90 seconds | 91.48 | 31.27 | 18 |
| Total time production | 1.11 | .28 | 18 |
| Average in years concept of a second | 1.30 | .20 | 18 |
| Long-term time estimation | -.78 | 12.67 | 18 |

***Note 1.*** *Gender*: men were coded 0, women 1.
***Note 2.*** The higher the mean, the higher the impulsivity.
***Note 3.*** The higher the mean, the more each trait is exhibited.
***Note 4.*** The higher the mean, the greater the number of "frontal" behaviours exhibited.
***Note 5.*** *Sadness, Anger, Fear, Happiness, Disgust*: the higher the mean, the more frequently each emotion is experienced. *Total subjective emotion score*: the higher the mean, the more emotional.
***Note 6.*** *Sadness, Anger, Fear, Happiness,* and *Disgust*: -1 = decrease in emotion, 0 = no change in emotion, and 1 = increase in emotion. *Total number of emotions changed*: the higher the mean, the greater the number of emotions changed.
***Note 7.*** The higher the mean, the greater the number of BPD traits exhibited.
***Note 8.*** *Number of errors on the MFFT* and *errors per second on the MFFT*: the higher the mean, the more impulsive. *Time latency on MFFT*: the higher the mean, the less impulsive.
***Note 9.*** *Acquisition of positive stimulus*: the higher the mean, the greater the number of trials required to acquire the positive stimulus. *Total pounds earned on reversal task*: the higher the mean, the more money earned. *Number of trials until first reversal*: the higher the mean, the greater the number of trials completed until reaching the first reversal. *Total number of reversals*: the higher the mean, the greater the number of reversals achieved. *Punishment insensitivity, reward insensitivity*: the higher the mean, the more insensitive.
***Note 10.*** *Between errors on SWM, within errors on SWM*: the higher the mean, the greater the number of errors made. *Strategy for spatial working memory*: the higher the mean, the worse the strategy used.
***Note 11.*** *Retrograde time estimation at 10 seconds, time estimation at 10, 30, 60, and 90 seconds, and total time estimation*: the higher the mean, the greater the number of seconds estimated. *Time production at 10, 30, 60, and 90 seconds and total time production*: the higher the mean, the greater the number of seconds produced. *Average concept of a second*: the higher the mean, the greater the average concept of a second. *Long-term time estimation*: the higher the mean, the greater the number of minutes estimated.

### 3.2 Correlative findings

Pearson Correlations (2-tailed) were performed across all populations to see the way in which the different tests and variables interacted. Correlations were not performed within each participant group because the number of variables being tested was too large compared to the number of participants in each group to yield reliable statistically significant results. Further, only the most salient variables from each test and questionnaire were used for the correlation analysis since the number of correlations performed could not be too large in relation to the number of participants tested as this could create many false positives. In addition, a Bonferroni Correction was applied in order to avoid a lot of spurious positives. After applying the Bonferroni Correction, the alpha level was lowered to .0005 to account for the number of comparisons being performed. Some correlations are mentioned where $p < .01$ if they were deemed to be interesting. The variables tested were[48]: total self-report impulsivity score; extraversion; agreeableness; conscientiousness; neuroticism; openness to experience; Frontal Behaviour Questionnaire score ("frontal" behaviour); total subjective emotion score (subjective emotion); BPD Questionnaire score (BPD traits); total errors/second on the MFFT (behavioural impulsivity); total pounds earned on the reversal task (reversal performance); between errors on the SWM task (SWM performance); total time estimation (subjective sense of time); and total time production (subjective sense of time).

These particular variables were chosen by taking only the total score or main measure on each test and excluded the more specific sub-scores or sub-variables. Note that all variables *within* each test were significantly correlated with each other thus allowing the researcher to look only at the most salient variable within each test for the correlation analysis. Also, the Emotional Change Questionnaire was not included in the correlation matrix as it was not administered to normal subjects. However, number of emotions changed (in terms of feeling capacity; either increased or decreased) since brain injury or onset of BPD was positively correlated with "frontal" behaviours and BPD traits ($r = .382$, $p = .005$ and $r = .599$, $p = .000$) across all patient groups.

See Table 3.6 for the correlation matrix containing the respective $r$ and $p$ values of the most salient 14 variables across all participants. The following relationships between variables were found:

Neuroticism, self-report impulsivity, "frontal" behaviour, subjective emotion, and BPD traits were all highly positively correlated with each other, $p = .000$ (see Table 3.6 for the respective $r$ values). Thus, someone who is highly impulsive is likely to be neurotic, highly emotional and to exhibit "frontal" behaviours and BPD traits. It is interesting to note that "frontal" behaviours and BPD traits are positively correlated with each other, which is in line with the hypothesis that the BPD syndrome involves a frontal lobe brain deficit. Further, the following relationships were also found:

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[48] The names inside the parentheses next to each variable are what variables are also referred to as.

As self-report impulsivity increases, behavioural impulsivity and subjective sense of time (decreased time production) increase ($r = .325$, $p = .003$ and $r = -.333$, $p = .003$) while extraversion and openness to experience decrease ($r = -.319$, $p = .001$ and $r = -.371$, $p = .000$).

As behavioural impulsivity increases, self-report impulsivity and "frontal" behaviour increase ($r = .325$, $p = .003$ and $r = .347$, $p = .002$) while reversal performance and SWM performance decrease ($r = -.326$, $p = .004$ and $r = .355$, $p = .001$).

As "frontal" behaviour increases, behavioural impulsivity and subjective sense of time (decreased time production) increase ($r = .347$, $p = .002$ and $r = -.295$, $p = .009$) while agreeableness and conscientiousness decrease ($r = -.467$, $p = .000$ and $r = -.307$, $p = .002$).

As BPD traits increases, conscientiousness decreases ($r = -.473$, $p = .000$).

As subjective emotionality increases, extraversion, conscientiousness, and reversal performance decrease ($r = -.347$, $p = .000$; $r = -.292$, $p = .003$; and $r = -.276$, $p = .008$).

As reversal performance *decreases*, subjective emotion, behavioural impulsivity, and between SWM errors increase ($r = -.276$, $p = .008$; $r = -.326$, $p = .004$; and $r = -.537$, $p = .000$).

As spatial working memory performance *decreases*, behavioural impulsivity and subjective sense of time (increased time estimation total) increase ($r = .355$, $p = .001$ and $r = .299$, $p = .008$) while openness to experience and reversal performance decrease ($r = -.317$, $p = .004$ and $r = -.537$, $p = .000$).

As subjective sense of time increases (in terms of decreased total time production), self-report impulsivity and "frontal" behaviour increase ($r = .333$, $p = .003$ and $r = .295$, $p = .009$) and (in terms of increased total time estimation), openness to experience and SWM performance (more between errors) decrease ($r = -.388$, $p = .000$ and $r = .299$, $p = .008$).

Also, it worth noting that as subjective sense of time increases (in terms of increased time estimation total) non-planning impulsivity (a sub-category of the report impulsivity questionnaire) and behavioural impulsivity (in terms of decreased time latency on the MFFT) increase ($r = .344$, $p = 002$ and $r = -.230$, $p < .05$).[49]

[49] These findings are not reported in the correlation matrix (Figure 3.6), as they are sub-variables of the main tests.

**Table 3.6: Correlation matrix of the most salient variables of each test/questionnaire across all subjects.**

| | | SRI | E | A | C | N | O | FBQ | SE | BPD | BI | total £s | BtSWM | TE total | TP total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SRI | *r* = | 1 | | | | | | | | | | | | | |
| | *p* = | . | | | | | | | | | | | | | |
| | N | 101 | | | | | | | | | | | | | |
| E | *r* = | **-.319** | 1 | | | | | | | | | | | | |
| | *p* = | **.001** | . | | | | | | | | | | | | |
| | N | **101** | 101 | | | | | | | | | | | | |
| A | *r* = | -.245 | **.282** | 1 | | | | | | | | | | | |
| | *p* = | .014 | **.004** | . | | | | | | | | | | | |
| | N | 101 | **101** | 101 | | | | | | | | | | | |
| C | *r* = | -.669 | .395 | .345 | 1 | | | | | | | | | | |
| | *p* = | .000 | .000 | .000 | . | | | | | | | | | | |
| | N | 101 | 101 | 101 | 101 | | | | | | | | | | |
| N | *r* = | .459 | -.571 | **-.334** | -.475 | 1 | | | | | | | | | |
| | *p* = | .000 | .000 | **.001** | .000 | . | | | | | | | | | |
| | N | 101 | 101 | **101** | 101 | 101 | | | | | | | | | |
| O | *r* = | -.371 | .216 | .056 | .229 | -.251 | 1 | | | | | | | | |
| | *p* = | .000 | .030 | .576 | .021 | .012 | . | | | | | | | | |
| | N | 101 | 101 | 101 | 101 | 101 | 101 | | | | | | | | |
| FBQ | *r* = | .505 | -.196 | -.467 | **-.307** | .455 | -.235 | 1 | | | | | | | |
| | *p* = | .000 | .049 | .000 | **.002** | .000 | .018 | . | | | | | | | |
| | N | 101 | 101 | 101 | **101** | 101 | 101 | 101 | | | | | | | |
| SE | *r* = | .429 | -.347 | -.212 | **-.292** | .591 | -.102 | .473 | 1 | | | | | | |
| | *p* = | .000 | .000 | .035 | **.003** | .000 | .314 | .000 | . | | | | | | |
| | N | 100 | 100 | 100 | **100** | 100 | 100 | 100 | 100 | | | | | | |
| BPD | *r* = | .571 | -.279 | -.320 | -.473 | .602 | -.007 | .707 | .612 | 1 | | | | | |
| | *p* = | .000 | .031 | .013 | .000 | .000 | .958 | .000 | .000 | . | | | | | |
| | N | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | | | | | |
| BI | *r* = | **.325** | .061 | -.167 | -.156 | .264 | -.213 | **.347** | .188 | .209 | 1 | | | | |
| | *p* = | **.003** | .591 | .142 | .170 | .019 | .060 | **.002** | .096 | .118 | . | | | | |
| | N | **79** | 79 | 79 | 79 | 79 | 79 | **79** | 79 | 57 | 79 | | | | |
| total £s | *r* = | -.195 | -.153 | -.144 | -.044 | -.069 | .125 | -.180 | **-.276** | -.025 | **-.326** | 1 | | | |
| | *p* = | .061 | .143 | .168 | .673 | .513 | .233 | .085 | **.008** | .851 | **.004** | . | | | |
| | N | 93 | 93 | 93 | 93 | 93 | 93 | 93 | **92** | 58 | **78** | 93 | | | |
| SWM | *r* = | .109 | .086 | .094 | .069 | -.090 | **-.317** | .143 | .030 | -.054 | **.355** | -.537 | 1 | | |
| | *p* = | .333 | .443 | .402 | .543 | .424 | **.004** | .204 | .793 | .683 | **.001** | .000 | . | | |
| | N | 81 | 81 | 81 | 81 | 81 | **81** | 81 | 81 | 59 | **79** | 80 | 81 | | |
| TE total | *r* = | .187 | -.011 | .104 | -.049 | .133 | -.388 | .120 | .102 | -.064 | .108 | -.127 | **.299** | 1 | |
| | *p* = | .101 | .926 | .365 | .672 | .247 | .000 | .295 | .374 | .640 | .353 | .267 | **.008** | . | |
| | N | 78 | 78 | 78 | 78 | 78 | 78 | 78 | 78 | 56 | 76 | 78 | **78** | 78 | |
| TP total | *r* = | **-.333** | .060 | .110 | .230 | -.259 | **.346** | **-.295** | -.260 | -.105 | -.203 | .232 | -.122 | -.507 | 1 |
| | *p* = | **.003** | .605 | .338 | .043 | .022 | **.002** | **.009** | .022 | .443 | .078 | .041 | .289 | .000 | . |
| | N | **78** | 78 | 78 | 78 | 78 | **78** | **78** | 78 | 56 | 76 | 78 | 78 | 78 | 78 |

Key to Table 3.6: ……..=Correlation significant at $p < .0005$ (2-tailed)
Bold font=Correlation significant at $p < .01$ (2-tailed)
total self-report impulsivity score=SRI, extraversion=E, agreeableness=A, conscientiousness=C, neuroticism=N, openness to experience=O, Frontal Behaviour Questionnaire score=FBQ, total subjective emotion score=SE, BPD Questionnaire score=BPD, errors/second on the MFFT (behavioural impulsivity)=BI, total pounds earned on the reversal task=total £s, between errors on the SWM task=BtSWM, total time estimation =TE total, and total time production=TP total

### 3.3 Main Analyses

A one-way analysis of variance (ANOVA) was performed on each of the variables to determine if mean scores differed significantly by group. In the instance where an ANOVA yielded a significant F-value, a Fisher's Least Significant Difference (LSD) post-hoc test was performed to identify the specific source of the difference. In the case where an ANOVA did not yield a significant F-value, no post-hoc test was conducted. All histograms presented, based on ANOVAs, show standard error bars of the mean. The standard error of the mean (standard deviation/$\sqrt{n}$) measures the standard amount of difference between the sample mean and the population mean that is reasonable to expect simply by chance.

In addition to an ANOVA being performed on each variable *with* outliers included, another ANOVA was performed on the data with outliers *excluded* to determine the role of outliers. When results from both ANOVAs were significant only the ANOVA with outliers included was reported. In the instance that an ANOVA with outliers included was significant, but the same ANOVA done on data with outliers excluded was non-significant, a Kruskal-Wallis non-parametric test was performed as normality of the variable could not be presumed. In the instance that the Kruskal-Wallis test yielded significant results, only the original ANOVA with outliers included was reported. If the Kruskal-Wallis test yielded non-significant results, no results were reported for that variable.

To investigate whether age differences between groups were a factor that could have influenced the results, Pearson correlations with age were performed on all variables across and within groups. In instances where a dependent variable was significantly correlated with age (across or within groups at $p < .05$), an ANCOVA with age identified as the covariate was performed (so as to explore the data with the effect of age removed). Results of ANOVAs are reported only in cases where ANCOVAs demonstrated significant effects of group membership (where age is the covariate; i.e. the factor of age was removed and there were still significant group differences). In one instance an extreme outlier was removed when running the ANCOVA for the spatial working memory within errors and punishment insensitivity variables.

To investigate whether gender differences between groups were a factor that could have influenced the results, Pearson correlations with gender were performed on all variables. This was performed in the context that 18 of the 19 BPD patients were female [BPD is diagnosed predominantly (75%) in females (APA, 1994)]. The only variable with any significant correlation with gender was the cognitive impulsivity subscale of the self-report impulsivity questionnaire. ANCOVAs with gender identified as the covariate were performed on all variables (so as to explore the data with the effect of gender removed) in order to account for any possible gender effects. ANCOVA analysis revealed that none of the significant differences between groups were due to the effect of gender. Thus, the results of the all of the significant ANOVAs are reported.

In addition, a third check was made to ensure that effects of gender did not lead to misinterpretation of the results. In this third check, all the data were re-analysed with ANOVAs,

but with no males included in any group. This was expected to lead to overall reductions of the levels of significance, as there were fewer subjects in the analyses. Even though there were fewer subjects in the different groups, all the ANOVAs that had shown significant group differences when all subjects were included still showed significant group differences when only the females were included in the analyses, with the exception of three variables in which the significance levels fell sufficiently to become non-significant. These three variables were, time latency on the MFFT [$F(3,53) = 2.57$, $p = 0.064$], the total pounds earned in the reversal task [$F(3,57) = 2.01$, $p = 0.123$], and punishment insensitivity in the reversal task [$F(3,57) = 0.608$, $p = 0.613$].

Note that performance with only females considered on the MFFT was still significantly different on the other two measures (errors/sec and number of errors) and that the time latency became only slightly insignificant. Further, only 4 female OFC patients and 6 female non-OFC patients were tested on the MFFT, so the decrease in significance level was not surprising, and the means for the females on the time latency variable were still showing the same trends as those found across all subjects. With respect to the reversal task, it is emphasised that there is still a significant group difference within female subjects in terms of the total number of reversals [$F(3,57) = 3.15$, $p = 0.032$] and, as with the overall analysis across all subjects, the post-hoc test showed that it was the OFC group and no other group that was significantly impaired at the reversal compared to normal subjects on this variable ($p = 0.008$). The fact that the total number of pounds earned, which is related to the total number of reversals made, did not reach the level of significance when only females were tested, again can be explained by the fact that the number of subjects tested in the OFC and the non-OFC group fell to only 7 in each group. Finally, to determine whether there was any difference in punishment insensitivity between OFC and normal controls within only the female subjects, a pre-planned Mann-Whitney U test was performed with these two groups with a significant result ($z = -1.65$, $p = 0.05$, one-tailed). The lack of high significance with this comparison may be due primarily to the small number of female OFC patients tested (n=7), and indeed, the mean punishment insensitivity of the male OFC patients (n=13) was 10.54, and of the females was 7.57, compared to means for the males in the normal group (n=10) of 3.4, and for the females in the normal group (n=29) of 4.07, so the trend was still in the same direction as it is across all subjects. None of the other groups differed from the normal controls in terms of punishment insensitivity.

Overall, the results of the data checks with respect to gender showed that none of the effects described here could be ascribed to any confounding effect of gender. Even when the analyses were performed with only females in each group, every questionnaire and task that had a significant group difference when performed across all subjects, also had a significant group difference within only females. In the three cases where the results within just the female subjects became non-significant, this lack of significance was ascribable to the small number of subjects remaining, as the means showed the same trends as in the analysis across all subjects.

### 3.3.1 Similarities between Deficits in Orbitofrontal Cortex and BPD Patients

In this section, only those results are discussed where both OFC and BPD patients behaved similarly in that they both were significantly impaired on these variables when compared to normal and non-OFC participants regardless of whether or not they differed significantly from each other. In all cases, OFC and BPD participants behaved similarly in that they both differed significantly form normal participants, and on some tests, also from non-OFC participants.

Both BPD and OFC patients were more impulsive in terms of self-report impulsivity (including non-planning, motor, and cognitive subscales), reported more inappropriate/"frontal" behaviours, BPD characteristics, and subjective anger, and less subjective happiness than normal and non-OFC participants with BPD participants being significantly more impaired than OFC participants on all of these measures. Further, both OFC and BPD participants were more behaviourally impulsive (in terms of errors/second, total errors, and mean time latency on the MFFT), had a faster subjective sense of time in terms of time production (producing more time in total and specifically at 60 and 90 seconds) and were less open to experience than normal participants with OFC participants being more impaired than BPD participants on the behavioural impulsivity errors/sec and total number of errors variables. See details below.

#### 3.3.1.1 Self-Report Impulsivity

ANOVAs were performed on the self-report impulsivity (SRI) variables (total self-report impulsivity score, and the non-planning impulsivity, motor impulsivity, and cognitive impulsivity subscales), which were generated from scores on the BIS-11. Results indicated that participants' scores on all four measures were significantly related to their group, $F(3,97) = 25.89$, $p = .000$, $F(3,97) = 20.82$, $p = .000$, $F(3,97) = 10.83$, $p = .000$, and $F(3,97) = 13.42$, $p = .000$ respectively.

Subsequent LSD tests were conducted on each of the variables. The results show that OFC and BPD participants were significantly more impulsive than both normal and non-OFC participants on all self-report impulsivity measures and BPD participants were more impulsive than OFC participants on all SRI measures. Further, normal and non-OFC participants did not differ significantly from each other on all four SRI variables. More specifically:

LSD post-hoc results of the *total SRI score* revealed that: 1) BPD participants' total SRI was significantly higher than that of all other participants, $p = .000$ and 2) OFC participants' total SRI was significantly higher than that of normal and non-OFC participants, $p = .000$ and $p < .01$ respectively. The mean total SRI score for each group is shown in Figure 3.1.

Post-hoc analysis of the *non-planning impulsivity* variable indicated that: 1) BPD participants' non-planning impulsivity was significantly higher than that of normal, non-OFC, and OFC participants, $p = .000$, $p = .000$, and $p = .01$ and 2) OFC participants' non-planning impulsivity was significantly higher than that of normal participants and non-OFC, $p = .000$ and $p < .05$ respectively. The mean non-planning impulsivity score by group is shown in Figure 3.2.

Post-hoc analysis of the *motor impulsivity* variable revealed that: 1) BPD participants' motor impulsivity was significantly higher than that of normal, non-OFC, and OFC participants, $p = .000$, $p = .000$, and $p < .05$ respectively and 2) OFC participants' motor impulsivity was significantly higher than that of normal and non-OFC participants, $p < .05$. The mean motor impulsivity score for each group is shown in Figure 3.3.

Results of the *cognitive impulsivity* variable post-hoc analysis revealed that: 1) BPD participants' cognitive impulsivity was significantly higher than that of participants in all other groups, $p = .000$ and 2) OFC participants' cognitive impulsivity was significantly higher than that of normal participants, $p < .05$ but OFC participants were not significantly different than non-OFC participants. The mean cognitive impulsivity score for each group is shown in Figure 3.4.

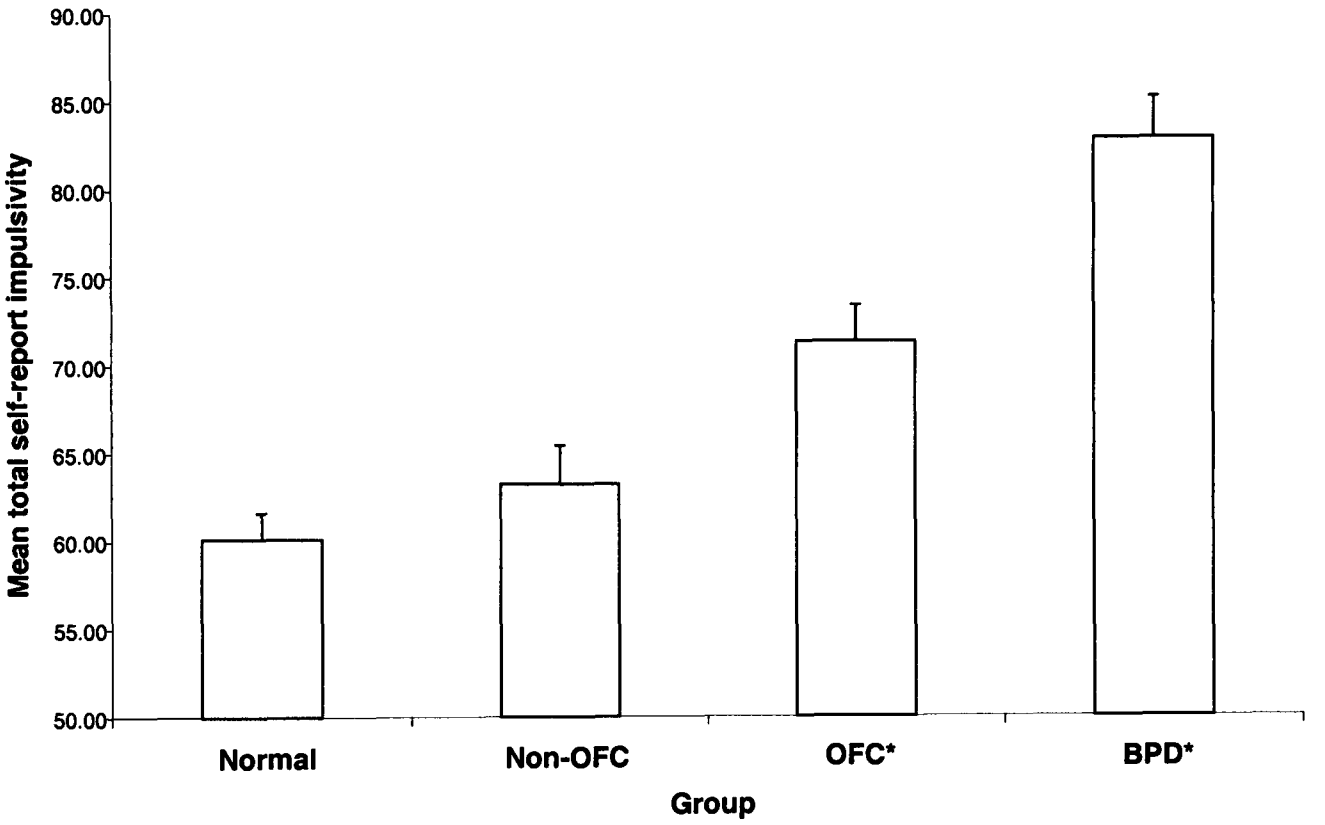



**Figure 3.1**: Histogram of the mean total score on the self-report impulsivity questionnaire across all four groups. OFC and BPD participants reported significantly more self-report impulsivity than did normal and non-OFC participants and BPD patients reported being significantly more impulsive than OFC patients.

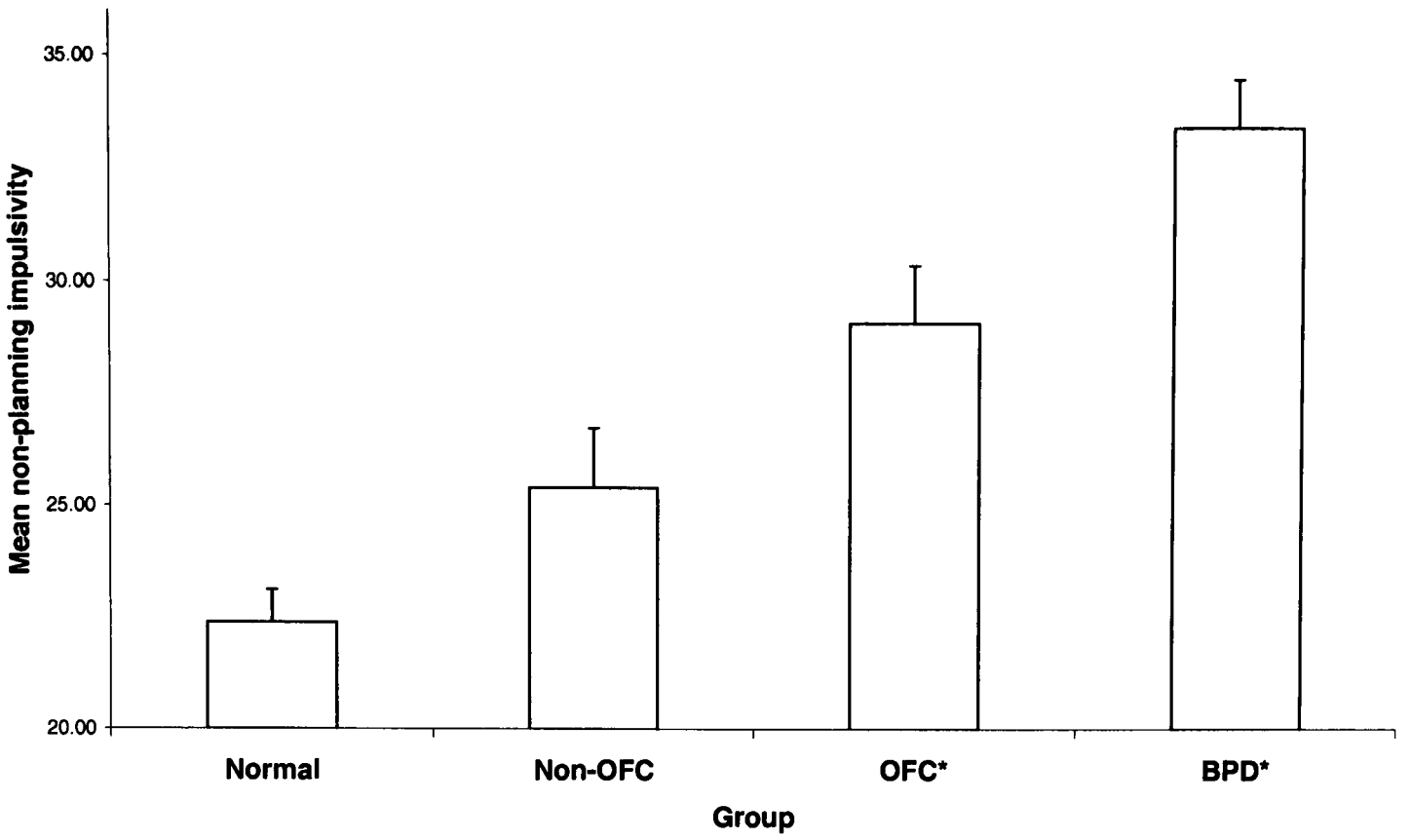



**Figure 3.2**: Histogram of the mean non-planning impulsivity sub-score on the SRI questionnaire across all four groups. OFC and BPD participants reported significantly more non-planning impulsivity than did normal and non-OFC participants and BPD patients reported significantly more non-planning impulsivity than OFC patients.




**Figure 3.3**: Histogram of the mean motor impulsivity sub-score on the SRI questionnaire across all four groups. OFC and BPD participants reported significantly more motor impulsivity than did normal and non-OFC participants and BPD patients reported significantly more motor impulsivity than OFC patients.

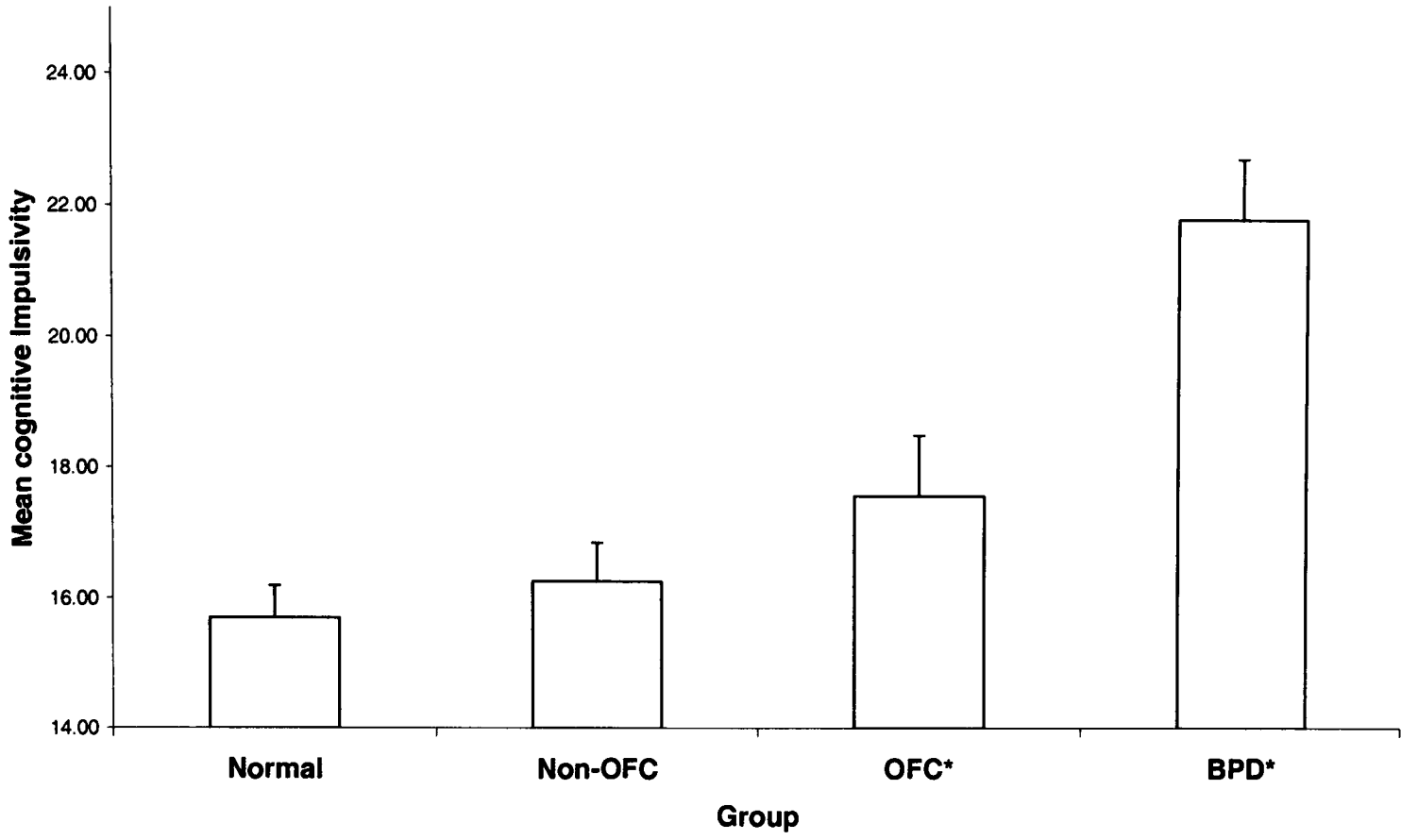



**Figure 3.4**: Histogram of the mean cognitive impulsivity sub-score on the SRI questionnaire across all four groups. BPD participants reported significantly more cognitive impulsivity than all other groups and OFC patients reported significantly more cognitive impulsivity than normal participants.

### 3.3.1.2 Behavioural Impulsivity

ANOVAs done on each of the Behavioural Impulsivity variables (errors per second on the Matching Familiar Figures Test [MFFT], number of errors on the MFFT, and time latency on the MFFT) indicated that participants' scores differed significantly by group on all three measures, $F(3,75) = 6.49$, $p = .001$, $F(3,75) = 11.49$, $p = .000$, and $F(3,75) = 5.28$, $p = .002$.

Subsequent post-hoc analysis revealed that OFC and BPD participants were more behaviourally impulsive than normal participants on all three measures with OFC participants being more impulsive than BPD participants on all but the time latency measure. Further, normal and non-OFC participants did not differ significantly from each other on all but the total number of errors variable where non-OFC participants were more impaired than normal participants. More specifically:

LSD post-hoc analysis of the *total errors per second* variable indicated that: 1) Participants with OFC damage were more behaviourally impulsive in terms of making significantly more errors and choosing the stimuli in a shorter amount of time than normal, non-OFC, and BPD patients, $p = .000$, $p < .05$, and $p < .05$ respectively and 2) BPD participants made significantly more errors and made faster choices of stimuli than normal subjects, $p < .05$. The mean total errors per second score for each group is shown in Figure 3.5.

LSD analysis of the *total number of errors* variable revealed that: 1) OFC, BPD, and non-OFC participants made significantly more errors on the MFFT than normal participants, $p = .000$, $p = .000$, and $p < .05$ respectively and 2) OFC participants made significantly more errors than BPD participants, $p = .004$. The mean total number of errors for each group is shown in Figure 3.6.

Post-hoc analyses of the *time latency* variable indicated that OFC and BPD participants time latency was significantly lower (indicating more impulsive behaviour) than that of normal participants, $p = .001$ and $p = .005$ respectively. The mean time latency (in seconds) to choose the first stimulus on each trial by group is shown in Figure 3.7.

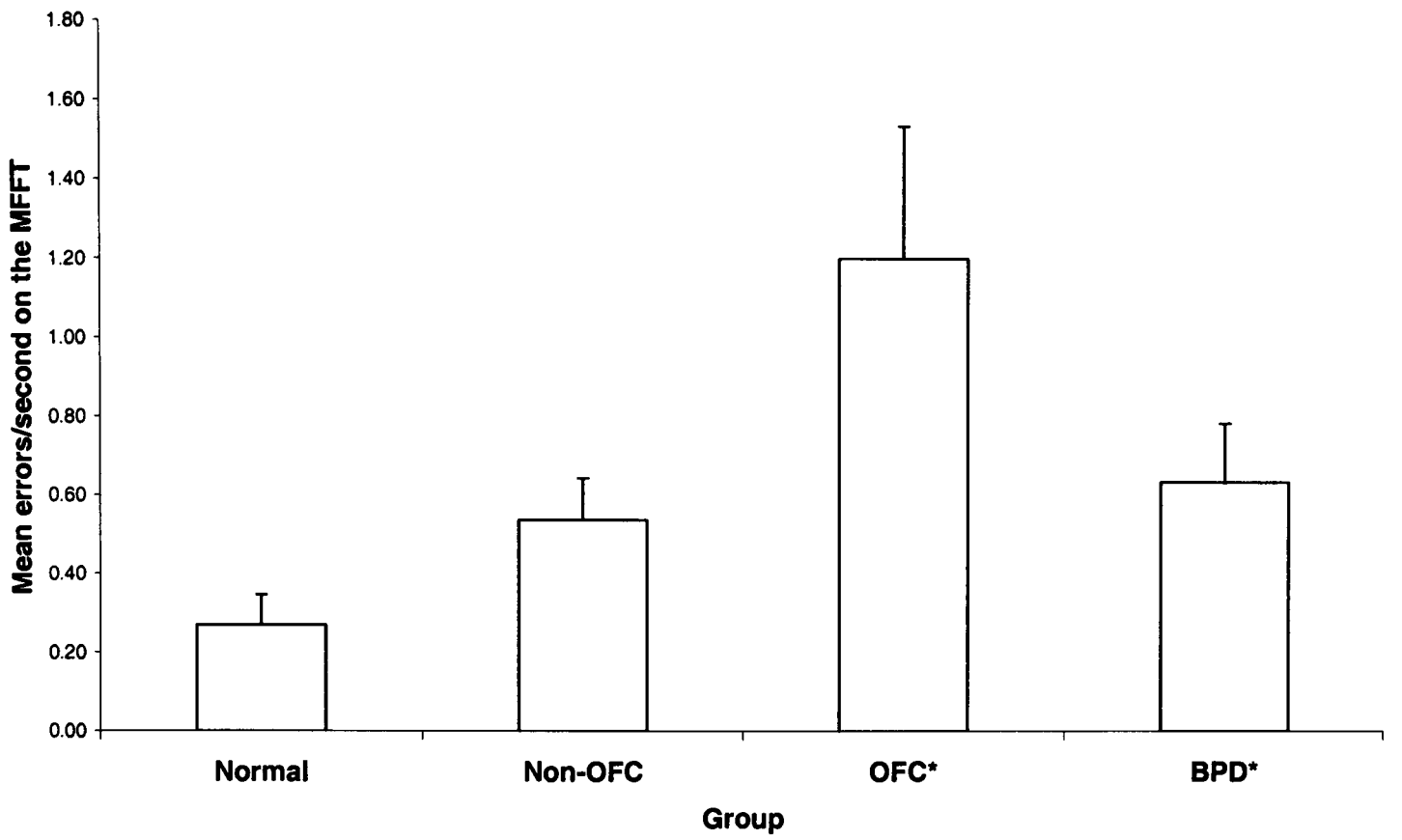



**Figure 3.5:** Histogram of mean total errors made divided by the average number of seconds taken to make the first choice of a stimulus on the MFFT across all groups. The higher the score the more behaviourally impulsive (i.e. the more errors made and the less time taken to choose a stimulus). Both OFC and BPD patients were significantly more impulsive than normal participants and OFC patients were more impulsive than non-OFC and BPD participants as well.

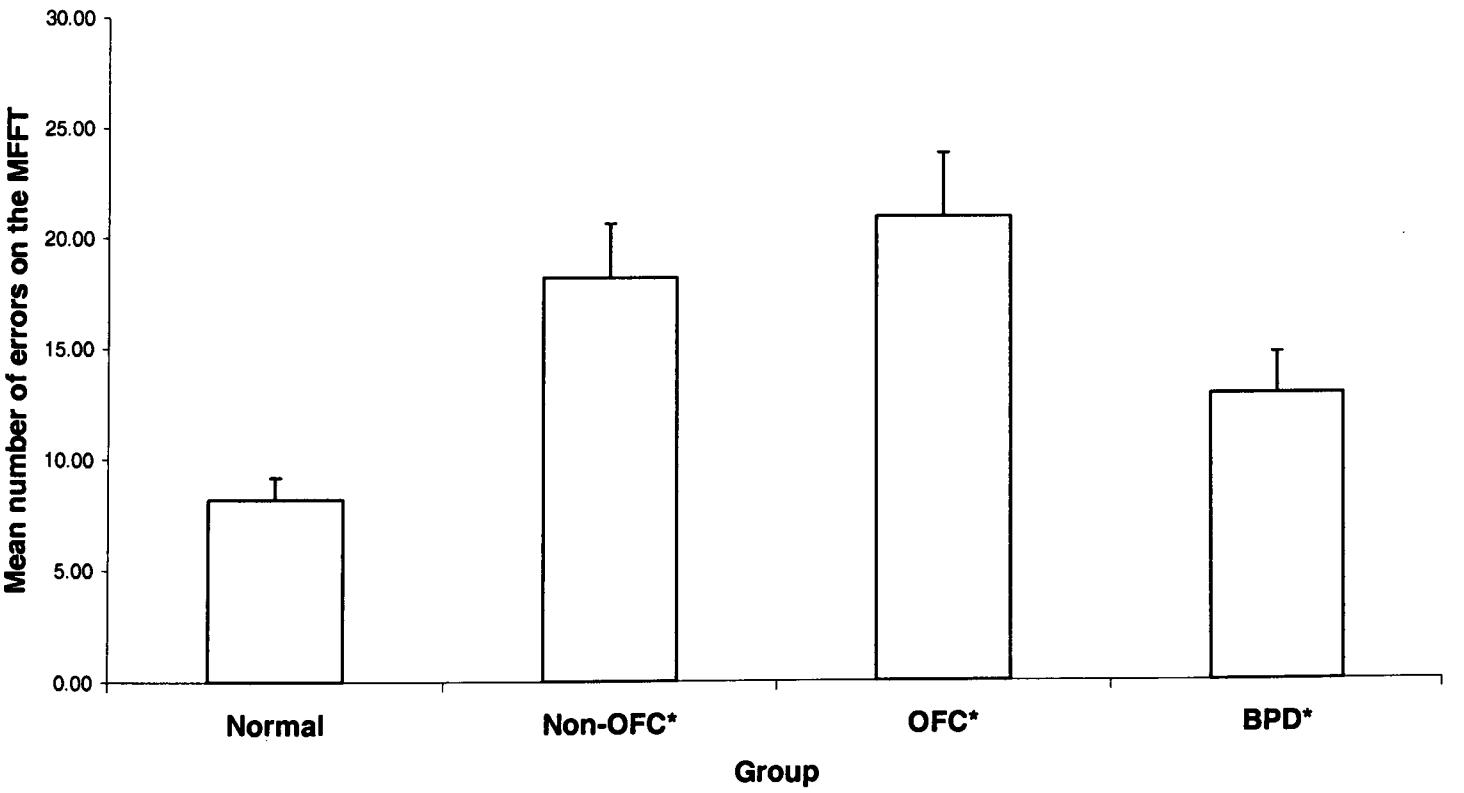



**Figure 3.6:** Histogram of mean total number of errors on the MFFT across all groups. The more errors made, the more behaviourally impulsive. OFC, BPD, and non-OFC participants made significantly more errors than normal participants and OFC patients made significantly more errors than BPD participants.

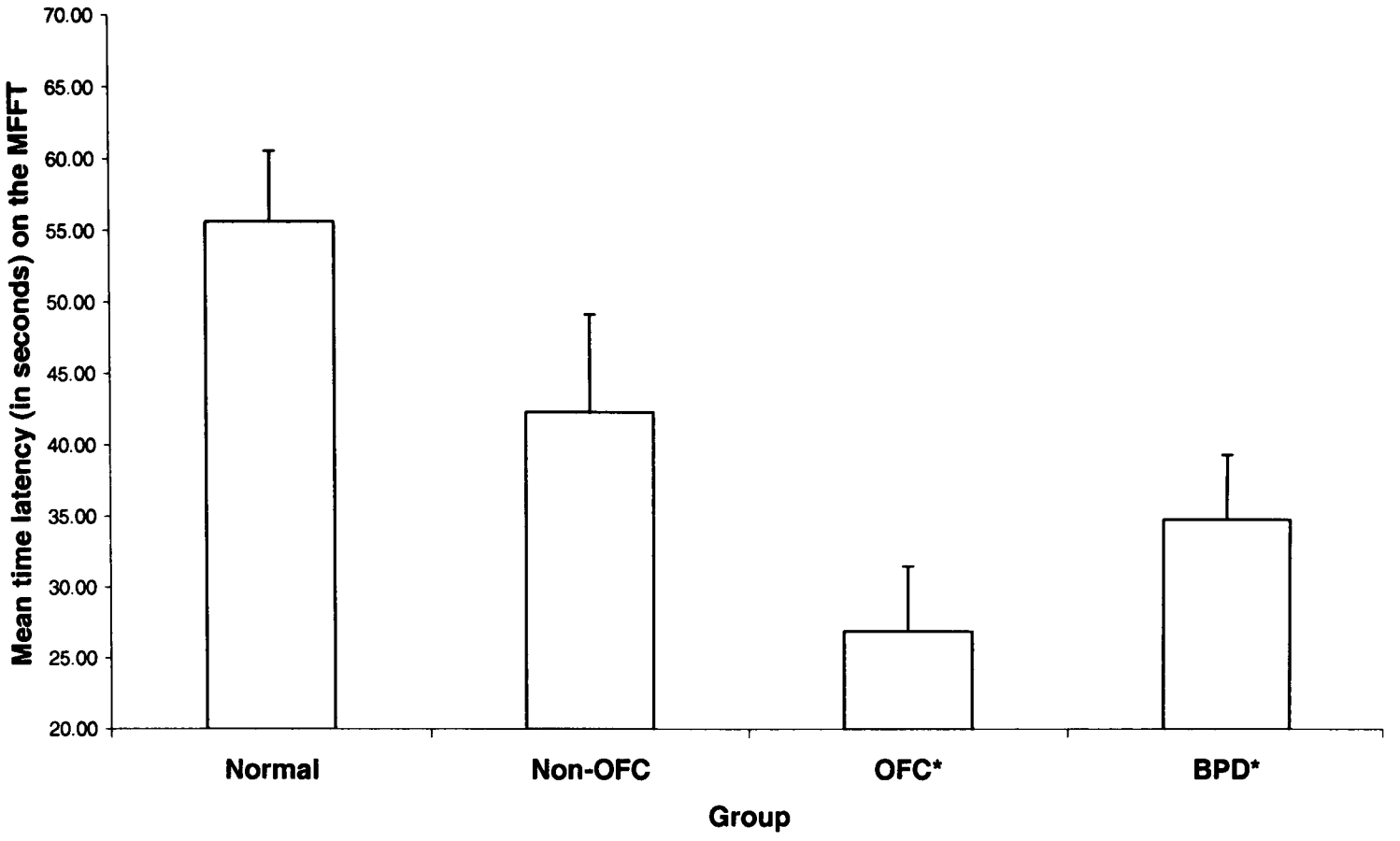



**Figure 3.7:** Histogram of mean time latency (in seconds) to choose the first stimulus on each trial on the MFFT across all groups. The less time taken to choose a stimulus, the more behaviourally impulsive. Both OFC and BPD had a significantly lower time latencies than normal participants.

### 3.3.1.3 Frontal Behaviour Questionnaire

An ANOVA was performed on participants' *Frontal Behaviour Questionnaire score*, and results indicated that participants' scores were significantly linked to their group, $F(3,97) = 12.40$, $p = .000$.

Subsequent post-hoc analysis revealed that OFC and BPD participants' mean Frontal Behaviour Questionnaire (FBQ) total scores were significantly higher than those of both non-OFC and normal participants and BPD participants mean total frontal behaviour score was significantly higher than that of OFC participants. Further, there was no significant difference on the FBQ mean score between normal and non-OFC participants. More specifically, 1) BPD participants scored significantly higher than normal, non-OFC, and OFC patients, $p = .000$, $p = .000$, and $p < .05$ respectively and 2) OFC participants scored significantly higher than normal and non-OFC participants, $p = .005$ and $p = .004$ respectively. The mean FBQ score for each group is shown in Figure 3.8.

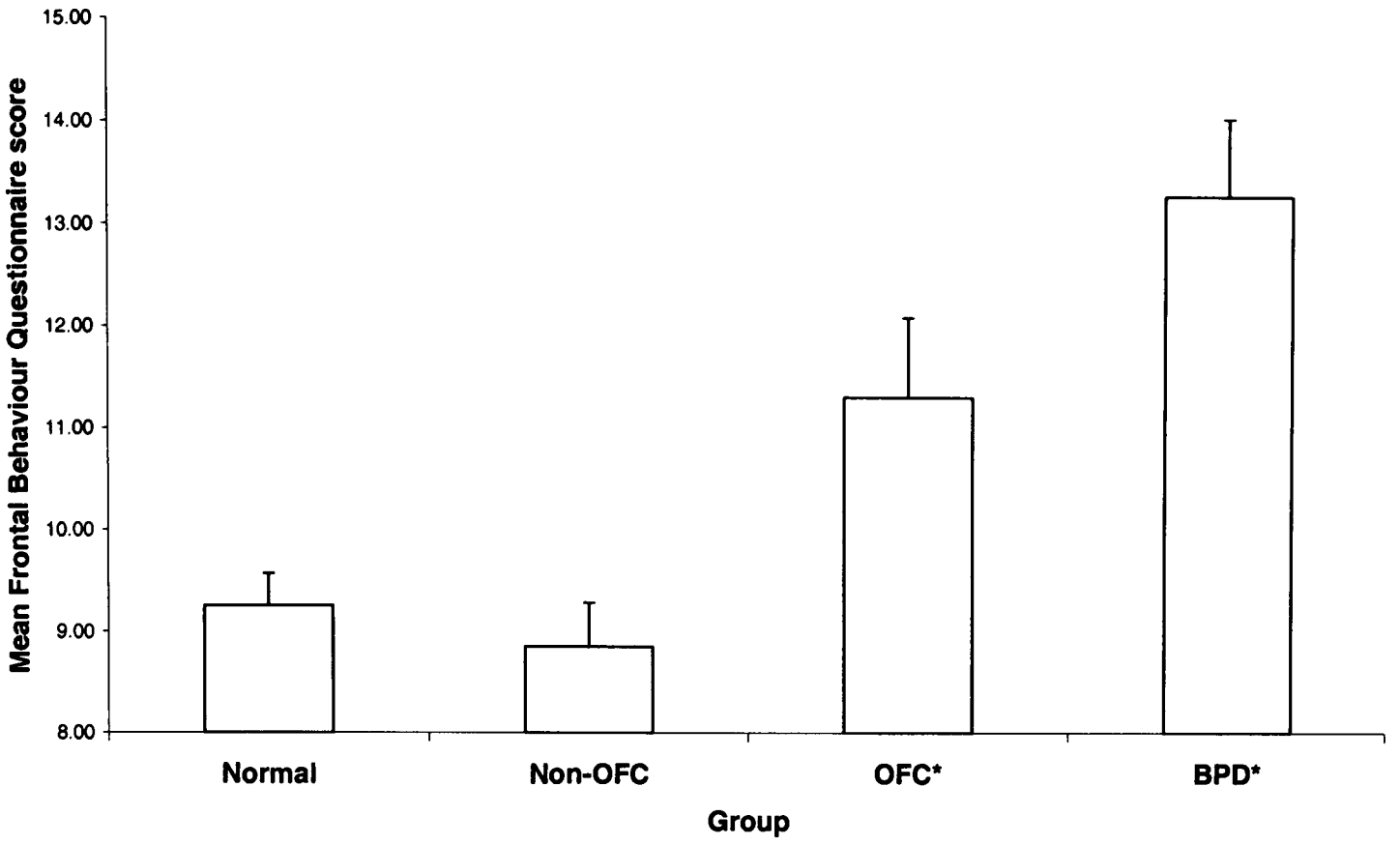



**Figure 3.8**: Histogram of participants' mean Frontal Behavioural Questionnaire (FBQ) total score by group. OFC and BPD participants' mean FBQ total scores were significantly higher than those of both non-OFC and normal participants and BPD participants' mean FBQ total score was significantly higher than that of OFC participants.

### 3.3.1.4 Borderline Personality Disorder Questionnaire

An ANOVA was performed on participants' *Borderline Personality Disorder Questionnaire score* (STB score), and results indicated that participants' scores were significantly linked to their group, $F(3,55) = 21.40$, $p = .000$.

Subsequent post-hoc analysis revealed that OFC and BPD participants' mean BPD Questionnaire total scores were significantly higher than those of both non-OFC and normal participants and BPD participants mean total BPD score was significantly higher than that of OFC participants. Further, there was no significant difference on the BPD Questionnaire mean scores between normal and non-OFC participants. More specifically, 1) BPD participants' scores were significantly higher than participants in all other groups, $p = .000$ and 2) OFC participants' scores were significantly higher than those of normal and non-OFC participants, $p < .05$. The mean BPD Questionnaire score for each group is shown in Figure 3.9.

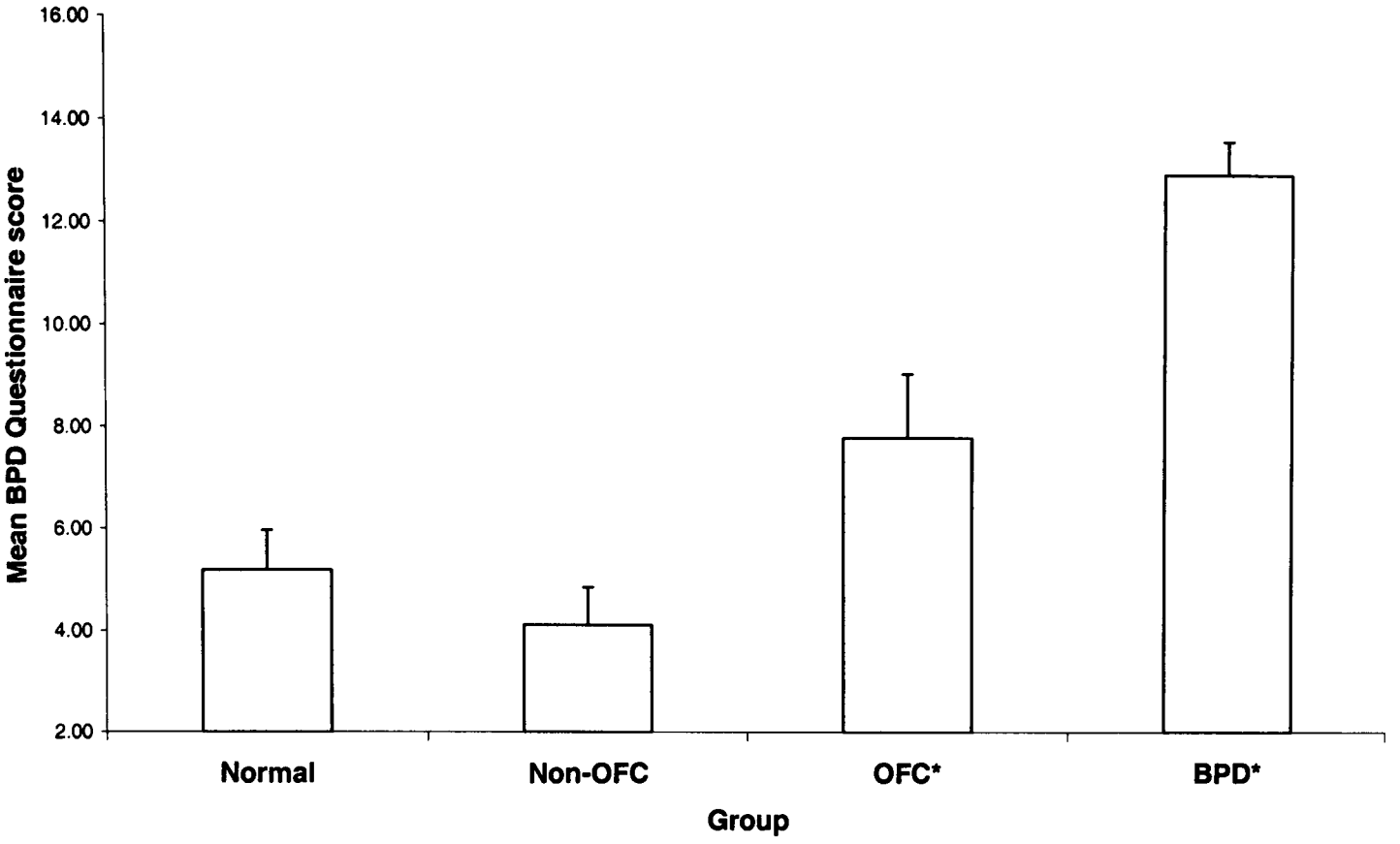



**Figure 3.9**: Histogram of participants' mean BPD Questionnaire total score by group. OFC and BPD participants' mean BPD total scores were significantly higher than those of both non-OFC and normal participants and BPD participants' mean BPD total score was significantly higher than that of OFC participants.

### 3.3.1.5 Time Perception

ANOVAs done on each of the time perception variables indicated that participants differed significantly by group in terms of *total time production* and specifically in *time production at 60 and 90 seconds,* $F(3,74) = 2.95$, $p < .05$, $F(3,74) = 2.82$, $p < .05$, and $F(3,74) = 5.04$, $p < .01$ respectively.

Whereas all subjects overproduced (except OFC participants at 90 seconds; overproduction indicates a slow subjective sense of time), LSD post-hoc analysis revealed that OFC and BPD participants produced significantly less time than normal participants (indicating a sped-up subjective sense of time) in total, $p < .05$, at 60 seconds, $p < .05$, and at 90 seconds, $p < .01$. The longer the time interval the more apparent the deficit became. The mean times produced for each group in total, at 60 seconds, and at 90 seconds are shown in Figures 3.10-3.12.

Independent, two-tailed t-tests were performed to determine if there were hemispheric differences between frontal patients on time perception. Left-sided OFC and non-OFC lesion patients overestimated time more than right-sided OFC and non-OFC lesion patients in total and at the short intervals of 10 and 30 seconds, $t = 1.62$, $p < .05$, $t = 1.79$, $p < .01$, and $t = 1.60$, $p < .01$ respectively. Also, left-sided OFC and non-OFC lesion patients underproduced time more than right-sided OFC and non-OFC lesion patients at the long intervals of 60 and 90 seconds, $t = -1.44$, $p < .01$ and $t = -.762$, $p < .05$ respectively. However, many of the lesion patients were not able to participate in the time perception tasks (explained in Section 2.2.2) and group size was uneven (n=4 left-sided and n=10 right-sided). Thus, more patients would need to be tested in order to achieve more reliable results concerning PFC laterality and time perception.

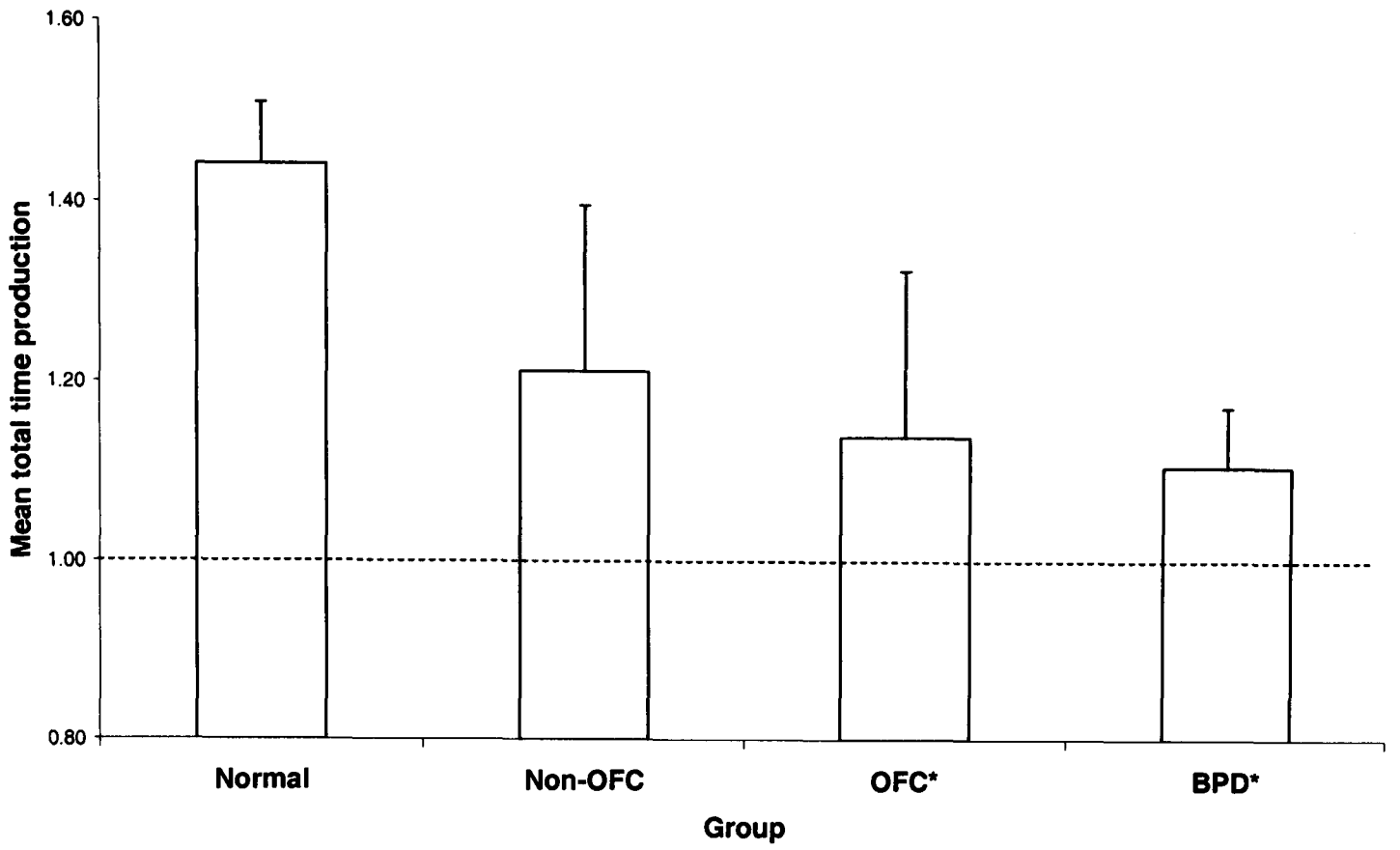



**Figure 3.10**: Histogram of participants' mean total time production score [total amount of seconds produced across all time intervals divided by 190 (total amount of seconds targeted to produce)] by group. While all groups overproduced, OFC and BPD participants' produced significantly less time (had a faster subjective sense of time) than normal participants did.

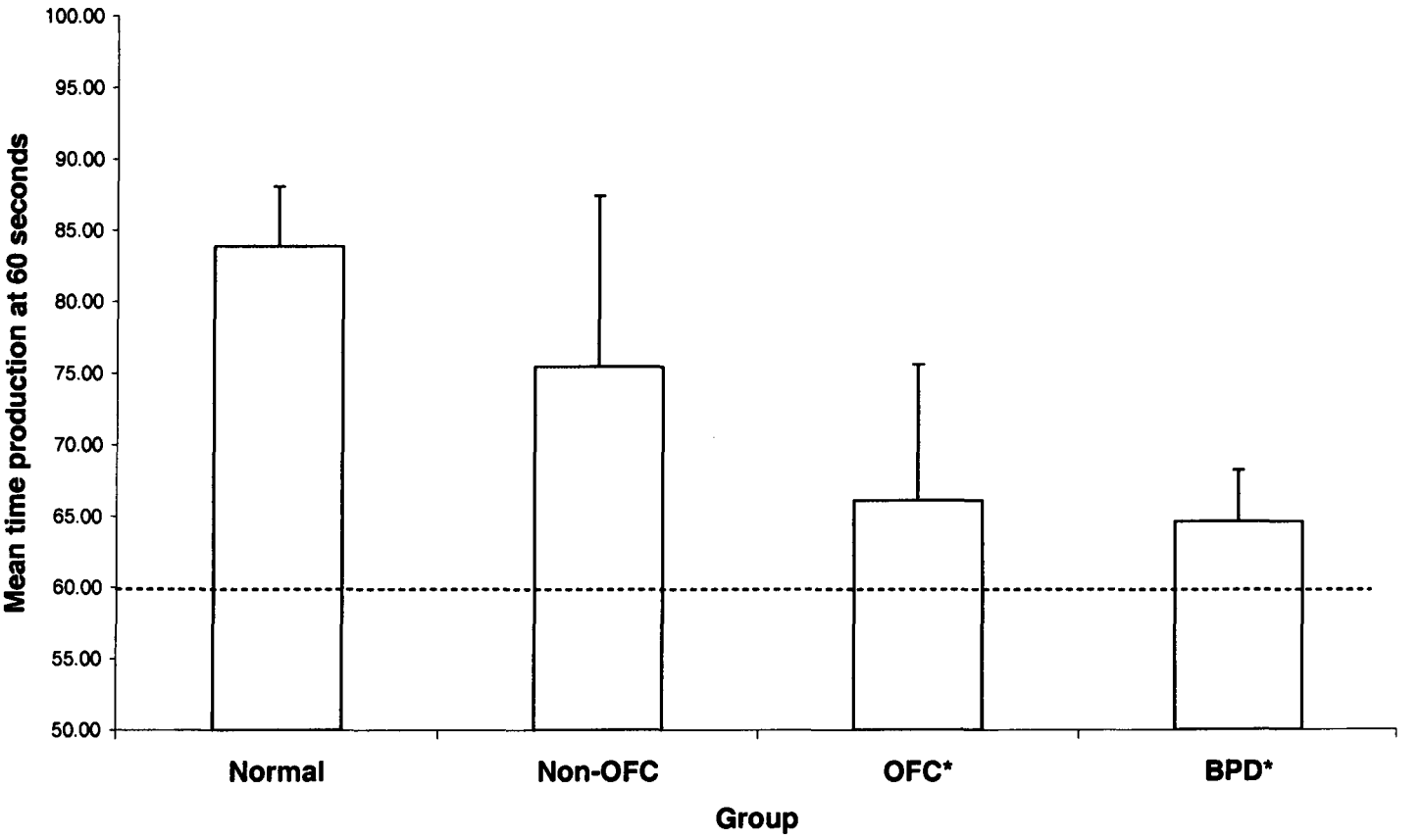



**Figure 3.11**: Histogram of participants' mean time production at 60 seconds by group. While all groups overproduced, OFC and BPD participants' overproduced significantly less (had a faster subjective sense of time) than normal participants did.

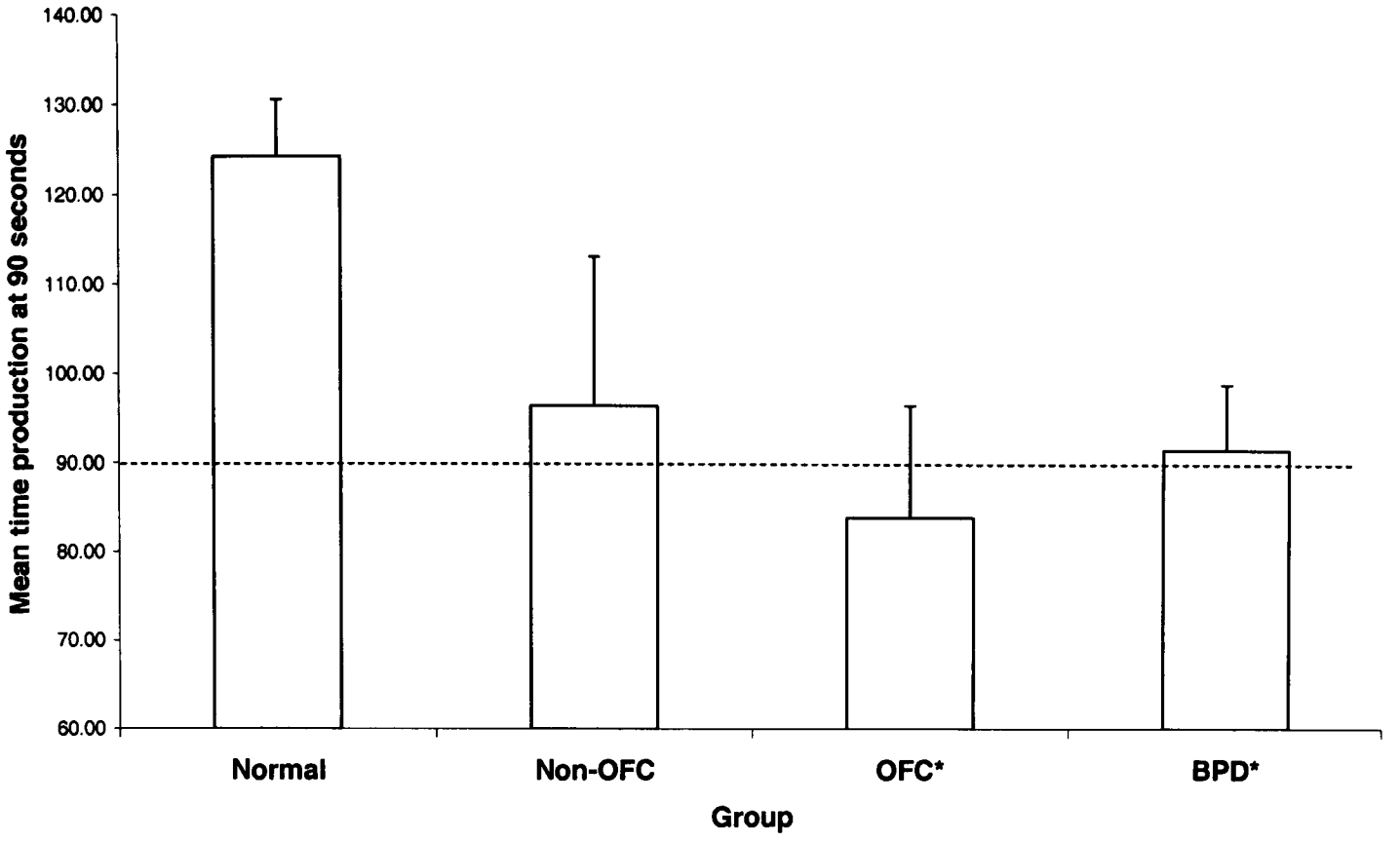



**Figure 3.12**: Histogram of participants' mean time production at 90 seconds by group. OFC and BPD participants' produced a significantly lower amount of time (had a faster subjective sense of time) at the 90 second interval than normal participants did. Further, while all other groups overproduced, OFC patients under-produced.

### 3.3.1.6 Personality

ANOVAs were performed on each of the personality variables of the Big Five Inventory (E = extraversion, A = agreeableness, C = conscientiousness, N = neuroticism, and O = openness to experience). There were significant group differences for E, C, N and O, $F(3,97) = 12.15$, $p = .000$, $F(3,97) = 12.71$, $p = .000$, $F(3,97) = 23.00$, $p = .000$, and $F(3,97) = 6.43$, $p = .001$ respectively. However, only the post-hoc results for the "openness to experience" variable will be reported in the current section since this was the only variable where OFC and BPD patients' results did not differ significantly from each other. The other variables for which they did differ significantly from each other are discussed in Section 3.3.2.1.

Results of the LSD post-hoc analysis for the *openness to experience* variable revealed that normal participants were significantly more open to experience than all other participants, $p < .005$. See Figure 3.13 for the mean openness to experience scores by group.

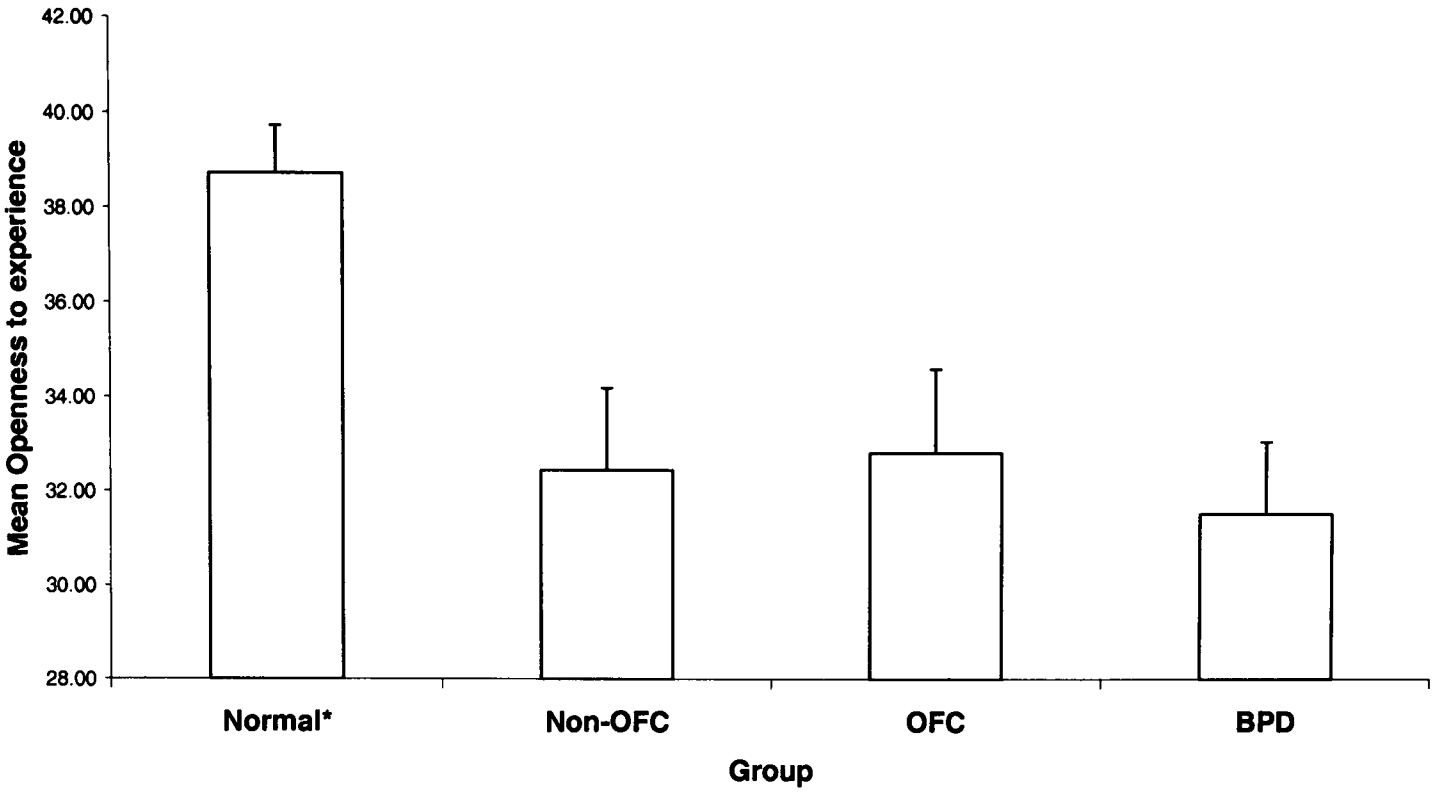



**Figure 3.13:** Histogram of participants' mean openness to experience score on the Big Five Inventory by group. Normal participants' were significantly more open to experience than participants in all other groups.

### 3.3.1.7 Subjective Emotion

ANOVAs performed on each of the Subjective Emotion Questionnaire variables (total subjective emotion score, sadness, anger, fear, disgust, and happiness) revealed that participants' scores on all six measures were significantly related to their group, $F(3,96) = 17.17$, $p = .000$, $F(3,96) = 10.84$, $p = .000$, $F(3,96) = 14.48$, $p = .000$, $F(3,96) = 23.78$, $p = .000$, $F(3,96) = 6.62$, $p = 000$, and $F(3,96) = 19.00$, $p = .000$ respectively. However, only the post-hoc analysis of anger and happiness variables will be reported in this section as BPD and OFC participants both differed significantly from normal and non-OFC participants on these variables. For all other variables, there was a dissociation between OFC and BPD participants' deficits and they are therefore discussed later in Section 3.3.2.2. For subjective anger and happiness, OFC and BPD participants reported being both significantly more angry and less happy than normal and non-OFC participants with BPD participants being significantly more angry and less happy than OFC participants. Further, there were no significant differences between normal and non-OFC participants' scores on these measures. More specifically:

Post-hoc results of the *subjective anger* variable indicated that 1) BPD participants' subjective anger was significantly higher than normal, non-OFC, and OFC participants, $p = .000$, $p = .000$, and $p < .05$ respectively and 2) OFC participants' subjective anger was significantly higher than normal and non-OFC lesion participants, $p < .01$. See Figure 3.14 for the mean subjective anger scores by group.

Post-hoc analysis of the *subjective happiness* variable indicated that: 1) BPD participants' subjective happiness was significantly lower than participants in all other groups, $p = .000$ and 2) OFC participants' subjective happiness was significantly lower than both normal and non-OFC

lesion participants, $p < .01$ and $p < .05$ respectively. See Figure 3.15 for the mean subjective happiness scores by group.

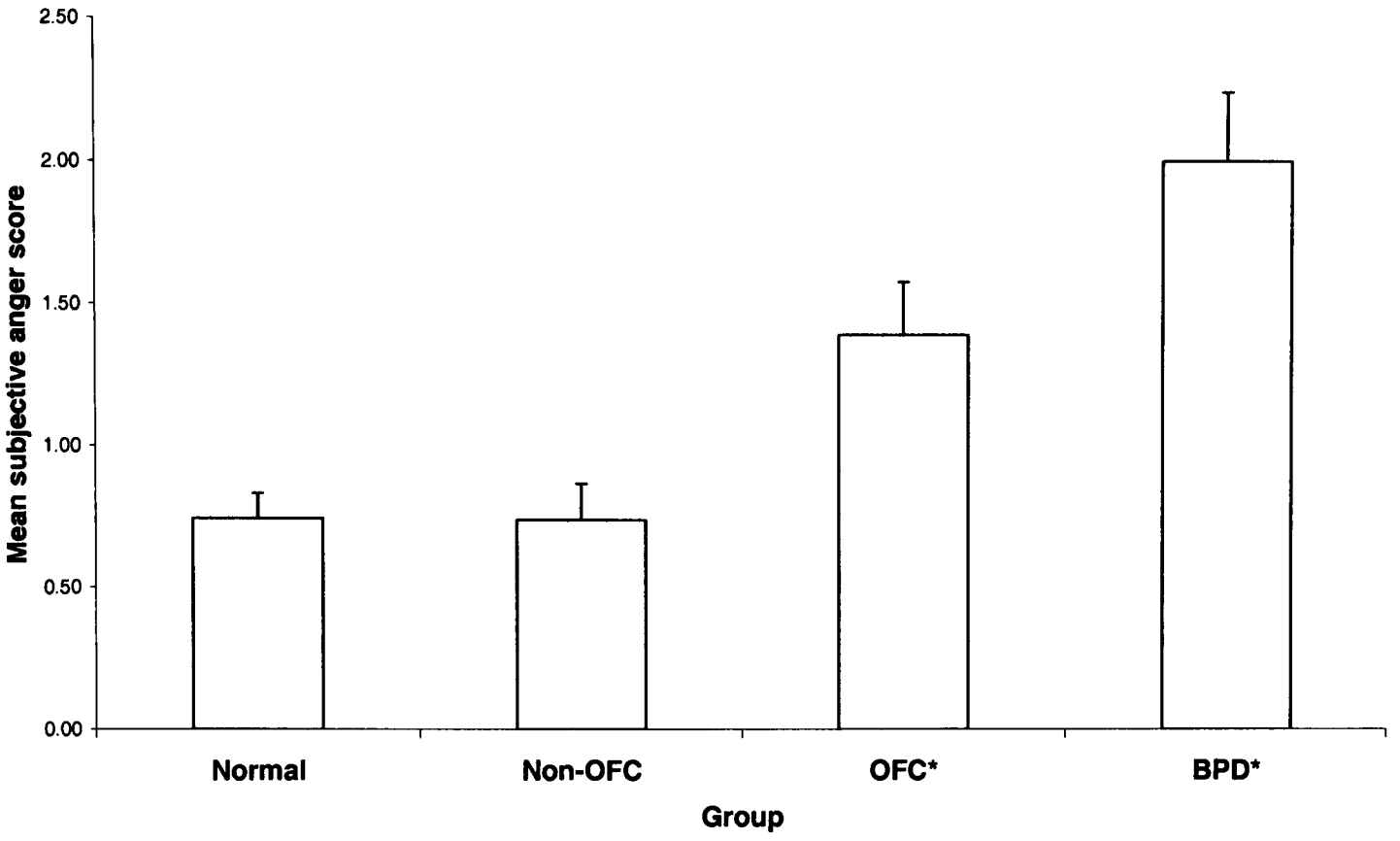



**Figure 3.14:** Histogram of participants' mean subjective anger score on the Subjective Emotion Questionnaire by group. OFC and BPD participants reported experiencing significantly more anger than non-OFC and normal participants and BPD participants experienced significantly more anger than OFC participants.

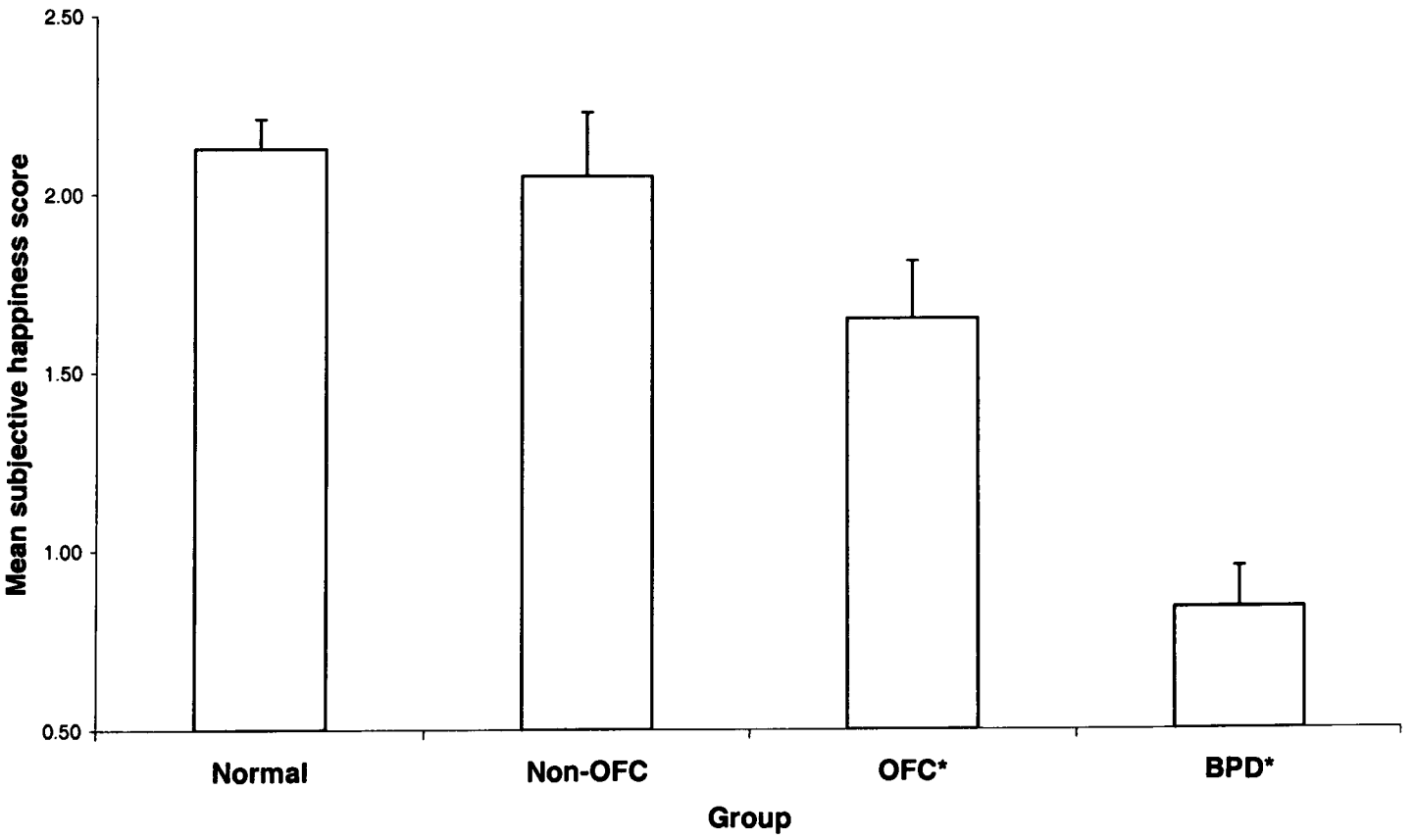



**Figure 3.15:** Histogram of participants' mean subjective happiness score on the Subjective Emotion Questionnaire by group. OFC and BPD participants reported experiencing significantly less happiness than non-OFC and normal participants and BPD participants experienced significantly less happiness than OFC participants.

### 3.3.2 Dissociations between Deficits in Orbitofrontal Cortex and BPD Patients

In this section variables are discussed in the following order, first variables in which only BPD participants have a deficit are discussed, then variables for which only OFC participants have a deficit are discussed, and finally the control SWM variables, where both lesion groups have a deficit, are discussed.

In sum, BPD participants were less extraverted, less conscientious, more neurotic, more emotional (in terms of total subjective emotionality and a higher frequency of sadness, fear and disgust), and had a bigger change in fear than all other groups. Further, BPD participants had a bigger change in sadness and anger than non-OFC participants.

OFC participants performed worse on the reversal task (made less money, fewer reversals, and were more insensitive to punishment) compared to all other groups. In addition, OFC participants had a significantly faster subjective sense of time in terms of total time estimation than normal participants while BPD participants did not have a deficit compared to normal participants.

Finally, both lesion patient groups, OFC and non-OFC, had a deficit on SWM compared to normal and BPD participants. This was expected as the SWM task was used to control for DLFC damage since it has been shown to be sensitive to DLFC damage (see Section 1.10.2). Therefore, since both lesion groups contained patients with mixed lesions which included DLFC damage, they were expected to perform poorly on this task. Since BPD participants were not impaired on this task it is inferred that their deficits on other tasks can not be attributed to DLFC/SWM dysfunction.

#### 3.3.2.1 Personality

ANOVAs performed on each of the personality questionnaire (BFI) variables (E = extraversion, A = agreeableness, C = conscientiousness, N = neuroticism, and O = openness to experience) indicated that participants' scores on E, C, N, and O were significantly related to their group, $F(3,97) = 12.15$, $p = .000$, $F(3,97) = 12.71$, $p = .000$, $F(3,97) = 23.00$, $p = .000$, and $F(3,97) = 6.43$, $p = .001$ respectively.

Post-hoc tests of the *extraversion* variable revealed that BPD participants were significantly less extraverted than participants in all other groups, $p = .000$ (see Figure 3.16).

Post-hoc results of the *conscientiousness* variable revealed that BPD participants were significantly less conscientious than participants in all other groups, $p = .000$ (see Fig. 3.17).

LSD analysis of the *neuroticism* variable indicated that BPD participants were significantly more neurotic that participants in all other groups $p = .000$ (see Figure 3.18).

(For "openness to experience" post-hoc analysis, see Section 3.3.1.6 above.)

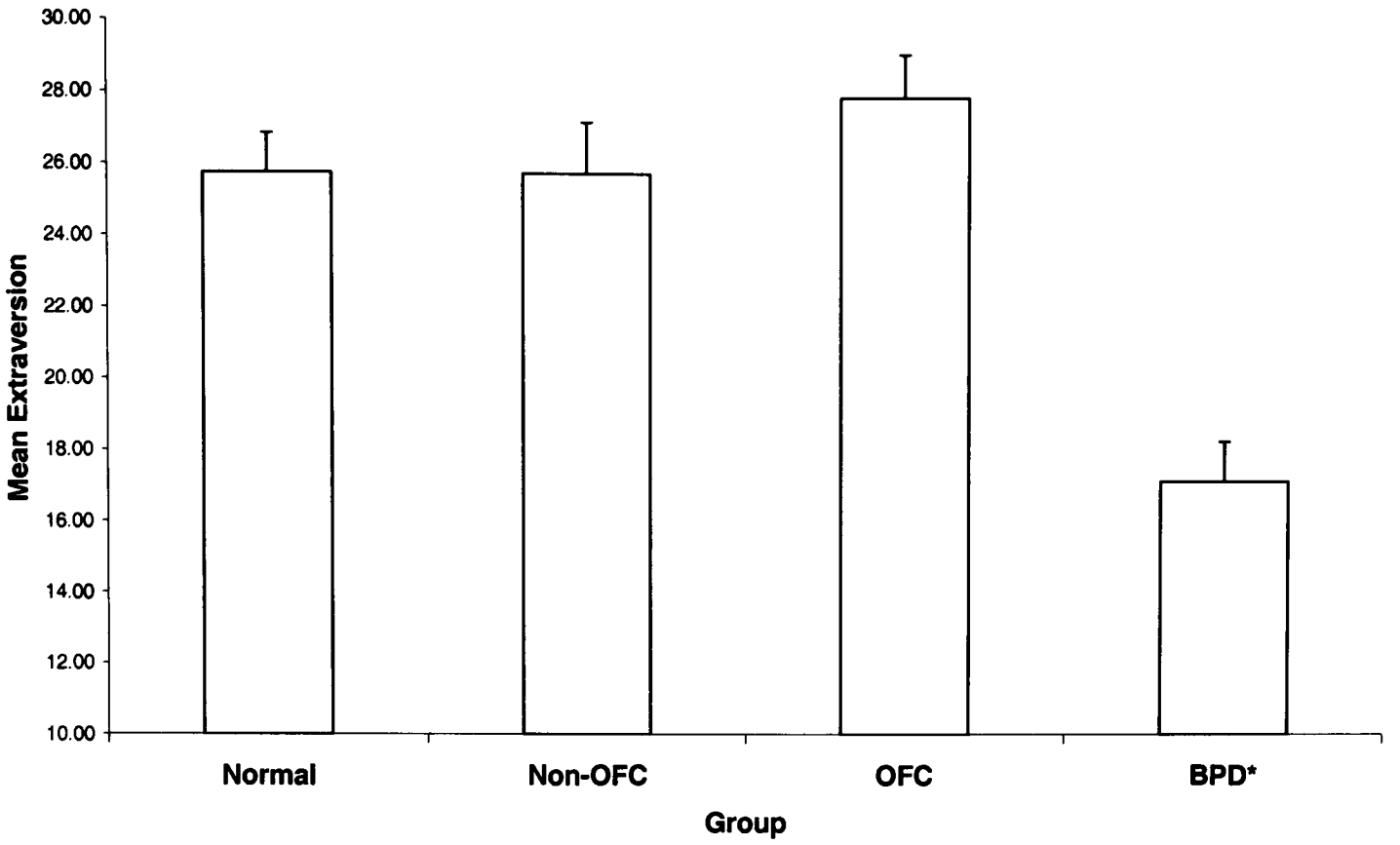



**Figure 3.16:** Histogram of participants' mean extraversion score on the Big Five Inventory by group. BPD participants' were significantly less extraverted than participants in all other groups.

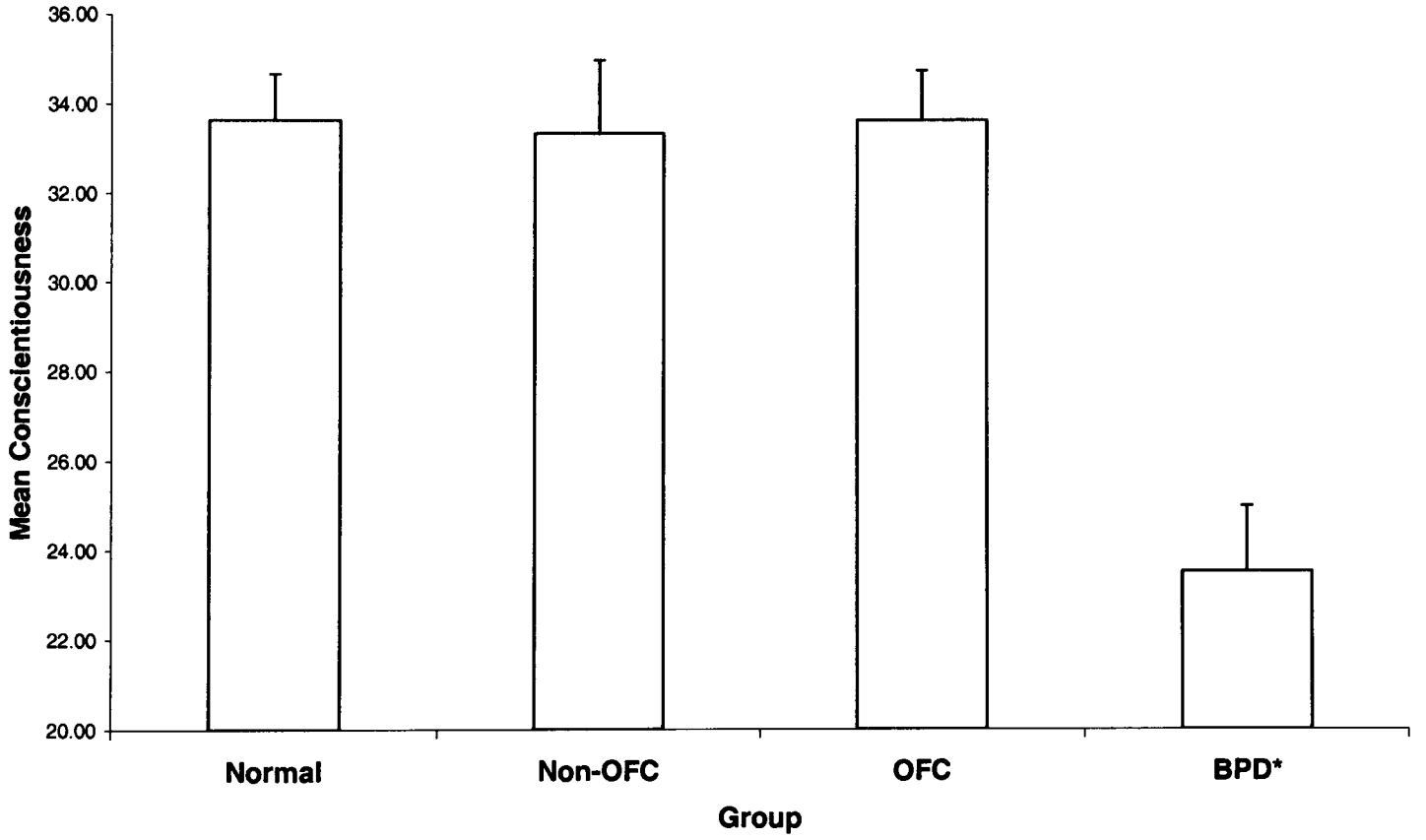



**Figure 3.17:** Histogram of participants' mean conscientiousness score on the Big Five Inventory by group. BPD participants' were significantly less conscientious than participants in all other groups.

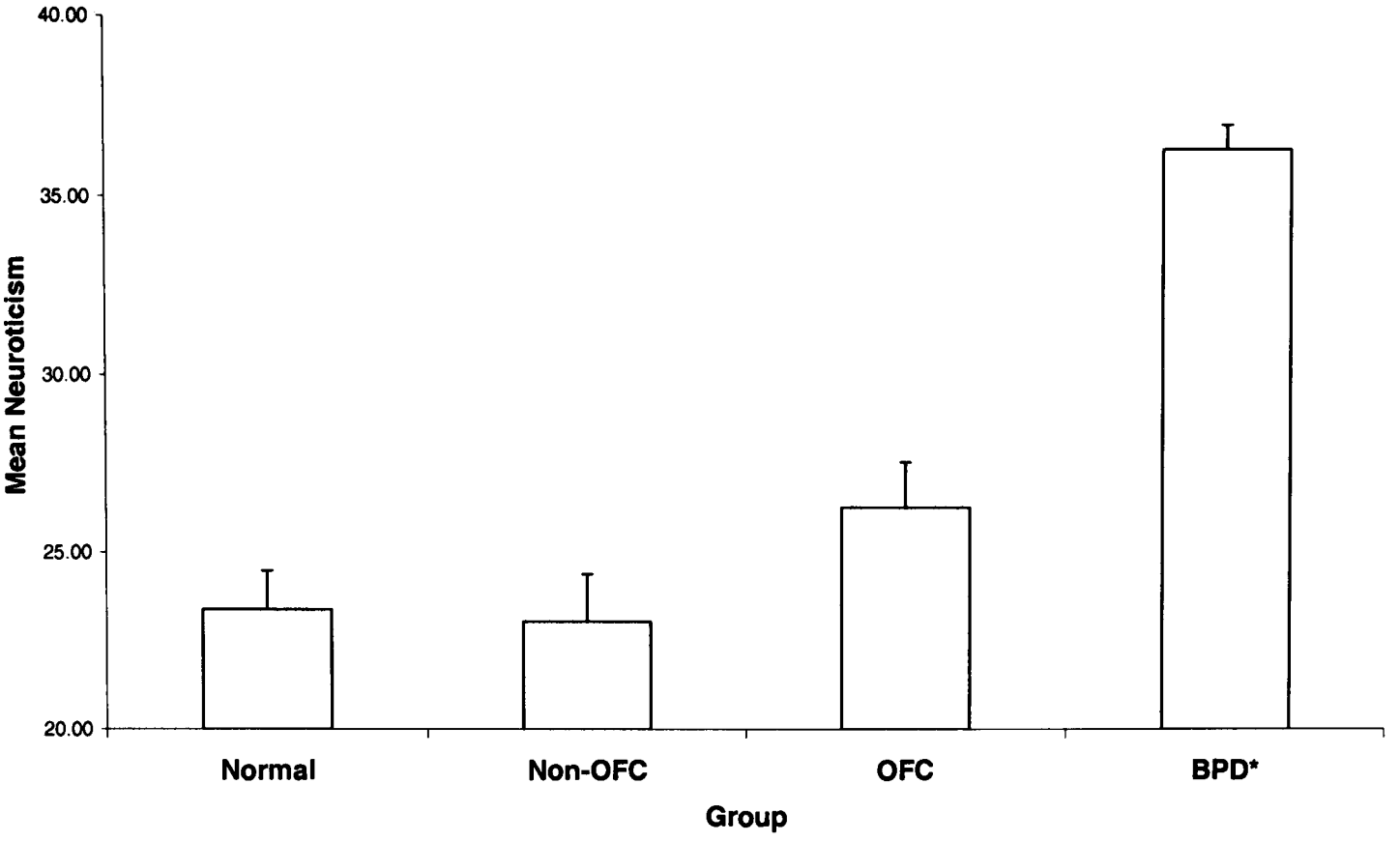



**Figure 3.18:** Histogram of participants' mean neuroticism score on the Big Five Inventory by group. BPD participants' were significantly more neurotic than participants in all other groups.

### 3.3.2.2 Subjective Emotion

ANOVAs performed on each of the Subjective Emotion Questionnaire variables (total subjective emotion, sadness, anger, fear, disgust, and happiness) revealed that participants' scores on all six measures were significantly related to their group, $F(3,96) = 17.17$, $p = .000$, $F(3,96) = 10.84$, $p = .000$, $F(3,96) = 14.48$, $p = .000$, $F(3,96) = 23.78$, $p = .000$, $F(3,96) = 6.62$, $p = 000$, and $F(3,96) = 19.00$, $p = .000$ respectively.

Subsequent post-hoc analysis of the *total subjective emotion* variable indicated that BPD participants' total subjective emotion score was significantly higher than participants in all other groups, $p = .000$ (see Figure 3.19).

Post-hoc analysis of the *sadness* variable indicated that BPD participants rated themselves as being significantly sadder that participants in all other groups, $p = .000$ (see Figure 3.20).

Results of the *fear* post-hoc showed that BPD participants' subjective fear was significantly higher than participants in all other groups $p = .000$ (see Figure 3.21).

LSD results of the *disgust* variable revealed that BPD participants' subjective disgust was significantly higher than that of all other participants, $p = .005$ (see Figure 3.22).

Anger and happiness variables were discussed previously in Section 3.3.1.7, as BPD and OFC patients *both* differed significantly from normal and non-OFC participants.

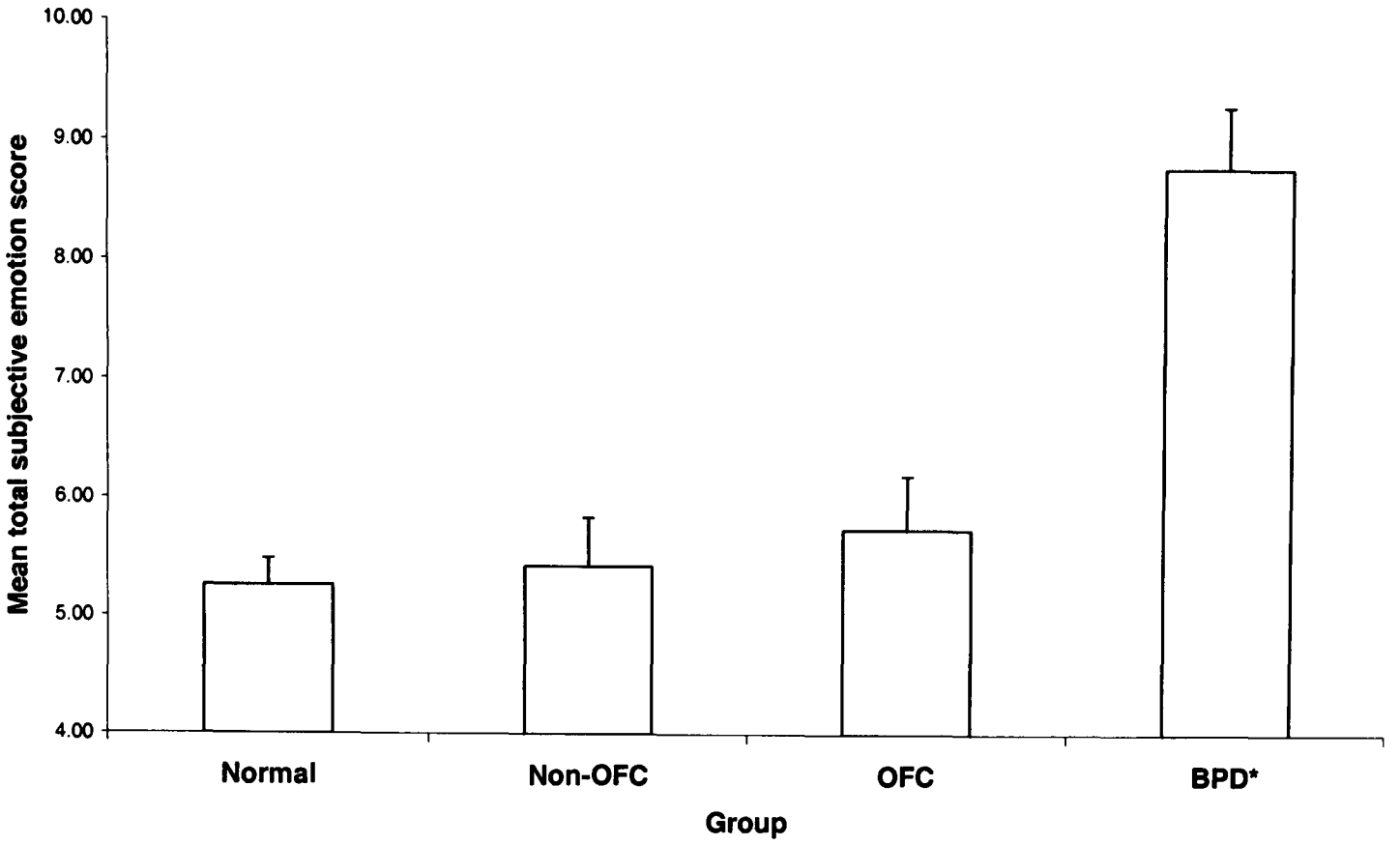



**Figure 3.19:** Histogram of participants' mean total Subjective Emotion Questionnaire score by group. BPD participants reported experiencing emotions significantly more frequently (were more emotional) than all other participant groups.

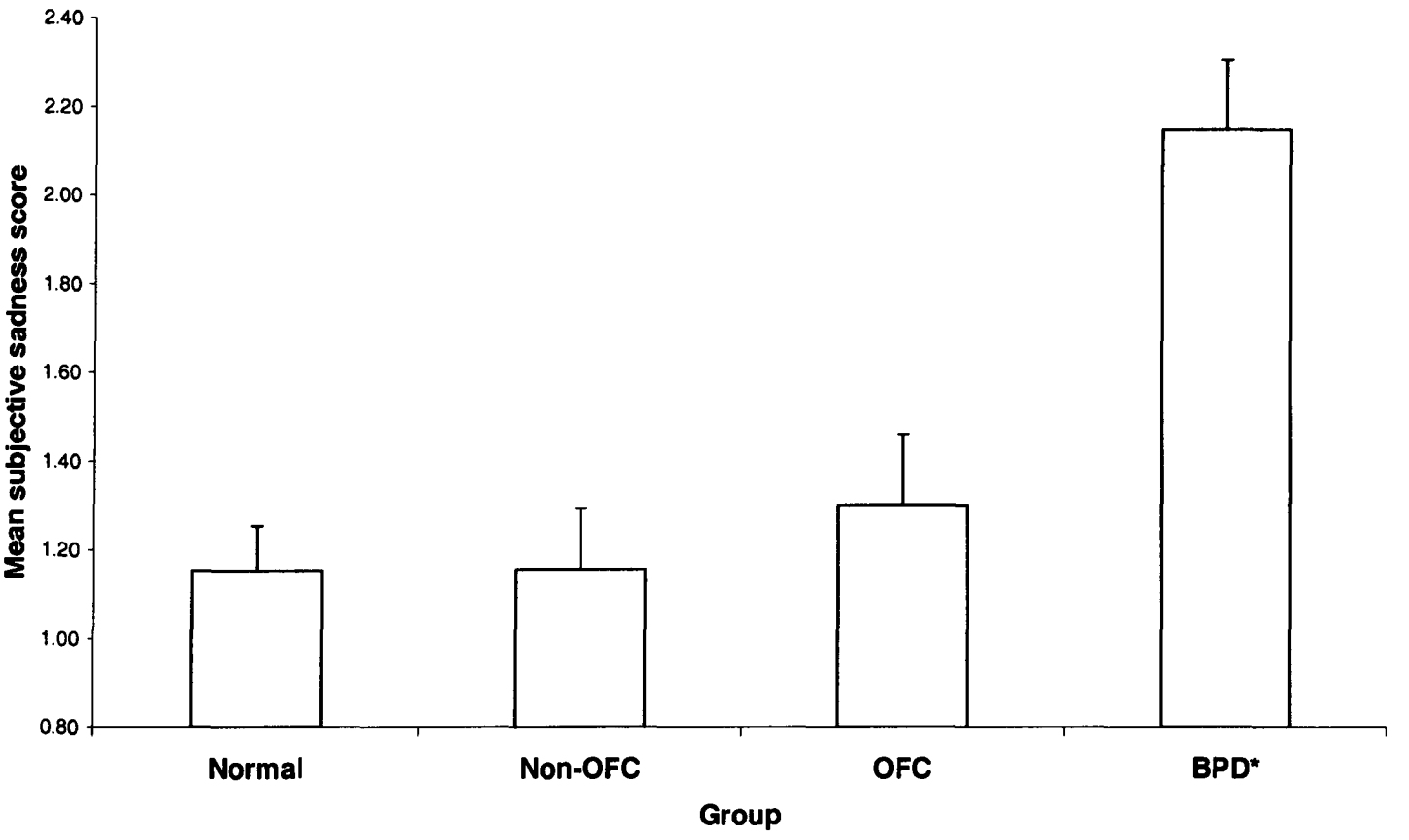



**Figure 3.20:** Histogram of participants' mean subjective sadness score on the Subjective Emotion Questionnaire by group. BPD participants reported experiencing significantly more sadness than all other participant groups.

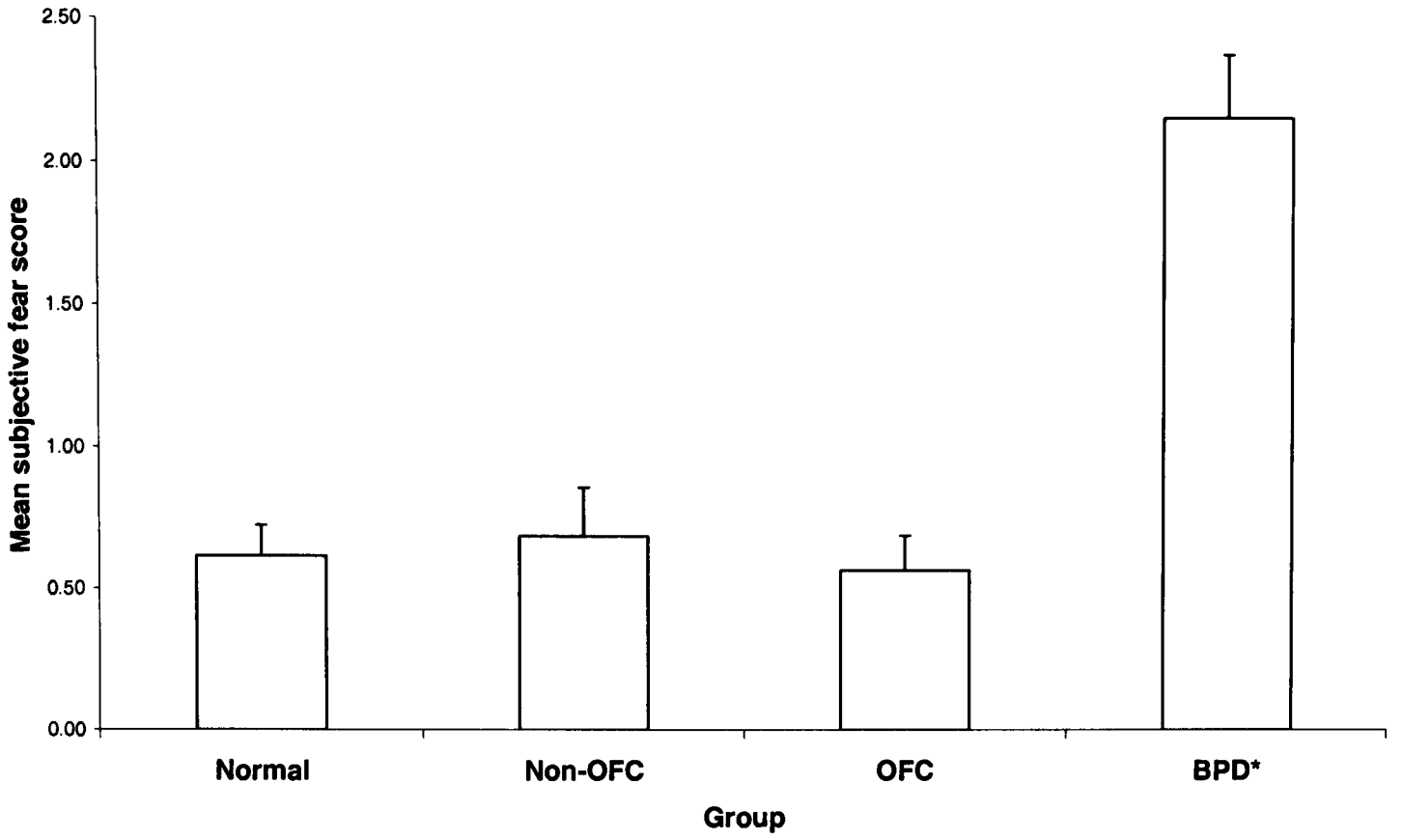



**Figure 3.21:** Histogram of participants' mean subjective fear score on the Subjective Emotion Questionnaire by group. BPD participants reported experiencing significantly more fear than all other participant groups.

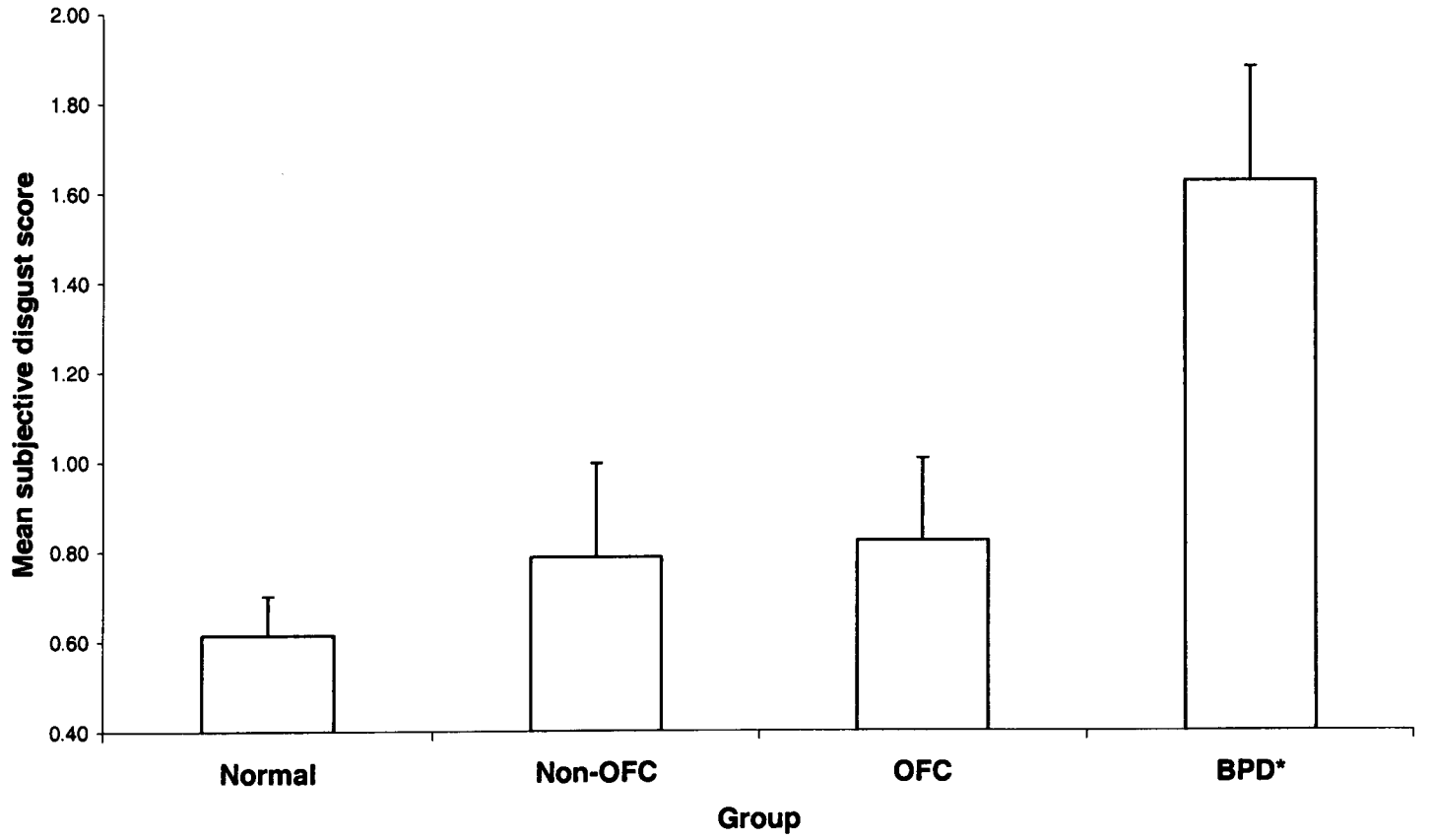



**Figure 3.22:** Histogram of participants' mean subjective disgust score on the Subjective Emotion Questionnaire by group. BPD participants reported experiencing significantly more disgust than all other participant groups.

### 3.3.2.3 Emotional Change

Only the non-OFC lesion, OFC lesion, and BPD participants completed the Emotional Change Questionnaire. ANOVAs performed on each of the related variables (total number of emotions changed, change in sadness, change in anger, change in fear, change in happiness, and change in disgust) indicated that participants' change in sadness, anger, and fear were significantly related to

their group, $F(2,49) = 5.12$, $p = .01$, $F(2,49) = 4.29$, $p < .05$, and $F(2,49) = 3.84$, $p < .05$ respectively. Participants' total number of emotions changed, change in happiness, and change in disgust did not differ significantly by group. LSD tests were then conducted on the change in sadness, anger, and fear variables respectively. Results indicated the following:

BPD participants' *sadness* increased significantly more than non-OFC participants' sadness increased, $p < .01$ and OFC participants did not differ significantly from non-OFC participants (see Figure 3.23).

There was a significant difference in the change of *anger* between BPD and non-OFC participants, $p < .01$: BPD participants' anger increased while that of non-OFC participants decreased and OFC participants did not differ significantly from non-OFC participants (see Figure 3.24).

BPD participants showed a significant change in *fear* from both non-OFC and OFC participants, $p < .05$ and $p < .01$ respectively: BPD participants' fear increased, whereas that of non-OFC and OFC participants decreased and OFC participants did not differ significantly from non-OFC participants (see Figure 3.25).

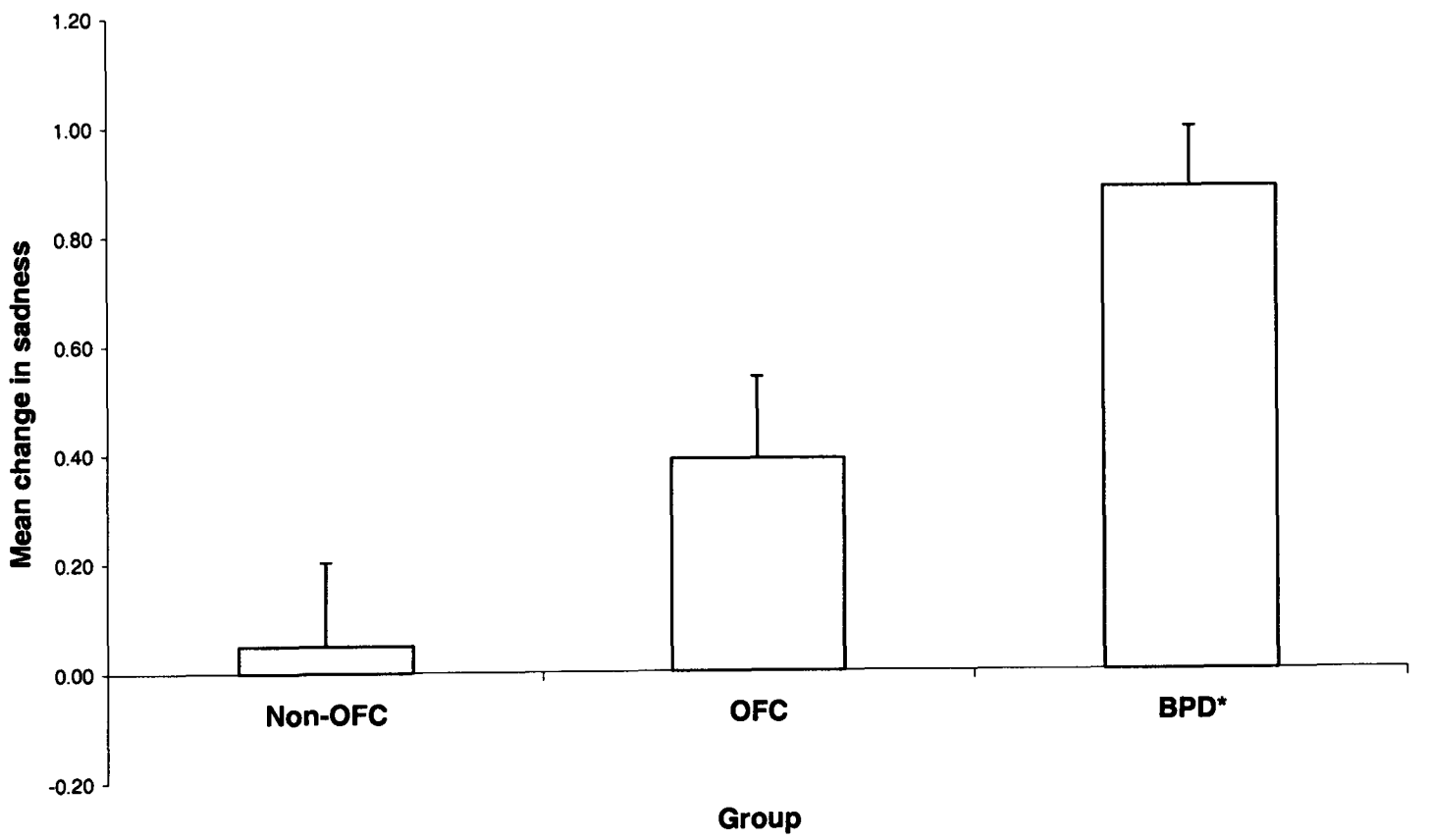



**Figure 3.23:** Histogram of participants' mean change in sadness score since their head injury or onset of illness on the Emotional Change Questionnaire by group. BPD participants' sadness increased significantly more than non-OFC participants' sadness increased.

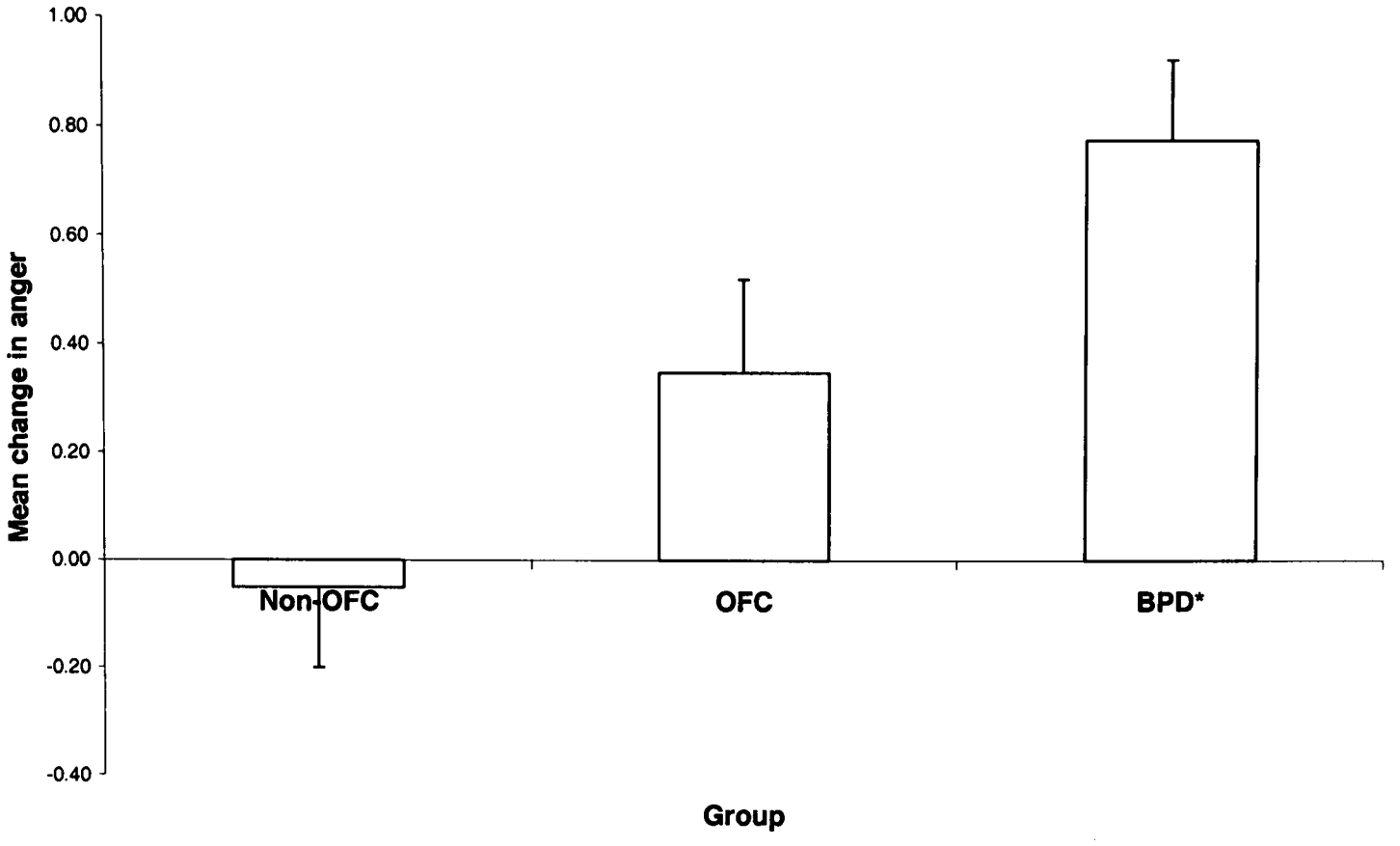



**Figure 3.24:** Histogram of participants' mean change in anger score since their head injury or onset of illness on the Emotional Change Questionnaire by group. There was a significant difference in the change of anger between BPD and non-OFC participants. BPD participants' anger increased while that of non-OFC participants decreased.




**Figure 3.25:** Histogram of participants' mean change in fear score since their head injury or onset of illness on the Emotional Change Questionnaire by group. BPD participants showed a significant change in fear from both non-OFC and OFC participants. BPD participants' fear increased, while that of non-OFC and OFC participants decreased.

### 3.3.2.4 Probabilistic Reversal

For the reversal data, 13 of the 35 (6/15 non-OFC and 7/20 OFC) lesion patients' scores on the reversal task were obtained from reversal data already collected on these subjects by Julia Hornak and John O'Doherty (Rolls et al., 1994). However, information for these 13 patients on the *number of trials to reach criterion (acquire S+)* on the acquisition task was unavailable, but it was known that they did successfully reach criterion on the acquisition task and understood the task demands.

ANOVAs done on each of the reversal variables (number of trials to reach criterion, total number of trials until the first reversal, pounds accumulated by the 100$^{th}$ trial, total number of reversals achieved by 100 trials, punishment insensitivity, and reward insensitivity) indicated that participants' scores differed significantly by group on all measures expect for the "number of trials to reach criterion" and the "number of trials until the first reversal" variables. Thus, there were significant group differences for the total pounds accumulated by the 100$^{th}$ trial, total number of reversals achieved by 100 trials, punishment insensitivity, and reward insensitivity variables (reward insensitivity was significant only when outliers were included, see Section 3.3.2.4.3) $F(3,89) = 7.05$, $p = .000$, $F(3,89) = 6.60$, $p = .000$, $F(3,89) = 3.85$, $p < .05$, and $F(3,89) = 3.22$, $p < .05$ respectively.

For the analysis of the *number of trials until first reversal* variable, four OFC participants' scores were excluded as they did not attain reversal at all over the 100 trials. The number of trials taken to achieve the first reversal was marked by the trial where the participant starting consecutively touching the new positive stimulus (S+). The one-way ANOVA did not reveal significant differences between groups on this measure.

#### 3.3.2.4.1 Acquisition Task

Although there were no significant differences between groups on the *number of trials to reach criterion*, all patients did eventually reach criterion on the acquisition task. This task was complete once the subject learned to consistently select the positive stimulus (to select S+ 16 out of the previous 18 consecutive responses) within 100 trials. Note that 2 normal participants completed the task at exactly 100 trials and one BPD was almost at criterion at 100 trials and did attain criterion when allowed to continue for another 6 trials. The finding that all participants successfully completed the acquisition task within 100 trials (with the one exception) and subsequently moved onto the reversal task, suggests that participants clearly understood the task demands and were able to follow the task instructions, thus controlling for those explanations for poor performance on the reversal task.

#### 3.3.2.4.2 Reversal Task

Post-hoc analysis of the relevant reversal variables showed that participants with OFC lesions were markedly impaired on the reversal task compared to all other participant groups. The fact that OFC participants were the only group impaired on the reversal task confirms previous findings with a

smaller sample of lesion patients (Rolls et al., 1994; see Section 1.7.3). However, BPD participants were not impaired on the reversal task.

Post-hoc analysis of the *total pounds accumulated* variable revealed that OFC participants accumulated significantly less "money" than did the normal, non-OFC, and BPD participants, $p$ = .000, $p < .01$, and $p < .01$ respectively. In fact, normal, non-OFC, and BPD participants earned "money", whereas OFC participants lost "money". The mean total pounds accumulated for each group is shown in Figure 3.26.

Post-hoc analysis of the *total number of reversals* achieved by 100 trials indicated that OFC participants made significantly fewer reversals than normal, non-OFC, and BPD participants, $p = .000$, $p = .005$, and $p < .05$ respectively. The mean number of reversals achieved in 100 trials for all four groups is shown in Figure 3.27. A successful reversal was considered choosing the new positive stimulus (S+) 9 out of the previous 10 responses. It was still counted as a reversal in cases where a reversal was started but was cut off in process by the 100$^{th}$ trial. This was true for all but two OFC participants who had chosen the new positive stimuli simply by random chance and never truly reversed.

**3.3.2.4.3 Insensitivity to Punishment and Reward**

A more detailed analysis of participants' performance was then carried out by examining the extent to which the participants demonstrated an "insensitivity" to reward and punishment. As described in Section 2.1.2.1.3 and shown in Figure 2.2 (Chapter 2), the magnitudes of reward and punishment that can be obtained on the S+ and S- are substantially different. On the S+, the minimum amount of money that can be won is £80, whereas the maximum that a participant can lose is £60. By contrast on the S- a participant can lose a minimum of £250 and win only up to a maximum of £60. Punishment insensitivity was measured by the total number of consecutive touches to a stimulus after having lost £250 or more. This is effectively a measure of the extent to which participants fail to *switch* immediately from a stimulus on the next trial following a large loss (£250 corresponds to the lower bound of the money that can be lost by touching S-). Reward Insensitivity was measured by the total number of times a participant touched a stimulus and won more than £80 but did not touch the same stimulus again on the next trial. This effectively measures the extent to which participants fail to *stick* to a stimulus following a large gain on that stimulus (£80 corresponds to the lower bound of the amount that can be won on the S+).

The ANOVA for *punishment insensitivity* showed significant group differences [$F(3,89)$ = 3.85, $p < .0$] and post-hoc analysis indicated that OFC participants showed significantly higher insensitivity to the magnitude of punishment than normal, non-OFC and BPD participants, $p$ = .001, $p < .05$, and $p < .05$ respectively. Thus, OFC participants returned to the same stimulus much more frequently following a large loss ($\geq$£250) on a previous trial than participants in all other groups. The mean punishment insensitivity for all groups is shown on Figure 3.28.

*Reward insensitivity* was significantly different between all four groups when an ANOVA was conducted with outliers included, $F(3,89) = 3.22$, $p < .05$. However, when an ANOVA with outliers excluded was run for the reward insensitivity variable, results were no longer significant. Further, when a subsequent non-parametric Kruskal-Wallace was run there were still no significant differences between groups. However, it is interesting to note that when the results were analysed with the outliers included, there was a significant difference between groups and post-hoc analysis revealed that OFC patients were significantly more reward insensitive than normal participants, $p = .003$ and there were no differences between normal participants and all other patient groups. Thus OFC patients failed to stick to a stimulus after receiving a positive reinforcer (a gain of $\geq$ 80£) more often than normal participants. Also, although the overall between group differences were no longer significant when the outliers were removed, the trends were still in same direction and perhaps would have reached the level of significance if more participants were tested. Unfortunately, time constraints did not allow for this. The mean reward insensitivity for all groups is shown in Figure 3.29.

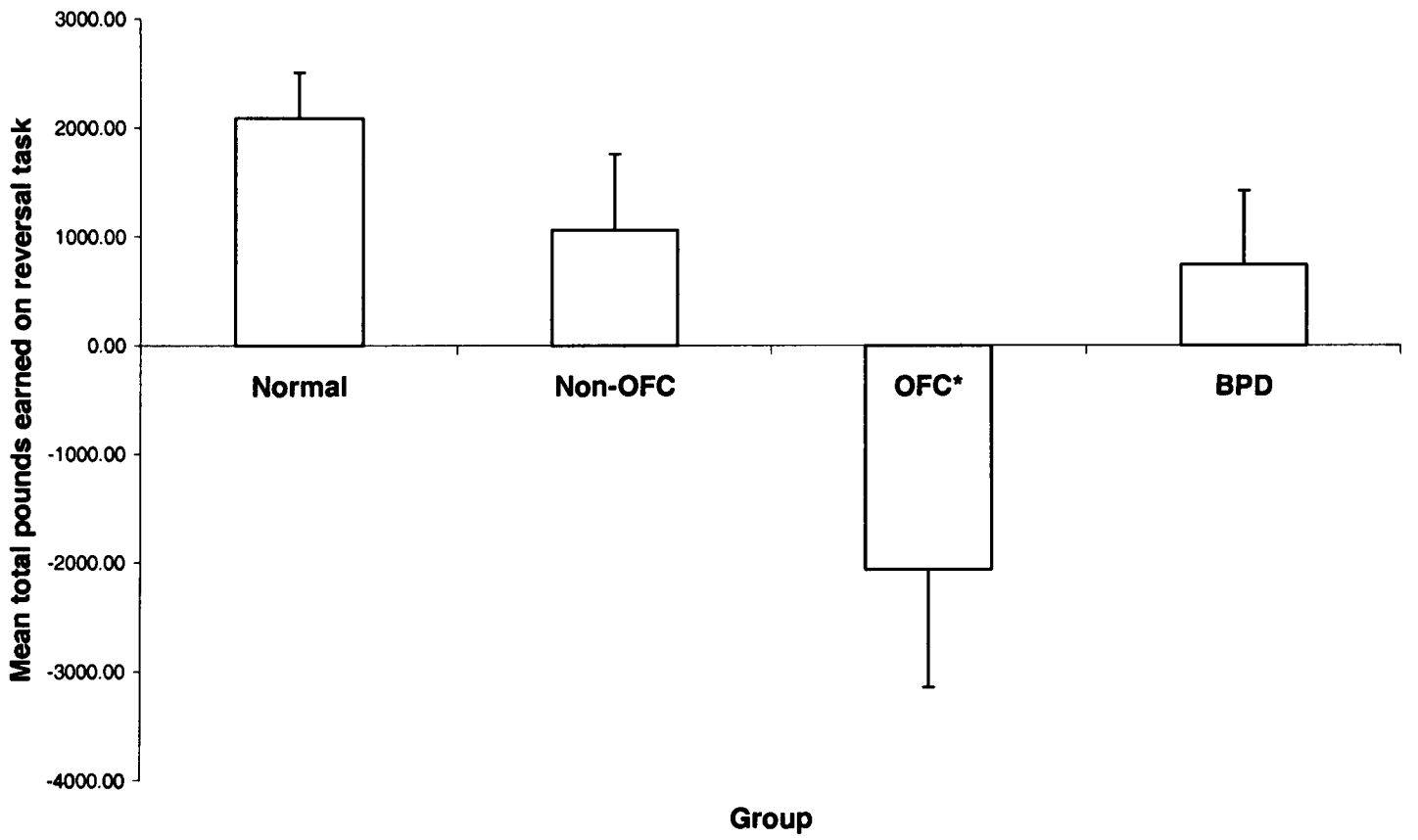



**Figure 3.26:** Histogram of participants' mean total pounds accumulated by the 100$^{th}$ trial on the reversal task by group. OFC participants earned significantly less "money" than did participants in all other groups. While normal, non-OFC, and BPD participants earned "money", OFC participants lost "money".

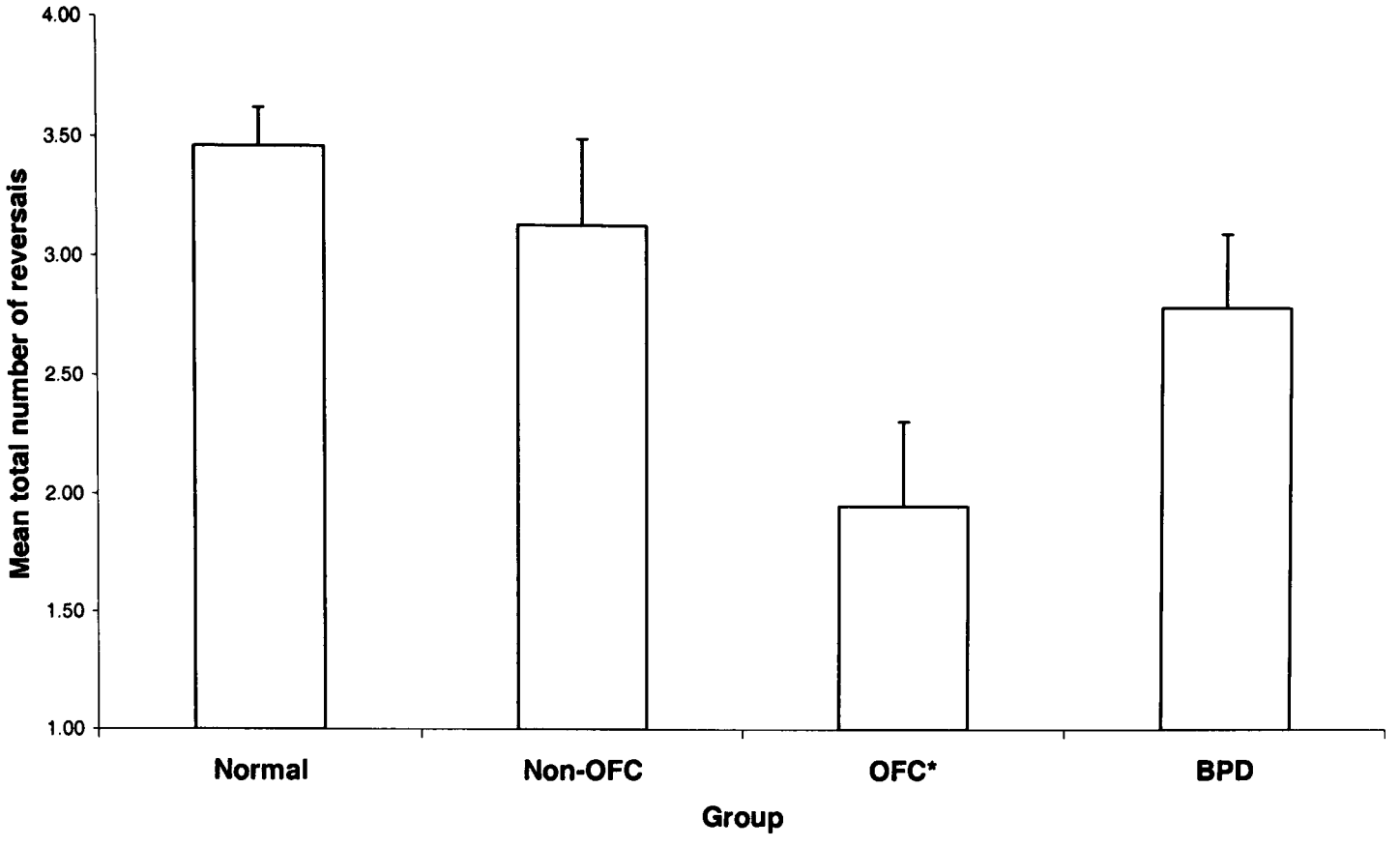



**Figure 3.27:** Histogram of participants' mean total number of reversals achieved by 100 trials on the reversal task by group. OFC participants made significantly less reversals than participants in all other groups.

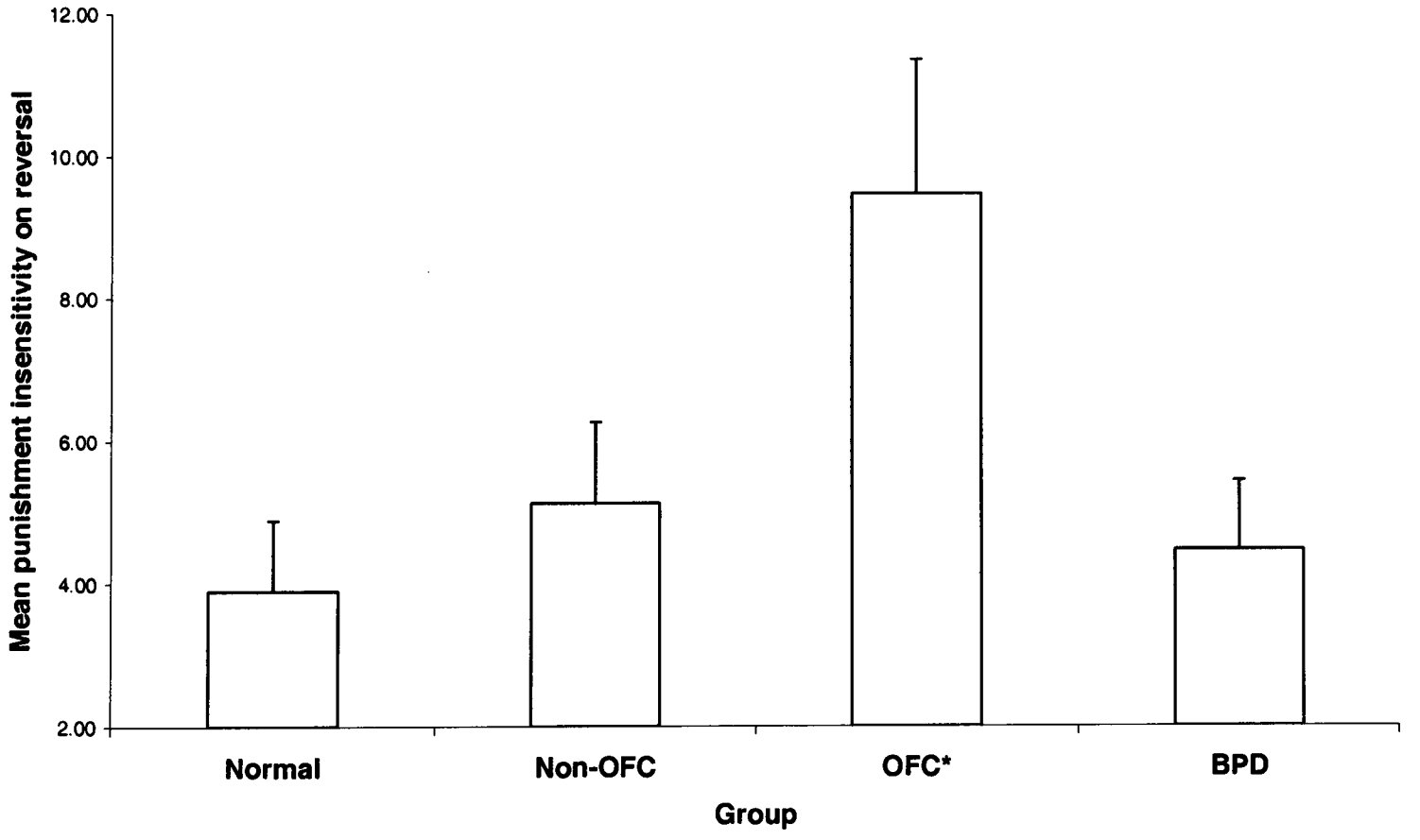



**Figure 3.28:** Histogram of participants' punishment insensitivity (the number of times a consecutive response is made to a stimulus following a monetary loss $\geq$ £250) on the reversal task by group. OFC participants showed significantly higher punishment insensitivity than participants in all other groups.

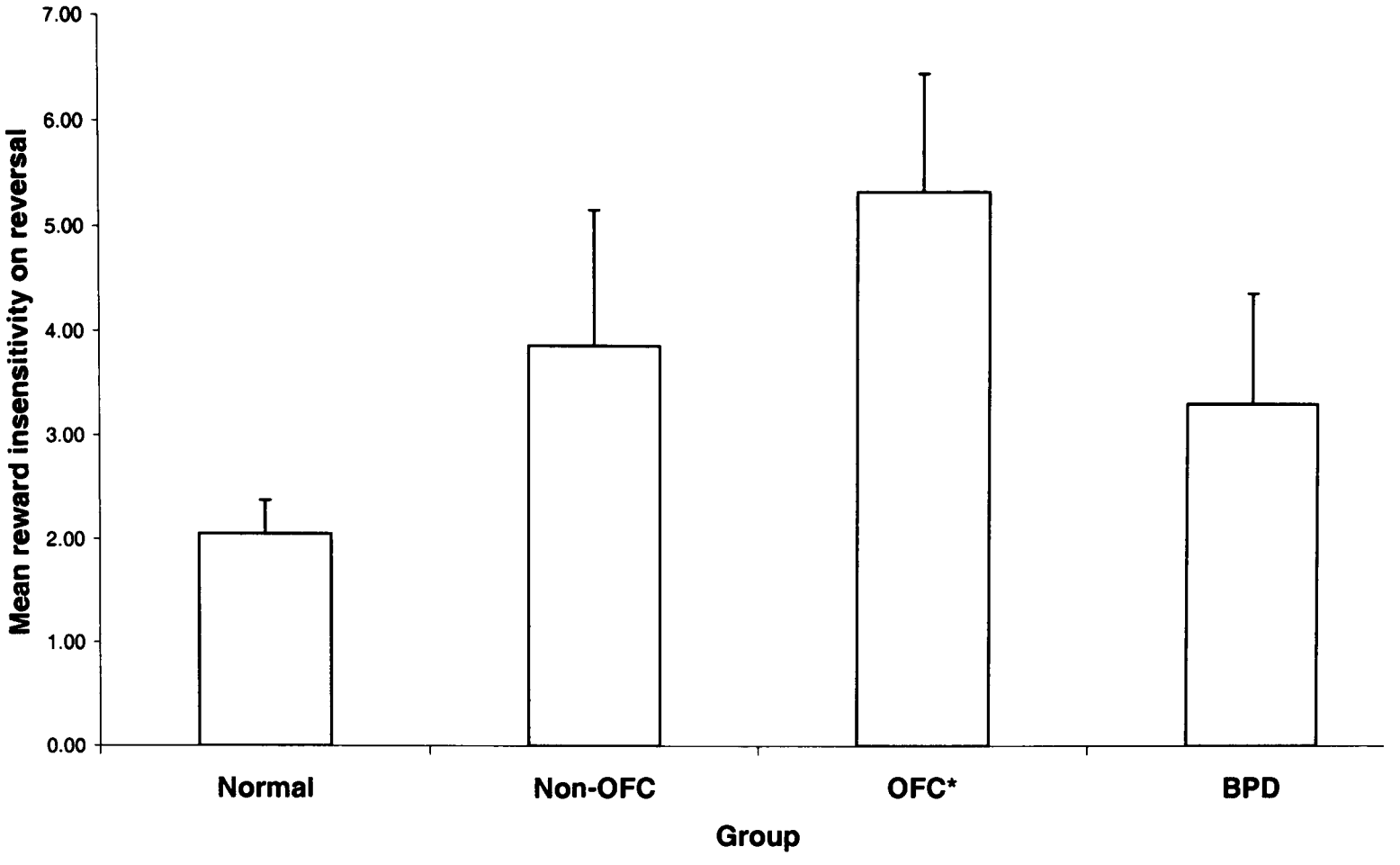



**Figure 3.29**: Histogram of participants' reward insensitivity (the number of times a participant failed to choose a stimulus following a monetary gain ≥ £80) on the reversal task by group. With outliers included, OFC participants showed significantly higher reward insensitivity than normal participants. However, when outliers were excluded the difference failed to reach a reasonable level of significance but the trends were still in the same direction.

### 3.3.2.5 Time Perception

ANOVAs done on each of the time perception variables indicated that participants differed significantly by group in terms of *total time estimation* $F(3,74) = 3.45$, $p < .05$.

LSD post-hoc analysis revealed that OFC participants estimated that significantly more time had past than normal participants did, $p = .002$. While OFC patients overestimated time, indicating a faster subjective sense of time, normal participants underestimated time, indicating a slower subjective sense of time and BPD participants did not differ from normal controls (see Figure 3.30).

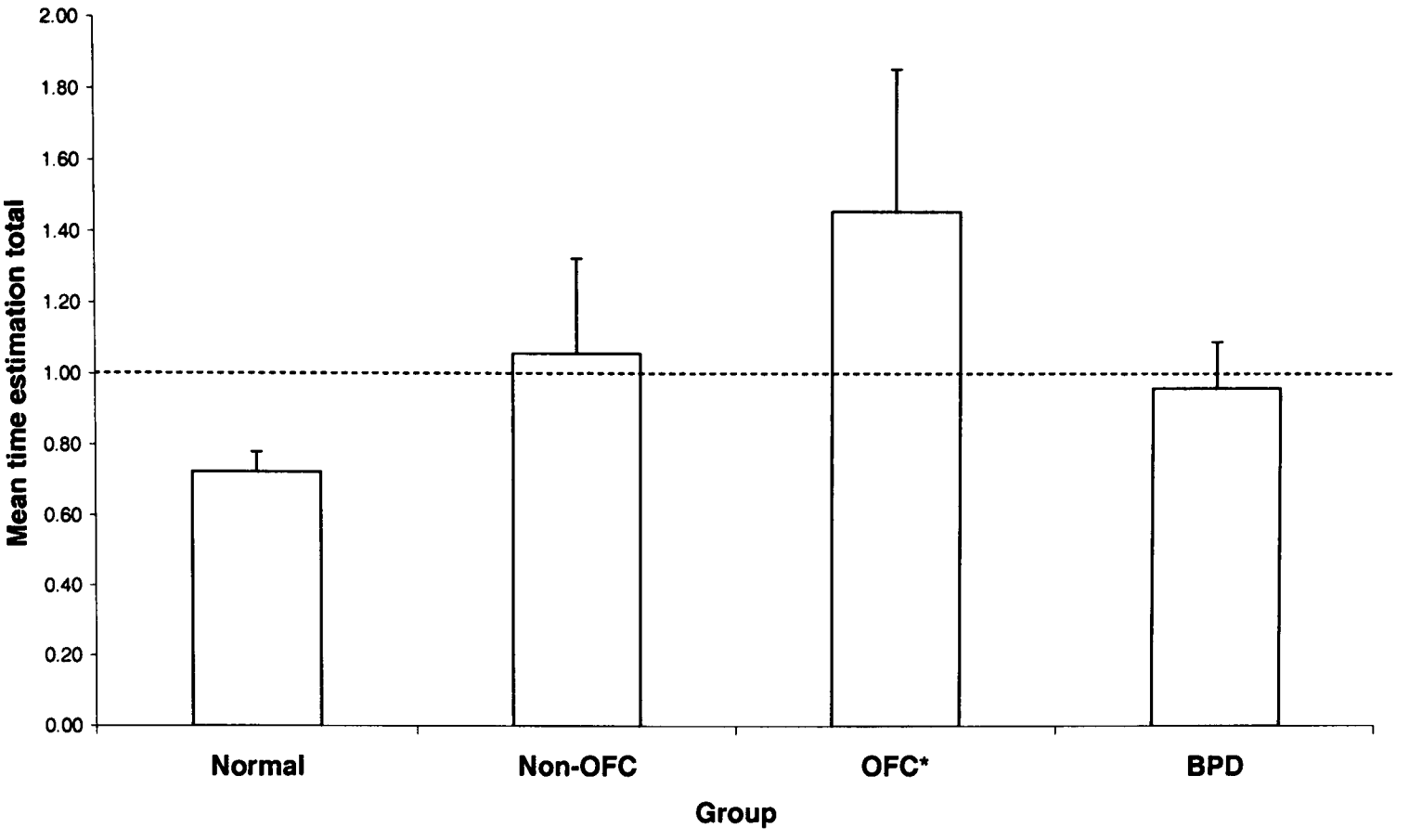



**Figure 3.30**: Histogram of participants' mean total time estimation score [total amount of seconds estimated across all time intervals divided by 190 (total number of seconds actually passed)] by group. OFC participants estimated that significantly more time had past than normal participants did. While OFC patients overestimated time, indicating a faster cognitive pace, normal participants underestimated time.

### 3.3.2.6 Spatial Working Memory

ANOVAs done on each of the SWM variables (between errors on SWM, within errors on SWM, and strategy errors on SWM) indicated that participants' scores differed significantly by group on all three measures, $F(3,77) = 19.27$, $p = .000$, $F(3,77) = 3.65$, $p < .05$, and $F(3,77) = 6.69$, $p = .000$ respectively.

Post-hoc analysis revealed that both non-OFC and OFC patients (most of whom had DLFC damage) made more *between SWM errors* than normal and BPD participants, p = .000 (see Figure 3.31).

LSD post-hocs have shown that non-OFC participants made significantly more *within SWM errors* than normal and BPD participants, $p < .01$ (see Figure 3.32). There was no significant difference between OFC, normal, and BPD participants.

Finally, LSD analysis revealed that non-OFC and OFC participants both used a worse *strategy* than normal ($p < .01$ and $p = .001$) and BPD participants, $p < .05$ (see Figure 3.33).

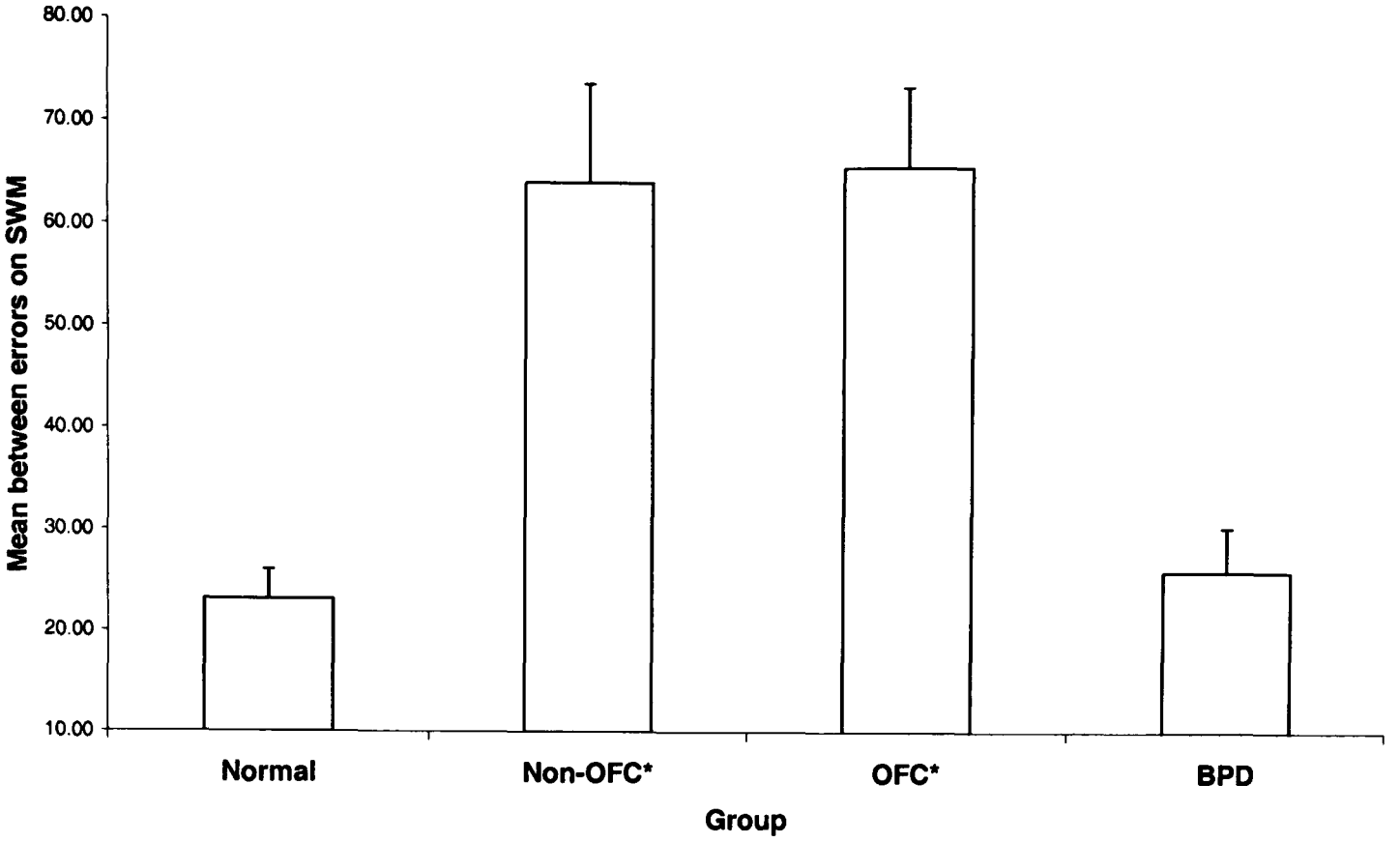



**Figure 3.31:** Histogram of participants' mean number of between errors on the spatial working memory task by group. Both non-OFC and OFC patients (most of whom had DLFC damage) made significantly more between SWM errors than normal and BPD participants.

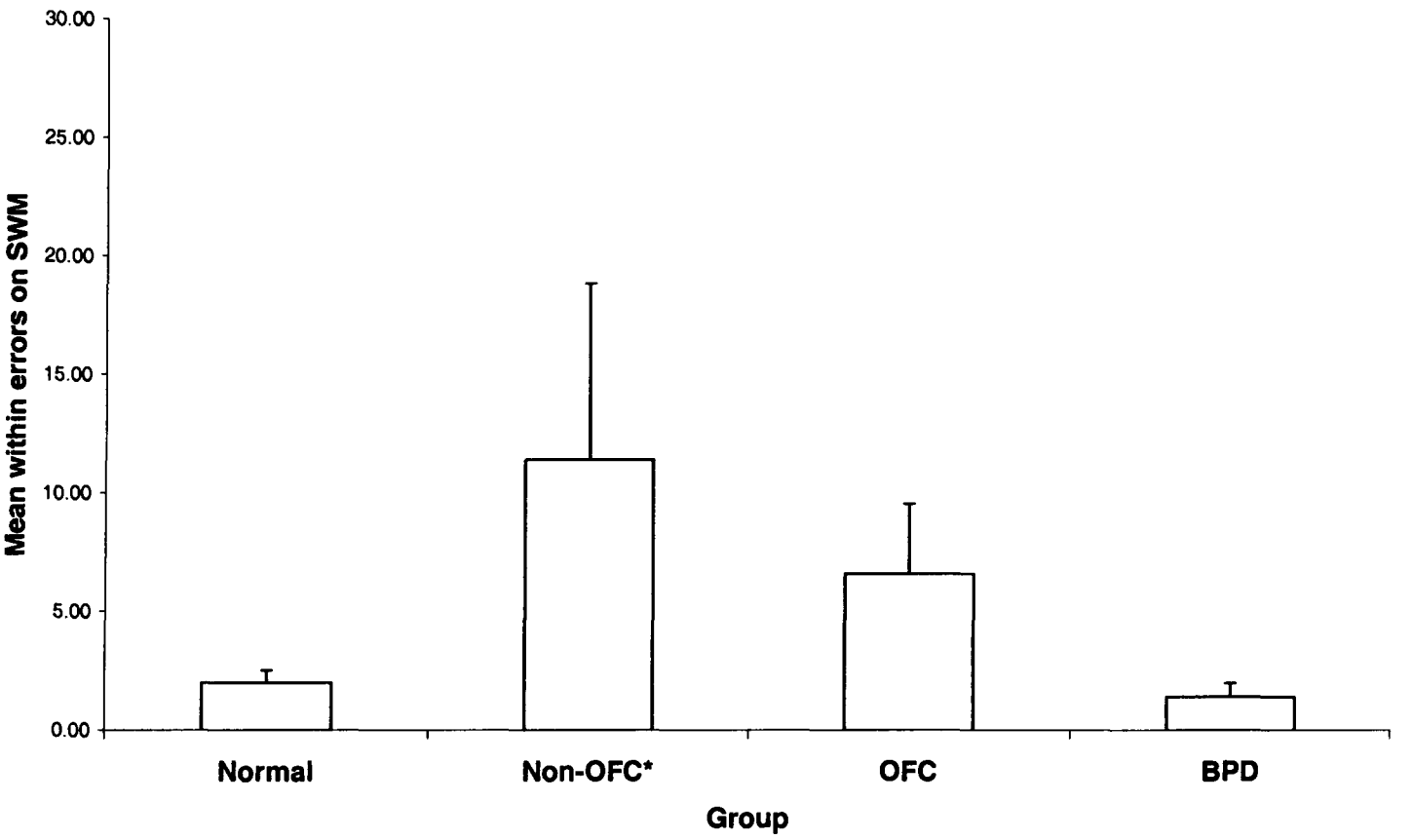



**Figure 3.32:** Histogram of participants' mean number of within errors on the spatial working memory task by group. Non-OFC participants made a significantly higher number of within errors than normal and BPD participants. There was no significant difference between OFC, normal, and BPD participants.

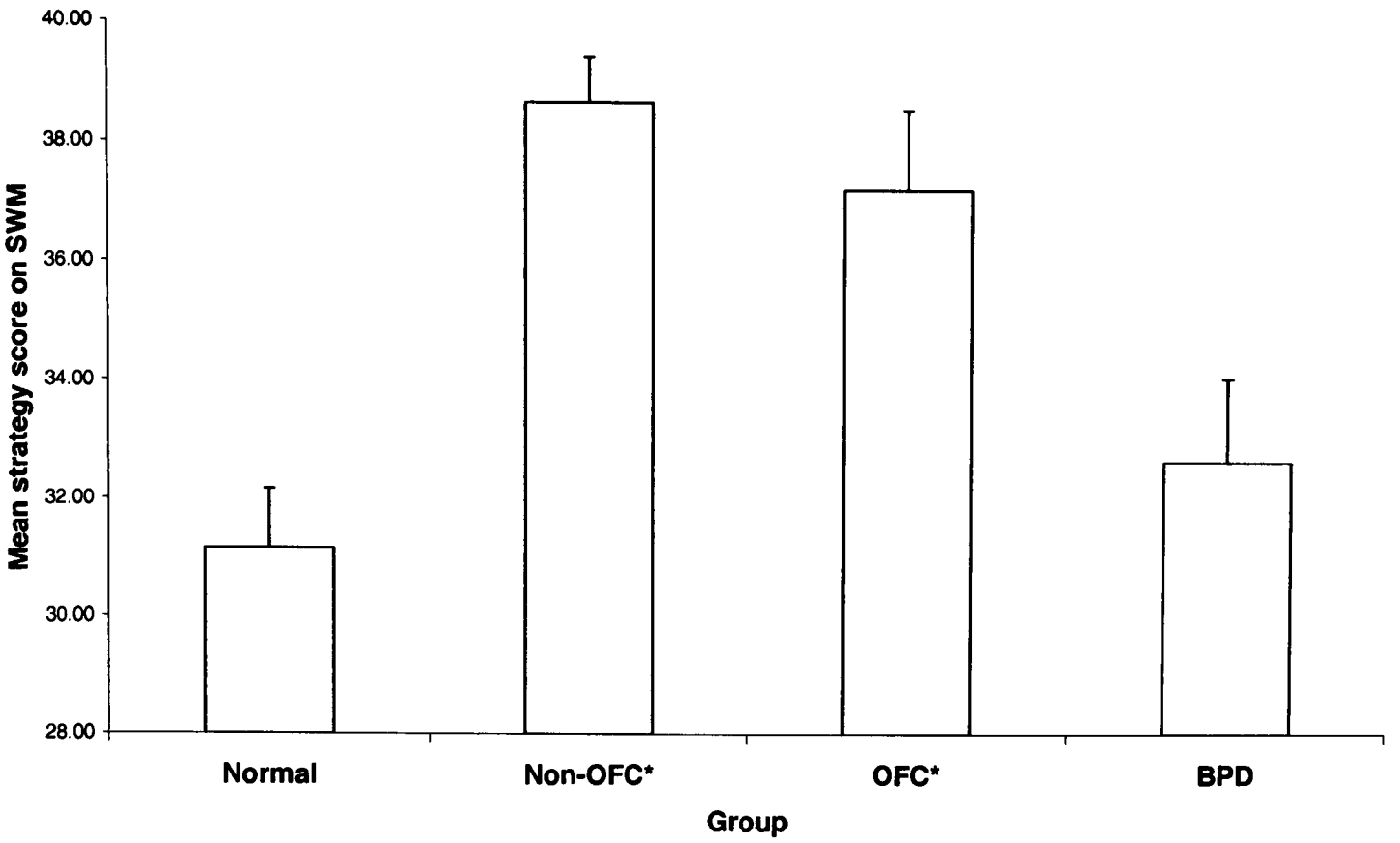



**Figure 3.33:** Histogram of participants' mean strategy score on the spatial working memory task by group. Both non-OFC and OFC patients (most of whom had DLFC damage) had a significantly higher strategy score, indicating a worse strategy used, than normal and BPD participants

### 3.3.3 Discriminant Function Analyses

A stepwise discriminant function analysis was performed using 14 variables as predictors of membership in the four groups; normal control, non-OFC lesion, OFC lesion, and BPD. The predictors included in the analysis were as follows:

1) Frontal Behaviour Questionnaire score

2) total self-report impulsivity score

3-7) personality variables (extraversion, agreeableness, conscientiousness, neuroticism, and openness to experience)

8) total Subjective Emotion Questionnaire score

9) BPD Questionnaire score

10) number of errors per second on the MFFT (behavioural impulsivity),

11) total pounds earned on the reversal task

12) number of between errors made on the spatial working memory task

13) total time estimation

14) total time production

The variables used were the summary variables rather than all the individual sub-components of each summary variable, because discrimination analysis requires that the number of subjects be larger than the number of variables (and if possible for the ratio to be larger than 3; Tabachnick & Fidell, 1996).

Although there were 101 participants in the study as a whole, not all could be included in the discriminant analysis because some patients could not be tested on all the measures. For example, due to logistical reasons, it was not possible to give the behavioural tests or the BPD

Questionnaire to any of the King's College discrete lesion patients (see Section 2.2.2). This reduced the number of subjects to 57 on whom complete or essentially complete data were available. Of these 57 participants, 17 were in the normal group, 8 in the non-OFC, 13 in the OFC, and 19 in the BPD group. The data were complete for 54 of these participants, and for three participants (two from the OFC group and one from the BPD group) data were missing for only one or two variables. As such, their missing values with replaced with variable-specific, within-group means. Evaluation of assumptions of normality and homogeneity of variance-covariance matrices revealed no threat to multivariate analysis.

Three discriminant functions were calculated, with a combined $\chi^2(12) = 112.25$, $p < .001$ (see Table 3.7). After removal of the first function, there was still a strong association between the groups and the predictors, $\chi^2(6) = 50.29$, $p < .001$. After the removal of the second function, $\chi^2(2) = 4.226$, $p > .05$, there was no longer a significant association between the groups and the predictors. As such, the third function will not be discussed further. The two main discriminant functions accounted for 60.3% and 37.5% respectively of the between-group variability (see Table 3.8). The first discriminant function maximally separates participants in the BPD group from participants in the other three groups. The second discriminant function discriminates the normal group from the other three groups (see Table 3.9 and Figure 3.34).

**Table 3.7: Wilks' Lambda**

| Test of Function(s) | Wilks' Lambda | Chi-Square | df | Sig. |
|---|---|---|---|---|
| 1 through 3 | .115 | 112.25 | 12 | .000 |
| 2 through 3 | .380 | 50.29 | 6 | .000 |
| 3 | .922 | 4.23 | 2 | .121 |

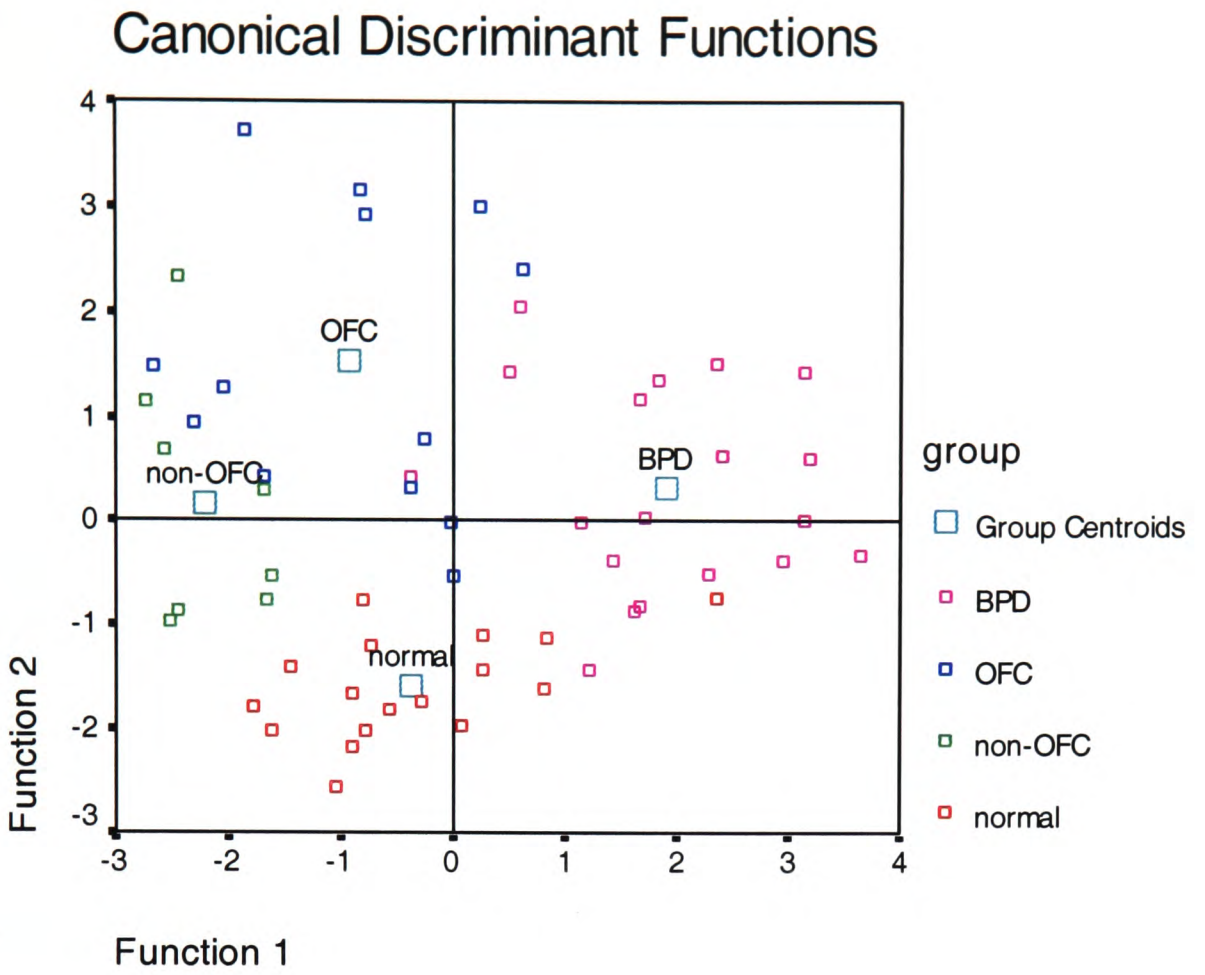
**Table 3.8: Eigenvalues**

| Function | Eigenvalue | % of Variance |
|---|---|---|
| 1 | 2.29 | 60.3 |
| 2 | 1.42 | 37.5 |
| 3 | .085 | 2.2 |

**Table 3.9: Functions at Group Centroids**

| Group | Function | |
|---|---|---|
| | 1 | 2 |
| Normal | -.37 | -1.59 |
| Non-OFC | -2.22 | .17 |
| OFC | -.93 | 1.53 |
| BPD | 1.90 | .31 |

**Figure 3.34:**




As shown in Table 3.10, the loading matrix of correlations between predictors and discriminant functions suggests that the best predictors for distinguishing between BPD participants and participants in the other three groups (the first function) were their BPD Questionnaire, total self-report impulsivity, and Frontal Behavioural Questionnaire scores (loadings < 0.50 were not interpreted; see Tabachnick & Fidell, 1996). First, the BPD group had higher scores on the BPD Questionnaire ($M$ [50] = 12.95) than the normal ($M$ = 5.18), non-OFC ($M$ = 3.63), and OFC groups ($M$ = 7.54). Second, the BPD group displayed more total impulsivity ($M$ = 83.00) than the normal ($M$ = 62.65), non-OFC ($M$ = 62.88), and OFC groups ($M$ = 73.15). Finally, the BPD group showed higher scores on the Frontal Behaviour Questionnaire ($M$ = 13.28) than the normal ($M$ = 8.35), non-OFC ($M$ = 9.44), and OFC groups ($M$ = 12.17).

Two predictors had loadings in excess of 0.50 on the second discriminating function, which separates the normal group and the other three groups: participants' total pounds earned on the reversal task and between errors on the spatial working memory task (see Table 3.10). First, the normal group earned more money on the reversal task ($M$ = 3330) than the non-OFC ($M$ = -274), OFC ($M$ = -4308), and BPD groups ($M$ = 748). Second, the normal group made fewer between SWM errors ($M$ = 10.71) than the non-OFC ($M$ = 63.5), OFC ($M$ = 64.31), and BPD groups ($M$ = 25.95).

[50] The means reported in this section are those for the 57 participants included in the discriminant function analysis, not for the total sample (n=101).

**Table 3.10: Structure Matrix**

| Variable | Function 1 | Function 2 |
|---|---|---|
| BPD Questionnaire score | **.67 *** | .35 |
| Total self-report impulsivity score | **.52 *** | .46 |
| Frontal Behaviour Questionnaire score | **.51 *** | .28 |
| Conscientiousness | -.37 * | -.29 |
| Agreeableness | -.25 * | -.11 |
| Neuroticism | .24 * | .14 |
| Total time production | -.05* | .02 |
| Total pounds earned on the reversal task | .17 | **-.76 *** |
| Between errors on the SWM task | -.39 | **.74 *** |
| Total Subjective Emotion Questionnaire score | .23 | .40 * |
| Errors per second on the MFFT | .17 | .28 * |
| Openness to experience | .14 | -.05 |
| Total time estimation | -.17 | -.04 |
| Extraversion | .04 | .01 |

Key to Table 3.10: Numbers in bold = significant loadings (> 0.5)
* = largest absolute loading between each variable and any discriminant function

The results of the SPSS Version 11.0 classification procedure for the total usable sample of 17 normal participants showed that 16 (94.1%) were classified into the correct group on the basis of their scores on the tests. Of the 8 non-OFC participants, 6 (75%) were classified correctly. Of the 13 OFC participants, 8 (61.5%) were classified correctly. Finally, of the 19 BPD participants, 15 (78.9%) were classified correctly. Across all 57 participants, 45 (78.9%) of participants were classified correctly.

The stability of the classification procedure was checked by a cross-validation run, a process whereby each case included in the discriminant analysis is classified by the functions derived from all cases other than that case. In this instance, 16 (94.1%) of the normal participants, 5 (62.5%) of the non-OFC participants, 8 (61.5%) of the OFC participants, and 15 (78.9%) of the BPD participants were classified correctly. In total, 77.2% of the cross-validated grouped cases were classified correctly.

# Chapter 4: DISCUSSION

In this discussion I will attempt to evaluate and integrate the findings of this study in light the current literature. First, I will explore the functions of the OFC by discussing the key findings and the theoretical and therapeutic implications of the OFC patients' performance on all tests compared to non-OFC (DLFC) patients and normal controls. I will then discuss the performance of BPD patients compared to normal subjects. Next, the hypothesis that OFC dysfunction may contribute to some of the inappropriate behaviours displayed by self-harming BPD patients will be explored by discussing the key similarities and differences between OFC and BPD patients performance on all tests and the theoretical and therapeutic implications of the these findings. Finally, I will discuss the conclusions, strengths, and limitations of this study as well as possible directions for future studies based on this research. The relationship between the different tests, based on the correlation analysis of the most salient variables across all groups, and suggestions for future studies, will be discussed throughout this discussion as well. As there were many findings and I wanted to give a general discussion without repeating all of the details of the results, please refer back to the appropriate sections in Chapter 3 (Results) and any sections I explicitly refer to for further details when reading this discussion.

## 4.1 Orbitofrontal Cortex Patients' Performance - Key Findings

OFC patients' performance is discussed in this section in comparison to non-OFC PFC lesion patients and normal controls. Accordingly, OFC patients performed more impulsively on both self-report (including total score and non-planning, motor, and cognitive impulsivity subscale scores) and cognitive/behavioural (errors/second on the MFFT) measures of impulsivity, had more inappropriate "frontal" behaviours, BPD traits, experienced more subjective anger and less subjective happiness, and performed worse on the reversal task than non-OFC and normal controls. Further, OFC patients had a faster subjective sense of time (less time produced in total and at 60 and 90 seconds and increased total time estimation) than normal controls, while non-OFC patients did not differ from normals. Finally, both OFC and non-OFC patients made significantly more between spatial working memory (SWM) errors and were less open to experience than normal participants. There were no differences between OFC patients, non-OFC lesion patients, and normal controls on all other personality traits, most notably extraversion, or between OFC and non-OFC patients in their emotional changes since their injury.

In sum, OFC patients were impulsive (both self-report and behavioural), reported inappropriate behaviours (both of the frontal and of the BPD type), were angry, unhappy, closed to experience, insensitive to punishment (demonstrated by their poor reversal performance), had fast cognitive tempos, and poor SWM. These findings are discussed separately in more detail below.

### 4.1.1 Impulsivity

#### 4.1.1.1 Self-Report Impulsivity

OFC patients were more impulsive than normal and non-OFC lesion controls on both the self-report and the cognitive behavioural measure of impulsivity. OFC patients also scored higher in each of the self-report impulsivity subcategories (non-planning, motor, and cognitive impulsivity) than both control groups. Also, there was a significant positive correlation between both measures of impulsivity across all subjects, which is in contrast to the findings of Barratt & Patton (1983; Barratt, 1981; see Section 1.11.3) that behavioural and cognitive measures of impulsivity (the MFFT and the BIS) are not correlated. According to the findings in the current study, both types of measures of impulsivity seem to be measuring the same dysfunction but in different ways. This dysfunction seems to be related to the OFC as patients with OFC lesions, and not patients with other PFC lesions or normal controls, scored significantly high on both tests of impulsivity.

One of the arguments against self-report measures is that they rely on patients' insight and that their insight might be impaired because of their lesion. However, behavioural measures of impulsivity were also used and the self-report and behavioural (which does not rely on insight) measures of impulsivity were significantly correlated. OFC patients were significantly more impulsive on both measures than normal and non-OFC controls. Therefore, OFC patients' insight about their own impulsive behaviour does not appear to be impaired. That is, they are aware of their own shortcomings yet are still unable to stop themselves. This may have valuable therapeutic implications. For example, if patients are encouraged to stop and think before they act they may be able to modify their behaviour (discussed further in Section 4.1.10). In doing so, perhaps some of the socially inappropriate behaviours of OFC patients could be avoided.

Consistent with previous findings (see Section 1.11.3), impulsivity was also related to time perception problems. OFC patients had a faster subjective sense of time than both control groups in terms of less time produced in total and at 60 and 90 seconds and increased total time estimation. Further, across all subjects, total self-report impulsivity (SRI) score was positively correlated with a sped-up perception of time in terms of decreased total time production, and the non-planning subcategory of the SRI questionnaire (the BIS-11) was positively correlated with increased time estimation across all time intervals (10, 30, 60, & 90 seconds). OFC patients also had a significantly lower mean time latency than normals on the behavioural impulsivity task (see Section 4.1.1.2). This implies that impulsivity may be a result of a fast cognitive pace, which may lead to impatience or the inability to stop and think before acting (see Section 4.1.2). In fact, two of the questions on the Frontal Behaviour Questionnaire that OFC patients scored higher than control groups on and that were positively correlated with self-report and behavioural impulsivity, were: "Do you stop to think before you act?" and "Do you stop to think before you take a decision?"

Part of the reason that OFC patients are impulsive could also be related to an inability to delay responding when rewards or punishers are involved. As discussed in Section 1.7.7, the OFC may be involved in the representation of rewards and punishers and when damaged, sensitivity to

reward and punishment may be affected, causing patients to act immediately to gain a reward despite the negative consequences. Therefore, OFC patients may act without giving themselves enough time to think about their behaviours and to modify them accordingly.

It is also interesting to note that SRI and extraversion (E) were highly negatively correlated within normal controls and across all subjects. So, the more impulsive a participant, the less extraverted they are. However, OFC patients were *not* significantly more extraverted than both controls groups. These findings are in contrast to Barratt & Patton's (1983) finding that E correlated positively with the BIS (SRI) in normal subjects. However, they measured E using the Eysenck E scale, which may be sensitive to a different aspect of extraversion. The Eysencks originally considered impulsiveness to be an integral part of E (Eysenck & Eysenck, 1963), but they later decided that there were two distinct components of impulsivity: venturesomeness, which aligned with E, and impulsiveness, which was realigned to be part of the psychoticism (P) dimension (Eysenck & Eysenck, 1978, 1980; Eysenck et al., 1985b). The BIS then correlated significantly with the P subscale and not the E subscale of the Eysenck Personality Questionnaire-R among an inpatient psychiatric population (O'Boyle & Barratt, 1993).

As far as this study is concerned, SRI and extraversion are inversely related. This is in contrast to Eysenck's original theory that extraversion and by extension impulsivity is caused by low cortical arousal (Eysenck, 1967). Extraversion and impulsivity appear to be unrelated and therefore could not be caused by the same underlying feature of low cortical arousal. The findings in this study do however favour Gray's (1970) theory that introverts (anxious neurotic people) are more sensitive to punishment and non-frustrative reward than extraverts. Accordingly, OFC patients in this study, who were *not* introverted, were in fact *less* sensitive to punishment on the reversal task than BPD patients, who were introverted (see Sections 4.1.7.1 & 4.4.1.3).

#### 4.1.1.2 Behavioural Impulsivity

On the Matching Familiar Figures Test (MFFT), a cognitive/behavioural test of impulsivity, OFC patients made more errors per second than non-OFC lesion patients and normal participants. However, when broken down into number of errors and time latency, OFC and non-OFC patients did not differ from each in terms of number of errors (they both made significantly more errors than normal controls) yet only OFC patients had a significantly lower mean time latency than normals. So the non-OFC lesion patients did not act impulsively in terms of low time latency to respond. Non-OFC lesion patients *did* take their time to respond. Thus the high number of errors non-OFC lesion patients made on this task could be due to other cognitive deficits like failure to pay attention. Most non-OFC patients had DLFC damage (17 out of 20) and some had parietal damage as well (4 out of 20) and both the DLFC and parietal cortex have been associated with attention (Iba & Sawaguchi, 2003; Kolb & Wishaw, 1996). In particular, non-human primates with DLFC lesions have shown an impaired ability to "monitor multiple stimuli" (Petrides & Pandya, 1999) and imaging studies have found that the DLFC is involved in dual-task performance

(Szameitat et al., 2002). Although some of the OFC patients also had DLFC damage (14 out of 23), which could contribute to some of the errors they made, their deficit also included responding impulsively in terms of decreased response times. So OFC patients' high number of errors may also be due to a failure to inhibit responding long enough to think about the task and respond correctly. This corresponds with the finding that OFC patients made more errors than non-OFC patients on the MFFT (21.00 versus 18.22 respectively), although this difference was not significant.

The behavioural impulsivity displayed by OFC patients on the MFFT may result from a problem with reinforcement sensitivity rather than a lack of motor response inhibition. So, impulsive behaviour, in terms of lower response latency and increased errors on the MFFT, could result from OFC patients' desire for an immediate reward (getting the correct answer) despite the consequences (making the wrong choice by choosing too quickly). Thus, they fail to inhibit responding even though it would be beneficial to take more time to think about the task before acting. Perhaps they become frustrated and want an immediate reward despite the benefits of waiting to respond. This coincides with the performance of OFC patients on the reversal task where they are more insensitive to punishment than all other groups[51]. In fact, behavioural impulsivity correlated negatively with pounds earned on the reversal task and positively with the Frontal Behaviour Questionnaire score across all subjects. So the more behaviourally impulsive a subject, the worse their reversal performance and the more inappropriate behaviours they displayed. Again, a beneficial therapeutic tactic might be to encourage patients to wait before responding and perhaps then they would make fewer errors on the MFFT and less socially inappropriate behaviours.

### 4.1.2 Time Perception

The intolerance of delay or inability to delay responding on impulsivity tasks may be related to a faster cognitive tempo in OFC patients. Accordingly, Barratt & Patton (1983) view impulsivity in terms of cognitive tempo and speculate that there are individual differences in the timing of cognitive and behavioural processes that characterise differences in impulsivity. They argue that arousal level is related in part to impulsivity and that action-oriented subjects have a faster cognitive tempo and respond more quickly in certain situations. That is, the internal clocks of impulsive individuals are faster than the internal clocks of non-impulsive individuals. So an impulsive individual would be likely to *overestimate* and *underproduce* time intervals.

Accordingly, when asked to produce set time intervals OFC patients produced less time in total and were particularly worse at the longer intervals of 60 and 90 seconds than normal controls while non-OFC lesion patients were no different from normal controls. So, for OFC patients, time production decreased the longer the time intervals became. In fact, at 90 seconds OFC patients were the only group to underproduce while both control groups overproduced. This could indicate

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[51] See Section 4.1.3.3; When outliers where included, OFC patients also failed to *maintain* responding to a rewarding stimulus after having received a large reward (an indication of reward insensitivity) more frequently than normal controls. However, this effect disappeared when outliers were removed.

that the longer the interval, the more frustrated OFC patients become. This frustration with waiting for the time interval to end may have caused OFC patients to say that the set time interval was over sooner than control groups in order to achieve the reward of having the task end.

Further, when asked to estimate how much time had passed in a set time interval, OFC patients overestimated in total significantly more than normal participants while non-OFC patients were no different from normal controls. Thus, the time intervals felt much longer to the OFC patients than they actually were. This could be due again to their frustration with waiting for the time interval to end. It may also be that OFC patients have a faster cognitive pace than all other groups in addition to being frustrated by non-reward (discussed further in Section 4.4.4). Another aspect of time that may be related to impulsivity and disruptive behaviours is reaction time. As mentioned above, impulsive OFC patients had quicker response times on the MFFT than both control groups. This might be due to their increased cognitive tempo or to their desire for an immediate reward despite the negative consequences.

Some evidence supports the theory that SWM and the DLFC are related to time perception problems (Miruma et al., 2000; see also Section 1.11.2.2). In the current study, increased time estimation, across all subjects, was positively correlated to the number of between errors on the SWM task. So, in a sense, the faster the subjective sense of time of a participant the worse they performed on the SWM task. However, there was no correlation between time production and SWM and time perception deficits did not seem to be related to DLFC deficits. For, both non-OFC (all 9 who took the time perception tasks had DLFC damage) and OFC (8 out of the 13 who took the test had DLFC damage) had deficits on the SWM task compared to normal controls however, non-OFC patients did not have time perception deficits while OFC patients did. Based on previous studies non-OFC (DLFC) patients were expected to have time perception deficits if time perception was related to working memory, however they did not. Thus, something else must be the cause of the time perception problems experienced by OFC patients. It could be that cognitive pace (Hoagland 1933; Carlson & Feinberg 1968) or decision making about abstract types of information, which have been related to OFC function (see Krawczyk, 2002 for a review), rather than working memory, underlie certain aspects of time perception.

There is also evidence that indicates that the right PFC is more involved in time perception than the left (see Section 1.11.2.1). The results of this study indicate that there were some differences between left- and right-sided OFC and non-OFC lesion patients, but the deficits were more severe for patients with left-sided as opposed to right-sided lesions. Left-sided OFC and non-OFC lesion patients tended to overestimate in total and particularly at short time intervals (10 and 30 seconds) and underproduce at long time intervals (60 and 90 seconds) significantly more than right-side lesion patients. However, the group sizes were not proportional between left-sided (n=4) and right-sided (n=10) patients and many lesion patients did not partake in the time perception tasks due to testing time constraints. More patients would therefore need to be tested in order to achieve more reliable results concerning PFC lateralisation and time perception.

In all, based on the current findings, OFC patients seem to have a faster cognitive pace and/or experience frustration with delay of reward, making time intervals feel subjectively longer than they actually are and causing them to overestimate and underproduce time. This may also explain some of the impulsive and inappropriate behaviours exhibited by OFC patients. Accordingly, OFC patients demonstrated a significantly faster subjective sense of time (underproduced and overestimated time) and reported more impulsive (both self-report and behavioural) and "frontal" behaviours than both control groups. Also, across all subjects, a faster subjective sense of time, in terms of decreased time production, correlated with increased SRI and "frontal" behaviours as well as decreased openness to experience (increased time estimation also correlated with decreased openness to experience).

It is interesting that SRI but not behavioural impulsivity correlated with time production while both SRI (the non-planning sub-score) and behavioural impulsivity (time latency on the MFFT) correlated with time estimation. The correlations were such that as impulsivity increased (higher SRI score, lower time latency on the MFFT, and higher non-planning SRI score), subjective sense of time sped-up (less total time produced and more total time estimated respectively). This could mean that although time perception appears to be related to impulsivity, two different brain mechanisms may underlie time production and time estimation (discussed further in Section 4.4.4).

The exact relationship between cognitive tempo and frustration to non-reward must be explored further. In may be that a fast cognitive tempo in OFC patients is the cause of or simply exacerbates the frustration to non-reward and intolerance of delay of reward (the ending of the time task) that is demonstrated by OFC patients on time perception tasks. Whatever the underlying cause, it appears that OFC participants have a problem with evaluating the passage of time at short intervals, which is related to measures of impulsivity and, which may lead to the behavioural deficits identified in these patients (see Sections 4.1.4 & 4.1.9).

### 4.1.3 Probabilistic Reversal

#### 4.1.3.1 Acquisition Task

The acquisition task enabled participants to familiarise themselves with the task demands and appreciate the probabilistic nature of the reward contingencies. This task was complete once the subject learned to consistently select the positive stimulus (to select S+ 16 out of the previous 18 consecutive responses) and there was no reversal. Since all participants successfully completed this task, it indicates that they understood the task demands and were able to adequately follow the instructions. Thus, those explanations could not explain poor performance on the reversal task. Further, since OFC patients were able to reach criterion on the acquisition task, their reversal impairments can not be explained by a failure to simply learn stimulus-reinforcement associations. Also, because OFC patients commented on the changing contingencies and described both the test and their performance after the test accurately, their poor performance on the reversal task could

not be attributed to a failure to comprehend or inability to retain the instructions given at the beginning long enough to achieve success. Since OFC patients' explicit system seems to be intact, their poor performance on the reversal task is most likely due to implicit deficits.

### 4.1.3.2 Reversal Task

OFC patients compared to patients with lesions outside of the OFC and normal controls, were significantly impaired on the reversal task: they earned less money in total, obtained fewer reversals, and were more punishment insensitive (number of times they choose a stimulus after having lost ≥250 pounds). These results confirmed the findings of Rolls et al. (1994) that lesions to the human ventral PFC can result in profound impairments in emotion-related reversal learning. By using patients with more delineated circumscribed PFC lesions and a larger number of patients than those used in Rolls et al. (1994), these results provide further evidence that, in humans, as in non-human primates, lesions of the OFC result in impairments in the ability to respond adaptively to the receipt of rewards and punishers that are made contingent upon a set of arbitrary stimuli or responses (Iversen & Mishkin, 1970; Bechara et al., 1994; Meunier et al., 1997).

The impairment of the OFC patients on the probabilistic reversal task can be interpreted in two ways. The repeated touching of the previously rewarded stimulus can be explained as simply motor perseveration (i.e. a failure of inhibitory control of the arm/hand with which patients reached out to the now incorrect stimulus) or a difficulty in altering stimulus-reward associations when the reward contingencies are reversed. The former explanation does not seem plausible as a response was required and made on every trial and the position of the old S+ was constantly changing. So the continued selection of the old S+ must reflect OFC patients' difficulty in forming new stimulus-reward associations when reinforcement contingencies are reversed. In other words, the failure to inhibit motor responses explanation can be ruled out, because in this present study the use of a concurrent visual discrimination design where S+ keeps switching position does not require the patient to inhibit a motor response on any trial, as they have to make a motor response on every trial. The design of this study therefore is consistent with the fact that the OFC patients' impairment at reversal learning (or extinction) was not due to a difficulty in inhibiting a motor response on "no-go" trials.

Since impairments of OFC patients on emotion-related reversal learning is not simply due to a difficulty in inhibiting motor responses, the current results are consistent with the hypothesis that one important function of the OFC is representing the reward and punishment value of stimuli and, more specifically, since all of the OFC patients succeeded in the acquisition stage of the reversal task (before the first reversal), in updating the associations between stimulus and reinforcers when the associations change. Also, the clear instructions explaining that reversals will occur and that the subject was to alter his/her choice of stimulus accordingly, and the fact that the patients made a selection on every trial, excludes an interpretation in terms of lack of initiative or failure to understand the task requirements.

These results complement the results of an fMRI study (O'Doherty et al., 2001b; see also Section 1.7.4), where the OFC in normal (non-lesioned) participants was activated during the performance of the same emotion-related reversal task. The activation was found during the receipt of rewards and punishers following the selection of each stimulus, and the magnitude of the rewards and punishments obtained was correlated with the magnitude of activation in the OFC. Medial OFC activation was correlated with the amount of money received and lateral OFC activation was correlated with the amount of money lost. The finding in this study of an impairment at the same task in patients with lesions to the OFC suggests that the role of the OFC in the representation of rewards and punishments is critical for successful performance of the task. This implies that damage to the OFC abolishes or alters a patient's ability to represent rewards and punishers, which can be a cause of some of their inappropriate behavioural problems (see Sections 4.1.4 & 4.1.9) as they may have a profound difficulty in responding adaptively to environmental reinforcers.

In this study, it was not possible to establish a dissociation between effects of medial OFC and lateral OFC lesions as most OFC patients' lesions were not restricted to either medial or lateral sectors. The fMRI study discussed above (O'Doherty et al., 2001b) would lead to the prediction that it may be possible to establish a dissociation between effects of lesions to the medial and lateral OFC in terms of the type of error that is produced. Based on the locus of activations to reward and punishment in the fMRI study, a lesion restricted to the medial OFC may produce a greater degree of errors of the reward insensitivity type (failing to stick to a stimulus after a gain of $\geq$ 80 pounds), whereas lesions to the lateral OFC may produce a greater degree of preservative errors of the punishment insensitivity type. Further research is needed to investigate this, perhaps by testing patients with discrete medial OFC and lateral OFC lesions on the reversal task.

#### 4.1.3.3 Insensitivity to Reward and Punishment

As discussed in the Section 3.3.2.4.3, OFC patients demonstrated punishment and some reward insensitivity. Not only did they fail to switch their choice of stimulus following a large punishment, but they also failed to stick to a stimulus following a large reward. This result further dispels the response inhibition theory of OFC function. The main prediction, as discussed above (Section 4.1.3.2), is that the predominant error made on reversal learning tasks are of a preseverative nature, where the patient continues to make consecutive responses to a previously rewarded stimulus even though it is no longer rewarded (Rolls et al., 1994; Robbins, 1996; Roberts & Wallis, 2000). This type of error was clearly made frequently by OFC patients, as they made consecutive responses to a stimulus following a large loss more often than both non-OFC lesion patients and normal participants. However, OFC patients (only when outliers were included) also failed to *maintain* responding to a rewarding stimulus after having received a large reward compared to normals. This type of response, although not as common as the punishment insensitive response, cannot be classed as perseverative, but instead as a difficulty in learning to respond to (or acquiring) the now

rewarded stimulus. This suggests that perseveration is not the only type of error associated with lesions to the OFC and thus a response inhibition hypothesis alone is not a sufficient explanation for the impairments found following OFC lesions. This type of non-perseverative error in reversal was first reported by Iversen & Mishkin (1970), who found that lesions to the medial OFC in macaques resulted in difficulty in learning to respond to (or acquire) the currently rewarded stimulus.

It is important to clarify that describing OFC patients as insensitive to rewards and punishments does not imply that patients are unable to experience an affective or emotional response immediately after receiving reinforcers. Rather, it is evident from observing patients' behaviour during the task that they often showed a strong affective response upon receipt of, for example, a large loss on a previously rewarded stimulus and often expressed their disappointment in a demonstrative way like sighing or wincing. In fact, in an investigation of the affective response in ventromedial PFC lesion patients to monetary rewards and punishers (see Section 1.7.3), Bechara et al. (1997) recorded galvanic skin responses (GSR) in response to a gambling task and found that patients did show a normal affective response (as shown by a change in skin conductivity) upon receipt of monetary rewards and punishments. The terms punishment and reward insensitivity are used here to describe the fact that patients seem unable to use the information about rewards and punishments obtained from a stimulus to guide the selection of subsequent responses. This effect was also observed in Bechara et al. (1997), who found that while the patients with OFC lesions did show normal GSR to the receipt of rewards and punishers, they did not show any "anticipatory" GSR when making decisions about which stimulus to choose next.

So, the present results provide further evidence of the dissociation described in the literature between what patients with frontal damage say or what they are aware of and what they do (Rolls et al., 1994; Damasio et al., 1990; Milner, 1964; Miller, 1992). This coincides with the finding that OFC patients report being impulsive on the SRI questionnaire yet, even though they are aware of their impulsive behaviours, continue to act impulsively as demonstrated by their impulsive behaviour on the MFFT. This again demonstrates that OFC patients have an implicit rather than explicit deficit. This implicit deficit may frustrate patients, as they are aware that they are choosing disadvantageously, yet are unable to do anything about it. Their explicit system seems to be monitoring and reacting to a failure of their implicit system to make adjustments to changing stimulus-reinforcement associations.

#### 4.1.3.4 Summary of Reversal

Overall, these findings suggest that the impairments at emotion-related reversal learning in OFC lesioned humans are best characterised as being due to a fundamental difficulty in processing rewards and punishments or in reversing stimulus-reinforcer associations, rather than being attributed simply to a difficulty in inhibiting previously relevant responses. Further, some of the reasons for the behavioural and emotional changes experienced by people following OFC damage

may be related to deficits in decoding the reward and punishment value of stimuli and using the results of the decoding to modify behaviour and emotional state (Rolls, 1990, 1999, 2001; Rolls et al., 1994). So, emotional and social problems may occur in OFC patients because the ability to respond appropriately to reinforcing stimuli and to learn when reinforcement associations change is of central importance to emotion and in social and emotional responses to behavioural stimuli.

### 4.1.4 Frontal Behaviour Questionnaire

In previous studies describing emotion and social functioning after frontal lobe lesions (Rolls et al., 1994; Hornak et al., 1996, 2003b; Bechara et al., 1994, 1998, 1999), the lesions covered a large territory of PFC on the ventral surface, and, in some cases, damage included rostal anterior cingulate and more medial PFC regions as well, making it impossible to evaluate separately the contributions of the OFC. Patients with much more circumcised surgical or stroke related lesions were tested in the current study in order to better differentiate the specific contributions of the OFC to emotion and social behaviour.

OFC patients reported significantly more inappropriate social behaviours than both non-OFC lesion and normal controls on the Frontal Behaviour Questionnaire, which was designed to quantify the social-behavioural abnormalities associated with PFC damage. Since OFC patients also scored significantly worse than both control groups on the reversal task, this suggests that the difficulty shown by OFC patients in rapidly altering stimulus-reinforcement associations may at least be partly responsible for their disinhibited and inappropriate behaviour. OFC patients' report of more impaired social behaviours coincides with the generally held view (Lezak, 1995; Barbas & Pandya, 1991) that lesions of the DLFC are more likely to affect planning and other higher cognitive functions like SWM, whereas lesions of the OFC, with its connections to the limbic system[52], have a greater effect on social behaviour and emotion (emotion is discussed further in Section 4.1.5). Further supporting the involvement of the OFC in both behaviour and emotion, the current study found a positive correlation between "frontal" behaviours and subjective emotions across all subjects: the more "frontal" behaviours reported, the more emotional one reports being. In addition, only OFC patients had significantly higher scores on both the Frontal Behaviour and Subjective Emotion Questionnaire (in terms of increased anger and decreased happiness; see Section 4.1.5.1) compared to normal and non-OFC participants.

Inappropriate "frontal" behaviours are also linked to impulsivity in that OFC patients behaved and reported being significantly more impulsive in addition to reporting significantly more "frontal" behaviours than both control groups. Further, SRI and Frontal Behaviour Questionnaire scores were positively correlated across all subjects, so the more impulsive, the more "frontal"

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[52] The limbic system is a group of brain structures (amygdala, cingulate gyrus, fornix, hippocampus, hypothalamus, olfactory cortex, and thalamus) that affect mood, various emotions including pleasure, fear, happiness, and motivation, and the endocrine and autonomic motor system. The limbic system is thought to be involved in controlling emotions and emotional responses, hormonal secretions, mood, motivation, and pain and pleasure sensations (Rolls, 1999).

behaviours reported. OFC patients' impulsivity in terms of increased response times on the MFFT and faster cognitive tempos on the time perception tasks, could contribute to their failure to interact with others appropriately. OFC patients may be too impatient to wait for appropriate feedback or to learn new stimulus-reinforcement associations and therefore fail to cooperate or respond appropriately in social situations. As such, the results of the present study have implications for the treatment of the problems OFC lesion patients are likely to face both within the family and when they return to work (discussed in Section 4.1.10).

### 4.1.5 Emotion

#### 4.1.5.1 Subjective Emotion (Anger and Happiness)

OFC patients reported experiencing more anger and less happiness than both lesion and normal control groups but there was no difference in sadness, fear, and disgust. As discussed in the introduction (Section 1.5.2), the OFC has been associated with emotion. If in fact, as Weiskrantz (1968), Gray (1975), and Rolls (1999) suggest, emotions are states produced by instrumental reinforcing stimuli, then sensitivity to reward and punishment, which was tested in the reversal task, should be important in determining emotion. Since sensitivity of OFC patients mostly to punishment and slightly to reward were impaired, it is not surprising that certain emotions were affected accordingly.

It is interesting that only anger and happiness were affected in patients with OFC lesions. Since OFC patients could report deficits for some emotions (anger and happiness), "lack of insight" can not fully explain why OFC patients did not report abnormalities for other emotions (i.e. sadness, fear, and disgust) compared to normals. OFC patients may be more angry and less happy because they are treated differently by others, or simply think of themselves as "handicapped", due to their brain damage. This, however, does not seem like a valid explanation for their emotional problems since non-OFC lesion patients, who also experience similar negative effects of having brain damage, do not experience more anger and less happiness than healthy controls.

The higher frequency of anger and lower frequency of happiness experienced by OFC patients may be attributed to a frustration from not getting appropriate social feedback because of their impulsive and inappropriate behaviours. Also, their insensitivity to positive reinforcers, demonstrated by their performance on the reversal task, may cause them to be less happy and more angry. Further, OFC patients reported a lack of concern for themselves and others on the Frontal Behaviour Questionnaire exemplified by negative answers to such questions as, "Do you ever worry about yourself?" and "If you see that someone else is upset, do you stop to help them?". This type of negative attitude toward oneself and others may cause or exacerbate OFC patients' emotional abnormalities or OFC patients' emotional abnormalities may cause these negative attitudes. Whatever the causal direction, there is most likely some sort of relationship between negative emotions and lack of concern for oneself and others. This is demonstrated by the positive correlation found across all subjects between subjective emotion score and "frontal" behaviour

score. Further, as discussed in Sections 4.1.1 & 4.1.3, OFC patients are aware that they are behaving impulsively and inappropriately, but are still unable to stop themselves. Being explicitly aware of their implicit deficits may cause OFC patients to be more angry and less happy than the non-impulsive controls.

Finally, perhaps the OFC patients' lesions were not large enough to affect all of their emotions. One would expect patients with OFC damage, with all of its connections to the limbic system, to have many emotional deficits. However, many of the OFC lesion patients in this study only had unilateral damage (16 out of 23). Hornak et al. (2003b, in press) found that although both bilateral and unilateral OFC lesions could impair emotional voice and/or face expression identification, significant changes in social behaviour and in subjective emotional state were related to bilateral OFC lesions only. The finding that anger and happiness were impaired in OFC patients in the current study implies that the OFC may be particularly involved with these two emotions so that even unilateral OFC damage can affect anger and happiness levels. However, perhaps only bilateral OFC damage is sufficient enough to affect the other emotions tested (sadness, fear, and disgust). Bilateral (n=7) OFC patients were not compared to unilateral (n=16) OFC patients in this study because the number of patients in each of these groups was uneven and only 1 of the 7 bilateral OFC patients had a precise surgical lesion. The others had closed head injuries and thus more diffuse damage which could confound the results.

Across all subjects, total subjective emotion score was positively correlated with "frontal" behaviour, neuroticism, self-report impulsivity, BPD traits, and poor reversal performance. Further, OFC patients behaved more impulsively, reported more impulsive and "frontal" behaviours, more BPD traits, and performed poorly on the reversal task. However, whether OFC patients' emotional abnormalities are a result of, a cause of, or intricately related with their impulsive and inappropriate behaviours is unknown. More studies are needed to investigate this issue. Also, longitudinal studies should be performed to determine if the emotional sensitivity of OFC patients changes over time.

#### 4.1.5.2 Emotional Change

While OFC patients report experiencing a subjectively higher frequency of anger and lower frequency of happiness than control groups, they do not report experiencing subjective *changes* in their emotions since their brain lesion any more than non-OFC lesion controls. This coincides with the work of Hornak et al. (2003b, in press) who used a similar subjective emotional change questionnaire and found that patients with unilateral medial lesions on either side in BA9 and/or in the ventral "affective" division of the anterior cingulate cortex (Aff ACC; Bush et al., 2000) reported significantly greater changes in the subjective experience of emotion since their surgery than those with medial lesions outside this region or with unilateral DLFC lesions. Further, patients with unilateral OFC lesions reported small amounts of emotional change, as would be expected from the presence of rich interconnections between the orbital and medial regions but they did not as a group differ significantly on this measure from the "Dorsolateral/Other Medial" group.

Patients with bilateral OFC lesions did report large changes in the subjective experience of emotion, showing that lesions of either the OFC bilaterally or of the medial BA9/ACC area unilaterally can alter subjective emotional state. There was no correlation between the total size of the PFC lesion and amount of emotional change reported, showing that these emotional changes cannot be explained as the consequence of having a large PFC lesion. Since most of the patients tested in the current study had unilateral OFC lesions (16 out of 23), it is not surprising that as a group they did not report having significant changes in their emotions since their injury.

So emotional *change* seems to be related to unilateral medial lesions in BA9 and/or Aff ACC and bilateral OFC damage and the patients in this study were not categorised according to that criterion and had mainly unilateral OFC lesions. However, subjective emotion *frequency* (in terms of anger and happiness) seems to be related to unilateral as well as bilateral OFC damage since most of the OFC patients tested had unilateral damage (16 out of 23) and reported experiencing significantly more anger and less happiness than both lesion and normal control groups. The discrepancy in the OFC patients tested between emotional change and emotional frequency may be related to underlying differences in neurology, or it may be that OFC patients simply have trouble remembering how emotional they were before their brain lesion, impeding their ability to report any changes in emotion they may have experienced since their brain lesion. This hypothesis could be tested by asking OFC, DLFC/other medial, and unilateral medial BA9 and/or Aff ACC surgical lesion patients to describe their emotions at two points, once before and once after surgery. If unilateral OFC and DLFC patients simply do not experience a significant change in emotions after their surgery, it would imply that the OFC lesion patients in this study were just as significantly more angry and less happy than controls before their head injury/surgery as they report being after their head injury/surgery. Thus, their emotional abnormalities may have predisposed them to acquire a head injury in the first place. The exact relationship between emotional change since PFC damage and the frequency with which certain emotions are experience after such damage requires further exploration.

### 4.1.6 Borderline Personality Disorder Questionnaire

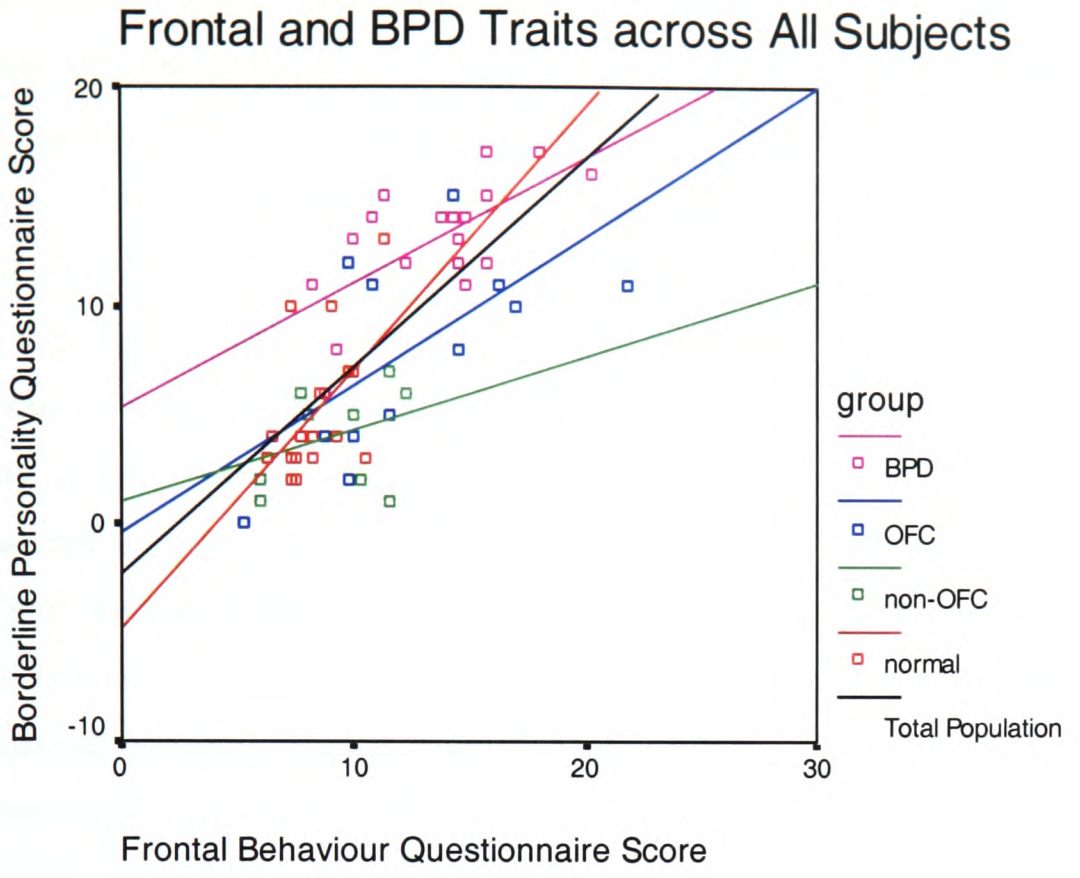
As far as I know, this was the first time that a test of BPD was given to OFC patients. The finding that OFC patients reported significantly more BPD behaviours than non-OFC lesion and normal controls supports the hypothesis that there is in fact a relationship between the BPD syndrome and OFC dysfunction. Further, across all subjects, "frontal" behaviours and BPD traits were highly positively correlated ($r$ = .707, $p$ = .000). More specifically, these two traits were not only significantly positively correlated with each other within OFC and BPD populations ($r$ = .616, $p$ = .019 and $r$ = .674, $p$ = .002 respectively), but they were also correlated within the normal population as well ($r$ = .531, $p$ = .028; see Figures 4.1 & 4.2). This implies that there is a relationship between OFC dysfunction and BPD symptoms. [Note that although there was still a

positive correlation between "frontal" behaviours and BPD traits amongst non-OFC lesion patients, it did not reach the level of significance in this patient group (see Figure 4.2)].

Finally, BPD traits, neuroticism, self-report impulsivity, "frontal" in the current study behaviour score, and subjective emotion total were all highly positively correlated with each other across all subjects. Thus, someone who is impulsive is likely to be neurotic, highly emotional, and to exhibit "frontal" behaviours and BPD traits. BPD traits are also related to subjective emotion, impulsivity, and "frontal" behaviour in that OFC patients experience significantly more of all of these traits compared to non-OFC and normal controls. This strengthens the relationship between OFC function and the BPD syndrome (discussed further in Section 4.3) and the possibility that impulsivity, emotionality, and behavioural inappropriateness are interrelated and have associated neurological aetiologies.

**Figure 4.1:**

**Figure 4.2:**




### 4.1.7 Personality

#### 4.1.7.1 Extraversion

An interesting finding in the data was that OFC patients differed from both non-OFC and normal control groups in terms of impulsivity, but not extraversion. This finding seems to support Gray's (1981) model of personality, which emphasises impulsivity as a main personality trait with biological underpinnings whereas Eysenck's (1967) model emphasises extraversion as a main personality trait related to reticulo-limbic and cortical circuits. Eysenck predicts that both E and N should relate to central nervous system and autonomic nervous system arousal. In Gray's theory, if both the "behavioural activation system" and the "behavioural inhibition system" activity feed into greater noradrenergic arousal, impulsives, as opposed to extraverts in Eysenck's theory, are expected to show more arousal in response to reward signals, whereas anxious individuals should be more responsive to punishment cues (see Section 1.3).

Gray (1987a) proposes that the neural system supporting impulsivity is the "behavioural activation system", which is sensitive to signals of reward and non-punishment and influences probability of approach behaviour. Thus, according to his theory impulsivity and sensitivity to reward and non-punishment signals should be related. In fact, it may be that impulsivity is caused by hypersensitivity or hyposensitivity to reward and non-punishment. Accordingly, the current study found that OFC patients were more impulsive (both in terms of self-report measures and behavioural measures) and were more insensitive to reward (however, only when outliers were included) than normal controls on the reversal task.

The current findings support Gray's theory, in terms of relating impulsivity to reward sensitivity, but differ from Gray's theory in certain respects. For instance, Gray (1987a) proposed that increased impulsivity should be related to *increased* reward sensitivity but in fact the current

study found that increased impulsivity was related to *decreased* reward sensitivity. Reward *in*sensitivity was positively correlated to both non-planning self-report impulsivity and behavioural impulsivity (increased number of errors/second and number of errors) across all subjects. Further, OFC patients were not only more insensitive to reward than normal controls on the reversal task, they were also more insensitive to punishment. According to Gray, *anxiety* (N+, E-) is associated with sensitivity of the "behavioural inhibition system", which is activated by fear, novelty stimuli, and signals of punishment or non-reward (see Figures 1.2 and 1.3). So, as anxiety levels increase, sensitivity to punishment, non-reward, and novelty signals should also increase. In the current study, anxiety was not measured but the equivalent to anxiety in Eysenck's theory, N and E, were measured and they were not correlated with punishment sensitivity. Further, even though OFC patients were not significantly less neurotic than controls, they were significantly less sensitive to punishment. However, neuroticism was positively correlated with "frontal" behaviour and SRI across all subjects. Future studies examining the relationship between anxiety, neuroticism, extraversion, impulsivity, and punishment sensitivity in OFC patients would be beneficial to improve the understanding of the neurological correlates and the complexities of this relationship.

As mentioned in the introduction (Section 1.3) the concept of impulsivity has developed from being thought of as a facet of E to being considered a trait in its own right that is highly correlated with E. In fact, E has been shown to correlate positively with the BIS (a self-report measure of impulsivity) (Barratt & Patton, 1983). However, in the current study, there was no relationship between E and behavioural impulsivity and E and SRI were significantly *negatively* correlated. Thus as SRI increased, E decreased (see Section 4.1.1.1 for a more detailed discussion). Therefore, introversion rather than extraversion seems to be related to impulsivity. This effect may have been caused by the finding that BPD patients were both significantly more introverted and more impulsive than normal and non-OFC controls despite the finding that OFC patients were more impulsive than, but were no different in terms of extraversion from normal and non-OFC controls. Yet, within normal controls there was also a negative relationship between SRI and E similar to that of BPD patients, although not at the level of significance (see Figure 4.3). Further, *across* BPD and normals controls there was a significant negative correlation between SRI and E ($r$ = -.519, $p$ = .000) with BPD patients at the high end of the relationship (see Figure 4.4) while there was no correlation across lesion patient groups. This implies that certain BPD symptoms, in this case introversion and impulsivity, may be behaviours at the extreme end of a continuum with the normal population (see Section 4.2).

Introversion may be related to increased cortical arousal (see Section 1.3). For example, Eysenck (1967; 1990) believes that there is a biological basis for introversion-extraversion, where introverts have higher levels of activity in the cortico-reticular loop, and thus are chronically more cortically aroused than extraverts. As arousal levels were not explored in the current study, further work is needed to examine the relationship between cortical arousal, impulsivity, and extraversion.

**Figure 4.3:**

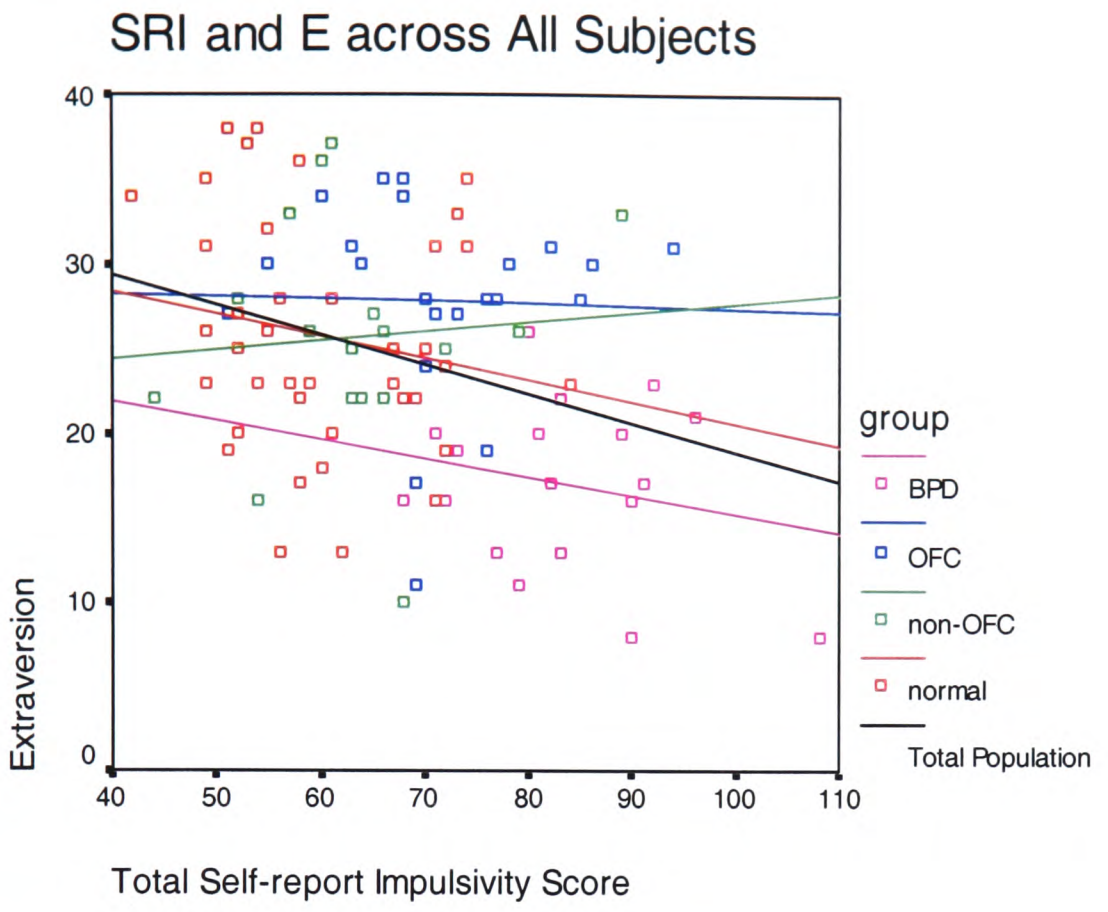
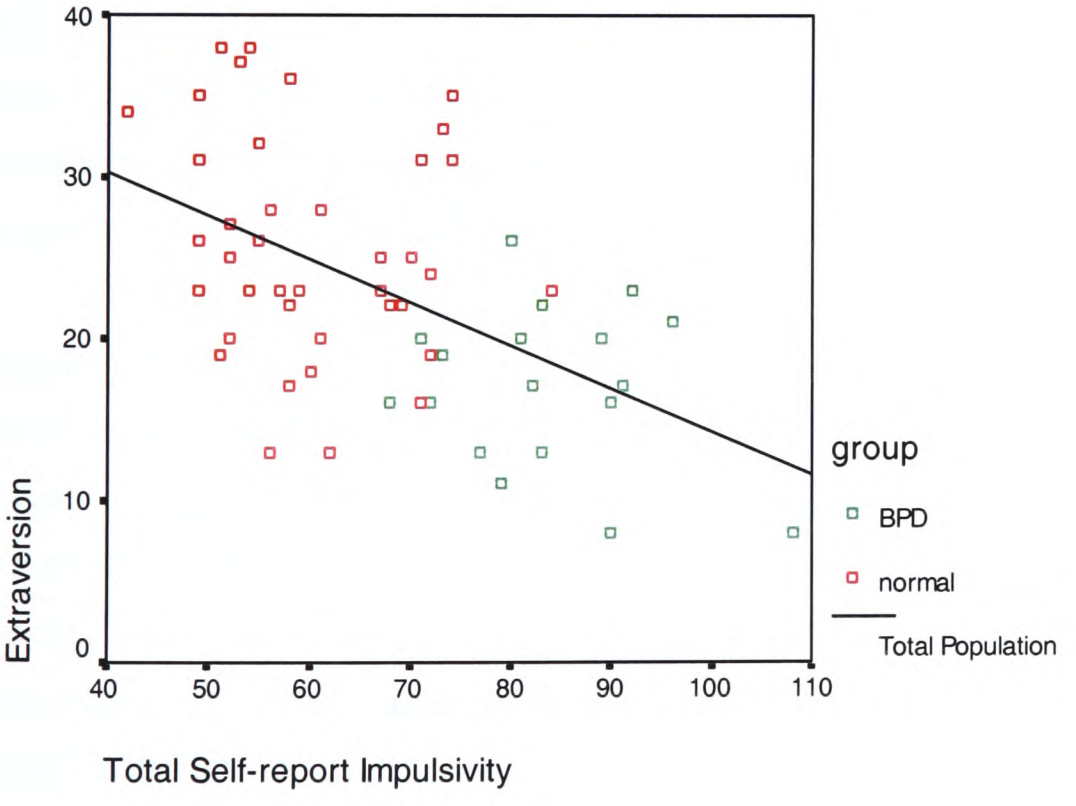



**Figure 4.4:**




### 4.1.7.2 Openness to Experience

OFC patients did not differ from non-OFC patients and normals on any of the personality dimensions except openness to experience, where *both* OFC and non-OFC lesions groups were significantly less open to experience than normal controls. The question is: What is it about PFC damage that leads patients to be less open to experience, but not significantly less conscientious, agreeable, extraverted, or more neurotic than normal patients?

It could be that OFC patients simply lack self-awareness or insight into their own condition. However, OFC patients report being impulsive, which correlates with the impulsive behaviours they display and they are aware of their inappropriate "frontal" behaviours and of their poor reversal performance. Thus, it seems that OFC patients are explicitly aware of their disruptive behaviours but they are simply unable to stop themselves. This observation can be important when considering rehabilitation methods (see Section 4.1.10). Further, the fact that OFC patients were aware that they are not open to experience makes "lack of self-awareness" as an explanation for why they did not report being significantly different on any of the other personality traits unlikely.

So, the question still remains as to why PFC patients are less open to experience than normal controls. It may be that the explanation for OFC patients is different from the explanation for why non-OFC patients are less open to experience than normal controls. The personality dimension of openness to experience has been described by the following trait adjectives: original, curious, artistic, imaginative, wide interests, inventive, idealistic, tolerance for new ideas and new ways of doing things, and experientially oriented (McCrea & Costa, 1996). Perhaps once OFC patients learn one way of behaving or thinking and associate positive attributes with that particular behaviour or thought pattern, it becomes difficult for them to relearn a new way of behaving or thinking. As demonstrated by their poor performance on the reversal task, OFC patients have a difficulty in reversing stimulus-reinforcer associations once they are learned. Therefore, once a particular behaviour or thought pattern is learned, OFC patients may be extremely inflexible to change. This, however, does not explain why *non-OFC* patients are not open to experience, as they demonstrated no problem on the reversal task. Non-OFC (mostly DLFC) patients may therefore be less open to experience because of other cognitive deficits.

The DLFC is known as one of the chief cortical areas responsible for maintaining and manipulating information in working memory (see Section 1.10.2). Working memory has obvious value in decision-making, as it is essential for maintaining a focus on goal hierarchies, monitoring the status of competing options, and possibly storing affective information relevant to attributes and assessments of options. In addition to working memory, the DLFC has also been implicated in different forms of reasoning. Other research into DLFC function implicates this region in the categorisation of novel stimuli (see Krawczyk, 2002). This process involves considerable comparison between exemplars, much like the comparison of attributes, or competing options one may undertake when making a decision. Novel categorisation is open-ended without objectively correct answers. Thus, people with DLFC damage might have difficulty with processing novel stimuli, making decisions, and reasoning. This makes open-minded thinking difficult, if not impossible, as ambiguity becomes much more difficult to deal with cognitively.

It is also possible that OFC and non-OFC patients are less open to experience because of the same underlying cause. It may be that SWM problems cause both sets of lesion patients to be less open to experience. Accordingly, both OFC and DLFC patients reported being significantly less open to experience than normal controls and both made significantly more between errors on

the SWM task than normal controls. Further, openness to experience was negatively correlated with between SWM errors across all subjects. So, the less open to experience a participant, the more between SWM errors he/she made. Perhaps having memory deficits makes novelty harder to deal with. If thoughts and behaviours remain predictable and unchanging, patients need to relay less on their memory system. This makes dogmatism rather than open-mindedness preferable in patients with SWM problems.

From the results of this study it is impossible to say whether the lack of openness to experience in OFC patients is due to their difficulty in reversing previously learned stimulus-reinforcement associations or due to their working memory deficits perhaps related to their DLFC damage (see Section 1.10.2) as 14 out of the 23 OFC patients also had DLFC damage. However, the fact that 9 out of the 23 OFC patients did *not* have DLFC damage suggests that the OFC group should be significantly *more* open to experience than the non-OFC group, where 17 out of the 20 patients had DLFC damage, if openness to experience is related to SWM and DLFC function. Yet, this was not the case. In fact, there was no significant difference between OFC and non-OFC patients on openness to experience score ($M = 32.83$ and $M = 32.45$ respectively). Thus, a stronger case can be made for the argument that deficits in reversing or changing previously learned stimulus-reinforcement associations cause OFC patients to be less open to experience. Yet, more research into the relationship between openness to experience, SWM, and reversal is needed to make definitive conclusions.

### 4.1.8 Spatial Working Memory

SWM has been associated with the DLFC in many studies (see Section 1.10.2). Therefore, the SWM task was used in this study as a control task to separate out OFC dysfunction from DLFC dysfunction. In other words, since many of the OFC lesion patients also had some DLFC damage (14 out of 23), the SWM task was given in order to ensure that any abnormalities demonstrated by OFC patients on the other tasks administered were in fact due to OFC impairments and not impairments in DLFC function. Both lesion groups made more errors (between and strategy) on the SWM task than normals, indicating that they both had some problems with SWM. However, only the OFC lesion group as opposed to the non-OFC (DLFC) lesion group acted impulsively, had a faster cognitive tempo, failed to reverse stimulus-reinforcement associations, was more emotional, and reported significantly more inappropriate BPD and "frontal" behaviours compared to normals. This supports the notion that these deficits shown by OFC patients are unique to OFC damage and are not related to DLFC deficits or SWM.

Both OFC and non-OFC patients used a poor strategy (see Section 2.3.2.3) and made significantly more between errors on the SWM task, but only non-OFC patients made significantly more within SWM errors than normal controls. As mentioned in Section 2.3.2.3, *between errors* are defined as the number of times the subject revisits a box in which a token has previously been found. *Within errors* are defined as the number of errors made within a search (i.e. the number of

times a subject revisits a box already found to be empty during the same search). Since 5 out of the 14 OFC patients who performed the SWM task did *not* have any DLFC, something other than simply SWM problems may have been at work and the dissociation between within and between errors could explain this. OFC patients' poor performance on this test could be related to a problem with altering reinforcement contingencies, which they demonstrate by their poor performance on the reversal task. OFC patients only made significantly more between and not within errors while non-OFC patients (all 9 who performed the SWM task had DLFC damage) made both types of errors. OFC patients may make more between errors, revisiting a box more often in which a token has already been found, because they associate that box with a reward and cannot relearn the new reinforcement contingency. Once a token has been found in a box, one can never be found in there again. Within errors, where a subject revisits a box that was already found to be empty, may be made less frequently by OFC patients because this type of error has more to do with simply remembering which boxes have already been touched. This implies that OFC patients may not have a problem with SWM but instead have a problem with relearning new reinforcement contingencies. This could further explain why OFC patients also acted impulsively, had faster cognitive tempos, failed to reverse stimulus-reinforcement associations, were more emotional, and reported more inappropriate BPD and "frontal" behaviours compared to normal controls while non-OFC patients did not.

So, the DLFC damage that some of the OFC patients had may have caused them to make more *within* errors, which may have more to do simply with memory, compared to normal controls ($M$ = 6.64 versus $M$ = 2.00) although not enough to reach the level of significance and not nearly as many as non-OFC (DLFC) patients ($M$ = 11.44). However, the OFC damage, that all of the OFC patients had, in conjunction with the DLFC damage, that some of them had, may explain why OFC patients did make significantly more *between* errors, which may be related to reversing stimulus-reinforcement associations, than normal controls and even slightly more than non-OFC patients ($M$ = 65.79 versus $M$ = 64.22). Future studies that try to separate out the possibly different reasons for why DLFC and OFC lesion patients both make between SWM errors would be beneficial.

### 4.1.9 Theoretical Implications for Orbitofrontal Cortex Function

Overall, the evidence seems to strongly support Rolls' view (Rolls, 1999) that the OFC is largely involved in representing and altering the reward value of primary and secondary reinforcers. Thus, behavioural impulsivity displayed by OFC patients, like the kind tested with the Matching Familiar Figures Test (MFFT), may result from a problem in modulating stimulus-reward associations rather than a lack of motor response inhibition. Hence, impulsive behaviour in terms of lower response latencies and increased errors on the MFFT could result from OFC patients' desire for an immediate reward despite the consequences. So, OFC patients fail to inhibit responding even though it would be beneficial to take more time to think about the task before responding. Accordingly, OFC patients' impairments on the reversal task may result from a problem in shifting

between old and new reinforcement contingencies leading to a failure to inhibit inappropriate responses to conditioned stimuli. Thus, the apparent failure to inhibit responses seen in OFC damaged humans (Rolls et al., 1994) and monkeys (Iversen & Mishkin, 1970) may be due to a failure to alter old stimulus-reinforcement associations (OFC patients were able to initially learn the associations as exemplified by their ability to reach criterion on the acquisition task), which contributes to the observed deficits on neuropsychological tests and the socially inappropriate behaviours exhibited by OFC patients. Further, this failure to alter stimulus-reinforcement associations may be exacerbated by the faster cognitive tempo exhibited by OFC patients, which causes them to respond quicker than controls, allowing for even less time to make appropriate reinforcement associations and accordingly appropriate behaviours.

OFC patients' impulsivity and reversal deficits may therefore affect their emotions and social behaviours. The OFC may be viewed as an integration centre for emotional content from other areas of the limbic system. It is involved in processing the reinforcement value of environmental stimuli that may underlie the affective component that accompanies decisions. Additionally, this area looks to be involved in adapting to rapid changes in reward contingencies and suppressing responses to stimuli that are no longer rewarding. These activities appear critical in deciding under time pressure and accommodating alterations in options. Further, the OFC seems to be involved in inhibiting responses when asked to wait in timing tasks, another aspect of the prominent role of the OFC in adjusting behaviour in accord with environmental reinforcement contingencies. Regions of the OFC are densely connected with many regions including the basal ganglia, amygdala, and other PFC areas. Both location and connectivity allow these OFC areas to receive perceptual and emotional information, code such information for reward and punishment value, and serve as an interface between affective information and the symbolic processing associated with the DLFC and ventrolateral PFC. These features place the OFC and its connected circuit components in a central position to contribute to the motivational and affective aspects of decision-making and perhaps more broadly to mediate the interface between emotions, behaviours, and cognition.

### 4.1.10 Therapeutic Implications for Orbitofrontal Cortex Patients

Since OFC patients performed more impulsively on self-report, cognitive-behavioural, and temporal measures of impulsivity than controls, and performance on the BIS and MFFT were positively correlated, it seems that impulsivity can be measured with multiple approaches. Even though almost all authors agree that impulsivity is multi-factorial, there is little agreement as to what these factors are (Evenden, 1999a). The different concepts of impulsivity cover a wide range of divergent behaviours. Considering impulsivity as a modulatory effect of several different factors on behaviour may provide the best pathology. The different aspects of impulsivity evident in different psychiatric and neurological syndromes may then be placed in a more satisfactory explanatory framework. Hope for a single treatment against all forms of pathological impulsivity

may be disadvantageous. Instead, more focused studies should be carried out that may help to identify treatments with a narrower profile of use for a better effect.

OFC patients' significantly high impulsivity, in terms of self-report and behavioural impulsivity and fast cognitive tempo, could be related to their inappropriate behaviour in social situations, as measured by the Frontal Behaviour Questionnaire and the BPD Questionnaire, and their experience of more anger and less happiness compared to both control groups. OFC patients may be in a vicious cycle of impulsive behaviour that leads to negative social feedback and feelings of anger and decreased happiness. Perhaps if patients were taught to use alternative measures to cope they would improve. For example, if they were taught to stop and explicitly evaluate situations before implicitly acting or taking decisions, perhaps they would act less impulsively and inappropriately, get better social feedback, and feel better about themselves.

Also, if OFC patients are in fact impaired at learning altering reinforcement associations. Perhaps they would be able to learn changes in reinforcement patterns if they took more time before simply responding based on old reinforcement patterns. It may be that they have two deficits, one being a failure to alter reinforcement contingencies, as demonstrated by poor performance on the reversal task, and the other being a propensity to act without thinking owing to frustration (i.e. impatience due to wanting a reward immediately despite the costs involved or a fast cognitive pace). Further, each type of deficit may exacerbate the other, intensifying behavioural impairments. However, if OFC patients were encouraged to wait before responding, perhaps they could override the desire for an immediate reward and actually respond in the most efficient way. Experiments can be done in the future that institute a long delay period between trials on the reversal task. Patients would be told to really think about which stimulus would be the best one to choose based on how much they just won or lost in the previous trial. Patients would then be forced to explicitly confront the stimulus-reinforcement associations and then perhaps be able to make more effective responses. By just responding instantaneously to avoid frustration in waiting for an award, while simultaneously having a deficit in associating stimuli with rewards and punishers, no improvements in behaviour can be made. However, if patients are encouraged to use their explicit system before implicitly responding, rather than simply explicitly reacting to their behaviour after they have already responded based on their impaired implicit system, then perhaps their behaviour would improve.

Thus, the present results have implications for rehabilitation. They suggest that one of the fundamental problems in OFC patients is in altering behavioural responses when environmental reinforcement contingencies change. In emotional and social interactions there is a continuous process of exchanging reinforcers (any reward or punishment) and reinforcing signals (like smiling or a disapproving look). Failure to respond normally to reinforcers may be a fundamental deficit that underlies impulsiveness, disinhibition, and misinterpretation of other peoples' moods. A fast cognitive tempo may also exacerbate OFC patients' inappropriate responses to environmental reinforcers as patients respond too fast to allow for ample time to properly evaluate reinforcement

contingencies and respond appropriately. Recognition of this could help with management of these patients. Explanation of these problems to OFC patients may help them to identify situations in which their behaviour may be inappropriate and then to take corrective measures. Given their ability to describe what responses should be made on the reversal task, patients could be encouraged to verbalise their intentions and then given explicit training in carrying them out. Training in a wide range of extinction and reversal situations may also be beneficial, as this might enable patients to produce more appropriate behaviours in a wide range of emotional and social situations in which such alteration of behaviour by learning normally occurs.

Finally, although serotonergic dysfunction has been extensively linked to clinical depression (e.g. Schildkraut, 1965; Smith et al, 1997; Moore et al, 2000; Cryan & Leonard, 2000; Arango et al., 2002), there is a substantial body of evidence implicating impaired functioning of serotonergic systems in impulsive behaviour (Linnoila et al., 1983; Harrison et al., 1997b; Puumala & Sirviö et al., 1998; Evenden, 1999c; Mobini et al., 2000). An enduring hypothesis underpinning research in this area is that reduced central serotonin (5-HT) activity, either directly or indirectly, predisposes a subject to impulsive tendencies (Linnoila et al., 1983; Wogar et al., 1993; Mobini et al., 2000; Fairbanks et al., 2001). Impulsiveness has been correlated to suicide and violent behaviour (Roy & Linnoila, 1988; Ho et al., 1998). Asberg et al. (1976) were among the first investigators to relate impulsive behaviour to dysfunction of the central 5-hydroxytryptaminergic (5-HTergic/serotonergic) system. They reported that depressed patients who had made violent, impulsive suicide attempts had reduced levels of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT, in their cerebrospinal fluid (Asberg, 1997). This finding has been replicated in some studies but not all (Deakin, 1989). Subsequent studies in alcoholics (Fils-Aime et al., 1996), violent offenders (Linnoila et al., 1983; Tiihonen et al., 2001), impulsive arsonists (Virkkunen et al., 1987), patients with personality disorders (Brown et al., 1982; Simeon et al., 1992), and healthy volunteers with impulsiveness as a personality trait (Roy et al., 1988) have shown that reduced baseline activity of the central serotonergic system is associated with aggressive/violent behaviour in general, and in particular with impulsive violent behaviour (Linnoila et al., 1983; Brown & Linnoila, 1990). In addition, the 5-HT-releasing drug d,l-fenfluramine has been found to decrease the number of impulsive and aggressive responses in groups of male subjects with a history of conduct disorders (Cherek & Lane, 1999, 2000). Thus, serotonergic functions seem to play a role in the inhibition of behaviour in humans (Soubrie, 1986). Animal studies have also found a clear link between impulsiveness and 5-HT. Manipulation of 5-HT levels in rats has resulted in a more impulsive response style in choice serial reaction time tasks (Harrison et al., 1997b, 1999; Carli & Samanin, 2000), lending further support for a link between impulsiveness and 5-HT. The use of neuroendocrine paradigms in humans, such as reduced prolactin responses to fenfluramine (Coccaro et al., 1989; see Footnote 41), has given a further demonstration of perturbed activity of central 5-HT systems in impulsiveness and aggression. Further, Walderhaug et al. (2002) found that a rapid lowering of tryptophan increased impulsiveness and decreased discriminating ability in

healthy young males (n=24)[53]. Tryptophan depletion resulted in a significantly more impulsive or disinhibited response style on the Continuous-Performance Test (CPT)[54].

In addition, lowered serotonin levels, specifically in the PFC, have been related to impulsive behaviour. Clinically speaking, aspects of impulsivity are both an important feature in several psychiatric conditions related to a low central serotonergic neurotransmission like aggressive behaviour and suicidality, and a core symptom of frontal lobe syndromes of various aetiologies. In an ERP study, Fallgatter & Herrmann (2001) found in 22 healthy subjects that impulsivity (measured by Eysenck's I(7)-scale; see Footnote 28) was correlated with a more anterior location in the PFC of the "Go" and the "No-Go" centroids[55] on the CPT[56]. These results indicate that in healthy subjects the amount of Eysenck's I(7) impulsivity is associated with differences in the PFC brain activation pattern during cognitive response control. Further, in a similar study, Fallgatter et al. (1999) found that the PFC participates in inhibitory motor control and is modulated by serotonergic activity. In 23 healthy subjects, lowered 5-HT function (measured by allele length) was associated with a significantly more anteriorly located "No-Go", but not "Go", centroid on the CPT. Rogers et al. (1999a) found that subjects with reduced tryptophan exhibited a deficit in the ability to learn changed stimulus-reward associations, but were still able to shift an acquired attentional set away from a now-irrelevant stimulus dimension towards a newly relevant dimension compared to subjects who received placebo. These results suggest that reduction in central serotonin leads to altered neuromodulation of the cortical and subcortical regions (e.g. the OFC and striatum) that mediate important aspects of associative learning, where stimulus-reinforcement associations are altered.

Thus, it may also be beneficial for OFC patients to take selective serotonin reuptake inhibitors (SSRIs) to treat their impulsivity. Such treatment would probably work best in extreme cases where OFC patients' impulsivity is causing major disruptions to their daily social and cognitive functioning. However, in extreme cases where people have extensive frontal lobe damage, there may be no substrate for the 5-HT to act on. Some studies that examine the efficacy of various selective SSRIs in the treatment of impulsive disorders are presented in Hollander & Rosen (2000). Further serotonin studies should be carried out on frontal lobe lesion patients with impulsive behaviours to see if such behaviours subside with increased levels of serotonin. In all, an eclectic approach to the treatment of impulsivity, among other inappropriate behaviors displayed

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[53] Rapid tryptophan depletion (RTD) reduces tryptophan [an essential amino acid that is converted into 5-Hydroxytryptophan (5-HTP), which is converted into serotonin (5-HT)] levels in the blood and increases the levels of the other five large neutral amino acids that compete with tryptophan for transportation over the blood-brain barrier. Animal and human studies of cerebral spinal fluid and brain tissue have confirmed that RTD lowers central nervous system levels of tryptophan, 5-HIAA (a metabolite of 5-HT), and 5-HT (Biggio et al., 1974; Gessa et al., 1974; Carpenter et al., 1998; Williams et al., 1999).

[54] The CPT is a typical test measuring rapid-response impulsivity. It requires the individual to make rapid evaluations/discriminations of presented stimuli to decide whether or not to respond.

[55] Centroids are centres of gravity of the brain electrical fields, in the case of this study, evoked by "Go" and "No-Go" responses.

[56] Within the CPT, execution is the "Go" condition and inhibition is the "No-Go" condition of a prepared motor response.

by OFC patients, using a combination of both cognitive-behavioural and pharmacological therapies, would probably be most beneficial.

### 4.2 Borderline Personality Disorder Patients' Performance - Key Findings

BPD patients compared to normal controls performed significantly more impulsively on both self-report and behavioural measures of impulsivity, had more inappropriate "frontal" behaviours, BPD traits, a sped-up subjective sense of time (produced less time in total and at 60 and 90 seconds), experienced more subjective emotions in total and specifically experienced more anger, fear, sadness and disgust, and less happiness, had an increase in anger, sadness, and fear since the onset of their illness, and reported significantly more negative personality traits on all personality measures (O, C, E, & N) except agreeableness. BPD patients were no different from normal controls on the reversal and the SWM memory tasks.

The current findings suggest that some of the behaviours that comprise the BPD syndrome, in particular impulsiveness and emotionality, may be on the high end of a continuum with the normal population. For example, as illustrated in Figure 4.5, there is a significant positive correlation between SRI and BPD traits across both normal controls and BPD patients ($r = .742$, $p = .000$) with BPD patients at the high end of the relationship. There was no correlation across lesion patient groups (not illustrated). Also, as demonstrated above in Figure 4.4, normal controls and BPD patients show a similar relationship (although negative) between SRI and extraversion (see Section 4.1.7.1), where again, BPD patients are at the extreme end of the relationship. Finally, the same relationship was found between emotion and BPD traits across normal controls and BPD patients where BPD patients were at the extreme end of the relationship ($r = .751$, $p = .000$) (see Figure 4.6). Thus, it seems likely that certain symptoms within the BPD syndrome are simply extreme behaviours on a continuum with the normal population. For example, impulsivity, emotionality, introversion, and BPD traits do occur in the normal population. However, these behaviours are considered pathological only after reaching a certain point, in this case, a score of >75 on the SRI questionnaire, >10 on the BPD Questionnaire, >7 on the Subjective Emotion Questionnaire, and <20 on the extraversion subscale.

**Figure 4.5**:

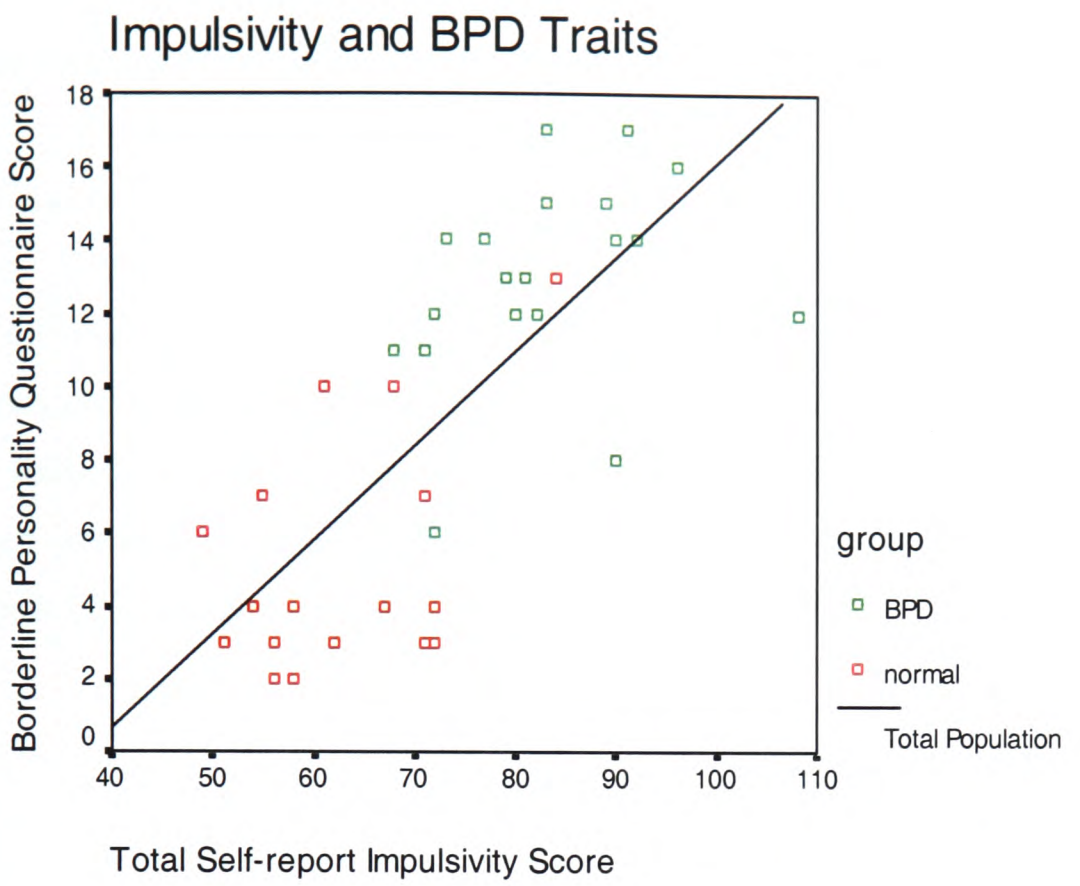
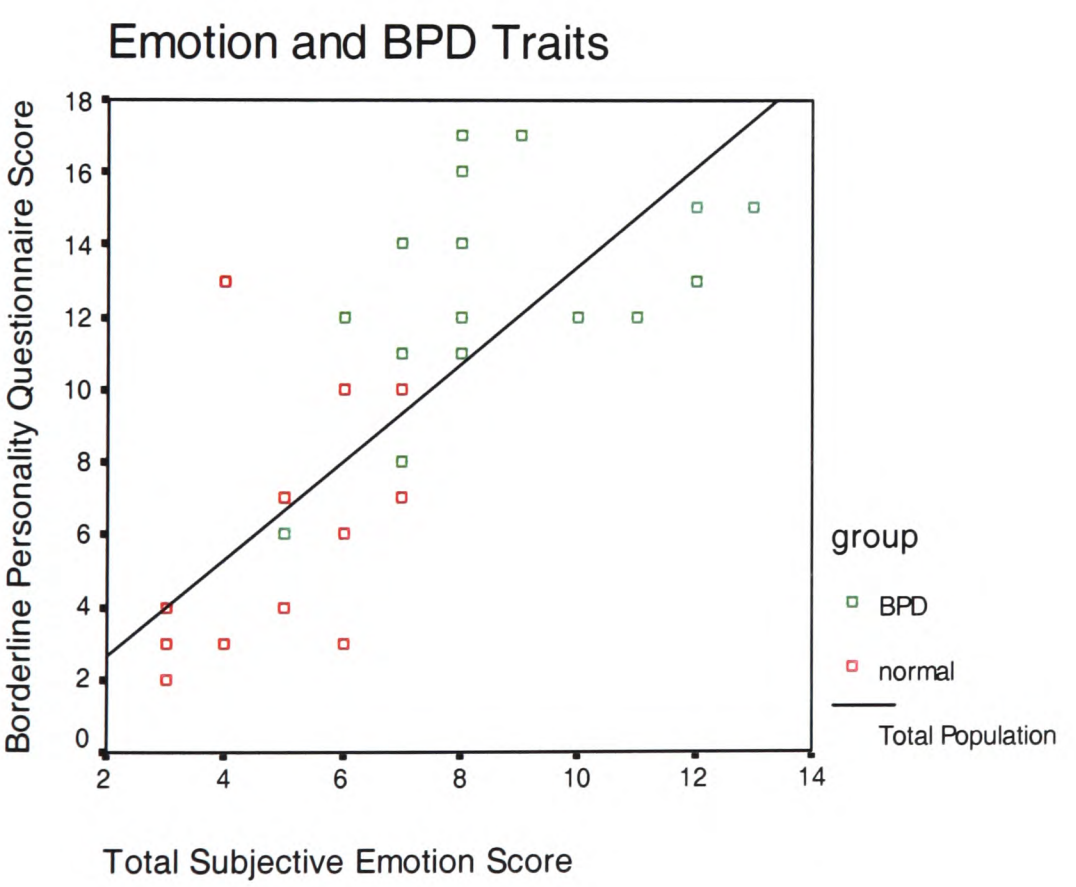



**Figure 4.6:**

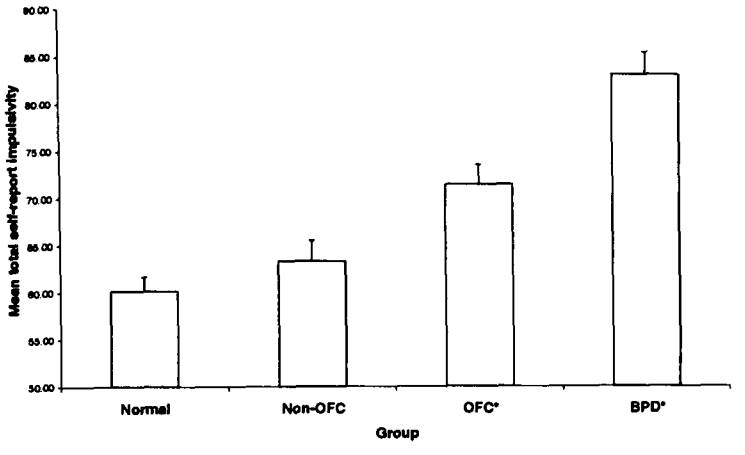


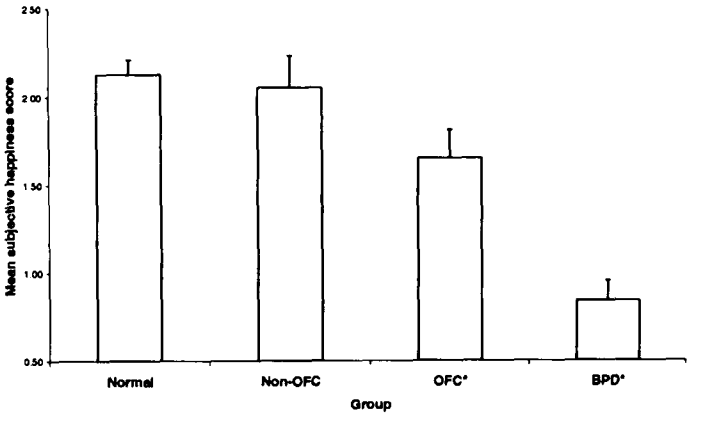

Rather than discussing in detail the BPD syndrome in relation to normal controls alone, I will discuss BPD patients' performance primarily in relation to that of OFC lesion patients on the same tests as this is the main focus of this thesis. In general, OFC and BPD patients performed similarly on certain tasks and differently on other tasks, which implies that some of the deficits seen in the BPD syndrome are related to OFC dysfunction while others are unrelated and are

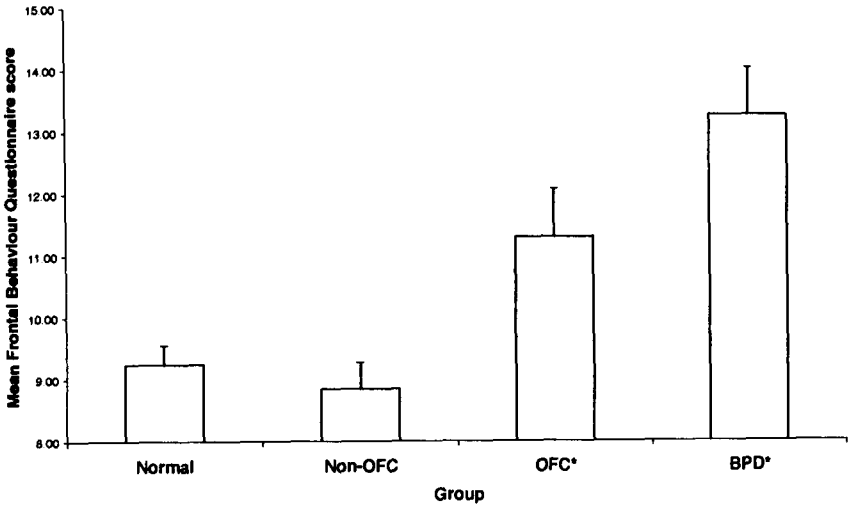
perhaps more related to limbic system dysfunction (discussed further in Sections 4.3.3, 4.4.2, & 4.7). This double dissociation between BPD and OFC on certain tasks may lead to a better understanding of both the aetiology of BPD and the functions of the OFC.

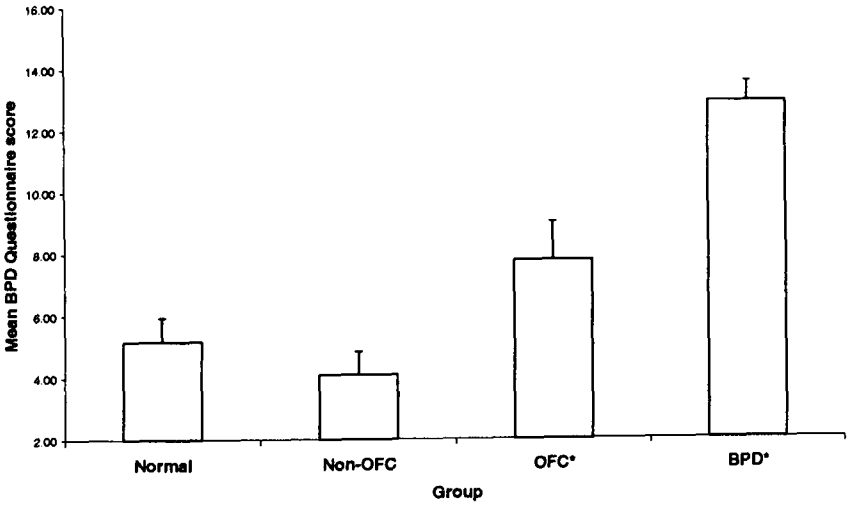
Figures 4.7 and 4.8 are composed of a summary of figures that are described in more detail in Chapter 3 (Results) and can be used as a quick reference when reading through the sections below. It is a visual summary of the similarities and differences between OFC and BPD patients on the different tests compared to non-OFC patients and normal controls. As the number of significant results and number of tests used is large, this summary of figures acts as a helpful way to organise the findings in order to make better sense of the data. This can make extrapolation of meaning based on trends or patterns in the data easier, which can lead to theories of aetiology of dysfunction in both OFC and BPD patient populations.

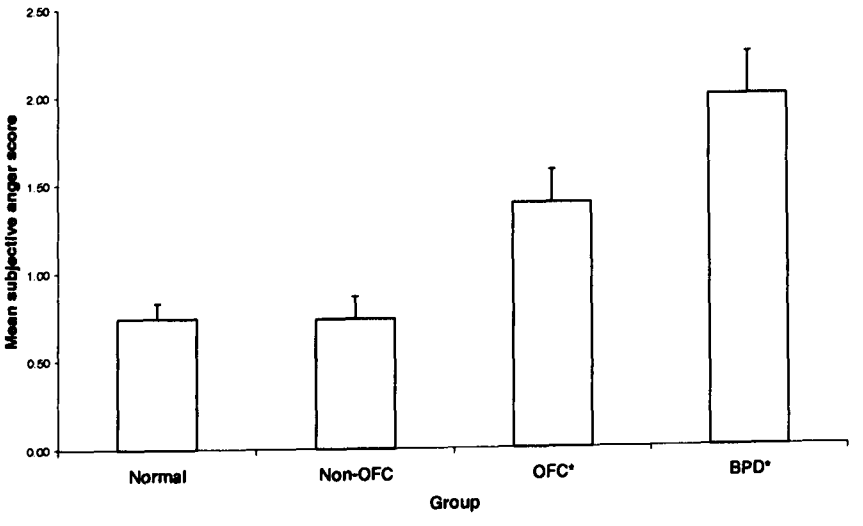
**Figure 4.7: Similarities between deficits in OFC and BPD patients**[57]; tests where:
**A)** Both are significantly different from non-OFC and normal controls, but BPD patients are significantly worse than OFC patients.



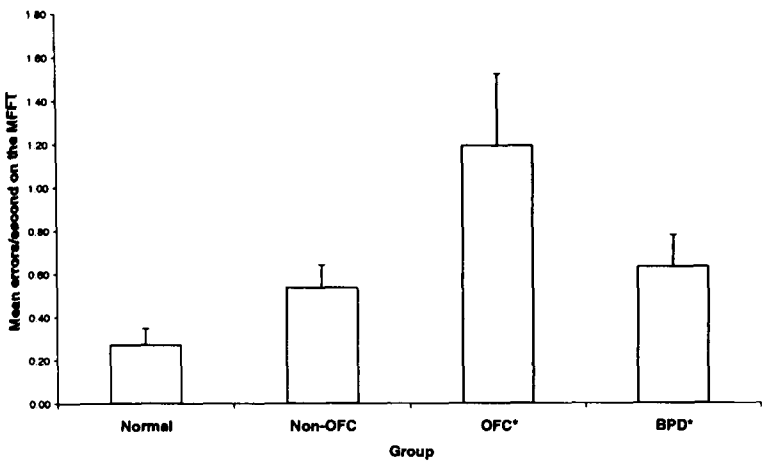



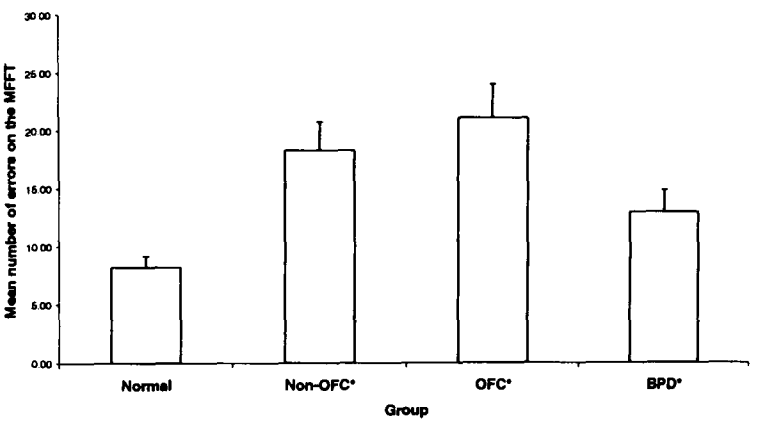



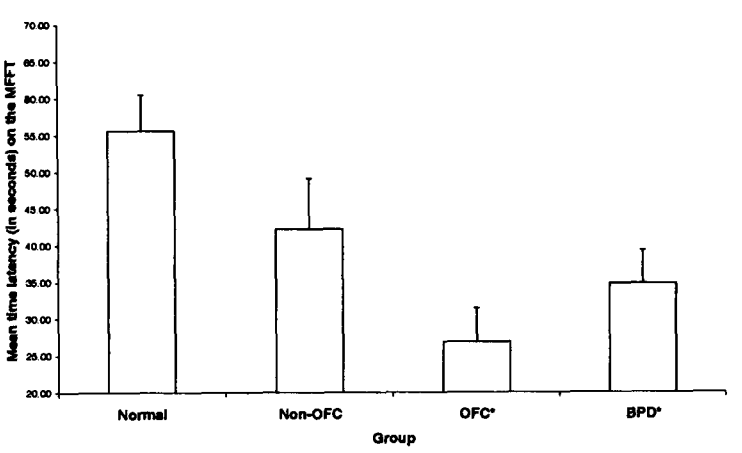

[57] For all histograms in Figures 4.7 & 4.8, error bars = the standard error of the mean (see Section 3.3).

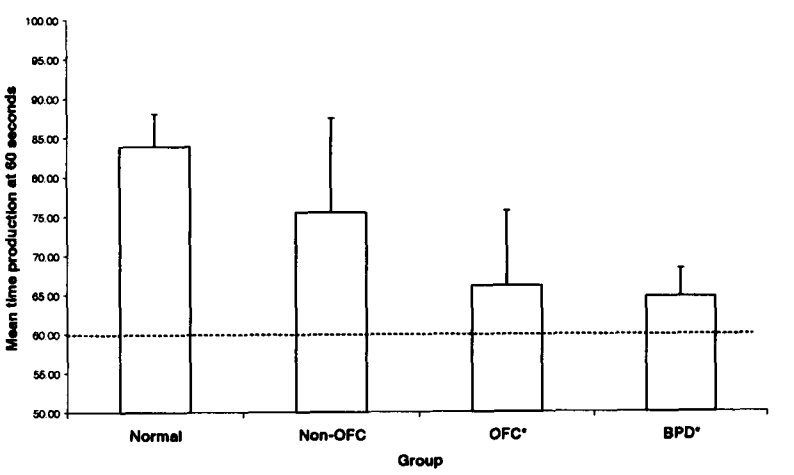
**B)** Both are significantly different than normal controls, but OFC patients are significantly worse than BPD patients (and non-OFC patients for errors/second).

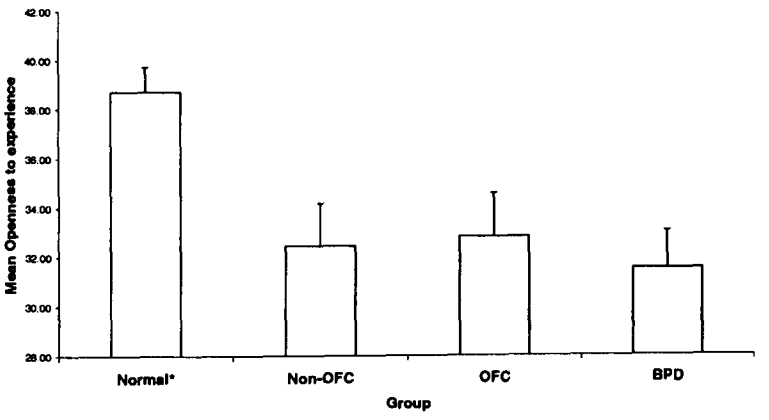


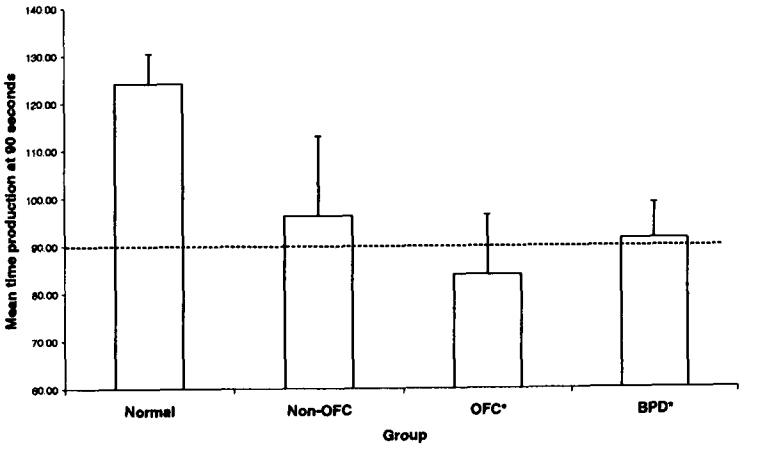




**C)** Both are significantly worse than normal controls but not different from each other.



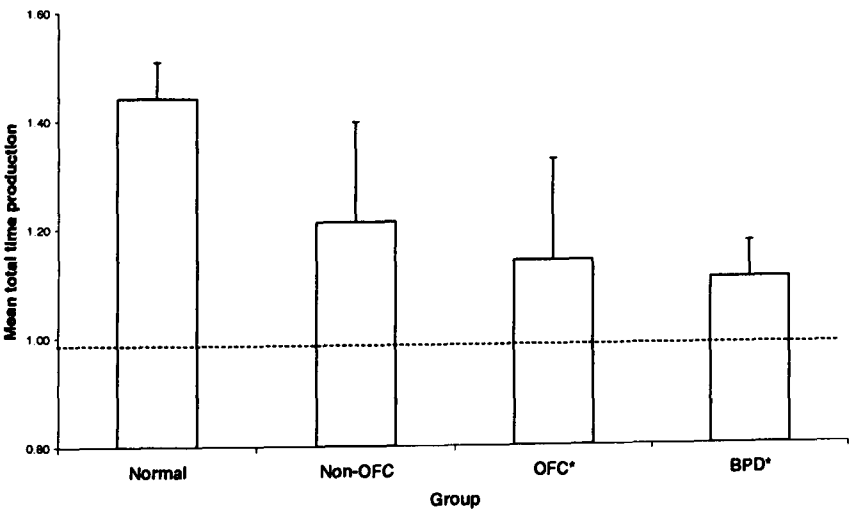
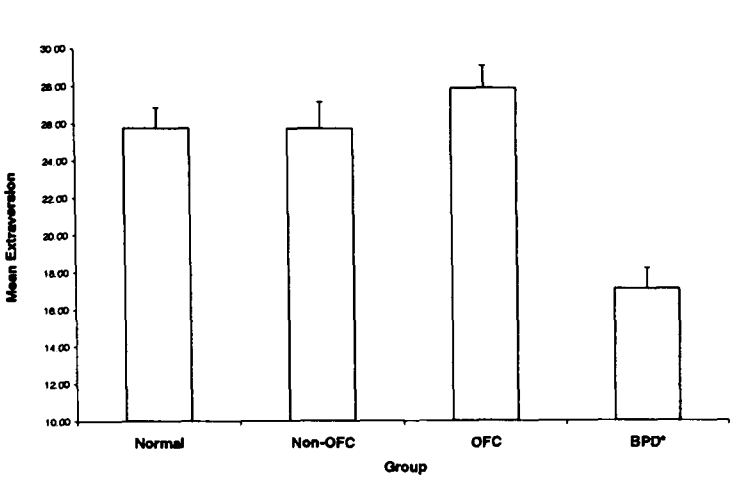
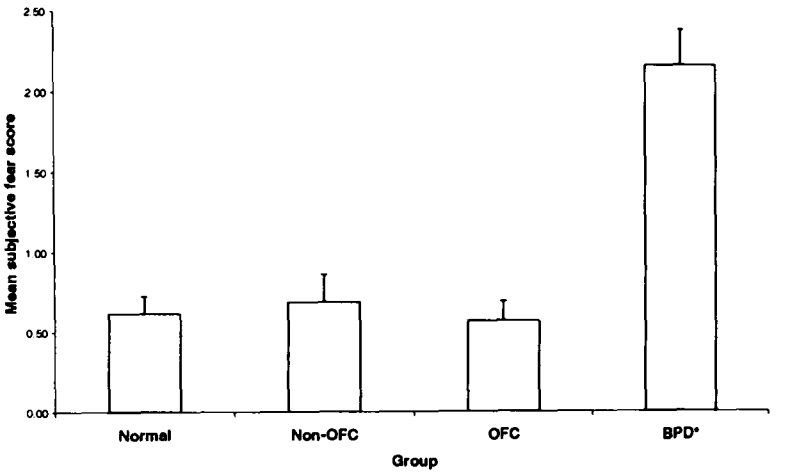
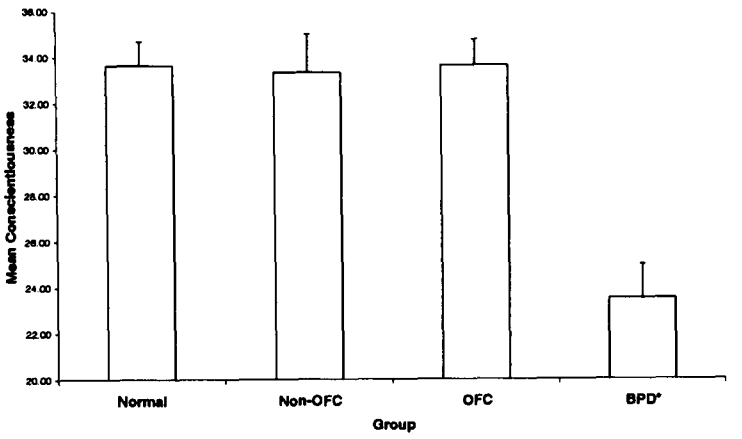
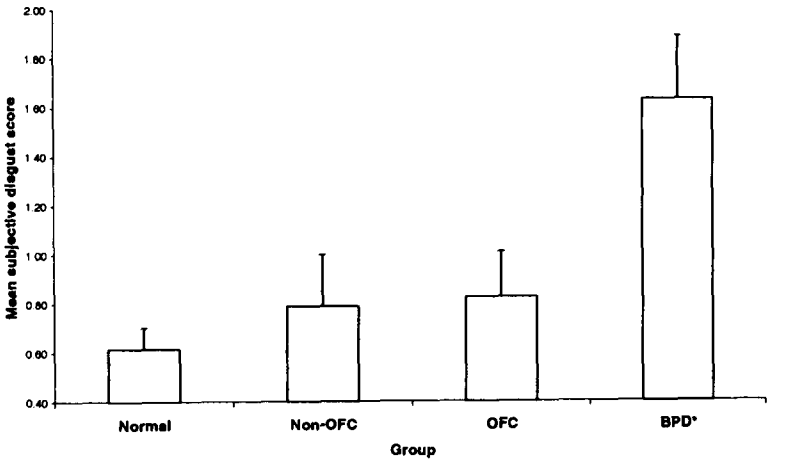



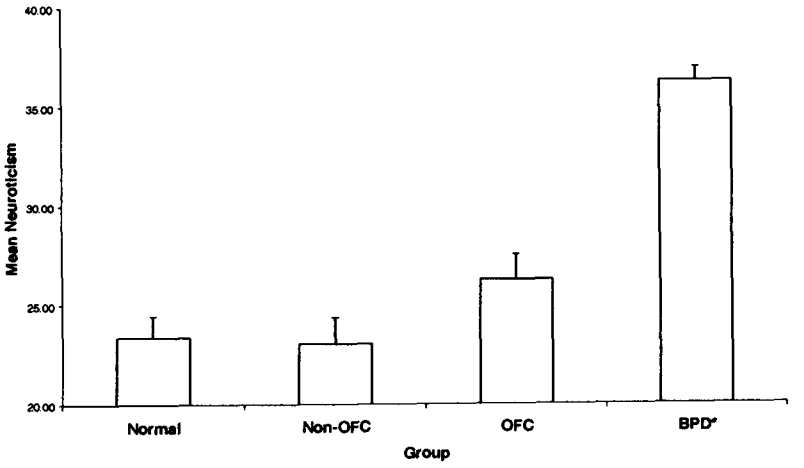
**Figure 4.8: Differences between deficits in OFC and BPD patients**; tests where:
A) BPD patients are significantly different than all other groups (and only from non-OFC patients for "change in anger" and "change in sadness" variables).

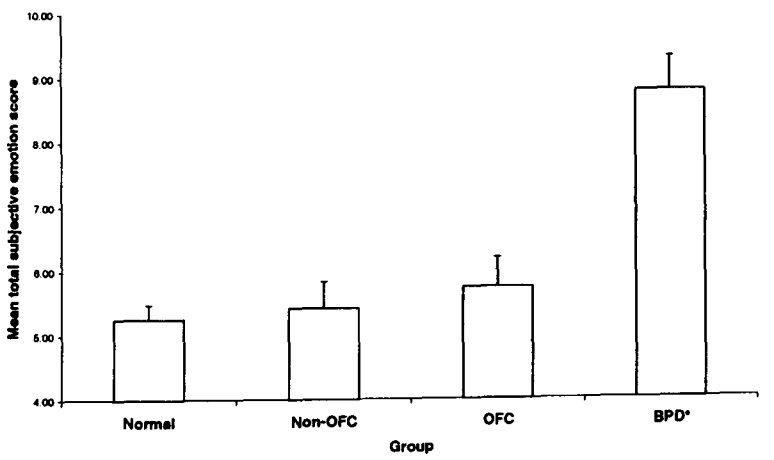


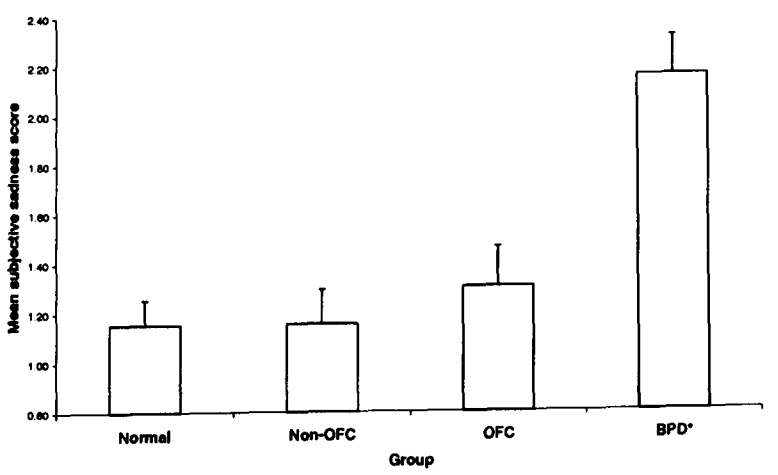



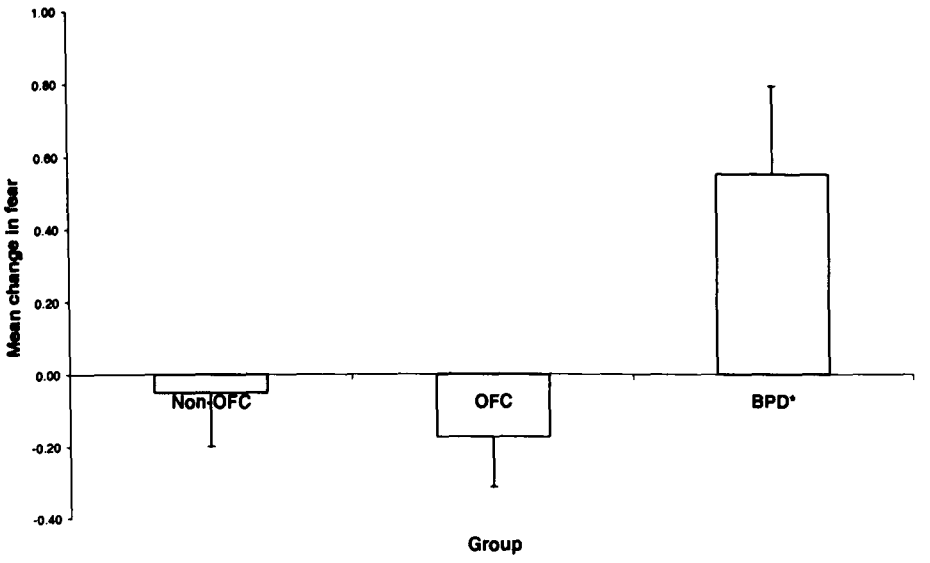



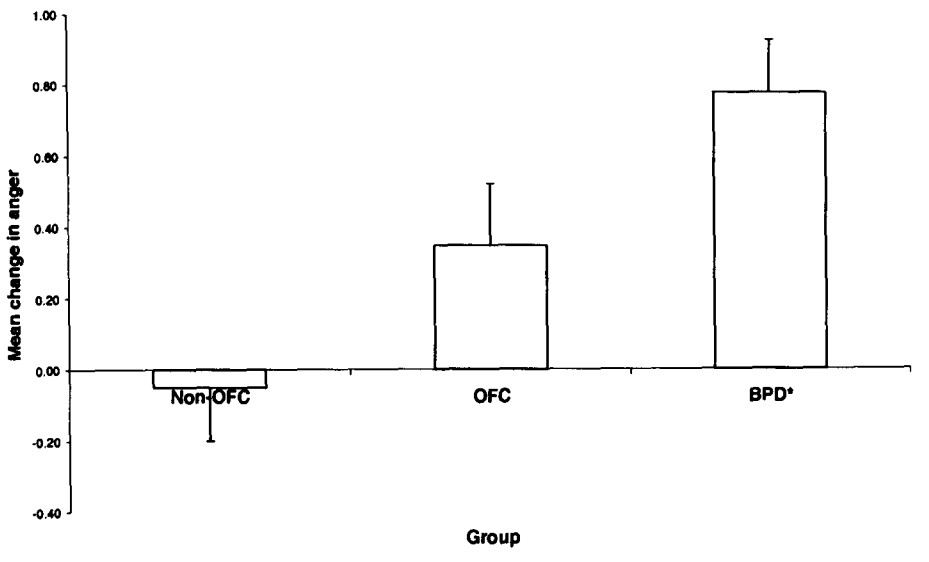



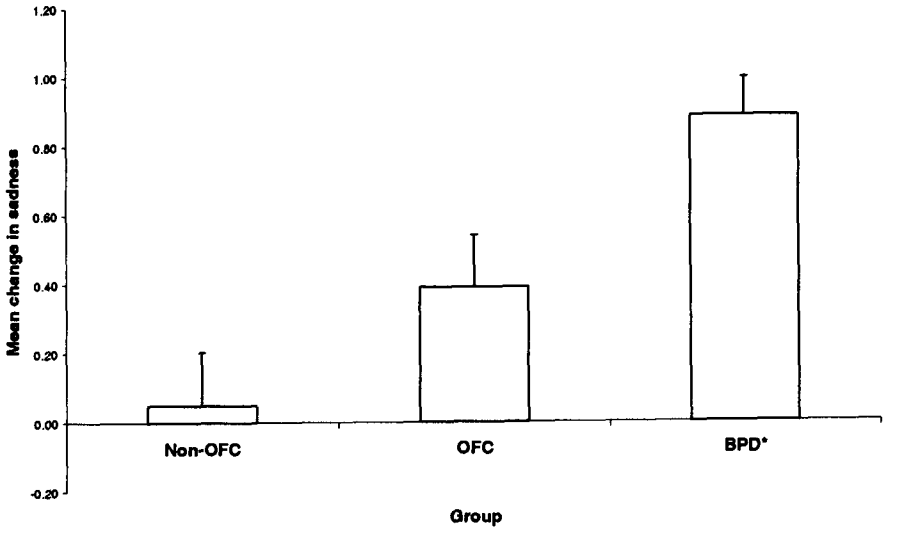



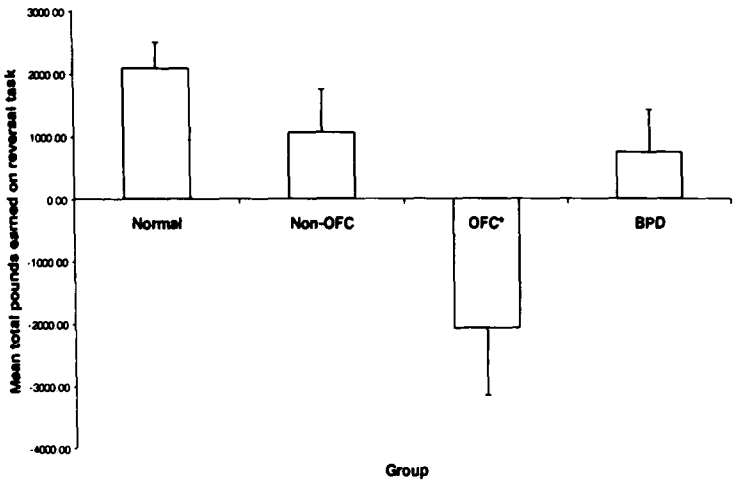



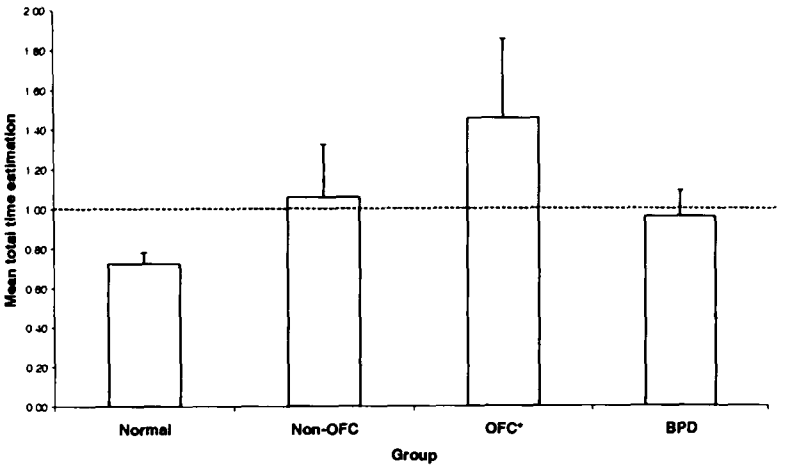

1.00
0.80
0.60
0.40
0.20
0.00
-0.20
-0.40
Mean change in fear
Non-OFC
OFC
BPD*
Group

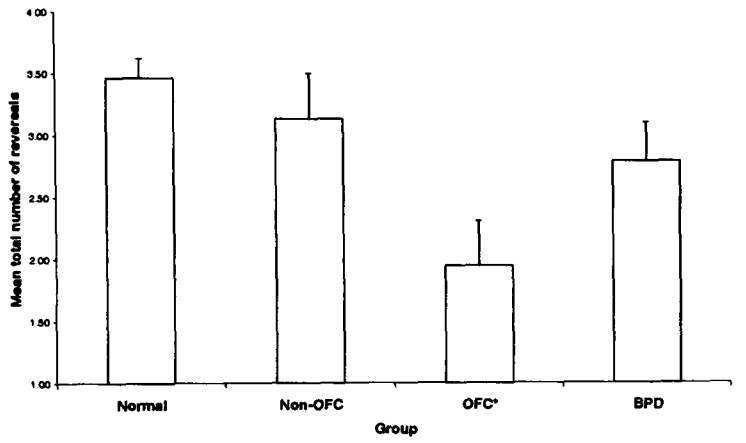

1.00
0.80
0.60
0.40
0.20
0.00
-0.20
-0.40
Mean change in anger
Non-OFC
OFC
BPD*
Group

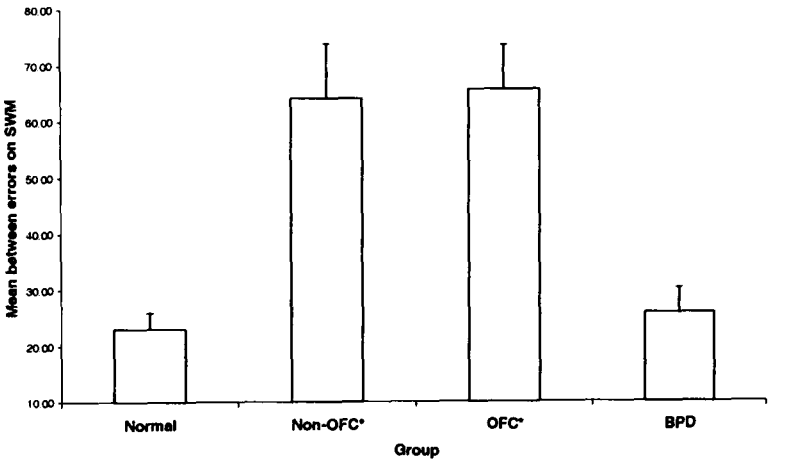

1.20
1.00
0.80
0.60
0.40
0.20
0.00
-0.20
Mean change in sadness
Non-OFC
OFC
BPD*
Group

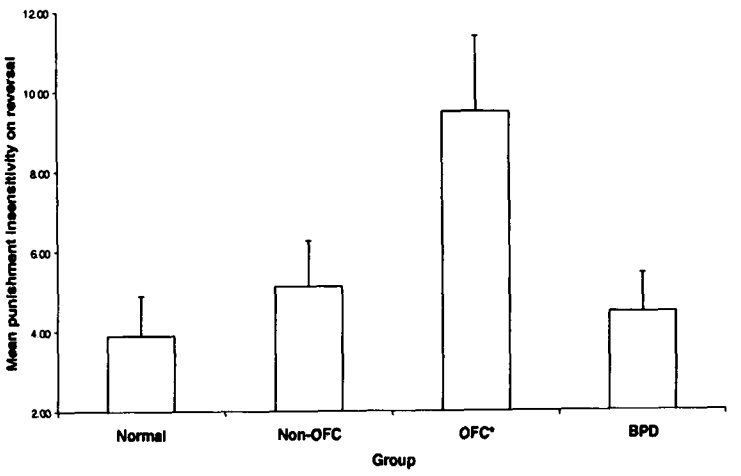
**B)** OFC patients are significantly different from all other groups (except non-OFC patients for SWM) and only from normal controls for reward insensitivity and total time estimation.

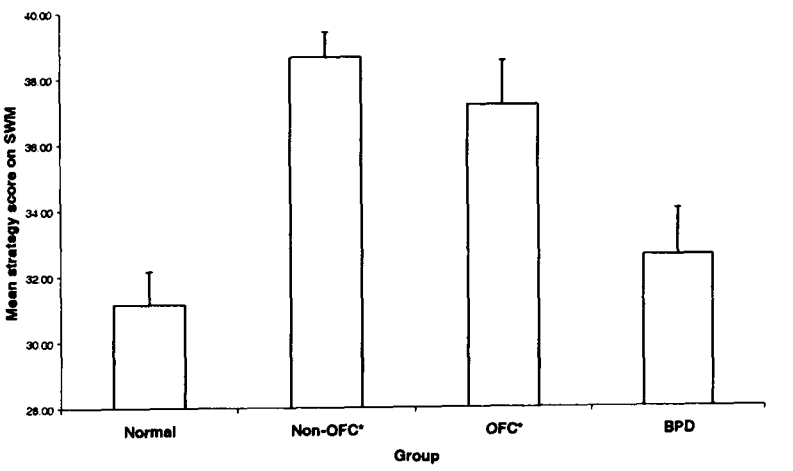


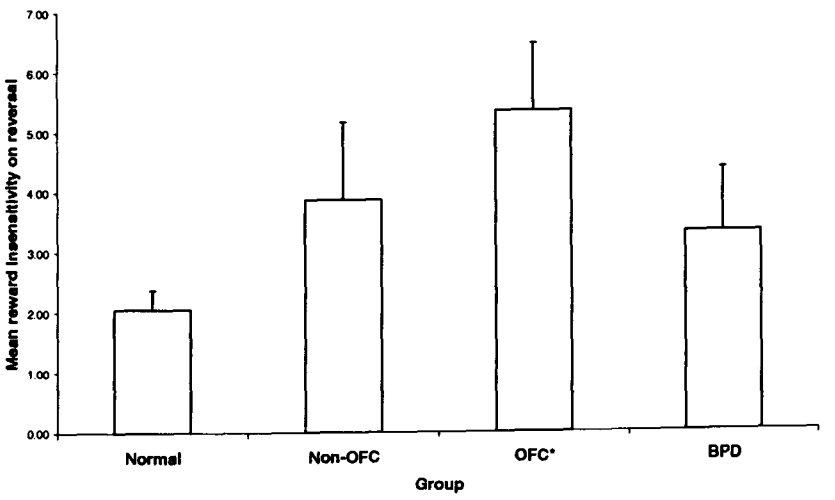



## 4.3 Similarities between Deficits in Orbitofrontal Cortex and BPD Patients

For all of the tests mentioned in this section, OFC and BPD participants behaved in the same way in that they were both significantly different, in the same direction, from normal participants, and on some tests, also from non-OFC participants.

Both BPD and OFC patients were more impulsive in terms of self-report impulsivity (including non-planning, motor, and cognitive subscales), reported more inappropriate/"frontal" behaviours, BPD characteristics, and subjective anger, and less subjective happiness than normal and non-OFC participants with BPD participants being significantly more impaired than OFC participants on all of these measures. Further, both OFC and BPD participants were more behaviourally impulsive (in terms of errors/second, total number of errors, and mean time latency on the MFFT), had a faster subjective sense of time in terms of time production (producing less time in total and specifically at 60 and 90 seconds), and were less open to experience than normal participants, with OFC participants being more impaired than BPD participants on the behavioural impulsivity errors/sec and total number of errors variables. See Figure 4.7 for a visual summary of the similarities between OFC and BPD patients.

### 4.3.1 Impulsivity (Self-report and Behavioural)

OFC and BPD patients are similar in that they were both significantly more impulsive, in terms of both behavioural and self-report impulsivity, than normal and non-OFC lesion patients. However, they differ in that BPD patients reported being significantly more impulsive than OFC patients while OFC patients behaved more impulsively in terms of errors per second than BPD patients. There are several possible explanations for this, a combination of which may explain the impulsive performance of BPD and OFC patients.

First, since self-report and behavioural impulsivity are most probably measuring different aspects of impulsivity, it could be that BPD patients are simply less behaviourally impulsive and/or experience more impulsivity of the kind the SRI questionnaire is measuring compared to patients with OFC damage. It may also be that OFC patients lack insight into their own condition thus they report less impulsivity yet act more impulsively than BPD patients. Or OFC patients could be performing worse than BPD patients on the behavioural test of impulsivity because of other deficits unrelated to impulsivity and perhaps related to their DLFC deficits like impaired SWM, ability to "monitor multiple stimuli" (Petrides & Pandya, 1999), or attention (Iba & Sawaguchi, 2003; discussed further in Section 4.1.1.2).

The latter explanation makes sense when behavioural impulsivity performance is broken down into number of errors made and time latency. Although both OFC and BPD patient groups did significantly worse on both of these measures than normal controls, OFC patients made significantly more errors than BPD patients, but they did not differ from each other in terms of time latency. So, OFC and BPD patients both responded equally impulsively in terms of time latency on the MFFT. However, OFC patients (half who participated in the task also had DLFC damage)

made significantly more errors in choosing stimuli than BPD patients, perhaps because of additional deficits related to DLFC damage, like SWM, causing them to forget which stimuli they had already chosen. Accordingly, non-OFC lesion patients (all tested had DLFC damage) also made significantly more errors than normal controls on the MFFT, but they did not differ from normal controls in terms of time latency. Therefore, the additional DLFC damage that many OFC patients had, and the SWM deficits that may derive from them, may account for the fact that, even though both BPD and OFC patients were equally impulsive in terms of lowered time latencies, OFC patients made significantly more errors than BPD on the MFFT. It is important to remember that both OFC and BPD patient groups made significantly more errors than normal controls. This explanation would rule out part of the first proposal that BPD patients are simply less behaviourally impulsive than OFC patients. For, OFC and BPD patients are no different in terms of time latency on the MFFT and the discrepancy in number of errors made could be caused by cognitive deficits related to the DLFC damage that some of the OFC patients had.

Further supporting this hypothesis, an ANOVA was run across all group when the OFC group was broken down into those with only OFC damage (n=6) and those with OFC plus DLFC damage (n=6). As was expected, there was no significant difference between OFC patients with DLFC damage, OFC patients without DLFC damage, and BPD patients on the time latency measure, and all three groups had significantly shorter time latencies than normal controls ($p < .05$). In terms of number of errors, non-OFC (DLFC) patients, OFC patients with and without DLFC damage, and BPD patients all made significantly more errors than normal controls ($p < .05$). However, OFC patients *with* DLFC damage made significantly more errors than BPD patients ($p < .05$). So, while OFC patients *without* DLFC damage and BPD patients both made significantly more errors than normal controls they did not differ from each other but OFC patients *with* DLFC damage did make significantly more errors than both normal controls *and* BPD patients. Also, non-OFC (DLFC) patients made more errors than normal controls. So, the fact that OFC patients as a group (both with and without DLFC) made more errors than BPD patients can most likely be explained by the fact that many of them also had DLFC damage. Therefore, OFC damage alone does not seem to make OFC patients significantly *more* behaviourally impulsive than BPD patients.

Lack of insight in OFC patients does not seem to be the best explanation for why OFC patients report being less impulsive than BPD on the SRI questionnaire (the BIS-11). For example, OFC patients still report being significantly more impulsive than both control groups, just not as much as BPD patients, and this correlates with the impulsive behaviours they display. Further, OFC patients are aware of their inappropriate "frontal" behaviours and of their poor reversal performance, even though they fail to stop themselves, and they report being less open to experience, less happy, and more angry than normal controls. So "lack of self-awareness" of their own disruptive or abnormal behaviours is an unlikely explanation for why OFC patients did not report being as impulsive as BPD patients.

It may be that BPD patients reported more impulsivity than OFC patients because of other mitigating factors related to their psychiatric disorder that OFC patients do not posses. For instance, BPD patients reported significantly more emotional and personality disturbances than OFC patients (discussed in Sections 4.4.1 & 4.4.2). Also, the BPD patients harmed themselves, which was not a behavioural feature of the OFC patients, and the BPD patients' behaviours were so severe that they were inpatients while the OFC patients were out-patients. Therefore, in accordance with the first proposal put forth, it may be that BPD patients simply do experience more impulsive behaviours of the self-report kind than OFC patients because, although their syndromes may be of a similar nature, BPD patients' self-report impulsivity may be slightly more severe than that of OFC patients. However, both patient groups are equally impulsive in terms of time latency on the behavioural impulsivity test. This could be explained by the fact that the SRI questionnaire and the behavioural impulsivity test are measuring different aspects of impulsivity. The SRI questionnaire relates to impulsivity in the context of the environment and to more broad or general non-planning, cognitive, and motor impulsive behaviours. BPD patients' emotional instability and negative personality characteristics may contribute more to these self-report types of impulsive behaviour than to the type measured by lowered response times. Conversely, OFC patients were not as characterologically and emotionally disturbed as BPD patients (see Chapter 3). Thus, although OFC patients reported being more impulsive than both controls groups, it was not as severe as BPD patients' self-report impulsivity.

In all, despite their differences it remains that both OFC and BPD patient groups were more impulsive, self-report and behaviourally, than normal and non-OFC controls. This indicates that OFC and BPD patients posses the common behavioural and cognitive feature of impulsivity, which I propose is likely to be a least partially related to OFC dysfunction.

### 4.3.2 "Frontal" Behaviours and Borderline Personality Disorder Traits

Both OFC and BPD patients reported experiencing significantly more inappropriate "frontal" and BPD behaviours than both control groups. In support of the hypothesis that OFC dysfunction contributes to at least some of the inappropriate behaviours displayed by BPD patients, not only did OFC patients report experiencing significantly more BPD traits than both control groups, but BPD patients reported experiencing significantly more "frontal" behaviours compared to both control groups. On both tests, BPD patients' scores were also significantly higher than those of OFC patients. These findings indicate that the emotional deficits and socially inappropriate behaviours of BPD patients are even more severe than those of OFC patients.

BPD patients significantly higher score on the BPD questionnaire compared to OFC patients coincides with the fact that this questionnaire was designed to measure the traits that are essential to the diagnoses of BPD (see Section 1.12.2). However, it is interesting that BPD patients experience significantly more inappropriate "frontal" behaviours than OFC patients, as the Frontal Behaviour Questionnaire was designed to measure types of behavioural problems generally

believed to result from frontal lobe damage (Levin et al., 1991) such as disinhibition, social inappropriateness, perseveration, and uncooperativeness. The additional emotional and personality problems that BPD have which OFC do not (discussed in Sections 4.4.1 & 4.4.2) may contribute to the higher number of inappropriate social behaviours that BPD patients experience. BPD patients may have dysfunctions in other parts of the brain, perhaps in the limbic system (discussed in Sections 4.3.3, 4.4.2, & 4.7), in addition to OFC dysfunction.

Another explanation may be that BPD patients simply have a better insight into their condition. So perhaps if people familiar with the OFC participants answered the questionnaires for them, they would have reported more inappropriate "frontal" behaviours and for that matter, perhaps more emotional and personality deficits as well. Again, the argument for lack of insight is not convincing, as OFC patients seem to have some awareness into their condition since they do report significantly more inappropriate behaviours and BPD traits than normal and non-OFC controls, just not as many as BPD patients who seem to be more severely disturbed. Thus, BPD patients who harm themselves seem to have some of the same kinds of impairments as OFC patients but simply to a greater degree. In accordance, the BPD patients were institutionalised while the OFC patients were living at home, either alone or with family members' assistance.

Despite their differences, the most important finding here is that OFC patients reported experiencing significantly more BPD traits and BPD patients reported experiencing significantly more "frontal" behaviours than both control groups. The finding that BPD patients exhibit inappropriate "frontal" behaviours supports the main hypothesis that BPD patients have some type of underlying PFC deficit. Further supporting the hypothesis that there is in fact a relationship between the BPD syndrome and OFC dysfunction, OFC patients report similar behaviours to those exhibited within the BPD syndrome. Additional support for the relationship between "frontal" behaviours and BPD traits comes from the finding of a highly significant positive correlation between scores on the Frontal Behaviour and the BPD Questionnaire both within normal controls and across all participants ($p$ =.000; see Figures 4.1 & 4.2 and Section 4.1.6). So the more "frontal" behaviours a subject reports, the more BPD traits they report as well.

Finally, the relationship between BPD and frontality (exemplified by disinhibited and inappropriate behaviours) and among other things, emotion, impulsivity, and personality should be explored further. In this study, across all subjects, BPD traits and "frontal" behaviours were both positively correlated with SRI, neuroticism, and total subjective emotion while only "frontal" behaviours were correlated with BI. Also, both BPD and OFC patients were significantly more impulsive (cognitively and behaviourally) and angry and less happy than both control groups and less open to experience than normal controls. The current evidence seems to strongly suggest that impulsivity, emotion, personality, and BPD and OFC traits are all intimately related. However, the underlying aetiology of these behaviours and how they are neurologically linked requires further clarification.

### 4.3.3 Subjective Emotion (Anger and Happiness)

On the Subjective Emotion Questionnaire, which measures frequency of emotions experienced, OFC and BPD patients both reported being significantly less happy and more angry than non-OFC lesion and normal controls. Further, BPD patients reported significantly more anger and less happiness than OFC patients. Only BPD patients reported being significantly more emotional on all of the other emotions tested (fear, sadness, and disgust), and reported significant changes in emotions on the Emotional Change Questionnaire (discussed further in Section 4.4.2) compared to control groups.

The first question is: Why are only anger and happiness affected in OFC patients and not the other emotions tested (fear, disgust, and sadness)? Possible explanations for this are discussed in detail above in Section 4.1.5.1. The second question is: Why do BPD patients report significantly more anger and less happiness than OFC patients? BPD patients' experience of more extreme emotions than OFC patients coincides with the fact that affective instability is a main symptom of the BPD diagnosis (see Appendix 6). BPD patients may also have a neurochemical imbalance, which OFC patients may not have, which exacerbates their emotional imbalance. Further, evidence (see Sections 1.12.7, 1.12.8 & Sections 4.4.2 & 4.7 below) supports the theory that BPD patients may have a limbic system imbalance, in particular, that they may have an overactive amygdala, which OFC patients may not have, causing more extreme emotions.

There is an abundance of evidence that the amygdala is involved with emotional processing. I will mention a few key findings. Lesion studies in monkeys have provided some of the most compelling evidence for the involvement of the amygdala in emotional and social behaviour (see Baxter & Murray, 2000). The amygdala has been associated with arousal, control of autonomic responses associated with fear, emotional responses, and hormonal secretions (Rolls, 1999). It has been suggested that the amygdala coordinates the actions of the autonomic and endocrine systems (Kelly & Dodd, 1991) and may be part of a "general-purpose defence response control network" (LeDoux, 1996, p.158). LeDoux (1987, 1994) defines the amygdala as a centre for emotional evaluation, specifically involved in fear conditioning. Animal and human studies show that the amygdala plays a role in conditioned fear (Davis, 1992; Davis & Whalen, 2001). A stimulus that predicts an aversive outcome will change neural transmission in the amygdala to produce the somatic, autonomic, and endocrine signs of fear, as well as increased attention to that stimulus (Davis & Whalen, 2001). The amygdala is also involved in learning about positively valenced stimuli as well as spatial and motor learning (Davis & Whalen, 2001). Bilateral lesions of the amygdala in monkeys produce tameness, abnormal exploratory and sexual behaviours, and incapacity to learn aversive stimuli (Weiskrantz, 1956; Kluver & Bucy, 1939). Monkeys voluntarily work to obtain electrical brain stimulation of the amygdala (Rolls et al., 1980). Researchers can now point to plausible circuits involved in the transmission of sensory inputs into the amygdala, between amygdaloid subregions, and to efferent targets in cortical and subcortical regions, for specific emotional learning and memory processes (LeDoux, 1992). Further, a number

of studies indicate that the amygdala is involved in a specific class of stimulus-reward associations (see Aggelton, 1993). In parallel with this, it appears increasingly likely that amygdala dysfunction contributes to the emotional changes that accompany certain neurological disorders including dementia, schizophrenia, and possibly BPD. A good review of studies examining the human amygdala, covering both lesion and electrical stimulation studies as well as the most recent functional neuroimaging studies, can be found in Davis & Whalen (2001).

Even though the OFC patients did not have any overt anatomical damage to their amygdala, one would still expect patients with OFC damage, with all of its connections to the amygdala (see Figure 1.7 and Section 1.6.2.1), to also have extreme emotions. The fact that OFC patients did not experience as extreme emotions as BPD patients may be due to the fact that many of the OFC lesion patients only had unilateral damage (16 out of 23). For example, Hornak (2003b, in press) found that significant changes in social behaviour and in subjective emotional state were related only to *bilateral* OFC lesions. So perhaps only bilateral OFC damage would be sufficient to produce emotional affects as extreme as those found in BPD patients (see also Section 4.4.2).

There may be many reasons why both sets of patient populations were more angry and less happy than controls; environmental/social, neuroanatomical, neurochemical, and/or neurophysiological. However, whatever the underlying cause, the main point is that both OFC and BPD patient populations had similarly abnormal frequencies of anger and happiness compared to normal and non-OFC lesion controls. Further, BPD and OFC patients also displayed similar behaviours in terms of impulsivity, inappropriate "frontal" and BPD behaviours, openness to experience, and time perception. Also, across all subjects, total subjective emotion score was positively correlated with "frontal" behaviour, neuroticism, self-report impulsivity, and BPD traits. Thus, it seems likely that there may be a common underlying cause in both OFC and BPD patient populations for their higher frequency of anger and lower frequency of happiness, namely OFC dysfunction. However, BPD patients' anger and happiness may also be affected by additional deficits, perhaps related to amygdala dysfunction. These possible additional brain abnormalities may mask the effects of OFC deficits or in fact exacerbate them. In all, it seems that the OFC and the limbic system are intricately interrelated and more studies should be carried out to further investigate the relationship between the amygdala, the OFC, and emotions in BPD patients.

### 4.3.4 Time Production

Both OFC and BPD patients had a sped-up perception of time in terms of time production (not time estimation[58]) compared to normal controls. They both produced less time in total and at the longer 60 and 90 second time intervals and there were no significant differences between OFC and BPD patients. Also, the deficit, underproduction of time intervals, became worse or more apparent the

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[58] A dissociation occurred where OFC patients had a sped-up perception of time in terms of both time estimation (discussed in Section 4.4.4) and time production, while BPD had a sped-up perception of time only in terms of time production.

longer the time interval they were asked to produce. It may that both BPD and OFC patients have a faster cognitive tempo, which causes them to truly believe that the set amount of time has actually passed even though they are responding (saying that the set amount of time has passed) prematurely compared to normal controls. Or it may be that patients become frustrated by waiting for the time interval to end and want the immediate reward of the session being finished making them unable to withhold responding especially at longer time intervals.

If a faster cognitive pace is the explanation, then both BPD and OFC patients would overestimate time intervals as well but in fact only OFC patients overestimated significantly more than normals. Thus, BPD patients may be underproducing time intervals because of frustration with waiting and a desire for the reward of the task being immediately over. OFC patients may also experience this frustrative non-reward, causing them to underproduce time intervals in addition to having a faster cognitive tempo, which is indicated by their overestimation of time intervals (i.e. thinking that more time has passed in a set interval than actually has). OFC patients' overestimation could also be related to boredom and the fact that time intervals feel longer the less active one is or the less interesting the task (Troutwine & O'Neal, 1981). However, no other group experienced this type of boredom.

This study supports the evidence that impulsivity and time perception are related (Barratt, 1985; see Section 1.11.3). The more self-report impulsivity reported the significantly less time was produced across all subjects. So, time perception was altered in impulsive subjects. Further, both BPD and OFC patients were impulsive (both self-report and behaviourally) and produced less time than normal controls (see also Sections 4.1.1.1, 4.1.1.2 & 4.1.2).

In all, both BPD and OFC patients had time perception deficits in terms of underproduction, especially at long intervals. The dissociation between time estimation and time production in BPD and OFC patients indicates that time production and estimation may involve different brain processes (discussed in Section 4.4.4). The processes that are involved in time estimation are apparently unaffected in BPD patients. The frustration in waiting and/or faster cognitive tempo that causes OFC and BPD patients to underproduce time intervals may also be related to some of the impulsive and inappropriate social and emotional behaviours they display, as demonstrated by their increased scores on the impulsivity, BPD, "frontal" behaviour, and emotion questionnaires compared to normal and non-OFC controls. In support of this relationship, decreased time production correlated with increased self-report impulsivity and "frontal" behaviours as well as decreased openness to experience across all subjects.

### 4.3.5 Personality (Openness to experience)

OFC and BPD patients were both less open to experience than normal controls and there was no significant difference between OFC and BPD patients. For all of the other personality traits, N, E, and C[59], only BPD patients differed significantly from normal controls (discussed in Section 4.4.1).

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[59] There were no significant differences between groups for the personality trait "agreeableness".

Several possible explanations as to why OFC patients are less open to experience than normal controls are discussed in detail in Section 4.1.7.2. Possible explanations as to why BPD patients are less open to experience than normal controls are discussed below.

The underlying reason why BPD patients are less open to experience than normals may be related to whatever makes BPD patients differ from normals on all of the other personality traits (N, E, and C). Thus, this explanation would differ from the reason OFC patients lack openness to experience since OFC patients are no different from normals on all of the other personality traits. Alternatively, BPD patients may in fact be less open to experience for the same reasons OFC patients are, and may have other deficits that cause them to be less conscientious, extraverted, and more neurotic. However, non-OFC patients were also significantly less open to experience than controls. So it is hard to say if BPD patients are less open to experience because of something related to their OFC, their DLFC, or to a dysfunction unique to BPD patients that is also the cause of their other personality deficits (perhaps amygdala dysfunction).

The latter explanation seems the most plausible, since it may be that SWM problems cause both types of PFC lesion patients (OFC and DLFC) to be less open to experience. As discussed in Sections 4.1.7.2 and 4.1.8, both OFC and DLFC patients reported being significantly less open to experience and made significantly more between errors on the SWM task than normal controls and decreased openness to experience was correlated with increased between SWM errors across all subjects. Further, as discussed in Section 4.1.7.2, the lack of openness to experience in OFC patients could be due to their difficulty in reversing learned stimulus-reinforcement associations in addition to or exclusive of their SWM deficits thought to be related to DLFC damage. In any case, since BPD patients do not have SWM or reversal deficits and the BPD Questionnaire is not correlated with SWM or reversal performance across all subjects, it seems unlikely that BPD patients are less open to experience for the same reasons that OFC patients are. In all likelihood, whatever is causing BPD patients to be less open to experience is related specifically to their disorder and perhaps to why they have other personality abnormalities that PFC lesion patients do not have. Further, BPD patients' personality abnormalities may be related to their emotional abnormalities (see Section 4.4.2), which PFC patients do not have either (excluding anger and happiness in OFC patients). In accordance, across all subjects, increased total subjective emotion score was correlated with decreased E and C and increased N. Since BPD patients were the only group significantly different from normals in terms of increased total subjective emotion score and N and decreased E and C, it is clear that the correlations between these factors across all subjects are due largely to the BPD patients' abnormalities. There is thus a strong link between emotionality and personality abnormalities in BPD patients and the most likely common cause for these deficits is amygdala dysfunction (discussed in Sections 4.3.3, 4.4.2, & 4.7). While amygdala dysfunction can affect OFC function due to their connectivity, it seems unlikely, based on the reasons provided above, that OFC dysfunction alone is the cause of BPD patients' closedness to experience.

Based on the results of this thesis, it is hard to say definitively what the underlying causes of closedness to experience are amongst the patient populations, but it is clear that patients with PFC damage (OFC and DLFC) and BPD are less open to experience than normal controls. Whether BPD patients' closedness to experience is caused by OFC, DLFC, or some other dysfunction related specifically to their disorder remains to be seen. Finally, correlation analysis across all participants has shown that the less open to experience a participant, the more impulsive (SRI), SWM deficits, and the faster the perception of time (increased time estimation total and decreased time production total). Investigations should be carried out in order to further explore the relationship between closedness to experience, impulsivity, SWM, and time perception.

## 4.4 Dissociations between Deficits in Orbitofrontal Cortex and BPD Patients

On some tests, BPD patients were significantly different from control groups while OFC patients were not and on other tests OFC patients were significantly different from control groups while BPD patients were not. In addition, on most of these tests, OFC and BPD patients were significantly different from each other.

BPD participants were significantly less extraverted and conscientious and more neurotic and emotional (in terms of total subjective emotionality and a higher frequency of sadness, fear and disgust) than all other groups. Further, BPD participants had a bigger change in fear, sadness, and anger than non-OFC participants (and OFC patients in the case of fear)[60] .

OFC participants performed worse on the reversal task (made less money, fewer reversals, and were more insensitive to punishment) compared to all other groups. Also, OFC participants had a significantly faster perception of time (in terms of increased total time estimation) than normal participants, while BPD patients were not significantly different from normal participants.

Finally, both lesion patient groups, OFC and non-OFC, had a deficit in SWM compared to normal and BPD participants. The SWM task was used to control for DLFC damage as SWM has been shown extensively to be related to DLFC function (see Section 1.10.2). Since both lesion groups contained patients with mixed lesions that included DLFC damage, they were expected to perform poorly on this task. Since BPD participants were not impaired on this task it is inferred that their deficits on other tasks can not be attributed to DLFC/SWM dysfunction. See Figure 4.8 for a visual summary of the dissociations between OFC and BPD patients.

### 4.4.1 Personality

BPD patients were significantly different from all other groups on all of the personality characteristics, except for openness to experience where they were only significantly different from normal participants (discussed in Section 4.3.5) and agreeableness where there were no between group differences. So, OFC and BPD patients were both significantly less open to experience than

[60] Normal participants did not complete the Emotional Change Questionnaire, as it measured emotional changes after a brain injury or onset of psychiatric illness.

normal controls and there was no difference between them, but for every other personality trait (except agreeableness), OFC and BPD patients were significantly from different from each other[61]. BPD patients were more neurotic, less extraverted, and less conscientious than all other groups. Since OFC patients were no different from normal controls on these personality traits, perhaps these traits are not related to OFC function, but instead are related to other intricate brain systems that are either neurochemically, neurophysiologically, or neuroanatomically imbalanced in BPD patients. Discovering the exact cause of these personality abnormalities in BPD patients requires further investigation.

Next, I will briefly discuss the relationship between BPD and N, C, and E and propose possible underlying causes of these personality disturbances.

#### 4.4.1.1 Neuroticism

The personality dimension of neuroticism (N) has been described by the following trait adjectives: emotional instability, gloomy, tense, worrying, moody, nervous tendency toward negative emotionality, and inability to cope (McCrea & Costa, 1996). BPD patients' significantly high neuroticism compared to all other groups coincides with the fact that emotional instability is one of the defining features of BPD (see Appendix 6). Since OFC patients are not neurotic while BPD patients are, it seems likely that BPD patients' neuroticism is linked to another type of brain dysfunction, perhaps within the limbic system, in addition to or perhaps separate from OFC dysfunction. For example, based on experiments with rats with bilateral amygdala damage, Simonov (1984) hypothesised that neurosis arises as a result of an impaired interaction between the frontal neocortex, hippocampus, amygdala, and hypothalamus. So perhaps something like hyperarousal of the amygdala, which has been shown to be involved in such emotions as fear, rage, and feelings of punishment (see Rolls, 1999), may act on its own or in conjunction with the OFC to produce emotional and personality instability. It may be that whatever causes one to be neurotic also causes one to be more emotional since, for example, according to Eysenck & Eysenck's (1969) theory, neuroticism raises the general intensity of emotional reactions. Eysenck associates N with arousibilty of the limbic circuit, such that neurotics become more aroused than stable individuals as a consequence of emotion-inducing stimulation. So, individual differences in N may only become apparent in an emotional or stressful context. N is thus thought to be founded on a biological system related to the visceral brain that produces autonomic arousal. This coincides with the fact that BPD patients were both more neurotic and more emotional than all other groups.

Experiments by Stenberg (1992) suggest that anxiety [high N and low E according to Gray (1987)] rather than impulsivity [high N and high E according to Gray (1987)] is related to emotionality. In an EEG study, Stenberg (1992) (see Section 1.3) manipulated positive and negative imagery in subjects classified by the Eysenck Personality Inventory and the Karolinska Scales of Personality (see Section 1.3). He found that more impulsive subjects showed signs of lower EEG

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[61] The link between open-mindedness, the OFC, and BPD is discussed in Section 4.3.5.

arousal than low impulsive subjects and more anxious subjects showed greater right-side frontal theta activity across all conditions, suggesting higher emotionality. Further, high anxious subjects showed higher beta rhythm activation to the negative emotional condition, but the high impulsives did not show a corresponding reaction to the positive emotional condition. Stenberg (1992) concludes that there is more support for the view that impulsivity is associated with low arousal than with facilitation of positive affect.

Eysenck (1967; 1990) proposed that introverts have higher levels of activity in the cortico-reticular loop, and thus are chronically more cortically aroused than extraverts, that introverts show greater conditionability than extraverts, and that neuroticism raises the general intensity of emotional reactions. As discussed in Section 1.3, Gray (1970, 1981) modified Eysenck's theory by rotating the dimensions of extraversion and neuroticism by 30 degrees, resulting in two new dimensions: impulsivity (N+, E+), and anxiety (N+, E-). The "behavioural activation system" is the neurophysiological basis of impulsivity, whereas the "behavioural inhibition system" is the neurophysiological basis of anxiety. According to Gray's (1981) theory, if "behavioural activation system" and "behavioural inhibition system" activity feed into greater noradrenergic arousal, impulsives (neurotic extraverts) are expected to show more arousal in response to reward or non-punishment, whereas anxious individuals (neurotic introverts) should be more responsive punishment, non-reward, and novelty. So, according to Gray, as anxiety levels increase, sensitivity to punishment, non-reward, and novelty signals should also increase. This coincides with the finding that BPD patients who were highly neurotic and introverted did not display *punishment insensitivity* (PI) when compared to both control groups on the reversal task. BPD patients were not significantly *more* sensitive to punishment on the reversal task (although they were expected to be according to Gray's theory) than normal controls. However, there was a floor effect based on the reversal test design where it was not possible to do any better than the normal controls. So, hypersensitivity to reinforcers may be related to BPD patients' emotionality (discussed in Sections 1.12.7, 1.12.8, 4.4.2 & 4.7) and neuroticism. BPD patients were also more impulsive than all other groups but were not extraverted so Gray's definition of impulsivity (highly neurotic and extraverted) must not correspond to the type of impulsivity measured by the tests in this study.

In sum, BPD patients were more neurotic and emotional than all other groups. So, whatever the causal relationship, based on the evidence, it seems likely that neuroticism and emotion are closely related and are most likely governed by common brain mechanisms. Further, these governing brain mechanisms seem to be affected in patients with BPD. The link between neuroticism, emotionality, and BPD is further supported by the correlation analysis which revealed that N, total subjective emotion score, and BPD Questionnaire score were all positively correlated with each other across all subjects.

#### 4.4.1.2 Conscientiousness

Conscientiousness is a personality dimension that has been described by the following trait adjectives: thorough, reliable, persevering, efficient, degree of organisation, and preference for goal-oriented activity *versus* careless, disorderly, lazy, and distractible (McCrea & Costa, 1996). Again, it is not surprising that BPD patients are less conscientious than normal controls as they tend to care less about themselves and others and lack energy as exemplified by their self-harming behaviour and by their high score on the Frontal Behaviour Questionnaire, which includes such questions as, "Do you ever worry about yourself? Do you ever feel listless?, Do you ever feel full of energy?, Do you ever find yourself saying things in an aggressive or abusive fashion to other people?, Are there occasions when you do not feel like co-operating when asked to?, and If you see that someone else is upset, do you stop to help them?". A high score on the Frontal Behaviour Questionnaire would indicate that participants do not worry much about themselves, feel listless often, rarely feel full of energy, and are verbally aggressive to and tend not to co-operate with or help others. Since OFC patients also had a high score on the Frontal Behaviour Questionnaire but were not unconscientious compared to control groups, perhaps OFC deficits in conjunction with other cognitive deficits contribute to the lack of conscientiousness in BPD patients. Further, there is a relationship between conscientiousness, emotionality, and BPD traits. As conscientiousness decreases, total subjective emotion, and BPD traits increase across all subjects. So perhaps whatever is causing BPD patients to be more emotional is also causing them to be less conscientious compared to OFC, non-OFC, and normal participants.

#### 4.4.1.3 Extraversion

Extraversion is a personality dimension that has been described by the following trait adjectives: talkative, energetic, enthusiastic, adventurous, outgoing, preference for social interaction, and activity for activity's sake (McCrea & Costa, 1996). It is interesting that, when compared to normal controls, BPD patients reported being introverted while OFC patients did not.

Eysenck & Eysenck (1969) suggest that introverts show greater conditionability than extraverts. This coincides with the finding that BPD patients, who were introverted, had no trouble on the reversal task involving conditioning, while OFC patients, who were not introverted, did. However, normal and non-OFC patients were not introverted either and they had no trouble on the reversal task. Gray (1970, 1981) modified Eysenck's theory by rotating the dimensions of extraversion and neuroticism by 30 degrees, resulting in two new dimensions: impulsivity (N+, E+), and anxiety (N+, E-) where high impulsivity leads to high sensitivity to reward and to non-punishment and high anxiety leads to high sensitivity to non-reward, to punishment, and to novelty. According to Gray's theory, since BPD patients were both more introverted and neurotic (anxious) than all other groups, they should also be more sensitive to punishment. As discussed above in Section 4.4.1.1, this coincides with the finding that BPD patients did not display punishment insensitivity compared to both control groups on the reversal task. So, hypersensitivity to

reinforcers may be related to BPD patients' impulsive behaviours and emotionality. BPD patients were also more impulsive than all other groups but were not extraverted so Gray's definition of impulsivity (highly neurotic and extraverted) must not correspond to the type of impulsivity measured by the tests in this study.

It may be that impulsivity (of the type measured in this study), interacting with introversion and high emotionality, causes BPD patients to harm themselves while OFC patients, who are impulsive but not introverted or extremely emotional, do not. OFC patients are not abnormally extraverted either which, combined with impulsivity, could lead patients to harm others. This theory is in line with that of Paris (1997) (see Footnote 37).

Finally, again, to link personality and emotion, introversion was correlated with increased subjective emotionality across all subjects. This implies that perhaps the same brain dysfunction is related to both introversion and emotionality. In fact, in physiological studies of animals, Eysenck (1990; Simonov 1981) found a biological basis for extraversion-introversion that is related to two Pavlovian types. In the "strong" type (choleric), related to extraversion, the frontal cortex and hypothalamus are dominant. In the "weak" type (melancholic), related to introversion, the hippocampus and amygdala are dominant. Thus, perhaps BPD patients who are introverted have some sort of hypothalamus or amygdala dysfunction, which could also explain their high emotionality.

Eysenck distinguishes arousal produced by reticular activity, the basis for extraversion, which he calls "arousal", from autonomic arousal, the basis for neuroticism, which he calls "activation". However, in reviewing EEG studies (O'Gorman & Lloyd, 1987), there is some evidence that impulsivity may be especially predictive of EEG, in line with Gray's theory, as opposed to E or N. Yet, in the absence of manipulation of motivational signals, those results have limited implications for the theory. Thus, more studies are needed.

#### 4.4.1.4 Summary of Personality

The evidence suggests that there is a strong relationship between certain personality traits and emotions, which may be related to the same underlying neurological correlates that are affected in patients with BPD. The relationship is made apparent by the fact that BPD patients have both personality and emotional abnormalities and by the strong correlations between total subjective emotion score, BPD traits, and N, C, and E across all subjects. Since OFC and DLFC patients were no different from normals in terms of N, C, E, and subjective emotion score, perhaps limbic system dysfunction is related to the personality and emotional abnormalities in BPD patients. The limbic system is a group of brain structures that affects mood, various emotions including pleasure, fear, happiness, and motivation, and the endocrine and autonomic motor system (Rolls, 1999; see Footnote 52 & Section 4.3.3). Since emotions are generally temporal inconsistent and usually focused on a particular event (see Section 1.5.1) while personality is temporally consistent and is more general in nature, perhaps an emotion is a brief, focused change in personality; or personality

is a permanent and global emotion. More research is needed in order to better understand the relationship between personality and emotion, which could lead to a clearer understanding of the emotional and personality abnormalities observed in BPD patients and to possible treatments.

### 4.4.2 Emotion (Subjective Emotion and Emotional Change)

BPD patients were more emotional than all other groups in terms of both frequency and amount of change since the onset of their illness. Compared to OFC patients, non-OFC patients, and normal controls, BPD patients had a significantly higher total subjective emotion score, experienced significantly more sadness, fear, anger, and disgust, and less happiness, and had a significant increase in sadness, anger, and fear since the onset on their illness. This is not surprising as a major criterion for the diagnosis of BPD is emotional instability (see Appendix 6). In fact, BPD is thought by some to arise from affective vulnerability (Linehan, 1993). The finding that BPD patients experienced more of each emotion (except happiness, which they experienced significantly less of) than all other groups coincides with previous studies (discussed in Sections 1.12.7 & 1.12.8) that imply that the affective vulnerability in BPD patients is caused by hyperarousal, including high sensitivity to emotional stimuli and high emotional intensity (Linehan, 1993). For example, Herpertz et al. (1997b) found that self-ratings indicated more intense emotional experiences and an increased sensitivity to even low-level emotional stimuli in personality disordered subjects with impulsive self-harming behaviour (14 out of 25 met the diagnostic criteria of BPD) compared to personality disordered subjects without impulsive self-harming behaviours. Self-mutilators exhibited an enduring pattern of impulsive behaviour, a deficit in future-oriented problem solving, and affective hyper-reactivity. So BPD patients' propensity for self-destructive behaviour could be associated with a failure to adequately process information about experienced emotions or a maladaptive response to intolerable affectivity.

In contrast to BPD patients, OFC patients did not report being very emotional except for being less happy and more angry than normal and non-OFC lesion participants (discussed in Section 4.1.5.1). In fact, while non-OFC and OFC lesion patients had a decrease in fear since the onset of their illness/head injury, BPD patients had an increase. In general, this implies that OFC patients are not likely to have amygdala dysfunction since, if they did, other emotions besides anger and happiness, in particular fear, (there is a wealth of data implicating the amygdala in fear conditioning; see Ledoux, 2000) would then be affected compared to normal controls. Accordingly, the OFC patients tested did not have any observable amygdala damage when their brain scans were reviewed. However, as mentioned earlier, the amygdala and OFC have reciprocal connections and OFC as well as amygdala damage can affect emotions (Rolls, 1999). Thus, further investigation is needed to fully understand the relationship between anger, happiness, the OFC, and the amygdala.

It may be that, BPD patients might have amygdala dysfunction in addition to OFC dysfunction, which could possibly explain the emotional irregularities that BPD patients reported that OFC patients did not. Sections 1.12.9.1.1 through 1.12.9.1.3 provide an overview of the

evidence that links BPD with PFC abnormalities. Concerning amygdala abnormalities, in an MRI study, Driessen et al. (2000) found that BPD patients (n=21) had nearly 16% smaller volumes of the hippocampus ($p < .001$) and 8% smaller volumes of the amygdala ($p < .05$) than healthy controls. As discussed in Section 1.12.7, Herpertz et al. (2001) found in an fMRI study that BPD (n=6), but not control, subjects had an elevated BOLD fMRI signal bilaterally in the amygdala and fusifrom gyrus and in the left medial and right ventrolateral PFC in response to aversive emotional stimuli. They suggest that the enhanced amygdala activation in BPD reflects the intense and slowly subsiding emotions commonly observed in response to even low-level stressors. Further, BPD subjects' perceptual cortex may be modulated through the amygdala leading to increased attention to emotionally relevant environmental stimuli. Also, the ventrolateral PFC, directly connected with the basal nucleus of the amygdala, has been regarded as a gateway for distinctive sensorial information and may modulate or inhibit amygdala-driven emotional responses and thus provide top-down control of the amygdala (Drevets, 1999; Morgan et al., 1994; Rauch et al., 1998). Thus, the OFC, with its strong inter-connections with subcortical areas implicated in emotional behaviour (see Section 1.6.2.1), may play a role in correcting emotional responses (Drevets, 1998; Rolls et al., 1994; Hornak et al., 1996). So, the abnormal emotionality, personality, and "frontal" behaviour, like behaving impulsively, demonstrated by BPD patients may be due to OFC dysfunction alone or to the combined effect of amygdala and OFC dysfunction.

In essence, BPD patients' emotion and impulsivity may be interrelated. Accordingly, impulsivity has been linked to affective dysregulation resulting in irritability and marked, rapid shifts of affective states like those seen in BPD patients (Van Reekum et al., 1994). So, intense affective instability has been regarded by some as an impulsive phenomenon (Western et al., 1992; Torgersen et al., 1994). One argument is that rapid mood shifts in reaction to even low-level stimuli show phenomenological similarities to impulsive behaviour, which has been defined as "an enduring tendency to react quickly instead of suppressing a response" (Buss & Plonin, 1975). The close relationship between impulsivity and affective hyperactivity is supported by the clinical observation that impulsive behaviours such as self-harm often occur in the context of intense episodic dysphoria (Herpertz, 1995) and are used as a maladaptive mechanism for relieving unbearable negative affect (Linehan, 1987). Herpertz et al. (1997b) found that patients suffering from personality disorders with impulsive self-harming behaviours (14 out of 25 were diagnosed with BPD) reported a higher intensity of affective experience in an affect-stimulation experiment in relation to non-impulsive patients and normal controls. These results suggest that poor affect regulation resulting from affective hyper-reactivity to environmental stimuli (positively or negatively valanced) is a crucial part of impulsivity in patients with self-harming behaviour and more generally in patients with BPD (Herpertz, 1997b). Finally, the finding that total subjective emotion score was positively correlated with SRI across all subjects, further supports a connection between impulsivity and emotion. However, the causal relationship, or in fact overlap, between these two factors remains to be discovered.

In sum, intense and rapidly changing mood states are a major feature of BPD although there have only been a few studies investigating affective processing in BPD, and, in particular, no definitive neurofunctional correlates of abnormal emotional processing have been identified so far (Herpertz et al, 2001). Therefore, further research to determine the exact neurofunctional abnormalities in patients with BPD is needed. In particular, more imaging studies should be done in order to investigate the activity of the OFC and the amygdala in BPD patients as each of these areas in conjunction or in isolation may be responsible for the various behavioural and emotional abnormalities observed in BPD patients.

### 4.4.3 Reversal

Only OFC patients had deficits on the reversal task compared to all other groups (discussed in detail in Section 4.1.3). OFC patients earned less money in total, obtained fewer reversals, and were more punishment insensitive (number of times they choose a stimulus after having lost $\geq$250 pounds) than all other groups while BPD patients were no different from control groups. So, OFC patients were insensitive to punishment while BPD patients were not. This coincides with Gray's (1970) theory that highly anxious individuals (neurotic introverts) should be more sensitive to punishment and frustrative non-reward than those who are not anxious. In accordance, BPD patients were neurotic and introverted while OFC patients were not. The discrepancy between BPD and OFC patients' performance on the reversal task, particularly in punishment sensitivity, is a key difference separating the two syndromes (discussed further in Sections 4.4.1.1, 4.4.1.3, & 4.7).

### 4.4.4 Time Estimation

Both BPD and OFC patients had time production deficits compared to normal controls, but only OFC patients had time estimation deficits compared to normal controls. This indicates that time production and estimation are regulated by two different brain mechanisms as there is a dissociation between BPD and OFC patients' deficits on these two types of time perception tasks.

OFC patients overestimated time in total significantly more than normal controls. This could imply that OFC patients have a faster cognitive pace than normal controls. This may be related to their inability to wait for the time interval to be over, as demonstrated by their tendency to underproduce time intervals compared to normals. However, OFC patients may simply underproduce time intervals because they have a faster cognitive tempo than normals. Overestimation of time intervals has to do with a fast cognitive pace because patients are required to wait for the whole time interval to pass before they respond, and the response is based on their perception of the time passed. However, in time production tasks, patients can end the interval whenever they wish. Therefore, there may be a different mechanism at work. Rather than a faster cognitive pace causing patients to produce less time than asked to, it may be that they are producing less time due to the incentive of having the test finish sooner. This is especially true of the BPD patients, most of whom, based on my own clinical observations, generally did not enjoy

being tested and wanted the testing to be over as soon as possible. Therefore, it may be that BPD and OFC patients both underproduced time compared to normal controls for two different reasons. It may be that OFC patients have a faster cognitive pace and BPD patients were experiencing frustration to non-reward causing them to respond (say the interval was over) sooner. However, OFC patients may also experience a frustration with delay of reward in addition to having a fast cognitive pace as the two may be related. OFC patients' overestimation could also be related boredom and the fact that time intervals feel longer the less active one is or the less interesting the task (Troutwine & O'Neal, 1981). Yet, no other group experienced this type of boredom. Further tests would have to be conducted on OFC patients to clearly determine why they underproduce time, but it is clear from the fact that they overestimate time that they do at least have a faster cognitive pace than normal controls.

It is interesting that both BPD and OFC patients had significantly lower time latencies than normal controls on the behavioural impulsivity task. Again, this probably has more to do with the desire to complete the task fast; in the case of OFC patients regardless of the punishers (making more errors by choosing the wrong stimuli) since, as revealed by their performance on the reversal task, OFC patients are less sensitive to punishment. In the case of BPD patients, who were not found to be insensitive to punishment, perhaps the reward of finishing the task sooner outweighs the punishment of making wrong choices on the MFFT since BPD patients do not make as many errors as OFC patients (see Section 4.3.1).

There are many theories concerning the mechanisms of timing (see Section 1.11.1). Some models suggest neuronal oscillations or interval based mechanisms like "biological clocks" (Wittman, 1999). While others suggest that timing deficits are due to impairments in various non-temporal processes such as motor implementation, attention, and memory (Harrington & Haarland, 1999; Rao et al., 2001). A faster subjective sense of time in terms of increased time estimation was correlated with increased between SWM deficits across all subjects while time production was not. This further emphasises the dissociation between time estimation and production and between BPD and OFC patients as OFC patients had SWM problems while BPD patients did not. From this observation one might suspect that time estimation involves SWM while time production involves some other kind of cognitive process. However, non-OFC patients had SWM deficits but did not have time estimation deficits. So, it seems that SWM does not necessarily affect time estimation. This supports the idea that subjective sense of time passing at short time intervals (10 to 90 seconds) is read off of an internal clock-like device in the brain rather than being based on memory for previous events that occurred during a particular time interval.

Data from lesion patients and some preliminary neuroimaging studies suggest that prospective timing might be mediated by different neural structures depending on the nature of the task and, possibly, on the temporal range evaluated (for a review of this data, see Basso et al., 2003). The brain areas that have been commonly implicated across studies include the basal ganglia, the cerebellum, and the PFC (see Section 1.11.2). Yet, the specific role of each of these

brain regions remains to be elucidated. However, there does seem to be a connection between the PFC and time estimation. For example, in an fMRI study, Basso et al. (2003) found that time estimation, compared with control working memory and motor tasks, was associated with increased activity in the middle occipital gyri, the right inferior parietal lobe, and bilaterally in the PFC. And, more specifically, time estimation may be related to OFC function as, in the current study, OFC patients had time estimation abnormalities while DLFC patients did not (see Section 4.1.2).

So, although there may be many brain processes involved in time perception, it is clear that dysfunction of different brain mechanism produces different types of time perception problems, namely time estimation and production. While the same underlying brain dysfunction may be causing both BPD and OFC patients to underproduce time, something else seems to be causing OFC patients to overestimate time, which remains unaffected in BPD patients. In all, as indicated by the underproduction and low response times (on the MFFT) of OFC and BPD patients and the overestimation of time by OFC patients, there seems to be a relationship between a fast subjective sense of time, increased cognitive tempo, and/or a lack of inhibitory control due to frustrative non-reward (e.g. wanting the task to end) (see also Sections 4.1.2 & 4.3.4).

### 4.4.5 Spatial Working Memory

Both OFC and non-OFC patients performed poorly on the SWM task compared to normal controls and BPD patients. This was expected, as it is well established that the DLFC is related to SWM (see Sections 1.10.2.2 and 1.10.2.3) and all 9 non-OFC lesion and 9 out of the 14 OFC lesion patients who participated in the SWM task had DLFC damage. The results of the SWM task in relation to frontal damage are discussed in more detail above in Section 4.1.8.

SWM was used as a control task to factor out DLFC deficits as reasons for the abnormalities displayed by OFC and BPD patients on other tests. In contrast to some evidence linking BPD to memory deficits (see Section 1.12.9), BPD patients did not have SWM deficits compared to normals and there was no significant correlation between BPD traits and SWM ability across all subjects. This indicates that the deficits displayed by BPD patients can not be attributed to SWM memory deficits and by extension to DLFC dysfunction. This implies that any frontal dysfunctions observed in BPD patients may instead be due to OFC dysfunction. Further, although both OFC and non-OFC patients displayed SWM deficits, non-OFC patients did not perform abnormally on other tests that OFC patients did (see Section 4.1). So, SWM/DLFC deficits alone can not explain the abnormal performance of OFC patients on those tests. In all, the SWM task did act as a control, ruling out SWM and DLFC deficits as possible explanations for the abnormal behaviours of OFC and BPD patients, allowing for the real aetiology of these behaviours to be separated out.

## 4.5 Discriminant Function Analysis

The discriminant function analysis was performed in order to identify interesting trends in the data and it provided an independent way to detect group differences. Two main functions were identified that separated out the four groups tested. For the first function, the discriminating variables that separate the groups maximally, and had loadings that are 0.5 or above and significant, are related to measures that reflect BPD. They are the BPD Questionnaire score, the total self-report impulsivity score, and the Frontal Behaviour Questionnaire score (as shown in Table 3.10). The first function separates the BPD group at one extreme from the other groups, with the normal and OFC lesion groups relatively close to each other, and the non-OFC lesion group a little further away in the direction away from the BPD group (see Table 3.9). The distances between groups in Figure 3.34 indicate how far apart the centroids of each group are from each other (Tabachnick & Fidell, 1996).

The second function, because it is orthogonal to the first, shows, in general, lower loadings on the variables related to the first function. The discriminating variables that separate the groups maximally with respect to the second function and that have loadings that are 0.5 or above, are related to effects of brain damage that separate normal controls from the other groups. The discriminating variables are performance on the reversal task (total pounds earned) and performance on the SWM task (between errors). Table 3.9 shows that the second function separates the normal group from the other groups in that the value for the centroid of the normal group is far, in the opposite direction along function 2, from that of the BPD, the non-OFC lesion, and especially the OFC lesion group (see Figure 3.34).

One of the main conclusions that can be made from this analysis is that normal participants can be separated out from all of the patient groups based on their performance on the reversal and SWM tasks. Both of these tasks are related to PFC damage as OFC patients and OFC and non-OFC patients performed poorly on each of these tasks respectively. Supporting the hypothesis that BPD is related to PFC dysfunction, BPD patients were grouped together with the PFC lesion patients on these tasks. This analysis also showed that BPD participants can be separated out from all other groups based on the BPD, Frontal Behaviour, and SRI questionnaires. This coincides with the finding that BPD patients scored significantly higher on all three of these tests than all other groups. It is interesting that "frontal" behaviours, which are behaviours commonly found in frontal lesion patients, separated out BPD patients from the other groups. This is consistent with the idea that part of the aetiology of BPD involves some sort of PFC abnormality, either neurochemical, neurophysiological, neuroanatomical, or some combination of the three.

## 4.6 Therapeutic Implications for BPD patients

The present results have implications for rehabilitation. Possible therapeutic strategies for OFC patients are discussed in detail in Section 4.1.10 above. It is suggested that if OFC patients are encouraged to stop and think before they act and given explicit feedback, perhaps some of their

implicit behavioural problems would resolve. Since OFC and BPD patients have many of the same behavioural and cognitive deficits, in particular impulsivity, perhaps the same types of therapeutic techniques that are proposed to be beneficial for OFC patients, as discussed in Section 4.1.10, would also help BPD patients. Further, BPD patients were found to have a faster subjective sense of time, which could lead to some of their frustration and impulsivity. Perhaps if carers were informed of this deficit in BPD patients they could take it into account when working with BPD patients and modify their responses accordingly.

The literature implies that there is a strong link between serotonergic dysfunction in the PFC and impulsivity (discussed in Sections 1.12.9.1.4 & 4.1.10). The PFC is the main source of input to midbrain serotonergic neurons of the dorsal raphe nucleus (Mayberg et al., 1990) and serotonin system dysfunction is thought to be involved in the production of impulsiveness in BPD (Brown et al., 1982; Coccaro et al., 1989; Hollander et al., 1994; see Section 1.12.9.4.1). So, it is logical that selective serotonin reuptake inhibitors (SSRIs) are recommended for treatment of the affective lability, impulsivity, and aggression found in patients with BPD. This recommendation is based on positive findings in at least 10 open studies and one small double-blind study of SSRIs for patients with BPD and one study of impulsive aggressive patients with different personality disorders (for a review, see Rinne et al., 2002). Studies that examine the efficacy of various SSRIs in the treatment of impulsive disorders such as BPD are presented in Hollander & Rosen (2000). Since OFC patients are also impulsive, treatment with SSRIs might help improve their impulsivity as well (see Section 4.1.10).

Results of the current study support the view that impulsivity, affective dysregulation, and personality abnormalities seem to be the psychopathological nuclear dimensions of BPD. Psychopharmacological treatment may become necessary during episodes of acute decompensation in which suicidal or self-destructive behaviour erupts. Some classes of psychotropic drugs have demonstrated efficacy in diminishing symptom severity and optimising functioning, such as antidepressants, mood stabilisers, benzodiazepines, opiate antagonists, and anti-psychotics. Conventional anti-psychotics are the best-studied psychotropic medications for BPD. However, non-adherence often occurs due to their severe side effects. Thus, perhaps SSRIs would be the best treatment for BPD patients' impulsive/self-harming behaviours in addition to any possible comorbid depression (see Section 4.1.10 & 4.9). There is a clear need for further controlled studies to evaluate pharmacological treatment options for this disorder (Hilger et al., 2003). Moreover, a diminished frontal metabolism could cause, parallel, or exacerbate impaired serotonergic function and therefore be related to impulsivity in BPD and OFC patients (De la Fuente, 1997).

In the current study, BPD patients had additional emotional and personality disturbances, which OFC patients did not. It is proposed that perhaps in addition to OFC deficits, BPD are more sensitive to reinforcers, perhaps due to an overactive amygdala and therefore are more emotional, neurotic, introverted, and less conscientious. As BPD patients may be extra sensitive to reinforcers

(see Sections 1.12.7, 1.12.8, 4.4.1.1, 4.4.1.3, 4.4.2, & 4.7) perhaps carers should be encouraged to emphasise positive feedback when working with BPD patients.

The cause of BPD is unknown at this time, but several theories are being looked at. There is some evidence that inheritance and other biological or biochemical factors may be involved in some people (Siever et al., 2002). For example, family, adoptive, and twin studies converge to support an underlying genetic component to the disorder (for a review, see Siever et al., 2002). However, although it is generally acknowledged that BPD has a complex, multi-factorial aetiology with interacting genetic and environmental substrates, the specific genetic underpinnings of this disorder have not been extensively investigated. Family aggregation studies suggest the heritability for BPD as a diagnosis, but the genetic basis for this disorder may be stronger for dimensions such as impulsivity/aggression and affective instability than for the diagnostic criteria itself (Skodol et al., 2002). Understanding the biological triggers of impulsivity or SIB, in conjunction with genetic predictors, may eventually help with the early prediction and prevention of suicidal behaviours.

Psychological factors are also involved for most patients. For example, having had childhood trauma (physical, sexual, or emotional abuse or neglect, or prolonged separation) is far more common in people with this disorder than in the general population (Paris, 1996). In fact, after reviewing an array of studies, Figueroa & Silk (1997) conclude that BPD patients' hyper-reactivity to the environment, which often manifests itself as hypersensitivity in interpersonal situations, is probably mediated through noradrenergic mechanisms, and these processes may be most closely related to a history of childhood sexual abuse. On the other hand, impulsivity, which is related to serotonergic mechanisms, is the major constitutional predisposition to BPD, regardless of whether or not there is a history of trauma. Combining environmental hyperactivity with impulsivity may lead to a clinical picture, often seen in BPD, where impulsivity and self-destructive behaviour are employed in order to deal with the stress, distress, and dysphoria of being hypersensitive to interpersonal and other environmental stimuli.

Treatment of BPD may include individual, group or family therapy, structure (e.g. scheduling their day), support, medicines, limit-setting, consistent rules, education about the illness, social skills training, behaviour modification, psychodynamic psychotherapy, and learning healthy communication and coping skills. Inpatient or day hospitalisation may be necessary when symptoms make the patient a danger to themselves or others. Patients should be encouraged to set clear, realistic goals, make and adhere to a written schedule every day so as to structure their time, develop methods to manage specific problem behaviours, be patient with themselves and others, learn to express their feelings directly and appropriately, control their reactions to their emotions, avoid alcohol and illegal drugs, and take their prescribed medications. In all, it seems that the best treatment for BPD is a combination of specific interventions, including medication and psychotherapeutic strategies. The overall treatment model should be an eclectic approach with an integrated framework based on an understanding of the borderline pathology that emerges from recent research.

## 4.7 Summary and Conclusions

This investigation aimed to determine if certain aspects of the borderline personality syndrome, in particular impulsivity, are associated with OFC dysfunction and to answer the question: To what extent do BPD patients with impulsive symptoms, who often are characterised by executive dysfunction, in the absence of overt neurological disorders and psychosis, also display evidence of PFC brain dysfunction and if so, exactly which areas of the PFC are associated with which aspects of the BPD syndrome? This issue was explored by administering selected basic questionnaires of personality, emotion, and impulsivity together with a number of computer based tasks sensitive to frontal lobe dysfunction that assess possible underlying factors related to impulsivity, including time perception, SWM, and sensitivity to reinforcers, to OFC lesion, non-OFC PFC lesion, and BPD patients as well as normal controls.

In accordance with the main hypothesis of this investigation that BPD is associated with OFC dysfunction, BPD patients were expected to have neuropsychological deficits similar to those of OFC patients. OFC and BPD patients performed similarly on certain tasks and differently on other tasks. This implies that some of the cognitive/behavioural deficits commonly found in BPD patients are related to OFC dysfunction while others are unrelated and are perhaps related to other brain systems (perhaps to an amygdala dysfunction as discussed below and in Sections 1.12.7, 4.3.3, & 4.4.2,). This dissociation between BPD and OFC patients on certain tasks may lead to a better understanding of both the aetiology of BPD and the functions of the OFC.

In support of the main hypothesis, OFC and BPD participants behaved in the same way on certain tasks in that they were both significantly different, in the same direction, from normal participants, and on some tests, also from non-OFC participants. Both BPD and OFC patients were more impulsive in terms of self-report impulsivity (including non-planning, motor, and cognitive subscales), reported more inappropriate/"frontal" behaviours, BPD characteristics, and subjective anger, and less subjective happiness than normal and non-OFC participants with BPD participants being significantly more impaired than OFC participants on all of these measures. Further, both OFC and BPD participants were more behaviourally impulsive (in terms of errors/second, total number of errors, and mean time latency on the MFFT), had a faster perception of time in terms of time production (producing more time in total and specifically at 60 and 90 seconds), and were less open to experience than normal participants with OFC participants being more impaired than BPD participants on the behavioural impulsivity "errors/sec" and "total number of errors" variables.

BPD and OFC patients behaved differently in that BPD participants were significantly less extraverted and conscientious and more neurotic and emotional (in terms of total subjective emotionality and a higher frequency of sadness, fear, and disgust) than all other groups. Further, BPD participants had a bigger change in fear, sadness, and anger than non-OFC participants (and OFC patients in the case of fear)[62]. OFC participants performed worse on the reversal task (made

[62] Normal participants did not complete the Emotional Change Questionnaire, as it measured emotional changes after brain injury or onset of psychiatric illness.

less money, fewer reversals, and were more insensitive to punishment) compared to all other groups. In addition, OFC participants had a significantly faster perception of time in terms of time estimation total than normal controls while BPD participants were not significantly different from normal controls. Finally, both lesion patient groups, OFC and non-OFC, had a deficit in SWM (more between errors and used a poorer strategy) compared to normal and BPD participants. The SWM task was used to control for DLFC damage (see Section 1.10.2). Since both lesion groups contained patients with mixed lesions that included DLFC damage, they were expected to perform poorly on this task. Since BPD participants were not impaired on this task it is inferred that their deficits on other tasks can not be attributed to DLFC/SWM dysfunction.

The finding that BPD patients reported significantly more BPD traits, were more emotional and impulsive, and had impaired personality traits compared to normal controls, coincides with the definition of the borderline syndrome (see Appendix 6). However, it is interesting that BPD patients reported significantly more "frontal" behaviours, had time production problems compared to controls, and had similar deficits to OFC patients in terms of impulsivity, time production, emotion (anger and happiness), personality (openness to experience), "frontal" behaviours, and BPD traits. This supports the theory that some BPD patients, in particular self-harmers, have similar deficits to OFC patients and accordingly perhaps some type of OFC dysfunction. This OFC dysfunction may be neuroanatomical (BPD patients may have decreased grey matter in their OFC), neurophysiological (BPD patients may have hyper- or hypoarousal of their OFC), or neurochemical (BPD may have a lack of serotonin or in their OFC; see Section 1.12.9.1.4). More research is needed to discover the exact nature of this dysfunction.

It may be that OFC dysfunction causes the same cognitive and behavioural abnormalities in OFC lesion and BPD patients, but does so in two different ways. For example, OFC patients may be less sensitive to reinforcers, as demonstrated by their poor reversal performance, while BPD patients may be more sensitive to reward and punishment, as they were unimpaired on the reversal task (see Sections 4.4.1.1 & 4.4.3), and thus more emotional[63] and introverted (possibly caused by overactivity of the amygdala; discussed below). Impulsivity may be a result of both types of dysfunction (hyper- and hypo- sensitivity to reinforcers). Further, impulsivity interacting with introversion and high emotionality may cause BPD patients to harm themselves while OFC patients, who are impulsive but not introverted or extremely emotional, do not. OFC patients were not abnormally extraverted either, which combined with impulsivity could lead patients to harm others, in line with Paris' (1997) theory (see Footnote 37).

Some of the differences in performance between OFC and BPD patients may be explained by abnormal amygdala function in addition to OFC dysfunction in BPD patients. Evidence of hyper-responsivity of the amygdala in BPD patients is discussed in detail in Herpertz et al. (2001) (see also Sections 1.12.7, 1.12.8, & 4.4.2). Herpertz et al. (2001) found that BPD subjects, but not

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[63] According to Weiskrantz (1968), Gray (1975), and Rolls (1999), emotions are simply states elicited by rewards and punishments.

control subjects, were characterised by an elevated BOLD fMRI signal bilaterally in the amygdala and fusiform gyrus and in the left medial and right ventrolateral PFC in response to aversive emotional stimuli. The hyper-responsivity of the amygdala in BPD patients might represent an oversensitisation to aversive emotional stimuli (Herpertz et al., 2001). So, perhaps BPD patients' emotional and personality abnormalities are related to amygdala dysfunction while their impulsivity, inappropriate behaviours, and time production deficits are related to OFC dysfunction or a combination of both. BPD patients' OFC dysfunctions (demonstrated by their similar performance to OFC patients on certain tasks) may also be exacerbated by amygdala dysfunction, thus explaining the worse performance of BPD compared to OFC patients on impulsivity, frontal behaviour, BPD, emotion, and personality questionnaires[64]. Therefore, it is plausible that a dysfunction of the limbic-orbitofrontal axis is involved in BPD, at least in a subgroup of patients (Van Reekum, 1993). The "lesions" that contribute to BPD may include increased limbic discharge and decreased OFC function.

The amygdala is thought to be related, among other things (discussed below), to fear (LeDoux 1987, 1994) and while non-OFC and OFC lesion patients had a decrease in fear since the onset of their illness/head injury, BPD patients had a significant increase in fear and BPD patients experienced significantly more subjective fear than all other groups. Neuroimaging studies in normal and depressed patients indicate a crucial role for the amygdala in processing negative emotions (Irwin et al., 1996; Morris et al., 1998; Schneider et al., 1997 ; Schneider et al., 1995) and a number of PET and fMRI studies showed left-sided (Morris et al., 1998; Schneider et al., 1997) or bilateral activation in the amygdala (Breiter et al., 1996; Irwin et al., 1996) based on volunteers' response to negative affect inducing visual stimuli. Activation of the amygdala may be regarded as a manifestation of a neurobiological fear reaction, as the BPD subjects of Herpertz et al's (2001) study also had high trait anxiety[65]. Amygdala involvement has also been reported in depressive subjects, in which increased activity has been found in the limbic-thalamo-cortical circuit, comprising the amygdala, the thalamus, and the OFC (Drevets, 1998; Drevets, 1999). Therefore, amygdala activation may be a biological indicator of intense aversive emotions. Enhanced amygdala activation in BPD patients is suggested to reflect the intense and slowly subsiding emotions commonly observed in these patients in response to even low-level stressors (Herpetz et al., 1997b). BPD patients' OFC may be modulated through the amygdala leading to increased attention to emotionally relevant environmental stimuli.

The findings in this study coincide with previous studies (Butter 1969; Iversen & Mishkin, 1970; Rolls et al., 1994; Hornak et al., 2003a, in press) in that the OFC has been shown to be

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[64] BPD patients scored worse than OFC patients on all questionnaires, even when they both scored worse than normal controls. However, on the behavioural tasks, when both BPD and OFC patients did worse than normal controls, BPD patients were never worse than OFC patients and OFC patients were often worse than BPD patients. This could indicate that OFC patients' performance on the questionnaires was affected by a slight lack of insight.

[65] Measured by the State-Trait Anxiety Scale (Spielberger et al., 1970) and the State-Trait Anxiety Expression Scale (Spileberger et al., 1985).

involved in the reversing of learned stimulus-reinforcement associations. Patients with OFC damage were severely disrupted on the reversal task in that their responses to changes in rewards and losses of rewards were impaired, which may contribute to their everyday behavioural difficulties (Hornak et al., 2003a, in press). This builds on previous work that found patients with ventral frontal lobe lesions to be impaired at emotion-related reversal learning and measures of behavioural and emotional change (Rolls et al., 1994; Hornak et al., 1996). Previous studies have also shown that OFC lesioned monkeys perseverate in responding to a formerly rewarded stimulus that is no longer rewarded (Butter, 1969) and respond on the inappropriate ("no-go") trials in a "go/no-go" task (Iversen & Mishkin, 1970). Dias et al. (1996b, 1997) found that performance of a reward reversal within a pair of stimuli was impaired for monkeys that had received OFC lesions, whereas DLFC lesioned monkeys were unable to properly focus selective attention, a finding that behaviourally separates these two PFC regions (see Section 1.10.1). The OFC is well suited to participate is associative learning, as it receives visual, taste, olfactory, and somatosensory inputs, giving it the essential representations necessary to form stimulus-reinforcement associations and to make behavioural adjustments in response to changes in these associations.

In considering the unique nature of the OFC's capacity to learn and reverse stimulus-reinforcement associations, it is useful to compare it with a similar response from the amygdala. The amygdala is known to receive major visual input from sensory areas of the cortex which provide fast responses to simple perceptual and associative aspects of external stimuli (LeDoux, 1996). So, in addition to subcortical pathways of emotional processing, which are thought to act automatically even without awareness of the stimuli (Whalen et al., 1998), the OFC, with its strong interconnections with subcortical areas implicated in emotional behaviour (see Section 1.6.2.1), may play a role in correcting emotional responses (Drevets, 1998; Rolls; Hornak et al., 1996). An abnormal elevation of cerebral blood flow in the ventrolateral PFC, which was found in four out of six BPD subjects in Herpertz et al. (2001) (see Section 1.12.7), was also reported during induced aversive emotional states in patients suffering from anxiety disorders or depression (Drevets, 1999). This part of the PFC is directly connected with the basal nucleus of the amygdala, has been regarded as a gateway for distinctive sensorial information, and may modulate or inhibit amygdala-driven emotional responses and thus provide top-down control of the amygdala (Drevets, 1999; Morgan et al., 1993; Rauch et al 1998).

Further, both the OFC and amygdala are involved in aspects of emotional processing (Rolls, 1999; Hornak et al., 1996), show neural responses to the processing of faces and facial expressions (Rolls, 1999; George et al., 1999), and respond to reward and punishment situations (Rolls, 1999; Rolls, 2000e). Also, both OFC and amygdala neurons are able to code reward associations and reversals (Cador, 1989; Burns et al., 1993; Whitelaw et al., 1996; Rolls, 1999), although the OFC neurons appear to have greater plasticity in forming these associations (Rolls, 1999). While amygdala neurons that are responsive to rewards tend to require many trials to reverse response after a reward change, OFC neurons appear to code reward reversals very rapidly

(Rolls, 1999). These rapid reversals would give a behavioural advantage to organisms capable of such responses, as this could allow for escape from dangerous or noxious stimuli and improved social abilities due to the learning flexibility that such responses allow. Such abilities may be particularly relevant in facial expression detection in primates, which is critical in making social decisions. This may explain why patients with OFC damage behave inappropriately in social situations. So, although the amygdala receives similar inputs and is involved in some of the same functions as the OFC, there is evidence that it may function less effectively in the rapid learning and reversal of stimulus-reinforcement associations, as indicated by the greater difficulty in obtaining reversal from amygdala neurons (Rolls, 1992, 2000d), and by the greater effect of OFC lesions in the continuing choice of no longer rewarded stimuli (Jones & Mishkin, 1972). In primates, the need for very rapid stimulus-reinforcement re-evaluation and the development of powerful cortical learning systems may result in the OFC effectively taking over this aspect of amygdala function (see Rolls, 1992, 1999).

The OFC reward system can be further understood from investigations of its interactions with the amygdala in processing reward. Baxter et al. (2000) demonstrated the importance of such interactions in appropriate associative learning. Rhesus monkeys were to choose between two objects that were paired with different food rewards. One of the foods was then devalued, leading healthy monkeys to choose the object not associated with this particular food. After learning the associations, the monkeys received unilateral lesions to the amygdala or OFC. Following these lesions, both groups were still competent at choosing the object associated with the non-devalued reward. A second complementary lesion followed so that those monkeys with amygdala lesions received a contralateral OFC lesion, while those monkeys with OFC lesions received contralateral amygdala lesions. Following the second lesion, both groups of monkeys were unable to appropriately choose between the objects. This suggests that the amygdala and OFC act as part of an integrated neural system, as well as alone, in guiding decision-making and adaptive response selection based on stimulus-reinforcement associations. So, there seems to be an interaction between the OFC and amygdala which could explain many of the abnormalities that are found in BPD patients as well as some of the abnormalities of OFC patients.

Impulsivity is generally considered a dimensional personality trait that covers a wide range of different behaviours (Evenden, 1999a). Based on findings from different areas of research including animal behaviour, human psychology, and psychiatry, different concepts of impulsivity have been developed (for a review see Evenden, 1999a & Section 1.4). Impulsivity can often be an important clinical problem in psychiatry and neurology. A pathological increase of different types of impulsivity plays a major role in frontal lobe syndromes of manifold aetiologies and personality disorders associated with impulse-control problems and aggressive behaviour (Fallgatter & Herrmann, 2001). The manifestation of impulsive behaviour in syndromes such as personality disorders may be extreme examples of impulsive behaviours on a continuum with the normal population (see Section 4.1.7.1 & Figure 4.4). Many different biological systems have been

proposed to contribute to the neurobiological basis of impulsivity. The serotonergic neurotransmitter system has recently received the most attention, with evidence of its involvement coming from animal as well as psychiatric patient studies (see Sections 1.12.9.1.4 & 4.1.10). While there is extensive literature on the links between impulsivity, frontal brain dysfunction and low serotonergic transmission (see Section 4.1.10) there are also indications that dopaminergic neurotransmission is involved in deficits in response inhibition mediated by frontal brain regions (Jentsch & Taylor, 1999).

The frontal lobes have therefore been proposed to play an important role in regulating impulsivity, as was demonstrated in this study, although it is unclear as to exactly how this occurs. None of the biological knowledge to date has led to reliable pharmacotherapy for excessive impulsivity. Further, there is little understanding to date of the mechanisms by which those drugs that have been found empirically to have some efficacy (e.g. the psychomotor stimulants in attention deficit hyperactivity disorder) exert their therapeutic effect. By bringing together knowledge from different areas of research it is hoped that a cross fertilisation will be achieved that will lead to a sharpening of concepts, an improvement in methodology, the stimulation of biological studies, and effective treatments of impulsivity (Evenden, 1999c) in both psychiatric and neurological populations.

## 4.8 Strengths of this Study

This study is unique in comparing the clinical population of BPD patients to PFC brain lesion patients and perhaps will start a trend in that direction. Comparing psychiatric to brain damaged/neurological patients can be an excellent way to increase understanding of the biological aetiology of certain psychiatric disorders as well as the functions of the brain. Patients with psychiatric disorders may not have overt anatomical deficits. Their neurological dysfunctions may be more subtle and therefore best measured by comparing their performance to that of patients with known areas of brain damage on the same neuropsychological tests. This can help establish exact anatomical correlates related to psychiatric disorders and is a step forward for future studies.

This type of study can also help in making dissociations between different pathological symptoms within a particular psychiatric syndrome. By comparing psychiatric patients with lesion patients with known precise areas of damage, one can fractionate or separate out certain aspects of a syndrome and relate them to certain brain functions. For instance, this study was beneficial in making dissociations between different personality traits. BPD patients were less extraverted, conscientious, open to experience, and more neurotic than all other groups, while PFC lesion patients were less open to experience, but unaffected on the other personality traits compared to normal controls. This implies that different personality traits are related to different brain systems. Linking symptoms within a psychiatric syndrome with underlying brain dysfunction not only adds to our understanding of certain behavioural, emotional, and cognitive abnormalities, but it can lead to affective treatments.

Other strengths of this study were the highly significant results (many at $p = .000$ and most at $p < .01$) and the large number of subjects that were tested. As patients with discrete brain lesions are hard to obtain, the fact that 23 OFC and 19 non-OFC patients were tested increases the statistical power of the results. In addition, many of the patients were surgical lesion patients (19 out of 43) with very precise lesions that were definitively identified by neurosurgeons. This type of patient sample is quite uncommon, as it is difficult to acquire. Also, as DSM-IV classification of BPD alone can be subjective, the fact that the BPD patients tested had the objective, impulsive behavioural feature of self-harm was beneficial in obtaining a homogeneous patient group. Furthermore, the careful recruitment of clinical subjects with severe BPD, but without a major comorbid psychosis or overt neurological deficits, strengthens the findings.

Finally, a unique combination of different types of test were used, for example, personality, emotion, impulsivity, and time perception, which allowed for new and interesting comparisons to be made between cognitive and behavioural traits that were hypothesised to be related. This helps to increase our understanding of how these particular traits are related to each in the general population and to identify patterns and make dissociations between different types of dysfunctions within a particular syndrome. Also, behavioural tests of impulsivity were used in addition to self-report measures so as to account for any lack of insight participants may encounter.

In all, this type of study helps to discover how the brain functions by seeing how different kinds of tests are related and what cognitive and behavioural functions are affected in patients with precise brain damage. It also helps to increase understanding of the neurological aetiology of psychiatric illnesses, in this instance BPD, which can lead to more effective treatment programs.

### 4.9 Limitations of this Study

There were several limitations to this study. First, the design of the study preludes any concrete causal explanation of the findings. Next, the ecological validity[66] of many of the tasks is questionable as many paradigms in this study were tasks using the written word. For example, the emotional change, subjective emotion, "frontal" behaviour, and BPD traits measures were verbal self-report questionnaires. The ecological validity of these stimuli as "emotional" and "social/ behavioural" is questionable as emotional and behavioural reactions are more likely to involve interpersonal interactions. Further, questionnaire measures have limitations as they rely on patients' insight into their own condition, which may be slightly skewed due to their condition.

Although the OFC group was fairly well balanced for lateralisation (n=9 right-sided, 9 left-sided and 7 bilateral lesions), the non-OFC lesion group contained only 1 patient with bilateral damage and the majority of the patients had right-sided (n=13) as opposed to left-sided (n=5) lesions. There are two reasons why this imbalance occurred. First, there were simply more right-sided lesion patients available in the sample tested. Secondly, some left-sided lesion patients had to

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[66] Ecological validity is the extent to which generalisations from observed behaviour in the laboratory can be made to natural behaviour in the world.

be excluded because their lesion extended to language areas of the brain causing them to have linguistic deficits that would interfere with testing. As a result of this imbalance, it was not viable to compare left versus right-sided lesions. Bilateral (n=7) versus unilateral (n=16) OFC patients were not analysed either, because the number of patients in each of these groups was uneven and only one of the 7 bilateral OFC patients had a precise surgical lesion. The others had closed head injuries and thus more diffuse damage which could confound the results. However, some studies suggest hemispheric and uni- versus bilateral specialisation within in the PFC (see Appendix 18 & Sections 1.11.2.1, 4.1.5.1, & 4.1.5.2).

Many of the patients had mixed lesions, making specific brain-behaviour relationships more difficult to unravel. Some non-OFC patients' lesions extended into temporal and parietal lobes that are involved in, amongst other things, attention and auditory and visual analysis of information (Kolb & Whishaw, 1996). In addition many of the OFC patients had medial and/or DLFC damage in addition to their OFC damage. So, although the SWM task was used to control for the effects of DLFC damage, patients with even more precise lesions perhaps restricted to the OFC would have been even better in helping to identify precise brain-behaviour relationships.

As it was almost impossible to find BPD self-harmers who were not on any medication, most BPD participants tested were on prescription drugs such as mood stabilisers, anti-psychotics, and anti-depressants, which could have affected some of the results. However, even though they were on medication aimed at improving many of the behaviours that were being tested, BPD patients still showed significant deficits on almost all variables. For example, mood stabilizers (e.g. lithium) and some antipsychotics work to stabilise emotional lability and extremes and some negative personality traits (e.g. psychoticism) (Soloff, 2000). Further, most antidepressants (e.g. SSRIs) are targeted at increasing serotonin levels in the brain, and low serotonin levels, particularly in the PFC, have been linked to increased impulsivity, while increased levels of serotonin have been linked to decreased levels of impulsivity (see Sections 1.12.9.1.4 & 4.1.10). Thus, the antidepressives and antipsychotics that many of the BPD patients were on, aimed at increasing serotonin levels, should have a negative effect on their impulsiveness. Yet, despite being medicated with drugs targeted at decreasing their impulsiveness, emotionality, and some negative personality traits, BPD patients still showed significant deficits on almost all variables compared to normal controls (see Chapter 3-Results). Also, not all BPD patients were on of the same combinations of drugs, yet the BPD patients as a group still performed significantly worse than normals on many tasks. Finally, many of the known side effects of the medications such as dry mouth, runny nose, nausea, and weight gain or loss, should not affect task performance dramatically. It could be that BPD patients did *not* show significant deficits on the reversal task due to improved performance because they were medicated. However, this cannot be know unless further studies are done on unmedicated BPD patients, which are extremely difficult to find in clinical settings.

Finally, all but one BPD patient was female and some of the patients may have had comorbid depression as BPD often co-occurs with Mood Disorders (see Appendix 6), which could

influence the results. Further, although using a relatively large number of different tests can be beneficial in understanding behavioural and cognitive relationships (discussed in Section 4.8), it also increases the chances of finding significant results purely by chance and makes interpretation of the results more difficult.

### 4.10 Future Directions

Future research directions based on the findings in this study are proposed throughout this discussion, but I will mention a few more here. Even though almost all authors agree that impulsivity is multi-factorial, there is little agreement as to what these factors are (Evenden, 1999a). Accordingly, a clear understanding of the distinct brains function associated with impulsive behaviour is not available. Therefore more studies are needed.

There is still relatively little structural or functional brain imaging data on impulsive patients without overt neurological lesions and, to my knowledge, only one fMRI study with BPD patients (Herpertz et al., 2001). The preliminary findings of the current study encourage the use of functional neuroimaging techniques in future research on BPD patients, OFC patients, and healthy controls while engaged in tasks related to impulsivity and reinforcement sensitivity in order to illuminate the brain systems related to impulsivity and other inappropriate behaviours and emotions. Since the specific brain systems implicated in impulsivity, emotion, and personality in BPD patients are still poorly understood, brain imaging offers a powerful tool with which to characterise the brain mechanisms underlying their vulnerability to impulsive behaviours and their abnormal personality, emotionality, and processing of emotional stimuli. Functional neuroimaging can help to localise abnormal functioning in the brain of impulsive BPD individuals, which could lead to advances in the treatment of such disorders. It can also help clarify preliminary findings of a significant association between decreased metabolic rates in the OFC and impulsivity (De la Fuente et al., 1997; Section 1.12.9.1.2) and help to delineate fully the functional neuroanatomy of impulsivity. Finally, conducting imaging studies on healthy subjects while they are performing tasks related to impulsivity and reinforcement sensitivity would help clarify brain-behaviour relationships in the healthy brain and give clues as to what is going wrong in neurological and psychiatric populations.

As discussed in Section 4.1.10, OFC patients could be asked to stop and think and verbally respond before choosing between stimuli on the reversal task to see if reversal performance improves when this explicit strategy is used. It may also be useful to image both normal and OFC patients while using both the explicit and non-explicit strategies and make comparisons between respective brain area activations. In a new study to eliminate confounding explanations of lack of insight into their own condition, perhaps lesion patients as well as their spouses or someone close to them could fill out the questionnaires. Since, OFC patients may have done slightly better on all questionnaires than BPD patients because of a slight lack of insight into their own condition. Future work should also consider changes in emotional and behavioural functioning pre- and post-

localised lesions, by for example testing patients both before and after neurosurgery to determine if in fact their abnormal behaviours and emotions are caused by their brain damage or if they are unchanged from their premorbid condition.

More ecological validity studies could be conducted like studying, for example, emotion by using physiological measures like skin conductance responses or using observers' ratings of subjects' facial, vocal, and gestural reactions after hearing arousing stories or seeing affective images (Bechara et al., 2000). Future studies could also compare left versus right-sided and uni- versus bilateral PFC lesions on tests of emotion, timing, impulsivity, and inappropriate social behaviour, as some studies suggest hemispheric and uni- versus bilateral specialisation within in the PFC (see Appendix 18 & Sections 1.11.2.1, 4.1.5.1, & 4.1.5.2) with regard to these functions. Further, many of the patients had mixed lesions making specific brain-behaviour relationships difficult to unravel. Testing patients with even more precise lesions, perhaps restricted to only the OFC, will be even more helpful in identifying precise brain-behaviour relationships. This could help rule out opposing findings like for example, that stop-signal inhibition is disrupted in patients with right inferior gyrus damage more than patients with OFC damage (Aron et al., 2003).

Since most BPD participants were on prescription medication and all but one BPD patient was female, perhaps more male and, if possible, unmedicated BPD patients could be tested on the tasks given in this study to rule out any gender or medication effects on their performance. Further, as BPD often co-occurs with Mood Disorders (see Appendix 6) perhaps BPD patients can be compared to depressed patients on the same tasks in a future study. Additionally, although the use of many different kinds of tests is beneficial in understanding the relationship between emotion, impulsivity, personality, reinforcement sensitivity, and time perception, perhaps using fewer tests in specific combinations would allow for clearer interpretations of the data. Also, perhaps other personality tests could be used in future studies with BPD and PFC lesion patients to assess different personality traits that are thought to be related to impulsivity like, for example, the psychoticism dimension of the Eysenck Personality Questionnaire-R (Eysenck & Eysenck, 1992; measures E, N, and P). Eysenck identified three dimensions of personality, extraversion (E), neuroticism (N), and psychoticism (P) (Eysenck & Eysenck, 1985), based upon self-report questionnaires. He found that items that intuitively reflected impulsivity are often associated with different personality factors on the Eysenck Personality Questionnaire-R. Eysenck originally considered impulsiveness to be an integral part of E (Eysenck & Eysenck, 1963), but later decided that there were two distinct components of impulsivity: venturesomeness, which aligned with E, and impulsiveness, which was realigned to be part of the psychoticism (P) dimension (Eysenck & Eysenck, 1978, 1980; Eysenck et al., 1985b). So, Eysenck (Eysenck, 1981; Eysenck & Eysenck, 1985) defines lower-order traits of extraversion that include sensation seeking, venturesomeness, carefreeness, and liveliness, whereas impulsivity itself is included in the higher-order trait psychoticism (Eysenck et al., 1985a). Further, perhaps an IQ test, such as the National Adult

Reading Test (NART) (Nelson, 1982), could be given in conjunction with tests of impulsivity, emotion, and personality to determine if IQ affects these factors.

Future studies should continue the trend of comparing psychiatric to brain damaged or neurological patients on various neuropsychological tests as it is an excellent way to decipher brain-behaviour relationships and the biological aetiology of certain psychiatric disorders. This type of study can also help in making dissociations between different symptoms within a particular psychiatric syndrome. Linking symptoms within a psychiatric syndrome with underlying brain abnormalities adds to our understanding of certain behavioural, emotional, and cognitive abnormalities and can lead to effective treatments.

Finally, neglecting the psychosocial factors in the aetiology of impulsive behaviour would be naïve. The effect of environmental events on brain structure requires further exploration. Future research on the neuropsychiatry of impulsivity should combine and integrate both neurobiological and psychosocial variables. It is also important to correlate neuroanatomical findings with neurochemical ones. It seems particularly important, for example, that serotonergic neurons innervate frontal areas and therefore useful to explore whether serotonin reuptake inhibitors exert inhibitory effects by altering the functional neuroanatomy of this area (Stein et. al., 1998). Similarly, it is interesting to note reports that anticonvulsants (Valproate; Stein et al., 1995) and dopamine antagonists (Winchel & Stanley, 1991) may be helpful in patients with impulsive personality disorders as well. Thus, it is evident that determining optimal medical treatment of impulsive personality disorders requires further pharmacological studies.

Although there are limitations to neuropsychological tests, brain imaging techniques, and pharmacological studies, they are nevertheless able to contribute to an understanding of the cognitive, affective, physiological, anatomical, and chemical processes that are related to impulsive behaviour. It is clear that elucidating the underling brain processes that are impaired in impulsive behaviour as a personality dimension, in the context of frontal lobe dysfunction, and within the context of illnesses like BPD, requires further elaboration, which is the goal of this research. It is hoped that this study has contributed to our understanding of the association between frontal dysfunction and impulsive behaviour, the behavioural changes exhibited by patients with PFC damage, and the cognitive and biological processes that are impaired in impulsive people in the context of BPD. Ideally, this research will lead to future studies that discover and further delineate brain-behaviour relationships, contribute to the prevention and treatment of neurological and psychological disorders, and expand our knowledge of the complex interactions of the human brain and mind.

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## APPENDIX 1: Consent form for all participants

University of Oxford
Department of Experimental Psychology
South Parks Road
Oxford OX1 3UD

*Tel direct*: (01865) 271375
*Fax*: (01865) 310447
*Email*: *heather.berlin@psy.ox.ac.uk*

*Head of Department: Prof. O. Braddick*
*Administrator: Dr R M Plummer*

CONSENT FORM

**Project Title:** Learning impairments and behavioural changes in patients with head injury, stroke, and other conditions*

1. I confirm that I have read and understand the information sheet dated ..... for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I agree to take part in the above study.

| | | |
|---|---|---|
| Name of patient | Date | Signature |
| Name of person taking consent (if different from researcher) | Date | Signature |
| Researcher | Date | Signature |

* *"Impulsiveness and Brain Function" and "Personality and Cognition" were the titles on the consent forms for the BPD and normal participants respectively, as they were under different ethics committees' approval than the lesion patients.*

## APPENDIX 2: Information for normal participants

University of Oxford
Department of Experimental Psychology
South Parks Road
Oxford OX1 3UD

*Tel direct*: (01865) 271375
*Fax*: (01865) 310447
*Email*: *heather.berlin@psy.ox.ac.uk*

*Head of Department: Prof. O. Braddick*
*Administrator: Dr R M Plummer*

### INFORMATION FOR VOLUNTEERS

**Project Title**: Personality and Cognition

We invite you to take part in this research project. Here is some information to help you decide whether or not to do so. Please take time to read it carefully. If there is anything you do not understand, or if you would like more information, please ask us.

We are interested in understanding the relationship between different aspects of peoples' personality and how they think and feel. This may help us understand how different kinds of people seem more or less vulnerable to certain psychiatric illnesses and may lead to better treatment programs. We need healthy volunteers to help us with this research.
To take part, we would like you to:

- Be aged 18-75
- Have normal or corrected vision (glasses or contact lenses)
- Have no history of or current neurological illness
- Have no current major psychiatric illness
- Have no current substance or alcohol abuse

This study would consist of one approximately 1 and ½ hour visit to the Department of Experimental Psychology. If you agree to take part, we would first ask you to complete some simple, short questionnaires which are in standard clinical use. We would then ask you to complete some straight forward tasks of learning and memory. None of these are particularly difficult and should not pose any problems. In general, people enjoy completing these tasks. If you take part in this study you will receive £3.50 per hour for your participation and any travel expenses will be reimbursed.

Your results in the study will not be seen by anyone outside of the team conducting the research. If you decide to take part, you are still free to withdraw at any time and without giving a reason.

If you have any questions about the study, please contact: Heather Berlin, Department of Experimental Psychology, South Parks Road, Oxford, OX1 3UD.
Telephone: (01865) 271 375
E-mail: heather.berlin@psy.ox.ac.uk

Date _____

## APPENDIX 3: Information for lesion participants

University of Oxford
Department of Experimental Psychology
South Parks Road
Oxford OX1 3UD

*Tel direct*: (01865) 271375
*Fax*: (01865) 310447
*Email: heather.berlin@psy.ox.ac.uk*

*Head of Department: Prof. O. Braddick*
*Administrator: Dr R M Plummer*

### INFORMATION FOR VOLUNTEERS

**Project Title**: Learning impairments and behavioural changes in patients with head injury, stroke, and other conditions

We invite you to take part in this research study. Here is some information to help you decide whether or not to do so. Please take time to read it carefully. If there is anything you do not understand, or if you would like more information, please ask us.

This research is intended to investigate changes in learning, memory, and behaviour after head injury, stroke, or other conditions. We are also interested in understanding the relationship between different aspects of peoples' personality and how they think and feel. This may help us understand how different kinds of people seem more or less vulnerable to certain psychiatric illnesses. If you agree to take part, you would be asked to make at least one visit to the Rivermead Rehabilitation Centre or Oxford University's Department of Experimental Psychology (which ever is more convenient for you) for an approximately 1 and 1/2 hour testing session. We would first ask you to complete some short, simple questionnaires which are in standard clinical use. We would then ask you to complete some straight forward tasks of learning and memory. None of these are particularly difficult and should not pose any problems. In general, people enjoy completing these tasks.

If you agree to participate, this might involve having a magnetic resonance brain image (MRI) if you have not already done so. This would mean an appointment at the John Radcliffe Hospital lasting approximately ½ hour. It is similar to a CT scan which you might have had before but, it provides more accurate information and it does not involve x-rays or any injections. There are no known harmful effects although, some people might find it claustrophobic and it is quite noisy. Having an MRI scan is completely optional.

We need both healthy and brain lesioned volunteers as well as people diagnosed with borderline personality disorder to help us with this research. You have been selected because you fulfil one of these requirements.

To take part, we would like you to:

- Be aged 18-70
- Have normal or corrected vision (glasses or contact lenses)
- Have no current major psychiatric illness
- Have no current substance or alcohol abuse

If you decide to take part in this study, you will be given this information sheet to keep and be asked to sign a consent form which you would be given a copy of to keep. If you decide to take part, you are still free to withdraw at any time and without giving a reason. This would not affect the standard of care you receive.

All information which is collected about you during the course of this research would be kept strictly confidential. Any information about you which leaves the facilities would have your name and address removed so that you can not be recognised from it and you will not be identified in any report or publication.

For all patients who agree to participate, your GP will be notified of your participation in the study. If you take part in this study, any travel expenses will be reimbursed.

This study has been reviewed by the Central Oxfordshire Research Ethics Committee and the Oxfordshire Psychiatric Research Ethics Committee.

Thank you for carefully reading the information sheet.
If you have any questions about the study, please contact: Heather Berlin, Department of Experimental Psychology, South Parks Road, Oxford, OX1 3UD.
Telephone: (01865) 271375.
E-mail: heather.berlin@psy.ox.ac.uk

Date: _____

## APPENDIX 4: Information for BPD participants

University of Oxford
Department of Experimental Psychology
South Parks Road
Oxford OX1 3UD

*Tel direct*: (01865) 271375
*Fax*: (01865) 310447
*Email*: *heather.berlin@psy.ox.ac.uk*

*Head of Department: Prof. O. Braddick*
*Administrator: Dr R M Plummer*

## INFORMATION FOR VOLUNTEERS

**Project Title**: Impulsiveness and brain function

We invite you to take part in this research study. Please take time to read the information below carefully. If there is anything you do not understand, or if you would like more information, please ask us.

We are interested in understanding the relationship between different aspects of peoples' personality and how they think and feel. This may help us understand how different kinds of people seem more or less vulnerable to certain psychiatric illnesses and may lead to better treatment programs. If you agree to take part, we would first ask you to complete some simple, short questionnaires, which are in standard clinical use. We would then ask you to complete some straight forward tasks of learning and memory. None of these are particularly difficult and should not pose any problems. In general, people enjoy completing these tasks. The entire session should last approximately two hours separated by five minute brakes.

To take part, we would like you to:

- Be aged 18-75
- Have normal or corrected vision (glasses or contact lenses)
- Have no history of or current neurological illness
- Have no current substance or alcohol abuse

It is up to you to take part. If you decide to take part, you would be given this information sheet to keep and be asked to sign a consent form which you would be given a copy of to keep. If you decide to take part, you are still free to withdraw at any time and without giving a reason. This would not affect the standard of care you receive or your future treatment.

All information which is collected about you during the course of this research would be kept strictly confidential. Any information about you which leaves the facilities would have your name and address removed so that you can not be recognised from it and you will not be identified in any report or publication. Further, if you wish, you may obtain the result of this study when all of the information is gathered and analysed in about two years time.

For all patients who agree to participate, your psychiatrist will be notified of your participation in the study. If you take part in this study, you will be reimbursed for any travel expenses and inconveniences.

This study has been reviewed by the Ethical Committee (Research) of the Institute of Psychiatry (King's College London) and will make up part of the D.Phil. thesis of Ms. Heather Berlin of Oxford University. Thank you for carefully reading the information sheet.
If you have any questions about the study, please contact: Heather Berlin, Department of Experimental Psychology, South Parks Road, Oxford, OX1 3UD.
Telephone: (01865) 271375 E-mail: heather.berlin@psy.ox.ac.uk
Date: _____

## APPENDIX 5: Letter to lesion patients' general practitioner

Professor Edmund T. Rolls D.Sc.
UNIVERSITY OF OXFORD
DEPARTMENT OF EXPERIMENTAL PSYCHOLOGY
SOUTH PARKS ROAD
OXFORD OX1 3UD, ENGLAND

Telephone +44-1865-271375
Secretary +44-1865-271323
Fax +44-1865-310447
Email Address: heather.berlin@psy.ox.ac.uk
Web Address: www.cns.ox.ac.uk

Date .....

Dear Dr. ..... ,

I am writing to inform you that your patient ..... has been asked to take part in a research project which we are conducting. We are investigating changes in learning, memory, and behaviour after head injury, stroke, or other conditions. We are also interested in understanding the relationship between different aspects of peoples' personality and how they think and feel. This may help us understand how different kinds of people seem more or less vulnerable to certain psychiatric illnesses. If your patient agrees to take part, he/she will be asked to make one visit to Oxford University's Department of Experimental Psychology, the Rivermead Rehabilitation Centre or we will visit them at home for an approximately 1 ½ hour testing session. They will be asked to complete some short, simple questionnaires which are in standard clinical use and some straight forward tasks of learning and memory. None of these are particularly difficult and should not pose any problems. In general, people enjoy completing these tasks. If you have any questions concerning this study, please feel free to contact us.

Yours Sincerely,

Ethics approval on 22/11/01: O01.038-Learning Impairments in Patients after Head injury, Stroke and Other Conditions

Collaborators:
Prof. Edmund Rolls, Department of Experimental Psychology, University of Oxford
Heather Berlin, MA, Department of Experimental Psychology, University of Oxford
Dr. Udo Kischka, Rivermead Rehabilitation Centre
Prof. Derrick Wade, Rivermead Rehabilitation Centre
Dr. Molyneux, Neuroradiology, Radcliffe Infirmary
Prof. Robin Morris, Institute of Psychiatry
Dr. Michel Crowe, Bethlem Royal Hospital

# APPENDIX 6: BPD DSM-IV Criteria

**DSM-IV Criteria: Borderline Personality Disorder** (APA, 1994)
"A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:
1. frantic efforts to avoid real or imagined abandonment. Note: Do not include suicidal or self-mutilating behaviour covered in Criterion 5.
2. a pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation.
3. identity disturbance: markedly and persistently unstable self-image or sense of self.
4. impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating). Note: Do not include suicidal or self-mutilating behaviour covered in Criterion 5
5. recurrent suicidal behaviour, gestures, or threats, or self-mutilating behaviour
6. affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
7. chronic feelings of emptiness
8. inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights)
9. transient, stress-related paranoid ideation or severe dissociative symptoms" (p.654)

**The DSM IV goes on to say:**
"The essential feature of Borderline Personality Disorder is a pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity that begins by early adulthood and is present in a variety of contexts.

Individuals with Borderline Personality Disorder make frantic efforts to avoid real or imagined abandonment (Criterion 1). The perception of impending separation or rejection, or the loss of external structure, can lead to profound changes in self-image, affect, cognition, and behavior. These individuals are very sensitive to environmental circumstances. They experience intense abandonment fears and inappropriate anger even when faced with a realistic time-limited separation or when there are unavoidable changes in plans (e.g. sudden despair in reaction to a clinician's announcing the end of the hour; panic of fury when someone important to them is just a few minutes late or must cancel an appointment). They may believe that this "abandonment" implies they are "bad." These abandonment fears are related to an intolerance of being alone and a need to have other people with them. Their frantic efforts to avoid abandonment may include impulsive actions such as self-mutilating or suicidal behaviors, which are described separately in Criterion 5.

Individuals with Borderline Personality Disorder have a pattern of unstable and intense relationships (Criterion 2). They may idealize potential caregivers or lovers at the first or second meeting, demand to spend a lot of time together, and share the most intimate details early in a relationship. However, they may switch quickly from idealizing other people to devaluing them, feeling that the other person does not care enough, does not give enough, is not "there" enough. These individuals can empathize with and nurture other people, but only with the expectation that the other person will "be there" in return to meet their own needs on demand. These individuals are prone to sudden and dramatic shifts in their view of others, who may alternately be seen as beneficent supports or as cruelly punitive. Such shifts often reflect disillusionment with a caregiver who nurturing qualities had been idealized or whose rejection or abandonment is expected.

There may be an identity disturbance characterized by markedly and persistently unstable self-image or sense of self (Criterion 3). There are sudden and dramatic shifts in self-image, characterized by shifting goals, values, and vocational aspirations. There may be sudden changes in opinions and plans about career, sexual identity, values, and types of friends. These individuals may suddenly change from the role of a needy supplicant for help to a righteous avenger of past mistreatment. Although they usually have a self-image that is based on being bad or evil, individuals with this disorder may at times have feelings that they do not exist at all. Such experiences usually occur in situations in which the individual feels a lack of meaningful

relationship, nurturing and support. These individuals may show worse performance in unstructured work or school situations.

Individuals with this disorder display impulsivity in at least two areas that are potentially self-damaging (Criterion 4). They may gamble, spend money irresponsibly, binge eat, abuse substances, engage in unsafe sex, or drive recklessly. Individuals with Borderline Personality Disorder display recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior (Criterion 5). Completed suicide occurs in 8%-10% of such individuals, and self-mutilative acts (e.g., cutting or burning) and suicide threats and attempts are very common. Recurrent suicidality is often the reason that these individuals present for help. These self-destructive acts are usually precipitated by threats of separation or rejection or by expectations that they assume increased responsibility. Self-mutilation may occur during dissociative experiences and often brings relief by reaffirming the ability to feel or by expiating the individual's sense of being evil.

Individuals with Borderline Personality Disorder may display affective instability that is due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days) (Criterion 6). The basic dysphoric mood of those with Borderline Personality Disorder is often disrupted by periods of anger, panic, or despair and is rarely relieved by periods of well-being or satisfaction. These episodes may reflect the individual's extreme reactivity troubled by chronic feelings of emptiness (Criterion 7). Easily bored, they may constantly seek something to do. Individuals with Borderline Personality Disorder frequently express inappropriate, intense anger or have difficulty controlling their anger (Criterion 8). They may display extreme sarcasm, enduring bitterness, or verbal outbursts. The anger is often elicited when a caregiver or lover is seen as neglectful, withholding, uncaring, or abandoning. Such expressions of anger are often followed by shame and guilt and contribute to the feeling they have of being evil. During periods of extreme stress, transient paranoid ideation or dissociative symptoms (e.g., depersonalization) may occur (Criterion 9), but these are generally of insufficient severity or duration to warrant an additional diagnosis. These episodes occur most frequently in response to a real or imagined abandonment. Symptoms tend to be transient, lasting minutes or hours. The real or perceived return of the caregiver's nurturance may result in a remission of symptoms.

**Associated Features and Disorders**

Individuals with Borderline Personality Disorder may have a pattern of undermining themselves at the moment a goal is about to be realized (e.g., dropping out of school just before graduation; regressing severely after a discussion of how well therapy is going; destroying a good relationship just when it is clear that the relationship could last). Some individuals develop psychotic-like symptoms (e.g., hallucinations, body-image distortions, ideas of reference, and hypnotic phenomena) during times of stress. Individuals with this disorder may feel more secure with transitional objects (i.e., a pet or inanimate possession) than in interpersonal relationships. Premature death from suicide may occur in individuals with this disorder, especially in those with co-occurring Mood Disorders or Substance-Related Disorders. Physical handicaps may result from self-inflicted abuse behaviors or failed suicide attempts. Recurrent job losses, interrupted education, and broken marriages are common. Physical and sexual abuse, neglect, hostile conflict, and early parental loss or separation are more common in the childhood histories of those with Borderline Personality Disorder. Common co-occurring Axis I disorders include Mood Disorders, Substance-Related Disorders, Eating Disorders (notably Bulimia), Posttraumatic Stress Disorder, and Attention-Deficit/Hyperactivity Disorder. Borderline Personality Disorder also frequently co-occurs with the other Personality Disorders.

**Specific Culture, Age, and Gender Features**

The pattern of behavior seen in Borderline Personality Disorder has been identified in many settings around the world. Adolescents and young adults with identity problems (especially when accompanied by substance abuse) may transiently display behaviors that misleadingly give the impression of Borderline Personality Disorder. Such situations are characterized by emotional instability, "existential" dilemmas, uncertainty, anxiety-provoking choices, conflicts about sexual orientation, and competing social pressures to decide on careers. Borderline Personality Disorder is diagnosed predominantly (about 75%) in females.

**Prevalence**
The prevalence of Borderline Personality Disorder is estimated to be about 2% of the general population, about 10% among individuals seen in outpatient mental health clinics, and about 20% among psychiatric inpatients. In ranges from 30% to 60% among clinical populations with Personality Disorders.

**Course**
There is considerable variability in the course of Borderline Personality Disorder. The most common pattern is one of chronic instability in early adulthood, with episodes of serious affective and impulsive dyscontrol and high levels of use of health and mental health resources. The impairment from the disorder and the risk of suicide are greatest in the young-adult years and gradually wane with advancing age. During their 30s and 40s, the majority of individuals with this disorder attain greater stability in their relationships and vocational functioning.

**Familial Pattern**
BPD is about five times more common among first-degree biological relatives of those with the disorder than in the general population. There is also an increased familial risk for Substance-Related Disorders, Antisocial Personality Disorder, and Mood Disorders.

**Differential Diagnosis**
BPD often co-occurs with Mood Disorders, and when criteria for both are met, both may be diagnosed. Because the cross-sectional presentation of Borderline Personality Disorder can be mimicked by an episode of Mood Disorder, the clinician should avoid giving an additional diagnosis of Borderline Personality Disorder based only on cross-sectional presentation without having documented that the pattern of behavior has an early onset and a long-standing course.

Other Personality Disorders may be confused with Borderline Personality Disorder because they have certain features in common. It is, therefore, important to distinguish among these disorders based on differences in their characteristic features. However, if an individual has personality features that meet criteria for one or more Personality Disorders in addition to Borderline Personality Disorder, all can be diagnosed. Although Histrionic Personality Disorder can also be characterized by attention seeking, manipulative behavior, and rapidly shifting emotions, Borderline Personality Disorder is distinguished by self-destructiveness, angry disruptions in close relationships, and chronic feelings of deep emptiness and loneliness. Paranoid ideas or illusions may be present in both Borderline Personality Disorder and Schizotypal Personality Disorder, but these symptoms are more transient, interpersonally reactive, and responsive to external structuring in Borderline Personality Disorder. Although Paranoid Personality Disorder and Narcissistic Personality Disorder may also be characterized by an angry reaction to minor stimuli, the relative stability of self-image as well as the relative lack of self-destructiveness, impulsivity, and abandonment concerns distinguish these disorders from Borderline Personality Disorder. Although Antisocial Personality Disorder and Borderline Personality Disorder are both characterized by manipulative behavior, individuals with Antisocial Personality Disorder are manipulative to gain profit, power, or some other material gratification, whereas the goal in Borderline Personality Disorder is directed more toward gaining the concern of caretakers. Both Dependent Personality Disorder and Borderline Personality Disorder are characterized by fear of abandonment, however, the individual with Borderline Personality Disorder reacts to abandonment with feelings of emotional emptiness, rage, and demands, whereas the individual with Dependent Personality Disorder reacts with increasing appeasement and submissiveness and urgently seeks a replacement relationship to provide caregiving and support. Borderline Personality Disorder can further be distinguished from Dependent Personality Disorder by the typical pattern of unstable and intense relationships.

BPD must be distinguished from Personality Change Due to a General Medical Condition, in which the traits emerge due to the direct effects of a general medical condition on the central nervous system. It must also be distinguished from symptoms that may develop in association with chronic substance use (e.g., Cocaine-Related Disorder Not Otherwise Specified).

BPD should be distinguished from Identity Problem...which is reserved for identity concerns related to a developmental phase (e.g., adolescence) and does not qualify as a mental disorder." (p.650-654)

## APPENDIX 7: Behavioural Impulsivity Scale (BIS-11)

Name _____ Date _____

Directions: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement carefully and darken the appropriate circle to the right of the statement. Answer quickly and honestly.

| | Rarely | Occasionally | Often | Almost always |
|---|---|---|---|---|
| 1. I plan tasks carefully | O | O | O | O |
| 2. I do things without thinking | O | O | O | O |
| 3. I make up my mind quickly | O | O | O | O |
| 4. I am happy-go-lucky | O | O | O | O |
| 5. I don't "pay attention" | O | O | O | O |
| 6. I have "racing" thoughts | O | O | O | O |
| 7. I plan trips well ahead of time | O | O | O | O |
| 8. I am self-controlled | O | O | O | O |
| 9. I concentrate easily | O | O | O | O |
| 10. I save regularly | O | O | O | O |
| 11. I "squirm" at plays or lecture | O | O | O | O |
| 12. I am a careful thinker | O | O | O | O |
| 13. I plan for job security | O | O | O | O |
| 14. I say things without thinking | O | O | O | O |
| 15. I like to think about complex problems | O | O | O | O |
| 16. I change jobs | O | O | O | O |
| 17. I act "on impulse" | O | O | O | O |
| 18. I get easily board when solving thought problems | O | O | O | O |
| 19. I act on the spur of the moment | O | O | O | O |
| 20. I am a steady thinker | O | O | O | O |
| 21. I change where I live | O | O | O | O |
| 22. I buy things on impulse | O | O | O | O |
| 23. I can only think about one problem at a time | O | O | O | O |
| 24. I change hobbies | O | O | O | O |
| 25. I spend or charge more than I earn | O | O | O | O |
| 26. I have outside thought when thinking | O | O | O | O |
| 27. I am more interested in the present than in the future | O | O | O | O |
| 28. I am restless at lectures and talks | O | O | O | O |
| 29. I like puzzles | O | O | O | O |
| 30. I plan for the future | O | O | O | O |

## APPENDIX 8: Big Five Inventory (BFI)

Name _____ Date_____

Instructions: Here are a number of characteristics that may or may not apply to you. For example, do you agree that you are someone who *likes to spend time with others?* Please write a number next to each statement to indicate the extent to which you agree or disagree with that statement.

1. Disagree strongly
2. Disagree a little
3. Neither agree nor disagree
4. Agree a little
5. Agree strongly

*I See Myself as Someone Who ...*

____ 1. Is talkative
____ 2. Tends to find fault with others
____ 3. Does a thorough job
____ 4. Is depressed, blue
____ 5. Is original, comes up with new ideas
____ 6. Is reserved
____ 7. Is helpful and unselfish with others
____ 8. Can be somewhat careless
____ 9. Is relaxed, handles stress well
____ 10. Is curious about many different things
____ 11. Is full of energy
____ 12. Starts quarrels with others
____ 13. Is a reliable worker
____ 14. Can be tense
____ 15. Is ingenious, a deep thinker
____ 16. Generates a lot of enthusiasm
____ 17. Has a forgiving nature
____ 18. Tends to be disorganised
____ 19. Worries a lot
____ 20. Has an active imagination
____ 21. Tends to be quiet
____ 22. Is generally trusting
____ 23. Tends to be lazy
____ 24. Is emotionally stable, not easily upset
____ 25. Is inventive
____ 26. Has an assertive personality
____ 27. Can be cold and aloof
____ 28. Perseveres until the task is finished
____ 29. Can be moody
____ 30. Values artistic, aesthetic experiences
____ 31. Is sometimes shy, inhibited
____ 32. Is considerate and kind to almost everyone
____ 33. Does things efficiently
____ 34. Remains calm in tense situations
____ 35. Prefers work that is routine
____ 36. Is outgoing, sociable
____ 37. Is sometimes rude to others
____ 38. Makes plans and follows through with them
____ 39. Gets nervous easily
____ 40. Likes to reflect, play with ideas
____ 41. Has few artistic interests
____ 42. Likes to co-operate with others
____ 43. Is easily distracted
____ 44. Is sophisticated in art, music, or literature

## APPENDIX 9: BPD Questionnaire (STB)

Name_____ Date_____

Please read each question carefully and answer each by circling yes or no. Please answer quickly and honestly.

1) Do you often feel the impulse to spend money which you know you can't afford?
   YES NO
2) Do you often change between intense liking and disliking of the same person?
   YES NO
3) Do you frequently have difficulty in starting to do things?
   YES NO
4) Do you hate being alone?
   YES NO
5) Do you often experience an overwhelming sense of emptiness?
   YES NO
6) Do you at times have an urge to do something harmful or shocking?
   YES NO
7) Do you at times have fits of laughing or crying that you can't control?
   YES NO
8) Do you often have periods of such great restlessness that you aren't able to sit still for more than a very short time?
   YES NO
9) Do you frequently gamble money?
   YES NO
10) Does life seem entirely hopeless?
   YES NO
11) Do you often have the urge to hit someone?
   YES NO
12) Have you ever felt the urge to injure yourself?
   YES NO
13) Do you often overindulge in alcohol or food?
   YES NO
14) Do often feel like doing the opposite of what other people suggest, even though you know that they are right?
   YES NO
15) Do you often feel that there is no purpose to life?
   YES NO
16) Do you ever have the urge to break or smash things?
   YES NO
17) Do you ever have suicidal thoughts?
   YES NO
18) Are your thoughts about sex often odd or bizarre?
   YES NO

## APPENDIX 10: Frontal Behaviour Questionnaire

Name _____ Date _____

Instructions: Below are things that people sometimes feel are a problem. Please read each statement carefully and circle the number which best applies to you. If you think that the item does not apply to you, please circle 5 (never). Please answer quickly and honestly.

1. Do you ever feel that you do or say things but would rather stop yourself?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

2. Do you ever do things in the company of other people that they find somewhat inappropriate?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

3. Do you ever feel like acting violently when you don't get what you want?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

4. Do you ever find yourself saying things in an aggressive or abusive fashion to other people?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

5. Do you ever get angry or irritable?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

6. Do you ever misinterpret people's moods?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

7. When you feel that you are right, do you stick to your point no matter what?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

8. If you don't get an expected reward that you want do you try harder to get it?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

9. If you don't get an expected reward that you want do you try something else?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

10. Do you ever worry about yourself?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

11. Do you ever feel listless?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

12. Do you ever feel full of energy?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

13. Are there occasions when you do not feel like co-operating when asked to?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

14. Do you show your emotions in your facial expressions?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

15. Can you predict someone else's mood from their facial expression?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

16. If you see that someone else is upset, do you stop to help them?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

17. Do you stop to think before you act?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

18. Do you stop to think before you take a decision?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

19. Do you like gambling?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

20. When you gamble, do you take big risks?

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Almost always | Often | Occasionally | Rarely | Never |

## APPENDIX 11: Subjective Emotion Questionnaire

Name _____ Date _____

How often do you experience each of the following emotions?
Please circle the number that most applies to you.

1. Sadness

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Almost always | Often | Occasionally | Rarely/Never |

2. Anger

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Almost always | Often | Occasionally | Rarely/Never |

3. Fear

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Almost always | Often | Occasionally | Rarely/Never |

4. Happiness

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Almost always | Often | Occasionally | Rarely/Never |

5. Disgust

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Almost always | Often | Occasionally | Rarely/Never |

## APPENDIX 12: Emotional Change Questionnaire

Name _____ Date _____

Have you experienced any change in your capacity to feel each of these emotions since your illness (head injury/stroke/surgery/other)?

If so, has this increased or decreased? Please circle one.

1) Sadness:

Increased Decreased Unchanged

2) Anger:

Increased Decreased Unchanged

3) Fear:

Increased Decreased Unchanged

4) Happiness:

Increased Decreased Unchanged

5) Disgust:

Increased Decreased Unchanged

## APPENDIX 13: Instructions for the Acquisition part of the reversal test

The following instructions are read aloud by the researcher to the participant "Two patterns will appear together on the screen. On each trial you are to choose on by touching it. When you do so you will either win or lose some money (this will be shown on the screen). It will show you when you touch a pattern how much you won or lost on the last go and the cumulative score will be shown in the middle of the screen on the bar (histogram) on the right side of the screen. Both patterns can either give or take away varying amounts of money when you touch them, but one pattern, the 'good' pattern, gives more than it takes overall. If you keep choosing the good one you will gradually win lots of money. The other pattern, the 'bad' pattern, takes more than it gives overall, if you keep touching the bad one you will soon get more and more into the red.

Your aim is to find out by trial and error which is the good pattern. You are free to switch back and forth as often as you like but once you think you have worked out which is the good pattern you should stick with it. The position of the patterns (whether they appear above or below) is irrelevant to whether together will win or lose you money. Do you understand?" If the participant answers "no", the researcher elaborates further and answers the participant's questions.

## APPENDIX 14: Instructions for the Reversal part of the reversal test

The following instructions are read aloud by the researcher to the participant "Two new patterns will now appear on the screen. As before one is the 'good' pattern and the other is the 'bad' pattern. However in this task, once you have found out which is the good pattern and have touched it consistently a certain number of times, it will gradually change and become the 'bad' pattern (and vice-versa: the 'bad' pattern will gradually become the 'good' pattern).Your aim is to adjust your choices accordingly- to start choosing the pattern that had been 'bad' at the beginning and avoid choosing the pattern which started out being 'good'. Once you have successfully switched your choice of pattern and have chosen it consistently a certain number of times, there will be a second reversal- back to how things were at the beginning. Whenever a pattern changes from being 'good' to being 'bad' 9 (and vice-versa) this will happen gradually and you might lose a lot on both during the transition phase.

Your aim is to win as much money as possible by keeping track of which pattern is currently the 'good' pattern and choosing it consistently until you think it is changing and becoming the 'bad' pattern. Do you understand?" If the participant answers "no", the researcher elaborates further and answers the participant's questions.

## APPENDIX 15: MFFT instructions

The following instructions are read aloud by the researcher to the participant "I am going to show you a picture of a familiar item and then items that look like it. You will have to point to the picture on this bottom page (point) that is just like the one on this top page (point). Let's do some for practice" Experimenter (E) shows practice items and the participant (P) selects the correct item. "Now we are going to do some that are a bit harder. You will see a picture on the top and eight pictures on the bottom. Find the one that is just like the one on the top and point to it."

E will record latency to the first response to the half second, total number of errors for each item and the order in which the errors are made. If P is correct, E will indicate this to him. If wrong, E will say, "No, that is not the right one. Find the one that is just like this one (point)." Continue to code responses (not times) until P makes a maximum of eight errors or gets the item correct. If incorrect, E will show the right answer.

## APPENDIX 16: SWM instructions

The following instructions are read aloud by the researcher to the participant "For this test you will see some coloured boxes on the screen. What you have to do on each go is to look for the blue token that the computer has hidden inside one of the boxes. Only one blue token will be hidden at a time. You have to collect enough blue tokens to fill the black hole (home) on the right of the screen. To look inside of a box all you have to do is touch it like this." The experimenter (E) then touches a box on the screen and the box does not contain a blue token. "This box does not have a blue token in it so I shall try a different box." E then touches another box and there is a blue token inside of it. "Now I have found a blue token in this box and there will never be one in there again so I must not go back to it and I will place the blue token into home on the right of the screen. Now there are two more blue tokens to find, but the computer never uses the same box twice for a blue token. So I must touch another." E touches another box. "There is no blue token in this box so I will try another one" The token is then found. "now the last blue token must be here" E touches the last box that contains the blue token and places it into home completing the task and the computer displays "COMPLETED" and plays a short tune and after a pause, the words "NEW SET" appear. "Now you have a go." E takes the participant through all of the steps again and repeats this process four more times until the participant is familiar with the task and then the actual test begins. Participants are told to press the space bar every time the computer reads "NEW SET" and this promotes them onto the next trial.

## APPENDIX 17: Time perception test instructions

Retrospective time estimation

The following instructions are read aloud by the researcher to the participant "Please read each consecutive number aloud that appears on the middle of the screen."

After the time interval has finished, the experimenter (E) then asks "How much time do you feel has passed from the moment you saw the green cross until the moment you saw the red cross disappear?"

Prospective time estimation

E then states, "From now on, at the end of each time interval, you will be asked how much time has passed from the moment the green cross appears on the screen until the moment the red cross disappears. Please continue to read each consecutive number off of the screen."

After the time interval has finished, E then asks "How much time do you feel has passed?"

Time production

E then instructs, "Please read the numbers off of the screen and press 'Q' when you think that (state the time interval being tested) X seconds have passed."

Time pacing

E then instructs, "Please start counting upward consecutively at what you feel is a one per second rate from the moment I say 'start' until the moment I say 'stop' and I will record the number you have reached at the end of each time interval."

Long-term Time Estimation

At the end of the time estimation experiment (at about 20 minutes), participants were asked "How much time do you think has passed from the moment we started the time task until now?"

## APPENDIX 18: Some evidence of hemispheric and uni- versus bilateral PFC specialisation

Hornak (2003a, in press) found that only bilateral as opposed to unilateral OFC lesion patients were impaired at a reversal task. Hornak (2003b, in press) also found that although both bilateral and unilateral OFC lesions could impair emotional voice and/or face expression, significant changes in social behaviour and in subjective emotional state were related to bilateral OFC lesions only. Starkstein & Robinson (1991) found that patients who have suffered left-sided frontal cortex strokes had a high probability of becoming depressed, whereas those with right-sided frontal cortex stroke damage were more likely to exhibit symptoms of mania. Further, Benson (1983) suggested that left frontal cortex damage leads to a pseudo-depressive condition, characterised by psychomotor inhibition, apathy, indifference, lack of drive, and emotional reactivity, while right frontal cortex damage leads to pseudo-psychopathic behaviour such as, disinhibition, sexual and personal hedonism, and lacked concern for others. Finally, Grafman (1986) found that right-sided OFC lesion patients were more likely to have increased edginess, anxiety, depression, and a higher incidence of psychiatric treatment than non-OFC lesion controls. However, left-sided OFC lesion patients did not differ from lesioned controls in their mood state, but did have a more cavalier attitude toward interpersonal problems.