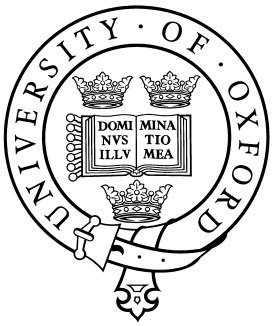
Vulnerability to Depression and Emotional Processing

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ABSTRACT

Risk factors for depression have long been identified. However, it remains unclear what are the *mechanisms* whereby these risk factors lead to depression. Therefore the current research examined cognitive and neurophysiological functioning in a sample of high risk vs. low risk never-depressed young adults. Risk for depression was defined by high neuroticism (N) scores on the Eysenck Personality Questionnaire (EPQ). Results indicated that, compared to low N volunteers, high N volunteers show widespread negative biases across emotional processing tasks, including self-referent words categorization and memory, facial expression recognition, and emotion potentiated startle. The neural substrates of these negative biases were further illustrated by our brain-imaging experiments using fMRI. In these studies, high N is associated with increased neural signals for negative self-referent personality attributes and fearful facial expressions in a distributed network known to be involved in emotional processing, including the fusiform-amygdala circuitry, anterior cingulate, and the superior parietal cortex. By contrast, these neurocognitive biases did not seem to be accompanied by impairments in more global executive function or disturbances in biological response to stress measured by awakening salivary cortisol. Consistent with the idea that emotional processing biases represent key mechanisms underlying vulnerability to depression, our final longitudinal study showed that depression symptoms in high N volunteers were well predicted (up to 91%) at an 18 month follow up by a combination of these negative biases and stressful life events. Taken together, the current investigations therefore suggest that neurocognitive biases in emotional processing are *trait* vulnerability markers for depression prior to illness onset.

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Chapter Seven

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To my parents and my husband

CHAPTER ONE

Research Background

1.1 GENERAL INTRODUCTION

Depression is a serious mood disorder that affects nearly all aspects of normal functioning, with the core features as persistent dysphoric mood and/ or anhedonia (i.e. inability to experience pleasure), which coexist with disturbances of motivated and psychomotor behaviour, sleep, appetite, energy and libido, and in some occasions suicide. Sadly, it is a relatively common mental health problem with lifetime prevalence rates estimated between 2.9 and 12.6 per 100 and lifetime risk estimated at 17-19% (Kessler et al 1994). This illness is highly recurrent even in this modern age of maintenance medication (Yiend et al 2007). Those who suffer from one depressive episode will experience an average of four lifetime depressive episodes of 20 weeks duration each (Judd 1997). Given this high relapse rate, the illness is now viewed as a chronic lifelong mental health condition. Very often, this battle starts quite early in life, with more than 50% of individuals having their first depressive episode by the age of 25, and 25% by the age of 18 (Sorenson et al 1991). All in all, prevention of illness onset must be made one of the top priorities in clinical psychological research.

To effectively prevent the first onset of depression, we need a thorough understanding of the aetiology of the illness. So far, research has identified the key high risk factors as family history of psychiatric illnesses, childhood abuse / neglect and the personality trait of neuroticism. These factors are believed to increase depression when triggered by major stressful life events (e.g. Kendler et al 1993, 2002, 2004, 2006). These research studies convincingly demonstrate factors involved

in risk for depression. However, they do not inform us of the exact *mechanisms* whereby these high risk factors lead to depression.

In contrast, cognitive and biological theories of depression suggest mechanisms without necessarily the same emphasis on a coherent causal model. Specifically, cognitive theories emphasise the role of negative biases in information processing in the aetiology and maintenance of depression (Beck 1979). In support of this, selective attention, interpretation and memory for negative materials have been reported in depressed patients and to a certain extent recovered patients (see section 1.2). Moreover, depressed patients are often found to have global cognitive deficits, with memory and executive functions deteriorating through the course of depression (see section 1.3). In parallel to these cognitive findings are biological dysfunctions found in depression. The hypothalamic-pituitary-adrenal (HPA) axis, which serves to regulate stress responses, is found to be particularly disturbed during depression (see section 1.4). Finally, recent advancement in the functional brain imaging technique has enabled research on neural mechanisms underlying these dysfunctions in depression. Neural networks for emotional processing have been mapped out, and dysfunctions in some of these structures have been associated with the cognitive biases seen in depression (see section 1.5).

Taken together, depression has been characterised with a range of neurocognitive and biological abnormalities. However, it is unclear whether these are *state* or *trait* factors of depression, that is, whether they are correlates of current depressed mood or whether they are long term vulnerability markers preceding the onset of depression. Therefore, the present research sought to identify vulnerability markers for depression preceding illness onset. As noted earlier, this line of research

will provide the prerequisite for developing effective strategies for preventing depression.

In this introductory chapter, the existing literature on the characteristics of depression, including negative biases in information processing, global cognitive impairments, disturbances of biological stress responses and neural abnormalities, will be discussed. Although depression is often studied alongside other affective disorders such as anxiety, wherever possible the current review will be focused primarily on the research relevant to depression. Each section will be concluded with a discussion regarding the state vs. trait debate. The last section will summarise the findings on high risk factors for depression, and finally, it will outline the objectives and methodology of the current thesis investigation.

1.2 NEGATIVE BIASES IN INFORMATION PROCESSING

As noted earlier, cognitive theories of depression emphasise the role of negative biases in information processing in the aetiology and maintenance of the disorder. Specifically, Beck proposed that, in depression, there are dysfunctional schemas which contain information about loss and failure, and the activation of such schemas results in selective processing of schema-congruent information (Beck et al 1979). Bower (1981, 1987) proposed an alternative model, in which each emotion is represented as a node in an associative network, and the activation of the emotion will increase the accessibility of the mood-congruent materials. These two theories differ in the way emotions are represented in our cognitive system. Nevertheless, both of them predict mood-congruent biases in information processing. In support of this, biases for memory and interpretation of emotional information have been reported in depression, although results regarding attentional biases are relatively inconclusive. These findings will be discussed in further details in the following subsections.

1.2.1 Attention to Emotional Stimuli

In everyday life, we encounter an abundance of information, thus selective attention is needed to maintain ongoing activities without being interfered by irrelevant information. In the case of depression and other mood disorders, however, this selective attention is usually biased towards negative valenced materials. This selective attention is believed to play a key role in the aetiology and maintenance of mood disorders (Williams et al 1997). In particular, there has been robust evidence of an attentional bias for threat in anxiety, as commonly illustrated by the modified Stroop and dotprobe tasks.

On the dotprobe tasks, an emotional word (e.g. threat related) and a neutral word are displayed simultaneously, one of them is then replaced by a dot. Anxious patients are typically faster in detecting the dot when it is presented to replace the threat word rather than the neutral word (e.g. MacLeod et al 1986, Mogg et al 1992), which is consistent with their processing resources being selectively allocated to the threat word content. On the modified Stroop tasks, subjects are asked to name the colour of the presented word, which is emotional or neutral. Here, anxious patients are typically slower in naming the colour of threat words (Mathews and MacLeod 1985, Mogg et al 1989, McNally et al 1990). This greater interference is again due to their selective allocation of attention to the emotional content of the word. These attentional biases are evident even when the stimuli are presented in subliminal level (e.g.14ms) both in dotprobe tasks (Mathews et al 1996, Mogg et al 1994, 1995) and Stroop tasks (Bradley et al 1997, Mogg et al 1993, Macleod and Rutherford 1992, Macleod and Hagan 1992), suggesting that anxiety is highly associated with a bias in pre-conscious attentional processes.

By contrast, research findings on depression have been mixed, leading some to propose that selective attention is a marker for anxiety rather than depression (Williams et al 1988, Mathews 1990). Nevertheless, the modified Stroop tasks have yielded some evidence for the presence of attentional biases in depression (Gotlib and McCann 1984, Williams and Nulty 1986, Gotlib and Cane 1987). Furthermore, recent studies using dotprobe tasks have found positive results when the stimuli were presented with a longer duration. For example, Mogg and colleagues (1995) reported evidence for attentional bias towards negative words in depressed patients, with this finding exclusive to the long-exposure condition (1 second) but not the short-exposure subliminal condition (14ms). In a similar study Mathews and colleagues (1996) found

that depressed patients selectively attend to socially threatening words, with a non-significant trend towards a stronger effect in the long exposure condition (500 ms) than the short exposure (50 ms). Consistent with this, increased attention to depression-related words has been reported in dysphoric patients and healthy volunteers undergoing a negative mood induction when longer stimulus durations (500ms, 1000 ms) were used (Bradley et al 1997).

Although not all studies using longer stimuli exposure yielded positive results (e.g. Hill and Dutton 1989, MacLeod et al 1986, Mogg et al 1993), wherever they have been found in depression, these have tended to occur on tasks using relatively long exposure duration. Indeed, it has been proposed that attention can be divided into components of shifting and maintenance (Posner and Petersen 1990, Allport 1989), with short and long exposure times capturing initial orienting and maintenance respectively. Therefore, the overall findings suggest that, unlike anxiety, depression is not associated with an attentional bias during the initial orienting, but instead may be characterised by the difficulty in disengaging attention from such materials.

1.2.2 Memory of Emotional Stimuli

While the findings of attentional biases in depression are controversial, mood-congruent memory is regarded as a reliable marker of depression. Mood-congruent memory refers to the tendency for depressed individuals to remember information consistent with their mood, that is, negative or unpleasant memories (Blaney 1986). This negative bias has been demonstrated in both explicit and implicit memory. Explicit memory refers to the strategic process of recollecting past events (or studied information), which is normally tested by free recall or recognition tasks. By contrast, implicit memory is manifested as a priming effect in which a past experience (e.g.

previous exposure of a word) facilitates performance on a task which does not require deliberate recollection of that experience (Graf and Schacter 1985). Such priming effects have been most often demonstrated in word stem completion tasks (Graf and Mandler 1984) and lexical decision tasks (Schacter 1987, Richardson-Klavehn and Bjork 1988). Performances on explicit and implicit memory tasks are thought to represent two distinctive processes underlying integration and elaboration respectively (Graf and Mandler 1984).

Earlier studies suggested that the mood-congruent memory is manifested in different patterns in depression and anxiety. Specifically, depressed patients have been found to show a bias favouring depression-relevant words on free / cued recall tasks, but not on word completion tasks (e.g. Denny and Hunt 1992, Watkins et al 1992). Using similar tasks, anxiety disordered patients showed the opposite pattern, in which they produced more threat words in primed stem word completion tasks but not in the free recall tasks (e.g. Mathews et al 1989). These results are consistent with the proposal that memory biases in depression and anxiety are respectively mediated by greater elaboration and integration for mood congruent information (Williams et al 1988).

Although there has been robust evidence for explicit memory biases in depression (Blaney 1986), there has also been increasing evidence supporting the role of implicit memory biases in depression. Bradley and colleagues (1995) found that, compared to anxiety disordered patients and healthy controls, depressed patients have greater priming effects for depression-related words in a primed lexical decision task and recall more words of the same kind. Specifically, the greater priming effects were evident in subthreshold condition (i.e. 14-ms stimulus exposure), suggesting that the depressed patients are biased towards negative memory without conscious awareness.

Similar findings of implicit memory biases were reported in another group of depressed patients (Watkins et al 1996) and non-clinical dysphoric subjects (Bradley et al 1994). In this latter study, the high negative affect group (i.e. healthy volunteers who scored on the high range of state / trait anxiety and depressed mood) displayed greater subliminal priming of depression-related words, which was further shown to be more closely associated with depression than anxiety.

Taken together, explicit and implicit memory biases are robust phenomena in depression. This mood-congruent memory is believed to play a key role in the maintenance of depression (Teasdale 1983). During depressed mood, negative memories become more accessible for recall, which in turn maintain or exaggerate the depressed conditions, leading to a vicious cycle. The presence of mood-congruent bias in implicit memory further suggests that an unconscious and automatic processing is involved in mediating the negative view of reality characterised in depression.

1.2.3 Affective Facial Expression Processing

Affective facial expression is an important component of social signals, thus the ability to accurately perceive facial expressions is crucial to effective interpersonal communication and social functions. This processing of others' facial expressions can be affected by own affective states, as illustrated in mood induction experiments (Bouhuys et al 1995) and naturally occurring mood disordered patients. In particular, depressed mood is associated with two impairments in facial expression processing, namely the general deficits in discriminating between emotions, and specific biases favouring the perception of negative relative to positive stimuli.

Evidence for a generalised deficit in the recognition of all emotions was found in a number of studies. For example, deficits have been demonstrated in the

recognition of faces expressing fear, anger, surprise, disgust, happiness, sadness, and indifference (Persad and Polivy 1993, Rubinow and Post 1992). Depressed patients also showed difficulty in verbal labeling of emotional and neutral faces (Feinberg et al 1986), suggesting a deficit in the expressive domain in addition to recognition impairments. These deficits are believed to be associated with the restricted range of affective states observed in severe depression.

Apart from deficits in recognising facial expressions in general, depression is consistently characterised by a specific processing bias towards negative and/ or away from positive facial stimuli. This abnormality is of particular relevance to the poor social functions of depressed individuals, who tend to appraise social events more negatively and experience less social support. While increased perception of sad faces was demonstrated (e.g. Bouhyus et al 1999, Hale 1998, Matthews and Antes 1992), other studies found reduced perception of happy faces (e.g. Suslow et al 2001, Sloan et al 1997, 2001). This discrepancy regarding the exact manifestation of negative bias in facial expression processing can be explained by different depression subtypes and methodology (such as the emotional valence, intensity, and presentation duration of stimuli) across studies (Surguladze et al 2004).

In fact, a few studies found both effects in depressed patients, suggesting that increased processing of negative and reduced processing of positive materials are not at all mutually exclusive. For example, Gur and colleagues (1992) found that depressed patients have higher tendency to misinterpret neutral faces as sad, but happy faces as neutral. In another study (Surguladze et al 2004), depressed patients were found to have poorer performance in discriminating sad and happy from neutral faces when the stimuli were presented rapidly (100ms). While the stimuli exposure was longer (2000ms), depressed patients showed a bias away from labeling mild

happy faces (50% intensity) as happy. These results thus supported the notion that generalised deficits in discriminating facial expressions and emotion-specific biases are two distinctive impairments in depression, which could be characterised separately by varying the intensity and exposure duration of the stimuli.

Overall, deficits in facial expression processing, especially a systematic bias favouring negative relative to positive stimuli, are robust markers of depression. These abnormalities are likely to underlie the poorer interpersonal problem solving (Gotlib and Asarnow 1979) and social competence (Fisher-Beckfield and McFall 1982) seen in depression.

1.2.4 Negative Cognitions Regarding the Self

As discussed so far, depressed patients have negative biases across a range of cognitive processes including attention, memory, perception and interpretation of emotional information. Not only do these biases serve to maintain a negative view of the world, more importantly, they sustain the negative sense of self that characterizes the core depressive symptoms of self reproach, guilt, and remorse.

This association between depression and negative cognitions regarding the self has been illustrated by experiments that employ self-referent materials. In particular, depression has been strongly associated with memory biases favouring negative information about the self, especially upon the theme of personal loss and failure (Blaney 1986, Teasdale 1988, Mathews and MacLeod 1994). These self-referent biases have been similarly revealed in attention using the Stroop paradigm. In these studies, depressed patients showed greater interference for self descriptive words than non self descriptive adjectives (Segal and Vella 1990, Segal et al 1995).

Furthermore, the effects of self-reference can also be assessed in facial expression processing. Bouhuys and colleagues (1995) introduced 'rejection' and 'invitation' to facial expression recognition task to capture the self-directed bias. They found that, following a depressive mood induction, subjects perceive more rejection but less invitation. This result clearly suggests that depressed mood can increase the perception of self-directed negative social signals. This also echoes an earlier study, in which negative biases in interpretation of social interactions were found to be more prominent when subjects imagine that these interactions were directed towards themselves rather than towards someone else (Hoehn-Hyde et al 1982).

Taken together, this robust phenomenon of negative bias in self-referent processing is consistent with the theory of Beck (1979), which suggests that negative cognition regarding the self is one of the key mechanisms underlying persistent depressed mood.

1.2.5 Emotion-Potentiated Startle

Apart from negative biases in cognitive processes, depression is also characterised by abnormal physiological reactivity to emotional information. Thus, the emotion-potentiated startle paradigm was introduced to measure the physiological correlates of emotional reactivity (Vrana et al 1988). Startle is an automatic reflexive response to fear, which can be elicited experimentally by an acoustic probe (typically a 50-ms burst of white noise around 95 dB) and measured by the magnitude and latency of eyeblink (Lang et al 2000). This response is normally potentiated (i.e. increased) by the presence of unpleasant stimuli (e.g. pictures of guns and death) but attenuated by pleasant stimuli (e.g. pictures of happy babies and erotica). This 'affect modulation' phenomenon is widely illustrated across studies using different stimuli,

though previous studies indicate inconsistent results regarding the inhibition effect by pleasant material and the use of imagery stimuli (Grillon and Bass 2003). Thus, this paradigm provides a reliable physiological measure of emotional reactivity, unaffected by subjective response bias or demand characteristics that often confound self rated reports.

In application to studies of psychiatric disorders, abnormal affect-modulation startle response has been widely demonstrated in anxiety disordered patients with phobias (e.g. Sabatinelli et al 1996, Hamm et al 1997), psychopathic prisoners (e.g. Patrick et al 1993, Pastor et al 2003), and depression (e.g. Allen et al 1999, Kaviani et al 2004, Dichter et al 2004). Specifically, anxiety disordered patients and healthy volunteers with high trait of fear show increased startle response both at baseline and under affect modulation (Grillon and Bass 2003, Cook et al 1991). Studies on depressed patients, however, have yielded inconsistent results, which appear to be varied according to different severity level and symptom profile.

In general, severely depressed patients with high levels of anhedonia do not display the typical pattern of affect modulation; instead they showed either no effects of modulation (Kaviani et al 2004) or potentiated response (rather than attenuated) to pleasant stimuli (Allen et al 1999). In contrast, patients with less severe depression and lower level of anhedonia showed the typical affect modulation effect, though the overall response was elevated (Kaviani et al 2004). These results suggested that severity of depression is associated with reduced physiological reactivity to emotional stimuli. The potentiated response to pleasant materials found in Allen et al (1999) further suggested that severely depressed patients may experience pleasant stimuli as aversive, although they subjectively rated the pleasant stimuli more positively than unpleasant stimuli. This dissociation subjective rating and physiological response

highlighted the advantage of including affect modulated startle response as an additional measure of emotional reactivity.

In summary, previous studies have illustrated abnormal affect modulation startle in depression, although the exact manifestation of this abnormality has yet to be clarified.

1.2.6 State vs. Trait

Hence, as reviewed above, depression is characterised by predominate negative biases in attention, memory, perception, and physiological reactivity for emotional information. However, it is not at all clear whether they are state or trait markers for depression.

Mood induction experiments provide one way to disentangle state and trait factors. For example, following negative mood induction, healthy volunteers were found to display increased attention to negative stimuli in dot probe tasks (Bradley et al 1997, Gotlib and McCann 1984), increased perception of sadness and reduced perception of happiness in ambiguous facial stimuli (Bouhuys et al 1995), and increased memory for negative materials (Mathews and Bradley 1983, Sutton et al 1988). These results suggest that mood directly modulates emotional processing, thus rendering support for the ‘state’ hypothesis.

Consistent with this, the evidence that negative biases disappear following successful treatment also suggests a mood-dependent characteristic. For example, in a longitudinal study, Mikhailova and colleagues (1996) showed that depressed patients are impaired in recognising sad and happy faces during the acute phase, but these impairments disappear during the remitted phase. Similarly, attention biases have also been shown to resolve following treatment (Gotlib and Cane 1987). However, this

line of evidence has been challenged by new findings that antidepressants could directly modulate emotional processing in healthy volunteers without changing their mood (Harmer et al 2003, 2004, 2006). In other words, resolution of dysfunction following treatment may not be mediated by mood states. An alternative explanation is that these cognitive biases have not been fully resolved; but rather, they may represent a latent vulnerability such that these biases would become apparent again when activated by stress or negative mood.

By contrast, cognitive biases that persist following recovery give strong support for the trait hypothesis. In particular, residual biases have been found in recovered patients in the facial expression recognition tasks (Hayward et al 2005, Bhagwagar et al 2004; Bouhuys et al 1999). In a longitudinal study, increased perception of sad faces during admission and discharge was found to predict subsequent relapse in six months (Bouhuys et al 1999). There has also been evidence that the abnormal affect modulation startle response persists after treatment (Dichter et al 2004).

Thus, measurable cognitive abnormality may be present in recovery, but we cannot rule out a scar effect, so-called because the residual biases may be a consequence of depression, rather than implying occurrence before the onset of the first episode. Previous research on individuals with sub-clinical mood disturbance provides a means to measure cognitive biases outside a depressive episode without being confounded by potential scar effects. For example, Bradley and colleagues (1997) indicated the presence of attentional bias towards negative words in dysphoric subjects (Beck Depressive Inventory scores >10). Specifically, this attention bias was correlated with the scores on Depression Proneness Questionnaire (Mathews and Bradley 1983). In another study, individuals with high negative affect (defined by

high scores on state and trait anxiety and depressed mood) were found to have greater subliminal priming of depression related words in implicit memory tasks, with further analyses suggesting that this implicit memory bias is more closely associated with depressed mood than anxiety (Bradley et al 1994). Using emotion-potentiated startle paradigm, individuals with high risks of anxiety, identified through high levels of trait fearfulness (Cook et al 1991, 1992) or harm avoidance (Corr et al 1995), showed enhanced affective startle modulation of negative materials similar to that observed in clinical anxiety.

These studies on sub-clinical depression and anxiety suggest that cognitive biases are present in individuals who are at high risk of mood disorders, and as such, they may represent vulnerability markers preceding illness onset. However, these studies provided only cross sectional measures and did not systematically control for previous experience of depression or anxiety. Only few studies have investigated the prediction of depression by cognitive mechanisms (see MacLeod & Hagan 1992, Alloy et al 2006). More research is needed to explore cognitive mechanisms underlying vulnerability to depression, and specifically longitudinal studies will be useful to examine whether cognitive biases would predict illness onset.

1.3 GLOBAL COGNITIVE DEFICITS

The previous section has reviewed research findings of negative biases in information processing in depression. In this section, the existence of more generalised cognitive deficits in depression will be reviewed.

1.3.1 Memory and Executive Functions Impairments

Cognitive deficits are well described in depressed patients, across a variety of tests measuring memory, attention, psychomotor functions, and executive functions (e.g. Goodwin 1997, Austin et al 2001). Executive functions refer to 'cognitive processes that control and integrate other cognitive activities' (Bryan and Luszcz 2000), which can be separated into subcomponents including set-shifting, planning, inhibition, working memory and fluency (Pennington and Ozonoff 1996). Amongst all, the most consistently reported cognitive deficit in depression is set-shifting. This has been illustrated across studies ranging from older (Beats et al 1996) to younger age (Purcell et al 1997), and more severe (Beats et al 1996) to less severe (Purcell et al 1997, Channon 1996, Channon and Green 1999) depression. The exception to this finding is relatively rare (e.g. Elliott et al 1996). Thus, it has been postulated that depression is characterised by deficits in shifting attentional focus whereas mania is shown by lack of inhibitory control (Murphy et al 1999).

Memory function is another key domain affected by depression, although there is inconsistency regarding different types of memory. In general, explicit memory appears to be most affected (Austin et al 1999) while deficits in implicit memory are not often indicated (Hertel and Hardin 1990, Denny and Hunt 1992, Bazin et al 1994, Danion et al 1995, Ilsley et al 1995). Moreover, there is evidence that cognitive impairments are more often observed in effortful tasks (e.g. recall) than automatic

tasks (e.g. recognition) (Roy-Byrne et al 1986). Thus, it has been postulated that the cognitive deficits in depression could be secondary to an underlying motivational deficit, rather than arising in their own right (Weingartner et al 1981, Cohen et al 1982, Roy-Byrne et al 1986). Although this effortful-automatic hypothesis was challenged by the finding of similar performance in recall and recognition (Frith et al 1983, Wolfe et al 1987, Golinkoff and Sweeney 1989, Austin et al 1992, 1999), it highlighted the importance of the role of motivation in cognitive functions.

Indeed, reduced motivation is one of the defining features of depression and could lead to cognitive deficits in several ways (Austin et al 2001). Previous studies proposed that reduced motivation in depressed patients is linked to their non-responsiveness to rewards, which in turn leading to a 'conservative response bias' i.e. a tendency to require a greater degree of certainty before they respond (Miller and Lewis 1977, Layne 1980, Henriques et al 1994). In particular, response bias to negative feedback is of particular relevance (Elliott et al 1996). Specifically, their results found that depressed patients' task performance drastically deteriorates after perceived failure on the preceding problem. The authors interpreted that as an indication of either an inadequate response to negative feedback or, quite the opposite, a stronger negative reaction to negative feedback manifesting cognitively as a 'negative cognitive set' (Beck 1963).

Another factor associated with cognitive deficits is illness severity. Significant correlations between severity of depression and cognitive deficits have been reported in some studies (e.g. Stromegren 1977, Cohen et al 1982, Wolfe et al 1987, Austin et al 1992, 1999, Elliot et al 1996), but not all (e.g. Rush et al 1983, Abas et al 1990, Brown et al 1994, Purcell et al 1997). Wherever correlations were found, they are often selectively for the more demanding tasks, consistent with the effortful-automatic

hypothesis discussed above. Moreover, cognitive deficits have been found to be more severe in patients with recurrent episodes (Stordal et al 2004, Basso and Bornstein 1999) and psychotic symptoms (Jeste et al 1996, Shatzberg et al 2000).

Clearly, widespread cognitive impairments are a reliable marker for acute depression. However, many of the studies discussed above were conducted on medicated patients. This could be seen as a confounding factor, especially when the state vs. trait question is confronted. This will be further discussed later in this section (sub-section 1.3.3). Meanwhile, the next sub-section will review the relationship between depression and deficits in another aspect of memory functions, known as 'over-general autobiographical memory'

1.3.2 Over-General Autobiographical Memory

Autobiographical memory refers to the recollection of past events that are personally experienced, and is central to a person's sense of self. Autobiographical memory was first implicated in depression in the context of selective recall of unpleasant past events in naturally occurring depression (Lloyd and Lishman 1975) and experimental mood induction experiments (Clark and Teasdale 1982, Teasdale and Fogarty 1979). When Williams and Broadbent (1986) attempted to study this phenomenon in suicidal patients, they observed that apart from the negative biases in memory, these patients consistently failed to recall specific past events. Rather, they tended to respond with a memory that summarised a category of events (e.g. 'I used to walk the dog everyday').

This phenomenon, known as 'over-general autobiographical memory', has been quickly replicated in other studies on suicidal patients (Williams and Dritschel 1988, Evans et al 1992, Williams et al 1996, Pollock and Williams 2001), and further

extended to other psychiatric groups. Amongst all, this over-general autobiographical memory has been most replicated in depressive disorders and posttraumatic stress disorders (Williams et al 2007). In contrast, the absence of such memory impairment has been consistently found in anxiety related disorders (Burke & Mathews 1992, Wenzel et al 2002, 2003, Wessel et al 2001), suggesting that over-general autobiographical memory is a relatively specific marker for depression and trauma rather than general psychiatric conditions.

Indeed, the connection between over-general autobiographical memory and depression has been robustly illustrated. In most of the studies, the 'autobiographical memory test' ('AMT': Williams and Broadbent 1986) with a cueing methodology was used, in which subjects were given a cue word (normally positive and negative valence) and asked to recall a 'specific event' that the word reminds them of. Specific events were defined as any single event that happened at a particular time and place and lasted for a day or less. In the last two decades, more than 10 studies found that depressed patients have more over-general memories (e.g. Moore et al 1988, Kuyken and Dalgleish 1995, Barnhofer et al 2002) or less specific memories (e.g. Williams and Scott 1988, Puffet et al 1991, Goddard et al 2001) than matched controls, depending on which parameter was used as the outcome variable. The effect of the valence of cue words was however less consistent. While a majority found that over-general autobiographical memory is present in both conditions, there is evidence that positive cue words elicit more over-general memory (e.g. Moore et al 1988, Williams and Scott 1988, Puffet et al 1991).

Furthermore, over-general autobiographical memory has been illustrated in sub-clinical depression. Using a variation of AMT, Moffitt and colleagues (1994) demonstrated that healthy undergraduates with high scores on depressive mood wrote

down more summary memories than those with low scores. This was replicated in later studies on dysphoric subjects (Goddard et al 1997, Ramponi et al 2004).

Despite the robust observations, there were a few exceptions where over-general autobiographical memory was not found in depressed group. However, these samples appear to be comorbid with other psychiatric conditions such as delusional disorders (Kaney et al 1999) and seasonal affective disorders (Dalgleish et al 2001). Overall, over-general autobiographical memory is a reliable cognitive marker for depression. It has been further suggested that over-general autobiographical memory is associated with other psychological functions, including poorer problem solving (Evans et al 1992, Goddard et al 1996, 1997, Raes et al 2005, Scott et al 2000), problems in imagining future events (Williams et al 1996), ruminative tendencies (Watkins and Teasdale 2001, Ramponi et al 2004), and elevated cognitive reactivity to mood changes (Williams et al 2005, 2006).

1.3.3 State vs. Trait

Although cognitive deficits are robust phenomena in depressed patients, again, it is relatively unclear whether they represent state or trait characteristics of depression. As noted before, one of the common methods to tease apart the state vs. trait effects is to assess patients before and after recovery. In general, results suggested that many cognitive deficits resolve upon full recovery, including set-shifting tasks (Paradiso et al 1997), verbal fluency (Trichard et al 1995), and memory functions (Peselow et al 1991). These studies lend support for the state hypothesis, although these results are far from conclusive. The major problem is that most of these studies failed to show recovery across all tasks. More problematic, there was low consistency across studies regarding which cognitive dysfunctions resolve or

persist. For example, in the study of Beats et al 1996, measures on simple and choice reaction time, set-shifting, and verbal fluency did not fully recover. Sternberg and Jarvik (1976) reported improved performance on immediate memory but not learning or short-term memory tasks.

Moreover, these studies on remission or recovery suffered considerable methodological limitations. While improvement upon recovery was reported, the task performance did not necessarily reach the normative range (Tarbuck and Payke 1995). Another key confounding factor, as mentioned earlier, is the lack of control over the effects of medication. The relationship between cognitive impairments and history of depression may also be mediated by other factors such as age, duration of illness, and number of episodes (Kessing 1998), which remains to be determined.

Just as the state vs. trait question remains unanswered for executive function impairments, the same question is confronting the phenomenon of over-general autobiographical memory. Illustrations of over-general autobiographical memory in recovered depressed patients (Mackinger et al 2000a, 2000b) gave partial support for the trait hypothesis. Consistent with this, over-general autobiographical memory assessed during non-depressed mood was found to predict future mood disturbances, such as premenstrual dysphoria (Mackinger et al 2001), postpartum depressed mood (Mackinger et al 2000a), depressive symptoms following negative life events in students (Gibbs and Rude 2004). However, many of these studies did not control for past experience of trauma and depression, thereby they may again be confounded by scar effects.

In summary, the state vs. trait question remains unanswered. Longitudinal studies assessing these cognitive functions before and after depression are required to reveal the interaction between cognitive functions and vulnerability to depression.

1.4 BIOLOGICAL RESPONSES TO STRESS

The cognitive biases and impairments in depression are often accompanied by dysfunctional stress responses within key biological systems. This section will briefly review these findings.

1.4.1 Hypothalamic-Pituitary-Adrenal (HPA) Axis

Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis has been well described in mood disorders. Briefly, this axis comprises of tissues of the hypothalamus, pituitary and adrenal cortices, regulatory neuronal inputs, and a variety of releasing factors and hormones (Young 2004). With its anatomical and functional connection with the amygdala, hippocampus, and other brain regions involved in emotional processing (Harrison 2002), the HPA axis is a chief modulator of stress reactions. Specifically, cortisol, a hormone released from the adrenal cortex, is elevated under chronic stress conditions (Wust et al 2000, Pruessner et al 1997). Thus, cortisol level has been often used as an indicator for HPA axis activity.

There are a variety of methods to assess cortisol level. Pruessner and colleagues (1997) proposed that free cortisol level after awakening is a more reliable assessment of the HPA axis activity, relative to the fixed time sampling method commonly used in earlier studies. In this publication, the authors presented data of the free cortisol responses to waking in 152 subjects repeatedly measured across three age groups: children, adults and elderly. Results showed a good intra-individual stability of this measure over days and weeks, which is similar across age groups. In general, free cortisol levels increase by 50%-75% within the first 30 minutes after waking followed by a decline and eventual return to baseline at about 1 hour after waking. Thus, unlike the conventional ways of fixed time point single assessments, this

method provides a dynamic measurement of the HPA activity with strict reference to time of waking. This method has quickly become one of the most widely used assessment tools of HPA activity.

1.4.2 Abnormality in Cortisol Secretion

Indeed, cortisol hypersecretion has been widely studied as a neurobiological marker for depression. The first observation of abnormalities of cortisol levels in depression was made in the 1950s by Board and colleagues (Board et al 1956). Over decades, increased baseline cortisol secretion in depressed patients has been illustrated in a number of studies (e.g. Carroll et al 1976, Halbreich et al 1985, Pfohl et al 1985, Rubin et al 1987, Sachar et al 1973). Hypersecretion of cortisol is believed to be resulted from impairments in the negative feedback mechanism of the HPA axis (Pariante and Miller 2001). Prolonged exposure to elevated cortisol may cause deficits in cognition, particularly learning and memory (Young et al 1999, Kirschbaum et al 1996, Lupien et al 1998, Wolowitz et al 1990, Newcomer et al 1994). Thus, it has been postulated that the HPA dysfunction reported in depressed patients is causally associated with the cognitive impairments also often seen in this population (Barden et al 1995, Young et al 1999).

In recent years, however, this well established phenomenon has become less consistent especially amongst less severely depressed samples recruited from the community or primary care source. Although some studies continued supporting the presence of cortisol hyperactivity in sub-clinical populations (Bhagwagar et al 2003, 2005; Cleary et al 1995, Young et al 2002), others have yielded contradictory results. For example, Stetler and Miller (2005) found blunted cortisol response to waking in a group of mildly and moderately depressed individuals. This study also found that,

unlike the healthy control group, cortisol response to waking in this depressed group was not correlated to waking time and social interaction. With this, the authors argued that HPA dysfunction in depression can be manifested as an insensitivity towards external (social interaction) and internal cues (waking time), resulting in a loss of regulatory control over HPA activity. Consistent with this, another sample of mildly depressed individuals was reported to have reduced plasma cortisol amplitude (Posener et al 2000). These were in line with other studies that found no evidence for cortisol hypersecretion in depression (Strickland et al 2002, Young et al 2002).

In the face of this controversy, two plausible explanations were suggested. First, cortisol hypersecretion may be confined to severely depressed patients (Maes et al 1994). However, as noted above, a few studies have illustrated cortisol hypersecretion in milder form of depression (Bhagwagar et al 2003, 2005; Cleary et al 1995, Young et al 2002). The second explanation, perhaps more convincing, is the different methodology employed by different studies. In particular, cortisol was measured at different times of the day across different studies. Nevertheless, HPA axis dysfunction is widely accepted as a prime biological marker for depression, although whether cortisol increases or decreases remains to be resolved.

1.4.3 State vs. Trait

For a long time, HPA axis dysfunction has been considered as a state condition (Plotsky et al 1998); mainly based on the evidence that cortisol levels normalise following successful treatment. However, recent studies with healthy volunteers have demonstrated that antidepressants could directly modulate HPA axis without mood change (Hennig et al 2000, Bhagwagar et al 2002, Hill et al 2003, Harmer et al 2003). This suggests that resolution of HPA dysfunctions following

effective treatment does not necessarily imply that HPA dysfunction is a state condition of acute depression. An alternative explanation is that such normalization of HPA function may only be temporary; i.e. they may persist as a latent vulnerability that would be activated in the face of stressful life events.

Indeed, research on recovered patients has yielded evidence supporting HPA dysfunction as a trait marker of depression. For example, Bhagwagar and colleagues (2003) found that fully recovered patients have overall increase in waking salivary cortisol, although this elevation normalised after one hour of waking. In a longitudinal study, Zobel and colleagues (2001) showed that the cortisol response at remission predicts relapse at six-month follow-up. Specifically, the probability of a relapse was more than 4-fold higher in the patients with an elevated cortisol response at discharge than in those with a normal cortisol response. Young and colleagues (2000) also found increased baseline cortisol in subjects with past major depression. These results provide strong support for the trait hypothesis. However, it is unclear from these data whether the HPA dysfunction is a residual symptom of past depressive episodes or a stable trait marker for depression preceding illness onset.

To avoid a scar effect, high risk populations have been studied. In these studies, high risk subjects were commonly identified through family history of depression or high neuroticism, two of the most well described risk factors of depression. For example, Mannie and colleagues (2007) illustrated increased waking salivary cortisol levels in young adults at familial risk of depression, which was not accounted for by parental attachment, life events, personality, or current mood states. Thus, the authors argued that HPA dysfunction is a trait vulnerability marker for depression, and is in part genetically mediated. Indeed, there is good evidence that genetic influences are involved in various aspects of HPA axis regulation including

waking salivary cortisol (Wust et al 2000, 2004, Young et al 2000). This study replicated previous findings on HPA dysfunction and familial risk for depression (Holsboer et al 1995, 2000), although there have also been negative findings (e.g. Le Masurier et al 2007). The interaction between neuroticism and HPA dysfunction is again inconclusive. While a few studies illustrated the link between cortisol hypersecretion and neuroticism (Portella et al 2005, Zobel et al 2004), at least one study found reduced cortisol response in high neuroticism (McCleery and Goodwin 2001). In the light of these contradictory results it remains unclear whether HPA dysfunction is a vulnerability marker preceding depressive illness.

In summary, HPA axis dysfunction is a well documented biological marker for depression. However, the state vs. trait question has yet to be resolved. More research effort is needed to elucidate the complex interaction between HPA dysfunction and risk for depression.

1.5 NEURAL MECHANISMS OF EMOTIONAL PROCESSING

As discussed in section 1.2, depression is characterised by pervasive negative biases in emotional processing. In parallel to this cognitive research, neuropsychological approach has sought to investigate the neural basis of emotional processing both in normal individuals and patients suffering from psychiatric disorders. In this section, I will first outline the existing findings regarding the neural system of emotional processing, followed by a review on the neuropsychological findings on depression.

1.5.1 Neural System of Emotional Processing

To outline the neural system underlying emotional processing, Phillips and colleagues (2003a) suggested that, in the face of a stimulus, the neural system will first identify its emotional importance before generating affective states and emotional behaviour, which are subjected to further regulatory processes. The authors further suggested neural circuitry linked to each of these specific processes. Overall, amygdala and insula are implicated for both appraisal of emotional significance and generation of emotional behaviour, whereas prefrontal areas are engaged in the regulation processes, with the division of dorsal vs. ventral regions specified for effortful and autonomic processes respectively.

While this theoretical framework provides an integrated approach for understanding emotional processing, a wide range of experimental paradigms has been employed to outline the neural networks for specific cognitive functions. Facial expression recognition, for example, has been widely studied for its implications in social cognition. A core system consisting of temporal and occipital cortical areas has been illustrated, with which emotional content is processed via its projections with

amygdala, insula and associated limbic structures known for emotional processing (Haxby et al 2000, 2002). This emotional processing can be performed unconsciously without explicit knowledge, which is illustrated by masked presentations of stimuli (Whalen et al 1998). Moreover, the neural network involved in facial expression recognition appears to be valence specific. In general, the amygdala is most implicated in perception of fear (e.g. Breiter et al 1996, Morris et al 1996, Phillip et al 1997, 2003a, Wright et al 2001, Sheline et al 2001, Surguladze et al 2003) though it has also been implicated in other emotions such as sadness (Blair et al 1999, Surguladze et al 2003) and happiness (Breiter et al 1996). There has also been increasing evidence for the role of insula in the perception of disgusted expression (Phillips 1997, Surguladze et al 2003). Furthermore, the fusiform gyrus has been highlighted in facial expression recognition across a wide range of emotions including fear, disgust, happiness and sadness (Surguladze et al 2003).

Sense of self is another fundamental process widely studied in psychology. Previous observations suggested that materials processed in self referent fashion are better remembered (e.g. Rogers et al 1977). Neuropsychological studies have supported the role of prefrontal cortex in this self referent processing (e.g. Gusnard et al 2001, Keenan et al 2001, Stuss 1991), specifically the medial prefrontal cortex (Craik et al 1999, Kelly et al 2002). In two recent studies, Fossati and colleagues (2003, 2004) clearly demonstrated the distinctive neural networks involved in the encoding and retrieval of self referent words. The conclusion from both studies suggested a predominate role of the dorsomedial prefrontal cortex in self reference processing, as implicated in both encoding and retrieval processes, as well as a number of other frontal and parietal areas. Indeed, the major role of a frontoparietal

network in self reference processing has also been illustrated using other stimuli type such as self-face (Uddin et al 2005, Kircher et al 2000).

Taken together, emotional processing recruits distinctive neural circuitry for specific functions. Abnormalities in the functioning of these structures or networks may be associated with abnormalities in emotional behaviour and regulation resulting in mood disturbances.

1.5.2 Neural Processing of Emotion in Depression

Indeed, a wide range of structural and functional neural dysfunctions have been reported in patients suffering from depression (Phillips et al 2003b, Drevets 2000, 2001). Using the same framework as discussed above (Phillips et al 2003a), Phillips and colleagues highlighted the evidence for neural impairments in the areas known to be involved in each of the components in emotional processing (Phillips et al 2003b). In particular, reduced volume and increased activity have been found within amygdala, insula, subgenual anterior cingulate, and other areas known for identification of the emotional significance of stimuli and generation of emotional behaviour. The authors suggested that these may result in a restricted emotional range, but with a bias towards the predominant role of the amygdala in perception of negative rather than positive emotions, resulting in symptoms of depressed mood and anhedonia. Similarly, by illustrating findings of reduced volume and decreased activity within prefrontal cortical areas, the authors further suggested a weakened top down emotion regulatory process in depression (Phillips et al 2003b).

Consistently, abnormalities within similar areas have also been highlighted in a large body of literature. In terms of structural abnormalities, neuroimaging studies have found reduced volume in amygdala (Sheline et al 1999), hippocampus (Bremner

et al 2000, Sheline et al 1999), subgenual anterior cingulate (Botteron et al 2002, Drevets et al 1997) and orbitofrontal cortex (Bremmer et al 2002). These results are consistent with evidence from postmortem studies in which a reduced density of glia cells was found in amygdala (Bowley et al 2002), subgenual anterior cingulate and orbitofrontal cortex (Cotter et al 2001, Drevets et al 1997).

In terms of functional abnormalities, depression is characterised by elevated resting cerebral blood flow and metabolism within amygdala (Drevets 1992), thalamas (Drevets et al 1992), and ventral limbic regions including the anterior insula and ventral striatum (Mayberg et al 1999).Using positron emission tomography (PET) the magnitude of this elevated activity in amygdala has been estimated as 5%-7%, which, after correcting for spatial-resolution effects, reflect an increase in the actual cerebral blood flow and metabolism of about 50-70% (Drevets 1992, 2001). There is evidence that this abnormality is positively correlated with severity of depression (Abercrombie et al 1996, Drevets 1992, 1995). Furthermore, abnormal elevations in orbital and ventrolateral prefrontal cortical activity have also been implicated in depression (Drevets 1992, 2000).

While the above data suggests structural pathology and baseline abnormal activity, functional imaging data reveals neural dysfunctions linked with specific cognitive-behavioural manifestations. For example, using facial expression recognition tasks, depression has been associated with increased amygdala, insula and ventral striatum responses during the presentation of negative expressions particularly fearful and sad faces (e.g. Sheline et al 2001, Davidson et al 2003, Fu et al 2004, Surguladze et al 2005, Drevets 2000, Keedwell et al 2005). Neural activity in extrastriate areas such as the fusiform gyrus and cuneus also show a differential pattern of response to emotional faces in depression, with reduced responses to happy

facial expressions and increased responses to negative facial expressions compared to healthy volunteers (Surguladze et al 2005, Keedwell et al 2005, Lawrence et al 2004, Fu et al 2007). In contrast, some studies have found increased activations to both positive and negative expressions in depression. For example, elevated activation to both happy and sad expressions has been reported in depressed patients in the subgenual anterior cingulate cortex (Gotlib et al 2005).

Evidently, facial processing is modulated by the affective content and significance of the faces. These effects have been hypothesized to be mediated through direct feedback connections from the amygdala, which could be performed without voluntary control, acting as a mechanism for increasing attention and associated visual processing to emotionally salient cues (Morris et al 1998, Vuilleumier 2005). Such unconscious automatic biases in early visual processing of emotional information in depression may be important in the underlying aetiology and maintenance of this disorder, with the patient assigning more salience and attention to negative vs. positive social cues, thereby fuelling negative thinking and poorer social function.

Apart from the facial expression paradigm, neural mechanisms underlying attentional biases were also revealed. During an affective go/no-go task, depressed patients showed reduced neural responses to emotional stimuli (both positive and negative) in ventral cingulate and posterior orbitofrontal cortices, but increased activity within rostral anterior cingulate gyrus specifically to negative stimuli (Elliot et al 2002). This study highlighted the role of medial and orbital prefrontal regions in mediating the mood-congruent processing biases in depression, especially increased attention towards negative stimuli. Consistently, similar hypoactivity in anterior cingulate was found in depressed patients using Stroop task, and again this

hypoactivity was not seen in the ventral part (George et al 1997). Indeed, rostral-ventral part of the anterior cingulate cortex, sometimes known as the 'affective division', is believed to play an important role in generation and regulation of emotional behaviour, and dysfunctions of this network have been robustly found in depression (Phillips et al 2003a, b, Bush et al 2000, Drevets 2001). It has also been postulated to be the brain's error detection and correction device (Bush et al 2000), thus dysfunctions in anterior cingulate reported in depressed patients may be related to their pathological guilt and self criticism.

Furthermore, neural processing of self-referent information has been explored in depression. In particular, increased and sustained amygdala activity was demonstrated in unmediated patients during self referent ratings to negative words (Siegle et al 2002, 2007). Amygdala activation has also been implicated in memory for emotionally charged life events (Halgren 1981, Brothers 1995). This excessive amygdalar stimulation of cortisol structures involved in declarative memory may account for the ruminative tendency of depressed patients (Drevets 2001).

Taken together, these studies have highlighted multiple neural abnormalities in depressed patients, which may underlie the aetiology and maintenance of the disorder. However, it is unclear from these data whether these neural pathologies arise during the depressive episode or whether they develop before illness onset.

1.5.3 State vs. Trait

Neuroimaging studies on patients during symptom remission, as well as healthy volunteers following an experimental mood-induction, to a certain extent distinguish between mechanisms that are dependent or independent on current mood states. In general, neural activities that could be normalised by treatment or induced

by experimental mood induction procedure appear to be mood-dependent and thus may be a result of depressive mood symptoms.

Indeed, some neural abnormalities reported in depressed patients could be induced in healthy volunteers following a sad mood induction, suggesting that these neural mechanisms are highly mediated by current mood. For example, Mayberg and colleagues (1999) illustrated increased regional cerebral blood flow within the insula and subgenual anterior cingulate, and decreased regional cerebral blood flow within the dorsomedial prefrontal cortex in volunteers experiencing transient sad mood.

Neuroimaging studies on recovered patients have also provided support for the state hypothesis. Phillips and colleagues (2003b) suggested that recovery following successful treatment is characterised by increased activity in brain areas involved in emotional regulation including multiple structures in prefrontal cortex (Baxter et al 1989, Brody et al 1999, Buchsbaum et al 1997, Kennedy et al 2001, Mayberg et al 1999, 2000), as well as decreased activity in areas involved in the generation of emotional states including ventral / subgenual anterior cingulate, thalamas, ventral striatum, insula, and hippocampus (Drevets et al 2002, Mayberg et al 1999, 2000, Nobler et al 1994, Smith et al 1999). Moreover, a study assessing facial processing before and after antidepressant treatment in a group of depressed patients found that the increased amygdala response to masked emotional faces (especially fear) resolves with treatment (Sheline et al 2001). Similar reductions in amygdala response were found for sad faces (Fu et al 2004). These findings of resolved neural abnormalities following treatment are, however, undermined by the recent findings that antidepressants can directly modulate neural activity in healthy volunteers without inducing mood changes (e.g. Harmer et al 2006). In other words, this line of evidence does not necessarily support the state hypothesis. Moreover, these data with recovered

patients do not necessarily suggest a full resolution of neural abnormalities upon recovery. Rather, they may persist as a latent vulnerability that could be activated in the face of stressful life events or negative mood.

In fact, not all neural abnormalities can be resolved by treatment or experimentally induced. There is evidence that some neural abnormalities persist after symptom withdrawal, and as such they may represent trait vulnerability to depression that precedes illness onset. For example, amygdala hyperarousal has been implicated in untreated remission and associated with depressive relapse (Drevets 2003). These 'residual abnormalities' could represent long term vulnerability markers for depression, but they could also simply be scars of previous depressive experiences.

To understand the aetiology of mood disorders, studies assessing neural functions in high risk samples before illness onset are particularly useful. Schwartz and colleagues (2003) observed that exaggerated amygdala responses to emotional faces occur in adults identified in childhood as having anxiety-related temperamental risk, in the absence of a current anxiety disorder diagnosis. Similar increased reactivity in amygdala and insula during presentation of emotional faces has been reported in healthy but anxiety-prone college students identified through high scores in trait anxiety and neuroticism scales (Stein et al 2007). Specifically, the magnitude of amygdala activity was significantly correlated with these temperamental and personality related risk factors. These results highly suggest that vulnerability to mood disorders could be characterised by abnormal neural mechanisms underlying emotional processing. However, experience of previous psychiatric conditions and / or sub-clinical symptoms in these high risk volunteers has not been controlled for. Further studies are required to clarify the exact relationship between vulnerability and emotional processing in depression and other affective disorders.

1.6 VULNERABILITY TO DEPRESSION

All in all, depression is characterised by pervasive abnormalities across a range of cognitive and neurobiological processes. The question here is whether these abnormal processes are the mechanisms underlying vulnerability to depression. A straightforward way to answer this question is to assess whether the vulnerable individuals (i.e. people who have high risk for developing depression) resemble depressed patients in these cognitive and biological functions. Thus, let us first consider the literature regarding high risk factors for depression.

1.6.1 High risk factors identified by twin studies

The aetiology of depression in community samples has been intensively investigated in twin studies that can broadly distinguish genetic from environmental factors. Kendler's group has published an unparalleled account of the risk factors together with a comprehensive model of how they may be related. In a very broad outline, the key vulnerability factors appear to be neuroticism, family history of depression and early abuse / neglect or trauma, whereas the precipitating factors are adverse life events and difficulties. Working with these variables, episodes of major depression are moderately well predicted at 12 month follow up similarly in women (Kendler et al 2002) and men (Kendler et al 2006a), although childhood parental loss and low self-esteem appeared to be more potent variables in the model of men than in women.

Amongst all, neuroticism is one of the best described predictors for depression. Neuroticism is a major personality dimension measuring an individual's tendency to experience negative emotions (Eysenck 1964, John 1990). This personality trait is stable over adulthood (McCrae and Costa 1990), and has a

heritability of approximately 50% (Eysenck 1990). High levels are associated with risk for depression when measured both cross-sectionally and prospectively. Specifically, in a large sample of female twins, Kendler and colleagues (1993) found a 1-SD difference in neuroticism to translate into a 100% difference in the rate of first onsets of depression over 12 months. Similarly, in a recent report based on a large Swedish twin sample (>20 000 individuals; Kendler et al 2006b), neuroticism strongly predicted the risks for lifetime and first onset depression assessed in 25-years follow up. Although extraversion was also (inversely) correlated with depression in this sample, this was shown to be mediated by the correlation between neuroticism and extraversion, thus the overall results identified neuroticism as the exclusive personality risk factor for depression. Furthermore, the twin modelling conducted in these studies suggested that the association between neuroticism and risk for depression is largely due to shared genetic determinants.

Indeed, family inheritance has been defined as one of the most reliable risk factors for depression. It has been estimated that by young adulthood up to 40% of children of parents with a clinical mood disorder will have suffered a personal episode of depression (Weissmann et al 1992, Beardslee et al 1998), which appears to be partially transmitted by genetic factors (Sullivan et al 2000). Based on a large twin sample containing more than 3000 same-sex and different-sex twins, Kendler and Prescott (1999) estimated the heritability of liability to depression as 39%, which is similar for men and women, while individual-specific environment accounts for the remaining 61% of variance.

Clearly, environmental factors also play a crucial role in the aetiology of depression. The social origins of depression have been extensively investigated (see Brown and Harris, 1978) and it has been suggested that depression is more common

amongst those from the lower social classes (e.g. Murphy 1982). The higher rates of depression within the lower social classes were in part due to their lack of social support and higher exposures to life stress (Brown and Harris, 1978, Murphy 1982, Dennis et al 2005). Indeed, there has been growing evidence that depression is often preceded by stressful life events (Hammen 1991, Kendler et al 1999, 2004, Simons et al 1993). However, many people faced with similar environmental stressors do not develop depression. This realization is consistent with the diathesis-stress model, which states that depression is caused by a genetic vulnerability combined with the experience of stressful life events. In support for this, Caspi and colleagues (2003) found that a polymorphism in the 5-HT transporter gene interacts with stressful life events to predict depression. Neuroticism, as a genetically-mediated risk factor, has also been found to interact with adverse life events, such that individuals with a high neurotic trait are more sensitive to the depressogenic effects of adversity (Kendler et al 2004).

Overall, research suggests that individuals who are genetically predisposed to depression are most likely to develop depression in face of major stressful life events. While the above findings are robust and convincing, the approach is essentially observational. Thus, further investigation is needed to unveil the mechanisms whereby depression emerges in high risk individuals.

1.6.2 Cognitive vulnerability models

According to the cognitive theories of depression, vulnerability to depression is related to cognitive styles. Both Hopelessness (Abramson et al 1989) and Beck's (1967) theories of depression contain a 'cognitive vulnerability hypothesis' in which individuals who have certain maladaptive thinking patterns are at increased risk for

depression in the face of adverse life events. In support of this, Alloy and colleagues (2006) recruited a sample of high risk vs. low risk college students by virtue of cognitive styles. They found that depression was well predicted by these cognitive vulnerability factors in a 2.5 years follow-up. In another study, rumination was found to be a predictive of suicidal ideation in a community sample at 1-year follow-up (Miranda and Nolen-Hoeksema 2007).

While the above studies directly tested the cognitive vulnerability hypothesis, earlier studies that illustrated cognitive biases in high risk populations recruited through personality risk factors have also shed light on this hypothesis. For example, individuals with higher scores on neuroticism tend to recall more self-depreciatory adjectives (Young and Martin 1981) and sentences with negative tones (Lishman 1972) than those with lower scores. Similarly, the speed for recalling unpleasant personal experience was found to be correlated with neuroticism scores (Lloyd and Lishman 1975). However, as neuroticism is often linked to dysphoric mood, it is unclear whether the cognitive bias observed is a correlate of the personality vulnerability or dysphoric mood conditions of these individuals. Studies examining this state vs. trait question have yielded controversial results. While some reported cognitive biases in highly neurotic subjects independent of mood states (e.g. Martin et al 1983), a few studies suggested that cognitive biases are an interactive function of neuroticism and sad mood (Bradley et al 1993, Bradley and Mogg 1994).

More recently, functional imaging studies have yielded evidence for neural abnormalities related to neuroticism. For example, there was evidence that neuroticism is linked with reduced grey matter concentration in the amygdala (Omura et al 2005) and increased brain activation in the temporal and frontal gyri in response to negative or frightening pictures (Canli et al 2001, 2004). Together with the

cognitive findings noted above, these results suggested that vulnerability to depression could be mediated by cognitive and neural biases in emotional processing.

However, this line of evidence has to be treated with caution. Most of these studies on neuroticism were based on non-selective community samples. Thus, the association between high neuroticism and emotional processing biases was established by correlations with neuroticism scores or comparison between high vs. low scorers (on neuroticism scale) using median split. By contrast, a more ideal design to identify cognitive and neural vulnerability markers for depression would be to compare individuals specifically selected to represent high vs. low vulnerability, such as individuals who score at the extreme range of the neuroticism scale. Furthermore, many of the previous studies did not systematically control for previous experience of depression. Future studies improving upon these aspects are required to provide a more accurate account of the mechanisms underlying vulnerability to depression.

1.6.3 Thesis Investigation

Therefore, the present study set out to determine the cognitive, biological, and neural mechanisms underlying vulnerability to depression. We recruited a sample of high risk vs. low risk volunteers, identified through high vs. low scores on the Eysenck Neuroticism Scale (Eysenck et al 1985). All participants were screened by Structural Clinical Interview for DSM-IV (SCID) to be free of any past or current axis I disorders. They were all first year undergraduate students at the time of recruitment.

Five cross-sectional experiments were designed to compare different aspects of emotional processing of these high risk and low risk individuals. First, a battery of neuropsychological tests was used to assess negative biases in information processing,

including self-referent categorisation and memory, facial expression recognition, dot-probe task, and emotion-potentiated startle paradigm. Second, working memory, executive functions, and specificity of autobiographical memory were respectively assessed by Auditory Verbal Learning Test, Tower of London, and Autobiographical Memory Test. Third, biological stress responses were measured by morning salivary cortisol. Finally, two brain imaging experiments using fMRI were conducted to examine neural activities during self-referent processing and facial expression recognition. In addition to these cross-sectional measures, two longitudinal studies were conducted, which took place in 6 month and 18 months following the first assessment. These follow up studies were included to provide a prospective measure of whether emotional processing can predict future development of depressive symptoms.

This project was approved by Oxfordshire Research Ethics Committee (OXREC Number: 05/Q1606/1). Details of the methodology and results of each study will be reported in the subsequent chapters. The final chapter will provide a general discussion of the findings across all five experiments, as well as their limitation and implications for further research.

CHAPTER TWO

Negative Biases in Information Processing and Vulnerability to Depression

2.1 INTRODUCTION

As reviewed in Chapter One, cognitive theories of depression emphasise the role of negative biases in information processing in the aetiology and maintenance of the disorder (Beck et al. 1979). Consistently, negative biases have been seen across the domains of attention, interpretation and memory for emotional information in depression and dysphoria. For example, in facial expression recognition tasks, depressed patients show reduced recognition of positive expressions and/or increased perception of negative expressions (Bouhuys et al 1999, Gur et al 1992, Surguladze et al 2004). Negative biases in emotional memory have also been revealed in depression (e.g. Bradley et al 1995). Although attentional biases are less consistently found, dot-probe tasks have shown increased attention to negative stimuli in dysphoric patients and healthy volunteers undergoing a negative mood induction when longer stimulus durations are used (Bradley et al 1997).

Thus, these data suggest that negative biases play a causal role in depression and as such may be seen outside of major depressive episodes. Indeed, some of these biases have been reported to persist into periods of remission (Bouhuys et al 1999, Bhagwagar et al 2004, Hayward et al 2005) and predict subsequent relapse (Bouhuys et al 1999), suggesting that they could be trait vulnerability markers for depression. However, findings from recovered patients are confounded by the 'scar effect', so-

called because the residual biases may be a consequence of depression, rather than implying occurrence before the onset of the first episode.

The present study was designed to examine whether negative biases in emotional processing are trait vulnerability markers for depression. We recruited young euthymic college students with high vs. low scores for neuroticism (N), and *without a history of depression*. A battery of tasks was chosen to assess different components of emotional processing, including categorisation and memory of self-referent words, facial expression recognition, dot probe tasks, and emotional potentiated startle paradigm. Overall, we hypothesised that high N volunteers would display affective processing biases favouring negative versus positive information, compared to low N volunteers.

2.2 METHODS

2.2.1 Subjects

The study was approved by the local ethics committee. Seventy-two healthy college students with high or low N scores (see below) gave written informed consent to the study, and received payment for their participation. The Structured Clinical Interview for DSM-IV was used to screen for axis I disorders and seven volunteers were excluded from the study because of current or previous depression or anxiety disorders.

N scores for screening were derived from the 12-item neuroticism scale of the shortened Eysenck Personality Questionnaire (Eysenck et al. 1985). Thirty-three (22 women) were in the high Neurotic group (H: mean score= 9.58, range =8-12), and 32 (18 women) in low Neurotic group (L: mean score= 1.25, range=0-3). The two groups were matched for age (18.82 ± 0.98 vs. 19.06 ± 0.88), gender, verbal IQ (119.92 ± 2.57 vs. 118.12 ± 5.09) and spatial IQ (26.19 ± 11.37 vs. 22.43 ± 9.37) (assessed with NART [Nelson 1982] and WAIS-R [Wechsler 1981]).

2.2.2 Characterization of State and Trait Variables

To assess mood, personality, attitudes and thinking style, family psychiatric history and personal life experience, participants were interviewed with the Hamilton Depression Rating Scale (HAMD: Hamilton 1967) and filled in the following questionnaires: State-Trait Anxiety Inventory (STAI: Spielberger et al. 1970), Beck Depression Inventory (BDI: Beck et al. 1961), Befindlichkeits Scale of Mood and Energy (Bf-S: von Zerssen et al. 1974), Fear of Negative Evaluation Scale (FNE: Watson and Friend 1969), Buss-Durkee Hostility Inventory (Buss and Durkee 1957),

Social Adaptation Self-Evaluation Scale (SASS: Bosc et al. 1997), Dysfunctional Attitude Scale (DAS: Weissmann 1979, factors taken from Cane et al.1986), ruminative items of the Response Styles Questionnaire (modified by Treynor et al. 2003), Eysenck Personality Questionnaire (EPQ: Eysenck and Eysenck 1975), Parental Bonding Inventory (PBI: Parker et al. 1979), stressful life events (adopted from Goodyer et al. 1997), and family history of psychiatric disorders. Two participants did not complete all the questionnaires.

2.2.3 Emotional Categorisation

Self referent task - personality characteristics categorisation

This task was used to assess processing of self-referent emotional information. Sixty personality characteristics chosen to be extremely desirable (e.g. honest) or undesirable (e.g. rude) (Anderson 1968, matched on word length, frequency and meaningfulness) were presented on a computer screen for 500 ms. Participants were asked to categorise these traits as likable or dislikeable by pressing the labelled key on the keyboard as quickly as possible. To encourage self-referent judgment, participants were asked to imagine whether they would be pleased or displeased if they overheard someone describing them in this way.

Non self-referent (control) task - animal attributes categorisation

A similar task was carried out as a control, which used 60 attribute words (30 per valence). This time participants were asked to classify each attribute as an "advantage" (e.g. strong) or "disadvantage" (e.g. weak) for a predatory animal, thus the judgment is not self-referent. In both tasks classifications and reaction times for the correct identifications were recorded.

2.2.4 Emotional Memory

A surprise memory task comprising a free recall and recognition (60 target words plus 60 distracters) was conducted 15 minutes after completing each of the categorisation tasks. The number of correctly and incorrectly recalled words was counted. Recognition data were analysed using signal detection theory (Green and Swets 1966, Grier 1971) to derive a measure of accuracy corrected for subjects' response tendency. The proportion of correctly recognised words (y) and the proportion of falsely recognised words (x) were entered into the following equations to give the sensitivity measure d'= 0.5 + ((y-x) (1+y-x)/4y (1-x)), and response bias β = y (1-y)-x (1-x)/y (1-y) +x (1-x). This allows an assessment of accuracy (hits) unconfounded by the response criterion used by the volunteer.

2.2.5 Facial Expression Recognition

This task was chosen to assess processing of social emotional information using facial expression stimuli. Pictures of faces representing six basic emotions (happiness, surprise, sadness, fear, anger, and disgust) were taken from the Pictures of Affect Series (Ekman and Friesen 1976). These were morphed between each full emotion (100%) and neutral (0%) in 10% steps (Young et al. 1997): four examples were given per intensity per emotion. Each face was also presented in a neutral expression, giving a total of 250 stimuli. Each stimulus flashed up on a computer screen for 500 ms followed by a blank screen. Participants were asked to recognise the emotion by pressing the appropriate key as quickly and accurately as possible. Accuracy and reaction times for correct choices and misclassifications were recorded. Accuracy was defined by the threshold, i.e. the intensity level at which the participant

gives 3 or more (i.e. ≥75%) correct responses across three consecutive intensity levels.

2.2.6 Dot Probe task

This task was chosen to assess preconscious and conscious attention to emotional information using masked and unmasked design respectively. The emotional stimuli included 30 social threatening negative words and 30 positive words, each of which was paired with a matched neutral word. Another 30 neutral-neutral word pairs were given as fillers. Preceded by a fixation cross (500ms), a word pair was presented on the screen having one word above another. In the unmasked condition the word pair was presented for 500ms, whereas in the masked condition it appeared for 14 ms followed by the display (186 ms) of a mask. After that, a probe (one or two stars) appeared in the position of either preceding word, and participants were asked to indicate the number of stars. These 180 trials were presented in three blocks in random orders. Incorrect responses were excluded from the analysis of reaction time. Reaction times that exceed 1500 ms and / or 2 standard deviations away from the individual mean were considered as outliers and excluded from subsequent analyses. Attentional vigilance scores were calculated for each participant by subtracting the mean reaction time of "congruent trials" (where the probe and emotional word appeared in the same position) from that of the "incongruent trials" (where they appeared in opposite position).

2.2.7 Emotion-Potentiated Startle (EPS)

<u>Stimuli</u>

Sixty-three pictures of three categories (pleasant, unpleasant, neutral) were taken from the International Affective Picture System (gender-specified, Larson et al. 2000). Each picture was presented for 13 s (mean inter-trial interval = 13 s) on a computer screen. The pictures were presented in three blocks in a fixed order such that no two of the same category would appear successively.

Procedure and recording

The eye-blink component of the startle response was recorded from the orbicularis oculi using electromyography (EMG startle response system, San Diego Instruments, Inc., San Diego). Acoustic probes were 50-ms, 95-dB bursts of white noise with a nearly instantaneous rise time (generated through the noise generator and amplifier of the EMG startle response system) and were delivered binaurally through headphones at 1.5, 4.5, or 7.5 s following picture onset. To minimise expectation, startle probes were skipped from two trials per valence per block, and three probes were given within the inter-trial interval. A practice session presenting nine neutral pictures and startle probes was used in the beginning to habituate participants to the startle probes.

EMG signals were filtered (low cutoff: 0.5 Hz; high cutoff: 100 Hz) and rectified. Eye-blink reflex magnitudes in μV were calculated by subtracting the amount of integrated EMG at reflex onset from the first peak amplitude of integrated EMG between 20 and 120 ms following probe onset. Trials with no traceable eye-blink reflex were assigned a magnitude of zero and included in the analysis. Eye-blink reflexes with an excessively noisy baseline (within 20 ms after the probe) were rejected. Four participants (two from each group) were excluded from the analysis

because they displayed fewer than 25% blink responses. Magnitude and latency of the eye-blink reflex were recorded.

Subjective rating

After the recording, participants were asked to review the pictures and rate the valence and arousal levels of each picture on a 1-10 scale (from negative to positive, low arousal to high arousal).

2.2.8 Statistical Analysis

Assumptions of normal distribution and homogeneity of variance were checked using Kolmogorov-Smirnov Test and Levene's Test respectively. Independent-samples T tests were used to reveal group differences in psychological questionnaires. Other data were analysed by analyses of variance (ANOVAs): For facial expression recognition and emotional potentiated startle, two-way ANOVAs were used with between-subjects variable as group (H vs. L) and within-subjects variable as emotion (7 for facial recognition, 3 for emotion potentiated startle task). For emotional categorisation and memory, three-way ANOVAs were used with the same between-Ss variable as group (H vs. L) and two within-Ss variables as emotion (likeable vs. dislikeable or advantage vs. disadvantage) and task (self-referent vs. non self-referent). For dot probe task, three-way ANOVA was used with between-Ss variable as group (H vs. L) and two within-Ss variables as emotion (positive vs. negative) and trials (masked vs. unmasked). Significant interactions were clarified by post hoc ANOVAs and t tests. BDI was included as a covariate to assess whether differences might be due to low grade mood symptoms. Due to the exploratory nature

of the study, the above analyses were primarily hypothesis-driven and hence Bonferroni tests were not performed to correct for multiple comparisons.

2.3 RESULTS

2.3.1 Psychological Characteristics

Using the full EPQ scale, the two groups were confirmed to have significant difference in neuroticism scores (17.91 ± 2.84 vs. 5.72 ± 3.27, $p<0.01$). Although none of the volunteers had ever met criteria for DSM-IV depression, and mean scores on clinical symptom scales did not exceed usual levels for remission, H participants showed a significantly higher level of depressed mood, anxiety and hostility than L. They also reported more rumination, dysfunctional attitudes, parental over-protectiveness, and lower social adaptation. In contrast, the two groups did not differ in family history of psychiatric disorder, parental care, and stressful life experience (all $p>0.10$) (Table 2.1).

2.3.2 Self-referent Categorisation

There was a significant group x task x emotion interaction ($F(1,63)=4.73$, $p=0.03$) for reaction time in the self-referent vs. animal categorisation tasks. Sensitivity analyses showed a significant group x emotion interaction in the emotional categorisation (Figure 2.1/ left: $F(1,63)=3.88$, $p=0.05$) but not in the control task (Figure 2.1/ right: $F(1,63)=0.51$, $p=0.48$). H volunteers were quicker at classifying negative versus positive personality characteristics than L. Furthermore, within the H group, the reaction time for positive items was significantly correlated with N scores ($r(33)=0.37$, $p=0.04$), so reaction time for positive items increased with neuroticism.

For accuracy data there was neither a group difference ($F(1,63)=0.45$, $p=0.51$) nor a group x emotion x task interaction ($F(1,63)=0.51$, $p=0.48$) but both groups

achieved more than 90% accuracy in both categorisation tasks, implying a potential ceiling effect.

2.3.3 Self-referent Memory

Free Recall: The two groups performed similarly in terms of correct recall (Figure 2.2A: group: $F(1,63)=0.47$, $p=0.50$; task x emotion x group: $F(1,63)=0.87$, $p=0.35$). However, H volunteers produced fewer positive memory intrusions than L (Figure 2.2B: group x emotion: $F(1,63)=7.54$, $p=0.01$) for self-referent information, but not in the control task (group x emotion: $F(1,63)=0.01$, $p=0.92$).

Recognition: The two groups had similar accuracy (d') (group: $F(1,63)=0.07$, $p=0.79$; task x emotion x group: $F(1,63)=3.09$, $p=0.09$) and response bias (β) (group $F(1,63)=0.03$, $p=0.87$; task x emotion x group $F(1,63)=0.50$, $p=0.48$).

2.3.4 Facial Expression Recognition

There were no significant effects on accuracy, reaction time or misclassifications in this task (all p-values >0.10). However, differences in recognition of each emotion were further explored using independent t tests, given a strong *a priori* hypothesis for individual emotions. This revealed a significant group difference for accuracy of happy faces (Figure 2.3: $t(63)=2.05$, $p=0.04$) but not in any other emotions (all p values >0.40). Specifically, H had a higher threshold in identifying happy faces than did L; i.e. they needed higher intensity levels to be able to correctly identify happy facial expressions.

2.3.5 Dot Probe Task

Both groups achieved overall high accuracy (high N: 97.9% ± 2.2 % vs. low N: 97.6% ± 3.8 %) suggesting a ceiling effect with accuracy data. As mentioned above, incorrect responses were excluded from subsequent analyses. There were no significant effects on the vigilance scores of reaction time (group: $F(1,63)=0.12$, $p=0.73$; group x emotion x mask: $F(1,63)=1.18$, $p=0.28$). This was also true when only the unmasked trials were considered (group: $F(1,63)=0.14$, $p=0.71$, emotion x group: $F(1,63)=0.46$, $p=0.50$). See Table 2.2.

2.3.6 Emotion-Potentiated Startle

Eye-blink magnitude: The standardized (z-transformed) data revealed the expected potentiation effect in both groups (Figure 2.4A: overall effect of emotion: $F(2,118)=10.17$, $p=0.001$) with volunteers showing a greater response to unpleasant than neutral or pleasant pictures. However, this was not affected by neuroticism (group: $F(1,59)=0.86$, $p=0.40$; emotion x group: $F(2,118)=0.85$, $p=0.43$). Examination of raw startle amplitudes showed a similar pattern (emotion: $F(2,118)=7.19$, $p=0.001$; group: $F(1,59)=1.33$, $p=0.25$; emotion x group: $F(2,118)=0.36$, $p=0.70$). The average amplitudes were similar between H and L (mean=1416.20 vs. 1674.83; $t(59)=-1.15$, $p=0.25$).

Eye-blink latency: There was a significant group x emotion interaction (Figure 2.4B: $F(2,116)=3.08$, $p=0.05$). Despite this significant interaction, post-hoc comparisons failed to reveal group difference within each emotional category (all $p>0.10$). As shown by paired-samples t tests, the interaction was mostly driven by H responding more slowly to pleasant than unpleasant pictures ($t(29)=2.04$, $p=0.05$).

Subjective ratings: There was no group difference in terms of rating for

valence (group: F(1,58)=0.12, p=0.73; emotion x group: F(2,116)=1.10; p=0.34) or arousal (group: F(1,58)=0.43, p=0.52; emotion x group: F(2,116)=1.14, p=0.32).

2.3.7 Covariate Analyses with BDI Scores

To assess whether group differences on the various tasks might be due to low grade mood symptoms, analyses were performed with BDI as a covariate. Results showed that the effects remained significant for emotional memory false recalls (emotion x group: F(1,62)=5.215, p=0.026), and emotion-potentiated startle latency (emotion x group: F(2,114)=4.097, p=0.019), suggesting that these effects are unrelated to low mood experienced by H volunteers. Results on emotional categorisation were mixed: after controlling for BDI score, the correlation between neuroticism and reaction time for positive words in H group remained significant (r(30)=0.395, p=0.013), but the group-by-emotion interaction became insignificant (F(1,62)=0.755, p=0.388).

Apart from depression scores, our results also suggested a significant group difference in other mood measures such as state anxiety (Table 2.1), which may potentially confound the current comparisons in cognitive biases. This could be statistically tested by including state anxiety scores and / or other mood measures as covariate(s), which, however, were not performed here due to the relatively small sample.

Table 2.1: Psychological Characteristics of High N and Low N Volunteers. Values represent group means ± standard deviations. Asterisks represent significance of group comparisons * $p \leq 0.05$, ** $p \leq 0.01$.

Variable	High N	Low N	t	P ≤
HAMD	3.55 (3.33)	1.34 (2.36)	3.08	0.00**
BDI	8.33 (5.97)	2.59 (2.67)	5.03	0.00**
STAI				
State	37.82 (9.90)	27.56 (6.33)	4.99	0.00**
Trait	47.18 (11.84)	28.75 (5.19)	8.17	0.00**
Bf-S	45.97 (28.43)	14.88 (13.96)	5.62	0.00**
FNE	21.88 (6.13)	8.31 (4.73)	9.91	0.00**
SASS	41.66 (5.47)	47.34 (4.09)	-4.71	0.00**
Hostility	32.00 (9.03)	24.13 (8.94)	3.51	0.00**
Rumination	51.75 (8.95)	39.31 (8.51)	5.70	0.00**
DAS				
Overall	142.81 (20.93)	105.59 (21.12)	7.08	0.00**
Perfectionism	46.91 (10.61)	33.22 (11.75)	4.89	0.00**
Approval by Others	44.81 (8.54)	32.47 (8.20)	5.90	0.00**
EPQ				
Neuroticism	17.91 (2.84)	5.72 (3.27)	16.04	0.00**
Psychoticism	2.88 (2.12)	4.25 (4.17)	-1.67	0.10
Lie	7.39 (3.69)	7.75 (4.18)	-0.36	0.72
Extraversion	8.97 (5.60)	15.00 (4.26)	-4.88	0.00**
Stressful Life Events	1.44 (1.24)	1.16 (1.55)	0.80	0.43
Family History				
Anxiety disorders	0.25 (0.62)	0.19 (0.47)	0.45	0.65
Bipolar disorders	0.00 (0.00)	0.09 (0.39)	-1.36	0.18

Depressive disorders	0.06 (0.25)	0.13 (0.42)	-0.73	0.47
Psychotic Disorders	0.00 (0.00)	0.00 (0.00)	N/A	N/A
PBI- Father				
Caring	26.19 (6.48)	27.72 (6.24)	-0.95	0.35
Overprotection	11.87 (6.36)	6.13 (4.07)	4.29	0.00**
PBI- Mother				
Caring	31.68 (4.21)	31.06 (5.87)	0.48	0.64
Overprotection	12.90 (6.77)	9.53 (6.86)	1.96	0.05*

Table 2.2: Attentional Bias as Measured by Dot-Probe Task under Masked and Unmasked Conditions. Values represent group means ± standard deviations.

		High N	Low N
Masked condition			
Reaction Time Vigilance (ms)	Positive	-12.21 (31.65)	-1.01 (41.51)
	Negative	-4.19 (31.26)	-5.02 (38.73)
Unmasked condition			
Reaction Time Vigilance (ms)	Positive	8.97 (43.03)	1.50 (33.53)
	Negative	2.08 (34.89)	4.45 (48.32)

Figure 2.1: Categorisation of Self-Referent Personality Characteristics and Non Self-Referent Animal Attributes. Values represent mean difference scores of reaction time to identify positive minus negative words ± SEM. Asterisks represent statistical significance of group comparisons *p<0.05

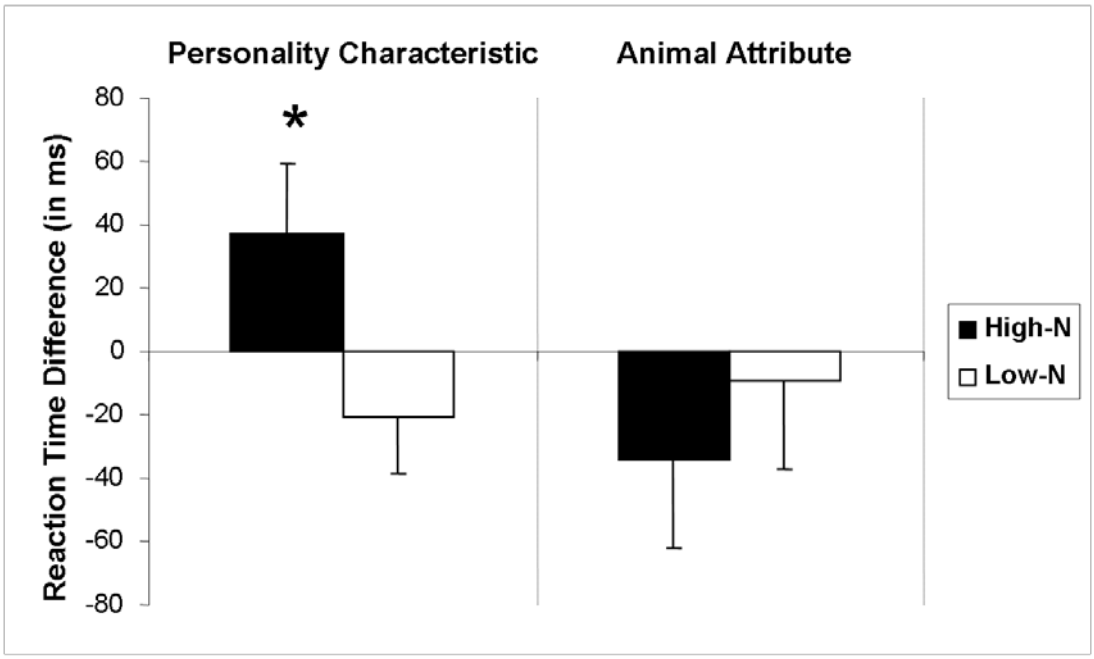


Figure 2.2: Memory of Self-referent Personality Characteristics and Non self-referent Animal Attributes. Values represent mean difference scores of number of words recalled for positive minus negative words ± SEM. Asterisks represent statistical signifcance of group comparisons * $p<0.05$.

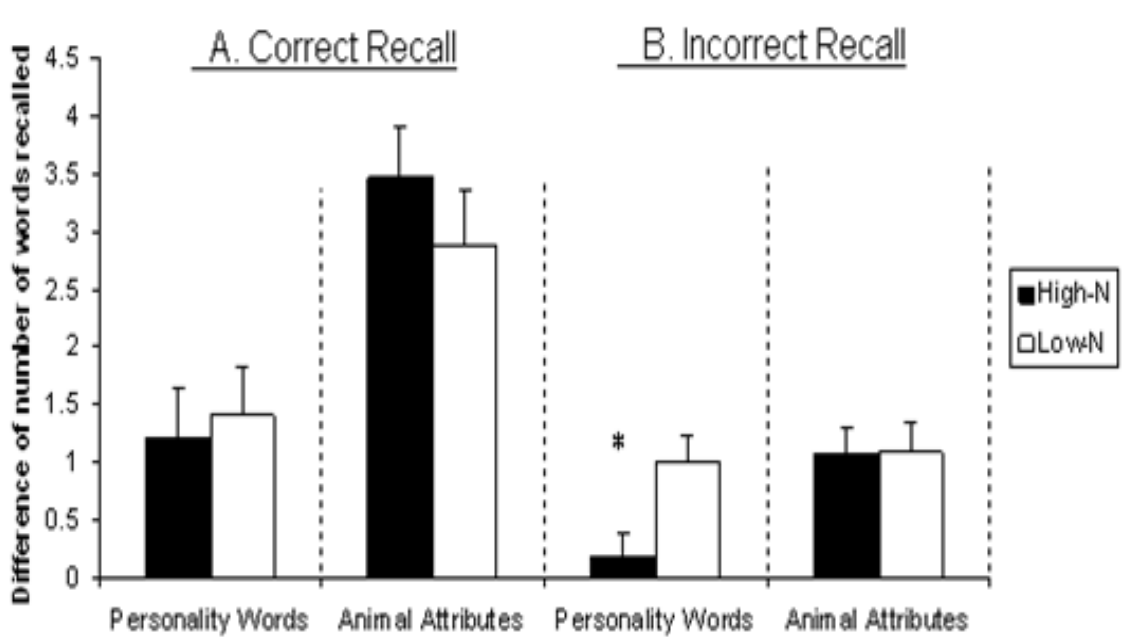


Figure 2.3: Threshold for Correct Identification of Facial Expressions by High N and Low N Volunteers. Values represent mean threshold levels (± SEM) required to correctly identify each emotion at a level of > 75%. Asterisks represent statistical significance of group difference *p<0.05.

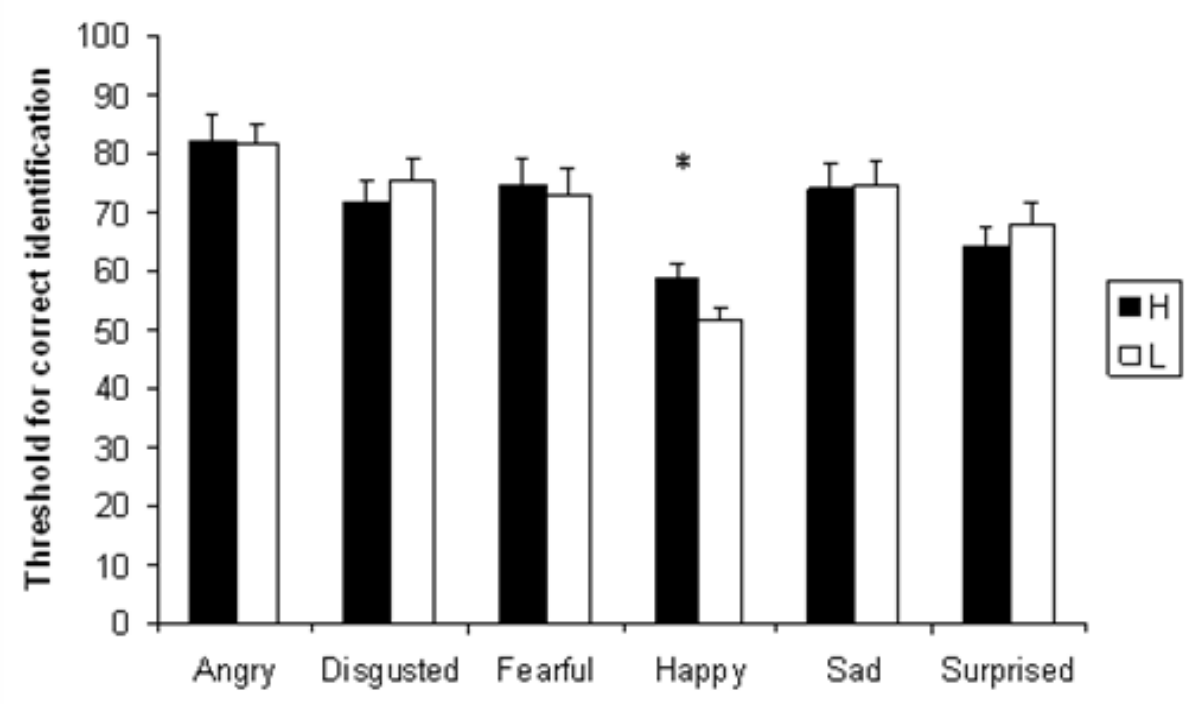
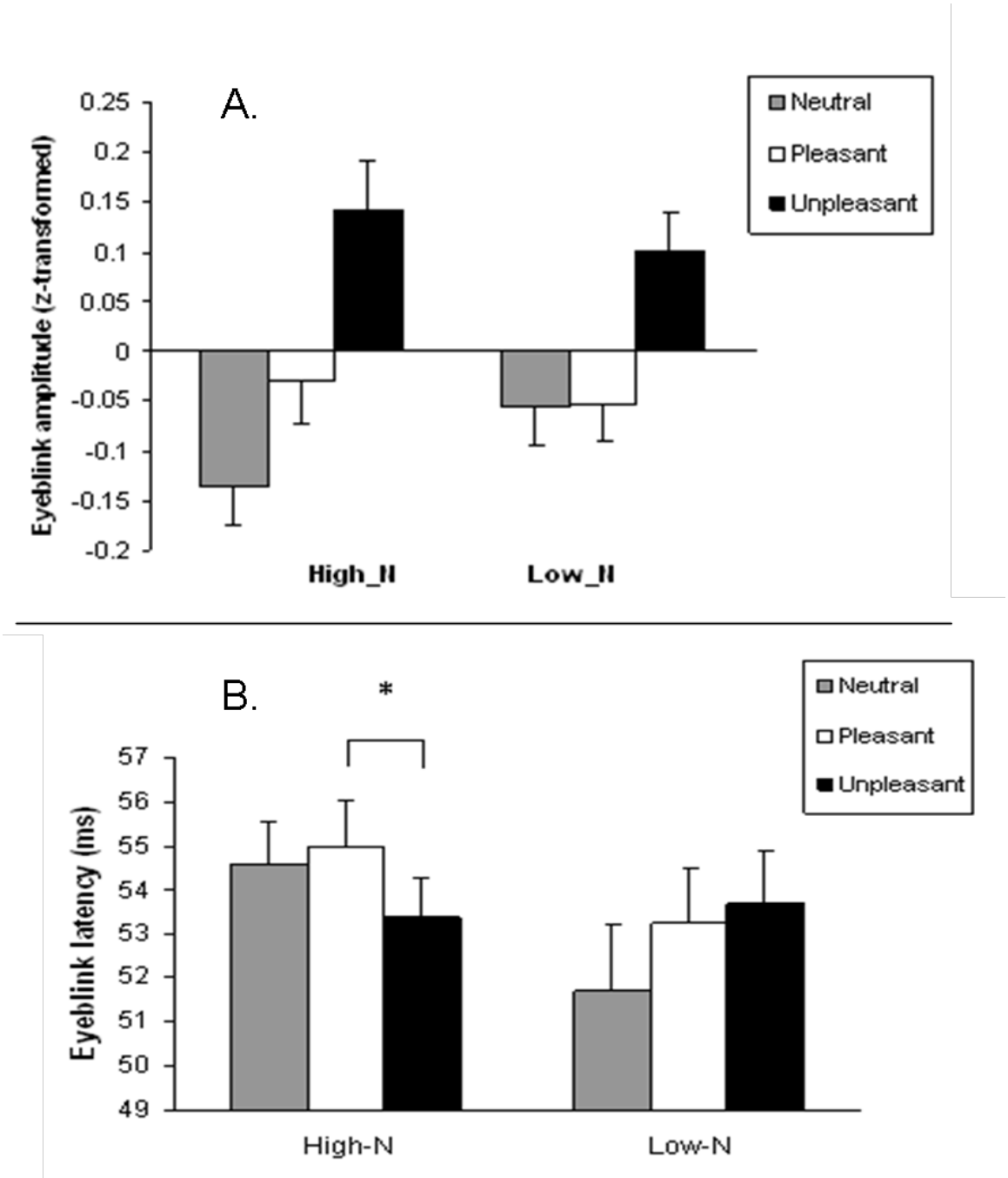


Figure 2.4: Emotion Potentiated Startle Responses to Pleasant, Unpleasant, and Neutral Pictures. (A) Average amplitude of eye-blink (Z scores) while viewing the pictures. (B) Average latency of startle response while viewing the pictures. Values represent group means ± SEM. Asterisks represent statistical signifcance of comparisons between startle responses during pleasant and unpleasant pictures within each group * $p<0.05$.



2.4 DISCUSSION

In this study, results showed that biases in information processing are present in students high in neuroticism, who are at risk of depression but have not been depressed. Decreased positive or increased negative processing was seen across a number of tasks including emotional categorisation and memory, facial expression recognition and emotion-potentiated startle. Covariate analyses with BDI scores suggested that these biases are mostly independent from low grade mood symptoms experienced by the H participants. By contrast, there was no evidence for effects of neuroticism on attentional bias as measured with dot-probe task.

As noted earlier, Beck's cognitive theory emphasises the role of depressogenic schemas in the aetiology and maintenance of depression (Beck et al 1979). Specifically, cognitive models suggest that these depressogenic schemas represent a diathesis that can increase risk for depression. Therefore, we included the Dysfunctional Attitude Scale to provide a questionnaire measure of dysfunctional schemas (Weissman and Beck 1978). Indeed, our high N subjects endorsed significantly higher scores on this scale than low N subjects, suggesting that identifiable differences at the level of cognitive schemas exist between high risk and low risk individuals. This demonstration of dysfunction schemas in high risk individuals was consistent with the findings of negative biases also found in this sample, providing strong support for the cognitive vulnerability model.

In the emotional categorization and memory tasks, H volunteers were faster to classify dislikeable self-referent personality characteristics and produced fewer positive memory intrusions. This bias towards the negative and away from positive information was not seen in the control task, suggesting that this negative bias is mostly related to self-referent processing. Furthermore, the memory bias away from

the positive was consistently revealed in the perception of social information, as measured by the facial expression recognition task. H volunteers had a higher threshold for identifying happy faces than the control volunteers. A reduction in positive facial perception echoes previous experimental findings in depressed patients (Murphy et al. 1999, Suslow et al. 2001) and healthy volunteers undergoing a negative mood induction (Bouhuys et al. 1995). In contrast, recovered patients tend also to show an *increased* perception of *negative* expression such as fear, disgust and sadness (Bouhuys et al. 1999, Bhagwagar et al. 2004, Hayward et al. 2005). This suggests the hypothesis that risk for depression is largely manifest as reduced positive processing of emotional information, which is accompanied by increased negative processing only after the actual experience of depression.

Emotion-potentiated startle (EPS) was used to give a physiological measure of reactivity to emotional information. Our sample, regardless of group membership, exhibited the expected EPS pattern with enhanced eye-blink during the presentation of aversive pictures relative to neutral or pleasant pictures, which is widely demonstrated in laboratory work (e.g. Bradley et al. 1990, Cook et al. 1991, Grillon and Bass 2003, Lang et al 2000). The two groups gave similar pleasantness ratings for the pictures. Unexpectedly, while amplitude was unaffected, there was an effect of neuroticism on blink latency. H volunteers showed a significant delay in their reflexive response to pleasant pictures. A reduced physiological reactivity to positive stimuli in the absence of differential subjective rating implies that neuroticism involves biases in mechanisms that are highly automatic and thus not influenced by self-report. The current result is compatible with the theory that low activity in appetitive emotional systems are the core deficits in depression (Fowles 1988, Depue and Iacono 1989, Clark and Watson 1991), although previous findings on affect-modulated startle in

depression are variable and appear to be influenced by factors such as depression severity, subtype of depression and anxiety (Grillon and Baas 2003). In addition, as latency is less frequently reported as a variable of EPS than magnitude data, further studies are required to confirm the validity of the current effects on the EPS task.

The effect sizes for the significant effects discussed above ranged between medium (self-referent categorisation 0.44; facial expression recognition task 0.46; emotion-potentiated startle 0.47; corresponding to powers of 0.42, 0.46 and 0.48 respectively) and large (self-referent memory 0.73; power 0.83). Future studies that aim to robustly replicate these effects would require a larger sample size: a sample of 81 subjects per group is required to achieve at least power 0.80 for *all* four of the above tasks.

The negative findings in this study may indicate domains in which deficits are simply not associated with depression vulnerability or, instead, may arise solely from the experience of depression. Thus, the dot probe task provides evidence that attentional biases play no role in neuroticism and, as noted in Chapter One, measures of attentional biases have yielded inconsistent results in depression too. There is also a possibility that vulnerability to depression is associated with attentional biases in the elaboration stage of information processing which could be seen in longer presentation of stimuli (Williams et al 1988). Indeed, previous studies indicating attentional biases in depression tended to be using long exposure durations of 1 second or more (e.g. Mogg et al 1995, Gotlib and McCann 1984, Gotlib and Cane 1987). When medium duration was used, such as 500 ms as in this study, the results have been variable (e.g. Mathews et al 1996) suggesting that this duration is unsuitable for interrogating attentional processes in depression. Further investigation varying the duration of stimuli presentation is needed to clarify the current findings.

Hence, in summary, the present results suggest that negative biases in emotional processing are present in individuals who are at high risk for developing depression but have not been depressed. These biases are widespread across a range of cognitive processing including perception and memory of self-referent information, processing of facial expression, and automatic startle responses. As such, these could represent long term vulnerability markers for depression. Results from the covariate analyses with BDI scores further confirm that the effects observed here is a function of high neuroticism per se, unconfounded by group differences in dysphoric mood. Our longitudinal studies (Chapter Seven) will investigate whether, and to what extent, such cognitive vulnerability predicts subsequent depression. If so, this could pave the way for further studies evaluating the efficacy of early interventions targeting the dysfunctional cognitive styles of the high-risk population.

CHAPTER THREE

Global Executive Functions and Vulnerability to Depression

3.1 INTRODUCTION

Results from the preceding chapter show that negative biases in emotional processing are found in volunteers at high risk for depression, suggesting that they may be trait vulnerability markers for this disorder. Depression is also characterised, however, by impairment in more general executive and memory function and the current chapter considers whether these deficits may also be apparent before the onset of the disorder.

As reviewed in Chapter One, a wide range of cognitive impairment has been readily demonstrated in depression. Depression is associated with poorer performance in verbal fluency, inhibition, working memory, set-maintenance and set-shifting (Stordal et al 2004). Of these impairments, deficits in learning, memory and executive function are most consistently found across studies (Elliott et al 1996). Furthermore, lack of specificity in autobiographical memory has also been implicated in depression. There is robust evidence of depressed patients being over-general in their autobiographical memory, i.e. an inability to recall specific past events, although previous findings using cue words with positive and negative valence did not show a consistent valence effect (Williams et al 2007). This impairment is believed to be related to other symptoms such as poorer interpersonal problem-solving (Goddard et al 1996, Pollock and Williams 2001), ruminative tendencies (Watkins and Teasdale

2001, Ramponi et al 2004), and elevated cognitive reactivity to mood changes (Williams et al 2005).

In general cognitive impairments tend to resolve following recovery (Peselow et al. 1991, Austin et al. 2001), although over-general autobiographical memory has been found in patients during periods of remission/ recovery (Williams and Dritschel, 1988; Mackinger et al 2000a and b; Peeters et al 2003). However, as emphasised in previous chapters, findings from recovered patients could be affected by the 'scar effect' and therefore they may not necessarily reflect vulnerability mechanisms before first illness onset.

The current study was designed to compare global cognitive functions of individuals at high risk vs. low risk for depression. As described in section 2.2, high risk and low risk samples were identified through neuroticism (N) scores. Three tasks: Auditory Verbal Learning Test (AVLT: Rey 1964), Tower of London (TOL), and Autobiographical Memory Test (AMT: Williams and Broadbent 1986) were chosen to assess learning and memory, problem solving, and autobiographical memory. Based on previous findings on depression, we hypothesised that high N subjects would have reduced specificity in their autobiographical memory. However, we predicted no group difference for overall cognitive performance assessed by AVLT and TOL based on the resolution of these impairments seen during remission.

3.2 METHODS

3.2.1 Subjects

The same sample of high N and low N volunteers as the previous study (Chapter Two) was recruited to participate in this study. Thus, there were 33 high N volunteers and 32 matched low N volunteers. The volunteers gave written informed consent, and received payment for their participation. All volunteers were screened to be free of previous or current Axis I disorders. Their demographic details as well as personality and mood variables were reported in the last Chapter (section 2.3).

3.2.2 Auditory Verbal Learning Test (AVLT)

The AVLT (Rey 1964) was used to assess learning and memory. In the immediate recall phase, participants were read aloud a 15-item word list and asked to recall immediately as many words as possible (in any word order). This procedure was repeated five times. A distracter list was then presented to create a short delay, after which free recall of the first list was measured. Fifteen minutes later, participants were tested again with a free recall, followed by a recognition test where they made a 'Yes / No' response to a list of 50 words (15 target items plus 35 distracters). For the immediate and delayed recall tests, number of correct recall (out of 15) was counted. For the recognition test, the number of correct ('hits') and incorrect ('false alarm') responses were counted.

3.2.3 Tower of London (TOL)

This is a test of planning which requires central executive function, based on the test by Shallice and McCarthy (Shallice 1982). This task was taken from the

Cambridge Neuropsychological Test Automated Battery (CANTAB; Robbins et al 1994), which has been widely used in previous studies with depressed patients (e.g. Stordal et al 2004, Elliott et al 1996). In this task, two sets of three coloured balls (red, blue, green) were presented on a touch-sensitive computer screen, with one at the top and the other at the bottom part of the screen. Each set of balls was arranged like snooker balls hanging in three pockets. Participants were asked to rearrange the balls in the bottom set to match the top set under certain rules. For example, a ball could not be moved to a higher position in a pocket unless there was another ball beneath it. The trials varied in terms of difficulty level, which was manipulated by the number of moves (two, three, four, five) required to complete the problem. The minimum number of moves required for each trial was indicated at the side of the screen. As the task was aimed to measure motor planning competence, participants were instructed to work out the whole solution in mind before making the first move. Number of moves required by the subject to rearrange the balls, and selection, and movement latencies for both the initial and subsequent moves were recorded. For each test problem, a 'yoked control' condition was employed to provide baseline measures of motor initiation and execution times. In this condition, the actual solutions the subject has generated for the two, three, four, and five move problems are played back on the computer screen one move at a time. The subject was instructed to simply follow these moves by touching them.

Task performance was assessed by four variables: (1) 'number of perfect solutions' refers to the number of problems solved with the minimum possible number of moves, (2) average number of moves used for each difficulty level, (3) 'initial thinking time' refers to the time between presentation of the problem and the first touch of the screen, and (4) 'subsequent thinking time' refers to the time between

the first move of the solution and completion of the problem, divided by the number of moves taken for that problem. Both thinking times were subtracted by the simple movement times derived from the yoked control conditions. Specifically, 'motor initiation' times were subtracted from the initial thinking times, and 'motor execution' times from the subsequent thinking times. Any negative values produced by this subtraction were corrected to zero, assuming minimal thinking time. Thus, the thinking time reflects an estimate of pure mental planning time unconfounded by individual differences in motor speed.

3.2.4 Autobiographical Memory Test (AMT)

This task (Williams and Broadbent 1986) was chosen to assess the specificity of autobiographical memory. In this task participants were presented with 18 cue words (9 positive and 9 negative), one at a time, and asked to recall a memory of a specific event that the cue word reminds them of. Instructions defined a specific event as any event that took place on a particular day at a particular place and no more recent than a week ago, and that participants should not recall the same event for more than one cue word. Each word was shown on a card and read aloud by the experimenter. If a participant did not respond after 30 seconds, this will be considered as 'omission' and the next word would be presented. A practice trial with a neutral word ("chicken") was used in the beginning to check that the participant understood instructions.

Responses were classified into four categories (Williams and Dritschel 1992): (1) 'specific memory' refers to responses that fulfill the definition of specific memory as specified above (e.g. to the word 'enjoy': 'I went to Jane's party last month'); (2) 'extended memory' refers to a single event that lasted more than a day (e.g. 'travelling

to Scotland last summer); (3) 'categorical memory' refers to a whole class of events (e.g. 'having parties with friends all the time'); and (4) 'semantic associates' refers to an object or concept associated with the cue word but not a personal event (e.g. 'movies'). Number of responses for each category was counted, separately to positive and negative cue words. The main outcome variables were the number of specific memory and the proportion of specific memory after discounting omissions.

3.2.5 Statistical Analyses

Assumptions of normal distribution and homogeneity of variance were checked using Kolmogorov-Smirnov Test and Levene's Test respectively.

For AVLT, data of the 5 immediate recall trials were entered into a two-way ANOVA with between-Ss variable as group (2: H, L) and within-Ss variable as trial (5: 1^{st}, 2^{nd}, 3^{rd}, 4^{th}, 5^{th}). Results of the short- and long- delayed recall trials were similarly analysed by a group x trial ANOVA. Group difference in the recognition test ('hits' and 'false alarm') was tested by independent samples t tests.

For TOL, the number of perfect solutions was analysed by independent samples t tests. Number of moves required and thinking times were each analysed by a two-way ANOVA with between-Ss variable as group and within-Ss variable as difficulty (4: two-move, three-move, four-move, five-move).

For AMT, the number and proportion of specific memories recorded were each analysed by a two-way ANOVA with the between-Ss variable as group and within-Ss variable as valence (2: positive, negative). Given the inconsistent valence effect indicated from previous studies, group comparison was also examined for the overall number and proportion of specific responses (i.e. regardless of valence) using t tests. To further investigate the effect of neuroticism on different degree of specificity,

an additional analysis was carried out, whereby the number of responses for each type of memory was entered into a three-way ANOVA with between-Ss variable as group and within-Ss variables as specificity level (4: specific, extended, categorical, semantic associates) and valence.

For all the above analyses, significant interactions were clarified by *post hoc* t tests. BDI was included as a covariate to assess whether differences might be due to low grade mood symptoms. Due to the exploratory nature of the study, the above analyses were primarily hypothesis-driven and hence Bonferroni tests were not performed to correct for multiple comparisons.

3.3 RESULTS

3.3.1 Auditory Verbal Learning Test

For the immediate recall trials there was a significant group x trial interaction (Figure 3.1: $F(4,253)=3.27$, $p=0.01$), with subsequent t tests suggesting that H outperformed L only in the first trial ($t(63)=2.21$, $p=0.03$). For the short- vs. long-delayed recalls there were no group difference ($F(1,63)=0.02$, $p=0.89$) or interaction ($F(1,63)=1.77$, $p=0.19$), nor was there any group difference on long-delayed recognition (hits: $t(63)=-1.14$, $p=0.26$; false alarms: $t(63)=1.26$, $p=0.21$). See Figure 3.2.

3.3.2 Tower of London

High N volunteers produced more 'perfect solutions' than did low N volunteers (mean 10.52, SD 1.37 vs. mean 9.78, SD 1.36; $t(63)=2.16$, $p=0.03$). However, among H volunteers, this measure was negatively correlated with N score ($r(33)=-0.35$, $p=0.05$), suggesting that the higher a participant scored in neuroticism the fewer problem s/he managed to solve in minimum moves.

In terms of number of moves required to solves the problems, there was a significant group effect (Figure 3.3: $F(1,63)=5.75$, $p=0.02$) and a group x difficulty interaction ($F(3,189)=3.32$, $p=0.02$). Subsequent t-tests found that H was better than L in the four-move problems ($t(63)=-2.29$, $p=0.03$). In contrast, there were no effects on initial thinking time (Figure 3.4: group: $F(1,63)=0.57$, $p=0.45$; interaction: $(3,189)=0.47$, $p=0.71$) or subsequent thinking time (Figure 3.5: group: $F(1,63)=0.01$, $p=0.93$; interaction: $F(3,189)=0.64$, $p=0.59$).

3.3.3 Autobiographical Memory Test

In the primary analyses on specific memories, there was no significant group difference or group x valence interaction in either the response count (group: $F(1,63)=2.20$, $p=0.14$; interaction: $F(1,63)=0.65$, $p=0.42$) or proportion (group: $F(1,63)=1.97$, $p=0.17$; interaction: $F(1,63)=0.31$, $p=0.58$). Similarly, there was no group difference for these variables when responses for positive and negative cues were combined (number of specific memory: $t(63)=-1.48$, $p=0.14$; proportion: $t(63)=-1.40$, $p=0.17$).

In the analysis across all responses, there was a marginally significant specificity x group interaction ($F(3,189)=2.52$, $p=0.059$). Separate ANOVAs for each specificity level revealed a significant group difference for extended memory ($F(1,63)=5.33$, $p=0.02$), whereby high N subjects produced more extended memory regardless of valence. See Figure 3.6 and Table 3.1.

3.3.4 Covariate Analyses

When including BDI as a covariate, the group effect for the number of extended memories in AMT disappeared ($F(1,62)=1.63$,$p=0.21$). In contrast, the effects remained significant for AVLT immediate recalls (group x trial: $F(4,248)=2.651$, $p=0.034$) and TOL number of moves (group difference: $F(1,62)=4.576$, $p=0.036$), suggesting that these effects are unrelated to low mood experienced by H volunteers.

However, as reported in previous chapter, H volunteers had significantly higher scores on perfectionism (measured through the Dysfunctional Attitude Scale: mean 46.91, SD 10.61 vs. mean 33.22, SD 11.75; $t(63) = 4.89$, $p<0.001$; see Table 2.1). We therefore hypothesised that the overall cognitive improvement in H

volunteers seen in AVLT and TOL is associated with an increased motivation. Hence, we conducted additional analyses using this perfectionism score as a covariate. As predicted, the differences were lost (AVLT Immediate Recall group x trial: $F(4,244)=1.33$, $p=0.26$; TOL Number of Moves group effect: $F(1,61)=3.08$, $p=0.08$; group x trial $F(3,183)=2.21$, $p=0.09$). This suggested that the better performance observed here in H volunteers was due to their increased higher motivation for achievements.

Table 3.1: Autobiographical Memory Test. Number of responses across different levels of specificity to positive and negative cues. Values represent group means ± standard deviations.

	HIGH N	LOW N
Specific Memory		
Positive Cues	5.85 (1.89)	6.69 (1.82)
Negative Cues	5.61 (1.87)	6.09 (2.39)
Extended Memory		
Positive Cues	1.21 (1.39)	0.66 (0.75)
Negative Cues	1.30 (1.33)	0.75 (0.98)
Categorical Memory		
Positive Cues	0.39 (1.00)	0.28 (0.63)
Negative Cues	0.39 (0.79)	0.53 (0.80)
Semantic Associates		
Positive Cues	0.30 (0.59)	0.28 (1.02)
Negative Cues	0.30 (0.77)	0.16 (0.51)

Figure 3.1: Auditory Verbal Learning Test Immediate Recall. Values represent group means ± SEM. Asterisks (*) represent statistical signifcance of group difference at $p<0.05$.

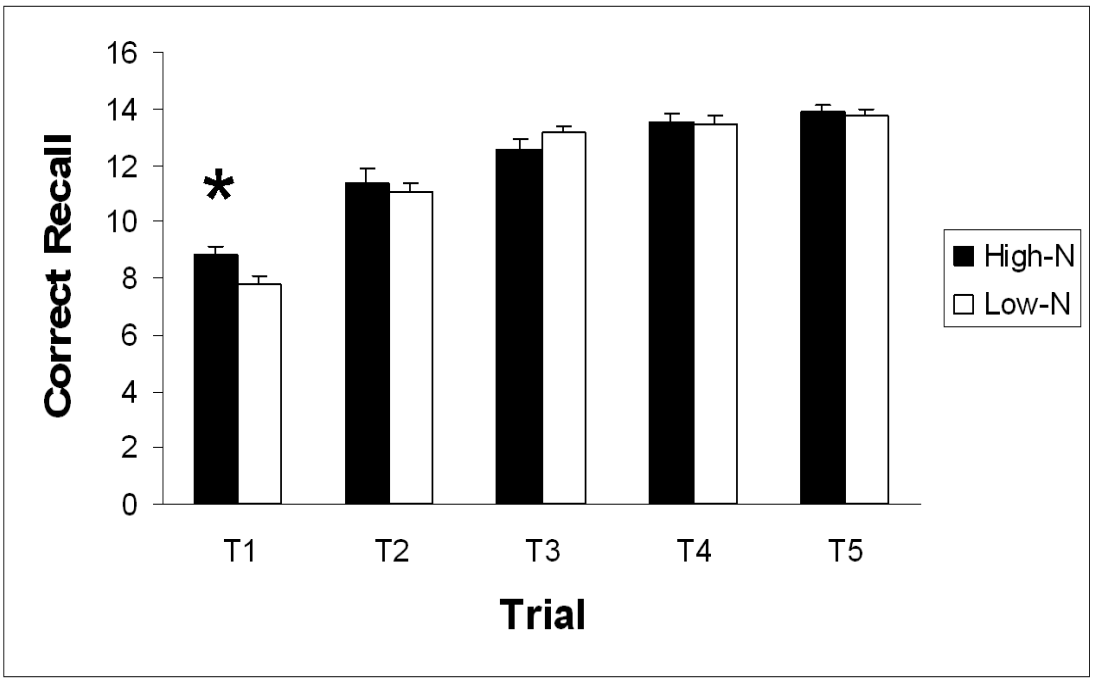


Figure 3.2: Auditory Verbal Learning Test Delayed Recall (left) and Recognition (right). Values represent group means ± SEM.

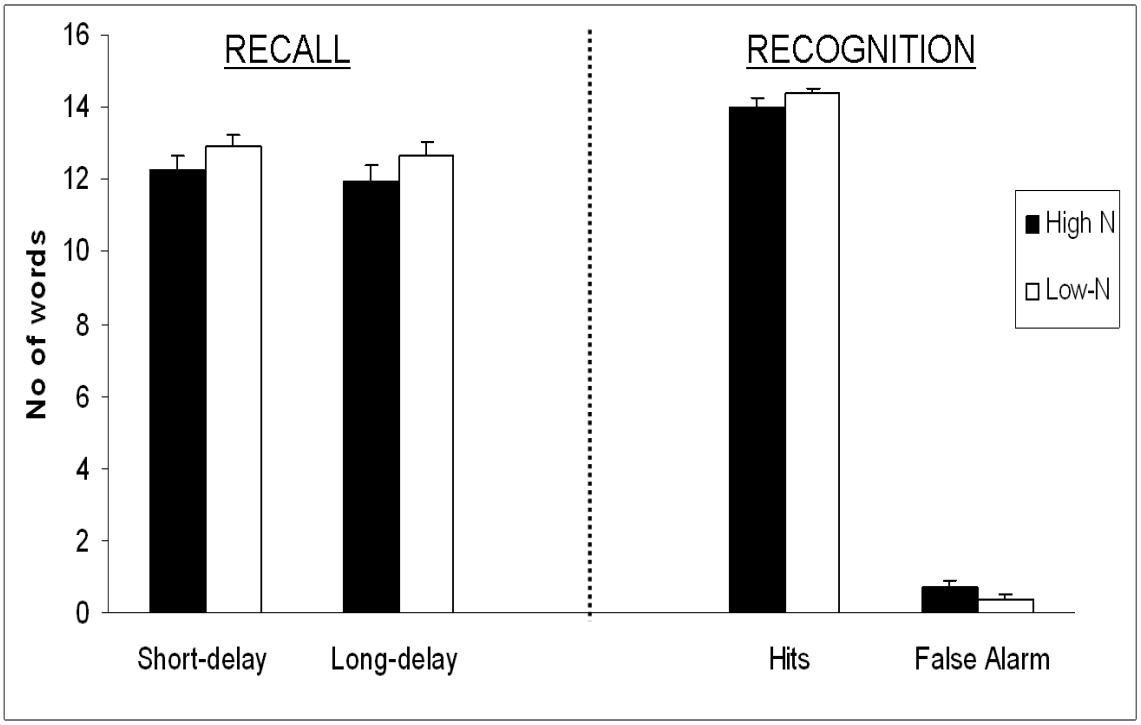


Figure 3.3: Tower of London Number of Moves Required. Values represent group means ± SEM. Asterisks (*) represent statistical signifcance of group difference at $p<0.05$.

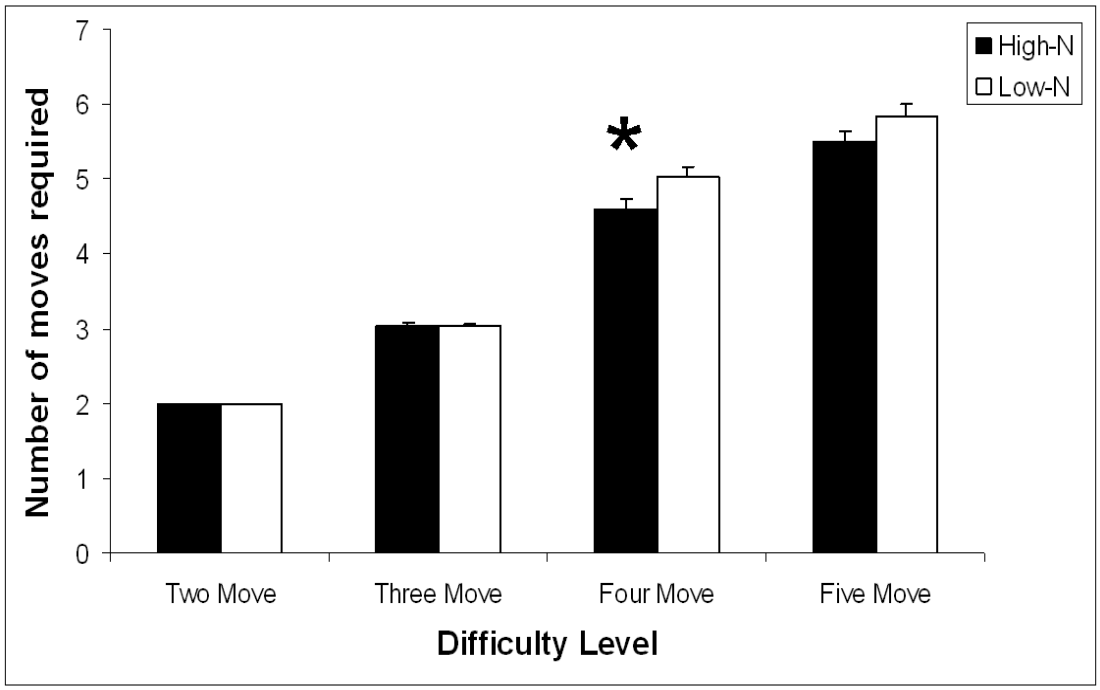


Figure 3.4: Tower of London Initial Thinking Time. Values represent group means ± SEM. Asterisks (*) represent statistical signifcance of group difference at $p<0.05$.

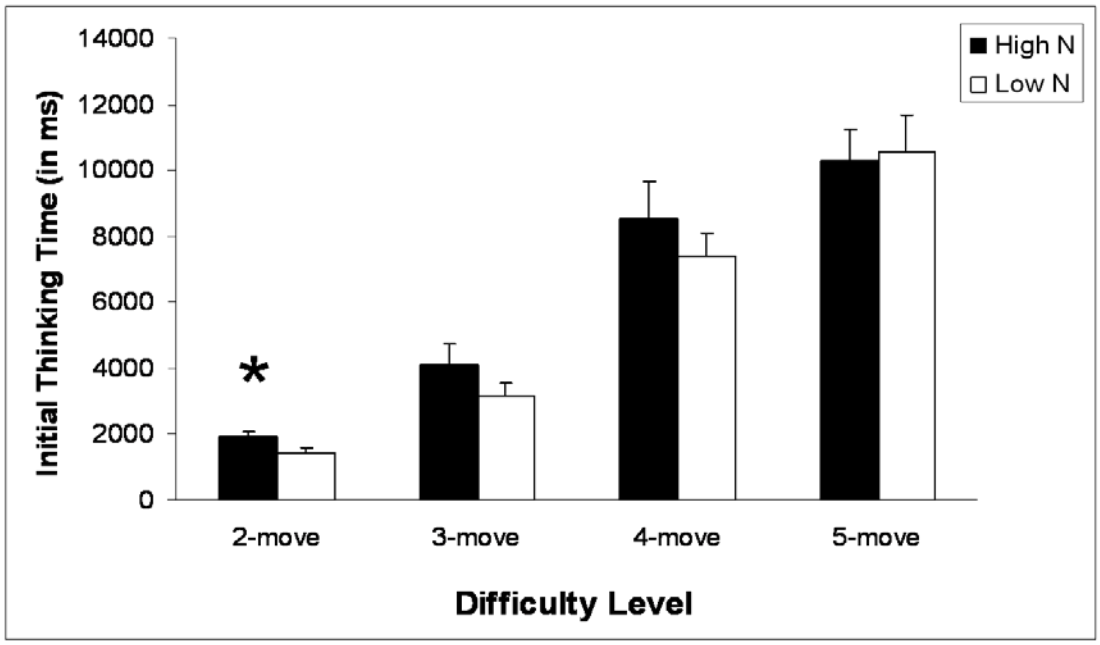


Figure 3.5: Tower of London Subsequent Thinking Time. Values represent group means ± SEM (presented in ms).

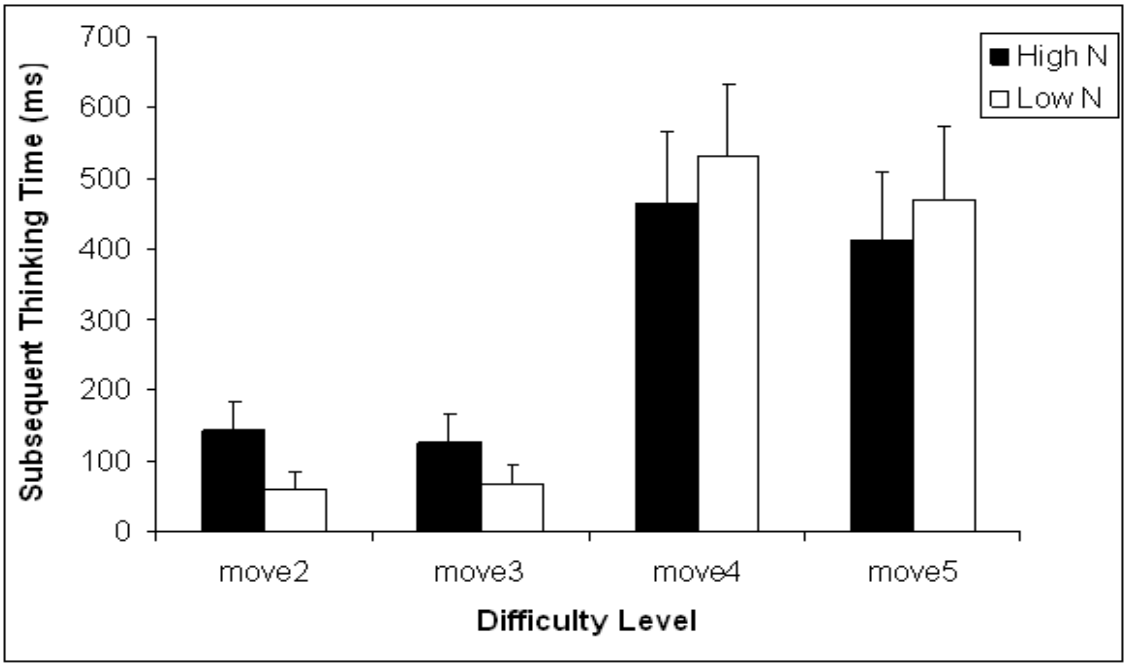
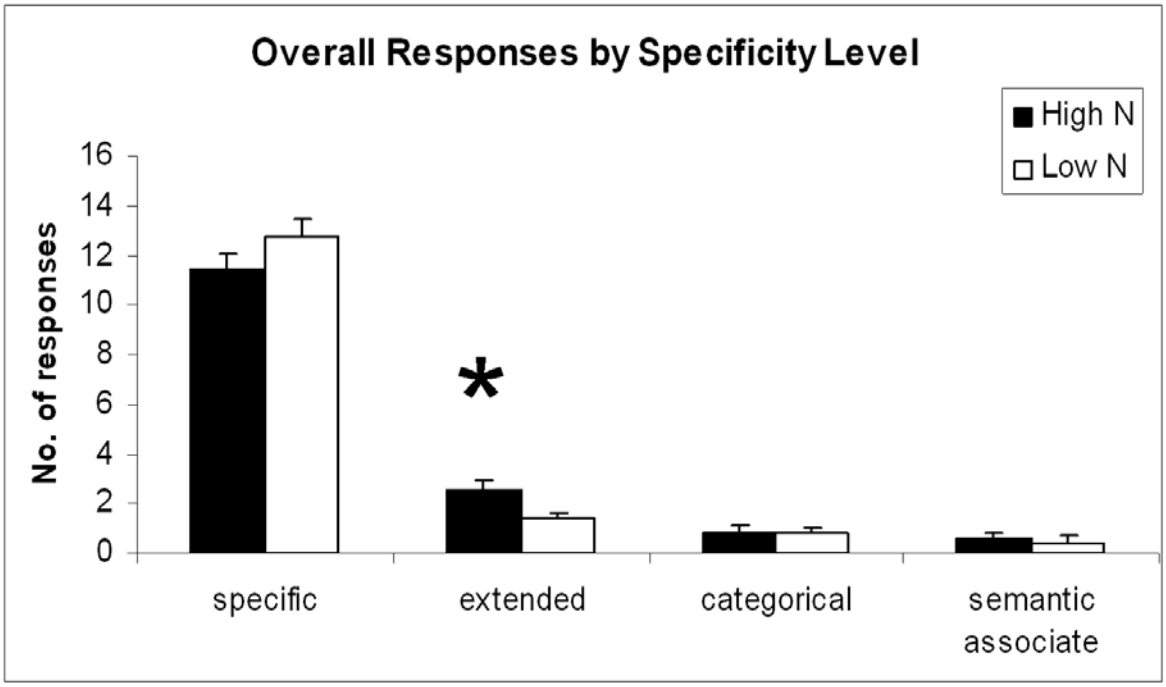


Figure 3.6: Autobiographical Memory Test. Figure showing the overall responses (i.e. positive and negative cue words combined) for each specificity level. Values represent group means ± SEM. Asteriks (*) represent group difference at significance level $p<0.05$.



3.4 DISCUSSION

In partial support of our hypotheses, the current results suggest that high neuroticism has no deteriorating effect on global executive functions. In fact, high N subjects showed modest improvements in Auditory Verbal Learning Test and Tower of London compared to low N subjects. In terms of specificity of autobiographical memory, high N subjects produced similar amount of specific memory as low N subjects. However, further analyses suggested that high N subjects produced more extended memory, suggesting a mild tendency towards being over-general.

As noted in Chapter One, global impairments of cognitive functions are largely confined to periods of illness in depression rather than as a more general trait factor (Austin et al 2001, Peselow et al 1991). Consistent with this, we found that high neuroticism does not impair simple learning and working memory (assessed by AVLT) and executive functions (assessed by TOL), suggesting that global cognitive impairments are not trait vulnerability markers for depression. As noted in Chapter One, cognitive impairments in depressed patients are in part caused by their reduced motivation (Weingartner et al 1981, Cohen et al 1982, Roy-Byrne et al 1986). Our high N subjects were healthy college students who, unlike depressed patients, did not suffer from motivational deficits. It is therefore unlikely that high risk for depression alone would lead to observable cognitive deficits. In fact, there was a tendency for high N volunteers to perform better in these tasks, which appeared to be related to their enhanced drive or perfectionism. This enhanced cognitive function makes the specific reduction in positive processing previously found in this group (Chapter Two) more noteworthy. The joint implications of our observations in emotional processing biases and the absence of general cognitive impairments in high risk volunteers will be discussed further in the final chapter. Meanwhile, it should be noted that AVLT

and TOL do not measure all processes of global cognitive functions. Future studies may consider using other tasks such as Wisconsin Card Sorting Test (WCST), a task specifically designed to measure set-shifting, a cognitive process that has been found to be most affected during depression (see 1.3.1).

In contrast to our hypothesis, high N volunteers did not replicate previous findings on depression regarding reduced specificity in autobiographical memory. Although this phenomenon has been robustly illustrated across clinical populations, as noted in Chapter One (section 1.3.2), their implications for vulnerability to depression are relatively unknown. Amongst the existing literature, there were only a limited number of longitudinal studies that have examined autobiographical memory before depression (e.g., Mackinger et al. 2000a & b, Van Minnen et al. 2005). However, their results were confounded by prior trauma experiences and/or unclear history of depression. Recently, a study conducted by Gibbs and Rude (2004) found that over-general memory interacts with stressful life events to predict subsequent depression symptoms in randomly selected college students. Indeed, stressful / traumatic life events are closely related to the development of over-general autobiographical memory (e.g. Kuyken and Brewin 1995, Harvey et al 1998, Henderson et al 2002). The current data therefore suggests that in young college students, without differences in life events, over-general autobiographical memory is not an obvious trait among high risk individuals.

Meanwhile, our data could not rule out the possibility of over-general autobiographical memory as a trait vulnerability marker. The specific increase in extended memories in high N subjects was particularly interesting. Extended memories represent the level of specificity in-between specific memories and categorical memories. Thus, it appears that risk for depression may be manifested by a

modest degree of reduced specificity in autobiographical memory. However, as the data of extended memory has been rarely reported, future studies are required to confirm this finding.

In summary, the current study showed that high risk for depression is not associated with global impairments in memory and executive functions, although there was a trend for reduced specificity in autobiographical memory in high risk individuals. Thus, the current finding showed that global cognitive impairments are not trait vulnerability marker for depression but instead may arise only during a depressive episode.

CHAPTER FOUR

Waking Salivary Cortisol and Vulnerability to Depression

4.1 INTRODUCTION

Results from Chapter Two revealed that negative biases in emotional processing are associated with neuroticism thereby suggesting that they may represent a vulnerability marker for depression. In Chapter Three, the same high risk sample showed enhanced executive function, most probably driven by higher perfectionism. Taken together, vulnerability to depression appears to be associated with cognitive abnormality focusing on emotional processing rather than a global impairment. As a next step, we aimed to explore whether abnormalities in biological function reported in depression are also seen as a risk factor for this disorder.

One of the most frequently reported biological abnormalities in depression is the hypothalamic-pituitary-adrenal (HPA) axis dysfunction, which can be indicated by an elevated cortisol response to awakening (Pruessner et al 1997, Young 2004). Consistent with this, elevated waking salivary cortisol has been demonstrated during acute depressive episodes (Bhagwagar et al 2005). Further, recent studies indicated that this dysfunction is also apparent in recovered patients (Bhagwagar et al. 2003), and can predict subsequent relapse (Zobel et al 2000). However, these data from recovered patients could not differentiate whether this cortisol hypersecretion is a consequence of previous illness / treatment or a long term vulnerability marker preceding illness onset. One study has reported enhanced morning cortisol responses

in a high N group without depression (Portella et al., 2005). However, volunteers in this study were typically past the peak age of onset for depression and so the implications for vulnerability to depression are difficult to interpret.

The current study was therefore designed to assess whether cortisol hypersecretion is seen in young high risk volunteers without a personal history of depression. Waking salivary cortisol levels of a sample of high risk vs. low risk never depressed volunteers identified through neuroticism scores were compared. Based on previous findings on high risk samples with high neuroticism (Portella et al 2005) we predicted that high neuroticism would be associated with HPA dysfunction as indicated by elevated morning salivary cortisol.

4.2 METHODS

4.2.1 Subjects

Fifty-four participants from the previous studies gave their written informed consent to collect salivary samples, and received payment for their participation. The current sample therefore consisted of 25 high N (16 women) and 29 low N (14 women) volunteers. N scores for recruitment were derived from the 12-item neuroticism scale of the shortened Eysenck Personality Questionnaire (Eysenck et al. 1985): the range of N scores was 8-12 vs. 0-3 for the high N and low N groups respectively. The two groups were matched for age (mean 18.88, SD 1.09 vs. mean 19.10, SD 0.90, $t(52)=-0.82$, $p=0.41$). Six female subjects (4 from high N and 2 from low N) were taking oral contraceptives. As noted earlier, they were screened to be free of current or previous Axis I disorders using the Structured Clinical Interview for DSM-IV. Their self-rated mood and personality variables were summarised in Table 4.1. As expected, high N subjects had higher scores on depressive and anxiety mood, dysfunctional attitudes and rumination than low N subjects, but the two groups did not differ in the number of stressful life events.

4.2.2 Materials & Procedures

Participants were carefully instructed to collect five salivary samples at home in the following morning: the first sample was taken immediately upon waking (Time 1) and continuing at 15-minute intervals for the next hour (Time 2, 3, 4 and 5 respectively). During the sampling, participants were not allowed to eat or drink. Alcohol consumption was not permitted the night before. Saliva samples were collected by using a salivette device (Sarstedt, Leicester, U.K.) in which saliva is

absorbed into a cotton roll and then expressed into a sterile vial. Salivary cortisol was measured, blind to subject status, by an in-house double antibody radioimmunoassay with intra- and inter-assay coefficients of variation of 3% and 10%, respectively.

4.2.3 Data Analysis

Two way repeated-measures analysis of variance (ANOVA) was carried out using group as between-subject variable (2: high N vs. low N) and time as within-subject variable (5: T1, T2, T3, T4, T5). Significant interactions were clarified by *post hoc* t tests. Salivary cortisol level was also measured as an area under curve (AUC) using the following formula (Pruessner et al 2003): $[(T_2 + T_1) + (T_3 + T_2) + (T_4 + T_3) + (T_5 + T_4)] \times 15/2$. Group difference was then examined by independent samples t tests. Finally, correlations were performed to explore the relationship between salivary cortisol level, neuroticism score, current mood state and stressful life events. Due to the exploratory nature of the study, the above analyses were primarily hypothesis-driven and hence Bonferroni tests were not performed to correct for multiple comparisons.

4.3 RESULTS

There was no significant group difference for time of awakening (high N: 8:38 am ± 55 min, low N: 8:38am ± 103 min, p=0.99) or hours of sleep (high N: 8.05 ± 1.27 hr, low N: 7.57 ± 1.48 hr, p=0.20).

As expected, salivary cortisol was affected by time of sample ($F(4,208)=12.02$, $p=0.00$). Overall, the volunteers showed a rise in salivary cortisol level within the first 30 minutes upon waking, which then gradually decreased and levelled off in the next 30 minutes. However, the salivary cortisol level was not affected by group (Figure 4.1: $F(1,52)=1.42$, $p=0.24$) or group-by-time interaction ($F(4,208)=0.22$, $p=0.93$). These group and interaction effects remained non-significant after including gender as covariate ($p>0.10$), although there was a significant main effect of gender ($F(1,51)=7.31$, $p=0.01$). *Post hoc* analyses showed that females had higher cortisol levels than males at all time points except T1 (Figure 4.2: T2 – T5: all p's <0.05).

Consistent with this, the cortisol area under curve (AUC) was not affected by group (Figure 4.1: 1376 ± 552 nmol x minutes/ litre vs. 1568 ± 594; $t(52) = -1.23$, $p=0.23$), but was higher in females than males (Figure 4.2: 1647 ± 660 vs. 1253 ± 343, $t(52)=-2.61$, $p=0.01$). The AUC was not correlated with overall age, duration of sleep or waking time (all p's > 0.30). Across the entire sample, the AUC measure was positively correlated with the number of lifetime stressful events ($r(54)=0.269$, $p=0.049$), which was also significant within the low N group ($r(29)=0.462$, $p=0.012$). However, the salivary cortisol level was not correlated with other psychosocial variables shown in Table 4.1, either across the entire sample or within each group separately. See Table 4.2.

Table 4.1: Personality, Mood, and Other Psychosocial Variables of High N and Low N Volunteers. Values represent group mean (standard deviation). Asterisks represent group comparison ** $p<0.001$, * $p<0.01$.

Task	High N	Low N	t (52)	P ≤
N score (as measured by full EPQ)	17.56 (2.65)	5.62 (3.33)	14.41	0.001**
HAMD	3.08 (2.98)	1.07 (1.65)	3.00	0.005 *
BDI	7.60 (5.10)	2.21 (1.92)	5.00	0.001**
STAI				
State	37.68 (10.64)	27.10 (5.86)	4.42	0.001**
Trait	46.12 (11.95)	28.45 (4.73)	6.94	0.001**
Bf-S	42.60 (26.88)	12.79 (9.97)	5.24	0.001**
FNE	21.56 (6.04)	8.07 (4.67)	9.25	0.001**
Hostility	31.72 (8.76)	24.28 (9.34)	3.01	0.004 *
Rumination (total)	52.08 (9.34)	38.76 (7.70)	5.75	0.001**
DAS (total)	142.16 (20.24)	105.45 (20.81)	6.55	0.001 **
Stressful Life Events	1.48 (1.36)	1.17 (1.56)	0.77	0.447

Table 4.2: Correlation between Salivary Cortisol Levels (Measured as AUC) and Psychosocial Variables across the Entire Sample and within High N and Low N Groups Separately. Values represent correlation coefficients and p value (in brackets). Asterisks represent significant correlations * $p<0.05$.

Task	Overall Sample	High N	Low N
N score (as measured by full EPQ)	-0.091 (0.514)	0.030 (0.888)	0.201 (0.296)
HAMD	-0.083 (0.551)	-0.251 (0.226)	0.317 (0.094)
BDI	-0.061 (0.660)	-0.030 (0.888)	0.230 (0.230)
STAI *State* *Trait*	 -0.187 (0.175) -0.180 (0.192)	 -0.141 (0.503) -0.064 (0.759)	 -0.098 (0.614) -0.165 (0.393)
Bf-S	-0.143 (0.303)	-0.127 (0.546)	0.088 (0.649)
FNE	-0.137 (0.322)	0.098 (0.641)	-0.119 (0.540)
Hostility	0.004 (0.976)	-0.168 (0.423)	0.257 (0.178)
Rumination (total)	-0.079 (0.568)	-0.023 (0.912)	0.087 (0.653)
DAS (total)	-0.016 (0.909)	0.012 (0.955)	0.226 (0.238)
Stressful Life Events	0.269 (0.049) *	0.049 (0.816)	0.462 (0.012) *

Figure 4.1: Salivary Cortisol Levels of High N and Low N Volunteers within the First Hour of Waking. Values represent group mean ± SEM.

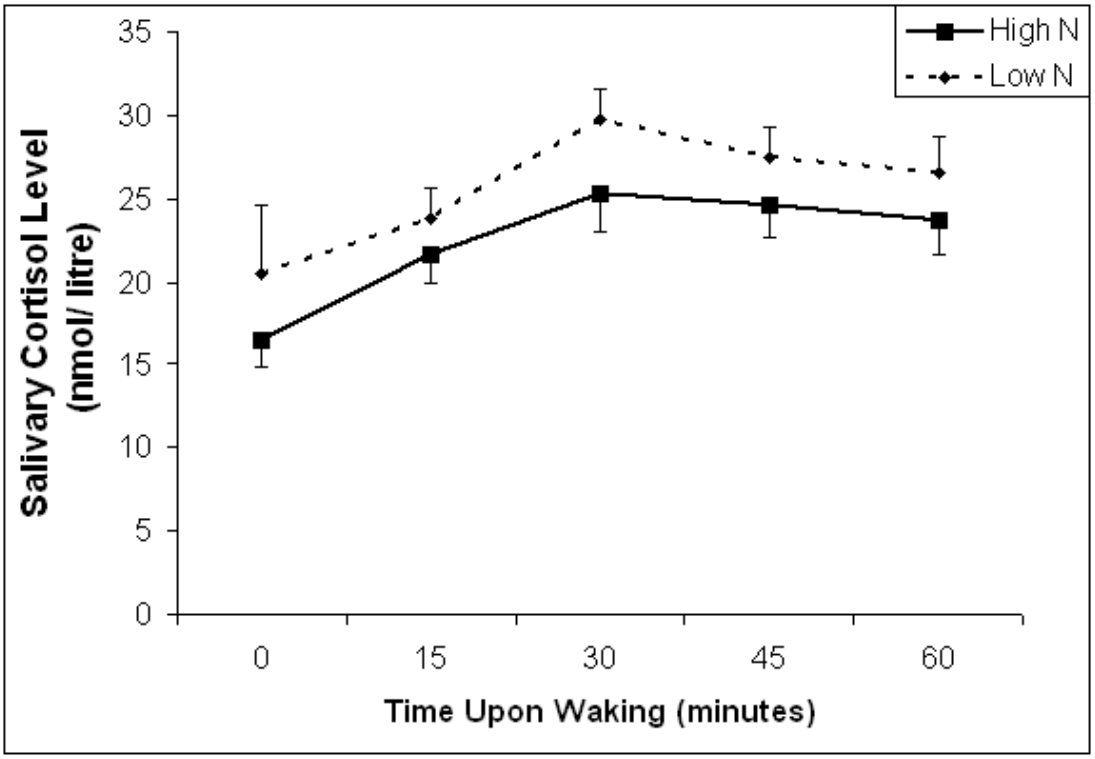
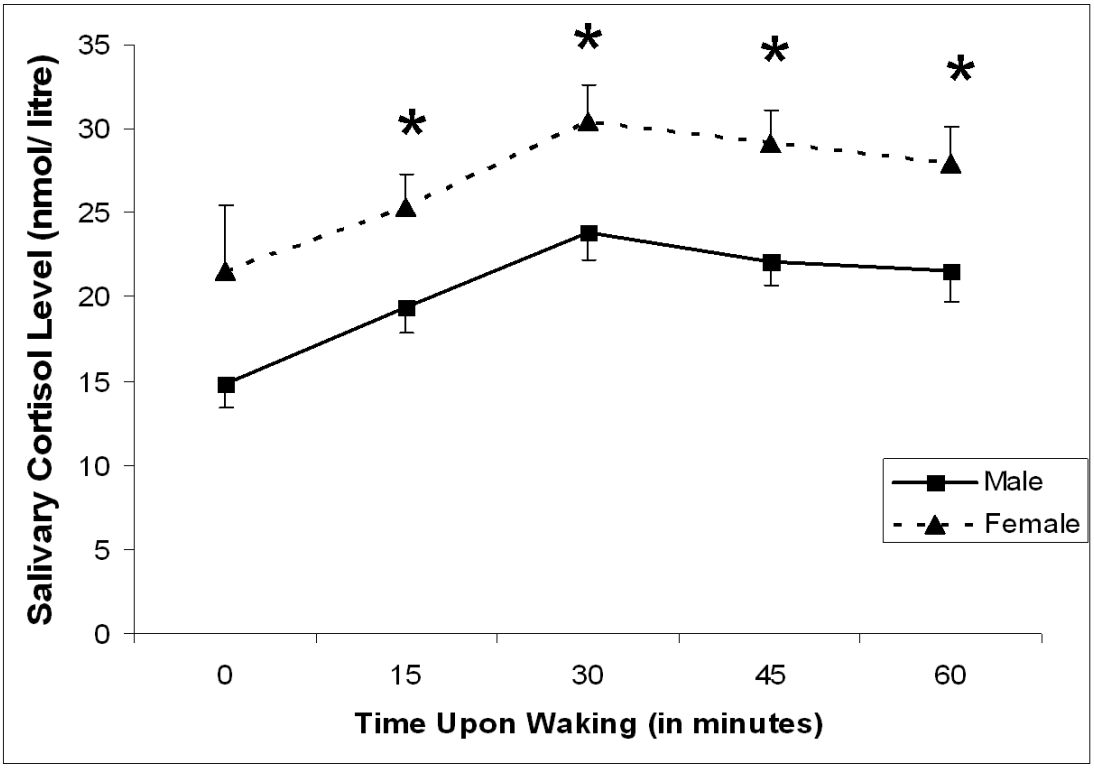


Figure 4.2: Salivary Cortisol Level of Male and Female Volunteers within the First Hour of Waking. Values represent group mean ± SEM. Asterisks (*) represents significant gender difference $p<0.05$.



4.4 DISCUSSION

Overall, our participants showed the typical pattern of waking salivary cortisol with an initial rise within the first 30 minutes followed by a gradual decrease, consistent with the robustly demonstrated phenomenon (Pruessner et al 1997). However, the cortisol level was not affected by neuroticism as shown by the absence of group effects and the absence of a correlation with neuroticism scores. In contrast, results showed that waking salivary cortisol is associated with gender and the experience of stressful life events.

Our negative findings for wakening salivary cortisol in high N students contrasted with the hyperactivity of HPA axis previously reported in other high risk samples. For example, Portella and colleagues (2005) reported enhanced early morning salivary cortisol in a group of high N, again never depressed, adults. However, their high N sample was substantially older than our high N sample (mean age: 40 vs. 19). Indeed, the effect of age on cortisol level was clearly illustrated in another study (Zobel et al 2004) where increased cortisol response in high neuroticism was mainly driven by the older subgroup. With a young adult sample (age <25) another study illustrated a reduction in cortisol response related to high neuroticism (McCleery and Goodwin 2001). With this, the authors argued that high N individuals may have a down-regulated HPA axis to prevent harmful over-activation. Taken together, these results suggest that dysfunction of HPA axis may be variably associated with neuroticism but that overactivity tends only to be seen with increasing age in vulnerable individuals, possibly as an interaction between risk and exposure to adverse life events.

Alternatively, our negative findings in waking salivary cortisol could be in part explained by the absence of group difference in the experience of stressful life

events. Morning cortisol response is primarily sensitive to current and prolonged subjective experience of stress (Pruessner et al 1999, Wust et al 2000), and consistent with this our results showed a significant correlation between cortisol levels and stressful life events. Our data therefore suggest that in young adults, with average level of life stress, elevated morning cortisol is not an indicator for vulnerability to depression.

As reviewed in Chapter One, the interaction between HPA dysfunction and vulnerability to depression is far from conclusive. In particular, the state vs. trait hypotheses has yielded both supportive and contradictory evidence. Recent studies focusing on high risk populations have raised interesting, but again inconclusive, findings. For example, familial risk for depression has been associated with greater cortisol secretion through twin studies (Young et al 2000) and people with family history of depression (Mannie et al 2007), although inconsistent results have also been reported (e.g. Le Masurier et al 2007). Our negative findings suggest that more attention needs to be paid to the role of life events, current stress and worry in mediating the association between risk for depression and heightened cortisol responses. It also raises the possibility that temperamental (neuroticism) and familial risks for depression may be manifested via different biological substrates. Future studies directly comparing different high risk groups are required to uncover this complex nature of vulnerability to depression.

Above all, previous findings appear to be varied according to severity of depression and methodology of measuring HPA activity. Indeed, salivary cortisol response to waking represents only a single aspect of HPA axis function; although previous studies have shown that this is a reliable and dynamic assessment of adrenocorticol activity (Pruessner et al 1997). Using a fixed time sampling method,

for example, some researches found no evidence for cortisol hypersecretion in depression (e.g. 8 am and 8pm in Young et al 2002; 9am and 9pm in Strickland et al 2002). The combined dexamethasone / corticotrophin-releasing hormone (DEX/CRH) test has also been widely used as another sensitive indicator of HPA activity. Our results therefore suggested that neuroticism is not associated with elevated cortisol response to waking, but they could not rule out the presence of HPA dysfunction that may be indicated by other methods.

Furthermore, it has been suggested that evidence for HPA axis hyperactivity is less consistent in less severe depression recruited from community and primary care sources (e.g. Strickland et al 2002, Watson et al 2002), where comparable or reduced levels of HPA axis activity were indicated. For example, Stetler and Miller (2005) found a blunted cortisol response to awakening in mild to moderate depression, suggesting that HPA dysfunction could be characterised as a dysregulation rather than hyperactivity. Therefore, again, our negative findings of waking cortisol responses could not rule out HPA axis dysfunction as a biological marker for depression.

Finally, our results replicated previous studies in revealing a sex difference in waking salivary cortisol response, which was independent of waking up time and duration of sleep (Pruessner et al 1997). However, this study did not control for the stage of the menstrual cycle or the use of oral contraceptives in female subjects. Although these are unlikely explanations to our results (Kirschbaum et al 1999, Kudielka and Kirschbaum 2003), control for these variables may improve the precision of the current findings.

In summary, the current results show that high neuroticism is not associated with salivary cortisol response to waking in young adults. However, it cannot be ruled out from our data set that HPA dysfunction may be seen in a subpopulation of high

neurotic subjects who will eventually develop depression, possibly as an interaction of risk and exposure to stressful life events. Our longitudinal studies have tested this hypothesis, which will be discussed fully in Chapter Seven. Meanwhile the next two chapters will examine the neural substrates of neuroticism that may also give rise to increased risk for depression.

CHAPTER FIVE

Neural Biases in Self-Referent Processing and Vulnerability to Depression

5.1 INTRODUCTION

Results from previous chapters showed that high neuroticism is associated with negative biases in emotional processing, but it does not affect global executive functions or early morning cortisol responses. To further investigate these emotional processing biases, the current study explored their neural substrates using a functional brain imaging technique. Specifically, this investigation focused on the self-referent processing biases reported in Chapter Two. Briefly, high N volunteers showed increased speed to categorise negative vs. positive self-referent personality adjectives and reduced positive memory intrusion in the subsequent recall (refer to sections 2.3.2 – 2.3.3 for details).

Negative biases for self-referent information have been identified as one of the key characteristics of depression (Mathews and Bradley 1983), which may in part contribute to the self reproach and negative self image observed in depressed patients. It is therefore of great theoretical and clinical importance to understand the nature of these processes and find out whether they develop prior to first illness onset.

Thus, similarly to our previous studies, the current study recruited a sample of high-risk (high N) vs. low risk (low N) individuals without personal history of depression. Functional Magnetic Resonance Imaging (fMRI) was acquired during self-referent categorisation and memory for positive and negative personality trait

words. Previous studies on healthy volunteers have shown that self-referent processing tasks induce activation in the medial prefrontal, parietal and occipital cortex (Fossati et al 2003, 2004, Kircher et al 2000, Lane et al 1997, Craik et al 1999, Gusnard et al 2001, Johnson et al 2002). Based on these results, we hypothesised that, compared to low N subjects, high N subjects would display greater activation in medial prefrontal, parietal and occipital cortex during categorisation of negative vs. positive words. Furthermore, we anticipated that retrieval of these negative adjectives might be facilitated in high N volunteers, and be associated with reduced activation in prefrontal areas (Norbury et al submitted, Miskowiak et al 2007).

5.2 METHODS

5.2.1 Subjects

Twenty-six right-handed healthy volunteers with high or low N scores (see below) gave written informed consent to the study, and received payment for their participation. The Structured Clinical Interview for DSM-IV (Spitzer et al 1995) was used to verify that all subjects were free of current or past axis-1 disorders. Due to a technical problem with response collection, five subjects were excluded prior to data analysis. Thus, the data presented here represented 21 subjects (14 women, aged 18-21).

N scores for screening were derived from the 12-item neuroticism scale of the shortened Eysenck Personality Questionnaire (EPQ: Eysenck et al 1985). Eleven (8 women) were in the high Neurotic group (N range 8-12), and 10 (6 women) in low Neurotic group (N range=0-4). The two groups were matched for age (mean 19.91, SD 0.54 vs. mean 19.90, SD 1.20), gender, verbal IQ (mean 119.42, SD 2.92 vs. mean 117.51, SD 3.54) and spatial IQ (in ms: mean 2578, SD 982 vs. mean 1842, SD 631) as assessed by NART (Nelson 1982) and WAIS-R (Wechsler 1981).

5.2.2 Mood and Personality Variables

To obtain a wider range of N scores across the sample, the full version of EPQ (Eysenck and Eysenck 1975) was administered. In addition, Beck Depression Inventory (BDI: Beck et al 1961) and State-Trait Anxiety Inventory (STAI: Spielberger et al 1970) were used to measure self-rated mood.

5.2.3 Verbal Stimuli

For the emotional categorisation task, a list of 90 personality-trait adjectives was constructed, of which half were unambiguously positive and half negative (Anderson 1968). Positive and negative words were matched on length, frequency (Francis et al 1982) and meaningfulness. Ten presentations of each of 'left' and 'right' were included as a baseline control condition. The words 'left' and 'right' were selected in order to control for the sensorimotor aspects of the task without requiring subjective assessment of the positive or negative aspects of the word. Thus, 110 words were presented in total, with the order randomised across subjects.

For the surprise incidental emotional memory task, the previously encoded words (old words) were mixed with 45 positive and 45 negative distracters (new words) taken from Anderson's list (Anderson 1968). The new words were unambiguously positive or negative and matched to the old words on length, frequency and meaningfulness. Thus, 180 words were presented in total, with the order randomised across subjects.

5.2.4 Task Design

Functional MRI scans were acquired while subjects performed both the emotional categorisation and recognition tasks. Stimuli were presented on a personal computer using E-Prime (version 1.0; Psychology Software Tools Inc., Pittsburgh, PA) and projected onto an opaque screen at the foot of the scanner bore, which subjects viewed using angled mirrors.

During the categorisation condition subjects were instructed to characterise the words as likeable or dislikeable in a self-referential fashion as quickly and accurately as possible. Specifically, subjects were asked to imagine whether they would be pleased or displeased if they overheard someone referring to them as possessing this

characteristic. Subjects indicated their decision as 'likeable' or 'dislikeable' by pressing a button with the right index and middle finger, respectively. For the control words 'left' and 'right', subjects responded with their right index and middle finger respectively. Subject responses were recorded using an MRI-compatible keypad. Accuracy and reaction times were recorded by E-Prime. Each trial consisted of a fixation cross (500ms) immediately followed by a personality-trait or control word (500ms). The duration of the intertrial interval (ITI) varied between 4000 and 8000ms according to a Poisson distribution, with a mean ITI of 5000ms. Total duration of the catergorisation experiment was 550s.

Emotional categorisation was immediately followed by an unexpected recognition task. Subjects were instructed to discriminate between studied (old) words and unstudied (new) words. Subjects indicated their decision of "yes" (old) or "no" (new) by pressing a button with the right index and middle finger, respectively. Trial presentation was identical to that during the categorisation condition. The total duration of the recognition experiment was 900s.

5.2.5 Functional MRI Data Acquisition

Imaging data were acquired at 1.5 Tesla on a Siemens Sonata scanner located at the Oxford Centre for Clinical Magnetic Resonance Research (OCMR). Functional imaging consisted of 30 contiguous T_2*-weighted echo-planar image (EPI) slices [TR/TE; 3000ms/50ms, matrix size/field of view; 64 x 64/192 x 192, slice thickness = 4 mm]. A Turbo FLASH sequence (TR = 12ms, TE = 5.65, voxel size = $1mm^3$) was also acquired to facilitate later coregistration of the fMRI data into standard space. The first two EPI volumes in each run were discarded to ensure T_1 equilibration.

5.2.6 Data Analyses

Functional MRI data was preprocessed using FSL version 3.2β (Smith et al 2004), which included slice acquisition time correction, within-subject image realignment (Jenkinson et al 2002), non-brain removal (Smith 2002), spatial normalisation (to Montreal Neurological Institute [MNI] 152 stereotactic template), and spatial smoothing (5mm FWHM). The time series were high pass-filtered (to a maximum of 0.025Hz).

Analyses of data from individual subjects were computed using the general linear model with local autocorrelation correction (Woolrich et al 2001). For the categorisation task three explanatory variables were modelled: 'negative', 'positive' and 'control' words. For the recognition condition two explanatory variables were modelled: 'positive remembered' and 'negative remembered'. In addition, temporal derivatives were included in the model as covariates of no interest to increase statistical sensitivity. All variables were modelled by convolving the onset of each word with a heamodynamic response function, using a variant of a gamma function (i.e. a normalisation of the probability density function of the gamma function) with a standard deviation of 3 s and a mean lag of 6 s.

Individual data were combined at the group level using a mixed effects analyses (Woolrich et al 2004). This mixed effects approach accounts for intra-subject variability and allows population inferences to be drawn. Significant activations were identified using cluster-based threshold of statistical images with a height threshold of $Z = 2.0$ and a (corrected) spatial extent threshold of $P < 0.05$ (Friston et al 1994). Corresponding Brodmann Areas (BA) were identified by transforming MNI coordinates into Talairach space (Talairach and Tournoux 1988).

The main contrasts of interest were main effects of task and group x valence interactions. For the categorisation task we contrasted activation during correct categorisation of emotional words (positive, negative) versus control words, as well as between positive and negative words. For the recognition task we contrasted correctly remembered positive words versus correctly remembered negative words. Significant interactions were further explored by extracting percent Blood Oxygen Level Dependent (BOLD) signal change within the areas showing significant difference in the above contrasts. In a secondary analysis, neuroticism was explored as a continuous variable, so N score was correlated with brain activation for correct categorisation and recognition of positive and negative words across the entire sample. The above whole brain analyses have corrected for multiple comparisons.

Behavioural data (accuracy and mean reaction time) were analysed using repeated measures analysis of variance (ANOVA, SPSS v.14.0) with group as the between-subject factor and valence as the within subjects factor (positive, negative and control words for categorisation task; positive and negative words for recognition task). Here, accuracy is defined as percent of correct responses. Due to technical difficulties, accuracy data were not available for two subjects (one from each group). Independent sample t tests were performed to clarify any significant interactions, as well as to examine group differences in mood ratings.

5.3 RESULTS

5.3.1 Behavioural Results

As expected, high N subjects had significantly higher scores on neuroticism (N), depressive mood (BDI), trait and state anxiety (STAI) (all p's <0.05). The two groups did not differ in terms of accuracy or response time to correctly categorised positive and negative self-referent words (all p's >0.05). For the recognition task there was no group difference for accuracy (p>0.05), although high N subjects showed reduced latency in recognising both positive and negative words than did low N subjects (group effect: p<0.01). See Table 5.1.

5.3.2 Functional Imaging Results: Main Effects of Task

Emotional categorisation

Relative to control words, encoding of negative and positive words both elicited greater activation in right lingual and left inferior frontal gyrus. In addition, negative vs. control words elicited greater activation in left precentral gyrus and anterior cingulate. For positive vs. negative and negative vs. positive words, increased activation was observed in right postcentral and left superior frontal gyri respectively. See table 5.2.

Emotional recognition

The recognition of positive and negative words activated a similar network of areas. Thus, there was no significant difference between these two emotional conditions across the whole sample.

5.3.3 Between-Group Differences

Emotional categorisation

Whole-brain analyses revealed greater activity in high N subjects in right superior parietal cortex (BA7, MNI: 20, -64, 64, z=2.94; Figure 5.1A) while encoding negative vs. positive words. Post hoc analyses of percent BOLD signal change for positive and negative words revealed a significant group-by-valence interaction ($F(1,19)=16.722$, $p=0.001$; Figure 5.1B), which was driven by high N subjects having greater activation for negative words than the low N group ($t(19)=3.180$, $p=0.005$). By contrast, the two groups had similar activation for positive words ($t(19)=0.417$, $p=0.681$). In addition, this group-by-valence interaction remained significant after including BDI or STAI scores as covariates (all $p<0.01$).

Emotional recognition

There were no between-group differences for the recognition of positive vs. negative words in this analysis.

5.3.4 Correlation between N Score and Neural Activity

Emotional categorisation

Across the entire sample, N was positively correlated with BOLD responses in left cingulate (BA24, MNI: -8,-8,52, Z=3.43; Figure 5.2A) and left parietal cortex (BA4, MNI: -20,-28,66, Z=3.28; Figure 5.2A) during successful categorisation of negative words. A positive correlation was also found in left inferior frontal gyrus (BA47, MNI:-46, 26,-6, z=3.28; Figure 5.2B) during successful categorisation of positive words.

Emotional recognition

N was negatively correlated with activity in the left cingulate (BA6/32, MNI: -10, 8, 54, Z-3.31; Figure 5.3A) during the correct recognition of negative words. Notably, this area overlapped with the cingulate activation reported above, although the correlation was in the opposite direction. To further explore these findings, we constructed a binary mask including only those voxels that were significantly correlated with both categorisation and recognition of negative words (BA6, MNI:-10, 26, 46, z=5.37, volume=312 $mm^{3,}$ Figure 5.3A). ANOVA analyses of the percent BOLD signal change of this overlap area found a significant group-by-valence interaction ($F(1,19)=16.431$, $p=0.001$; Figure 5.3B), which was driven by high N subjects having greater activation in encoding of negative words ($t(19)=3.181$,$p=0.005$) and reduced activation in recognition ($t(19)=-3.909$, $p=0.001$) of negative words compared to the low N subjects. Moreover, N was found to be negatively correlated with activity in the right precentral gyrus during successful recognition of positive words (BA6, MNI: 48, 0, 12, Z=3.45).

TABLE 5.1: Mood Ratings and Behavioural Data of High N and Low N Volunteers. Values represent group mean ± standard deviations. Asterisk (*) represents statistical significance p <0.05.

Measures	High N	Low N	Statistics
Mood and Personality Ratings			
N as full EPQ	16.45 (2.54)	5.50 (3.21)	t(19)=8.72; p=0.000*
BDI	2.55 (2.02)	0.90 (1.45)	t(19)=2.13; p=0.047*
State Anxiety	32.73 (7.06)	24.70 (3.47)	t(19)=3.35; p=0.004*
Trait Anxiety	39.55 (8.31)	26.30 (3.47)	t(19)=4.84; p=0.000*
Self referent Word Categorisation			
Accuracy % Control Positive Negative	 99.00 (2.11) 98.45 (2.80) 97.55 (1.28)	 100.00 (0.00) 97.25 (2.42) 96.23 (3.87)	Group effect: F(1,17)=0.498; p=0.490 Group x valence: F(2,34)=1.653; p=0.207
Reaction time Control Positive Negative	 756.31 (146.92) 865.85 (198.61) 929.71 (173.04)	 748.01 (88.16) 902.24 (89.73) 939.56 (116.21)	Group effect: F(1,19)=0.047; p=0.831 Group x valence F(2,38)=0.641; p=0.532
Self referent Word Recognition			
Accuracy % Positive Negative	 82.52 (6.93) 73.89 (14.17)	 80.51 (9.66) 72.24 (16.19)	Group effect: F(1,17)=0.143; p=0.710 Group x valence: F(1,17)=0.004; p=0.951
Reaction time Positive Negative	 954.84 (185.27) 999.75 (194.14)	 1189.72 (181.57) 1210.85 (153.04)	Group effect: F(1,19)=9.114; p=0.007* Group x valence: F(1,19)=0.199; p=0.661

TABLE 5.2: Main Effects of Task. The brain regions that show differential activations for correctly categorised positive, negative, and control words across the entire sample.

Brain Regions	Left/ Right	Brodmann Area	MNI	Z Value
Negative vs. control				
Lingual gyrus	R	17	14 -84 6	4.3
Precentral gyrus	L	6	-4 56 24	4.03
Inferior frontal gyrus	L	47	-44 28 -10	4.27
Anterior cingulate	L	32	-2 18 42	3.72
Positive vs. control				
Lingual gyrus	R	18	14 -82 4	4.48
Inferior frontal gyrus	L	47	-56 28 -2	3.75
Positive vs. negative				
Postcentral gyrus	R	43	66 -18 30	3.04
Negative vs. positive				
Superior frontal gyrus	L	6	-24 14 66	3.17

FIGURE 5.1 The image (A) and percent BOLD signal change (B) of the right superior parietal cortex (BA7, MNI: 20, -64, 64) which shows increased activation for correctly categorised negative vs. positive words in high N (black) vs. low N (white) subjects. Values represent group mean ± SEM. Asterisk (*) indicates significant group difference $p<0.05$.

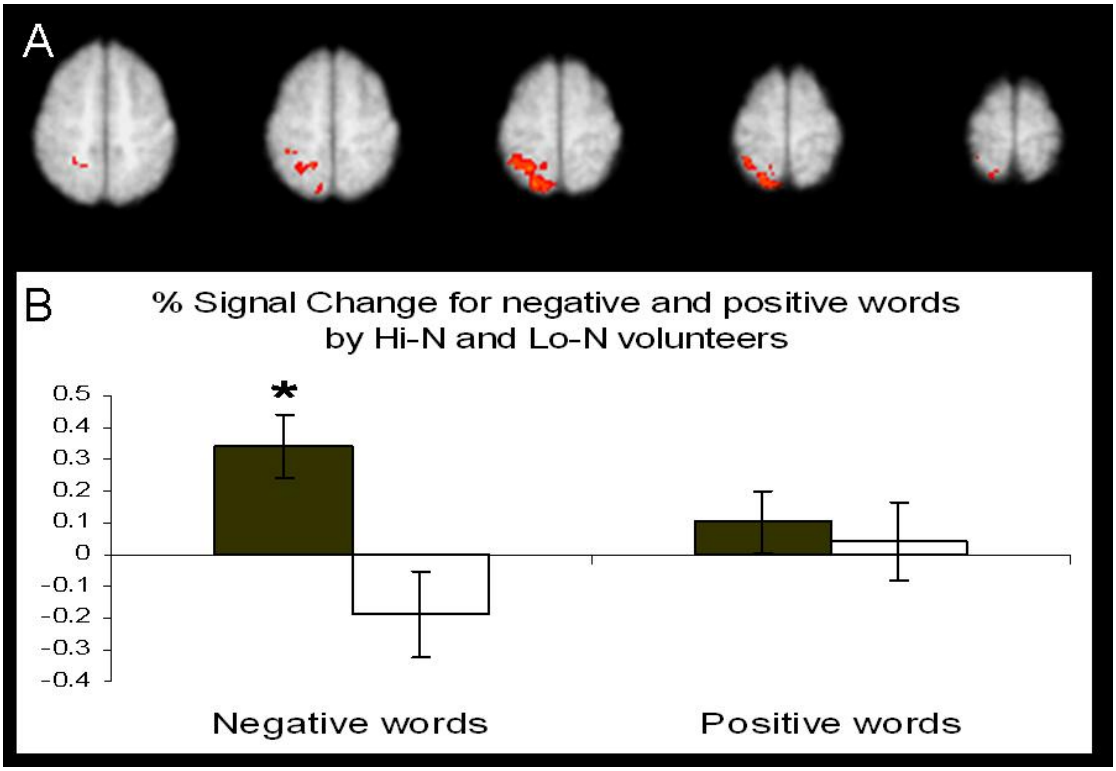


FIGURE 5.2 (A) Activations in left cingulate and parietal cortices were positively correlated with N during categorisation of negative words. (B) Activations in inferior frontal gyrus were positively correlated with N during categorisation of positive words.

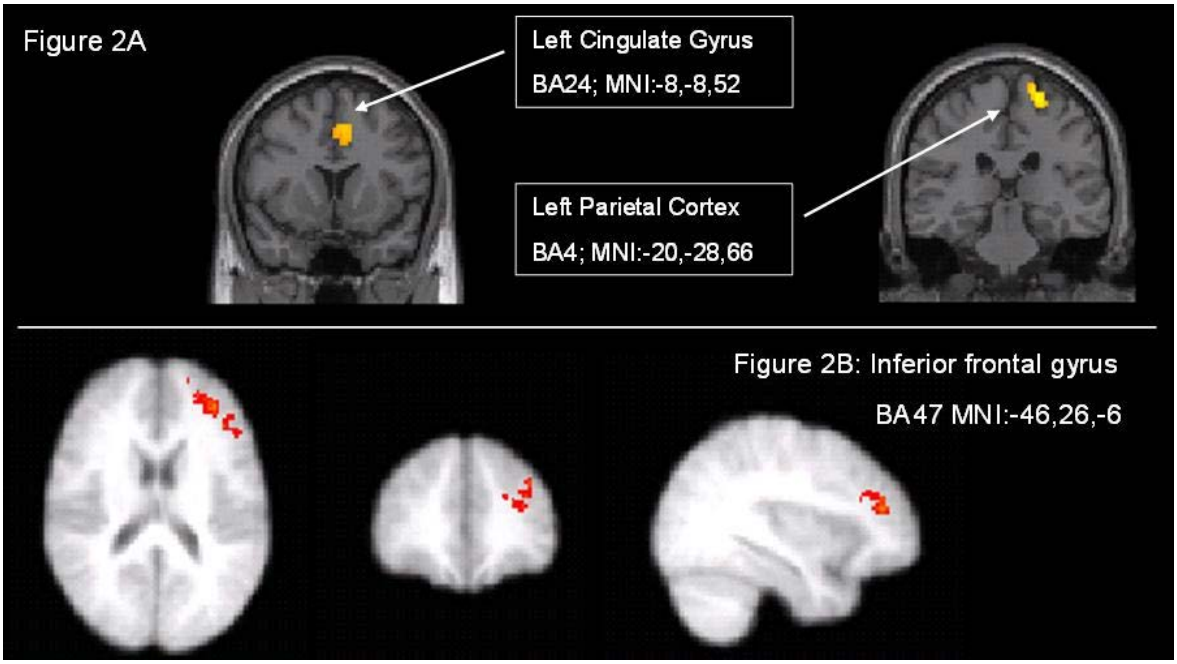
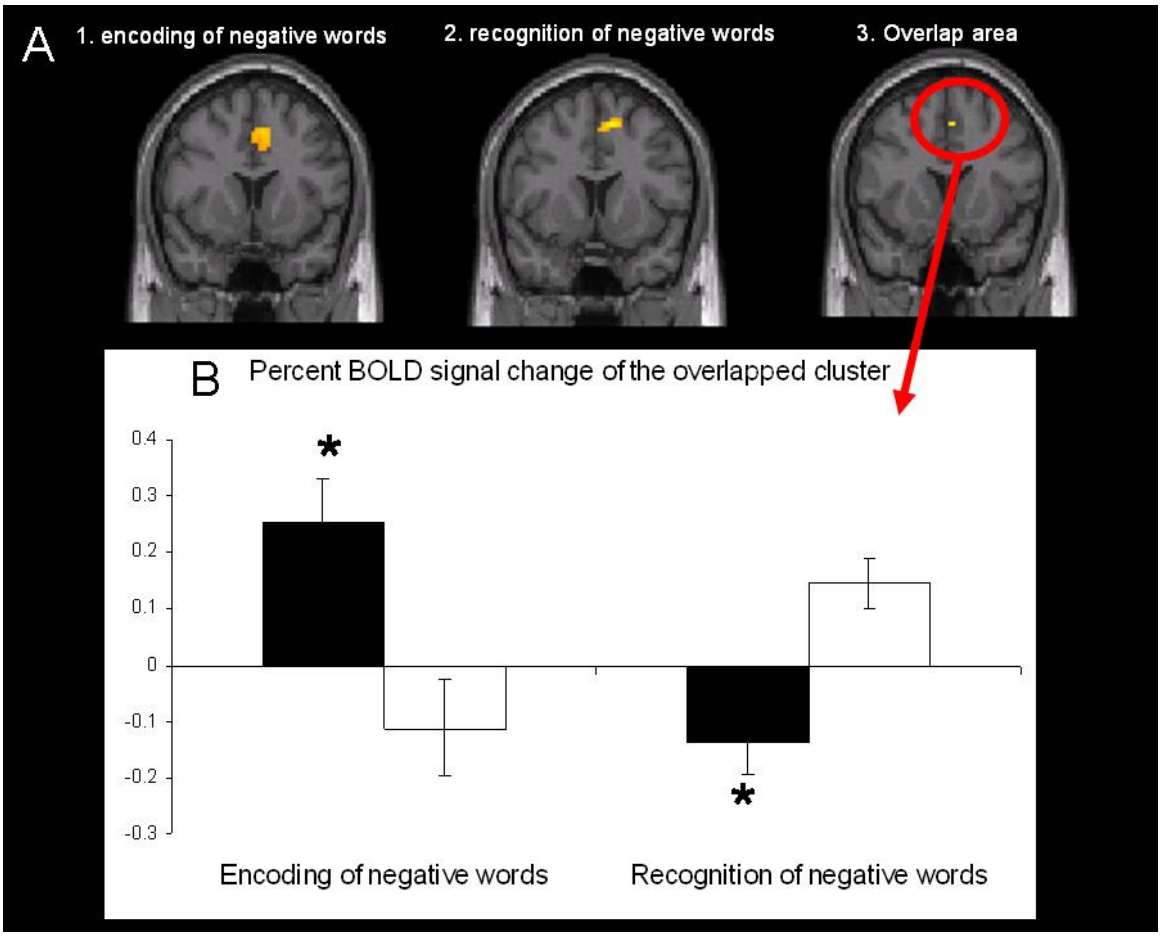


FIGURE 5.3 (A) The cingulate cortical area which was (1) positively correlated with N during categorisation of negative words; (2) negatively correlated with N during recognition of negative words; (3) overlapped between the two clusters above. (B) Percent BOLD signal change within the overlapped cluster of high N (black) and low N (white) subjects. Values represent group mean ± SEM. Asterisk (*) indicates significant group difference $p<0.05$.



5.4 DISCUSSION

The current study illustrates a neural basis for negative biases in self-referent emotional processing in subjects at high risk for depression. Our high-risk, never depressed volunteers exhibited greater activity in the right superior parietal cortex during encoding of negative personality traits compared to low-risk volunteers. Activation in the left cingulate was shown to increase with neuroticism during encoding of negative words but decrease with neuroticism during subsequent retrieval of negative words. In addition, neuroticism was found to correlate with activations in left parietal, left inferior frontal and right pre-central gyri during encoding and recognition of emotional self-referent words. These areas have been implicated in self-referent processing and depression in previous studies, thus our results suggest that these neural and associated cognitive processes could also play a role in vulnerability to depression.

Analyses across all subjects revealed that categorisation of emotional self-referent words engaged the lingual, precentral, inferior frontal, anterior cingulate, superior frontal and postcentral gyrus. Replicating previous research findings (Fossati et al 2003, 2004; Kircher et al 2000, Vuilleumier 2005), our results confirmed an extensive network to be involved in self-referent processing.

The present study further highlighted specific areas that appear to underlie the self-processing biases in vulnerability to depression, in particular in superior parietal cortex. First, our high-risk group showed significantly increased activation in the right superior parietal cortex during categorisation of negative words compared to low-risk group. Second, left parietal activation was found to increase with neuroticism score during encoding of negative words. Taken together, the results suggested that bilateral

hyperactivity in parietal cortex is a feature of high neuroticism whether explored as a categorical risk factor or continuous personality variable.

Parietal cortex is believed to play a key role in attentional processes to biologically significant or personally relevant events (Vuilleumier 2005). Although its function in self-referent word processing has not been previously explored, previous studies have indicated its direct involvement in self-face recognition, concept of self, and perception of social relationship (Uddin et al 2005, Feinburg 2001, Decety and Sommerville 2003, Carr et al 2003, Farrer and Frith 2002, Iacoboni et al 2004). Consistent with this, our results suggested that high neuroticism is linked to an increased self-awareness of negative personality traits, which could in part contribute to the excessive self criticism observed in high N individuals and depressed patients.

The current observation of hyperactivity in parietal cortex seems to reflect the neural basis of vulnerability to depression *per se*, not simply dysphoric mood. Symptoms of low mood are often observed in neuroticism, and it is sometimes proposed that N is simply a measure of usual mood. Although the high N volunteers displayed higher scores on current depression and anxiety scales, the range of these mood scores was well below that in syndromal states and was low compared with other high N samples that have been studied. Furthermore, analyses with BDI and STAI as covariates confirmed that current mood scores could not explain the imaging findings.

Just as current mood cannot account for the findings, behaviour in the scanner was similar in both groups and does not explain the neural differences. Our previous study of behavioural biases in high N subjects could demonstrate modest effects of N on self-referent categorisation and recall in a larger sample studied in less demanding conditions than a scanning environment (Chapter Two). These differences were

compatible with enhanced encoding and more efficient recall. However, differences in performance will always be potentially confounded by strategy and motivation so a scanning approach gives a more precise estimate of the actual functional locus of experimental effects, as is illustrated here.

The current study also supported an involvement of the cingulate in vulnerability to depression. Sometimes called the 'error detector', the anterior cingulate modulates the autonomic response to emotional experience and processes information concerning reward-punishment reinforcement contingencies (Bush et al 2000, Drevets 2001). Structural and functional abnormality of cingulate cortex has been implicated in depression (Gotlib et al 2005, Mayberg et al 1997), which is potentially related to heightened sensitivity to personal failure and pathological guilt in depressed individuals. In this study, activity of the cingulate cortex increased with N during encoding of negative words, while in the subsequent retrieval of these negative words activation within this same area fell. Thus, better encoding of negative trait words during categorization led to a reduced retrieval effort at recognition.

The processing of positive words was also interesting: high N was related to greater activation in a left inferior frontal area during the encoding of positive words. Inferior prefrontal cortex has previously been implicated in emotional control and inhibitory processes during inhibition of distracting information (Dolcos et al 2006, Dolcos and McCarthy 2006, Ochsner and Gross 2005, Aron et al 2004, Jha et al 2004, Jonides et al 1998). Thus, high neuroticism may imply greater inhibitory processes over positive information, and thus reduced positive emotional processing in high N individuals. These effects are hypothesis generating and must be regarded with caution until replicated.

The areas related by N in the current study overlap with those previously suggested to be implicated in trait vulnerability for depression from the study of remitted patients (e.g. Damasio et al 1998, Mayberg et al 1997). The current findings extend the existing literature by suggesting that abnormalities within cingulate and parietal cortex are apparent even in high risk individuals who have never suffered or been treated for depression; as such they cannot represent scar effects of prior illness.

In conclusion, in support of our hypothesis, self-reference processing biases underlying vulnerability to depression are associated with changed neuronal activity in parietal, cingulate and prefrontal areas. Consistent with our earlier finding (Chapter Two), negative biases in self-referent processing were revealed in high neuroticism. The next chapter will explore the neural correlates of facial expression processing biases in neuroticism.

CHAPTER SIX

Neural Biases in Facial Expression Processing and Vulnerability to Depression

6.1 INTRODUCTION

Facial expression processing bias is one of the most remarkable cognitive-social impairments in depression. In our previous behavioural study (Chapter Two), we observed high N volunteers to have reduced perception of happy facial expressions. This negative bias is similar to that observed in depressed patients (Bouhuys et al 1999, Gur et al 1992, Surguladze et al 2004, Suslow et al 2001) and to a certain extent recovered patients (Bouhuys et al 1999, Hayward et al 2005; Bhagwagar et al 2004), suggesting that this emotional processing bias may play a crucial role in the aetiology and maintenance of depression. Behavioural abnormalities are likely to be the expression of complex underlying mechanisms. Therefore, this study explored the neural mechanisms that may serve to maintain this facial expression processing bias in high risk volunteers.

Functional imaging studies have outlined the neural network that underlies affective facial processing (Haxby et al 2001, Phillips et al 2003a) and abnormality within this network has been implicated in depression (Phillips et al 2003b). As noted in Chapter One, the role of amygdala in fear perception and depression has been robustly illustrated (Sheline et al 2001, Davidson et al 2003, Fu et al 2004, Surguladze et al 2005, Drevets 2000, Keedwell et al 2005). Extrastriate areas such as the fusiform gyrus and cuneus also show a differential pattern of neural response to emotional

faces in depression, with reduced responses to happy facial expressions and increased responses to negative facial expressions compared to healthy volunteers (Surguladze et al 2005, Keedwell et al 2005, Lawrence et al 2004, Fu et al 2007).

Similar to our study outlined in the last chapter, the current study examined the neural substrates of facial expression processing in high-risk (high N) vs. low risk (low N) volunteers without a personal history of depression using functional Magnetic Reasonance Imaging (fMRI). Previous work has suggested that linear modeling of the neural response to different intensities of positive and negative emotions is a sensitive method to identify biases in depression (e.g. Surguladze et al 2004, 2005; Fu et al 2004). Thus, we sought to explore whether similar biases would be seen as a function of vulnerability *per se*. We hypothesized that high N would be associated with increased activation to increasing intensity levels of fear and / or reduced activation to increasing intensity of happiness within the amygdala and fusiform gyrus. We also predicted that high N volunteers would show greater activation for fearful vs. happy expressions than low N volunteers within these areas.

6.2 METHODS

6.2.1 Subjects

Twenty-five right-handed healthy volunteers (17 female, aged 18-22) gave written informed consent to the study, which was approved by the Oxford Research Ethics Committee. The Structured Clinical Interview for DSM-IV (Spitzer et al 1995) was used to verify that all subjects were free of current or past axis-1 disorders. Participants received payment for their participation.

N scores for screening were derived from the 12-item neuroticism scale of the shortened Eysenck Personality Questionnaire (EPQ: Eysenck et al 1985). Twelve (9 women) were in the high Neuroticism group (N range 8-12), and 13 (8 women) in the low Neuroticism group (N range=0-3). The two groups were matched for age (mean 20.00, SD 0.60 vs. mean 20.15, SD 0.99), gender, verbal IQ (mean 119.10, SD 3.03 vs. mean 118.66, SD 4.26) and spatial IQ (in ms, mean 2584, SD 941 vs. mean 1974, SD 610) assessed by NART (Nelson 1982) and WAIS-R (Wechsler 1981) respectively.

6.2.2 Mood and Personality Variables

To obtain a wider range of N scores, the full version of EPQ (Eysenck and Eysenck 1975) was administered. In addition, Beck Depression Inventory (BDI: Beck et al 1961) and State-Trait Anxiety Inventory (STAI: Spielberger et al 1970) were used to assess self-rated mood.

6.2.3 Stimuli and Task

Each volunteer participated in a single 16 minute experiment employing rapid event-related fMRI. Eight faces (4 male, 4 female) displaying prototypical expressions of fear and happiness were taken from a standardized series of facial expressions (Ekman and Friesen 1976). In addition to the prototypic or high intensity (100%) facial expression, lower intensity expressions were created using morphing software to manipulate the 8 different prototypic expressions to 30% (low intensity) and 60% (medium intensity) along the neutral-prototypic continuum. Each face was also presented in a neutral facial expression. Thus, there were eight facial stimuli representing each of the following categories: high fearful (fear-H), medium fearful (fear-M), low fearful (fear-L), high happy (happy-H), medium happy (happy-M), low happy (happy-L), and neutral. Each of these faces was presented three times and 24 presentations of a fixation cross were included as baseline, giving a total of 192 trials. Stimuli were presented in a random order for 500ms each, and the intertrial interval varied according about a Poisson distribution with a mean of intertrial interval of 5000ms. Subjects were asked to indicate the gender of each face by pressing one of two keys on an MRI compatible keypad. No motor response was required for baseline trials of fixation cross. Stimuli were presented on a personal computer using E-Prime (version 1.0; Psychology Software Tools Inc., Pittsburgh, PA) and projected onto an opaque screen at the foot of the scanner bore, which subjects viewed using angled mirrors. Behavioural responses were recorded using a MRI-compatible keypad. Accuracy and reaction times were recorded by E-Prime.

6.2.4 Functional MRI Data Acquisition

Imaging data was collected by a 1.5T Siemens Sonata scanner located at the Oxford Centre for Clinical Magnetic Resonance Research (OCMR). Functional

imaging consisted of 30 contiguous T_2*-weighted echo-planar image (EPI) slices [repetition time (TR) = 3000ms, echo time (TE) = 50ms, matrix = 64 x 64, field of view (FOV) 192 x 192, slice thickness 4mm]. A Turbo FLASH sequence (TR = 12ms, TE = 5.65, voxel size = $1mm^3$) was also acquired to facilitate later coregistration of the fMRI data into standard space. The first two EPI volumes in each run were discarded to ensure T_1 equilibration.

6.2.5 Data Analyses

Functional MRI data analysis was carried out using FSL version 3.2β (Smith et al 2004). Preprocessing included slice acquisition time correction, within-subject image realignment (Jenkinson et al 2002), non-brain removal (Smith 2002), spatial normalisation (to Montreal Neurological Institute [MNI] 152 stereotactic template), spatial smoothing, and high-pass temporal filtering (to a maximum of 0.025Hz).

In the first-level analysis, individual activation maps were computed using the general linear model with local autocorrelation correction (Woolrich et al 2001). Eight explanatory variables were modelled, including each intensity (low, medium, high) of fear and happy as well as neutral and fixation. The main contrasts of interest were fear vs. happy expressions (and vice versa) for each intensity level, i.e. fear-H vs. happy-H; fear-M vs. happy-M, fear-L vs. happy-L. In addition, each individual activation map was analysed by fitting linear trends at each voxel at the three intensity levels of fear and happy, separately, with orthogonal polynomial trend analysis. Positive linear trends modelled responses for increasing emotional intensity while negative linear trends modelled responses for decreasing emotional intensity. All variables were modelled by convolving the onset of each stimulus with a heamodynamic response function, using a variant of a gamma function (i.e. a normalisation of the probability

density function of the gamma function) with a standard deviation of 3s and a mean lag of 6s.

In the second-level analysis, individual data were combined at the group level (high N vs. low N) using a mixed-effects analysis (Woolrich et al 2004). This mixed effects approach accounts for intra-subject variability and allows population inferences to be drawn. We aimed to establish (1) the main effect of task across the entire sample; (2) the effect of neuroticism on the responses to fear vs. happy facial expressions at each intensity level; and (3) the effect of neuroticism on the linear trend across increasing / decreasing intensity of fear and happy expressions. Significant activations were identified using a cluster-based threshold of statistical images [height threshold of $Z = 2.0$ and a (corrected) spatial extent threshold of $p < 0.05$ (Friston et al 1994)]. Significant interactions were further explored by extracting percent BOLD signal change within the areas of significant difference, which were then analysed using repeated measures ANOVA (between Ss variable = group; within Ss variable = intensity or valence) followed by appropriate *post-hoc* t-tests (SPSS v.14.0). Corresponding Brodmann Areas (BA) were identified by transforming MNI coordinates into Talairach space (Talairach and Tournoux 1988). The above whole brain analyses have corrected for multiple comparisons.

Due to the strong *a priori* evidence implicating the amygdala in the processing of facial expressions (Sheline et al 2001, Davidson et al, Fu et al 2004, Surguladze et al 2005, Drevets 2000), we also performed a region-of-interest (ROI) analysis. Amygdala masks (left and right) were segmented for each individual using a robust fully automated Integrated Registration and Segmentation Tool ("FIRST"; Patenaude et al 2007). To examine any structural differences in amygdala between the high N and low N groups, volume was extracted from each individual amygdala (left and

right) which were then analysed by a 2x2 repeated measures ANOVA (2 variables: group, hemisphere). To examine the functional differences, percent BOLD signal change for each emotional stimulus (fear and happy) was then extracted from each individual amygdala. These data were entered into 2x2x3 repeated measures ANOVA (between Ss variable = group; within Ss variables = valence and intensity). Significant three-way interaction was clarified by two-way ANOVA and subsequent t-tests. Time series data were also extracted from each individual amygdala for each stimulus type.

For the behavioural data, independent sample t-tests were used to examine group difference for subjective mood ratings, overall accuracy and reaction time of the gender discrimination responses. Due to technical difficulties, reaction time and accuracy data (measured during fMRI) from four low N subjects were not recorded.

6.3 RESULTS

6.3.1 Mood Ratings and Behavioural Data

As expected high N subjects had significantly higher scores on neuroticism (high N: 16.50 ± 2.43, low N: 5.69 ± 2.93) and trait anxiety (39.00 ± 8.15 vs. 27.47 ± 4.91, p=0.00). State anxiety (32.08 ± 7.09 vs. 26.46 ± 7.02, p=0.06) and depressive mood scores (BDI: 2.50 ± 1.93 vs. 1.23 ± 1.92, p=0.11) had the expected trend, but were not statistically different. Behaviourally, both groups achieved higher than 90% correct for gender discrimination of all facial expressions, with no between-group difference (94.29 ± 5.62 vs. 92.80 ± 9.51, p=0.66) and did not differ in overall reaction time (674.38 ± 87.29 ms vs. 725.97 ± 161.84 ms, p=0.36).

6.3.2 Functional Imaging Results

Main effects of task

Across the entire sample, increased activation was found in right middle temporal gyrus (BA21, MNI: 58, -12, -6, z=3.03) for fear vs. happy expressions at low intensity. There were no significant differential responses for fear vs. happy expressions, or vice versa, for high or medium intensities. Furthermore, there was a linear trend of increasing responses in lingual gyrus (BA19, MNI: 6, -52, -6, Z=3.21) and inferior frontal gyrus (BA47, MNI: 48, 32, -14, Z=3.56) for expressions of increasing happiness. By contrast, there was a linear trend of decreasing responses in nucleus accumbens (MNI: -4, -6, 18, Z=2.98) for expressions of increasing fear.

Neural Responses for Fearful vs. Happy Expressions: Between-group Differences

Our primary hypothesis was that fearful and happy faces would be differentially processed by the subject groups. Indeed, high N vs. low N subjects exhibited greater activity for fear vs. happy expressions with medium intensity (i.e. fear-M vs. happy-M) in the following areas: cerebellum (MNI: 0, -64, -26, z=3.91, Figure 6.1), left middle frontal gyrus (BA10, MNI:-30, 58, 2, z=3.46, Figure 6.2), left superior parietal (BA7, MNI:-18, -66, 60, z=3.25, Figure 6.3) and right superior parietal cortex (BA7, MNI: 4, -48, 68, z=3.25, Figure 6.4). Analysis of percent BOLD signal change for fear-M and happy-M stimuli in each of these clusters revealed increased responses during presentation of fearful facial expressions, which in some areas was accompanied by relatively reduced responses during the presentation of happy facial expressions (see Figures 6.1 - 6.4 for simple main effect analyses). These effects remained significant after including BDI or STAI scores as covariates (all $p<0.01$).

Linear Trend for Increasing Intensity of Fear or Happy: Between-group Differences

For fearful expressions, high N subjects demonstrated a significant positive linear trend in right fusiform (Figure 6.5. BA 19, MNI: 26, -66, -14, Z=3.48) and left middle temporal gyri (Figure 6.6. BA21, MNI: -56, -32, 0, z=3.51) relative to low N subjects. Further analyses of percent BOLD signal change confirmed a significant group-by-intensity interaction in both fusiform gyrus ($F (2, 46) = 14.155$, $p<0.001$) and middle temporal gyrus ($F (2, 46) =18.736$, $p<0.001$), which remained significant after including mood scores (BDI, STAI) as covariates (all p's ≤ 0.001). In right fusiform gyrus, high N subjects showed greater activation for increasing fearful intensity whereas low N subjects showed the opposite effect (Figure 5). *Post hoc* t-tests revealed greater activation in high N subjects for the high intensity of fear

(p=0.006) and a marginal reduction in activation for low intensities of fear (p=0.060). A similar pattern was found in middle temporal gyrus (Figure 6), in which high N had greater activation for high intensity (p<0.001) and reduced activation for low intensity (p=0.001) fearful facial expressions. By contrast, there was no between-group difference in terms of linear trends for happy expressions.

ROI analysis for amygdala

Amygdala volumes were not significantly affected by group (Right: high N 1907 ± 282 vs. low N 1843 ± 353; Left: high N 1856 ± 198 vs. low N 1738 ± 428; main effect of group: F(1,23)=0.563, p=0.461; group x hemisphere: F(1,23)=0.261, p=0.614), allowing functional responses to be examined in the absence of potentially confounding structural differences. In the right amygdala there was a non-significant trend for an emotion x intensity x group interaction (p=0.092). Due to a strong *a priori* hypothesis regarding the effects on ambiguous facial expressions, two-way ANOVAs were run for each intensity level. These revealed a significant group x valence interaction for medium intensity (i.e. fear M vs. happy M; p=0.024). This interaction was driven by high N having greater amygdala activation for medium fearful expression relative to the low N group (p=0.029; see Figure 6.7). By contrast, there was no significant effect in left amygdala.

A functional connectivity analysis was carried out to assess whether the enhanced fusiform response to fear in our high N group was driven by the amygdala responses. Time series were extracted from the right amygdala and fusiform gyrus for each subject during the processing of high intensity of fear. Correlation analysis revealed significant interaction between the two areas across the whole sample (r=0.2, p<.001), which was largely driven by the high N group (r=0.2, p<.001) and absent in

the low N group (r=0.09, p=0.1). Thus, these results suggest that high N is associated with an increased coupling of this circuit in response to high threat stimuli.

Figure 6.1: The image and BOLD percent signal change of cerebellum, in which high N volunteers (black) showed greater activation for fearful vs. happy faces at medium intensity than low N volunteers (white). Colour bar represents Z score between 2.0 and 3.9. Asterisks (*) represent significant group comparisons $p<0.05$.

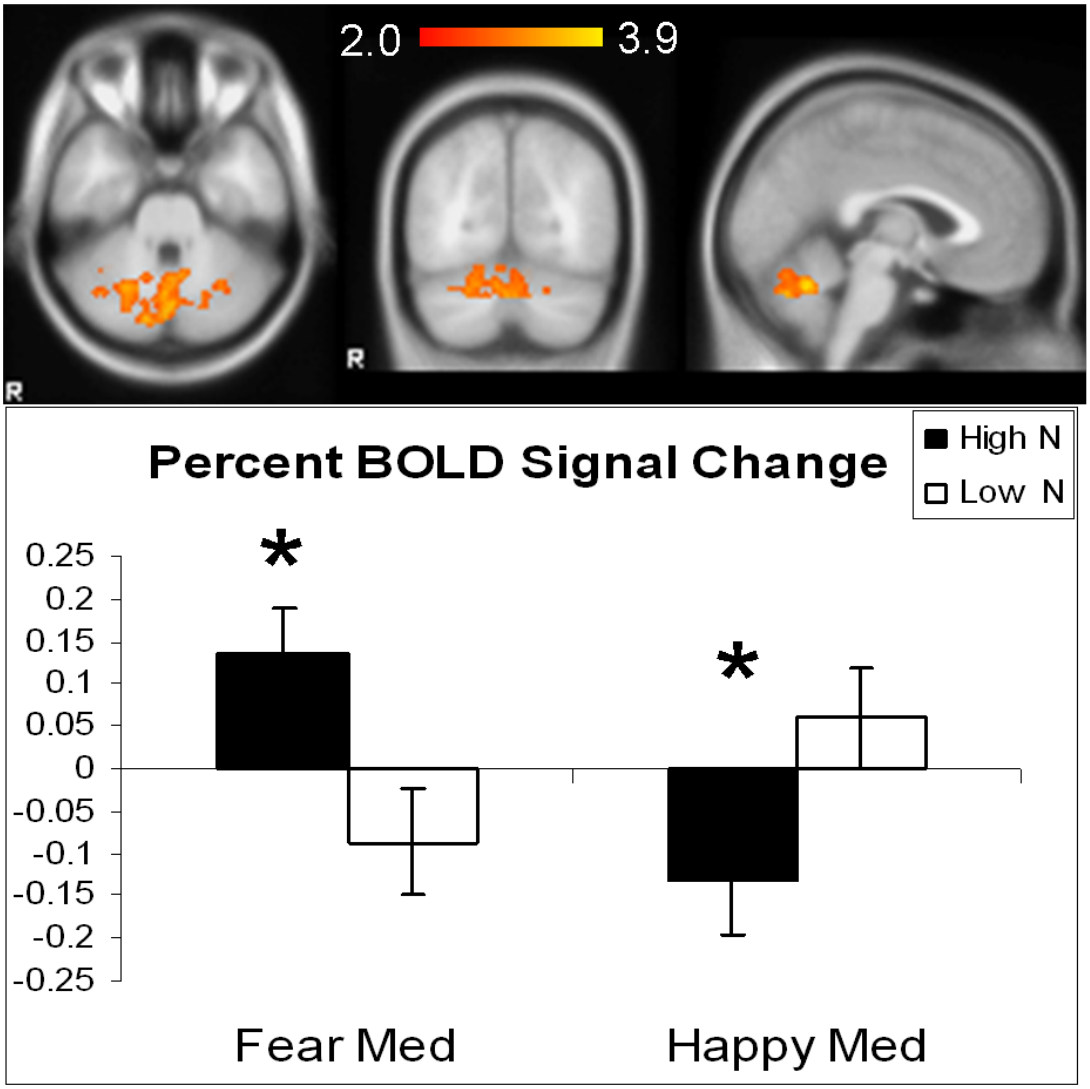


Figure 6.2: The image and BOLD percent signal change of left middle frontal gyrus, in which high N volunteers (black) showed greater activation for fearful vs. happy faces at medium intensity than low N volunteers (white). Colour bar represents Z score between 2.0 and 3.9. Asterisks (*) represent significant group comparisons $p<0.05$.

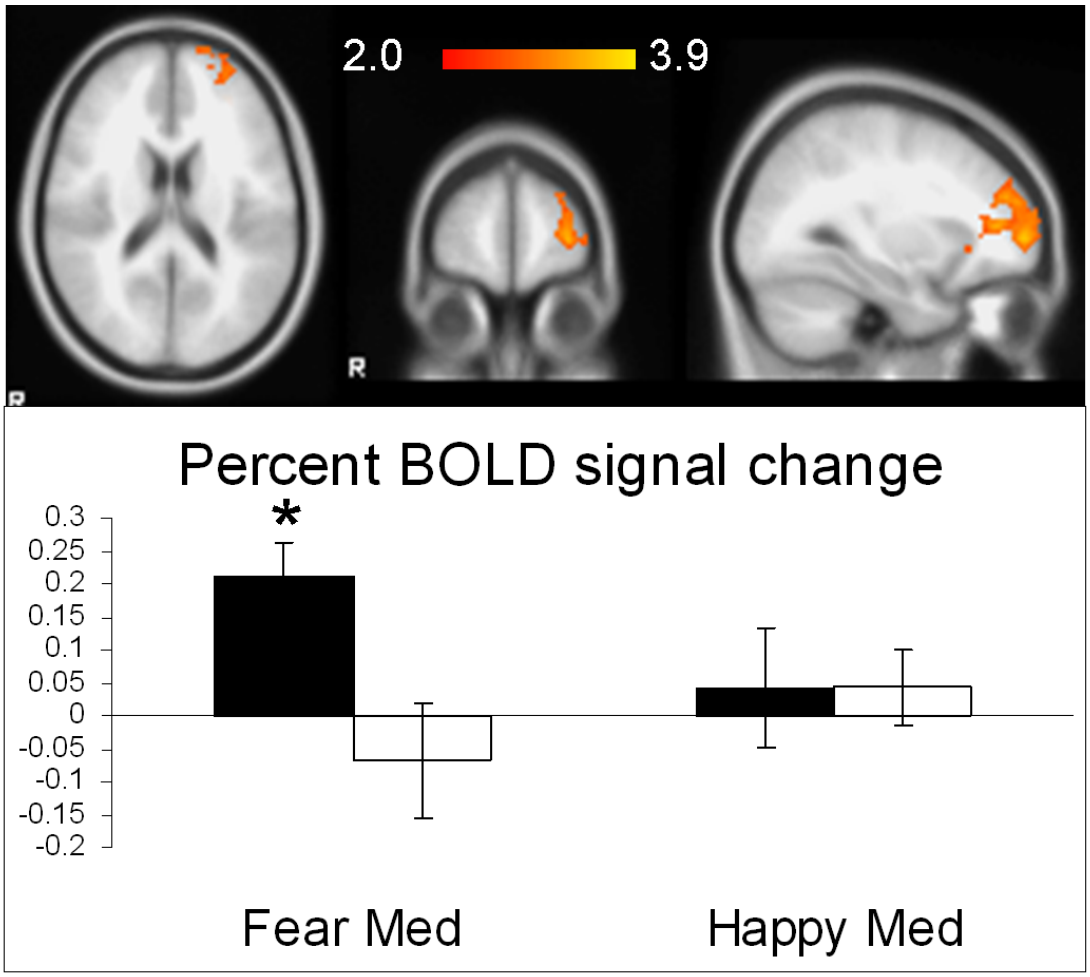


Figure 6.3: The image and BOLD percent signal change of left superior parietal cortex, in which high N volunteers (black) showed greater activation for fearful vs. happy faces at medium intensity than low N volunteers (white). Colour bar represents Z score between 2.0 and 3.9.

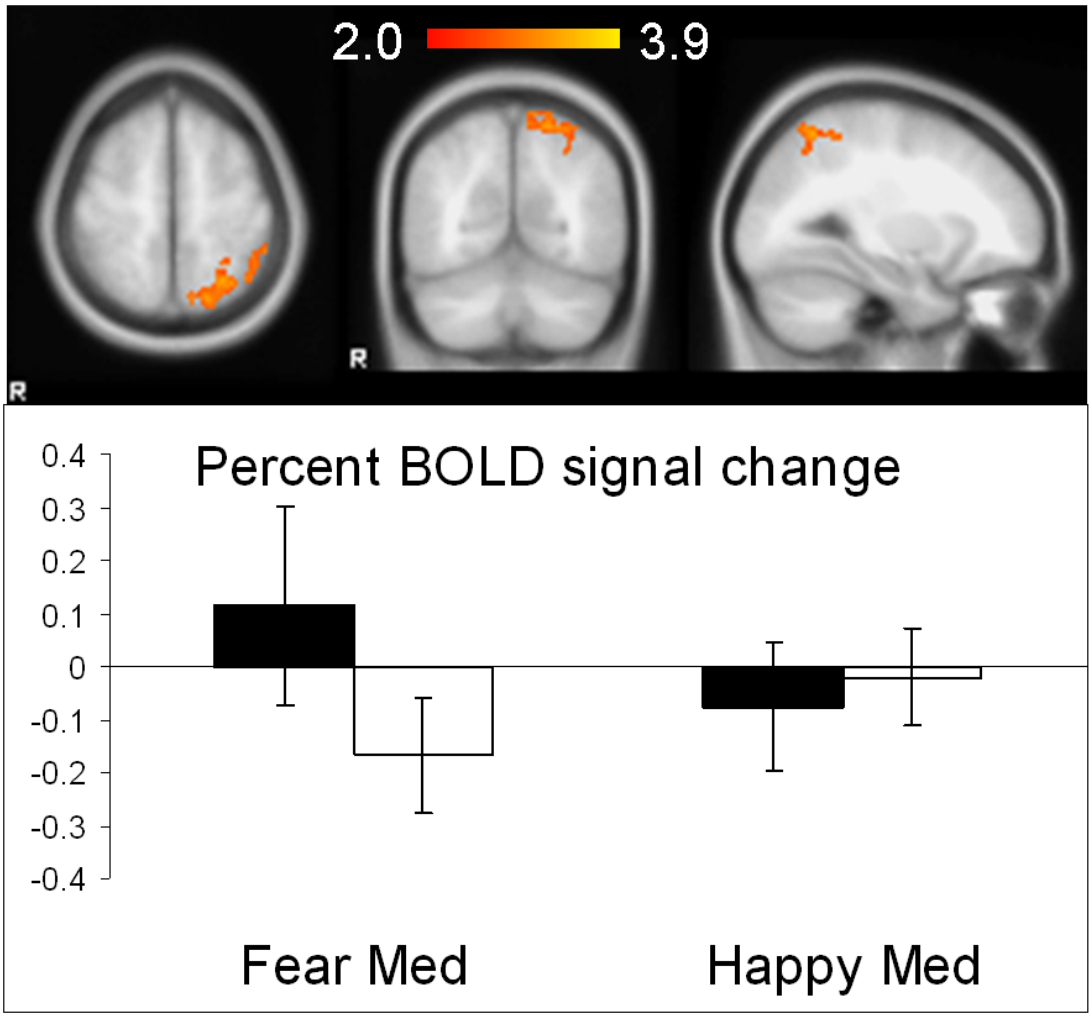


Figure 6.4: The image and BOLD percent signal change of right superior parietal cortex, in which high N volunteers (black) showed greater activation for fearful vs. happy faces at medium intensity than low N volunteers (white). Colour bar represents Z score between 2.0 and 3.9.

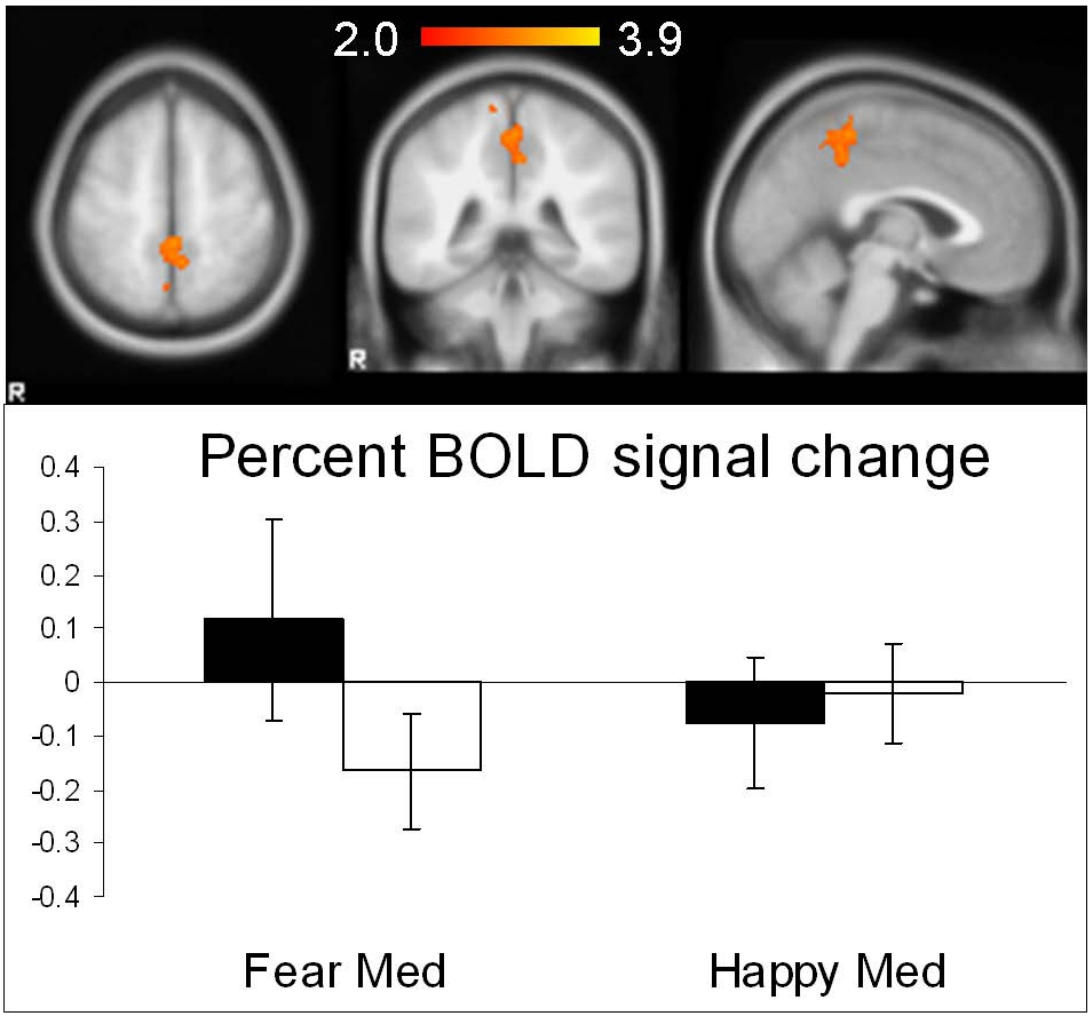


Figure 6.5: The image and BOLD signal change of right fusiform gyrus (MNI: 26, -66, -14), in which high N volunteers (black) showed increased signals for increasing intensity of fearful expressions whereas low N (white) showed the reversed pattern. Colour bar represents Z score between 2.0 and 3.5. Asterisks represent significant group comparison $p<0.05$.

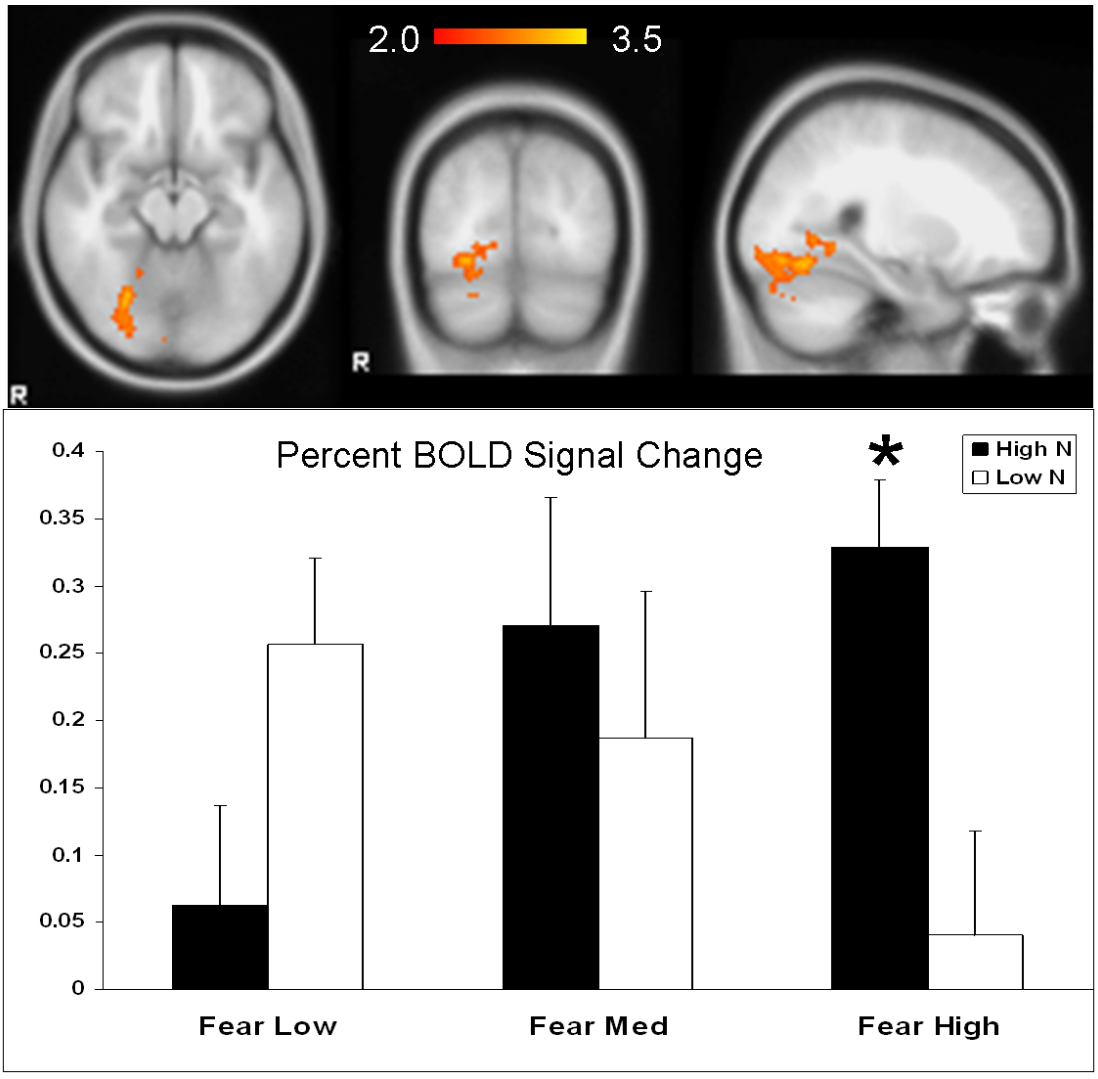


Figure 6.6: The image and BOLD signal change of left middle temporal gyrus (MNI: -56, -32, 0), in which high N volunteers (black) showed increased signals for increasing intensity of fearful expressions whereas low N (white) showed the reversed pattern. Colour bar represents Z score between 2.0 and 3.5. Asterisks represent significant group comparison $p<0.05$.

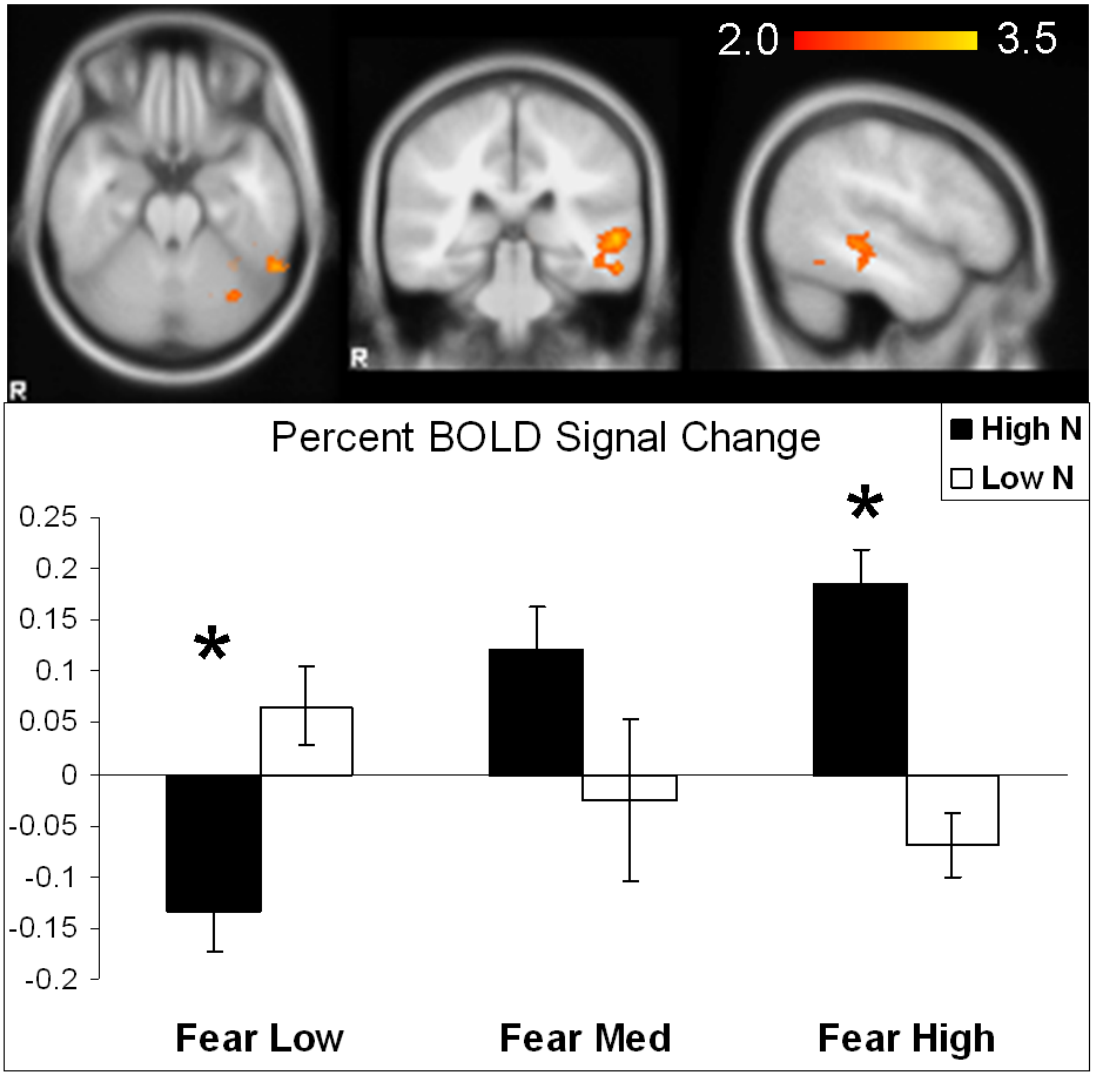
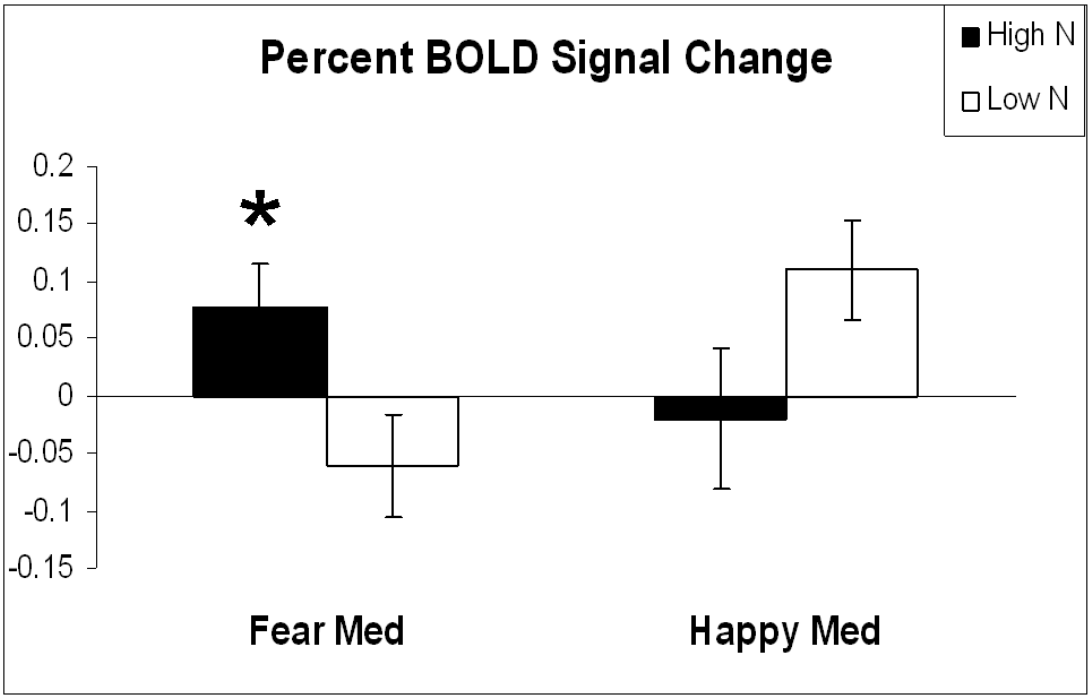


Figure 6.7: Percent BOLD signal change in right amygdala for fearful and happy expressions at medium intensity by high N (black) and low N (white) volunteers. Asterisks represent group comparison $p<0.05$.



6.4 DISCUSSION

The current study illustrates a neural basis for negative biases in emotional facial processing in subjects at high risk for depression by virtue of increased neuroticism. Our high N never-depressed volunteers exhibited a linear increase in neural signals in right fusiform gyrus and left middle temporal gyrus for increasing intensity of fearful expressions, whereas the low N volunteers showed the opposite effect. Analysis of the time series during fearful face presentation suggested that the enhanced fusiform response may be mediated, at least in part, via increased drive from the amygdala. Furthermore, high N volunteers showed a larger response in right amygdala, cerebellum, left middle frontal gyrus, and bilateral superior parietal cortex during the presentation of ambiguous medium levels of fearful vs. happy expressions. These areas have been implicated in facial expression processing and depression in previous studies, therefore we believe that these aberrant neural processes play a crucial role in both the aetiology and maintenance of depression.

A key role for both the amygdala and the fusiform gyrus has been proposed previously from studies of processing bias in currently depressed individuals compared with controls (Sheline et al 2001, Fu et al 2004, Vuilleumier et al 2006, 2007, Surguladze et al 2004, 2005) and a similar pattern of effects was seen here as a function of neuroticism. Thus, the increased signal shown by high N volunteers for increasing intensity of fear in the right fusiform gyrus and heightened amygdala responses to ambiguous fearful facial expressions is the same as for depressed patients (Surguladze et al 2004; Sheline et al 2001). Specifically, the fusiform gyrus has been suggested to be modulated by the level of facial expression processing through explicit orienting and / or automatic capturing of attention (Vuilleumier et al., 2006, 2007) and its response to emotional information is modulated, in part, via back-

projections from the amygdala .In line with this, our functional connectivity analysis suggested increased coupling between these two regions in the high N volunteers. Such findings support the idea that amygdala-extrastriate responses may be biased towards negative emotional information even before the onset of depression and could play a role in vulnerability to this disorder. These results are also consistent with recent evidence which suggests that amygdala responses to emotional information correlates with neuroticism score in unselected populations (Stein et al 2007, Baas et al 2007).

It is notable that while high N volunteers showed the expected increase in fusiform response as a function of increasing fear value, the low N volunteers showed the opposite pattern. This implies decreased visual processing with increasing threat in volunteers at low risk of developing depression. Such a pattern of effects could be explained by differential evaluation of threat value in high vs. low N volunteers, according to the curvilinear response function of the cognitive motivational account (Mogg and Bradley 1998). This theory suggests that low threat stimuli may be avoided in order to reduce distraction and high threat stimuli are monitored for potential importance. The observed pattern of results would be expected if low N volunteers estimated the face stimuli as having a lower threat value, leading to the high intensity fear faces being 'avoided' in the low N but not high N group.

In addition to the effects on the fusiform gyrus and amygdala, our results implicate a network of brain areas that are involved in facial processing and vulnerability to depression. First, the middle temporal gyrus revealed differential responses for fearful expressions in high and low N volunteers similar to the fusiform gyrus. The temporal gyrus is within the core system of face perception (e.g. Bruce and Young 1986, Haxby et al 2000, 2002) and the increased responses seen here in high N

volunteers also appears be consistent with greater processing of threat relevant facial stimuli in this group.

The medium intensity of fear versus happy expressions revealed group differences in the cerebellum, left middle frontal gyrus, and bilateral parietal cortex. Indeed, such a frontoparietal network plays a central role in concept of self, perception of social relationships and attention (Uddin et al 2005, Feinburg 2001, Decety and Sommerville 2003, Carr et al 2003, Farrer and Frith 2002, Iacoboni et al 2004). Activation in the superior parietal region has also been found in the same high N sample during processing of negative self-referent words (Chapter Five). Thus, the specific activations for fearful expressions in these regions by high N individuals could be explained by their greater tendency to view negative expressions as self-relevant or self-threatening and requiring activation of attentional systems. In line with this, the reduced activation for happy expressions may reflect their inclination to disregard positive social information as self-referent and deserving of further attention. In other words, these individuals are more likely to interpret negative social signals to be personally relevant or threatening, but at the same time unable to translate positive social signals for a positive self image. This interpretation is consistent with the self-referent and facial expression processing biases previously observed in our behavioural study of a similar high N sample (Chapter Two).

The current study demonstrated differential responses to emotional cues in the high N group in the absence of current or past history of Axis 1 psychiatric disorders from DSM-IV, thereby proving that these biases precede mood or anxiety disorder. Analyses including mood scores as covariates further confirmed that the current effects were a function of neuroticism *per se* independent of mood state. The study

implicates the networks underlying the attentional mechanism involved in social communication, which appear to underlie vulnerability to depression defined by N.

The current results also highlighted the effectiveness of using emotional stimuli with varying intensity. Notably, the differential responses for positive vs. negative expressions shown here were seen largely with the medium intensity level of facial expression. This probably represents maximal ambiguity which is particularly relevant for problematic social interaction and, experimentally, for differentiating group differences. The current findings were also obtained from direct contrast between positive and negative emotional stimuli, which avoided potential confounds linked to the interpretation of neutral stimuli.

Overall, this study suggests that risk for depression is associated with exaggerated neural responses to fearful expressions of emotion and, to a lesser extent, reduced neural responses to happy expressions. By contrast, our behavioural study on a similar high N vs. low N sample found a decrease in the recognition of happy facial expressions in the absence of differences in the threshold for perception of fear (Chapter Two). Possibly, the neural bias observed here is an early abnormality that has yet to be fully translated to behaviour, or is masked by compensatory strategies while the individuals are not depressed. In other words, the neural bias towards negative stimuli does not appear to be simply translated into a behavioural bias to detect negative expressions more easily. Future studies are required to clarify this complex interaction between neural mechanisms and behavioural biases.

In summary, in support of our hypothesis, our results illuminate a role for fusiform gyrus and amygdala in facial expression processing biases in volunteers at high risk for the development of major depression. In addition, a number of parietal and frontal areas were engaged suggesting a distributed neural network. These areas

overlap with those thought to be important in depression and the effects of antidepressants (Sheline et al 2001, Fu et al 2004, 2007, Harmer et al 2006). The current findings show that neurocognitive abnormalities in facial expression processing are apparent even in high risk individuals who have never suffered or been treated for depression.

CHAPTER SEVEN

LONGITUDINAL STUDIES

7.1 SIX MONTH LONGITUDINAL STUDY

In previous Chapters, high N volunteers were found to have negative biases in information processing across a wide range of tasks including self-referent word processing, facial expression recognition and emotion-potentiated startle response (Chapter Two); but had intact global cognitive functions of memory and learning, problem solving, autobiographical memory and biological response to stress indicated by morning salivary cortisol level (Chapters Three and Four). The preceding chapters further illustrated the neural substrates of the cognitive biases in self-referent processing (Chapter Five) and facial expression processing (Chapter Six), supporting our main hypothesis that negative biases in emotional processing are vulnerability markers of depression that occur at an early stage preceding illness onset. Finally, two longitudinal studies were carried out to assess whether, and to what extent, these negative biases in information processing found in high N group predict subsequent depression in these vulnerable individuals.

The first longitudinal assessment took place six months following the first test battery. It consisted of a short interview and the key self-rated mood questionnaires. The 'cognitive vulnerability hypothesis' of the cognitive theories (Beck et al 1967, 1979; Abramson et al 1989) suggests that individuals who exhibit particular maladaptive thinking patterns are at increased risk for depression when they experience negative life events. Based on these theories and previous research that predicted depression by cognitive risk factors (e.g. Alloy et al 2006), we hypothesized

that the emotional processing biases revealed by the first battery (T1) would predict subsequent depression in high N individuals in six months (T2).

7.2 METHODS

7.2.1 Subjects

Fifty-seven volunteers of the original sample (27 high N, 28 low N) gave written informed consent to take part in this study and received payment for their participation. The high N and low N groups were matched with age (19.44 ± 1.12 vs. 19.50 ± 0.79) and gender (18 F vs. 17 F). As expected, high N group had significantly higher N scores than did low N (shortened 12-item N scale: 9.52 ± 1.16 vs. 1.29 ± 1.05, $p<0.001$).

7.2.2 Measures

Participants were interviewed with the Structured Clinical Interview for DSM-IV (SCID) and the Hamilton Depression Rating Scale (HAM-D: Hamilton 1967). They also completed self-rated questionnaires of Beck Depression Inventory (BDI: Beck et al. 1961) and State-Trait Anxiety Inventory (STAI: Spielberger et al. 1970). The clinical interview suggested that only one subject (from high N group) developed depressive symptoms that met DSM-IV criteria of a depressive episode. Therefore, the following analyses used HAM-D and BDI scores as outcome variables of low mood

7.3 RESULTS

7.3.1 Mood Change over Time

Table 7.1 summarizes the mood scores of high N and low N volunteers at T1 and T2. To examine whether the two groups had mood change over time, a 2x2 ANOVA was carried out for all mood scores with between-Ss variable as group (high N vs. low N) and within-Ss variable as time (T1 vs. T2). Results indicated a significant group difference for all mood variables, such that high N has higher depressed and anxiety mood scores averaged across both times [HAM-D: $F(1,53)=15.81$; BDI: $F(1,53)=20.26$; State Anxiety: $F(1,53)=25.29$; Trait Anxiety: $F(1,53)=43.42$; all p's < 0.01]. Furthermore, there was a significant time effect for Trait Anxiety ($F(1,53)=5.95$, $p=0.02$) and BDI ($F(1,53)=5.58$, $p=0.02$), such that these mood ratings reduced over time across the entire sample. By contrast, there was no time x group interaction for any mood variable (all p's > 0.20), suggesting that the two groups did not have differential mood change over time.

7.3.2 Correlations

To obtain an initial idea of which measures best predict low mood in the vulnerable volunteers, correlations were analysed between T1 performance of each emotional processing task (key variables) and T2 depression and anxiety (HAM-D, BDI, State Anxiety) within the high N group. The correlation coefficients are presented in Table 7.2.

Results suggested that T1 rumination was positively correlated with T2 depression as measured by HAM-D and BDI, whereas T1 DAS was correlated with T2 State Anxiety. For T1 self-referent processing tasks, the reaction time for

categorising positive vs. negative words was positively correlated with T2 BDI and State Anxiety, suggesting that faster speed for negative words (vs. positive words) was associated with subsequent depression and anxiety.

For facial expression recognition task, the threshold for the perception of disgust was positively correlated with HAM-D, BDI, and State Anxiety, suggesting that high N individuals who required higher intensity to recognise disgust at T1 (i.e. reduced perception of these expressions) reported more depression and anxiety at T2. Similarly, threshold for sad expressions was positively correlated with HAM-D, suggesting that reduced perception for sad expressions was also associated with subsequent increase in depressed mood.

For the dotprobe task there was no correlation between T1 attentional bias and T2 mood in either the masked or unmasked condition. Similarly, performance in emotion-potentiated startle assessed at T1 did not have significant correlations with T2 depression or anxiety scores.

7.3.3 Multiple Regressions

The above correlations have identified four cognitive tasks related to T2 depression and / or anxiety mood: Rumination, DAS, Self-referent categorisation (RT positive vs. negative), and Facial Expression Recognition (Threshold for Disgust and Sadness). To further examine whether performances on these cognitive tasks predict T2 mood, hierarchical multiple regressions were run with each of the key mood scores (HAM-D, BDI or State Anxiety) as the outcome variables. Mood measured at T1 was first entered into the model to control for pre-existing depression or anxiety. Assumptions for multiple regressions were checked, including multicollinearity (using variance inflation factor), homoscedasticity (Levene's Test), Independence of errors

(Durbin-Watson Test) and normally distributed errors. Specifically, BDI scores at T2 were regressed first onto T1 BDI scores to control for pre-existing level of depression. The cognitive predictors were then added to the model by a 'stepwise' method. As expected, T1 BDI significantly predicted T2 BDI (β=.53, $p<.01$), accounting for 28% of the total variance in T2 BDI. The addition of T1 self-referent categorisation and rumination together accounted for an additional 25% of the total variance of T2 BDI. Thus, the best fit model accounted for 53% of the total variance. See Table 7.3.

Similarly, T2 HAM-D was regressed first into T1 HAM-D, followed by the cognitive predictors. T1 HAM-D only accounted for 10% of the total variance in T2 HAM-D in the initial model. However, the model significantly improved after including Rumination and Threshold for Sad Faces. This final best-fit model accounted for 48% of the total variance. See Table 7.4.

By contrast, T2 state anxiety was best predicted by T1 state anxiety. Results from multiple regressions suggested that T1 state anxiety alone accounted for 41% of the total variance in T2 state anxiety, and that none of the cognitive predictors significantly improved the predictability of the model. Thus, the best-fit model was consisted of the baseline State Anxiety alone. See Table 7.5.

In each of the above regression models, T3 mood scores (i.e. BDI, HAM, State Anxiety) were first regressed into T1 scores of the same measure to control for the effect of preexisting mood. This approach in part allows attribution of effects to the trait phenomena; however, the current results were potentially confounded by group differences in other state measures of mood. This could be statistically tested by including all baseline state measures in all regression models, which, however, were not performed here due to the relatively small sample.

Table7.2: Depression and Anxiety Mood Scores of High N and Low N volunteers at T1 and T2. Values represent group mean (standard deviation).

		High N	Low N
HAM-D	T1	3.56 (3.51)	1.36 (2.50)
	T2	3.85 (4.11)	0.61 (1.42)
BDI	T1	7.26 (5.19)	2.75 (2.80)
	T2	5.93 (4.91)	1.71 (2.68)
State Anxiety	T1	37.41 (10.37)	27.75 (6.60)
	T2	38.37 (11.12)	26.39 (8.23)
Trait Anxiety	T1	46.48 (12.64)	29.29 (5.10)
	T2	43.63 (12.54)	28.18 (5.96)

Table7.3: Correlation between T1 Cognitive Bias and T2 Mood Scores within the High N group. Values represent correlation coefficients. Asterisks represent statistical significance **p ≤ 0.01, *p ≤ 0.05 (two tails).

	HAM-D	BDI	State Anxiety
Rumination	0.50**	0.45*	0.34
DAS	0.20	0.25	0.41*
Self-referent Word Categorisation			
RT pos-neg	0.11	0.51**	0.46*
Acc pos-neg	-0.14	-0.06	-0.02
Self-referent Word Memory			
Recall Hit pos-neg	0.00	-0.14	-0.22
Recall FA pos-neg	-0.15	-0.17	-0.04
Recog Hit pos-neg	0.14	0.08	0.18
Recog FA pos-neg	-0.27	-0.15	-0.27
Facial Expression Recognition Task			
Threshold Anger	-0.07	-0.06	0.05
Threshold Disgust	0.38*	0.43*	0.45*
Threshold Fear	-0.01	-0.24	0.02
Threshold Happy	0.15	0.05	0.20
Threshold Sadness	0.48*	0.11	-0.04
Threshold Surprise	0.16	0.04	0.37
Dotprobe Task			

Mask RT pos-neg	0.14	0.11	0.00
Unmask RT pos-neg	-0.20	-0.26	-0.18
Emotion-potentiated Startle			
Peak Size pos-neg	-0.16	-0.10	0.15
Latency pos-neg	-0.09	-0.08	-0.05

Footnote: DAS= Dysfunctional Attitude Scale; RT = reaction time; Acc = accuracy, Hit = correct recall / recognition; FA = false alarm; Recog = recognition; Pos - Neg = positive minus negative; and in dotprobe task, RT refers to vigilance score.

Table7.4: Multiple Regression Models Predicting T2 BDI within the High N Group. Asterisks represent statistical significance ****p ≤ 0.01, *p ≤ 0.05**

	b	SE b	β	p
Model 1				
Constant	2.27	1.42		
BDI 1	0.50	0.16	.53 **	.004
Model 2				
Constant	2.50	1.29		
BDI 1	0.41	0.15	.44 **	.011
EW pos-neg	0.02	0.01	.40 *	.018
Model 3				
Constant	-5.61	3.94		
BDI 1	0.28	0.15	.30	.073
EW pos-neg	0.02	0.01	.43 **	.008
RUM	0.17	0.08	.34 *	.041

Note: $R^2 = .28$ for Step 1; $\triangle R^2 = .15$ for Step 2; $\triangle R^2 = .10$ for Step 3

Table7.5: Multiple Regression Models Predicting T2 HAM-D within the High N Group. Asterisks represent statistical significance ****p ≤ 0.01, *p ≤ 0.05**

	b	SE b	β	p
Model 1				
Constant	2.56	1.10		
HAM 1	0.36	0.22	.31	.12
Model 2				
Constant	-7.38	3.90		
HAM 1	0.27	0.20	.23	.20
RUM	0.20	0.08	.46 **	.01
Model 3				
Constant	-11.96	3.80		
HAM 1	0.17	0.18	.14	.37
RUM	0.20	0.07	.45 **	.01
Thres. Sad	0.07	0.03	.43 **	.01

R^2 = .10 for Step 1; △ R^2 = .20 for Step 2; △ R^2 = .18 for Step 3

Table7.6: Multiple Regression Models Predicting T2 State Anxiety within the High N Group. Asterisks represent statistical significance *** p<.001.

	b	SE b	β	p
Model 1				
Constant	12.59	6.37		
STATE 1	0.69	0.16	.64 ***	.000

R^2 = .41 for Step 1.

7.4 DISCUSSION

In this longitudinal study, results indicated that depressed mood amongst high N volunteers was significantly predicted by both questionnaire ratings and cognitive test performance measured six months before. Specifically, rumination, self-referent word categorisation (increased speed for categorising negative vs. positive self-referent words) and facial expression recognition (reduced perception for expressions of sadness and disgust) were found to be highly correlated with subsequent depression, whereas dysfunctional attitudes were correlated with subsequent anxiety. Multiple regressions further illustrated that rumination, self-referent processing biases and reduced perception of sad facial expressions predicted depression in six months even after controlling for the preexisting low mood. The best fit models explained up to about 50% of depression mood ratings in this six month follow-up (BDI: 53%; HAM-D: 48%). By contrast, baseline state anxiety alone accounted for 41% of the variance in subsequent anxiety scores, and this regression model did not improve by addition of any cognitive variables.

Overall, our results are consistent with the 'cognitive vulnerability hypothesis' developed from the cognitive theories of depression (Beck et al 1967, 1979; Abramson et al 1989). According to these theories, individuals who have maladaptive cognitive style are at higher risk for depression as they are more likely to appraise life events negatively. In support of this, the current study found that high risk volunteers by virtue of high neuroticism exhibit negative biases in information processing, and specifically, bias in processing self-referent words, reduced facial expression recognition and rumination predicted subsequent dysphoric mood in six months even after controlling for preexisting low mood.

That high neuroticism is associated with increased rumination has been implicated in Chapter Two. This longitudinal study illustrated directly that increased rumination elevated future psychological distress. Indeed, rumination has been found to prolong durations of depressive episodes, as rumination allows the depressed mood to negatively bias thinking and interferes with instrumental behaviour and problem solving (Nolen-Hoeksema 1991). Rumination has also been shown to predict suicidal ideation at one-year follow-up in a community sample, and this prediction was partially mediated by symptoms of depression (Miranda and Nolen-Hoeksema 2007). Consistent with this, rumination was found to be correlated with daily depressed mood (Hankin et al 2005) although in this study rumination was excluded from the regression models presumably due to substantial overlapping with neuroticism. The present study indeed found a strong association between neuroticism and rumination. Through investigation within the high N group alone, we established the prediction of depressed mood by rumination.

Similarly, increased processing of negative self-referent words was found to predict future depression. This suggested that negative biases in processing self-referent information are part of the vulnerability risk factors for depression. As noted in Chapter One, self-referent processing bias has been established as a well known characteristic of depression, and is believed to play an important role in maintaining depressive symptoms such as negative self and excessive guilt. Our current result strongly suggested that that this emotional processing bias occurs at an early stage in high risk individuals even before the development of full clinical depressive symptoms. However, it is also noteworthy that many of the other measures of negative bias were not significantly associated with depressed mood in this follow-up. This is therefore examined in more detail in the subsequent section.

Facial expression recognition task was another predictor identified in this study, although this appeared to represent difficulties in identification of others' emotional states rather than a negative bias *per se*. Specifically, reduced perception for sadness was found to predict subsequent increase in depressed mood. Similarly, reduced perception for disgusted expressions was found to correlate with subsequent depressed mood and anxiety although it did not survive correction for preexisting mood ratings. Hence it may be that deficits in social function are more important in risk for episodes of low mood than negative biases in interpretation. This is explored in more detail in the subsequent section.

The current study primarily investigated cognitive predictors for onset of depression in vulnerable young adults. Although no participant developed full-blown clinical depression in this six month follow-up, statistical regression models have yielded evidence for the prediction of dysphoric mood (assessed by HAM-D and BDI, both are instruments known to validly measure depression) by specific cognitive behaviour. The overall decrease in state anxiety and BDI over the entire sample was unexpected, but nonetheless made the prediction of depressed mood by specific cognitive behaviour more noteworthy. Finally, the study also yielded interesting findings regarding the aetiology of depression and anxiety. Results from the regression models appeared to suggest that risks for depression and anxiety involve both common and differential cognitive mechanisms. Though hypothesis-driving, the current study was not designed to categorise the differences between the risks for depression and anxiety. Further experiments are required to clarify whether, and to what extent, depression and anxiety arise from different vulnerability mechanisms.

In summary, this longitudinal study showed that a combination of preexisting depressed mood, rumination, and cognitive biases in self-referent categorisation and

facial expression recognition significantly predicts depressed mood up to 6 months. However, this study has not fully tested the 'cognitive vulnerability hypothesis' in that stressful life events were not measured. The low incidence of full-blown clinical depression amongst high N individuals might be due to low exposure to stressful life events. In other words, the cognitive vulnerability, as represented by negative biases in information processing in this study, had not been triggered by adverse life events. Thus, the effects of stressful life events on risk for depression will be explored in the next longitudinal study. Specifically, the next sections will examine whether, and to what extent, the emotional processing biases implicated in the first battery would interact with stressful life events in predicting depression in 18 months.

7.5 EIGHTEEN MONTH LONGITUDINAL STUDY

This final follow-up study (T3) took place eighteen months following the first battery (T1). This study aimed to measure any mood changes over the last 18 months. Similar to the last longitudinal study, we hypothesised that the emotional processing biases revealed in first battery would predict subsequent symptoms of depression. Specifically, based on previous findings of the effects of stressful life events on depression (Kessler 1997, Kendler et al 1999) and the 'cognitive vulnerability hypothesis' developed from cognitive theories (Beck et al 1967, 1979; Abramson et al 1989), we hypothesised that depression would be best predicted by an interaction between preexisting cognitive biases (Time 1) and the occurrence of stressful life events between Times 1 and 3. Furthermore, to explore whether the high risk and low risk groups have differential changes in cognitive and biological functions, the tasks of Facial Expression Recognition, Auditory Verbal Learning Test and the waking salivary cortisol were repeated in this study.

7.6 METHODS

7.6.1 Subjects

Thirty-eight volunteers (18 high N, 20 low N) gave informed consent to take part in this study and received payment for their participation. The high N and low N groups had similar age (20.50 ± 1.34 vs. 20.65 ± 0.88) and gender ratio (13 F vs. 12 F); and, as expected, the high N group had significantly higher N scores than did the low N group (shortened 12-item N scale: 9.61 ± 1.20 vs. 1.30 ± 1.03, $p<0.001$).

7.6.2 Measures

Participants were interviewed with SCID and HAM-D and completed self-rated mood questionnaires of BDI and STAI, as well as other questionnaires measuring rumination (RUM), dysfunctional attitudes (DAS), and stressful life events. Facial Expression Recognition Task and the Auditory Verbal Learning Task (AVLT) were used to measure emotional processing and global executive functions respectively. Finally, participants were given instructions and equipments to collect 5 salivary samples within the first hour of waking on the following morning. Details of these tasks and questionnaires have been noted in earlier chapters (Chapter Two for all questionnaires and Facial Expression Recognition Task; Chapter Three for AVLT; and Chapter Four for salivary cortisol).

No volunteer reported experiences of depressive episodes during the time between T1 and T3, but one high N volunteer received a diagnosis of obsessive-compulsive disorder. Due to the absence of clinical depression in the sample, similar to the T2 follow-up study, the following analyses will employ HAM-D and BDI scores as the main outcome variable of depression. In addition, the two groups did not

differ in terms of the number of stressful life events experienced between T1 and T3 (high N: 0.61 ± 0.85; low N: 0.70 ± 1.17; p=.79 ns).

7.7 RESULTS

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7.7.1 Mood Change over Time

Table 7.6 summarizes the mood scores at T1 and T3 of high N and low N volunteers. To examine whether the two groups have mood changes over time, a 2x2 ANOVA was carried out for all mood scores with between-Ss variable as group (high N vs. low N) and within-Ss variable as time (T1 vs. T3). Results indicated a significant group difference in nearly all mood variables, such that high N has higher depressed and anxiety mood averaged across both times [HAM-D: $F(1,36)=8.82$ $p<0.01$; BDI: $F(1,36)=7.90$ $p<0.01$; State Anxiety: $F(1,36)=11.22$ $p<0.01$; Trait Anxiety: $F(1,36)=25.59$; $p < 0.001$]. Furthermore, there was a significant time effect for BDI ($F(1,36)=4.31$, $p=0.05$), such that depressed mood reduced over time across the entire sample. However, there was no time x group interaction for any mood variable (all p's > 0.07), suggesting that the two groups did not have differential mood change over time.

7.7.2 Cognitive and Biological Change over Time

To examine whether the participants' cognitive and biological functions changed over time, ANOVAs were carried out for RUM, DAS, AVLT and Cortisol, with between-Ss variable as group (high N vs. low N) and within-Ss variable as time (T1 vs. T3). For Facial Expression Recognition Task, 'valence' was included as an additional within-Ss variable.

ANOVA for RUM suggested a main effect of group and time, such that high N had more ruminations than low N ($F(1,36)=12.18$, $p=0.001$) and that the overall rumination of the whole sample decreased over time ($F(1,36)=11.21$, $p=0.002$).

However, there was no group x time interaction (p=0.26). For DAS, there was a group effect such that high N had more dysfunctional attitudes than low N ($F(1,36)=30.15$, $p=0.000$), but there was no group x time interaction or time effect (both p's ≥ 0.20). See Table 7.7.

For AVLT, performance for the immediate recalls of the whole sample improved from T1 to T3 (Time Effect: $F(1,36)=10.54$, $p=0.003$) suggesting a modest practice effect, but there was no group x time interaction (p=0.09) or group effect (p=0.75). There was no main effect or interaction for the delayed recalls and recognition (all p's ≥ 0.16). See Table 7.7.

For the Facial Expression Recognition Task, accuracy was defined by the threshold, i.e. the intensity level at which the participant gives 3 or more (i.e. ≥75%) correct responses across three consecutive intensity levels (same as in Chapter Two, refer to Section 2.2.5). ANOVA results suggested a significant main effect of time ($F(1,36)=4.77$, $p=0.04$), valence ($F(5,180)=9.70$, $p<0.001$), and group ($F(1,36)=3.64$, $p=0.07$). These data suggested an overall lower threshold (i.e. higher accuracy) in high N volunteers, and that the overall threshold reduced over time across all volunteers, possibly due to a practice effect. However, there were no two-way or three-way interactions (all p's ≥ 0.21). See Figure 7.1.

In terms of salivary cortisol, five volunteers did not give sufficient salivary samples at T3 for analysis of cortisol. ANOVA for the Area-Under-Curve revealed no group x time interaction or group effect (both p's ≥ 0.70). However, there was a significant time effect such that the overall cortisol level reduced from T1 to T3 ($F(1,28)=27.83$, $p=0.000$). See Figure 7.2.

7.7.3 Correlations

Correlations were analysed between T1 cognitive tasks performance and T3 depression and anxiety mood (HAM-D, BDI, State Anxiety) within the high N group. The correlation coefficients are presented in Table 7.8.

For T1 self-referent processing tasks, the reaction time for categorising positive vs. negative words was positively correlated with T3 HAM-D, BDI and State Anxiety, suggesting that faster speed for negative words (vs. positive words) was associated with subsequent increase in depressed mood and anxiety. For facial expression recognition, the threshold for the perception of sadness was negatively correlated with T3 HAM-D, suggesting that individuals who required lower intensity to identify sadness (i.e. increased perception of sadness) reported more depression at T3. By contrast, dotprobe task, emotion-potentiated startle, self-referent word memory, DAS, and rumination measured at T1 had no significant correlations with T3 mood. In addition, stressful life events were positively correlated with depression and anxiety.

Due to a strong *a priori* hypothesis that cognitive bias would lead to depression and / or anxiety when triggered by stressful life events, interaction between each cognitive bias and stressful life events (e.g. Rumination x Stressful Life Events) was computed (after standardizing both scores). Correlations were run between these interaction variables and T3 mood. As summarised in Table 7.9, RUM, DAS, negative biases in self-referent processing, increased perception of sad expressions, and slower speed for startle response to positive vs. negative stimuli were significantly correlated with subsequent symptoms of depression and / or anxiety when interacting with stressful life events.

7.7.4 Multiple Regressions

Similar to the previous longitudinal assessment, hierarchical multiple regressions were used to predict T3 BDI, HAM-D, and State Anxiety from T1 cognitive bias, stressful life events and their interaction. The above correlation analyses have identified the potential predictors as 3 main factors and 5 interactions: (1) Self-referent Word Categorisation RT (2) Facial Expression Recognition Threshold for Sadness (3) Stressful Life Events (4) RUM x Life (5) DAS x Life (6) Self-referent Word RT x Life (7) Threshold for Sad x Life (8) Startle RT x Life. First, T3 mood was regressed onto T1 mood to control for pre-existing depression or anxiety. The three main factors were then entered into the model simultaneously by a 'stepwise' method. In the last block, the five interactions were entered into the model again by a 'stepwise' method. Appropriate tests have been performed to check that the assumptions involved in using multiple regressions are true (see section 7.3.3).

Results showed that T1 BDI significantly predicted T3 BDI (β=.60, $p<.01$), accounting for 36% of the total variance in T3 BDI. The final best-fit model consisted of four variables, including the baseline BDI, negative biases in self-referent word categorisation, stressful life events, and its interaction with the threshold for recognising sad facial expressions, accounting for up to 91% of the total variance. See Table 7.10. To create a graphical representation of the interaction of threshold for sad expressions x stressful life events, the sample was sub-divided into high vs. low threshold group (in recognising sad expressions) using a median split. As illustrated in Figure 7.3, depressed mood increased with increasing stressful life events, and this prediction was stronger within individuals with low threshold for recognising sad faces.

Multiple regression models for HAM-D revealed similarly high predictability of T3 depressed mood by cognitive biases. Unlike the case with BDI, T1 HAM-D did

not predict T3 HAM-D (β=-.003, p=.99 ns). However, the addition of Stressful Life Events, Threshold for recognising sad facial expressions, and the interaction of these two variables significantly improved the final model, which accounted for 87% of the total variance in T3 depressed mood measured by HAM-D. See Table 7.11. A graphical representation of the interaction of threshold for sad expressions x stressful life events similar to that with BDI results was created. As illustrated in Figure 7.4, depressed mood increased with increasing stressful life events, and this prediction was stronger within individuals with low threshold for recognising sad faces.

By contrast, similar to the previous follow-up study, T1 State Anxiety accounted for 27% of T4 State Anxiety, and none of the cognitive variables could improve the model significantly. See Table 7.12.

Finally, similarly to the previous longitudinal study, the current results were potentially confounded by group differences in other state measures of mood. This could be statistically tested by including all baseline state measures in all regression models, which, however, were not performed here due to the relatively small sample.

Table7.7: Depression and Anxiety Mood Scores of High N and Low N Volunteers at T1 and T3. Values represent group mean (standard deviation).

		High N	Low N
HAM-D	T1	2.67 (2.50)	0.60 (0.82)
	T3	2.17 (3.93)	0.70 (2.05)
BDI	T1	6.17 (5.04)	2.35 (2.16)
	T3	4.17 (5.65)	1.50 (2.95)
State Anxiety	T1	33.83 (7.51)	27.45 (7.06)
	T3	33.33 (10.09)	25.60 (6.44)
Trait Anxiety	T1	43.78 (13.09)	29.60 (5.34)
	T3	44.06 (10.33)	31.05 (7.39)

Table7.7: Cognitive Functions of High N and Low N Volunteers at T1 and T3.

Values represent group mean (standard deviation).

		High N	Low N
Rumination	T1	51.78 (9.95)	39.45 (9.13)
	T3	44.00 (11.35)	35.65 (11.63)
Dysfunctional Attitude Scale (DAS)	T1	141.22 (15.16)	107.65 (20.23)
	T3	133.72 (21.07)	106.60 (20.88)
Auditory Verbal Learning Test (AVLT)			
Average of the 5 immediate recalls	T1	12.43 (1.54)	11.92 (1.53)
	T3	12.79 (1.00)	13.08 (1.07)
Average of short and long delay recalls	T1	12.97 (1.83)	12.50 (2.25)
	T3	13.19 (1.74)	12.90 (1.92)
Recognition Hits	T1	14.39 (0.78)	14.35 (0.93)
	T3	14.39 (0.70)	14.00 (1.34)
Recognition FA	T1	0.39 (0.85)	0.55 (0.83)
	T3	0.33 (0.49)	0.25 (0.44)

Table7.8: Correlations between T1 Cognitive Bias and T3 Depressive Mood Scores within the High N Group. Values represent correlation coefficients. Asterisks represent statistical significance **p ≤ .01; *p ≤ .05.

	HAM-D	BDI	State Anxiety
Rumination	0.28	0.20	0.09
DAS	0.17	0.26	0.05
Self Referent Word Categorisation			
RT pos-neg	0.48*	0.57*	0.59*
Acc pos-neg	-0.45	-0.36	0.02
Self Referent Word Memory			
Recall Hit pos-neg	-0.03	0.01	-0.03
Recall FA pos-neg	0.04	-0.13	-0.10
Recog Hit pos-neg	0.15	0.25	0.13
Recog FA pos-neg	0.22	0.14	0.10
Facial Expression Recognition Task			
Threshold Anger	-0.28	-0.22	0.07
Threshold Disgust	0.20	0.23	0.44
Threshold Fear	0.03	-0.10	-0.06
Threshold Happy	-0.09	-0.04	0.31
Threshold Sadness	-0.58*	-0.45	-0.16
Threshold Surprise	0.03	0.08	0.21
Dotprobe Task			
Mask RT pos-neg	0.03	-0.02	0.20

Unmask RT pos-neg	0.06	-0.09	-0.37
Emotion-potentiated Startle			
Peak Size pos-neg	0.18	0.11	0.07
Latency pos-neg	0.32	0.36	0.21
Stress			
Stressful life events	0.80**	0.81**	0.60**

Footnote: DAS= dysfunctional Attitude Scale; RT = reaction time; Acc = accuracy, Hit = correct recall / recognition; FA = false alarm; Recog = recognition; Pos - Neg = positive minus negative; in dotprobe task, RT refers to vigilance scores.

Table7.9: Correlations between T3 mood and Cognitive Bias x Life Events within the High N Group. Values represent correlation coefficients. Asterisks represent statistical significance **p ≤ .01; *p ≤ .05.

x Stressful Life Event	HAM-D	BDI	State Anxiety
Rumination	0.48 *	0.49 *	0.21
DAS	0.46 *	0.44	0.43
Self Referent Word Categorisation			
RT pos-neg	0.70 **	0.74 **	0.59 **
Acc pos-neg	-0.40	-0.32	-0.08
Self Referent Word Memory			
Recall Hit pos-neg	0.06	-0.10	-0.25
Recall FA pos-neg	0.19	0.23	0.11
Recog Hit pos-neg	0.34	0.33	0.24
Recog FA pos-neg	0.18	0.25	0.20
Facial Expression Recognition Task			
Threshold Anger	-0.40	-0.42	-0.38
Threshold Disgust	0.34	0.35	0.23
Threshold Fear	0.12	0.08	-0.13
Threshold Happy	-0.35	-0.32	-0.38
Threshold Sadness	-0.80 **	-0.74 **	-0.52 *
Threshold Surprise	0.27	0.28	0.03
Dotprobe Task			
Mask RT pos-neg	0.28	0.34	0.16

Unmask RT pos-neg	0.15	0.25	0.34
Emotion-potentiated Startle			
Peak Size pos-neg	-0.06	-0.04	-0.10
Latency pos-neg	0.55 *	0.53 *	0.41

Footnote: DAS= dysfunctional Attitude Scale; RT = reaction time; Acc = accuracy, Hit = correct recall / recognition; FA = false alarm; Recog = recognition; Pos - Neg = positive minus negative; in dotprobe task, RT refers to vigilance scores.

Table7.10: Multiple Regression Models Predicting T3 BDI within the High N Volunteers. Asterisks represent statistical significance **p ≤ .01; *p ≤ .05.

	b	SE b	β	p
Model 1				
Constant	-0.15	1.82		
BDI 1	0.72	0.25	.60 **	.01
Model 2				
Constant	-0.77	1.23		
BDI 1	0.37	0.19	.31	.07
Life Events	4.45	1.02	.68 **	.00
Model 3				
Constant	-0.20	1.00		
BDI 1	0.30	0.15	.25	.07
Life Events	4.04	0.82	.61 **	.00
EW pos-neg	0.02	0.01	.35 **	.01
Model 4				
Constant	0.58	0.85		
BDI 1	0.22	0.12	.18	.11
Life Events	2.53	0.84	.38 **	.01
EW pos-neg	0.02	0.01	.37 **	.00
Thres Sad x Life	-1.73	0.60	-.37 **	.01

R^2 for Step 1 = .36; ΔR^2 for Step 2 = .37; ΔR^2 for Step 3 =.11; ΔR^2 for Step 4 =.07. R^2 squared for the final model =.91.

Table7.11: Regression Models Predicting T3 HAM-D within the High N Group.

Asterisks represent statistical significance **p ≤ .01; *p ≤ .05.

	b	SE b	β	p
Model 1				
Constant	2.07	1.48		
HAM-D 1	-0.01	0.45	-.003	.99
Model 2				
Constant	-0.96	1.07		
HAM-D 1	0.31	0.28	.18	.28
Life Events	3.85	0.74	.83 **	.00
Model 3				
Constant	3.31	2.02		
HAM-D 1	0.26	0.24	.15	.30
Life Events	3.28	0.68	.71 **	.00
Thres Sad	-0.05	0.02	-.34 *	.03
Model 4				
Constant	4.82	1.63		
HAM-D 1	-0.07	0.21	-.04	.74
Life Events	1.37	0.80	.30	.11
Thres Sad	-0.06	0.02	-.36 **	.01
Thres Sad x Life	-1.75	0.55	-.53 **	.01

R^2 for Step 1 = .00; ΔR^2 for Step 2 = .66; ΔR^2 for Step 3 = .10; ΔR^2 for Step 4 = .11; R^2 of the final model = .87.

Table7.12: Multiple Regression Models Predicting T3 State Anxiety within the High N Volunteers.

	b	SE b	β	p
Model 1				
Constant	10.17	9.75		
STATE 1	0.66	0.28	.52	.03

R^2 for Step 1 = .27.

Figure7.1: Thresholds for Recognising Each Emotional Facial Expression by High N and Low N Volunteers at T1 and T3. Values represent group mean.

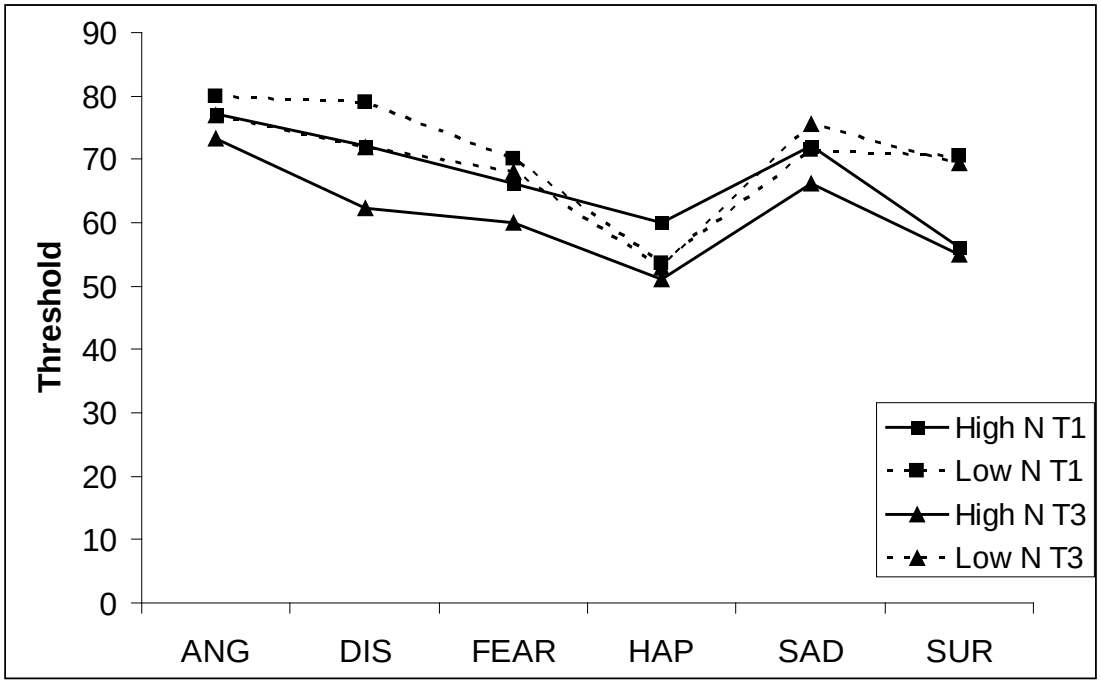


Figure 7.2: Morning Salivary Cortisol Levels of High N and Low N Volunteers at T1 and T3. Values represent group means ± standard errors of mean.

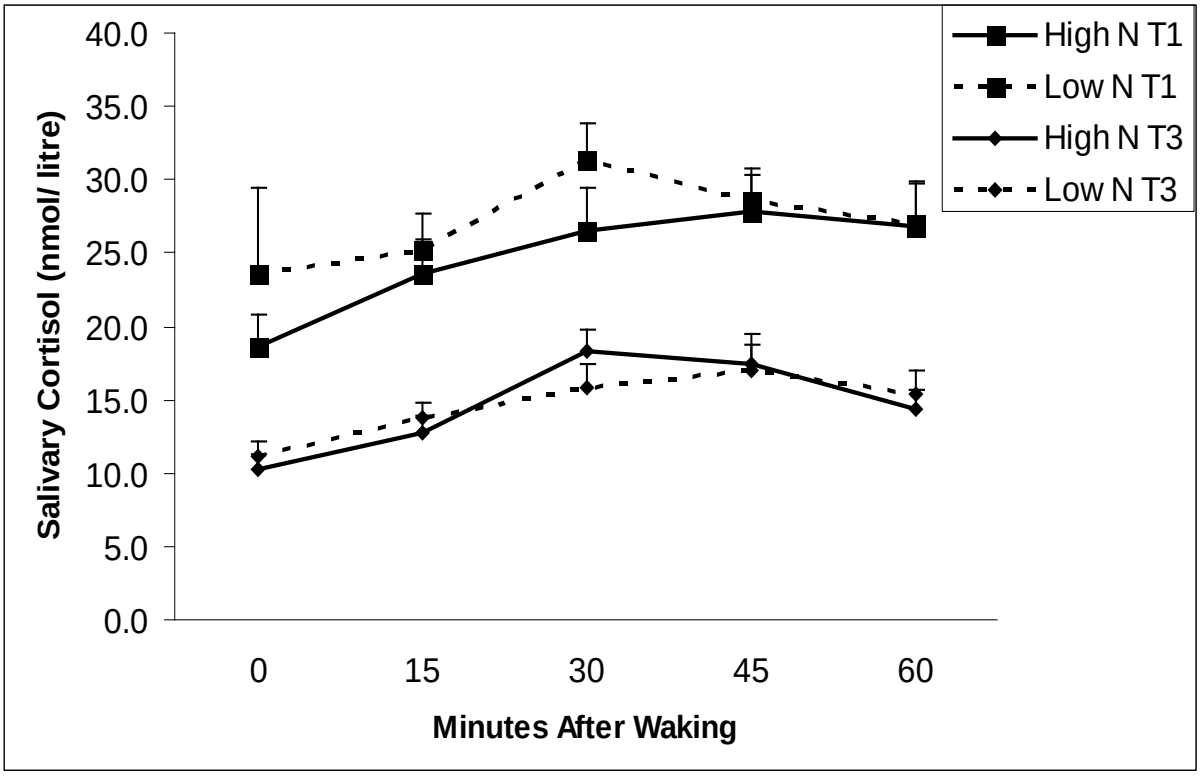
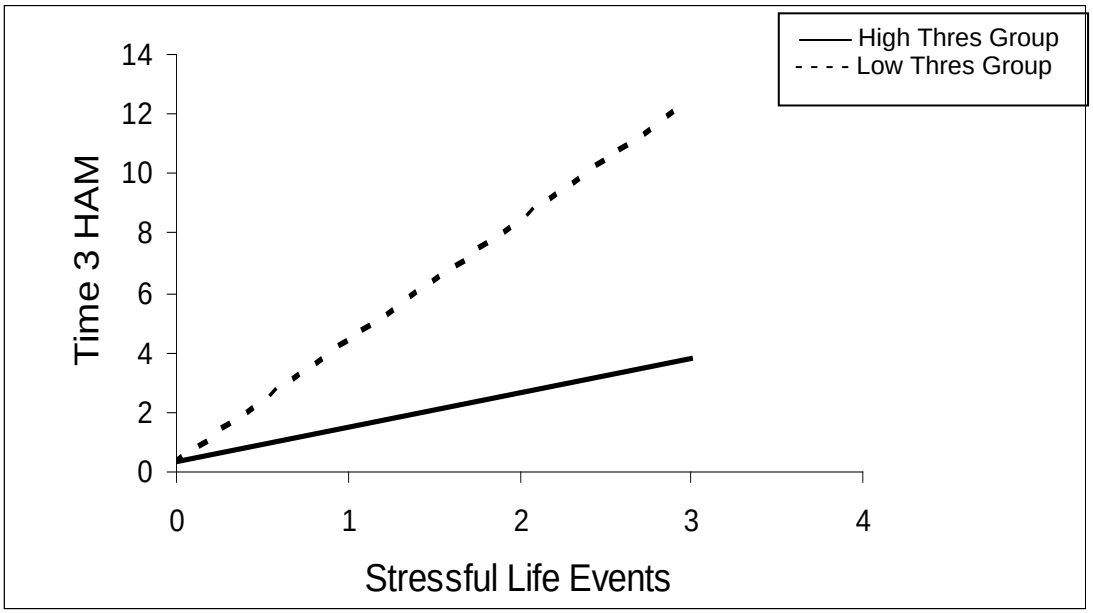


Figure7.3: Trend Lines Showing the Prediction of Time 3 BDI by Stressful Life Events in High vs. Low Threshold Groups in Recognising Sad Facial Expressions.



Figure7.4: Trend Lines Showing the Prediction of Time 3 HAM by Stressful Life Events in High vs. Low Threshold Groups in Recognising Sad Facial Expressions.



7.8 DISCUSSION

In this final eighteen-month longitudinal study, current depressed mood was highly predicted (up to about 90%) by a combination of negative cognitive biases and experiences of stressful life events in high-risk individuals. Specifically, increased speed for categorising negative self-referent words (vs. positive words) and increased perception for sad facial expressions were identified as the major cognitive predictors for subsequent psychological distress. In support of our hypothesis, the present findings suggested that negative biases in emotional processing constitute a cognitive vulnerability that predisposes high-risk individuals to emotional distress in the face of adverse life events. Though entirely predicted by cognitive models of depression (Beck et al 1967, 1979; Abramson et al 1989), very few previous studies have involved prediction of depression by cognition (see MacLeod & Hagan 1992, Alloy et al 2006). The current longitudinal design has the advantage of enabling us to make cause and effect conclusions about cognitive bias and onset of depression.

Overall, the statistical regression models showed that a vast majority of the total variance in depression (up to 91%) could be predicted by four major factors. Based on the presumptions that preexisting depressed mood is a key predictor for future depression, Time 1 depression (measured by BDI and HAM) was first entered into the regression models to control for this unhypothesized predictor. As expected, results showed that Time 1 BDI alone explained for 36% of the variance in Time 3 BDI. By contrast, Time 1 HAM did not predict Time 2 HAM, which was somewhat surprising. In fact, a similar result was found in the last longitudinal study. A plausible reason was that HAM was designed to measure episodes of clinical depression symptoms and therefore might be less sensitive to variations in depressed mood within the sub-clinical level. Although HAM and BDI are both valid measures of

depression, the two measures provide slightly different perspectives of depression: HAM is specifically designed for making diagnosis by a structured clinical interview whereas BDI is a self-reported questionnaire. The current study aimed to predict depressive episodes by cognitive risk factors, and therefore the results with HAM seemed to be a more relevant measure of depressive episode. However, our results with HAM and BDI have both interpretative constraints given the low variances in these measures.

Regression models predicting Time 3 depression measured by BDI and HAM yielded highly convergent results. Specifically, stressful life event and its interaction with threshold for recognising sad expressions were found to predict depression measured by both instruments. The present results suggested that increased perception for sad expressions (illustrated by reduced threshold) elevated psychological distress in the face of stressful life events. This result is consistent with previous finding that increased perception of sad facial expressions predict subsequent relapse in depression (Bouhuys et al 1999). The current result therefore suggested that increased perception of negative emotion constitutes a cognitive vulnerability that leads to depression when elevated by life adversity. By contrast, an opposite effect was found in our previous 6-month follow-up, in which reduced perception of sad expressions was associated with subsequent low mood (see 7.2.3). As discussed earlier, the last study yielded inconclusive findings in that it did not include a measure of life events. Therefore, we argue that the current study provided a more accurate measure of the effects of facial expression processing biases on depression when interacting with stressful life events.

Furthermore, the effects of self-referent processing biases on subsequent depression have been highlighted in both longitudinal assessments. The role of self-

referent processing biases in the aetiology and maintenance of depression has been emphasized in cognitive theories. In Beck's Theory (1967, 1979), negative self-schemata revolving around themes of failure, loss, inadequacy, and worthlessness, are hypothesized to provide cognitive vulnerability to depression. The Hopelessness Theory (Abramson et al 1989) also predicted that individuals who tend to infer negative self-characteristics in response to a negative life event are more likely to develop depression. Taken together, the current findings are consistent with cognitive theories of depression in suggesting that that negative biases in self-referent processing are key cognitive predictors for depression.

The current study has yielded highly significant results for the prediction of low mood by cognitive biases, thus supporting the main hypothesis of cognitive vulnerability. However, this study has also revealed some unexpected results. Specifically, high N and low N volunteers as a whole showed reduced BDI and salivary cortisol over time. They also showed improved overall accuracy in facial expression recognition task and auditory verbal learning test, plausibly due to a practice effect. These effects are not hypothesized and thus required further investigation. Nevertheless, these effects made the specific prediction of increased depression symptoms by cognitive biases noteworthy.

Finally, the two groups did not differ in their experiences of stressful life events in this period of 18 months. In fact, both groups have experienced very low level of stressful life events (average <1). This relatively low exposure of life adversity might in part explain why no high N participant developed full-blown depression. Longitudinal study with a longer duration will reveal whether these high N individuals will subsequently develop clinical depression when more stressful life events arise.

In conclusion, the current study identified negative biases in self-referent processing and facial expression recognition as the major cognitive mechanisms underlying vulnerability to depression. When interacting with stressful life events, these cognitive vulnerability factors together with baseline mood predicted up to 90% of the total variance in depression mood scores 18 months later. The significance and implications of this study will be discussed alongside our previous studies in the next and final chapter.

CHAPTER EIGHT

General Discussion

8.1 SUMMARY OF FINDINGS

The current series of investigations have yielded converging evidence for the presence of emotional processing biases in individuals who have high risk for depression (by virtue of high neuroticism, a well known risk factor) but have not been depressed. These emotional processing biases were illustrated across a wide range of cognitive functions including perception and memory for self-referent information, interpretation of facial expressions and physiological responses to emotional pictures measured by emotion-potentiated startle paradigm (Chapter Two). Overall, when compared to low risk individuals, high risk individuals showed a consistent pattern of biases favouring negative information such as negative self-referent words and away from positive information such as happy facial expressions.

This systematic selective processing of negative information, however, was not accompanied by impairments in more global executive function (Chapter Three), suggesting that emotional processing biases shown in high risk individuals cannot be attributed to global cognitive impairments. In fact, high risk individuals outperformed low risk individuals in the experimental tasks measuring general learning and memory (Auditory Verbal Learning Test) and motor planning and problem-solving (Tower of London), which was related to their higher trait of perfectionism. The same study revealed no clear evidence for high risk individuals having deficits in recalling specific autobiographical memory, suggesting that global cognitive functions are not

characteristics of risk for depression but instead may occur only during or after a depressive episode.

The potential association between risk for depression and dysfunctional biological stress responses has also been investigated (Chapter Four). Our results with waking salivary cortisol responses, a widely used indicator of the activity of hypothalamic-pituitary-adrenal (HPA) axis, suggesting that high risk individuals do not differ from their low risk counterparts in this function. Thus, similar to global cognitive functions, biological stress response does not appear to be part of the mechanisms that underlie high N's vulnerability to depression.

Taking together results from Chapters Two - Four, high risk individuals resembled depressed patients in that they are biased towards processing negative information. However, unlike in clinically depressed patients, global cognitive functions and biological stress responses remained intact in these high risk individuals. Thus, the primary finding of the present study was that negative biases in information processing are present in never-depressed high risk individuals, and as such they may represent long term vulnerability markers for depression preceding illness onset.

Our research further demonstrated the neural substrates of such emotional processing biases with two brain imaging experiments using fMRI (Chapters Five and Six). High risk individuals were found to have exaggerated neural responses while processing negative information including negative self-referent words and fearful facial expressions. These neural abnormalities were seen across a network of brain areas known to be involved in relevant emotional processing, including the superior parietal cortex, anterior cingulate, amygdala, and fusiform gyrus. These findings

suggested neural mechanisms underlying the negative biases observed behaviourally in high risk individuals.

Finally, our longitudinal studies illustrated that depressed mood in 18 months is highly predictable (up to 91%) by a combination of emotional processing biases and stressful life events, even after controlling for baseline mood (Chapter Seven). Specifically, the selective perception of negative self-referent words and sad facial expressions appeared to be the strongest cognitive predictors. Although no volunteer developed clinical depression within the 18 month time period of this study, statistical regression models have provided strong evidence that cognitive vulnerability elevated depression symptoms within a sub-clinical range. Our shorter follow-up study conducted at 6 months after the first study similarly identified negative biases in self-referent processing and facial expression recognition as the major cognitive predictors for subsequent increase in depressed mood. The significance and implications of these findings will be discussed in the following sections. The effectiveness and validity of the experimental design will also be critically evaluated.

8.2 NEUROCOGNITIVE VULNERABILITY TO DEPRESSION

Overall, the current investigations have consistently found that negative biases in emotional processing are major characteristics of risk for depression. Data from the longitudinal studies further confirmed that these biases elevated subsequent sub-clinical depression symptoms particularly in the face of stressful life events. These findings are consistent with the 'cognitive vulnerability hypothesis' developed from the cognitive theories of depression (Beck et al 1967, 1979; Abramson et al 1989), which suggests that individuals who exhibit particular maladaptive cognitive patterns are at increased risk for depression when they experience negative life events. The current research illustrated these maladaptive cognitive patterns in the form of negative biases across a wide range of cognitive functions in information processing. Specifically, increased perception of negative self-referent descriptions and sad facial expressions were suggested to be the best cognitive predictors for subsequent low mood. Thus, depression was best predicted by a *subset* of cognitive tasks and stressful life events, suggesting that the cognitive biases may not represent a single entity of cognitive vulnerability. Further analyses using correlations and / or factor analysis would be useful in clarifying the relationship amongst performance in different tasks and thus the nature of cognitive biases.

As predicted by the diathesis-stress model, we found that stressful life events interact with cognitive vulnerability mechanisms in predicting up to 91% of the total variance in dysphoric mood in 18 months. By contrast, in the 6-month follow-up where stressful life events were not included as a predictor, the predictive power of the models was much weaker. Although stressful life events were shown to play a key role in predicting depression in the last follow-up, our sample of young college students experienced relatively low levels of adverse life events (average <1). Thus,

the current models might have underestimated the effects of the cognitive vulnerability mechanisms, which may require the experience of more life stress to trigger illness onset.

While our longitudinal studies have established the prediction of subsequent low mood by cognitive vulnerability mechanisms, our fMRI experiments provided early evidence for the presence of neural vulnerability mechanisms in high risk individuals. Our brain-imaging results clearly illustrated that risk for depression is related to exaggerated neural response to negative information, particularly negative self-referent descriptions and fearful facial expressions. In particular, exaggerated response to threat within the amygdala-fusiform circuitry was seen as a function of risk for depression (Chapter Six). This is consistent with a large body of previous work which suggests a key role for the amygdala in depression (e.g. Sheline et al 2001, Davidson et al 2003, Fu et al 2004, Surguladze et al 2005, Drevets 2000, Keedwell et al 2005). Indeed, we observed differential amygdala responses to threat between high risk and low risk individuals (Chapter Six), suggesting that neural biases might be a *trait* vulnerability marker for depression that precede illness onset. Using a connectivity analysis it appeared that this elevated amygdala response was highly related to increased responses to negative affective information in the fusiform gyrus, providing a mechanism whereby risk for depression could lead to hypervigilance to threatening information.

Apart from the amygdala, functional abnormalities in other brain areas known to be involved in emotional processing have also been implicated as a function of risk for depression. Specifically, the superior parietal cortex was found to have increased responses while encoding negative self-referent words (Chapter Five). This result was consistent with previous suggestions of this area being involved in the processing of

personally relevant events (Vuilleumier 2005). It also echoed results of our first test battery where high N individuals were found to be faster in categorising negative self-referent adjectives. In fact, the parietal cortex has also been implicated in self-face recognition and perception of social relationships (Uddin et al 2005, Feinburg 2001, Decety and Sommerville 2003, Carr et al 2003, Farrer and Frith 2002, Iacoboni et al 2004). Consistent with this, abnormal activity within this area was observed in high N volunteers during facial expression processing task (Chapter Six).

Also highlighted in our fMRI findings was the activity of cingulate cortex, an area known to modulate the autonomic response to emotional experience and to process information concerning reward-punishment reinforcement contingencies (Bush et al 2000, Drevets 2001). Our findings established that risk for depression is related to heightened sensitivity to negative self-referent words, which was shown by enhanced responses within the cingulate cortex during the encoding of negative words and subsequent reduced responses (or reduced effort) during the retrieval of these words (Chapter Five). This hyperviligant response towards negative self-referent information in high risk volunteers is hypothesised to be related to their higher levels of social anxiety (measured by the Fear of Negative Evaluation questionnaire, Chapter Two) and self-criticism (measured as a symptom of depression by HAM-D, Chapters Two and Seven).

Taken together, results from our fMRI experiments suggested that risk for depression are related to widespread neural biases in emotional processing. Longitudinal studies with a large sample are required to establish a direct causal relationship between these hypothesised neural vulnerability mechanisms and subsequent depression.

Although our brain-imaging experiments aimed to identify the neural basis of the emotional processing biases observed in the first battery, they have also highlighted the neural processing biases that have not been observed behaviourally. Specifically, the differential neural responses to threat across different intensity between high N and low N volunteers suggested the hypothesis that high risk individuals assign a higher threat value to negative facial expressions compared with their low risk counterparts. Interestingly, this was not shown in their behaviour responses assessed outside the fMRI scanning. Likewise, the behavioural expression of the reduced activity in the cingulate cortex during the retrieval of negative self-referent words was not apparent in the first study. These suggested that neural processes are not always directly translated to observable behaviour, thus highlighting one of the advantages of using multidimensional measures within a single investigation. This will be discussed further in the next section.

8.3 THE EXPERIMENTAL DESIGN AND SELECTION OF TEST BATTERY

Indeed, the current research provided a large amount of data from both cross-sectional and longitudinal studies. The five cross-sectional studies (Chapters Two - Six) have employed a wide range of instruments assessing the neuropsychological behaviour in emotional processing, thus demonstrating within a single model the multifaceted mechanisms associated with risk for depression. This is in contrast to the majority of previous studies, which tend to be restricted to a specific domain (e.g. memory, attention) and have their hypotheses built upon a single theoretical approach. The current test battery was carefully selected to measure different key neural-cognitive behaviour hypothesised to be associated with risk for depression.

Specifically, the emotional categorisation task was used to measure processing of self-referent information. The inclusion of the control task using non self-referent information (animal attributes) enabled us to draw the conclusion that the differential behaviour of high vs. low risk individuals towards negative words is specific to a self-referent context rather than a general bias towards negative information (Chapter Two). The facial expression recognition task was selected to investigate the social context of emotional processing. As noted earlier, perceptions and interpretations of facial expressions play an important role in our social interactions in daily life. Likewise, the dotprobe task was included to measure attention to emotional information. The inclusion of both a short-exposure (masked) and long-exposure (unmasked) conditions was aimed to investigate the automatic and strategic stages of information processing respectively (Chapter Two). Also included in the first study was the emotion-potentiated startle, which, unlike the tasks discussed above, measured emotional reactivity from automatic reflexes and therefore avoided any subjective response bias or demand characteristics.

In addition, three tasks were selected to measure global executive functions in Chapter Three, including the Auditory Verbal Learning Test, Tower of London, and Autobiographical Memory Test. Waking salivary cortisol was used to measure the biological response to stress (Chapter Four). All of these measures have been used by previous studies with clinical populations. By employing the same instruments in the current investigation with high risk individuals, the findings here can be directly compared to previous observations on clinically depressed individuals.

The advantage of having such a wide range of diverse experimental instruments within one single investigation was further highlighted in Chapters Five and Six. As noted above, results from the fMRI experiments have not only suggested the neural mechanisms that underlie the negative biases observed in our first behavioural study, they also revealed negative biases in neural processing that were not revealed behaviourally. For example, the exaggerated responses towards fearful expressions in high risk individuals have only been observed during fMRI scanning but not in the behavioural study. Thus, it appeared that neural biases do not always simply translate to behavioural biases and it may be possible to pick up neural biases with more sensitivity than behavioural outputs which could be affected by many different processes. This clearly illustrates the importance of integrating data from experiments using different instruments.

The facial expression processing task used in the fMRI experiment (Chapter Six) was a simplified version of the task used in the behavioural study (Chapter Two) in that participants were only required to discriminate the gender of the emotional face rather than categorising the emotional expression. In addition, only happy and fearful expressions were selected for the fMRI experiments based on the findings of reduced perception of happy expressions in high N volunteers from our behavioural

experiment and heightened response to threat from previous studies on depression (e.g. Sheline et al 2001, Fu et al 2004, Surguladze et al 2005, Drevets 2000). With the use of emotional stimuli with different intensity levels we were able detect differences between high and low risk volunteers particularly when the facial expressions where at their most ambiguous.

The two-task design of the self-referent processing task (Chapters Two and Five), including the encoding of the self-referent words followed by a surprise memory test, provided a broad investigation into the different cognitive stages involved in the processing of self-referent information. Risk of depression was shown to be related to negative biases in both perception and memory for self-referent information. This was particularly evident from the fMRI finding that the same area within the cingulate cortex was involved in both tasks, thus generating consistent results concerning the involvement of this brain area in self-referent processing and risk for depression.

Finally, the scope of findings generated by the current investigation was highly expanded by its longitudinal design. The two longitudinal studies directly tested the cause and effect relationship between emotional processing and onset of depression. Sub-clinical depression symptoms measured by instruments such as BDI were shown to be highly predictable by a combination of emotional processing biases and stressful life events. To the best of my knowledge, very few previous studies have involved prediction of depression by cognition (see MacLeod & Hagan 1992, Alloy et al 2006). The present longitudinal design has therefore generated highly novel results suggesting that emotional processing biases elevated depression symptoms in high-risk individuals. However, the strength and generalization of the prediction models have been weakened by the relatively small sample especially in the final follow-up

study (n=18 in high risk group). The limitations related to the sample size will be further discussed in the next section.

Overall, the wide range of cross-sectional assessments accompanied by the longitudinal studies has generated highly integrated data illustrating the widespread neuropsychological mechanisms underlying the risk for depression.

8.4 THE HIGH N VERSUS LOW N SAMPLE

The present investigations used high neuroticism to define risk for depression. As noted in the Introductory Chapter, neuroticism is a stable personality trait that is highly predictive of subsequent depression (e.g. Kendler et al 1993, 2002, 2004, 2006). It has been estimated that each increase by a standard deviation in the neuroticism score (N) carries a hazard ratio for a depressive onset of 1.72 (Kendler 2004). Thus, the difference of N between our high N and low N groups (9.58 vs. 1.25), corresponding to 2.58 standard deviation units, represented about a four-fold difference in risk of depression. In addition, the two groups did not differ in personal or family history of psychiatric disorders, experience of stressful life events or childhood experience of adversity (see Chapter Two). The difference in emotional processing biases observed here can therefore be attributed to the difference of neuroticism unconfounded by other risk factors.

Although neuroticism is an instrument shown to reliably predict depression, it is not a specific marker for depression but rather it is a predictor for mood disorders in general. Indeed, we found that the high N individuals had consistently higher self-rated state and trait anxiety compared to their low N counterparts. However, our longitudinal studies showed that emotional processing biases measured by this test battery specifically predicted elevated depression but not anxiety. This suggested that although neuroticism is a common risk factor for both disorders, the neurocognitive mechanisms by which this risk factor leads to depression and anxiety disorder might be different. However, it should be noted that the primary interest of the present research is vulnerability to depression. Although depression and anxiety symptoms are often comorbid (e.g. Stein et al 2001), the experiments conducted here were not

specifically designed to characterise the differences between depression and anxiety. Further studies are required to test the hypothesis suggested above.

Another problem related to defining risk for depression by neuroticism is that highly neurotic individuals have often experienced depression symptoms, leading to a potential confound that the emotional processing biases observed here might be due to current or past depression symptoms rather than vulnerability *per se*. This problem has been exposed by previous studies, and therefore the current investigation has carefully selected the sample by excluding any individuals who have past or present depression symptoms that reach the clinical diagnostic criteria defined by DSM-IV. This exclusion of individuals with past or current clinical depression is an important feature of the current investigation, which enabled our results to be attributed to the risk for depression unconfounded by the so-called 'scar effects'. Though not clinically depressed, however, our high N individuals had significantly higher self-rated depression. This is inevitable as neuroticism is itself defined by tendency of mood swings. To disentangle the effects of neuroticism and depression symptoms, analyses using BDI as covariates have shown that the emotional processing biases observed in high N volunteers remained significantly different from low N volunteers even controlling for differences in depression symptoms. This provided strong evidence that emotional processing biases are related to risk for depression *per se*, rather than current experience of sub-clinical depression.

Indeed, our analyses including BDI as a covariate have allowed comparisons in neurocognitive behaviour without being confounded by differences in state mood of depression. However, as reviewed by Chapter Two (see Table 2.1) the groups also differed on other dimensions such as state anxiety. Thus, the current selection of high risk vs. low risk groups does not *per se* allow unambiguous attribution of effects to

trait phenomena. This confound could be statistically overcome by including all state mood scores as covariates, which, however was not performed here due to the relatively small sample.

An additional way to reduce potential confound due to current or past depression or anxiety symptoms experienced by high risk individuals is to use a younger sample. The current sample consisted of young adults with mean age 18 years at Time 1. As noted earlier, about 25% of the depressed population has had their first depressive episode by this age (Sorenson et al 1991). Indeed, we had excluded seven volunteers (out of 72) at the beginning due to prior experience of depression or anxiety disorders. Thus, a high risk sample with younger age may be more ideal for this kind of research.

Furthermore, the current research can be improved by increasing the sample size. The relatively low prevalence rates of depression implies that only a small proportion of the high N population will go on to develop depression, thereby potentially diluting any effects that we may have seen. While this might account for the lack of effect in waking salivary cortisol and autobiographical memory performance, it could not account for the emotional processing biases which were seen in the high N group as a whole. Indeed, although the effect size of the present findings might be limited by the sample size, the overall findings showed that emotional processing biases are detectable even in such a small sample. However, the problem related to the small sample size became more significant in the longitudinal studies. Specifically, this has limited the rate of clinical depression that could be observed in our high risk sample. Although results using sub-clinical measures such as BDI have generated highly significant findings, the current research failed to illustrate the prediction of the onset of clinical depression. Given the relatively low

prevalence rates of depression as noted earlier, future studies are required to confirm the current findings in a sample adequately powered for the detection of infrequent events.

It is also noteworthy that the current findings of mechanisms associated with risk for depression were based on the direct comparison between the high risk and low risk individuals. Although the primary aim of this research was to identify mechanisms in risk for depression, our studies have generated interesting observations about the low risk individuals. For example, low risk individuals showed reduced neural responses to fearful facial expressions with increasing intensity (Chapter Six). This 'positive bias' was not previously found in randomly selected control volunteers, therefore suggesting that the present observations in low N volunteers may represent potential protective mechanisms underlying low risk for depression. Future studies including a control group are required to further characterise the neurocognitive mechanisms underlying low risk for depression.

Finally, the current investigations did not differentiate between male and female high risk individuals, although the sex ratio was balanced between the high and low risk groups. There has been evidence that female sex increases the risk for depression (e.g. Kendler et al 2004). However, this excess risk in females almost disappeared in the face of high exposure to stressful life events, suggesting sex differences in the sensitivity to the depressogenic effects of stressful life events (Kendler et al 2004). Indeed, predictive models for onset of depression have been constructed separately for women (Kendler et al 2002) and men (Kendler et al 2006a). Although the models for men and women consisted of similar risk factors, childhood parental loss and low self-esteem appeared to be more potent variables in the model of men than in women. These results suggested potential sex differences in the

mechanisms underlying risk for depression. This hypothesis could not be fully investigated in the present study, however, due to the relatively small sample size.

8.5 IMPLICATIONS FOR PREVENTION OF DEPRESSION

A huge complex of mechanisms is potentially involved in the aetiology of depression. Although the present study has included a test battery with a wide range of assessments and a carefully selected sample of high risk individuals, the present results may represent only a part of this complex. Nonetheless, we believe that the current findings have high relevance to the aetiology of clinical depression and provide early evidence of the presence of neurocognitive abnormality in vulnerable individuals prior to illness onset.

As noted in the Introduction, major risk factors for depression have long been identified. However, the most crucial but often neglected question is: *How exactly do these factors lead to depression?* The research reported here aimed to answer this question by validating and extending previous knowledge of cognitive vulnerability factors. It has also opened up new questions for future research.

Following the current findings that negative biases in information processing predict subsequent depressive mood symptoms, one specific way forward for future research is to examine the potential effectiveness of early cognitive interventions in preventing depression in vulnerable individuals. One intriguing possibility for example is based on a recently developed technique known as 'cognitive bias modification' (Yiend & Mathews 2002) which has been found to effectively reduce negative bias and / or enhance positive bias for emotional information and subsequently produce enduring reductions in self-reported anxiety (Mathews et al 2007). Future research should explore how this experimental technique could be tailored specifically to depression, and whether it might be used preventatively to reduce illness onset in high risk populations.

Furthermore, strategies to prevent depression have also been explored from a pharmacological perspective. For example, the potential clinical use of omega-3 essential fatty acids (EFA) in prevention and treatment of depression and other psychiatric disorders has been explored. Preliminary results have showed that food supplementation with omega-3 fatty acids appears to reduce symptoms of depression (Freeman et al 2006, Ross et al 2007). The protective effects of other food supplements such as St John's Wort (*Hypericum perforatum*) in reducing symptoms of depression could also be explored as a potential early intervention strategy.

8.6 CONCLUSIONS

In conclusion, the present work has established that negative biases in information processing are present in individuals who have high risk for depression but have not been previously depressed. The neural basis of these negative biases was further suggested by our fMRI experiments. This emotional processing bias constituted to a cognitive vulnerability, which was shown to elevate depressive symptoms in high risk individuals up to 18 months follow-up, especially in the face of stressful life events. The present research has generated novel findings with high relevance to the aetiology of depression. It has also paved the way for future studies evaluating the efficacy of early interventions targeting the cognitive vulnerability mechanisms of high risk populations.

REFERENCES

Abas MA, Sahakian BJ, Levy R (1990): Neuropsychological deficits and CT scan changes in elderly depressives. *Psychological Medicine* 20:507-520.

Abercrombie HC, Larson CL, Ward RT (1996): Metabolic rate in the amygdala predicts negative affect and depression severity in depressed patients, an FDG-PET study. *NeuroImage* S217.

Abramson LY, Metalsky GI, Alloy LB (1989): Hopelessness depression: a theory-based subtype of depression. *Psychological Review* 96:358-372.

Allen NB, Trinder J, Brennan C (1999): Affective startle modulation in clinical depression: preliminary findings. *Biol Psychiatry* 46:542-50.

Alloy LB, Abramson LY, Whitehouse WG, Hogan ME, Panzarella C, Rose DT (2006): Prospective incidence of first onsets and recurrences of depression in individuals at high and low cognitive risk for depression. *Journal of Abnormal Psychology* 115:145-156.

Allport A (1989): Visual attention. In M. I. Posner (Ed.): *Foundations of Cognitive Science.* Cambridge, MA: MIT Press.

Anderson NH (1968): Likeableness rating of 555 personality trait words. *J Pers Soc Psychol* 9:272-279.

Aron AR, Robbins TW, Poldrack RA (2004): Inhibition and the right inferior frontal cortex. *Trends Cogn Sci* 8(4):170-7.

Austin M-P, Mitchell P, Goodwin GM (2001): Cognitive deficits in depression: possible implications for functional neuropathology. *British Journal of Psychiatry* 178:200-206.

Austin M-P, Mitchell P, Wilhelm K, Parker G, Hickie I, Brodaty H, *et al* (1999): Melancholic depression: a pattern of frontal cognitive impairment. *Psychological Medicine* 29:73-85.

Austin M-P, Ross M, Murray C, O'Carroll RE, Ebmeier KP, Goodwin GM (1992): Cognitive function in major depression. *Journal of Affective Disorders* 25:21-30.

Baas BW, Omura K, Constable RT, Canli T (2007): Emotional conflict and neuroticism: personality-dependent activation in the amygdala and subgenual anterior cingulate. *Behavioural Neuroscience* 121(2): 249-56.

Barden N, Reul JMHM, Holsboer F (1995): Do antidepressants stabilize mood through actions on the hypothamic-pituitary-adrenocortical system? *Trends Neurosci* 18:6-11.

Barnhofer T, Jong-Meyer R, Klleinpass A, Nikesch S (2002): Specificity of autobiographical memories in depression: an analysis of retrieval processes in a think-aloud task. *British Journal of Clinical Psychology* 41:411-6.

Berry WD (1993): Understanding regression assumptions. Sage university paper series on quantitative applications in the social sciences, 07-050. Beverly Hills, CA: Sage.

Basso MR, Bornstein RA (1999): Relative memory deficits in recurrent versus first-episode major depression on a word-list learning task. *Neuropsychology* 13:557-63.

Baxter LR, Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, *et al* (1989): Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Archives of General Psychiatry* 46:243–250.

Bazin N, Perruchet P, De Bonis R, Feline A (1994): The dissociation of explicit and implicit memory in depressed patients. *Psychological Medicine* 24:239-245.

Beardslee WR, Versage EM, Gladstone TRG (1998): Children of affectively ill parents: a review of the past 10 years. *Am J Child Adolsec Psychiatry* 37:1134-1141.

Beats BC, Sahakian BJ, Levy R (1996): Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. *Psychological Medicine* 26:591-603.

Beck AT (1963): Thinking and depression. *Archives of General Psychiatry* 9:324-333.

Beck AT (1967): *Depression: Clinical, Experimental, and Theoretical Aspects*. New York: Harper & Row.

Beck AT, Rush AJ, Shaw BF, Emery G (1979): *Cognitive Therapy of Depression*. New York: Guilford Press.

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh (1961): An inventory for measuring depression. *Arch Gen Psychiatry* 4:561-571.

Bhagwagar Z, Cowen PJ, Goodwin GM, Harmer CJ (2004): Normalization of enhanced fear recognition by acute SSRI treatment in subjects with a previous history of depression. *Am J Psychiatry* 161:166-168.

Bhagwagar Z, Hafizi S, Cowen PJ (2002): Acute citalopram administration produces correlated increases in plasma and salivary cortisol. *Psychopharmacology* 163:118-120.

Bhagwagar Z, Hafizi S, Cowen PJ (2003): Increased concentration of waking salivary cortisol in recovered patients with depression. *Am J Psychiatry* 160:1890-1891.

Bhagwagar Z, Hafizi S, Cowen PJ (2005): Increased salivary cortisol after waking in depression. *Psychopharmacology* 182(1):54-7.

Blair RJR, Morris JS, Frith CD, Perrett DI, Dolan RJ (1999): Dissociable neural responses to facial expressions of sadness and anger. *Brain* 122:883–893.

Blaney PH (1986): Affect and memory: a review. *Psychological Bulletin* 99(2):229-246.

Board F, Persky H, Hamburg DA (1956): Psychological stress and endocrine functions; blood levels of adrenocorticol and thyroid hormones in acutely disturbed patients. *Psychosom Med* 18:324-333.

Bosc M, Dubini A, Polin V (1997): Development and validation of a social functioning scale, the Social Adaptation Self-Evaluation Scale. *Eur Neuropsychopharmacol* 7 (suppl 1): S57-S70.

Botteron K, Raichle M, Drevets WC, Heath A, Todd RD (2002): Volumetric reduction in left subgenual prefrontal cortex in early onset depression. *Biol Psychiatry* 51: 342–344.

Bouhuys AL, Bloem GM, Groothuis TGG (1995): Induction of depressed and elevated mood by music influences the perception of facial emotional expressions in healthy subjects. *Journal of Affective Disorders* 33:215-226.

Bouhuys AL, Geerts E, Gordijn MC (1999): Depressed patients' perception of facial emotions in depressed and remitted states are associated with relapse: a longitudinal study. *J Nerv Ment Dis* 187:595-602.

Bower GH (1981): Mood and memory. *American Psychologist* 36:129-148.

Bower GH (1987): Commentary on mood and memory. *Behaviour Research and Therapy* 25:443-455.

Bowley MP, Drevets WC, Ongur D, Price JL (2002): Low glial cell numbers in the amygdala in major depressive disorder. *Biol Psychiatry* 52: 404–412.

Bradley BP, Mogg K (1994): Mood and personality in recall of positive and negative information. *Behaviour Research and Therapy* 32(1):137-141.

Bradley BP, Mogg K, Galbraith M, Perrett A (1993): Negative recall bias in neuroticism: state versus trait effects. *Behaviour Research and Therapy* 31:125-127.

Bradley BP, Mogg K, Lee SC (1997): Attentional biases for negative information in induced and naturally occurring dysphoria. *Behaviour Research and Therapy* 35(10):911-927.

Bradley BP, Mogg K, Williams R (1994): Implicit and explicit memory for emotional information in non-clinical subjects. *Behaviour Research and Therapy* 32:65-78.

Bradley BP, Mogg K, Williams R (1995): Implicit and explicit memory for emotion-congruent information in clinical depression and anxiety. *Behaviour Research and Therapy* 33(7):755-770.

Bradley MM, Cuthbert BN, Lang PJ (1990): Startle reflex modification: Attention or emotion? *Psychophyiology* 27:513-523.

Breiter HC, Etcoff NL, Whalen PJ, Kennedy WA, Rauch SL, Buckner RL, *et al* (1996): Response and habituation of the human amygdala during visual processing of facial expression. *Neuron* 17:875–887.

Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS (2000): Hippocampal volume reduction in major depression. *Am J Psychiatry* 157:115–118.

Bremner JD, Vythilingham M, Vermetten E, Nazeer A, Adil J, Khan S, *et al* (2002): Reduced volume of orbitofrontal cortex in major depression. *Biol Psychiatry* 51:273–279.

Brody AL, Saxena S, Silverman DH, Alborzian S, Fairbanks LA, Phelps ME, *et al* (1999): Brain metabolic changes in major depressive disorder from pre- to post-treatment with paroxetine. *Psychiatry Res* 91:127–139.

Brothers L (1995): Neurophysiology of the perception of intentions by primates. In Gazzaniga MS (Ed.): *The Cognitive Neurosciences*. Cambridge, MA: MIT Press, pp. 1107-1116.

Brown GW, Harris TO (1978): *Social Origins of Depression: A Psychiatric Study on Psychiatric Disorder in Women*. London: Tavistock.

Brown RG, Scott LC, Bench CJ, Dolan RJ (1994): Cognitive function in depression: its relationship to the presence and severity of intellectual decline. *Psychological Medicine* 24:829-847.

Bruce V, Young A (1986): Understanding face recognition. *British Journal of Psychology* 77:305–327.

Bryan J, Luszcz MA (2000): Measurement of executive function: considerations for detecting adult age differences. *J Clin Exp Neuropsychol* 22:40-55.

Buchsbaum MS, Wu J, Siegel V, Hackett E, Trenary M, Abel L, et al (1997): Effect of sertraline on regional metabolic rate in patients with affective disorder. *Biol Psychiatry* 41:15–22.

Burke M, Mathews A (1992): Autobiographical memory and clinical anxiety. *Cognition and Emotion* 6:23-35.

Bush G, Luu P, Posner MI (2000): Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences* 4(6): 215-222.

Buss AH, Durkee A (1957): An inventory for assessing different kinds of hostility. J *Consult Psychol* 21: 343-349.

Cane DB, Olinger LJ, Gotlib IH, Kuiper NA (1986): Factor structure of the dysfunctional attitude scale in a student population. *Journal of Clinical Psychology* 42(2):307-309.

Canli T (2004): Functional brain mapping of extraversion and neuroticism: learning from individual differences in emotional processing. *Journal of Personality* 72(6):1105-1132.

Canli T, Zhao Z, Desmond JE, Kang E, Gross J, Gabrieli JDE (2001): An fMRI study of personality influences on brain reactivity to emotional stimuli. *Behavioral Neuroscience* 115:33-42.

Carr L, Iacoboni M, Dubeau MC, Mazziotta JC, Lenzi GL (2003): Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. *Proc. Natl. Acad Sci* 100(9):5497–5502.

Carroll BJ, Curtis GC, Mendels J (1976): Neuroendocrine regulation in depression I. Limbic system-adrenocortical dysfunction. *Archives of General Psychiatry* 33:1039–1044.

Caspi A, Sugden K, Mottiff TE, Tayler A, Craig IW, Harrington H, *et al* (2003): Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 301:386-389.

Channon S (1996): Executive dysfunction in depression: the Wisconsin Card Sorting Test. *Journal of Affective Disorders* 39:107-114.

Channon S, Green PS (1999): Executive function in depression: the role of performance strategies in aiding depressed and non-depressed participants. *Journal of Neurology, Neurosurgery and Psychiatry* 66:162-171.

Clark DM, Teasdale JD (1982): Diurnal variations in clinical depression and accessibility of memories of positive and negative experience. *Journal of Abnormal Psychology* 91:87-95.

Clark LA, Watson D (1991): Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. *J Abnorm Psychol* 100:316-336.

Cleary AJ, Bearn J, Allain T, McGregor A, Wessely S, Murray RM, *et al* (1995): Contrasting neuroendocrine responses in depression and chronic fatigue syndromes. *Journal of Affective Disorders* 34:283-289.

Cohen R, Weingartner H, Smallberg S, Pickar D, Murphy DL (1982): Effort and cognition in depression. *Archives of General Psychiatry* 39: 593-598.

Cook EW III, Davis TL, Hawk LW, Spence EL, Gauiter CH (1992): Fearfulness and startle potentiation during aversive visuals stimuli. *Psychophysiology* 29:633-45.

Cook EW III, Hawk LW, Davis TL, Stevenson VE (1991): Affective individual differences and startle reflex modulation. *Journal of Abnormal Psychology* 100:5-13.

Corr P, Wilson G, Fotiadou M, Kumari V, Gray N, Checkley S, *et al* (1995): Personality and affective modulation of the startle reflex. *Personality and Individual Differences* 19:543-53.

Cotter D, Mackay D, Landau S, Kerwin R, Everall I (2001): Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. *Archives of General Psychiatry* 58:545–553.

Craik FIM, Moroz TM, Moscovitch M, Stuss DT, Winocur G, Tulving E, Kapur S (1999): In search of the self: a positron emission tomography study. *Psychol Sci* 10: 26–34.

Dalgleish T, Spinks H, Yiend J, Kuyken W (2001): Autobiographical memory style in seasonal affective disorder and its relationship to future symptom remission. *Journal of Abnormal Psychology* 110(2):335-40.

Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto LLB, Hichwa RD (1998): Neural Correlates of the Experience of Emotions. *Soc Neurosci Abstr*. 24:258

Danion JM, Kauffmann-Muller F, Grange D, Zimmermann MA, Greth P (1995): Affective valence of words, explicit and implicit memory in clinical depression. *Journal of Affective Disorders* 34: 227 -234.

Davidson RJ, Irwin W, Anderle MJ, Kalin NH (2003): The neural substrates of affective processing in depressed patients treated with venlafaxine. *Am J Psychiatry* 160:64-75.

Decety J, Sommerville JA (2003): Shared representations between self and other: A social cognitive neuroscience view. *Trends Cogn Sci* 7(12):527–533.

Dennis M, Wakefield P, Molly C, Andrews H, Friedman T (2005): Self-harm in older people with depression: comparison of social factors, life event and symptoms. *British Journal of Psychiatry* 186(6):538-539.

Denny EB, Hunt RR (1992): Affective valence and memory in depression: dissociation of recall and fragment completion. *Journal of Abnormal Psychology* 101:581-586.

Depue RA, Iacono WG (1989): Neurobehavioral aspects of affective disorders. *Annual Review of Psychology* 40:457-492.

Dichter GS, Tomarken AJ, Shelton RC, Sutton SK (2004): Early- and late-onset startle modulation in unipolar depression. *Psychophysiology* 41:433-440.

Dolcos F, Kragel P, Wang L, Mcarthy G (2006): Role of the inferior frontal cortex in coping with distracting emotions. *Neuroreport* 17(15):1591-4.

Dolcos F, McCarthy G (2006): Brain systems mediating cognitive interference by emotional distraction. *J Neurosci* 26(7):2072-9.

Drevets WC (2000): Neuroimaging studies of mood disorders. *Biol Psychiatry* 48:813-829.

Drevets WC (2001): Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Neurobiology* 11:240-249.

Drevets WC (2003): Neuroimaging abnormalities in the amygdala in mood disorders. *Ann N Y Acad Sci* 985:420-444.

Drevets WC, Price JL, Simpson JR, Todd RD, Reich T, Vannier M, *et al* (1997): Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 386:824–827.

Drevets WC, Bogers W, Raichle ME (2002): Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *Eur Neuropsychopharmacol* 12:527–544.

Drevets WC, Simpson JR, Raichle ME (1995): Regional blood flow changes in response to phobic anxiety and habituation. *J Cereb Blood Metab* 15:S856.

Drevets WC, Videen TO, Price JL, Preskorn SH, Carmichael ST, Raichle ME (1992): A functional anatomical study of unipolar depression. *J Neurosci* 12:3268–3641.

Ekman P, Friesen WV (1976): *Pictures of facial affect*. Palo Alto, Calif: Consulting Psychologists Press.

Elliott R, Sahakian BJ, McKay AP, Herrod JJ, Robbins TW, Paykel ES (1996): Neuropsychological impairments in unipolar depression: the influence of perceived failure on subsequent performance. *Psychological Medicine* 26:975-989.

Elliot R, Subinztein JS, Sahakian BJ, Dolan RJ (2002): The neural basis of mood-congruent processing biases in depression. *Archives of General Psychiatry* 59:597-604.

Evans J, Williams JMG, O'Loughlin S, Howerlls K (1992): Autobiographical memory and problem-solving strategies of parasuicidal patients. *Psychological Medicine* 22:399-405.

Eysenck HJ (1990): Genetic and environmental contributions to individual differences: the three major dimensions of personality. *J Pers* 58:245-261.

Eysenck HJ, Eysenck SBG (1964): *Manual of the Eysenck Personality Inventory*. London: London University Press.

Eysenck HJ, Eysenck SBJ (1975): *Manual of the Eysenck Personality Questionnaire.* London: Hodder and Stoughton.

Eysenck SBG, Eysenck HJ, Barrett P (1985): A revised version of the Psychoticism Scale. *Personality and Individual Differences* 6:21-29.

Farrer C, Frith CD (2002): Experiencing oneself vs. another person as being the cause of an action: the neural correlates of the experience of agency. *NeuroImage* 15(3):596–603.

Feinberg TE (2001): *Altered Egos: How the Brain Creates the Self*. New York: Oxford University Press.

Feinberg TE, Rifkin A, Schaffer C, Walker E (1986): Facial discrimination and emotional recognition in schizophrenia and affective disorders. *Archives of General Psychiatry 4*3:276-279.

Fisher-Beckfield D, McFall RM (1982): Development of a comprehensive inventory for college men and evaluation of relationships between competence and depression. *Journal of Consulting and Clinical Psychology* 50:697-705.

Fossati P, Hevenor SJ, Graham SJ, Grady C, Keightley ML, Craik F, Mayberg H (2003): In search of the emotional self: an fMRI study using positive and negative emotional words. *Am J Psychiatry* 160(11):1938-45.

Fossati P, Hevenor SJ, Lepage M, Graham SJ, Grady C, Keightley ML, *et al* (2004): Distributed self in episodic memory: neural correlates of successful retrieval of self-encoded positive and negative personality traits. *Neuroimage* 22(4):1596-604.

Fowles DC (1988): Psychophysiology and psychopathology: A motivational approach. *Psychophysiology* 25:373-391.

Francis WN, Kucera A (1982): *Frequency Analysis of English Usage: Lexicon and Grammar*. Boston, MA: Houghton Mifflin.

Freeman MP, Hibbeln JR, Wisner KL, Davis JM, Mischoulon D, Peet M, *et al* (2006): Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *J Clin Psychiatry* 67(12):1954-67.

Friston KJ, Worsley KJ, Frackowiak RSJ, Mazziotta JC, Evans AC (1994): Assessing the significance of focal activations using their spatial extent. *Human Brain Mapping* 1:210-220.

Frith CD, Steven M, Johnstone EC, Deakin JF, Lawler P, Crow TJ (1983): Effects of ECT and depression on various aspects of memory. *British Journal of Psychiatry* 142:610-617.

Fu CHY, Williams SC, Brammer MJ, Suckling J, Kim J, Cleare AJ, *et al* (2007): Neural responses to happy facial expressions in major depression following antidepressant treatment. *Am J Psychiatry* 164(4):599-607.

Fu CHY, Williams SCR, Cleare AJ, Brammar MJ, Walsh ND, Kim J, *et al* (2004): Attenuation of the neural response to sad faces in major depression by antidepressant treatment. *Archives of General Psychiatry* 61:877-889.

George MS, Ketter TA, Parekh PI, Rosinsky N, Ring HA, Pazzaglia PJ, *et al* (1997): Blunted left cingulate activation in mood disorder subjects during a response interferences task (the Stroop). *J Neuropsychiatry Clin Neurosci* 9:55-63.

Gibbs BR, Rude SS (2004): Overgeneral autobiographical memory as depression vulnerability. *Cognitive Therapy & Research* 28:511-526.

Goddard L, Dritchel B, Burton A (1996): Role of autobiographical memory in social problem solving and depression. *Journal of Abnormal Psychology* 105:609-616.

Goddard L, Dritchel B, Burton A (1997): Social problem solving and autobiographical memory in non-clinical depression. *British Journal of Clinical Psychology* 36:449-451.

Goddard L, Dritchel B, Burton A (2001): The effects of specific retrieval instruction on social problem-solving in depression. *British Journal of Clinical Psychology* 40:297-308.

Golinkoff M, Sweeney J (1989): Cognitive impairments in depression. *Journal of Affective Disorders* 17:105-112.

Goodwin GM (1997): Neuropsychological and neuroimaging evidence for the involvement of the frontal lobes in depression. *Journal of Psychopharmacology* 11:115-122.

Goodyer IM, Herbert J, Tamplin A, Secher SM, Pearson J (1997): Short-term outcome of major depression: II. Life events, family dysfunction, and friendship difficulties as predictors of persistent disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 36(4): 474-80.

Gotlib IH, Asarnow RF (1979): Interpersonal and impersonal problem-solving skills in mildly and clinically depressed university students. *Journal of Consulting and Clinical Psychology* 47:86-95.

Gotlib IH, Cane DB (1987): Construct accessibility and clinical depression: a longitudinal investigation. *Journal of Abnormal Psychology* 96:199-294.

Gotlib IH, McCann CD (1984): Construct accessibility and depression: an examination of cognitive and affective factors. *Journal of Personality and Social Psychology* 47:427-439.

Gotlib IH, Sivers H, Gabrieli JDE, Whitfield-Gabrieli S, Philippe G, Minor KL, Canli T (2005): Subgenual anterior cingulate activation to valenced emotional stimuli in major depression. *NeuroReport* 16:1731-1734.

Graf P, Mandler G (1984): Activation makes words more accessible, but not necessarily more retrievable. *Journal of Verbal Learning and Verbal Behaviour* 23:553-568.

Graf P, Schacter DL (1985): Implicit and explicit memory for new associations in normal and amnesic subjects. *Journal of Experimental Psychology: Learning, Memory and Cognition* 11:501-515.

Green DM, Swets JA (1966): *Signal Detection Theory and Psychophysics*. New York: Wiley.

Grier JB (1971): Nonparametric indexes for sensitivity and bias: computing formulas. *Psychol Bull* 75(6): 424-9.

Grillon C, Baas J (2003): A review of the modulation of the startle reflex by affective states and its application in psychiatry. *Clinical Neurophysiology* 114:1557-1579.

Gur RC, Erwin RJ, Gur RE, Zwil AS, Heimberg C, Kraemer HC (1992): Facial emotion discrimination: II behavioral findings in depression. *Psychiatry Research* 42: 241-251.

Gusnard DA, Akbudak E, Shulman GL, Raichle ME (2001): Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc. Natl. Acad. Sci. U. S. A.* 98: 4259–4264.

Halbreich U, Asnis GM, Schindledecker R, Zurnoff B, Nathan RS (1985): Cortisol secretion in endogenous depression I. Basal plasma levels. *Archives of General Psychiatry* 42:909–914.

Hale WW (1998): Judgment of facial expressions and depression persistence. *Psychiatry Research* 80:265-274.

Halgren E (1981): The amygdala contribution to memory and emotion: current studies in humans. In Ben-Ari Y (Ed): *The Amygdaloid Complex*, Amsterdam: Elsevier, pp. 395-408.

Hamilton M (1967): Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 6:278-296.

Hamm AO, Cuthbert BN, Globisch J, Vaitl D (1997): Fear and startle reflex: blink modulation and autonomic response patterns in animal and mutilation fearful subjects. *Psychophysiology* 34:87-107.

Hammen C (1991): Generation of stress in the course of unipolar depression. *Journal of Abnormal Psychology* 100:555-561.

Hankin BL, Fraley RC, Abela JRZ (2005): Daily depression and cognitions about stress: evidence for a traitlike depressogenic cognitive style and the prediction of depressive symptoms in a prospective daily diary study. *Journal of Personality and Social Psychology* 88(4):673-685.

Harey AG, Bryant RA, Dang ST (1998): Autobiographical memory in acute stress disorder. *Journal of Consulting and Clinical Psychology* 48:126-128.

Harmer CJ, Bhagwagar Z, Shelley N, Cowen PJ (2003): Contrasting effects of citalopram and reboxetine on waking salivary cortisol. *Psychopharmacology* (Berl) 167(1):112-4.

Harmer CJ, Hill SA, Taylor MJ, Cowen PJ, Goodwin GM (2003): Toward a neuropsychological theory of antidepressant drug action: increase in positive emotional bias after potentiation of norepinephrine activity. *Am J Psychiatry* 160(5):990-2.

Harmer CJ, Mackay CE, Reid CB, Cowen PJ, Goodwin GM (2006): Antidepressant drug treatment modifies the neural processing of nonconscious threat cues. *Biol Psychiatry* 59(9):816-20.

Harmer CJ, Shelley NC, Cowen PJ, Goodwin GM (2004): Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. *Am J Psychiatry* 161(7):1256-63.

Harrison PJ (2002): The neuropathology of primary mood disorder. *Brain* 125:1428-1449.

Haxby JV, Gobbini MI, Furey ML, Ishai A, Schouten JL, Pietrini P (2001): Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science* 293: 2425-2430.

Haxby JV, Hoffman EA, Gobbini MI (2000): The distributed human neural system for face perception. *Trend in Cognitive Sciences* 4(6):223-233.

Haxby JV, Hoffman EA, Gobbini MI (2002): Human neural systems for face recognition and social communication. *Biol Psychiatry* 51:59-67.

Hayward G, Goodwin GM, Cowen PJ, Harmer CJ (2005): Low-dose tryptophan depletion in recovered depressed patients induces changes in cognitive processing without depressive symptoms. *Biol Psychiatry* 57(5): 517-24.

Henderson D, Hargreaves I, Gregory S, Williams JMG (2002): Autobiographical memory and emotion in a non-clinical sample of women with and without a reported history of childhood sexual abuse. *British Journal of Clinical Psychology* 41:129-141.

Hennig J, Lange N, Haag A, Rohrmann S, Netter P (2000): Reboxetine in a neuroendocrine challenge paradigm: evidence for high cortisol responses in healthy volunteers scoring high on subclinical depression. *Int J Neuropsychopharmacol* 3:193-201.

Henriques JB, Glowacki JM, Davidson RJ (1994): Reward fails to alter response bias in depression. *Journal of Abnormal Psychology* 103: 460-466.

Hertel PT, Hardin TS (1990): Remembering with and without awareness in a depressed mood: evidence of deficits in initiative. *Journal of Experimental Psychology* 119:45-59.

Hill AB, Dutton F (1989): Depression and selective attention to self-esteem threatening words. *Personality and Individual Differences* 10:915-917.

Hill SA, Taylor MJ, Harmer CJ, Cowen PJ (2003): Acute reboxetine administration increases plasma and salivary cortisol. *Journal of Psychopharmacology* 17(3):273-5.

Hoehn-Hyde D, Rush AJ (1982): Perception of social interactions in depressed psychiatric patients. *Journal of Consulting and Clinical Psychology* 50:209-212.

Holsboer F (2000): The cortisosteroid receptor hypothesis of depression. *Neuropsychopharmacology* 23:477-501.

Holsboer F, Lauer CJ, Schreiber W, Krieg J (1995): Altered hypothalamic-pituitary-adrenocortical regulation in healthy subjects at high familial risk for affective disorder. *Neuroendocrinology* 62:340–347.

Iacoboni M, Lieberman MD, Knowlton BJ, Molnar-Szakacs I, Moritz M, Throop CJ, Fiske AP (2004): Watching social interactions produces dorsomedial prefrontal and medial parietal BOLD fMRI signal increases compared to a resting baseline. *NeuroImage* 21(3):1167–1173.

Ilsley JE, Moffoot APR, O'Carrol RE (1995): An analysis of memory dysfunction in major depression. *Journal of Affective Disorders* 35:1-9.

Jenkinson M, Bannister P, Brady M, Smith S (2002): Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage* 17(2):825-41.

Jeste DV, Heaton SC, Paulsen JS, Ercoli L, Harris MJ, Heaton RK (1996): Clinical and neuropsychological comparison of psychotic depression with nonpsychotic depression and schizophrenia. *Am J Psychiatry* 153:490-6.

Jha AP, Fabian SA, Aguirre GK (2004): The role of prefrontal cortex in resolving distracter interference. *Cogn Affect Behav Neurosci* 4(4):517-27.

John OP (1990): The 'big five' factor taxonomy: dimensions of personality in the natural language and in questionnaires. In Pervin L (Ed.): *Handbook of Personality Theory and Research*. New York: Guilford pp.66-100.

Johnson SC, Baxter LC, Wilder LS, Pipe JG, Heiserman JE, Prigatano GP (2002): Neural correlates of self-reflection. *Brain* 125(8):1808-14.

Jonides J, Smith EE, Marshuetz C, Koeppe RA, Reuter-Lorenze PA (1998): Inhibition in verbal working memory revealed by brain activation. *Proc Natl Acad Sci USA* 95(14):8410-3.

Judd LJ (1997): The clinical course of unipolar major depressive disorders. *Archives of General Psychiatry* 54:989-991.

Kaney S, Bowen-Jones K, Bentall RP (1999): Persecutory delusions and autobiographical memory. *British Journal of Clinical Psychology* 38:97-102.

Kaviani H, Gray JA, Checkley SA, Raven PW, Wilson GD, Kumari V (2004): Affective modulation of the startle response in depression: influence of the severity of depression, anhedonia, and anxiety. *Journal of Affective Disorders* 83:21-31.

Keedwell PA, Andrew C, Williams SCR, Brammer MJ, Phillips ML (2005): A double dissociation of ventromedial prefrontal cortisol responses to sad and happy stimuli in depressed and healthy individuals. *Biol Psychiatry* 58:495-503.

Keenan JP, Nelson A, O'Connor M, Pascual-Leone A (2001): Self-recognition and the right hemisphere. *Nature* 409: 305.

Kelley WM, Macrae CN, Wyland CL, Caglar S, Inati S, Heatherthon TF (2002): Finding the self? An event-related fMRI study. *J Cogn Neurosci* 14: 785–794.

Kendler KS, Gardner CO, Prescott CA (2002): Toward a comprehensive developmental model for major depression in women. *Am J Psychiatry* 159(7):1133-45.

Kendler KS, Gardner CO, Prescott CA (2006a): Toward a comprehensive developmental model for major depression in men. *Am J Psychiatry* 163(1):115-24.

Kendler CS, Gatz M, Gardner CO, Pedersen NL (2006b): Personality and major depression. *Archives of General Psychiatry* 63:1113-1120.

Kendler KS, Karkowski LM, Prescott CA (1999): Causal relationship between stressful life events and the onset of major depression. *Am J Psychiatry* 156:837-841.

Kendler KS, Kessler RC, Neale NC, Heath AC, Eaves LJ (1993): The prediction of major depression in women: toward an integrated etiologic model. *Am J Psychiatry* 150(8):1139-48.

Kendler KS, Kuhn J, Prescott CA (2004): The interrelationship of neuroticism, sex, and stressful life events in the prediction of episodes of major depression. *Am J Psychiatry* 161:631-636.

Kendler KS, Prescott CA (1999): A population-based twin study of lifetime major depression in men and women. *Archives of General Psychiatry* 56:39-44.

Kendler KS, Kessler RC, Neale NC, Heath AC, Eaves LJ (1993): The prediction of major depression in women: toward an integrated etiologic model. *Am J Psychiatry* 150(8):1139-48.

Kendler KS, Kuhn J, Prescott CA (2004): The interrelationship of neuroticism, sex, and stressful life events in the prediction of episodes of major depression. *Am J Psychiatry* 161:631-636.

Kennedy SH, Evans KR, Kruger S, Mayberg HS, Meyer JH, McCann S, *et al* (2001): Changes in regional brain glucose metabolism measured with positron emission tomography after paroxetine treatment of major depression. *Am J Psychiatry* 158:899–905.

Kessing LV (1998): Cognitive impairment in the euthymic phase of affective disorder. *Psychological Medicine* 28:1027-1038.

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, *et al* (1994): Lifetime and twelve-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Study. *Archives of General Psychiatry* 51:8-19.

Kessler RC (1997): The effects of stressful life events on depression. *Annu Rev Psychol* 48:191-214.

Kircher TTJ, Senior C, Phillips ML, Benson PJ, Bullmore ET, Brammer M, *et al* (2000): Toward a functional neuroanatomy of self processing: effects of faces and words. *Brain Res Cogn Brain Res* 10:133-144.

Kirschbaum C, Kudielka BM, Gaab J, Schommer NC, Helhammer DH (1999): Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamic-pituitary-adrenal axis. *Psychosomatic Medicine* 61:154-162.

Kirschbaum C, Wolf OT, May M, Wippich W, Hellhammer DH (1996): Stress and treatment induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. *Life Science* 58: 1475-1483.

Kudielka BM, Kirschbaum C (2003): Awakening cortisol responses are influenced by health status and awakening time but not by menstrual cycle phase. *Psychoneuroendocrinology* 28:35-47.

Kuyken W, Brewin CR (1995): Autobiographical memory functioning in depression and reports of early abuse. *J Abnorm Psychol* 104:585-591.

Kuyken W, Dalgleish T (1995): Autobiographical memory and depression. *British Journal of Clinical Psychology* 34:89-92.

Lane RD, Fink GR, Chau PM, Dolan RJ (1997): Neural activation during selective attention to subjective emotional responses. *Neuroreport* 8(18):3969-72.

Lang PJ, Davis M, Ohman A (2000): Fear and anxiety: animal models and human cognitive psychophysiology. *Journal of Affective Disorders* 61:137-159.

Larson CL, Ruffalo D, Nietert JY, Davidson RJ (2000): Temporal stability of the emotion-modulated startle response. *Psychophysiology* 37:92-101.

Lawrence AS, Williams AM, Surguladze S, Giampietro V, Brammer MJ, Andrew C, *et al* (2004): Subcortical and ventral prefrontal cortisol neural responses to facial expressions distinguish patients with bipolar disorder and major depression. *Biol Psychiatry* 55:578-587.

Layne C (1980): Motivational deficit in depression: People's expectations: the impact on outcome. *Journal of Clinical Psychology* 36:647-652.

Le Masurier M, Cowen PJ, Harmer CJ (2007): Emotional bias and waking salivary cortisol in relatives of patients with major depression. *Psychological Medicine* 37(3):403-10.

Lishman WA (1972): Selective factors in memory. Part 1: age, sex and personality attribute. *Psychological Medicine* 2:121-138.

Lloyd GG, Lishman WA (1975): Effects of depression on the speed of recall of pleasant and unpleasant experiences. *Psychological Medicine* 5:173-180.

Lupien S, de Leon M, de Santi S, Convit A, Tarshish C, Nair NPV, Thakur M, McEwen BS, Hauger RL, Meaney MJ (1998): Cortisol levels during human

ageing predict hippocampal atrophy and memory deficits. *Nature Neuroscience* 1: 69-73.

Mackinger HF, Kunz-Dorfer A, Scheider B, Leibetsder MM (2001): The prediction of premenstrual distress: autobiographical memory as a vulnerability marker. In Kallus KW, Posthumus N, Jimenez P (Eds.): *Current psychological research in Austria: Proceedings of the 4th Scientific Conference of the Austrian Psychological Society* (pp.57-60). Graz, Austria: Akademische Druck and Verlagsanstalt.

Mackinger HF, Loschin GG, Leibetsder MM (2000a): Prediction of postnatal affective changes by autobiographical memories. *European Psychologist* 5:52-61.

Mackinger HF, Pachinger MM, Leibetsder MM, Fartacek RR (2000b): Autobiographical memories in women remitted from major depression. *Journal of Abnormal Psychology* 109:331-334.

MacLeod C, Hagan R (1992): Individual differences in the selective processing of threatening information, and emotional responses to a stressful life event. *Behav Res Ther* 30(2):151-61.

MacLeod C, Mathews A, Tata P (1986): Attentional bias in emotional disorders. *Journal of Abnormal Pathology* 95:15-20.

MacLeod C, Rutherford EM (1992): Anxiety and the selective processing of threatening information: mediating roles of awareness, trait and state variables, and personal relevance of stimulus materials. *Behaviour Research and Therapy* 30:479-491.

Maes M, Calabrese J, Meltzer HY (1994): The relevance of the inversus outpatients status for studies on HPA-axis in depression: spontaneous hypercortisolism is a

feature of major depressed inpatients and not of major depression per se. *Progress in Neuropsychopharmacology and Biological Psychiatry* 18:503-517.

Mannie ZN, Harmer CJ, Cowen PL (2007): Increased waking salivary cortisol levels in young people at familial risk of depression. *Am J Psychiatry* 164: 617-621.

Martin M, Ward J, Clark DM (1983): Neuroticism and the recall of positive and negative personality information. *Behaviour Research and Therapy* 21:495-503.

Mathews A (1990): Why worry? The cognitive function of anxiety. *Behaviour Research and Therapy* 28:455-468.

Mathews A, Bradley B (1983): Mood and the self-reference bias in recall. *Behaviour Research and Therapy* 21:233-239.

Mathews A, MacLeod C (1985): Selective processing of threat in anxiety states. *Behaviour Research and Therapy* 23:563-569.

Mathews AM, McLeod C (1994): Cognitive approaches to emotion and emotional disorders. *Ann Rev Psychol* 45:25-50.

Mathews A, Mogg K, May J, Eysenck M (1989): Implicit and explicit memory bias in anxiety. *Journal of Abnormal Psychology* 98:236-240.

Mathews A, Ridgeway V, Cook E, Yiend J (2007): Inducing a benign interpretational bias reduces trait anxiety. *J Behav Ther Exp Psychiatry* 38(2):225-36.

Mathews A, Ridgeway V, Williamson DA (1996): Evidence for attention to threatening stimuli in depression. *Behaviour Research and Therapy* 34(9):695-705.

Mathews GR, Antes JR (1992): Visual attention and depression: cognitive biases in the eye fixation of the dysphoric and non-depressed. *Cognitive Therapy and Research* 16:359-371.

Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, Tekel JL, *et al* (1997): Cingulate function in depression: a potential predictor of treatment response. *Neuroreport* 8:1057-1061.

Mayberg HS, Brannan SK, Tekell JL, Silva A, Mahurin RK, McGinnis S, *et al* (2000): Regional metabolic effects of fluoxetine in major depression: Serial changes and relationship to clinical response. *Biol Psychiatry* 48:830–843.

Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jarabek PA, *et al* (1999): Reciprocal limbic-cortical function and negative mood: Converging PET findings in depression and normal sadness. *Am J Psychiatry* 156:675–682.

McCleery JM, Goodwin GM (2001): High and low neuroticism predicts different cortisol responses to the combined dexamethasone-CRH test. *Biol Psychiatry* 49:410-415.

McCrae RR, Costa PT Jr. (1990): *Personality in Adulthood*. New York: Guilford.

McNally RJ, Reimann BC, Kim E (1990): Selective processing of threat cues in panic disorder. *Behaviour Research and Therapy* 28:407-412.

Mikhailova ES, Vladimirova TV, Iznak AF, Tsusulkovskaya EJ, Sushko NV (1996): Abnormal recognition of facial expression of emotions in depressed patients with major depression disorder and schizotypal personality disorder. *Biol Psychiatry* 40:697-705.

Miller E, Lewis P (1977): Recognition memory in elderly patients with depression and dementia: a signal detection analysis. *Journal of Abnormal Psychology* 86:84-86.

Miranda R, Nolen-Hoeksema S (2007): Brooding and reflection: rumination predicts suicidal ideation at 1-year follow-up in a community sample. *Behaviour Research and Therapy*

Miskowiak K, O'Sullivan U, Harmer CJ (2007): Erythropoietin enhances hippocampal response during memory retrieval in humans. *Journal of Neuroscience* 27(11):2788-92.

Moffitt KH, Singer JA, Nelligan DW, Carlson MA, Vyse SA (1994): Depression and memory narrative type. *Journal of Abnormal Psychology* 103:581-583.

Mogg K, Bradley BP (1998): A Cognitive-motivational analysis of anxiety. *Behav Res Ther* 36(9): 809-48.

Mogg K, Bradley BP, Hallowell N (1994): Attentional bias to threat: roles of trait anxiety, stressful events, and awareness. *Quarterly Journal of Experimental Psychology* 47A:841-864.

Mogg K, Bradley B, Williams R (1995): Attentional bias in anxiety and depression: the role of awareness. *British Journal of Clinical Psychology* 34:17-36.

Mogg K, Bradley B, Williams R, Mathews A (1993): Subliminal processing of emotional information in anxiety and depression. *Journal of Abnormal Psychology* 102:304-311.

Mogg K, Mathews AM, Eysenck M (1992): Attentional bias to threat in clinical anxiety states. *Cog Emot* 6:149-159.

Mogg K, Mathews AM, Weinman J (1989): Selective processing of threat cues in anxiety states: a replication. *Behaviour Research and Therapy* 27:317-323.

Moore RG, Watts FN, Williams JMG (1988): The specificity of personal memories in depression. *British Journal of Clinical Psychology* 27:275-276.

Morris JS, Frith CD, Perrett DI, Rowland D, Young AW, Calder AJ, *et al* (1996): A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature* 383:812–815.

Morris JS, Ohman A, Dolan RJ (1998): Conscious and unconscious emotional learning in the human amygdala. *Nature* 393:467–470.

Murphy E (1982): Social origins of depression in old age. *British Journal of Psychiatry* 141:135-142.

Murphy FC, Sahakian BJ, Rubinsztein J S, Michael A, Rogers RD, Robbins TW, *et al* (1999): Emotional bias and inhibitory control processes in mania and depression. *Psychological Medicine* 29:1307-1321.

Nelson HE (1982): *National Adult Reading Test (NART): Test Manual*. Windsor: NFER-Nelson.

Newcomer JW, Craft S, Hershey T, Askins S, Bardgett ME (1994): Glucocoticoid-induced impairment in declarative memory performance in adult humans. *J Neuroscience* 14: 2047-2053.

Nobler MS, Sackeim HA, Prohovnik I, Moeller JR, Mukherjee SSDB, *et al* (1994): Regional cerebral blood flow in mood disorders, III treatment and clinical response. *Archives of General Psychiatry* 51:884–897.

Nolen-Hoeksema S (1991): Responses to depression and their effects on the duration of depressive episodes. *Journal of Abnormal Psychology* 100(4):569-582.

Norbury R, Mackay CE, Cowen PJ, GM Goodwin, Harmer CJ (submitted): The effects of noradrenergic manipulation emotional processing in healthy volunteers: An fMRI study.

Ochsner KN, Gross JJ (2005): The cognitive control of emotion. *Trends Cogn Sci* 9(5):242-9.

Omura K, Constable RT, Canli T (2005): Amygdala gray matter concentration is associated with extraversion and neuroticism. *NeuroReport* 16(17):1905-1908.

Paradiso S, Lamberty GJ, Garvey MJ, Robinson RG (1997): Cognitive impairment in the euthymic phase of chronic unipolar depression. *Journal of Nervous and Mental Disease* 185:748-754.

Pariante CM, Miller AH (2001): Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biol Psychiatry* 49:391-404.

Parker G, Tupling H, Brown LB (1979): A parental boding instrument. *Br J Med Psychol* 52: 1-10.

Pastor MC, Molto J, Vila J, Lang PJ (2003): Startle reflex modulation, affective ratings and autonomic reactivity in incarcerated Spanish psychopaths. *Psychophysiology* 40(6):934-948.

Patenaude B, Smith S, Kennedy D, Jenkinson M (2007): Bayesian Shape and Appearance Models. http://www.fmrib.ox.ac.uk/analysis/techrep/.

Patrick CJ, Bradley MM, Lang PJ (1993): Emotion in the criminal psychopath: startle reflex modulation. *Journal of Abnormal Psychology* 102:82-92.

Pennington BF, Ozonoff S (1996): Executive functions and developmental psychopathology. *J Child Psychol Psychiatry* 37:51-87.

Persad S, Polivy J (1993): Differences between depressed and non-depressed individuals in the recognition of and response to facial cues. *Journal of Abnormal Psychology* 102:358-368.

Peselow ED, Corwin J, Fieve RR, Rotrosen J, Cooper TB (1991): Disappearance of memory deficits in outpatient depressives responding to imipramine. *Journal of Affective Disorders* 21:173-183.

Pfohl B, Sherman B, Schlecte J, Stone R (1985): Pituitary/adrenal axis rhythm disturbances in psychiatric patients. *Archives of General Psychiatry* 22:897–903.

Phillips ML, Drevets WC, Rauch SL, Lane R (2003a): Neurobiology of emotion perception I: the neural Basis of normal emotion perception. *Biol Psychiatry* 54(5):504-14.

Phillips ML, Drevets WC, Rauch SL, Lane R (2003b): Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biol Psychiatry*. 54(5):515-28.

Phillips ML, Young AW, Senior C, Calder AJ, Perrett D, Brammer M, et al (1997): A specific neural substrate for perception of facial expressions of disgust. *Nature* 389: 495–498.

Plotsky PM, Owens MJ, Nemeroff CB (1998): Psychoneuroendocrinology of depression- Hypothalamic-pituitary-adrenal axis. *Psychiatr Clin North Am* 21:293–307.

Pollock, L. R. & Williams, J. M. G. (2001): Effective problem solving in suicide attempters depends on specific autobiographical recall. *Suicide and Life-Threatening Behavior* 31: 386-396.

Portella MJ, Harmer CJ, Flint J, Cowen P, Goodwin GM (2005) : Enhanced early morning salivary cortisol in neuroticism. *Am J Psychiatry* 162(4):807-9.

Posener JA, DeBattista C, Williams GH, Chmura KH, Kalehzan BM, Scatzberg AF (2000): 24-hour monitoring of cortisol and corticotropin secretion in psychotic and nonpsychotic major depression. *Archives of General Psychiatry* 57:755-760.

Posner MI, Petersen SE (1990): The attention system of the human brain. *Annual Review of Neuroscience* 13:25-42.

Pruessner JC, Helhammer D, Kirschbaum C (1999): Burnout, perceived stress, and cortisol responses to awakening. *Psychosomatic Medicine* 61:197-204.

Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH (2003): Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology* 28: 916-931.

Pruessner JC, Wolf OT, Hellhammer DH, Buske-Kirschbaum A, von Auer K, Jobst S, Kaspers F, Kirschbaum C (1997): Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. *Life Science* 61(26):2539-49.

Puffet A, Jehin-Marchot D, Timsit-Berthier M, Timsit M (1991): Autobiographical memory and major depressive states. *European Psychiatry*

Purcell R, Maruff P, Kyrios M, Pantelis C (1997): Neuropsychological function in young patients with unipolar major depression. *Psychological Medicine* 27:1277-1285.

Raes F, Hermans D, Williams JMG, Eelen P (2005): Autobiographical memory specificity and emotional abuse. *British Journal of Clinical Psychology* 44(Pt 1):133-8.

Ramponi C, Barnard PJ, Nimmo-Smith I (2004): Recollection deficits in dysphoric mood: an effect of schematic models and executive mode? *Memory* 12(5):655-70.

Rey A (1964): *L'examen de Clinique en Psychologie*. Paris: Presses Universitaires de France.

Richardson-Klavehn A, Bjork RA (1988): Measures of memory. *Annual Review of Psychology* 39:475-543.

Robbins TW, James M, Owen A, Sahakian BJ, McInnes L, Rabbitt PM (1994): Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor

analytic study of a large sample of normal elderly volunteers. *Dementia* 5:266-281.

Rogers TB, Kuiper NA, Kirker WS (1977): Self-reference and the encoding of personal information. *J. Pers. Soc. Psychol.* 35:677–688.

Ross BM, Seguin J, Sieswerda LS (2007): Omega-3 fatty acids as treatments for mental illness: which disorder and which fatty acid? *Lipids in Healthy and Disease* 6(1):21.

Roy-Byrne PP, Weingartner H, Bierer LM, Thompson K, Post RM (1986): Effortful and automatic cognitive processes in depression. *Archives of General Psychiatry* 43:265 -267.

Rubin RT, Poland RE, Lesser IM, Winston RA, Blodgett N (1987): Neuroendocrine aspects of primary endogenous depression I. Cortisol secretary dynamics in patients and matched controls. *Archives of General Psychiatry* 44:328–336.

Rubinow DR, Post RA (1992): Impaired recognition of affect in facial expression in depressed patients. *Biological Psychiatry* 31:947-953.

Rush AJ, Weissenburger J, Vinson DB, Giles DE (1983): Neuropsychological dysfunction in unipolar nonpsychotic major depression. *Journal of Affective Disorders* 5:281-287.

Sabatinelli D, Bradley MM, Cuthbert BN, Lang PJ (1996): Wait and see: aversion and activation in anticipation and perception. *Psychophysiology* 33:S72.

Sachar EJ, Hellman L, Roffwarg HP, Halpern FS, Fukush DK, Gallagher TF (1973): Disrupted 24 hour patterns of cortisol secretion in psychotic depressives. *Archives of General Psychiatry* 28:19–24.

Schacter DL (1987): Implicit memory: history and current status. *Journal of Experimental Psychology: Learning, Memory and Cognition* 13:501-518.

Schatzberg AF, Posener JA, DeBattista C, Kalehzan BM, Rothschild AJ, Shear PK (2000): Neuropsychological deficits in psychotic versus nonspsychotic major depression and no mental illness. *Am J Psychiatry* 157:1095-100.

Scott J, Stanton B, Garland A, Ferrier IN (2000): Cognitive vulnerability in patients with bipolar disorder. *Psychological Medicine* 30:467-472.

Schwartz CE, Wright CI, Shin LM, Kagan J, Rauch SL (2003): Inhibited and uninhibited infants 'grown up': adult amygdalar response to novelty. *Science* 300:1952-1953.

Segal ZV, Gemar MC, Truchon C, Guirguis M, Horowitz LM (1995): A priming methodology for studying self-representation in major depressive disorder. *Journal of Abnormal Psychology* 108:205-213.

Segal ZV, Vella DD (1990): Self-schema in major depression: replication and extension of a priming methodology. *Cog Ther Res* 14:161-176.

Shallice T (1982): Specific impairments of planning. *Philos. Trans. Roy. Soc. Lond. B* 298:199–209.

Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA (2001): Increased amygdala responses to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol Psychiatry* 50:651-658.

Sheline YI, Sanghavi M, Mintun MA, Gado MH (1999): Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci* 19: 5034–5043.

Siegle G, Steinhauer SR, Thase ME, Stenger A, Carter CS (2002): Can't shake that feeling: Event-related fMRI assessment of sustained amygdala activity in

response to emotional information in depressed individuals. *Biol Psychiatry* 51:693–707.

Siegle GJ, Thompson W, Carter CS, Steinhauer SR, Thase ME (2007): Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. *Biol Psychiatry* 61:198-209.

Simons AD, Angell KL, Monroe SM, Thase ME (1993): Cognition and life stress in depression: cognitive factors and the definition, rating, and generation of negative life events. *Journal of Abnormal Psychology* 102:584-591.

Sloan DM, Strauss ME, Quirk SW, Sajatovic M (1997): Subjective and expressive emotional responses in depression. *Journal of Affective Disorders* 46:135-141.

Sloan DM, Strauss ME, Wisner KL (2001): Diminished response to pleasant stimuli by depressed women. *Journal of Abnormal Psychology* 110:488-493.

Smith GS, Reynolds CF, Pollock B, Derbyshire S, Nofzinger E, Dew MA, *et al* (1999): Cerebral glucose metabolic response to combined total sleep deprivation and antidepressant treatment in geriatric depression. *Am J Psychiatry* 156:683–689.

Smith S (2002): Fast robust automated brain extraction. *Human Brain Mapping* 17:143-155.

Smith SM, Jenkinson M, Woolrich MW, Beckmanna CF, Behrensa TEJ, Johansen-Berga H, *et al* (2004): Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 23:S208-S219.

Spielberger CD, Gorsuch RL, Lushene RD (1970): *STAI Manual.* Palo Alto, Calif: Consulting Psychologists Press.

Spitzer RL, Williams JBW, Gibbon M, First MB (1995): *Structural Clinical Interview for the DSM-IV (SCID-I/P), Version II.* Washington, DC: American Psychiatric Press.

Sorenson SB, Rutter CM, Aneshensel CS (1991): Depression in the community: an investigation into age of onset. *Journal of Consulting and Clinical Psychology* 59:541-546.

Stein MB, Fuetsch M, Mullen N, Hofler M, Lieb R, Wittchen HU (2001): Social anxiety disorder and the risk for depression: a prospective community study of adolescents and young adults. *Archives of General Psychiatry* 58:251-256.

Stein MB, Simmons AN, Feinstein JS, Paulus MP (2007): Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. *Am J Psychiatry* 164:318-327.

Steler C, Miller GE (2005): Blunted cortisol response to awakening in mild to moderate depression: regulatory influences of sleep patterns and social contacts. *Journal of Abnormal Psychology* 114(4):697-705.

Sternberg DE, Jarvik ME (1976): Memory functions in depression. *Archives of General Psychiatry* 33:219-224.

Stetler C, Miller GE (2005): Blunted cortisol response to awakening in mild to moderate depression: regulatory influences of sleep patterns and social contacts. *Journal of Abnormal Psychology* 114:697-705.

Stordal KI, Ludervold AJ, Egeland J, Mykletun A, Asbjornsen A, Landro NI, *et al* (2004): Impairment across executive functions in recurrent major depression. *Nordic Journal of Psychiatry* 58(1):41-47.

Stromgren LS (1977): The influence of depression on memory. *Acta Psychiatrica Scandinavica* 56:109-128.

Strickland PL, Deakin JF, Percival C, Dixon J, Cater RA, Goldberg DP (2002): Bio-social origins of depression in the community: Interactions between social adversity, cortisol and serotonin neurotransmission. *British Journal of Psychiatry* 180:168-173.

Stuss DT (1991): Self, awareness, and the frontal lobes: a neuropsychological perspective. In Strauss, J. and Goethals, G.R. (Ed.): *The Self: Interdisciplinary Approaches*, New York: Springer-Verlag, pp. 255–278.

Sullivan PF, Neale MC, Kendler KS (2000): Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry* 157:1552-1563.

Surguladze SA, Brammar MJ, Keedwell P, Giampietro V, Young AW, Travis MJ, *et al* (2005): A differential pattern of neural responses toward sad versus happy facial expressions in major depressive disorder. *Biol Psychiatry* 57:201-209.

Surguladze SA, Brammer MJ, Young AW, Andrew C, Travis MJ, Williams SCR, *et al* (2003): A preferential increase in the extrastriate response to signals of danger. *NeuroImage* 19:1317-1328.

Surguladze SA, Young AW, Senior C, Brebion G, Travis MJ, Philips ML (2004): Recognition accuracy and response bias to happy and sad facial expressions in patients with major depression. *Neuropsychology* 18(2):212-8.

Suslow T, Junghanns K, Arolt V (2001): Detection of facial expressions of emotions in depression. *Perceptual and Motor Skills* 92:857-868.

Sutton LJ, Teasdale JD, Broadbent DE (1988): Negative self-schema: the effects of induced depressed mood. *British Journal of Clinical Psychology* 27:188-190.

Talairach J, Tournoux P (1988): *Co-Planar Stereotaxic Atlas of the Human Brain: Three-dimensional Proportional System.* New York: Thieme Medical.

Tarbuck AF, Paykel ES (1995): Effects of major depression on the cognitive function of younger and older subjects. *Psychological Medicine* 25: 285 -296.

Teasdale JD (1983): Negative thinking in depression: cause, effect, or reciprocal relationship? *Advances in Behaviour Research and Therapy* 5:3-25.

Teasdale (1988): Cognitive vulnerability to persistent depression. *Cognition and Memory* 2:247-274.

Teasdale JD, Fogarty SJ (1979): Differential effects of induced mood on retrieval of pleasant and unpleasant events from episodic memory. *Journal of Abnormal Psychology* 88:248-257.

Treynor W, Gonzalez R, Nolen-Hosksema S (2003): Rumination reconsidered: a psychometric analysis. *Cognitive Therapy and Research* 27(3):247-259.

Trichard C, Martinot JL, Alagille M, Masure MC, Hardy P, Ginestet D (1995): Time course of prefrontal lobe dysfunction in severely depressed in patients: a longitudinal neuropsychological study. *Psychological Medicine* 25: 79-85.

Uddin LQ, Kaplan JT, Molnar-Szakacs I, Zaidel E, Iacoboni M (2005): Self-face recognition activates a frontoparietal "mirror" network in the right hemisphere: an event-related fMRI study. *Neuroimage* 25(3):926-35.

von Minnen A, Wessel I, Verhaak C, Smeenk J (2005): The relationship between autobiographical memory specificity and depressed mood following a stressful life event: a prospective study: *British Journal of Clinical Psychology* 44:405-415.

von Zerssen D, Strian F, Schwarz D (1974): Evaluation of depressive states, especially in longitudinal studies. In Pichot P (Ed.): *Psychological Measurements in Psychopharmacology*. Basel, Switzerland: Karger, pp 189-202.

Vrana SR, Spence EL, Lang PJ (1988): The startle probe response: a new measure of emotion? *Journal of Abnormal Psychology* 97:487-91.

Vuilleumier P (2005): How brains beware: neural mechanisms of emotional attention. *Trends Cogn Sci* 9(12):585-94.

Vuilleumier P, Pourtois G (2006): Distributed and interactive brain mechanisms during emotion face perception: evidence from functional neuroimaging. *Neuropsychologia* 45:174-194.

Watkins E, Teasdale JD (2001): Rumination and overgeneral memory in depression: Effects of self-focus and analytic thinking. *Journal of Abnormal Psychology* 110:353-357.

Watkins PC, Mathews A, Williamson DA, Fuller RD (1992): Mood congruent memory in depression: emotional priming or elaboration? *Journal of Abnormal Psychology* 101:581-586.

Watkins PC, Vache K, Verney SP, Mathews A (1996): Unconscious mood-congruent memory bias in depression. *Journal of Abnormal Psychology* 105(1):34-41.

Watson D, Friend R (1969): Measurement of social-evaluative anxiety. *Journal of Consulting and Clinical Psychology* 33:448-457.

Watson S, Galagher P, Del Estal D, Hearn A, Ferrier IN, Young AH (2002): Hypothalamic-pituitary-adrenal axis function in patients with chronic depression. *Psychological Medicine* 32:1021-1028.

Wechsler D (1981): *Wechsler Adult Intelligence Scale—revised (WAIS-R) Manual*. New York: Psychological Corporation.

Weingartner H, Cohen RM, Murphy DL, Martello C, Great C (1981): Cognitive processes in depression. *Archives of General Psychiatry* 38: 42 -47.

Weissmann A (1979): The Dysfunctional Attitude Scale: A validation study. Unpublished doctoral dissertation. University of Pennsylvania, Philadelphia.

Weissmann A, Beck AT (1978): The Dysfunctional Attitudes Scale. Paper presented at the Annual Meeting of the Association for the Advancement of Behaviour Therapy, Chicago, IL, November.

Weissman M, Fendrich M, Warner V, Wickramaratne P (1992): Incidence of psychiatric disorder in offspring at high and low risk for depression. *Am J Child Adolsec Psychiatry* 31:640-648.

Wenzel A, Jackson LC, Brendle JR, Pinna K (2003): Autobiographical memories associated with feared stimuli in fearful and non-fearful individuals. *Anxiety Stress and Coping* 16:1-15.

Wenzel A, Jackson LC, Holt CS (2002): Social phobia and the recall of autobiographical memories. *Depression and Anxiety* 15(4):186-9.

Wessel I, Meeren M, Peeters F, Arntz A, Merckelbach H (2001): Correlates of autobiographical memory specificity: the role of depression, anxiety and childhood trauma. *Behaviour Research and Therapy* 39(4):409-21.

Whalen PJ, Rauch SL, Etcoff NL, McInerney SC, Lee MB, Jenike MA (1998): Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J Neurosci* 18:411–418.

Williams JMG (1996): Depression and the specificity of autobiographical memory. In Rubin DC (Ed.): *Remembering Our Past: Studies in Autobiographical Memory* (pp. 244-267). Cambridge: Cambridge University Press.

Williams JMG, Barnhofer T, Crane C, Beck AT (2005): Problem solving deteriorates following mood challenge in formerly depressed patients with a history of suicidal ideation. *Journal of Abnormal Psychology* 114:421-431.

Williams JMG, Barnhofer T, Crane C, Hermans D, Raes F, Watkins E, Dalgleish T (2007): Autobiographical memory specificity and emotional disorder. *Psychological Bulletin* 133(1):122-48.

Williams JMG, Broadbent K (1986): Autobiographical memory in suicide attempters. *Journal of Abnormal Psychology* 95: 144-149.

Williams JMG, Chan S, Crane C, Barnhofer T, Eade J, Healy H (2006): Retrieval of autobiographical memories: the mechanisms and consequences of truncated search. *Cognition and Emotion* 20:351-382.

Williams JMG, Dritschel BH (1988): Emotional disturbance and the specificity of autobiographical memory. *Cognition and Emotion* 2:221-234.

Williams JMG, Dritschel BH (1992): Categoric and extended autobiographical memories. In Conway MA, Rubin DC, Spinnler H, Wagenaar WA (Eds): *Theoretical Perspectives on Autobiographical Memory*, pp. 391-412. Dordecht, Boston & London: Kluwer Academic Publishers.

Williams JMG, Ellis NC, Tyers C, Healy H, Rose G, MacLeod AK (1996): The specificity of autobiographical memory and imageability of the future. *Memory & Cognition* 24: 116-125.

Williams JMG, Nulty DD (1986): Construct accessibility, depression, and the emotional Stroop task: transient mood or stable structure? *Personality and Individuals Differences* 7:485-491.

Williams JMG, Scott J (1988): Autobiographical memory in depression. *Psychological Medicine* 18:689-695.

Williams JMG, Watts FN, MacLeod C, Mathews A (1988): *Cognitive Psychology and Emotional Disorders.* New York: Wiley.

Williams JMG, Watts FN, MacLeod C, Mathews A (1997): *Cognitive Psychology and Emotional Disorders 2nd Ed.* Chichester: Wiley.

Wolfe J, Granholm E, Butters N, Saunder SE, Janowsky D (1987): Verbal memory deficits associated with major affective disorders: a comparison of unipolar and bipolar patients. *Journal of Affective Disorders* 13:83-92.

Wolkowitz OM, Reus VI, Weingartner H, Thompson K, Brier A, Doran A, Rubinow D, Pickar D (1990): Cognitive effects of corticosteroids in man. *Am J Psychiatry* 147: 1297-1303.

Woolrich MW, Behrens TE, Beckmann CF, Jenkinson M, Smith SM (2004): Multilevel linear modelling for FMRI group analysis using Bayesian inference. *Neuroimage* 21(4):1732-47.

Woolrich MW, Ripley BD, Brady M, Smith SM (2001): Temporal autocorrelation in univariate linear modeling of FMRI data. *Neuroimage* 14(6):1370-86.

Wright CI, Fishcer H, Whalen PJ, McInerney SC, Shin LM, Rauch SL (2001): Differential prefrontal cortex and amygdala habituation to repeatedly presented emotional stimuli. *NeuroReport* 12:379–383.

Wust S, Federenko I, Hellhammer DH, Kirschbaum C (2000): Genetic factors, perceived chronic stress, and the free cortisol response to awakening. *Psychoneuroendocrinology* 25:707-720.

Wust S, Federenko IS, Van Rossum EF, Koper JW, Kumsta R, Entringer S, Hellhammer DH (2004): A psychobiological perspective on genetic determinants of hypothalamus-pituitary-adrenal axis activity. *Ann NY Acad Sci* 1032:52-62.

Yiend J, Mathews A (2002): Induced biases in the processing of emotional information. In Shohov SP (Ed.): *Advances in Psychology Research (Vol. 13, pp. 43-68).* New York: Nova Science Publishers, Inc.

Yiend, Paykel, Merritt, Lester, Doll & Burns (submitted, *BMJ*). Long term outcome of depression: 23 year follow up.

Young AH (2004): Cortisol in mood disorders. *Stress* 7(4):205-208.

Young AH, Gallagher P, Porter RJ (2002): Elevation of the cortisol-dehydroepiandrosterone ratio in drug-free depressed patients. *American Journal of Psychiatry* 159:1237-1239.

Young AH, Sahakian BJ, Robbins TW, Cowen PJ (1999): The effects of chronic administration of hydrocortisone on cognitive function in normal male volunteers. *Psychopharmacology* 145:260-266.

Young AW, Rowland D, Calder AJ, Etcoff NL, Seth A, Perrett DI (1997): Facial expression megamix: tests of dimensional and category accounts of emotion recognition. *Cognition* 63: 271-313.

Young EA, Aggen SH, Prescott CA, Kendler KS (2000): Similarity in saliva cortisol measures in monozygotic twins and the influence of past major depression. *Biol Psychiatry* 48(1):70-4.

Young GCD, Martin M (1981): Processing of information about self by neurotics. *British Journal of Clinical Psychology* 20:205-212.

Zobel A, Barkpw K, Schulze-Rauschenbach S, von Widdern O, Metten M, Pfeiffer U, Schnell S, Wagner M, Maier W (2004): High neuroticism and depressive temperament are associated with dysfunctional regulation of the hypothalamic-pituitary-adrenocortical system in health volunteers. *Acta Psychiatrica Scandinavica* 109: 393-399.

Zobel AW, Nickel T, Sonntag A, Uhr M, Holsboer F, Ising M (2001): Cortisol response in the combined dexamethasone/ CRH test as predictor of relapse in patients with remitted depression: a prospective study. *J Psychiatr Res* 35:83-94.