LINKING ACTIONS TO OUTCOMES IN THE FRONTAL LOBE

MaryAnn P. Noonan

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Oxford

Keble College

Michaelmas Term 2010

LINKING ACTIONS TO OUTCOMES IN THE FRONTAL LOBE

MaryAnn P. Noonan

Keble College, Oxford **Michaelmas Term 2010**

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Oxford

ABSTRACT

Behaviour is guided by accumulated experience, valuation and comparison. While many aspects associated with these functions are mediated by the frontal lobes, the precise contribution from particular regions remains debated. This thesis will deal with how an organism comes to select an option and will specifically focus on the role of the orbitofrontal cortex (OFC) in two mechanisms in this process: learning of outcome specificities and selecting between multiple options based on their expected values. Despite evidence emphasizing anatomical and connective heterogeneity within this structure, the OFC is often regarded as a uniform region. This thesis aims to resolve some of this uncertainty by assuming that the medial and lateral regions of the OFC contribute differentially to learning and decision-making. Two distinct methodologies were used in these investigations. First, the contribution of the medial OFC to social and emotional processing was examined. The findings from this study disprove previously held beliefs that the medial regions of the OFC guide social and emotional behaviours, but indicted a role for this region in value-guided decision-making. The second study examined functional differences between the lateral and medial OFC by making circumscribed lesions to either region in macaque monkeys. The animals performed a number of 3-armed bandit tasks which were designed to investigate different aspects of value assignment and comparison. The results show that while lateral OFC was required for "credit assignment" – the correct assignment of values to visual cues – medial OFC was critical for comparison of the cues' values during decision-making. In unchanging probabilistic environments, mOFC lesions induced decision-making impairments when value comparison was difficult without affecting credit assignment and associative learning. By contrast, lateral OFC lesions caused the opposite pattern of impairment. The final study used human-neuroimaging techniques to investigate the differential representation of outcome-specific contingency learning and found not only that the expectation of a unique outcome facilitated learning and memory recall but that this was supported by a neural network which included the lateral regions of the OFC and the anterior cingulate cortex. Activity in the mOFC did not correlate with outcome-specific contingency learning but instead reflected both the value associated with the receipt and expectation of a reward. Taken together, the results from this thesis suggest that specific parts of the OFC make markedly different contributions to these very different cognitive functions.

This work was funded by a 4 year Wellcome Trust studentship

ACKNOWLEDGEMENTS

This work would not have been possible without my supervisor, Matthew Rushworth. He is a brilliant scientist, a wonderful teacher and amazing mentor. I lack the adjectives to thank him sufficiently for his constant support and patient encouragement. I feel incredibly fortunate to have been his student, having him to guide me through this work. From every broken joystick to every single first level Feat analysis, I have enjoyed every moment in the Rushworth lab and am so grateful to have been a part of it.

The success of the animal projects in this thesis relied so heavily on Mark Walton and Tim Behrens. I am so very grateful to Mark for showing me the ropes and training me to train. I have taken up countless hours of his time. His support, knowledge and advice (task-related and otherwise) have been invaluable. I am indebted to Tim. His enthusiasm is inspirational and his modelling and analytical skills are daunting.

Throughout my PhD I have lucky enough to share an office with Rogier Mars. Rogier has been invaluable to the fMRI project described in this thesis. From concept, programming and analysis, I thank him not only the big things but also for having endured with me the everyday scientific grind: every high and every low.

Thanks too must be paid to Jerome Sallet and Peter Rudebeck. I am grateful for Jerome's support and company in darkened rooms and video editing suites. Pete has been a cross-Atlantic angel of mercy on so many occasions. I thank him for his time in answering anxious emails, his impeccable organisational skills and his thesis.

I would like to thank the F-level/level 3 technicians and veterinary staff for providing first-rate care for the animal subjects in this thesis. Special mention should also go to Mark Buckley for his excellent surgical skills, Greg Daubeny Taylor for his superb histology, Peter Rhone in electronics for his amazing ability to fix the aforementioned joystick. Also thanks to Steve Knight at OCMR for scanning my 39 participants and for training me in radiography.

I would like to thank Laurence Hunt and Sarah Rudebeck: wonderful colleagues and amazing friends. Thanks also to James Unwin, his contribution to this thesis and his faith in me must be acknowledged sincerely and gratefully. I would also like to thank (in no particular order) Jacinta O'Shea, Erie Boorman, Ethan Buch, Jill O'Reilly, Carinne Piekema, Charlie Stagg, Paula Croxson and Debbie Clarke. Without these good people my thesis and life would be less interesting.

I am indebted to my family: my wonderful parents Terry and Philomena and my dear brothers and sisters, Jo, David, Katy and Philip. They mean the world to me and I appreciate so much their faith and love. I am also grateful to my friends on the outside. They not only offer me a life beyond the lab, but critically they do no judge when I so often fail to take it.

Finally, my acknowledgement of Ross McAdam - here again I can't find the right words. Put simply, this work and its author would be missing without him. He is never at a loss for words of support, encouragement and perspective. He wrote many of my analysis scripts, troubleshooted countless problems and even read chapters of this thesis, despite having his own to write. I will endeavour to return the favour, but for now all I can do is thank you.

LONG ABSTRACT

The ventromedial prefrontal cortex (vmPFC) in humans is associated with emotional processing, learning and decision-making. However, whilst the nature of these functions has been examined the anatomical foci of function have tended to be overlooked. The vmPFC is composed of a number of distinct anatomical subregions; the orbitofrontal, the anterior cingulate and frontopolar cortex. For many years the orbitofrontal cortex (OFC) was believed to support emotional and social processing through its role in representing primary reinforcement or punishment (Rolls, 1999). However recent evidence suggests the contributions of the anterior cingulate cortex (ACC) to normal social evaluative processes and the frontal polar cortex (FPC) to relative choice valuation should not be overlooked. Moreover, detailed analysis of the anatomical structure and connectivity of the OFC has demonstrated that it is far from a homogeneous structure and instead is composed of a mosaic of areas. Based on cortico-cortical and cortico-subcortical connections these subregions have been broadly divided into two connectional networks: the 'medial' and the more lateral 'orbital' prefrontal network. As cortical function is critically dependent on the intrinsic and extrinsic connective patterns of a brain region as well as its anatomical structure it is possible that functional differences exist within OFC subregions. Chapter 1 will review a number of animal and human studies which have contributed to the understanding of the role of the OFC in emotional and emotional processing, learning and decision-making. Chapter 2 will discuss the anatomy of the OFC. Describing cyctoarchitectonic and connective differences between medial and lateral regions of the OFC and how these may relate to differences in regional function. Collectively, these chapters will consider the hypothesis that learning and decision-making are functionally separable within the OFC and set

out a number of experiments described in detail in the subsequent chapters which support this hypothesis.

The first experiment set out to address the alterations in socially guided behaviour after damage to parts of the vmPFC. The debate over the loci of social and emotional processing in humans is complicated by the nature of stroke damage: being rarely restricted to a well defined cortical area. Various theories have argued that changes in personality following frontal brain injury were due to damage to the OFC and were supported by this region's role in stimulus-reinforcement learning (Rolls, 1999). However vmPFC damage in patients usually includes mOFC, as well as affecting subgenual/perigenual ACC. Recent work shows that only emotional processing relies on the OFC (Rudebeck et al., 2006a). Social valuation, in contrast, is mediated by the ACC. If changes in emotional processing are attributed to reinforcement guided learning mechanisms, and these mechanisms are only supported by the lOFC (Walton et al., 2010), only damage to lateral areas should contribute to impairments in emotional processing. Therefore, the purpose of the study described in Chapter 3 was to investigate the specific contribution of mOFC to emotional and social valuation. Four macaque monkeys were tested on a species-specific task measuring the animals' valuation of emotional and social stimuli (Rudebeck et al., 2006a), prior to and after focal lesions of mOFC. This group of animals was compared to previously collected data on the same task with animals with lesions to the ventral and lateral regions of the prefrontal cortex as well as animals with lesions to the anterior cingulate gyrus (ACCg). These comparisons revealed that only animals whose lesions included the lOFC were impaired in emotional valuation and only animals with ACCg lesions were impaired in using social information to guide subsequent actions. This chapter does however implicate the mOFC in value-guided decision-making as mOFC lesions deficits were identified in a probabilistic 2-choice decision

task. These deficits were not seen after ACCg lesions. In summary, the double dissociation between the patterns of impairment suggests that vmPFC involvement in decision-making, emotional and social valuation may be mediated by distinct subregions centred on mOFC, lOFC and ACCg respectively.

In order to directly address the uncertainty surrounding the role of the OFC in value-guided learning and decision-making, the second experiment explored the hypothesis that the lOFC is involved in the assignment of value to a previously selected option (Walton et al., 2010), while the mOFC contributes to value comparison between multiple competing options. Macaques performed 3-armed bandit tasks designed to probe these different aspects of learning and choice behaviour and the effects of selective mOFC lesions were contrasted against lOFC lesions. The results described in Chapter 4 confirmed the specificity of impairments in value assignment to the lOFC, as mOFC-lesioned animals were still able to learn stimulus values. However, mOFC-lesioned animals demonstrated deficits in comparing the stimulus cues' values during decision-making. In unchanging probabilistic environments, mOFC lesions induced decision-making impairments when value comparison occurred in difficult multi-option environments. In contrast, lOFC-lesioned animals showed no such impairment in decision-making. These results therefore describe a double dissociation within the OFC.

Chapter 5 attempts to clarify the nature of the impairment experienced by mOFC-lesioned animals by comparing their choice behaviour in dynamically-changing environments relative to their control performance. The results suggest that, contrary to axiomatic assumptions of decision theory, the mOFC-lesioned animals' value comparisons were no longer independent of context or the presence of alternative options. MOFC-lesioned animals were beguiled into choosing the second best option partly as a function of there being a large difference in value

between it and the worst option. The pattern of impairment suggests the mOFC is critical for maintaining a uniformly scaled "decision-making space" for rational decision-making.

The final experiment initially investigated whether outcome-specific expectations of a forthcoming reward were associated with improved learning and memory. This concept has been demonstrated in numerous animal learning experiments (Schmidtke et al.; Carlson and Wielkiewicz, 1972; Trapold and Overmier, 1972; Jones and White, 1994; Miyashita et al., 2000; Kelly and Grant, 2001; Easton and Gaffan, 2002; Urcuioli, 2005; Ramirez and Savage, 2007). Such studies suggest that this process relies on a number of cortical and subcortical regions including the OFC, temporal cortex and the amygdala. However, this network is still not well understood, particularly in humans. The current study sought to investigate learned expectations acquired through an outcome-specific contingency learning mechanism, using a novel version of the Differential Outcomes Procedure adapted for humans. Pre-conditioning Stimulus-outcome (S-O) and Response-outcome (R-O) exposure phases were combined with final Stimulus-response (S-R) learning and during each phase the consistency of the outcomes which followed individual stimuli and actions were manipulated. Chapter 6 describes how predicable outcomes were found to significantly improve learning and recall of visuomotor associations and implied that a specific expected outcome can act to guide a selective human behavioural response.

The second objective of the experiment described above was to investigate the neural basis of underlying the behavioural advantage associated with outcome consistency. Functional magnetic resonance imaging (fMRI) measured the blood-oxygen-level dependent (BOLD) responses during the final S-R learning phase and it was anticipated that the OFC would show increased activation in subjects with access to outcome-specific information to guide choice behaviour. This hypothesis was based on rat lesion (Ostlund and Balleine, 2005, 2007a, b;

Ramirez and Savage, 2007) as well as human neuroimaging experiments (Valentin et al., 2007; de Wit et al., 2009) which implicated this region in outcome-specific contingency and goal-directed S-O learning. The results presented in Chapter 7 indicated that the lateral orbitofrontal cortex showed differential activation for error related feedback and the knowledge of the rewarding environment when consistent S-O and R-O mappings were available to guide action selection. Furthermore, the ACC also showed differential activation in proportion to the subject's knowledge about which response to select. Critically though, this experiment distinguishes between the contributions of the mOFC and lOFC to outcome-specific learning. Previous studies emphasize the role of more medial regions of frontoventral cortex in outcome-specific or goal-directed learning (Valentin et al., 2007; de Wit et al., 2009). However, this chapter will argue that for various reasons these studies misattribute mOFC activation that is really related to valuation and choice, to the updating of stimulus-outcome values.

Chapter 8 brings all the work in this thesis together and discusses the markedly different contributions of the lOFC and mOFC to learning and decision-making. This chapter also explores a number of potential avenues for further research and discusses potential reasons to explain why some of the results conflict with previous studies.

TABLE OF CONTENTS

CHAPTER 1: THE CONTRIBUTION OF THE VENTROMEDIAL PREFRONTAL CORTEX TO EMOTIONAL AND SOCIAL PROCESSING, LEARNING AND DECISION-MAKING

Damage to the ventromedial prefrontal cortex (vmPFC) in humans is associated with impaired learning, decision-making and emotional processing. However, whilst attention has been focused on the nature of these impairments, the anatomical foci of function has tended to be overlooked. For a number of years it was suspected that sub-region of the vmPFC, the orbitofrontal cortex (OFC), was the critical foci for all of these deficits, as it was thought to underlie emotional and social processing through its role in representing primary reinforcement or punishment. However, recent evidence suggests that the contributions of the anterior cingulate cortex (ACC) to normal social evaluative processes, and the frontal polar cortex to relative choice valuation should not be overlooked. As a result research is beginning to consider the importance of anatomical differences between the subregions of the frontal cortex. This thesis presents evidence that the anatomical subdivisions within the OFC are functionally meaningful, with relatively independent regions uniquely contributing to specific aspects of learning and decision-making.

1.1 Introduction

What an apple must be to Newtonian physicist, a tamping iron is to a frontal lobe cognitive neuroscientist. Just as the apple is said to have fallen from the sky, striking the head of Issac Newton and inspiring a branch of physics for the following 500 years, a tamping iron is reported

to have exploded through the medial frontal lobe of one Phineas Gage and inspired the theory that the frontal lobes play a distinct and critical role in guiding behaviour. This thesis is inspired by the latter event and aims to contribute to the developing theories of frontal lobe function.

The reason why this and so many previous theses can be inspired from a single event in medical history is that it is so well documented. In 1848, Phineas Gage, a 25-year-old New England railway foreman, attempted to push an explosive charge into solid rock with a tamping iron. Unfortunately, his choice of actions set off an uncontrolled explosion that drove the iron into the left side of his skull. Remarkably, Gage survived and was delivered to John Harlow who treated and recorded the subsequent recovery. Over the next 12 years, until Gage's death, Harlow detailed the severe changes in emotion, social behaviour and decision-making. In the years since various attempts have been made to localise the lesion Gage suffered. Using his still-existing skull and modern neuroimaging techniques (Figure 1.1) it is suggested that the damage involved bilateral anterior and right mesial OFC, bilateral polar and mesial frontal cortices and bilateral anterior ACC gyrus (Damasio et al., 1994). These conclusions are not without controversy and so the precise locus of the damage, as well as the extent of the personality changes following the injury, remain in debate. Despite this, Gage's case retains its status as the first to demonstrate the importance of the frontal lobes in normal emotional, social processing as well as decision-making. It therefore stands in history as an event which shaped the theory and understanding of brain function.

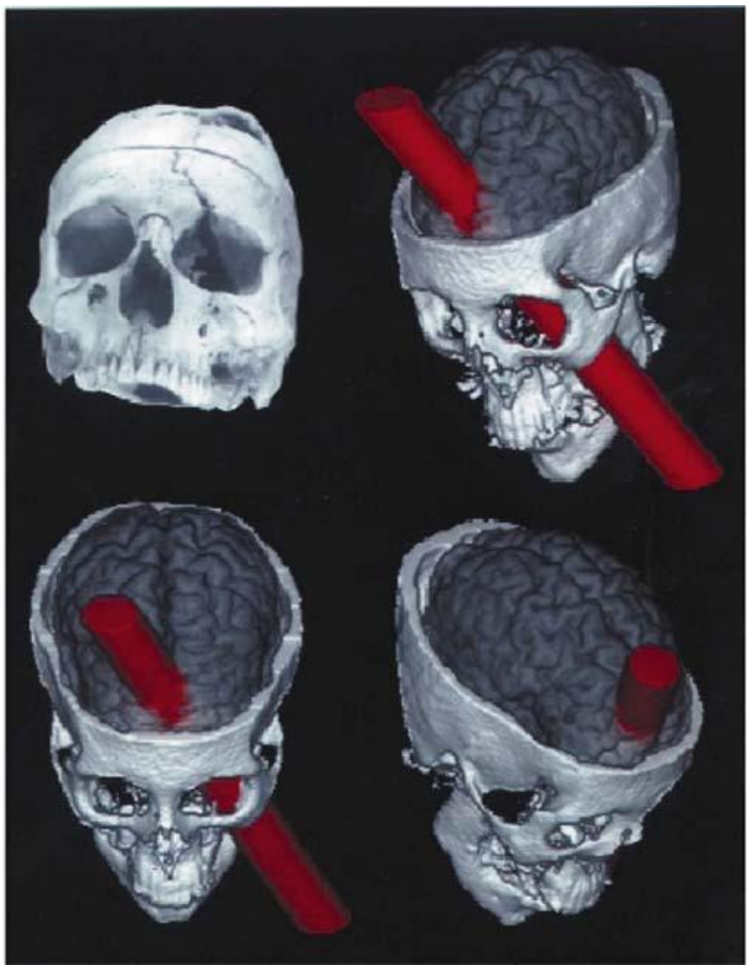

Figure 1.1. A reconstruction of the passage of the tamping iron through the head of Phineas Gage. The images are based on scans from the skull (top left) and show that the tamping iron entered through his left cheek and exited close to the midline, predominantly damaging the left ventral and medial frontal cortex. Permission to adapt and reprint granted by Damasio et al (1994) and the American Association for the Advancement of Science.

Since Gage, another patient with a more selective vmPFC lesion has been studied extensively (Eslinger and Damasio, 1985; Saver and Damasio, 1991). Patient EVR had a large orbitofrontal meningioma surgically removed and, despite the evidence of his intelligent remaining intact, EVR developed profound personality changes. The surgery removed bilateral OFC and right mesial Brodmann areas 32, 10, 8, 9, 24 and the anterior portion of area 6.

Similarly, on the left mesial damage included areas 8, 9 and 24. The lesion also affected the right dorsolateral cortex (prefrontal fields 8, 9, and 46). In tests of language, memory, visual perception, construction, abstraction, calculation and orientation EVR showed above average functioning. His social judgement was deemed sensible; his reasoning logical and his Minnesota Multiphasic Personality Inventory (MMPI) profile did not indicate psychopathology. Yet, the authors argued, there was a dissociation between the intact cognitive abilities, as measured by standardised testing, and the actual utilisation of those abilities in the real environment. When EVR was called to act on the real-life equivalent of the problems he was posed with in the laboratory he usually took the wrong action. In his life since the surgery this manifested in bankruptcy, two divorces, a potentially new bad marriage, the loss of numerous jobs and continued employment problems. Eslinger and Damasio coined the term "acquired sociopathy" to describe EVR's dramatic change in personality.

Case studies, while considerably informative, require corroboration. Subsequent to the discovery of EVR, groups of patients with damage localised within the ventromedial frontal cortex have been studied and compared to patients with lesions outside of the vmPFC, such as the dorsolateral PFC (dlPFC), and to normal healthy control subjects. Collectively, these patients are described as showing alterations in personality, learning and decision-making. Patient studies can be broadly divided into two groups. First, there are those which emphasise the social impairments and personality changes, such as increases in the expression of socially inappropriate behaviour, aggression and impulsivity, as well as the tendency to misinterpret other people's moods (Hornak et al., 1996; Hornak et al., 2003; Berlin et al., 2004). Patients often show impairments in the judgement of other people's intimacy through non-verbal cues (Mah et al., 2004), as well as in their ability to interpret facial and vocal emotional expressions (Hornak

et al., 1996; Mah et al., 2005; Heberlein et al., 2008) and processing of moral violations (Ciaramelli et al., 2007).

Second, there are those studies that describe vmPFC patients impairments in learning and decision-making (Rolls, 2005). In what are now considered seminal studies in frontal lobe psychology conducted at the University of Iowa, vmPFC patients, including EVR and normal healthy controls, played a probabilistic game for monetary reward (Bechara et al., 1994; Bechara et al., 1997; Bechara et al., 1999). In the Iowa gambling task (IGT) participants choose between four decks of cards that lead to either monetary gains or losses at different rates. Two of the decks are described as "safe", because choosing cards from them yields small but constant gains with minimal losses. The other two decks are described as 'risky', as picking cards from them leads to large payoffs but even greater monetary losses. Bechara and colleagues (1994) showed that vmPFC patients initially behave like normal controls by exploring all decks. However, while the controls gradually begin to select more and more frequently from the overall advantageous decks, vmPFC patients continue to select frequently from the disadvantageous decks. Subsequent experiments measured skin conductance while the subjects played the game. Normal subjects were found to begin to generate anticipatory skin conductance responses (SCR) whenever they pondered a choice that turned out to be risky, before they knew explicitly that it was a risky choice, whereas vmPFC patients never developed anticipatory SCRs, although some eventually realised which choices were risky (Bechara et al., 1997; Bechara et al., 1999). Along with the impairments described by the Iowa group, vmPFC patients are also described as impaired in flexible stimulus-reinforcement learning. Patients have great difficulty in extinguishing their response to a now no longer rewarded stimulus in preference for the stimulus which was previously unrewarded (Rolls et al., 1994). This

impairment is particularly apparent in probabilistic environments and manifests in patients who have OFC and vmPFC damage, and who tend to accumulate less money over the course of a testing session (Rolls et al., 1994; Hornak et al., 2004).

Deficits are not only apparent in value-guided learning, but also in many aspects of value-guided decision-making, such as choice, risk, regret and guilt. Patients are significantly more inconsistent in their hypothetical paired choice preferences for food, famous people and colours than controls and non-vmPFC patients (Fellows and Farah, 2007). Furthermore, the deficits in relative value judgment did not correlate with deficits in reversal learning in these patients, suggesting two potentially dissociable functions of the vmPFC (Fellows, 2007). Additionally, they also show increased risky behaviour, often being more likely than controls to make risky choices when gains are small and losses high (Weller et al., 2007), and betting regardless of the chance of winning (Clark et al., 2008). Regret also appears to be processed differently after damage to the vmPFC. In the context of gambling, OFC patients show no discrimination in SCRs when viewing a better unchosen option compared to controls who do show discriminatory SCRs (Camille et al., 2004). vmPFC patients also appear to employ maximising strategies less often than normal subjects, consistent with the hypothesis that such damage affects the influence of regret on decision-making (Fellows, 2006). Similarly, patients are less sensitive to guilt, being less likely to donate money in economic games and less trustworthy in their play (Krajbich et al., 2009).

Deficits found in the laboratory do translate to real-world impairments. Tranel and colleagues investigated vmPFC patients using the Multiple Errands Test, which requires patients to execute a series of unstructured tasks in a real-world setting. These tasks include purchasing a number of small items and determining a number of pieces of information. The patients were

impaired relative to controls in the number of tasks they completed and the number of errors they made (Tranel et al., 2007).

A number of theories have been proposed to account for the changes in patient behaviour following vmPFC damage. One theory, by Damasio and colleagues (Damasio et al., 1990), was based on the findings from the IGT described above. The Somatic Marker hypothesis suggests that during normal learning emotion-based biasing signals generated from the body (SCR or somatic markers) are associated with specific events or different response options. When making a decision the reactivation of the somatic marker indicates the emotional reaction to a response option and biases appropriate action selection. Bechara and colleagues (1994) argue that vmPFC patients who show a preference for selecting decks of cards that are risky and disadvantageous overall are insensitive to future consequences and driven primarily by immediate outcomes. The theory argues that the lack of skin conductance responses in vmPFC patients suggest their representation of future outcomes are not marked (positively or negatively) with a somatic state and, as a result, patients struggle to easily accept or reject options.

While the Somatic Marker hypothesis attempts to account for the social and decision-making impairments in vmPFC patients, more recent evidence suggests that the absence of somatic markers may not fully explain patients' deficits. Indeed, it has been suggested that the SCRs described as anticipatory may not actually reflect the end product of the decision (Dunn et al., 2006). Furthermore, studies have suggested that vmPFC patients are aware that certain decks in the IGT are more risky than others, and that their impaired decision-making may actually be due to an inability to flexibly assign reinforcement values to stimuli (Rolls, 1999; Maia and McClelland, 2004; Fellows and Farah, 2005; Fellows, 2007). The latter theory suggests that this ability is a basic prerequisite for normal patterns of emotion and social behaviour, as well as

decision-making. It draws its support from a number of studies described above that show patients with vmPFC lesions perform poorly on tasks that require altering stimulus reward associations, such as visual discrimination reversal learning (Fellows and Farah, 2003; Hornak et al., 2004).

Whilst both theories attempt to fuse the impairments in decision-making and social processing together, they often fail to consider the extent of damage caused by the patient's brain injury. Lesions in humans typically straddle a number of anatomically distinct boundaries, and such theories may become overly complicated by attempts to amalgamate numerous deficits into one account. The frontal lobes contain a number of anatomical divisions and as such it is possible that function changes between them. Therefore, lesions that affect more than one brain region may produce more than one impairment. This suggests that the impairments in social processing, learning and decision-making experienced by vmPFC patients can be explained by exploring the specific brain foci of each function. This thesis will present evidence for this theory, focusing almost exclusively on a sub-region of the vmPFC, the OFC, its medial and lateral division and their respective roles in learning and decision-making. The remainder of this chapter will discuss the contribution of this region to emotional and social processing, and learning and decision-making, as investigated in animal studies and with human neuroimaging techniques. One of the benefits of animal research is that lesions can be made in precise locations within the brain, unlike those in human patients, where lesions often encroach across the boundaries of anatomical areas. Similarly, many neuroimaging techniques have very high spatial resolution and so offer numerous advantages for exploring regional functional specialization. Although Chapter 2 will discuss the connections and cytoarchitecture of these two areas in the

human and macaque in detail, the following three sections will assume that there are genuine cross species correspondences in these areas' anatomical connections and functions.

1.2 Contribution of the mOFC to Social and Emotional Behaviour

Animal Studies

The previous discussion focused on the OFCs role in learning and decision-making, which is thought to underlie the social and emotional impairments experienced by patients with lesions in this area of the frontal cortex (Rolls, 1999). Yet despite the interest in the role of the frontal lobe few studies have objectively investigated impairments in social and emotional processing in animals and so much remains unknown about how the OFC contributes in isolation to these functions.

Those studies that have examined these issues have tended to focus on the effects of OFC lesions to fear responses in the macaque monkey and exploited their natural perception of unfamiliar humans as threatening. Monkeys have an innate aversion to snakes and this is typically assessed using variants of a task developed by Mineka and colleagues (1980). In this task a piece of food, desired by the animal, is placed near a toy snake. The macaques are then given the opportunity to retrieve the food, and their latency to do so acts as an index of how fearful they are of the snake. Normal macaques are slow to retrieve the food, if they do so at all. In contrast, macaques with lesions to the OFC are more reliable in taking the food, suggesting that they perceive the snake as less threatening (Kalin, 2003; Izquierdo et al., 2005; Rudebeck et al., 2006a). These same OFC-lesioned macaques also show more aggression to unfamiliar humans (Izquierdo et al., 2005) and less freezing behaviour (Kalin, 2003; Fox et al., 2010). In

more ecological settings OFC-lesioned animals show more aggression to other macaques during social interaction than control animals (Machado and Bachevalier, 2006).

Recent work has demonstrated a double dissociation between social and emotional processing in the vmPFC (Rudebeck et al., 2006a). Three groups of macaques performed a task similar to that described above, used by Mineka and colleagues (1980). One group of animals had lesions made to their ventrolateral and lateral orbital prefrontal cortex (PFv+o), one group had anterior cingulate gyrus (ACCg) lesions, while another group acted as the un-operated control group. The animals' reaching latencies to pieces of food were measured while they were exposed to either emotive snake stimuli; socially relevant stimuli, including images of other macaques; or staring unfamiliar humans; or neutral junk items. The authors reported that normal macaques respond fearfully in the presence of the snake and demonstrated differential interest in the different types of social stimuli, suggesting differential value estimations (Figure 1.2). Macaques with PFv+o lesions were only significantly different to control animals in how they reacted to the fearful stimuli, while they maintained similar differential reaching latencies to the different social stimuli. The authors therefore concluded that the valuation of emotional but not social information was supported by this region of the OFC. In contrast, they argued that the ACCg was a more likely candidate in social valuation, as the animals who received lesions to this region were uninterested in any of the videos of the other macaques and the pattern of differential interest seen in control animals was absent.

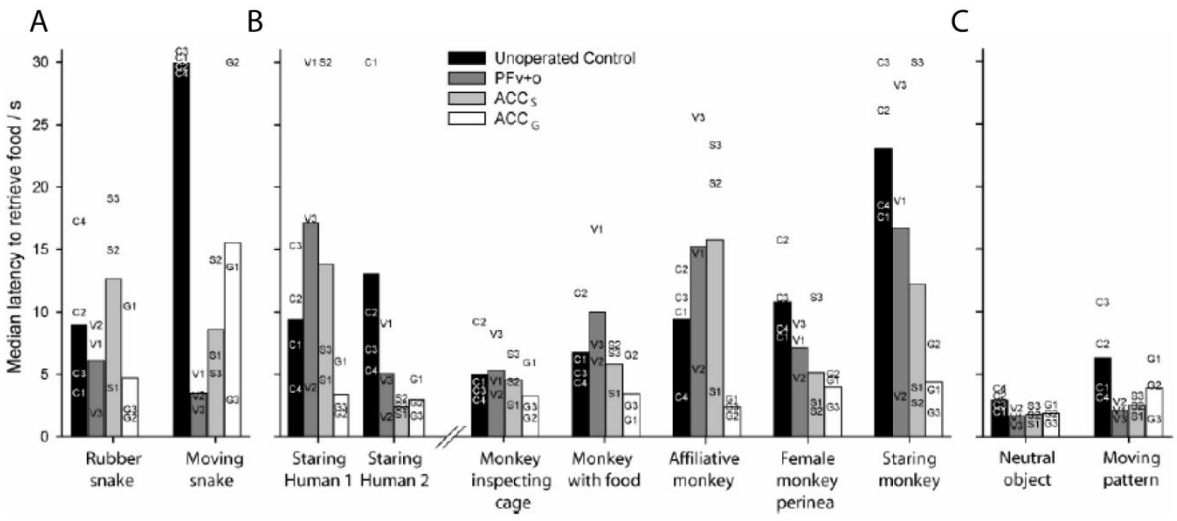

Figure 1.2. Median latencies to retrieve a piece of food in the presence of mildly fearful (**A**) or socially relevant stimuli (**B**) as well as neutral items (**C**) of PFv+o, ACC sulcus and gyrus lesioned monkeys compared to un-operated control animals. Symbols indicate scores from each individual. Permission to adapt and reprint granted by Rudebeck et al. (2006a) and the American Association for the Advancement of Science.

These impairments are not only restricted to humans and macaque monkeys; whilst rare, studies of OFC-lesioned rats report a similar pattern of emotional impairment. After OFC lesions, made either through aspiration or electrolyte, rats are more aggressive in tests of social interaction (Kolb, 1974; de Bruin et al., 1983; Rudebeck et al., 2007). Frontal lesions focusing on the OFC also show a decrease in anxiety-related behaviour in unconditioned fear condition paradigms, such as elevated maze or in the open field, as well as during social interactions, shock probe burying (Gonzalez et al., 2000; Lacroix et al., 2000; Shah and Treit, 2003) and decision-making tasks (Rudebeck et al., 2007).

As described, the similarity between OFC-lesioned animals and human patients with vmPFC damage underscores the important contribution of the OFC to emotional processing. Moreover, the close association between emotional impairment and the ability to flexibly learn

stimulus-reinforcement associations after OFC lesions has led to the argument that the latter inability may underlie the former (Rolls, 1999). According to this view, if an animal or person with an OFC lesion is unable to predict the reinforcement consequence of a stimulus, the mechanism which guides normal emotional response to the stimulus will be impaired as well.

Human neuroimaging studies

Discrete lesion studies can often neglect the neural network which operates to co-ordinate behavioural responses. Functional imaging studies in humans provide a useful tool for highlighting the contribution of other brains regions, including the amygdala, insula and striatum (Frey et al., 2000; Murphy et al., 2003; Schienle et al., 2006; Schafer et al., 2009). Morris and Dolan (2004), for example, investigated conditioned fear stimulus reversals in a human neuroimaging study. They demonstrated that the OFC flexibly responds to the stimuli after a reversal, but that the amygdala shows a persistent memory response that reflects the previous conditioning. Furthermore, the extinction of fear conditioning has been shown to activate the vmPFC and hippocampus (Phelps et al., 2004; Milad et al., 2007).

Collectively the studies described above implicate the OFC in emotional processing, but as discussed earlier the OFC is not a uniform structure. The anatomical and connective differences between the medial and lateral regions of the OFC have been extensively characterised (Carmichael and Price, 1994, 1996; Ongur et al., 2003), and it therefore may be that the different regions have differing contributions to emotional processing. Until recently the majority of animal OFC lesion studies remove cortex in both the lateral and medial regions. However, recently a macaque lesion study focused on the impact of lOFC lesions on associative S-R learning and found that post-operatively animals were impaired in assigning reinforcement

value to the appropriate stimuli (Walton et al., 2010). Moreover, this impairment was confined to the lateral regions as an independent study demonstrated that this impairment was not present after mOFC lesions (Chapter 5). If it is the case that impairments in stimulus-outcome (S-O) learning underlie the deficits in emotional processing (Rolls, 1999) one could hypothesise that emotional deficits should be seen only after lOFC lesions and not medial. Therefore tests that directly assess changes in emotional processing after mOFC and lOFC lesions are needed in order to identify the specific contribution of these brain regions. Chapter 3 describes an experiment that aimed to address this hypothesis. Using identical task set-up and stimuli as the Rudebeck and colleagues (2006a) study this chapter explored the contribution of specific mOFC damage to a macaque's ability to utilise socially or emotionally valuable information to guide actions.

1.3 Assigning and Comparing the Unique Contributions of the OFC to Reward-Guided Learning and Decision-Making

The OFC has a well documented involvement in learning and decision-making. Investigators have made use of various techniques and species in an attempt to define the specific regions' contributions to these complex and multifaceted cognitive functions. However, whilst substantial accumulated knowledge has evolved theories and understanding of this brain region, questions still remain over the precise nature of the OFC involvement. Difficulties in interpreting the role of the OFC in learning and decision-making may be due in part to the tasks used in the investigations. Many tasks inadvertently confound learning and decision-making; often, once a choice is made, the outcome is used to update reward expectancies. Likewise, during tasks designed to investigate learning subjects typically are choosing between stimuli and actions. For

example, an extinction test, which aims to assess choice in the absence of the confound of reward outcome, is alternatively confounded by violations of learned expectations: negative prediction errors. For these reasons, establishing the OFCs role in these two functions is challenging. However, the following sections will attempt to review studies of learning and of decision-making in the OFC and vmPFC. It draws on data obtained from a number of different species as well as with different methodologies.

The Contribution of the OFC to Reward-Guided Learning

Animal Studies

Aspiration lesions of the OFC in monkeys have been shown to affect tasks that assess the flexible reassignment of stimulus-reinforcement associations (Jones and Mishkin, 1972; Meunier et al., 1997; Izquierdo et al., 2004). Typically these tasks require macaques to perform two-choice visual object discriminations for food rewards. Once the animal learns that one object leads reliably to food, the object-reward contingency is reversed, such that the previously unrewarded object now yields reward. After a reversal normal monkeys are quick to learn the new associations. In contrast, OFC-lesioned animals perseverate and continue to choose the previously rewarded object, suggesting that OFC-lesioned animals are unable to flexibly assign reward value to the previously unrewarded objects. However, recent work indicates this is not the complete picture, as the OFC lesion impairment lies more particularly in the monkey's inability to use correctly performed trails to guide subsequent choice (Rudebeck and Murray, 2008). Furthermore, Walton and colleagues demonstrated that OFC lesions impair a monkey's ability in causally assigning reward value to a particular stimulus choice: *credit assignment* (Walton et al., 2010). The authors argue that normal monkeys learn to attribute value to a

stimulus as a function of the precise history of reward received in association with the choice of that particular stimulus. In contrast, animals with OFC lesions value a particular stimulus as a proximity-weighted function of the history of all rewards received approximately at the time of stimulus choice, even when the rewards were actually caused by choices of the alternative stimuli on preceding and subsequent trials, a phenomenon that Thorndike termed "Spread of Effect" (Thorndike, 1933). Thus these data imply that OFC monkeys, whilst able to process the outcomes of choices, are no longer able to associate these outcomes with the preceding choice on which they were contingent "Law of Effect". Instead the animals can only form associations between the overall integrated history of choices and an overall integrated history of outcomes.

The OFCs role in generating reinforcement or outcome expectancies associated with visual stimuli has been further emphasised by devaluation studies (Gallagher et al., 1999; Baxter et al., 2000; Pickens et al., 2003). One version of the outcome devaluation paradigm initially requires one set of stimuli to be paired with one specific outcome, such as a peanut, and another set of stimuli to be paired with a different outcome, such as a raisin (Izquierdo et al., 2004). In the training phases rewards are hidden beneath stimulus objects and the animals learn to push over the object to reveal the reward. Once these training phases have been completed the animals are allowed free access to one of the two rewards and allowed to consume it to satiety. Immediately after this experience the animals are tested in extinction but the two sets of stimuli associated with the different rewards are now paired against each other and the animals must choose between them. The consistent finding is that control animals select stimuli that are associated with the reward that has not been devalued, suggesting they have updated their expected reward values as a result of being sated with one of the outcomes. In contrast, animals

with complete OFC lesions do not show this bias and choose equally between the two sets of stimuli, suggesting that they are unable to manipulate or utilise outcomes expectancies.

These effects are not confined to primate species and are evident in OFC-lesioned rodents for both reversal learning and Delayed Non-match to Sample paradigms (Gallagher et al., 1999; Chudasama and Robbins, 2003; Schoenbaum et al., 2003b). Furthermore, lesions of the rat OFC have uncovered a very precise role in reinforcement devaluation (Rescorla, 1992; Gallagher et al., 1999). Pickens and colleagues manipulated whether reinforcement was devalued before or after lesions, and revealed that the OFC is essential for maintaining representations of the current value of reinforcement and the subsequent use of this information to guide choices (Pickens et al., 2003; Pickens et al., 2005). This role of the OFC in using outcome expectancies has been further supported by the finding that lesions disrupt the use of differences in outcome expectancies to guide learning of instrumental responses (McDannald et al., 2005).

In addition, detailed lesion work has distinguished the anatomical loci of Pavlovian (cue driven) from instrumental (action driven) reward contingency learning. In non-human primates OFC lesions typically impair stimulus-reinforcement learning tasks (Rolls, 1999; Murray et al., 2007; Rudebeck et al., 2008b; Walton et al., 2010), whereas more medial vmPFC and ACC lesions impair response-reinforcement learning tasks (Shima and Tanji, 1998; Hadland et al., 2003; Kennerley et al., 2006). The findings in rat lesion experiments, whilst more difficult to translate to humans also suggest a medial versus lateral difference in location for Pavlovian and instrumental learning mechanisms. Lesions to prelimbic cortex (PL; sometimes argued to correspond to human ACC/vmPFC) have been shown to impair instrumental contingency degradation learning, namely, the selective weakening of the predictive status previously trained conditioned stimulus by means of delivering its outcome with the same probability in its

presence as in its absence (Corbit and Balleine, 2003; Killcross and Coutureau, 2003), as well as abolishing sensitivity of instrumental performance to outcome devaluation, while leaving intact pavlovian-instrumental transfer (PIT) effects (Ostlund and Balleine, 2005). In contrast, lesions to rat OFC disrupt the tendency of Pavlovian cues to facilitate instrumental performance in a PIT task but do not influence the suppressive effects of instrumental outcome devaluation (Ostlund and Balleine, 2007a). Ostlund and colleagues argued that its role was therefore limited to encoding predicative S-O relationships that could bias action selection (Ostlund and Balleine, 2007a). Taken together these findings indicate that, while the ventromedial regions of cortex are important for encoding response-outcome (R-O) associations (Dickinson and Balleine, 1993; Corbit and Balleine, 2000; Balleine, 2005; Kennerley et al., 2006), the OFC is critical for representing S-O associations (Ostlund and Balleine, 2007a; Walton et al., 2010).

Devaluation studies demonstrate not only that the OFC plays an important role in reward expectation but that this region holds an outcome-specific representation of an expected reward. Additional evidence for this comes from studies using the Differential Outcomes Procedure (DOP). This task involves subjects learning to press either right or left levers in an operant chamber in the presence of discriminative auditory stimuli, for example, either an auditory tone or clicker. As trials progress subjects learn that if they press the left response in the presence of the clicker they are rewarded with sucrose solution. If the animal makes the right lever response in the presence of the tone, solid food is delivered to the rat. Incorrect responses on the levers in the alternative auditory context are never rewarded. The rat's ability to learn the stimulus-response (S-R) associations in the DOP condition is compared to a condition in which the same food type is delivered (Non-differential Outcomes Procedure, NOP). Under normal circumstances, animals in the differential-outcomes condition have more rapid learning curves

than animals in control conditions, where the outcome of the event provides no outcome-specific cue to the appropriate action (Trapold and Overmier, 1972; Urcuioli, 2005). This effect has become known as the differential outcomes effect (DOE).

The DOEs effect is reported to be dependent on a network of brain regions including the OFC and amygdala. Ramirez and Savage (2007) had groups of rats with lesions to the OFC perform this task and revealed that OFC lesions impair accuracy in maintaining and using outcome-specific expectations (Figure 1.3). By contrast, lesions made to the amygdala impaired the ability to acquire S-R associations, as indicated by the persistence of the impairment. Finally, animals with nucleus accumbens lesions tended to show improved learning across the session relative to sham controls. Chapters 6 and 7 describe a novel version of the DOP adapted for use in humans in order to investigate the behavioural evidence (chapter 6) of the use DOE in humans S-R learning as well as the neural mechanisms potentially underlying outcome-specific contingency learning (chapter 7). Specifically, chapter 7 investigates the precise role of three cortical brain regions, the lOFC, mOFC and ACC with fMRI.

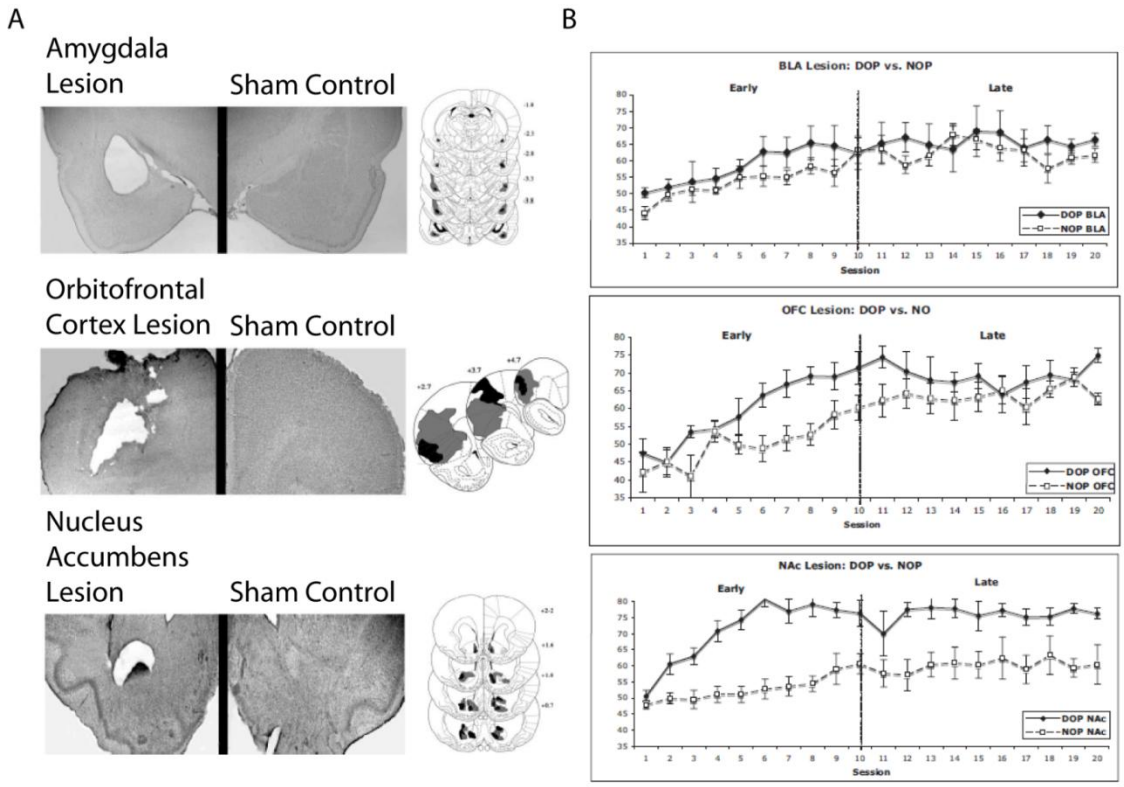

Figure 1.3. **A**. Photomicrographs showing stained sections, of amygdala, OFC and nucleus accumbens lesions (left panels), sham control (middle panel) and schematic representations of lesion extent (left panel). **B**. Mean percentage correct performance of the amygdala (top), OFC (middle) and nucleus accumbens (bottom) lesioned animals relative to sham controls for the acquisition and maintenance of conditional discrimination learning. From Ramirez and Savage (2007). Permissions for reprints are unnecessary for a single figure from the American Psychological Association.

Electrophysiological studies support the findings from ablative lesion studies. Recordings from macaque OFC neurons show that cells code reward upon receipt (Thorpe et al., 1983; Rolls et al., 1996; Hosokawa et al., 2004), as well as properties associated with external cues predictive of a forthcoming reward (Schoenbaum et al., 1998; Schultz et al., 2000; Schoenbaum et al., 2003a; Padoa-Schioppa and Assad, 2006) or punishment (Morrison and Salzman, 2009). With access to both critical pieces of information it is perhaps not surprising that cells have also been

shown to encode outcome-specific information, such as taste (Padoa-Schioppa and Assad, 2006), texture (Rolls et al., 2003b; Verhagen et al., 2003) and olfactory and gustatory sensation (Rolls and Baylis, 1994). More complex signals of anticipated magnitude of rewards or punishments (Padoa-Schioppa and Assad, 2006; Rolls et al., 2008; Kobayashi et al., 2010), probability (Kennerley and Wallis, 2009a), expected delay before reward onset (Wallis and Miller, 2003; Roesch and Olson, 2004, 2005a) and even reward preference (Tremblay and Schultz, 1999; Hosokawa et al., 2007) are also identified in neurons throughout the subdivisions of the OFC. Neuronal recordings during a S-O reversal suggest that OFC neurons code an error which requires a behavioural switch (Thorpe et al., 1983) and track visual or olfactory stimulus reinforcement across the reversal (Rolls et al., 1996). Similarly, in an olfactory discrimination task in rats, Schoenbaum and colleagues demonstrate that OFC neurons gradually develop specificity for different odour-outcome pairings, such that they fire in anticipation of either positive or negative outcomes (Schoenbaum et al., 1998; Schoenbaum et al., 2003a). Furthermore, after rats had learnt these pairings the activity of the cells encoded the value of the anticipated outcome following presentation of the different odour. Combining recording and lesion methods, these researchers demonstrate that through mutual interactions with the amygdala, the OFC is part of a system that is critical for integrating stimulus reward information to guide behaviour.

For learning to occur there must exist a difference between what is expected in the environment and what actually happens. This difference can often be quantified and has been termed prediction error (Sutton and Barto, 1998). Prediction errors can be bidirectional. If an outcome is more valuable than expected, the prediction error will be positive. In contrast, if the outcome fell short of expectations it would lead to a negative prediction error. Prediction errors

are particularly important signals and any brain regions critical for learning might be expected to modulate their neuronal firing rates in relation to such violations in expectations. Just such a signal can be identified in midbrain dopamine neurons (Schultz, 2000), which are known to project to a number of brain regions including the OFC (Ferry et al., 2000; Croxson et al., 2005; Haber et al., 2006). Whilst a number of studies tend to find weak or no evidence of positive or negative reward prediction error signals in the OFC (Kennerley et al., 2009; Takahashi et al., 2009), one very recent study shows neurons in the rat OFC which increase firing rates for both positive and negative reward prediction errors, encoding them at the same time (Sul et al., 2010). If verified, this finding suggests that prediction errors are encoded in multiple brain regions and potentially contribute to learning in a number of ways.

Collectively, the animal lesion and electrophysiological work suggests that the OFC plays a critical role in flexible and adaptive learning of S-O associations. Unfortunately, the methods described above have the tendency to neglect the anatomical and connective differences within this brain region. The OFC has some of the most studied anatomical and connection patterns in the frontal lobe and is far from a homogeneous structure (detailed in Chapter 2). Briefly, the OFC can be differentiated into two regions that lie mainly on the medial surface and on the ventral or orbital surface. The regions' connection profiles are distinct and there are relatively few connections between the two regions. Lesions in the OFC are often complete, removing both the medial and lateral surfaces and, due to the difficultly of accessing the medial surface with electrophysiological recording equipment, recordings are often restricted to only the more lateral parts of the orbital surface. This means that investigations of the OFC are often biased towards the lateral regions or fail to distinguish between the potentially different roles of lateral and medial OFC. One method without this potential bias is neuroimaging. The subsequent section

will present data acquired from functional magnetic resonance imaging (fMRI) and Positron Emission Topography (PET) experiments which have supported and expanded the interpretations of the function of the OFC in value-guided learning.

Human neuroimaging studies

Similar to the animal work described above, human neuroimaging studies have identified activity throughout the OFC and vmPFC associated with S-O reversal learning (O'Doherty et al., 2003a) and stimulus valence itself (O'Doherty et al., 2003a; Smith et al., 2010). Devaluation studies also implicate the OFC in the representation of changes in stimulus valuation. Activity in the OFC evoked towards predictive stimuli tends to decrease following outcome devaluation while activity associated with still-valuable stimuli is maintained (O'Doherty et al., 2000; Gottfried et al., 2003; Kringelbach et al., 2003). Furthermore, this decrease in OFC activation correlates with decreases in the subjective pleasantness of the food (Kringelbach et al., 2003). Collectively, these results suggest that the human OFC, just like the monkey, encodes stimulus-specific motivational and incentive values.

Devaluation studies have been taken as evidence that the OFC contributes to goal-directed learning (Valentin et al., 2007; de Wit et al., 2009). During value-guided learning, learned associations are dependent on an animal's specific reinforcement history of actions, stimuli or both, as well as the animal's subjective preference. Specific reinforcement history can be associated with environmental stimuli; such as visual cues, as is the case in Pavlovian learning, or individual actions; such as lever presses, as is the case in instrumental learning. In rats this has been localised to PL cortex and the OFC respectively (Killcross and Coutureau, 2003; Ostlund and Balleine, 2005, 2007a; Ramirez and Savage, 2007). Humans neuroimaging

studies show that this brain region encodes not only the valence of stimuli (O'Doherty et al., 2003a), but also action based and stimulus-response-outcome valence (Glascher et al., 2009). Valentin and colleagues scanned human subjects with fMRI while they learned to choose instrumental actions that were associated with the subsequent delivery of different food rewards (tomato juice, chocolate milk and orange juice). Following training, one of these foods was devalued by feeding to satiety on that food. The subjects were then scanned again while re-exposed to the instrumental choice procedure in extinction. Comparing BOLD response before and after stimulus-specific devaluation revealed changes associated with R-O information present in the medial and central OFC (Valentin et al., 2007).

Pavlovian and instrumental associations can both be contrasted with habitual responses, which are guided by a strong association between the stimulus and response in the absence of any explicit representation of the specific outcome generated by the response, and tend to activate more ventrolateral frontal cortex (as opposed to OFC), striatal (caudate nucleus), parahippocampal regions as well as middle temporal gyrus (Toni et al., 2001; Toni et al., 2002).

Together, these studies emphasise the importance of the OFC in monitoring and updating stimulus-specific reinforcement histories. However, these studies are not able to distinguish the source of the activation. Stimulus reversal and devaluation studies confound the factor of learning, i.e. updating value expectations on the basis of the presence or absence of a reward on that choice, with the act of then deciding between the two different options. Increasingly detailed fMRI studies have aimed to investigate the precise nature of value representation in the frontal cortex with the hope of determining which parts of the OFC play a role in learning the encoding of S-O or R-O associations (Tremblay and Schultz, 1999; Rolls, 2000) and which parts are

involved in guiding decisions, by encoding the value of alternative goals (Arana et al., 2003; Schoenbaum and Roesch, 2005; Padoa-Schioppa and Assad, 2006).

Many studies have found that the BOLD responses in the OFC correlate with the subjective value of expected, experienced and imagined outcomes. Various types of outcomes including positive and negative primary rewards (O'Doherty et al., 2001a; Gottfried et al., 2002; Plassmann et al., 2008), real and imaginary monetary reinforcements (Breiter et al., 2001; O'Doherty et al., 2001b; Bray et al., 2010), as well as socially rewarding stimuli such as the smile of an attractive face (O'Doherty et al., 2003b), have been shown to activate the OFC. These responses were predominantly observed in central and/or medial parts of OFC and there is some evidence that the experience of certain rewards and punishments can be dissociated to different OFC regions (O'Doherty et al., 2001a; Small et al., 2001; Ursu and Carter, 2005; Kim et al., 2006). In 2004, Kringelbach and Rolls reviewed this evidence and proposed two distinct trends of neural activity based on a meta-analysis (Kringelbach and Rolls, 2004). They argued for a posterior-anterior distinction in the OFC, with the more posterior regions involved in representing simple primary reinforcers, whilst more complex, abstract reinforcers were represented in more anterior structures. Similarly, they posited a medial-lateral trend, whereby mOFC was related to decoding and monitoring the reward value of reinforcers and the lOFC was involved in evaluating punishers, which when detected may lead to a change in current behaviour. Whilst this dissociation mirrors the functional segregation between gains and losses represented in prediction error coding in anterior and posterior ventral striatum respectively, the evidence in support of it in the OFC is not always consistent (Breiter et al., 2001; Elliott et al., 2003). O'Doherty and colleagues have suggested that the discrepancies relate to whether or not the negative reinforcement leads to a subsequent behavioural change and that this dissociation

may only be relevant during the receipt, rather than the expectation of reinforcement (O'Doherty, 2007).

There is strong evidence that the OFC and vmPFC encode the expectation of a forthcoming reward, called *expected value*. Activity in these regions has been shown to represent a number of components that contribute to the estimate of such an expected reward, such as magnitude (Elliott et al., 2000; Breiter et al., 2001; Galvan et al., 2005; Rolls et al., 2008), probability (Knutson et al., 2005), temporal delay (McClure et al., 2004; Tanaka et al., 2004; Kable and Glimcher, 2007; McClure et al., 2007) and uncertainty or risk (Tobler et al., 2007), even in the absence of choice (Knutson et al., 2005). Furthermore, OFC signals appear to integrate a number of these variables (Knutson et al., 2005). Knutson and colleagues demonstrate that activation in mesolimbic regions, including the mOFC and vmPFC correlate linearly with expected value in a probabilistic monetary incentive delay task (Knutson et al., 2005). Additional decomposition analyses indicate that distinct regions of the mesolimbic regions respond differently to particular components of expected value. Whilst the foci of activation for expected incentive value was the left anterior cingulate and bilateral nucleus accumbens, the main effect of reward magnitude was the OFC, and probability was encoded in the mesioprefrontal cortex. Finally, the authors showed that the interaction between the value and magnitude localised to the medial prefrontal cortex. In a separate experiment, Rolls and colleagues showed that mOFC represented both the actual amount of reward magnitude at the time of outcome, as well as the amount of reward expected probabilistically for a particular choice measured earlier in time (Rolls et al., 2008).

As discussed previously, the OFC has access to both the expectation of an outcome and the representation of the outcome itself, and as such has the potential to calculate prediction

error. Just as the dopamine system encodes this signal at the neural level in non-human primates (Schultz, 2000), investigations in human imaging experiments have similarly identified the presence of this key learning signal in the VTA (D'Ardenne et al., 2008), as well as regions targeted by dopaminergic neurons, including the striatum (Abler et al., 2006; Schonberg et al., 2007; den Ouden et al., 2009; Valentin and O'Doherty, 2009) and insula (Preuschoff et al., 2008). Specifically, studies have shown that activity in the nucleus accumbens correlates linearly with both positive and negative prediction errors (Abler et al., 2006) and that better learners have stronger BOLD activations, which correlate with reward prediction errors in the ventral and dorsal striatum (Schonberg et al., 2007). The OFC is anatomically networked with these regions (Ferry et al., 2000; Croxson et al., 2005; Haber et al., 2006) and, whilst the evidence for prediction error signals is still debated in the monkey, there is collective evidence of its presence in human OFC (Knutson and Cooper, 2005; Tobler et al., 2006; Bray and O'Doherty, 2007). Tobler and colleagues used a blocking paradigm in order to directly investigate the neural representation of reward prediction error (Tobler et al., 2006). In this task, a novel stimulus is blocked from learning by presenting it simultaneously with a stimulus which already fully predicts a subsequent outcome in a number of compound conditioning trials. By definition of its association, when subsequently presented on its own in test trials where no reward is delivered, the blocked stimulus would be expected to elicit no reward prediction error. Brain activity elicited by the blocked stimulus is compared to that of a stimulus which has come to acquire an association with an outcome, and on trials where the reward is withheld does produce a prediction error. The findings from this study showed that medial regions of the OFC show more activation to the stimulus that elicited a reward prediction error than the one that did not. Furthermore, activation in a more anterior region of the OFC increased towards the paired non-

blocked stimulus during learning trials which mirrored the increasing degree of associative strength between the stimulus and outcome. Finally, studies that model fMRI learning tasks with reinforcement learning algorithms find prediction error signals in the OFC which reflect the difference between the value of the outcome received on a given trial and the value of the expected outcome on that trial (Bray and O'Doherty, 2007).

As demonstrated in animal lesion experiments, contingency between outcomes and instrumental action or an external cue is a critical aspect of learning and has been localised to the PL and OFC of rats respectively (Ostlund and Balleine, 2005, 2007a). In humans, changes in OFC activity have also been demonstrated with regards to this aspect of associative learning. For example, Tanaka and colleagues investigated brain regions involved in contingency between actions (button presses) and outcomes (monetary reward) (Tanaka et al., 2008). Enhanced activity was found in dorsomedial striatum and vmPFC during blocks with greater contingency between actions and outcomes. Moreover, activity in vmPFC tracked local changes in contingency within blocks.

The Contribution of the OFC to Reward-Guided Decision-Making

Animal studies

Patients with vmPFC lesions not only display deficits in value-based learning, but also in value-guided decision-making. The classic report of patient EVR refers to his very laborious and often poor real-life decision-making which appeared to conflict with his evident access to the hypothetically correct course of action (Eslinger and Damasio, 1985). Similarly, patients are often more inconsistent in paired choice preferences for food, colours and famous people than controls and non-vmPFC patients, as well as in multi-attribute decisions, such as hypothetical

choices between rental apartments (Fellows, 2006; Fellows and Farah, 2007). Deficits in decision-making are less often studied in animal lesion experiments and the impairments in devaluation studies are typically attributed to an inability in updating current expected value. An alternative hypothesis suggests the deficit lies in the value-guided decision-making system. This account assumes subjects may still be able to update stimulus-value, but can no longer use these values for comparison between the options. The subsequent sections will explore the evidence from animal studies and human neuroimaging experiments that implicate the OFC in value-guided decision-making, and will ultimately propose that it might be possible to dissociate learning and decision-making within the OFC.

The previous sections detailed that neurons in the OFC encode expected and experienced rewards (Thorpe et al., 1983; Rolls et al., 1996; Schoenbaum et al., 1998; Schultz et al., 2000; Schoenbaum et al., 2003a; Padoa-Schioppa and Assad, 2006), and suggested that these signals are modulated by reward magnitude, probability and uncertainty (Padoa-Schioppa and Assad, 2006; Rolls et al., 2008; van Duuren et al., 2008; Kennerley and Wallis, 2009a; Kobayashi et al., 2010). As rewards act as basic goals of behaviour it is possible that the OFCs rich representation of the reward could serve to bias choice behaviour. OFC-lesioned animals demonstrate similar impairments to vmPFC patients in their altered representations of reward exceptions (Jones and Mishkin, 1972; Meunier et al., 1997; Izquierdo et al., 2004), as well as inconsistencies in reward preferences to paired food choices (Baylis and Gaffan, 1991). The specific nature of neuronal encoding of reward preferences was investigated by Tremblay and Schultz (1999). They proposed that preferences expressed by overt choice behaviour were relative and dependent on the available alternatives. For example, reward B preferred over reward C may be instantly neglected if alternatively paired against a more appetizing reward, A. To investigate whether

OFC neurons encoded this relative motivational value monkeys were presented with blocks of trials in which one of two visual cues, each associated a specific juice reward, in a standard delayed response task. Three different cue stimuli were used, paired with three distinct flavours of juice, but only two of them were presented in a given trial block. With independent verification of reward choice preferences (A over B and B over C) Tremblay and Schultz demonstrated that the activity of many OFC neurons in the posteriomedial areas 11, close to area 14, depended on the combination in which a particular reward occurred. Neurons were found which showed significantly higher activation preceding reward A when compared with reward B, but then would also elicit higher activation to reward B when paired in blocks with reward C. Neurons were also found which encoded the relative non-preferred juice option, and both types of activity were demonstrated during the receipt of the outcome, as well as with the reward-predicting cue stimulus. Subsequent investigations have shown that a similar pattern of relative encoding occurs with aversive outcomes (Hosokawa et al., 2007), and have also demonstrated changes in cerebral blood responses, as measured by PET, correlated with relative preferences (Obayashi et al., 2009). More recent studies have demonstrated that the time course of events is critical for the neuronal display of relative preference encoding. Padoa-Schippo and Assad intermixed alternative trials within blocks (a trial of B and C, followed by a trial of A and B), as opposed to the previous studies which compared alternatives across blocks (one block of A and B, followed by another block of B and C), while recording from area 13m and found that OFC neurons now only coded absolute economic value (Padoa-Schioppa and Assad, 2008).

As well as encoding some aspects of relative reward preferences OFC neurons also encode a number of aspects of economic choice, such as value of offer and chosen value. Economic choices are made when individuals select an option among many available

alternatives. These choices have no explicit "correct" answer but depend on subjective preferences. Padoa-Schioppa and Assad offered monkeys choices between different amounts of differentially preferred juice rewards. Monkeys' choices are based on a trade-off between juice type and juice quantity, and so relative value differences can be manipulated by systematically increasing the volume of the non-preferred juice (B), while keeping the preferred juice (A) volume constant. Neurons were identified in region 13 which encoded the *offer value* of the two juices during the period of time after the offer was presented to the animal; around the time value is being assigned to a particular choice. In order to choose between the two different offers their relative values must be encoded and compared. Behaviourally, choice preferences can be calculated by putting the different quantities of the two different juices on the same scale. Using a sigmoid function it is possible to estimate the value of the juice chosen by the animal and the point at which the volume of B is enough to cause the monkeys to choose it 50% of the time is called the indifference point. When the volume of B is below the indifference point its value is proportionally less than the value of A and the monkey is increasingly less likely to select it. In contrast, when the volume of B is above the indifference point its value is proportionally higher than that for A. Neurons have been identified that encode this *chosen value* of juice, showing decreased firing rates when the value of the chosen option is low and increasing its firing rates linearly as the chosen value increases. Chosen value signals were found at the time of the offer, as well as the periods before and after juice delivery. Finally, shortly after the delivery of the juice, *taste* neurons were identified which encoded the type of juice regardless of offer value or chosen value. These findings have been subsequently replicated and expanded by experiments from the same laboratory (Padoa-Schioppa and Assad, 2008; Padoa-Schioppa, 2009). Padoa-Schippa questioned whether these signals, which are intrinsically limited in their range of firing

rates, are capable of representing the huge range in potential goods (Padoa-Schioppa, 2009). From comparing values in their thousands of pounds, humans are able to switch to compare between values of just a few pounds. OFC neurons in the macaque solve this problem by dynamically adjusting their firing rate range to the range of values on offer (Padoa-Schioppa, 2009).

Taken together, these studies illustrate that context, as defined by the presence of preferred alternatives, as well as the value range of the options, modulate the firing rates of OFC neurons. Alternative contexts, defined by additional decision variables, are also encoded in the OFC. Neurons in both the rat and monkey adjust their firing rates according to the costs involved in acquiring the outcome (Roesch and Olson, 2004; Morrison and Salzman, 2009). Some costs are defined in terms of energy spent acquiring a reward or the time spent waiting for a reward, and both show increased firing rates in situations when costs are low. OFC neurons also encode the probability that a choice will be successful (Roesch and Olson, 2005b; Kennerley et al., 2009), as well as confidence in the choice, which itself correlated with an animal's willingness to wait for reward delivery (Kepecs et al., 2008).

Other than the devaluation and choice preference tests very few animal experiments have explicitly investigated choice behaviour while manipulating these types of complex decision-making variables after lesions to the OFC. To address this Chapter 4 and 5 describe a number of experiments in which macaques performed 3-armed bandit tasks designed to probe different aspects of learning and choice behaviour. Lesions made selectively to the lOFC have recently been shown to impair the particular aspect of causally assigning value to an appropriate stimulus (Walton et al., 2010). Therefore one of the aims of the present study was to investigate the effects of mOFC lesions on learning and decision-making tasks, specifically examine the role of

the mOFC in comparing expected value difference in order to bias choice. By contrasting the two different lesion groups these experiments were designed to investigate the possibility that the anatomical foci of learning and decision-making were distinct in the OFC. Chapter 4 details the resulting dissociation of learning and decision-making mechanisms while Chapter 5 will present findings which elaborate and clarify the nature of deficit experienced by the mOFC lesioned animals in decision-making. Whilst not able to establish causality, human neuroimaging experiments have the capacity to specify regional changes in cerebral activity and can indicate whether decision-making tasks selectively activate a particular subdivision of the OFC. The increasing interest in human decision-making from both a psychological, neuroscientific as well as neuroeconomical perspective has driven the flurry of recent neuroimaging studies investigating complex value computation and comparison. This work will be briefly reviewed in the following section.

Human neuroimaging studies

The human orbitofrontal cortex is typically activated by any task which involves an outcome. As detailed in the previous sections, that outcome could be primary reinforcement (O'Doherty et al., 2001a) or abstract monetary reinforcement (Breiter et al., 2001; O'Doherty et al., 2001b); it might even constitute socially rewarding attractive faces (O'Doherty et al., 2003b). Changes in OFC BOLD responses correlate with expected and experienced outcomes that are either positive, negative (Breiter et al., 2001; Gottfried et al., 2003; Rolls et al., 2008) or even imagined (Bray et al., 2010). OFC cerebral activity encodes particular decision variable which contribute to the formation of expected value, such as magnitude and probability (Elliott et al., 2000; Breiter et al., 2001; Galvan et al., 2005; Knutson et al., 2005; Rolls et al., 2008), but does not act alone in this

complex assessment of an outcome. The OFC is described as part of the reward circuit, networked with the striatum, amygdala, insula and hippocampus, as well as the ACC and sensory areas of temporal cortex (Croxson et al., 2005; Haber et al., 2006). The previous section described these studies in relation to the OFCs contribution to value-guided learning; however this does not preclude them from acting as decision-making signals. An animal seeking to satisfy a particular biological need might want to compare the values of alternative options that are present in a representation of the animals' reward environment in order to select the goal which has the capacity to satisfy its biological requirement. A number of neuroimaging experiments have provided evidence that many aspects of this process involve the OFC. For example, a comparator system might be expected to signal the relative, rather than the absolute expected reward value. Replicating the finding of Tremblay and Schultz (1999), Elliott and colleagues show that responses in a medial region of the human OFC to a perceptually identical stimulus are greater when the stimulus predicts the more valuable of two rewards than when it predicts the less valuable (Elliott et al., 2008). Specifically, the mOFC, amygdala and ventral striatum are more active towards a stimulus which predicts a 50p reward, when it is presented in the context of a stimulus associated with 10p, than when it is paired with a more valuable stimulus predictive of a £1 reward (Figure 1.4a). The nature of relative value encoding in the OFC has been explored further in a number decision based tasks for both monetary rewards (Boorman et al., 2009) and incommensurable items (FitzGerald et al., 2009), implying that this signal may code for a common currency of value during a complex decision. Boorman and colleagues used a two-armed bandit task and asked subjects to choose between two actions each associated with an explicit size of reward earnings (Boorman et al., 2009). The probability of the subject receiving a reward for each alternative response varied across the course of the scan, and the subjects

developed an estimate of this probability by exploring the different action, and learning through trial-and-error which action was currently more likely to be rewarded. As subjects were motivated to accumulate as much money as possible for their time, they were required to implicitly trade the size of reward with the probability of the action eliciting the reward. In order for subjects to select the optimal choice they had to compare the expected values associated with the two alternatives. Brain regions involved in making this decision are therefore expected to show activation correlated with the relative difference in chosen value (i.e. the difference between the chosen and unchosen expected values). Boorman and colleagues identified signals in the vmPFC that encoded relative chosen value during the period of contemplation, i.e. before a response had been made (Figure 1.4b). Moreover, the vmPFC encoded the component parts of the signal, showing a positive correlation with chosen action value and a negative correlation with unchosen action value. The study contrasted the relative chosen value signals found in the vmPFC with that of the relative unchosen *probability* signals found in the adjacent frontopolar region of cortex. Furthermore, while activity in the frontopolar cortex was found to encode the evidence in favour of subjects switching away from their current choice (Boorman et al., 2009), this study also found that activation in the vmPFC correlated with the likelihood that the subject maintained their current choice (Boorman et al., unpublished observations). These observations support the distinction between brain regions involved in exploitative and exploratory actions drawn by Daw and colleagues. Here the authors identified that the frontopolar cortex and intraparietal sulcus are preferentially active during exploratory decisions, i.e. choices during which a subject might be attempting to gather information about the state of their reward environment. In contrast, decisions which exploited this information to harvest rewards were associated with increased activations in regions of vmPFC and the striatum (Daw et al., 2006).

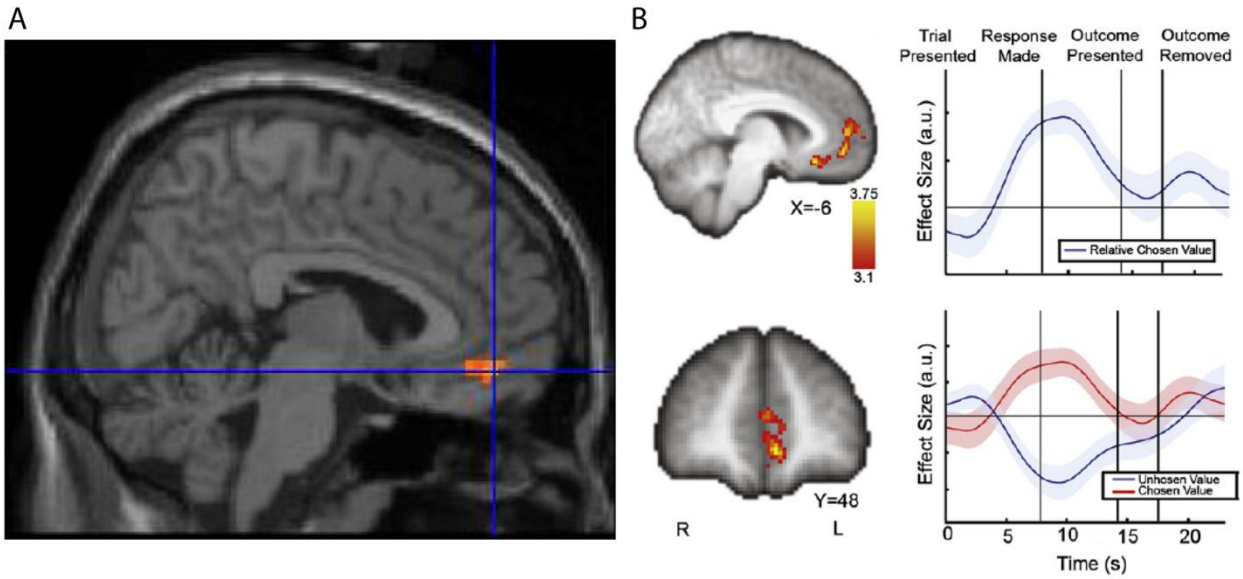

Figure 1.4. MOFC and vmPFC responses during relative reward processing **A**. mOFC is more active to cue B when it represents the better of two rewards (i.e. following an AB than BC pairing) from Elliott et al. (2008). **B**. vmPFC activity to relative chosen value (leftwards panel) and its time course (top right) decomposed into chosen and unchosen action values (bottom right) from Boorman et al. (2009). Permission to adapt and reprint granted by Elliott et al. (2008), Boorman et al. (2009), John Wiley and Sons and Elsevier.

Human decision-making is often remarkably irrational, being particularly susceptible to the context in which available choices are presented. Economists define one particular aspect of rationality as 'invariance', which is the assumption that logical consistency across decision is maintained regardless of the available choices. However, numerous studies suggest that human choice behaviour deviates from this description and choices are often influenced by the manner in which they are framed. The neural basis of the so-called *framing effect* was investigated by De Martino and colleagues (2006). The task asked subjects to either gamble a proportion of an endowment or chose a 'sure' option which was equally matched with the gamble. The choice was framed as either a Gain or a Loss, with the sure option stating that the subject would 'keep'

or ‘lose’ the stated amount of money, while the gamble was represented as a proportion of a pie chart. In real terms the value of choices were identical, yet subjects behaviour choices were significantly affected by the manner in which the choice was presented. In accordance with the predictions from prospect theory (Kahneman and Tversky, 1979; Tversky and Kahneman, 1981) subjects were risk-averse in the Gain frame, tending to choose the sure option over the gamble, and risk-seeking in the Loss frame, opting now to gamble. The authors reported that bilateral amygdala was more active when subjects chose in accordance with the frame effect than when choices went against it, while the ACC was identified in the reverse contrast, showing enhanced activity when choices went against the framing effect. Interestingly, vmPFC activity correlated with the degree to which subjects’ decisions were rational and uninfluenced by irrelevant features of the context in which they are made. Increased activation in the OFC and vmPFC was associated with a decreased susceptibility to the framing effect. These three brain regions are anatomically interconnected and together, it appears, they work in a functional network to bias choice behaviour.

A number of researchers have emphasised the importance of other neural signals which contribute to sound economic decision-making. As described above, learning occurs when there is a need to update a value assigned to a previously chosen option on the basis of deviations between the expected and actual reward, i.e. a prediction error. However, in order to choose between options, a brain region must compute a number of other value-related signals. In a manner the reward prediction error signal contributes to the calculation of the *goal value*, a measure of the predicted reward that result from the outcome generated by each of the option (choice or action) under consideration. Behaviourally, goal value can be estimated as a subject’s willingness to pay to acquire or avoid a particular outcome, and these signals have been

identified by a number of studies in medial regions of the OFC (Plassmann et al., 2007; Hare et al., 2008; De Martino et al., 2009; Hare et al., 2009; Plassmann et al., 2010). These signals are not modulated by a subject's role as buyer or seller in the transaction, and are therefore reference independent (De Martino et al., 2009). Once goal value has been established the system is able to measure the net value difference between taking either of alternative options and calculate the *decision value*. The OFC also encodes signals related to decision values, associated with different rewarding food choices (Hare et al., 2009), and during a task where subjects paid money to view attractive faces (Smith et al., 2010). Decision value signals were also notably present in the absence of an overt choice task (Smith et al., 2010).

Summary of Value-Guided Learning and Decision-Making in the Orbitofrontal Cortex

The OFC plays a critical role in both the learning of, and comparison between, multiple expected values. However, an important question is whether the specific anatomical foci of these two functions are dissociable in the brain. Kable and Glimcher have recently argued that they are and proposed a "basic model" for primate decision-making (Kable and Glimcher, 2009). Their review suggests a system for learning, storing and representing subjective values involves the ventromedial sectors of the PFC and associated regions of the striatum. In contrast, they claim that the choice of a single highly valued action from among a number under consideration relies on lateral prefrontal and parietal areas. This interpretation, which is largely based on electrophysiological recordings in non-human primates, where inference of influence and directionality is often challenging, has never been tested with methods which assign causality of function. Whilst, Kable and Glimchers (2009) argue against the strict interpretation of the neurons identified by Tremblay and Schultz (1999) as encoding relative value, suggesting

instead they are "condition-variant" (longer-term adaptive reward scaling), they neglect the increasing human imaging evidence which identifies vmPFC activity that correlates with relative subjective value (De Martino et al., 2006; Elliott et al., 2008; Boorman et al., 2009; Smith et al., 2010). The authors also fail to consider the effect of vmPFC and OFC lesions in both human and monkey lesions which impair the consistency of choice preference tests (Baylis and Gaffan, 1991; Fellows and Farah, 2007). An alternative hypothesis suggests that aspects of value-guided learning and decision-making can be dissociated within the OFC itself. The evidence presented above describing OFC activity in relative reward encoding, rational decision-making and the degree to which subjects are influenced by irrelevant aspects of context, often localize to the ventromedial regions of the PFC and mOFC. Interestingly, OFC lesions which don't include area 14 fail to produce food preference changes (Machado and Bachevalier, 2007). This suggests that the vmPFC and mOFC themselves may play a role in biasing choice behaviour. In contrast, although S-O learning is less clearly localized with neuroimaging or electrophysiological methods, potentially due to confounding variables and methodological difficulties respectively, the specific aspect of credit assignment can be localized to more lateral OFC regions (Walton et al., 2010). Chapter 4 explicitly investigates the hypothesis that the lOFC and mOFC are respectively, involved in learning and decision-making. The effects of mOFC and lOFC lesion in the macaque were compared while the animals perform 3-armed bandit tasks designed to probe different aspects of learning and choice behaviour. The first aim of the study was to confirm whether impairments of credit assignment were restricted to lOFC lesions, and if so what underpinned the deficits seen in mOFC lesioned animals. Chapter 5 went on to investigate the precise nature of the deficit experienced by mOFC lesioned animals in relative value comparison and the influence of irrelevant rewarding alternatives on choice behaviour. In an effort to

translate the principles of these findings into human subjects we explored whether outcome-specific contingency learning was mediated by specific regions of the frontal lobe. Given the lOFCs involvement in S-O credit assignment (Walton et al., 2010) we hypothesised that its role may extend from assigning value to a specific stimulus to assigning the expectation of a *specific* outcome to a specific stimulus. Chapters 6 and 7 will investigate this possibility in a human fMRI experiment which uses a stimulus-specific contingency learning paradigm based on the DOP (Ramirez and Savage, 2007).

1.4 Thesis experiments

Does the Macaque mOFC Support Social or Emotional Evaluation?

The first experiment, presented in Chapter 3, explores the contribution of specific mOFC damage to a macaque's ability to utilise socially or emotionally valuable information to guide actions. The methods are identical to those adopted by Rudebeck and colleagues, which dissociated the contributions of the ACC and PFv+o to social and emotional processing respectively (Rudebeck et al., 2006a). By comparing the results of these two studies, this chapter concludes that the mOFC makes no major contribution to social or emotional processing but does indicate a role in value-guided decision-making.

Assigning and Comparing the Roles of the lOFC and mOFC in Expected Value

A basic model of decision-making should address two key questions. Firstly, how are subjective values of options under consideration learned, stored, and represented in the brain? Secondly, how are these multiple values compared and one ultimately chosen from among various alternatives? Much research has gone into answering these two questions using

electrophysiological, animal lesion work, as well as human neuroimaging experiments. However, to date no experiment has been designed to explicitly investigate the possibility of dissociation between the two functions in a targeted lesion experiment. Chapters 4 and 5 will outline a set of experiments which aimed to address both of these issues. This study expanded a reward environment to a three-choice situation and in doing so identified a double dissociation between the contribution of the lateral and medial regions of the OFC to value assignment and value comparison. Chapter 4 will detail this dissociation while Chapter 5 will present findings which elaborate and clarify the nature of deficit experienced by the mOFC lesioned animals in decision-making.

Differential Reinforcement Learning: Identifying the Unique Contribution of the OFC to Outcome-Specific Contingency Learning.

As identified in the preceding section a question remains over the role of the human OFC and, more particularly, the regional specificity within this structure for the representation of outcome-specific associations. Many investigators have interpreted rat lesion studies as suggesting that the OFC is the area which learns, stores and represents expected and stimulus-specific value (Ostlund and Balleine, 2007a; Ramirez and Savage, 2007). This hypothesis has gained support from a number of studies that identified changes in BOLD responses during tasks which manipulate expected value (Gottfried et al., 2003; Valentin et al., 2007). However, in both types of experiments, learning is often confounded by the subjects using expected value to choose between different options. Whilst this is interpreted as goal-directed learning, it may in fact represent goal-directed decisions. One set of experiments in this thesis set out to determine whether this latter hypothesis could be considered. Chapters 6 and 7 describe a novel version of

the DOP adapted for use in humans. The behavioural results are presented in Chapter 6, while the neural mechanisms underpinning outcome-specific contingency learning are explored in Chapter 7.

CHAPTER 2: THE ANATOMY OF THE ORBITOFRONTAL CORTEX

Cortical function is critically dependent on the intrinsic and extrinsic connective patterns of a brain region, as well as its anatomical structure. Without clear knowledge of this information it is nearly impossible to interpret results from any functional method. Recently a series of detailed anatomical studies have demonstrated that the ventromedial prefrontal cortex in the macaque is far from a homogeneous structure, and is instead composed of a mosaic of areas. Based on differential cortico-cortical and cortico-subcortical connections these subregions have been broadly divided into two connectional networks; the 'medial' and the more lateral 'orbital' prefrontal network. This chapter will present the evidence for these two connective networks, and discuss how relative differences in connective inputs might serve to specialize functional roles. It will then compare the pattern of these connections with those of the human brain so that homologies between the two species can be drawn.

2.1 Introduction

The connections between neighbouring cortical regions and distinct cortical and subcortical structures determine the functional role of a brain area (Carmichael and Price, 1996; Passingham et al., 2002). Just as the inputs to a system will determine the types of processes possible within it, the outputs will determine the influence of processing in other networked systems. In the brain this translates to an influence on behaviour and serves to bias actions. As part of the ventromedial prefrontal cortex (vmPFC), the orbitofrontal cortex (OFC) has been implicated in

learning, decision-making, and social and emotional processing. However, in order to substantiate these claims it must be established that the OFC has access to the afferent inputs to assess the precursor elements of these complex behaviours, such as stimulus properties and value, which are processed elsewhere in the brain. Furthermore, it must be determined whether the OFC utilises this information to influence behaviour via interconnections with brain regions specialised for bodily sensations or action, such as motor, musculo-skeletal and subcortical systems.

2.2 Cytoarchitectonic Divisions of the Macaque Prefrontal Cortex

The OFC is on the ventral surface of the frontal lobe. It extends posteriorly from the frontal pole to the insula, and ventrally, from the rostral sulcus on the medial wall, it follows and includes the curvature of the frontal lobe above the eyes all the way to the lateral orbital sulcus (Walker, 1940; Carmichael and Price, 1994; Petrides and Pandya, 1994; Petrides, 2006). Variations in cytoarchitecture within the OFC have encouraged numerous researchers to divide this area up. Rostro-caudally, differences in the concentration of the granular layer IV have been observed with the most anterior parts of the OFC containing a well defined granular layer. Dysgranular and even agranular regions have been identified in central and posterior orbital cortex respectively.

Early classification, based on cell layer differences such as granulation, identified a number of prominent component structures. Brodmann (1905) was the first to parcellate the medial and orbital surfaces of the macaque brain, but subsequent improvements in staining and tracing techniques have led later researchers to differentiate these areas in increasingly more detailed ways. For example, Walker (1940) observed two fields within the posterior medial

orbital cortex (Figure 2.1). Area 13 was defined as cortex on the "posterior orbital gyrus", extending dorsally from the posterior portion of the medial orbital sulcus to the frontomarginal sulcus. Adjacent cortex, which encompassed the gyrus rectus, as well as cortex beneath, and medial to the olfactory tract, was labelled area 14. Area 11 was indentified as cortex that lay rostral to area 13 and lateral to area 14; being immediately posterior to the frontopolar region of area 10, and extending from the lateral to the medial orbital sulcus. On the medial wall, dorsal from area 14, Walker identified areas 24 and 25. He argued these regions represented the agranular and granular cingulate gyrus respectively.

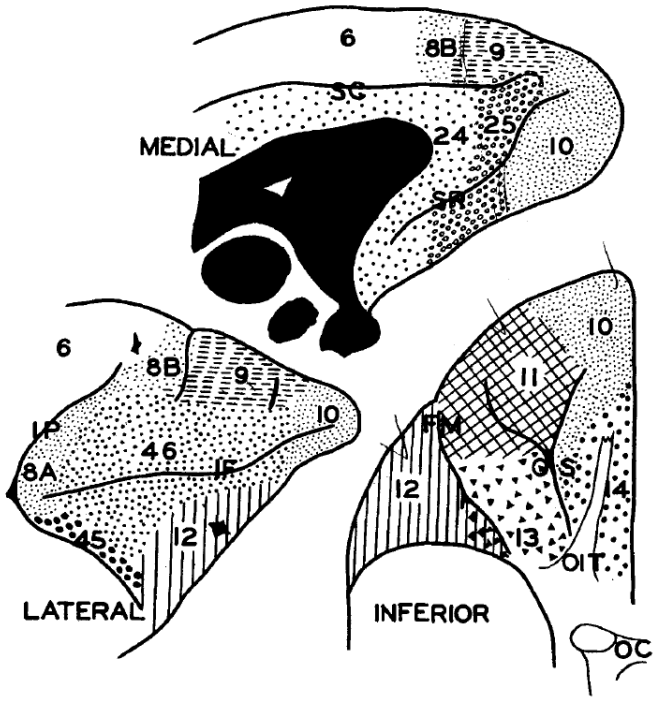

Figure 2.1. Cytoarchitectonic map of orbital and medial prefrontal cortex from Walker (1940). The orbital and medial cortex was subdivided into seven areas. Later parcellations would use this map as a template for more fine grain regional divisions. Permission to adapt and reprint granted by Walker (1940) and John Wiley and Sons.

Observed cyctotechonic differences within the PFC, in terms of layer IV granulation, pyramidal cell size, cell-packing densities and myelination, have led researchers to recognize

additional subdivisions in the OFC creating even more refined maps of the macaque OFC (Barbas and Pandya, 1989; Petrides and Pandya, 1994). For example, both Petrides and Pandya (1994) and Price and colleagues created parcellation maps (Figure 2.2) in which the nomenclature and analysis of architectonic subdivisions of the orbital and medial PFC was based on Walker (1940). Notably, Price and colleagues extended the subdivisions quite considerably. The group performed an extensive series of experiments investigating both the anatomical architectonic regional differences of the prefrontal cortex as well as the intrinsic and extrinsic cortico-cortical and cortico-subcortical connections (Ray and Price, 1993; Carmichael and Price, 1995a, b, 1996; An et al., 1998; Ongur et al., 1998; Ferry et al., 2000; Kondo et al., 2003, 2005; Hsu and Price, 2007). Carmichael and Price (1996) subdivided each of Walker's original six anatomical prefrontal areas, 10, 11, 12, 13, 14 and 24, and included the additional areas 25 and 32, into 16 cyctoarcitectonically distinct areas. On the medial wall they identified areas 10o, 10m, 24a, 24b, 32 and 25. Ventromedial to the gyrus rectus and extending around the ventromedial convexity to the medial orbital gyrus, area 14 is divisible into 14r and 14c. These two regions are distinguished along the caudo-rostral dimension by the introduction of a sparse dysgrandular layer IV in area 14r (Barbas and Pandya, 1989; Carmichael and Price, 1996). Lateral to the medial orbitfrontal sulcus, the central OFC (cOFC) can be subdivided into the dysgranular areas 13m and 13l, with more medial regions now classified as 13a and 13b. Area 13a distinguishes itself from its numerical classification by being the only agranular region of area 13, as well as having distinct anatomical connective patterns, which will be discussed further below. Similarly, granular area 11 has been divided into 11m and 11l. 11m can be seen to extend both laterally and rostrally from area 13b. Area 11l includes cortex lateral from area 11m and extends roughly to the lateral orbital sulcus. Lateral to area 11l, area 12 has been subdivided

and classified as areas 12r and 12m, 12o and 12l. Finally, Carmichael and Price's parcellation emphasizes the posterior agranular insular areas of orbital cortex and divides this grey matter into Iam, Ial, Iapm, Iapl and Iai (Carmichael and Price, 1996).

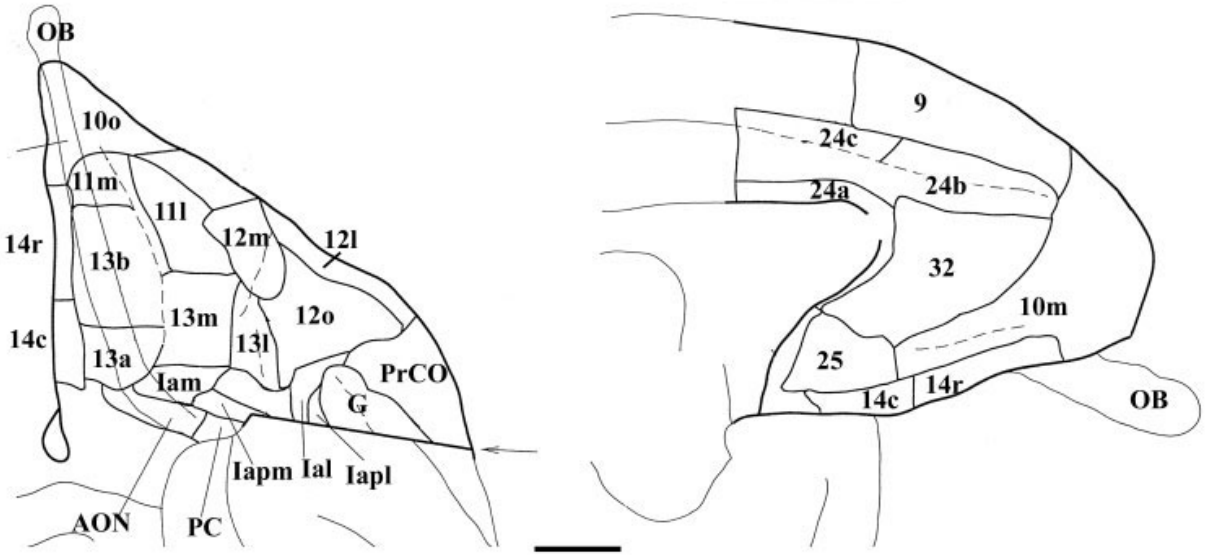

Figure 2.2. Architectonic subdivision of the macaque orbital (at left) and medial surface (at right) described by (Carmichael and Price, 1996). Walkers original six anatomical prefrontal regions were expanded and divided into 16 cyctoarcitectonically distinct areas. Permission to adapt and reprint granted by Carmichael and Price (1996) and John Wiley and Sons.

Whilst debates over the reliability and relevance of such fine grained subdivisions (Petrides, 2007) have been raised, the divisions proposed by Carmichael and Price appear to have some functional significance, as within these regions various distinct cortio-cortical connective patterns have been demonstrated (Barbas and Pandya, 1989; Carmichael and Price, 1995a, b). Moreover, Carmichael and Price (1996) suggest that differences between cortio-cortical connections segregate the architectonic areas into two connective networks (Figure 2.3). The 'medial' prefrontal network links most medial areas including 14r, 14c, 24, 25, 32 and 10m. In contrast the lateral 'orbital' prefrontal network selectively connects areas within lateral orbital

cortex, and includes posteriolateral areas Iam, Iapm, Ial, 13b, 13m, 13l and 11m, as well as 12m, 12l and 12r. Very few connections between the two networks were identified, but 'intermediate' areas 13a, 12o and Iai had substantial connections to both networks, and so were argued to serve as points of interaction.

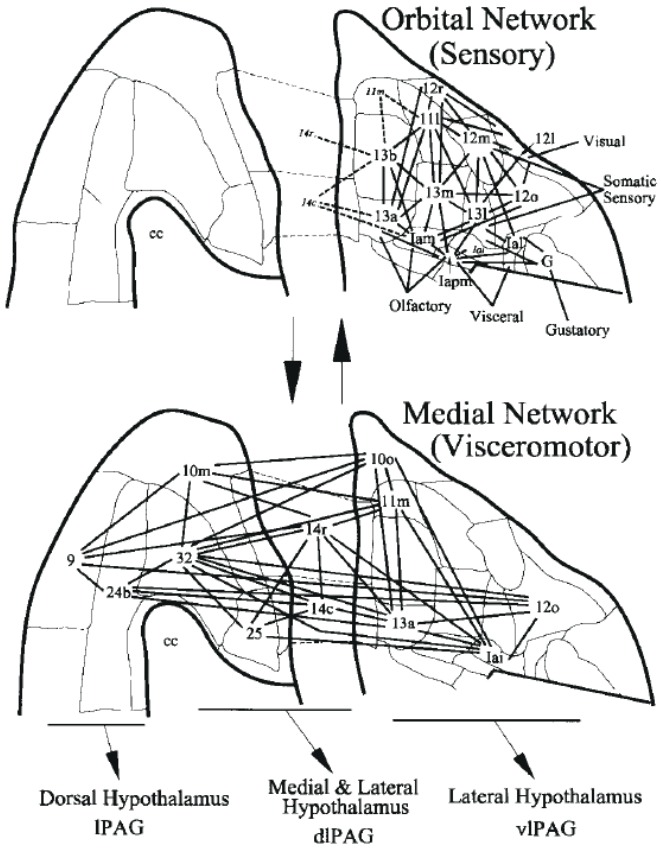

Figure 2.3. Summary of corticocortical connections within the OMPFC (from Ongur and Price (2000), modified from Carmichael and Price (1996)). Although the two networks are distinct there are several points of interaction especially through areas near the ventromedial corner of the frontal lobe. Permission to adapt and reprint granted by Carmichael and Price (1996) and Oxford University Press.

The prefrontal networks established by Carmichael and Price (1996) are further corroborated by a series of experiments investigating regional connections to distant cortical and

subcortical structures. The details of these distinct connectional networks will be presented in the subsequent section, with particular emphasis on their functional interpretations. However, whilst the discussion will aim to encompass each network as a whole, specific attention will be paid to areas; 24 and 14, as representatives of the medial network; and 13 and 11, as representative nodes in the orbital network.

2.3 Connectional Networks of the OFC

Carmichael and colleagues propose two distinct connective networks and argue that these two networks have differential reciprocal connections with a number of cortical and subcortical regions, including sensory and premotor regions, as well as limbic structures, such as the amygdala nuclei, hippocampus, parahippocampas and cingulate cortex (Ray and Price, 1993; Carmichael and Price, 1995a, b, 1996; An et al., 1998; Ongur et al., 1998; Ferry et al., 2000; Kondo et al., 2003, 2005; Hsu and Price, 2007). This proposed distinction will provide the framework of the subsequent sections in this chapter. Critically, because most connections described are reciprocal in nature, this chapter will tend not to focus on directionality of projections. In arguments about functions, however, the connections described with sensory and limbic regions are emphasized as important afferent connections, while connections with motor and premotor areas are described more in terms of efferent projections from the OFC.

The Stimulus: Sensory and Hippocampal Connections

The OFC is implicated in flexible learning of stimulus-reinforcement associations. Lesions to this region disrupt the ability to alter behaviour following a change in reward contingencies (Butter et al., 1970; Iversen and Mishkin, 1970; Izquierdo and Murray, 2004; Walton et al.,

2010). Extracellular recordings show that neurons track the integrative information of stimulus reward value (Thorpe et al., 1983; Rolls et al., 1996; Tremblay and Schultz, 2000). Furthermore, neuronal responses can discriminate stimuli on the basis of distinct outcomes and on outcome preference (Tremblay and Schultz, 1999). It is therefore essential that the OFC receives input from regions specialized for processing the independent elements of these associations in order to accurately represent distinct stimulus properties, and the associated hedonic or intrinsic reward value.

The OFC receives projections from visual and sensory related areas in the inferior temporal lobe (Pandya and Kuypers, 1969; Jones and Powell, 1970; Chavis and Pandya, 1976; Webster et al., 1994), as well as from other sensory modalities including somatosensory (Seltzer and Pandya, 1989), gustatory and olfactory cortex (Carmichael et al., 1994; Carmichael and Price, 1995b). However, the strength of connections to areas within the OFC are vastly disproportionate (Carmichael and Price, 1995b). Lateral regions of the OFC, such as area 11 and 13, receive input from nearly all sensory regions, while the more medial OFC, including area 14 and cingulate areas 24, receive almost none. The majority of connections with visual association cortex are directed to area 12l, but innovation is scattered to most lateral granular and dysgranular orbital frontal regions, including subregions of areas 13 and 11, in addition to caudual agranular insular areas. The lateral OFC also receives sensory information from somatosensory cortex. The second somatosensory area, the anterior infraparietal area and granular insula areas send strong projections to areas 12m, caudomedial regions of area 13 and Ial. Weaker projections are also seen to 11l. Gustatory, visceral and primary olfactory innovations are also strong projections to posteriolateral areas. Olfactory innovations of OFC are particularly unusual. Most primary sensory projections to OFC, and cortex in general, are

mediated via association areas or through thalamic structures, which act as relay stations. Primary olfactory cortex, including piriform, entorhinal, ventral tenia tecta and anterior olfactory nuclei receive direct projections from the olfactory bulb and project, many of them, via the uncinate fasciculus (Van Hoesen et al., 1972; Van Hoesen et al., 1975), directly to OFC regions, including lateral areas 13 and agranular insular areas, in addition to medial areas 14c and 25. Finally, the OFC has access to polysensory or multimodal sensory information from superior temporal gyral regions, which directly innervate intermediate areas 12o, 13a and Iai.

As described sensory projections are consistently strongest to lateral OFC structures, with virtually no projections to medial structures. One of the few exceptions to this pattern comes from auditory association cortex including ventrolateral and superior temporal cortex. Cingulate cortex in particular therefore has access to complex auditory information, as well as integrated and highly processed visual and auditory information, such as species-specific vocalizations and facial expressions (Bruce et al., 1981; Poremba et al., 2004; Ghazanfar et al., 2005).

The hippocampus also innervates OFC. The subiculum of the hippocampus sends projections exclusively to the medial structures, including area 14 and 10; with smaller projections to area 32. In contrast, the body of the hippocampus and area CA1 send projections to lateral 13a and 13b (Carmichael and Price, 1995a). The hippocampus is associated with perception, long-term memory and aspects of contextual memory (Parkinson et al., 1988; Smith and Milner, 1989; Eichenbaum et al., 1990; Mishkin et al., 1997; Murray and Richmond, 2001; Buckley and Gaffan, 2006). Hippocampal connections innervate the frontal cortex directly along the uncinate fasciculus (Van Hoesen et al., 1972; Van Hoesen et al., 1975), or indirectly via connections from cortical sites in the temporal lobe. The enthorhinal and perirhinal cortices, as well as the temporal pole and parahippocampal cortex, are all reciprocally connected to the OFC,

and here again, connective patterns serve to differentiate the frontal networks (Carmichael and Price, 1995b; Kondo et al., 2005). Projections from perirhinial and entorhinal cortex also connect with lateral OFC structures, including 13, 12l and agranular insular areas. However, whilst perirhinal cortex is relatively confined in its lateral innervation, with only 14c receiving light innovation, entorhinal cortex connects with a number of medial structures including 14 and 24. Meanwhile, the temporal pole innervates both networks relatively evenly, but differentiates between the networks based on the source of connections within itself (Kondo et al., 2003). Specifically, ventromedial regions of the temporal pole, TGvg and TGvd, project almost exclusively to lateral OFC structures such as 13b, 13l, 13m and 12m and agranular insular areas. In contrast, dorsolateral regions of the temporal pole, TGdg and TGdd, preferably innervate the medial network, including areas 10m, 14, 32 and 24. Similarly, the posterior parahippocampus, known for representing contextual information about stimuli, also connects more exclusively with medial and intermediate OFC regions (Vidyasagar et al., 1991; Salzmann et al., 1993).

The Value: Striatal and Amygdala Connections

In order to integrate flexibly encoded stimulus values, in addition to information regarding stimulus properties, the OFC also requires input representing the receipt of an outcome and the intrinsic value of that outcome. The acknowledged receipt of reward is critical to a system. Monkey physiological studies have identified neurons in the ventral striatum and nucleus accumbens, in addition to both medial and lateral structures of the OFC that fire in response to a rewarding event (Schultz et al., 1998). However, reward related responses are not homogeneous throughout the midbrain and cortical structures. Dopamine neurons in the accumbens fire in response to primary rewards, or reward-predicting stimuli, without discriminating between

rewarding stimuli. Meanwhile, striatal neurons respond to expectations of specific rewards, and may especially adapt expectation to new reward situations. However, OFC neuronal responses encode more complex factors such as monkeys' relative preference for each reward (Schultz et al., 1998; Tremblay and Schultz, 1999).

It is critical then that the OFC has access to dopaminergic and striatal reward-related input. Detailed analyses of the cortico-striatal network suggests that both medial and cingulate regions connect to the core of the nucleus accumbens, but whilst frontopolar and ventromedial areas (including rostral areas of 14) connect with the medial body of the caudate and rostral and ventral regions of the putamen, cingulate regions, 24b and 24c, connect with dorsal regions of the caudate and the putamen. In contrast, lateral structures of the OFC innervate lateral regions of the caudate and ventromedial regions of the putamen. Interestingly, these lateral regions do not connect with the nucleus accumbens; labelled axons were identified close to the edge of the accumbens nucleus, but rarely in the medial part itself (core or shell). Ferry and colleagues (2000) suggest that OFC and dopaminergic inputs to the ventral striatum determine its responses, and that the ventral striatum acts to choose between different reward-guided behaviours by suppressing inappropriate or undesired stimulus-reward associations. This mechanism is very similar to the dorsal striatum's proposed mechanism of action selection, choosing between different opposing actions, and allowing one pattern of activity to initiate one action by suppressing another antagonistic pattern (Mink, 1996).

Whilst this analysis emphasizes the distinct projection terminals from cortical regions, in line with the concept of parallel corticostriatal pathways (Alexander et al., 1990), more recent investigations of the innervation of the striatum from OFC and ACC show an organization that features a dual system for parallel and integrative network processing (Haber et al., 2006). Haber

and colleagues traced axonal projections from the OFC; areas 11 and 13, dACC; areas 24b and 32, and dlPFC; area 9/46, and found that whilst the focal projections from these regions occupied their own territory, at rostral levels of the striatum dlPFC terminals converged with those from both the dACC and OFC (Figure 2.4). Focal projections were complimented by a pattern of diffuse terminal fields, some invading fields some distance from their focal site into regions that receive their focal input from other PFC areas. The authors argued that functional coordination at the level of the striatal terminals between the OFC, ACC and dlPFC would be particularly valuable to a system involved in learning new procedures and associations.

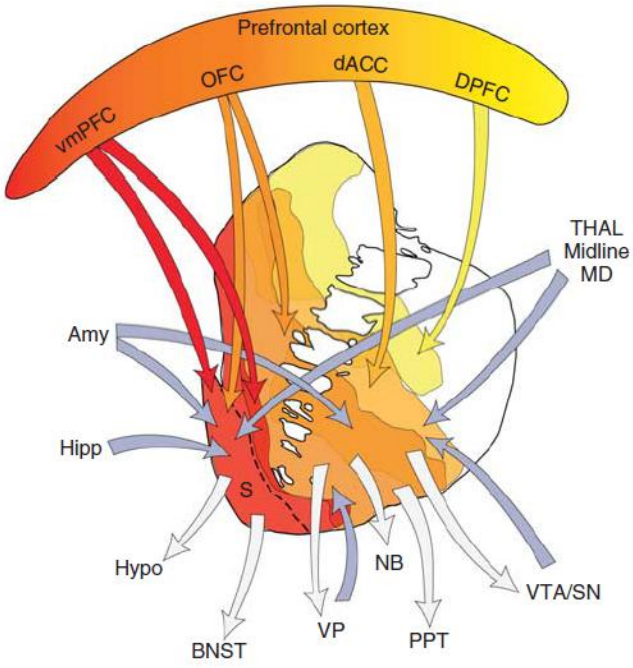

Figure 2.4. Schematic illustration of ventral striatal connections. Inputs and outputs are represented blue and gray arrows respectively. Abbreviations: Amy = amygdala; BNST= bed nucleus stria terminalis; Hipp=hippocampus; hypo=hypothalamus; MD=medio-dorsal nucleus of the thalamus; PPT=pedunculopontine nucleus; S=shell; SNc=substantia nigra, pars compacta; STN=subthalamic nucleus; Thal=thalamus; VP=ventral pallidum; VS=ventral striatum; VTA=ventral tegmental area; vmPFC=ventral medial prefrontal cortex. Permission to reproduce granted by Haber and Knutson (2010) and Nature Publishing Group.

Like the striatum, the amygdala has been implicated in several primate studies as having a critical role in generating associations between stimuli and rewarding or aversive events, in addition to learning and emotional responses (Aggleton and Passingham, 1981; Malkova et al., 1997; Baxter et al., 2000; Izquierdo et al., 2005; Paton et al., 2006). Therefore, in order for the OFC to integrate stimulus information from sensory regions with value-related information from medial temporal lobe nuclei, it is essential that the OFC receives input from these structures.

Both the medial and orbital networks, described by Carmichael and Price (1996), are connected to the basal nucleus of the amygdala, but the distribution of projections within this structure is different between the two networks. Areas defined as part of the medial, including both areas 24 and 14 and intermediate network, are relatively more connected to ventrolateral regions within the basal nucleus. In contrast, area 12l of the lateral network is connected to more dorsal regions of the basal nucleus. Similarly, the relative strength of projections from other amygloid nuclei also differentiates the two networks. Lateral structures such as 13a and 13b and posterior agranluar insular areas are relatively more connected to the lateral nucleus of the amygdala and the anterior cortical nucleus. In contrast, medial regions receive very few, if any, connection to these amygloid nuclei (Carmichael and Price, 1995a).

As well as presumably providing information about the value of an external event, the amygdala innervation to the OFC is also associated with focusing attention on relevant task features and suppressing distracters (Wang et al., 2004). Neurons from the amygdala typically terminate in the superficial layers I and II of the OFC; intermingling with local inhibitory neurons (Ghashghaei et al., 2007). Activity in these inhibitory neurons may serve to focus attention on stimuli with emotional importance and explain the behavioural changes seen in

macaques in terms of heightened aggressiveness directed to emotive stimuli (Izquierdo et al., 2005; Rudebeck et al., 2006a).

The Action: Motor Connections

The frontal lobe of the macaque contains several distinct areas that possess reciprocal connections with the motor cortex, spinal cord or superior colliculus. These are defined as premotor regions (Muakkassa and Strick, 1979; Godschalk et al., 1984; Matelli et al., 1986; Huerta and Kaas, 1990; Dum and Strick, 1991; Morecraft and Van Hoesen, 1992), and a number have been found to project directly to orbital and ventromedial areas. For example, the premotor region of rostral ACC, area 24c, projects to the face, digit and limb parts of the motor cortex in addition to dorsomedial pre-motor regions, such as the supplementary motor area and the spinal cord. This type of connective pattern is suggestive of an area that has direct influence over the motor system, and therefore of behaviour. In keeping with this interpretation it is not surprising that lesions to this region affect the integration of intrinsic costs and benefits of an action (Walton et al., 2003; Rudebeck et al., 2006b), and neuronal activity in this region reflect the valuation of a course of action (Kennerley et al., 2009).

Whilst the OFC does not project to cortical motor areas, it is connected to a number of cortical and sub-cortical motor related regions. Medial area 24b and agranular insular area Ial have been shown to connect to premotor cingulate area 24c. Likewise, premotor areas 6va, 6vb and the supplementary eye field connect to a number of subregions within lateral areas 12 and 13. The OFC is also connected to a number of subcortical motor related areas in the midbrain. The periaqueductal gray (PAG) is associated with the coordination of actions, and as such receives projections from a number of motor and premotor cortical regions including 6va and

6vb, 24c, 9 and 8. It is therefore situated in an appropriate connectional position to bias behaviour indirectly via its prefrontal efferent projections. Afferent connections towards PAG were detailed by An and colleagues (1998), and suggest a network with strong medial OFC connections. Both the dorsolateral and ventrolateral column of the PAG direct and receive projections from medial regions 10m, 14c, 25, 32 and 24b, as well as intermediate structures 13a, 12o and Iai. The only designated lateral prefrontal region even lightly innervated by the PAG is area 12l.

As well as connections to motor related areas in the midbrain the orbital and ventromedial also project to the hypothalamus. The hypothalamus is an area associated with autonomic control and homeostatic regulation, and just like the PAG the majority of projections to the hypothalamus come from medial regions. Medial and intermediate structures, such as area 10m, 14, 25 and 32, as well as 13a, 12o and agranular insula areas, send projections to both rostral and caudal regions of the hypothalamus. In contrast, area 24 and area 13 are more exclusive in their projections towards caudal regions. Collectively, the interconnections of the medial network with the hypothalamus, amygdala and PAG prompted Ongur and colleagues to propose the existence of a further three sub-networks (Ongur et al., 1998). They argued that as each network incorporates discrete compartments of the ventromedial cortex, the amygdala, hypothalamus and PAG allow visceral information to be processed in parallel, yet separate systems (Figure 2.5).

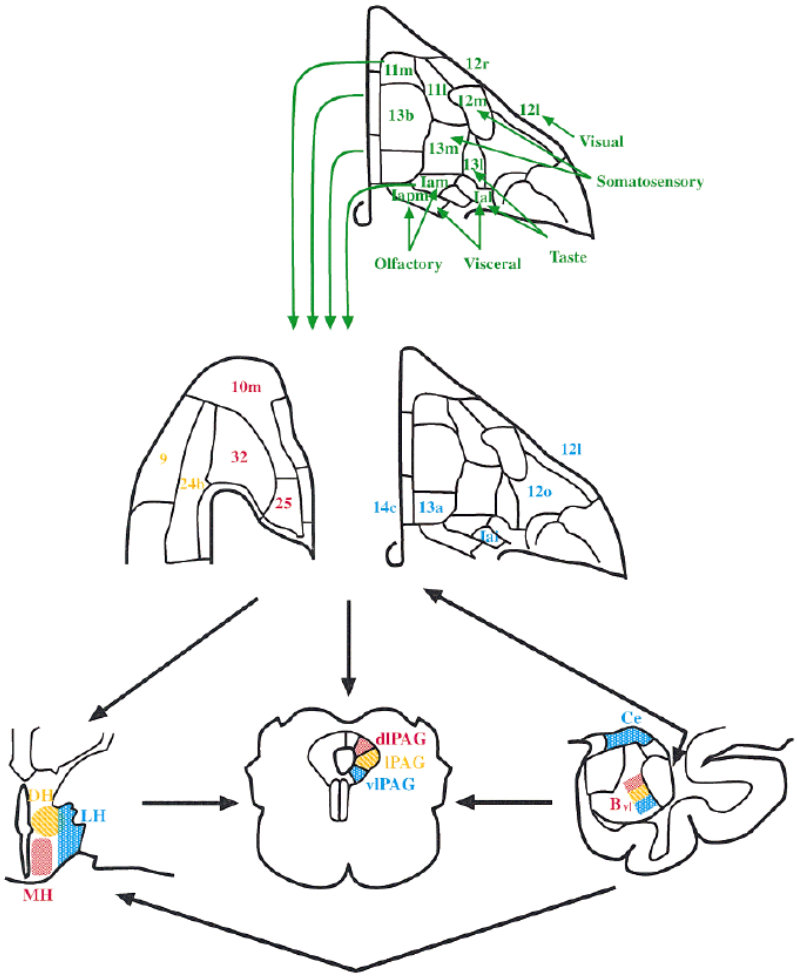

Figure 2.5. Connections between the medial "visceromotor" network, hypothalamus, periaqueductal grey and amygdala. Distinct parts of the medial network project to separable areas within limbic, autonomic and midbrain structures that are in turn interconnected. Permission to adapt and reprint granted by Ongur et al (1998) and John Wiley and Sons.

It is important to remember that claims of functional differentiation based on cytoarchitecture and connective patterns must also be tested directly with behavioural experiments. Price and colleagues used their anatomical studies to propose a functional division between lateral and medial networks as a "viscerosensory" system, dedicated to feeding and reward, and a "visceromotor" system devoted to visceral control and emotion. Whilst this

dissociation is plausible, it has never been explicitly tested with discrete lesion experiments. Moreover, despite broad differences between the connectional profiles of orbital structures described above, the two networks are far from mutually exclusive. Reciprocal connections from numerous cortical and subcortical structures innervate both networks, suggesting that these regions have access to similar information regarding value and stimulus properties (Barbas and Pandya, 1989; Carmichael and Price, 1995a, b). This implies that neighbouring structures perform interrelated functions either in parallel or in sequence.

Recently, a number of lesion studies have investigated the effects of lesions circumscribed lesions within the orbital and medial PFC. Walton and colleagues lesioned lateral areas 11 and 13, and argued that these structures are involved in credit assignment, the process by which value is casually and appropriately assigned to a particular stimulus (Walton et al., 2010). Similarly, recent lesion work in the ACC suggests that this structure is involved in monitoring the outcome of actions (Rudebeck et al., 2006a) and evaluating the importance of social information (Rudebeck et al., 2006a). However, a question remains over the function of cortex between these regions.

Area 14 lies ventral to the frontopolar area 10m and lateral to cingulate area 25, and is separated from areas 11 and 13 by the medial orbitofrontal sulcus. This region is considered part of Carmichael and Price's medial network; yet despite being intimately connected with areas 24, 25 and 32 there are a number of discrete differences in its connectivity profile from these cingulate regions (Barbas and Pandya, 1989; Carmichael and Price, 1995a, b). Specifically, area 14 lacks premotor connections, but is more connected with the anteriomedial thalamic and amygloid nuclei than cingulate regions (Carmichael and Price, 1995b). Area 14 and cingulate cortex also differ in their connections within the mediodorsal thalamus, as area 14 is more

connected to rostral regions of the pars caudodorsalis, whereas areas 24 and 32 are connected to neurons in more caudal regions (Ray and Price, 1993). Area 14 also receives additional innovation from the pars paramediana, whereas the cingulate does not. This connective pattern indicates that area 14 may play a less critical role in directly modulating behaviour than its cingulate neighbours, but, via its connections with areas 23, 32 and 24, area 14 may be able to bias behaviour to a greater extent than the more lateral component structures. Area 14 is not particularly innervated by sensory regions, suggesting that it may not share in the role attributed to adjacent areas 11 and 13 of assigning value to stimuli (Barbas and Pandya, 1989; Carmichael and Price, 1995a, b). However, this region does still have access to value information from the amygdala and so may still perform a role utilizing this information (Carmichael and Price, 1995a; Kondo et al., 2003, 2005). This thesis will investigate the functional differences between these three areas using aspiration lesions in macaque monkeys and functional magnetic resonance imaging (fMRI) in humans. The following section will detail the cytoarchitechonic similarities and differences between the human OFC and the macaque as described by Carmichael and Price (Carmichael and Price, 1994, 1996). Additionally, the distinct cortical connective patterns of the human OFC will also be illustrated.

2.4 Comparative Anatomy of Macaque and Human OFC

In recent years neuroscientists have made increasing use of new, non-invasive neuroimaging technologies. These methods include fMRI, position-emission topography (PET), as well as electroencephalography (EEG) and magnetoencephalography (MEG). However, whilst electrophysiological and lesion studies allow precise localisation through histological examination, the very nature of non-invasive methods means this is not possible in human

studies. The vmPFC, along with much of the prefrontal cortex has expanded disproportionally from the rest of the brain through evolution from monkey to man (Schoenemann et al., 2005). As such, it may be hypothesised that the cortical divisions of the human possess distinct connections profiles from macaques. Comparative studies of anatomy and connection are therefore critical in order to confidently compare the different primate species, and allow generalisation of proposed brain functions. Furthermore, if a goal of neuroimaging work is to investigate the fractionation of prefrontal function, it has never been more important to understand and appreciate anatomical and connective differences between neighbouring brain regions. Yet, despite the value of comparative studies very few have actually been performed in frontal lobe regions.

Brodmann was one of the first to complete a comprehensive cytoarchitectural analysis of the human and non-human primate brain (Brodmann, 1905, 1909). However, despite assigning unique numbers to different cytoarchitectonic areas, his investigation of the OFC was not particularly detailed. In the human map, Brodmann identified areas 24, 25, 32 on the medial wall, and described areas 10, 11 and 47 on the lateral OFC surface (Figure 2.6A). Whilst the human map resembled the monkey, Brodmann was clear in stating that the maps were not identical. Indeed, area 32 in the human map was highlighted as not being homologous to area 32 in the macaque. In recent years, subsequent parcellations have increasingly attempted to reconcile Brodmann's human prefrontal regions with Walker's (1940) macaque OFC divisions in terms of coordinating nomenclature, cytoarchitectonic boundaries and labelling schemes (Economo and Koskinas, 1925; Bailey and Bonin, 1951). For example, in one of the first direct comparative architectonic analyses, Petrides and Pandya (1994) specifically introduced the term 47/12 to refer to the lateral orbital areas in humans and monkeys, thereby creating a map with

good alignment between the gross cytoarchitecture of the orbital cortex of the two primate species (Figure 2.6B).

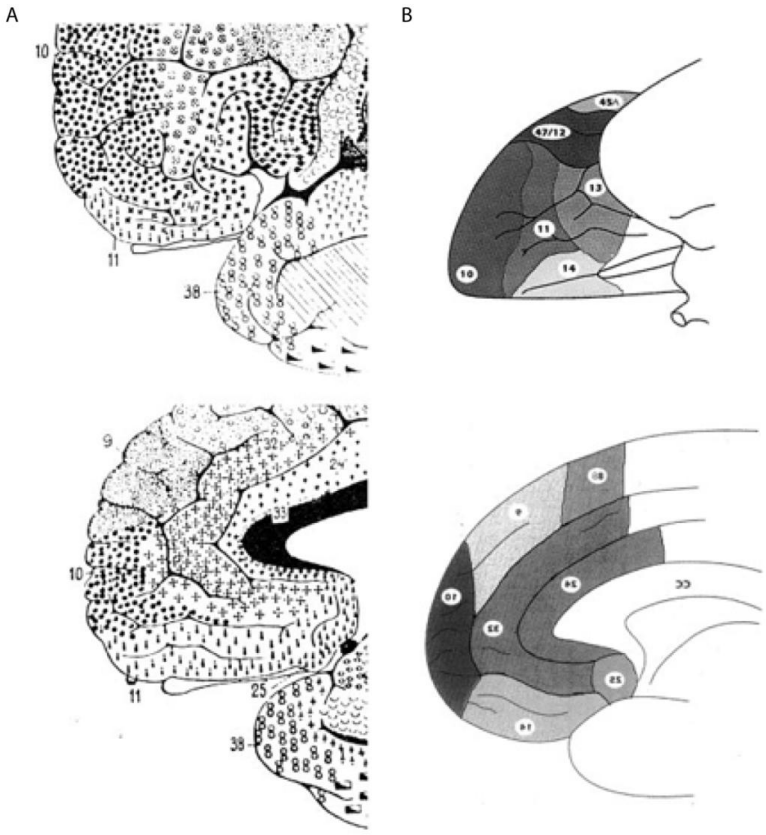

Figure 2.6. Subdivisions of the human orbital and medial PFC. A. Brodmann (1909) only labelled the OFC as area 11 and 47 and recognised areas 10, 32, 24 and 25 on the medial wall. B. Petrides and Pandya attempted to reconcile differences between Brodmann's human and Walkers monkey maps by introducing the term 12/47 and dissociating area 32. Permission to adapt and reprint granted by Ongur et al (2003) and John Wiley and Sons.

Ongur and colleagues have gone further by proposing a division of cytoarchitecture in the human brain, which closely matches the subdivisions of the monkey OFC by Carmichael and Price (Carmichael and Price, 1994; Ongur and Price, 2000; Ongur et al., 2003). Using a number of histological and immunohistochemical stains, Ongur and colleagues recognised all 21 areas identified by Carmichael and Price and two further subdivisions of area 10 and 32 (Figure 2.7).

Specifically, frontopolar area 10 was subdivided into 10m, 10p (equivalent to monkey area 10o), and the additional area 10r. Meanwhile, Brodmann's human dorsal anterior cingulate area 32 and his monkey prelimbic area of the same name were reconciled by defining the human area 32 as 32ac, and identifying a human OFC region, areas 32pl, as equivalent in structure and position to areas 32 in monkeys in the caudoventral zone of agranular cortex. Whilst expansions of human frontopolar cortex have pushed structures such as areas 25 and 32pl from their non-human primate locations, Ongur and colleagues believe the macaque and human brains to be cyctoarchietectonically similar (Ongur et al., 2003). However, this claim is difficult to substantiate without proof that the subregions' individual connection patterns are also comparable.

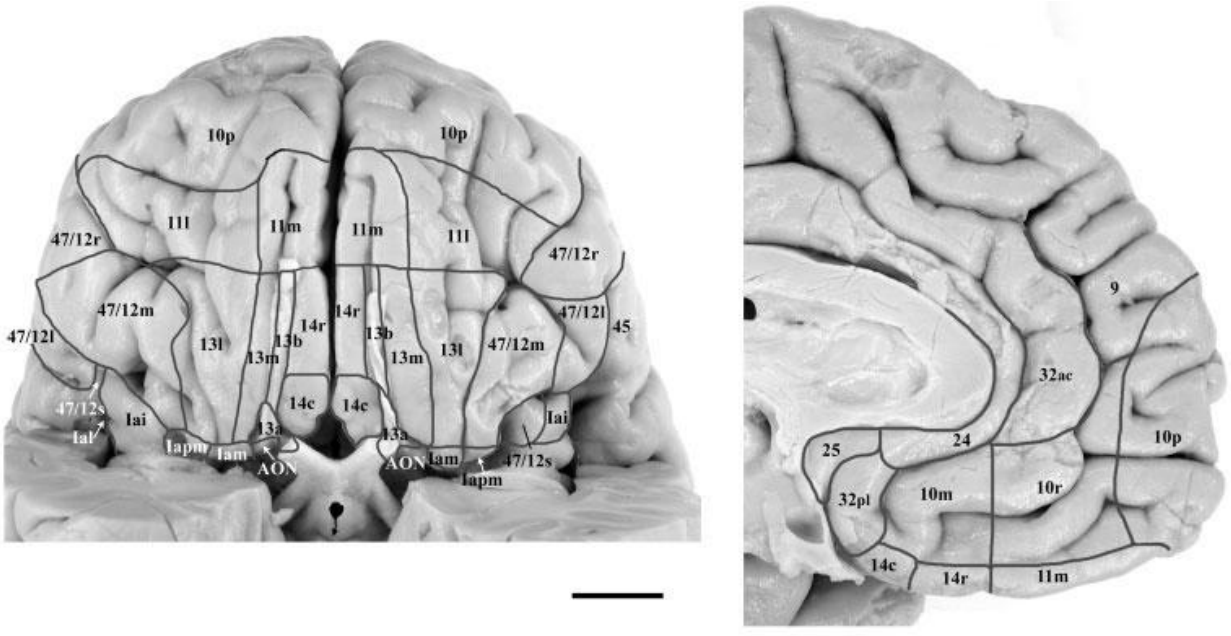

Figure 2.7. Architectonic subdivisions of the human orbital (left) and medial surface (right) as described by Ongar et al (2003). Permission to adapt and reprint granted by Ongar et al (2003) and John Wiley and Sons.

In humans, it has only recently become possible to perform comparative white matter tracing studies. Higher resolutions of MRI machines, in combination with the development of diffusion-weighted imaging (DWI) (Behrens et al., 2003), and the application of probabilistic diffusion tractography, now allows the quantitative analysis of human fibre tracts. DWI provides information about the orientation of brain fibre pathways; while applying the statistical analysis of probabilistic tractography generates estimates of the likelihood of a pathway existing between two brain areas. A number of studies have applied this approach to different structures and regions, and have compared across the human and non-human primate species. However, only one study to date has investigated the connective profiles of the prefrontal cortex (Croxson et al., 2005). Croxson and colleagues characterised the comparative connectivity profiles of PFC and found that each subcortical region had a distinct pattern of connectivity (Figure 2.8). Furthermore, these patterns of human PFC connectivity resemble those found in the DWI-based estimations of connections in macaques and the traditional tracer studies in macaques (Van Hoesen et al., 1972; Van Hoesen et al., 1975; Rosene and Van Hoesen, 1977; Barbas, 1988; Morecraft et al., 1992; Barbas, 1993; Barbas and Blatt, 1995; Carmichael and Price, 1995a). As seen in the macaque, different subregions of the vmPFC and OFC have differential cortico-cortical and cortico-subcortical connective patterns. In humans, all subregions of the OFC appear to have similar strength of connections to sensory brain regions such as posterior temporal cortex, via the extreme capsule (EC). However, central regions of the OFC are relatively more connected to anterior temporal cortex, via the uncinate fasciculus (UF). In contrast, the OFC is not especially connected to the parietal cortex, as very few tracts were indentified along the superior longitudinal fascicle (SLF). In macaques, probabilistic tractography (Croxson et al., 2005) and tracer injections (Van Hoesen et al., 1972; Van Hoesen et al., 1975; Rosene and Van

Hoesen, 1977; Barbas, 1988; Morecraft et al., 1992; Barbas, 1993; Barbas and Blatt, 1995; Carmichael and Price, 1995a) similar patterns of OFC connection with temporal and perirhinal structures. Observed connections along the cingulum bundle (CB) between lateral OFC and subcortical structures, such as the hippocampus, are both relatively sparse in humans and macaque (Croxson et al., 2005).

Comparisons of connective patterns towards value related regions, such as the amygdala and striatum, suggest a number of similarities exist across the two species (Croxson et al., 2005). There was evidence of a gradient of increasing strength of connections with the amygdala going from lateral to medial OFC in both humans and macaques. Similarly, fornix connections are evident in both species and are more prominent with mOFC. Evidence of stronger connection between the mOFC and ventral striatum was also found in both species.

The connectivity pattern of cingulate regions is also similar in both species (Croxson et al., 2005), as are the connections to the amygdala and hippocampus, along the CB and fornix. Cingulate regions are also connected to the striatum in both humans and macaques.

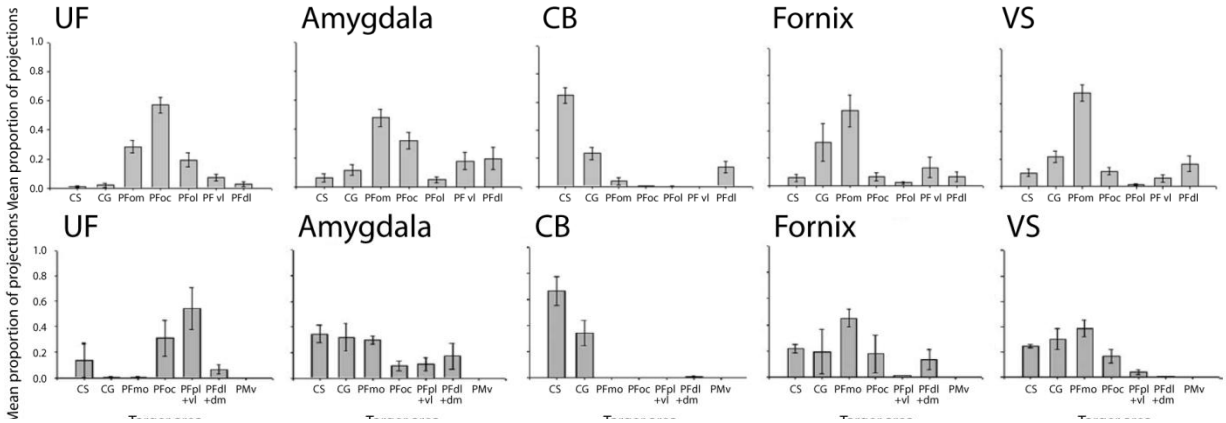

Figure 2.8. Comparative quantatative results of probabilistic tractography from seeds in human (upper) and macaque (lower) brain areas. Abbreviations; Uncinate fasciculus, UF; Cingulum bundle, CB; Ventral striatum, VS. Permission to adapt and reprint granted by Croxson et al (2005) and Society for Neuroscience.

Functional Considerations

Established comparative anatomical and connective similarities across human and non-human primate species are important for interpreting the functional similarities between the two species. Proposed mechanisms of behaviour from studies of discrete lesions and electrophysiological recordings in macaques can only inform human imaging studies (where neuronal responses can are only inferred from change in regional blood oxygenation ratios) if the brains across the species are relatively homologous. By being so they thereby validate the use of non-human primates as models of human brain function, and suggest that lesions can accurately represent and clarify the nature of impairments experienced by frontal lobe patients. For example, functional neuroimaging studies in humans have demonstrated changes in neuronal activity in the OFC in relation to sensory processes, such as olfaction (Zatorre et al., 1992; Zald and Pardo, 1997; Dade et al., 1998) and gustation (Small et al., 1997a, b; Zald et al., 1998; Small et al., 1999). In light of the OFCs mutual connections with primary olfactory cortex and gustatory responsive neurons (Carmichael et al., 1994) these functional experiments are relevant and interpretable. However, although these studies localise regional blood flow and oxygenation changes to the OFC, it has often been difficult to relate these changes to specific orbital subregions. This problem often stems from inconsistencies in the use of patterns of anatomical landmarks and the inherent intra-subject variability of gross anatomical organisation. Chiavaras and colleagues attempted to address this problem by assessing the patterns formed by individual sulci, and compared them to those of the less convoluted macaque brain (Chiavaras and Petrides, 2000; Chiavaras et al., 2001). They identified four sulci in both the human and macaque brain which formed a very similar set of patterns in both species. The olfactory, medial, lateral and transverse sulci often formed patterns resembling an “H”, “X” or “K”, and the division imposed

on the brains by such an arrangement resulted in four consistent major gyri: the medial, lateral, anterior and posterior orbital gyri. Whilst additional sulci in the human and intra-subject variability observed in both species added complexities to the organisation of the cortex, the pattern was very similar from macaques to humans. With a better understanding of anatomical landmarks, improvements in the localisation of functional activation should contribute to an overall advance in understanding of function in anatomically divisible regions of cortex.

The OFC has been described as a heterogeneous structure in both the human and non-human primates (Ongur et al., 2003; Croxson et al., 2005) and as such it is possible that the different categories of reported OFC deficit and task-specific changes in regional blood flow, as measured by neuroimaging studies, can be selectively associated with differing brain regions. One theory has proposed that medial and lateral OFC have distinct roles in representing rewarding and punishing events respectively, while a posterior-anterior gradient within the OFC distinguishes the representation of primary reinforcers to more complex abstract reinforcers, such as monetary gain and loss (Kringelbach and Rolls, 2004). This claim was made on the basis of a meta-analysis on a number of neuroimaging studies, where activation in the OFC was identified, but has never been tested directly in an animal lesion experiment. This thesis will argue that this proposed division of function does not capture the precise nature of regional contributions to learning and decision-making, and will therefore explore an alternative hypothesis.

Anatomically, the ACC is well located to bias actions based on the recent accumulated history of outcomes associated with a particular action (Rushworth et al., 2007a). It has multiple anatomical connections to motor and premotor brain regions, as well as receiving information about value from the amygdala and ventral striatum. Lesion work in monkeys has shown that animals with lesions to the cingulate sulcus have particular deficits in response-outcome (R-O)

reversal (Kennerley et al., 2006) and matching tasks (Rudebeck et al., 2008b), whilst being unimpaired in performing a stimulus-outcome (S-O) matching task (Rudebeck et al., 2008b). Human fMRI studies have also demonstrated a similar distinction between the two associative learning tasks, with the ACC showing activation in tasks involving monitoring performance and actions (Ridderinkhof et al., 2004; Walton et al., 2004). In contrast, the OFC is more typically activated in stimulus based learning tasks (O'Doherty, 2007), and both human patients and OFC lesioned macaques consistently report impairments in S-O reversal learning and stimulus devaluation (Baxter et al., 2000; Fellows and Farah, 2003; Izquierdo and Murray, 2004; Izquierdo et al., 2004; Walton et al., 2010). Recently this deficit has been found in macaques whose lesions were relatively confined to lOFC, and spared the mOFC. Indeed, the lateral structures of the OFC are particularly well suited to integrate stimulus and value information with multiple efferent inputs from sensory cortex and amyloid nuclei.

However, much less is known of the mOFC. Area 14 lies between the cingulate and lOFC, and many studies do not distinguish it from neighbouring orbital areas 11 and 13. Anatomically though, area 14 receives relatively more sensory input than the cingulate cortex, as well as relatively more cingulate connections than the lOFC. It is therefore possible that its function lies in utilising the S-O associations, created in the lOFC, to guide behaviour. It has been suggested that the mOFC has a role in relative reward representation (Elliott et al., 2008), and this may explain deficits experienced by patients in decision-making and consistency of choice preferences in human and macaques (Baylis and Gaffan, 1991; Fellows and Farah, 2007).

The subsequent experimental chapters will describe three experiments designed to investigate the hypothesis described above. However, whilst Carmichael and Price's (1996) medial and orbital connective networks have proved a useful framework for anatomical analyses,

due to this thesis' chosen methods, it will now be necessary to identify these regions based on gross anatomical architecture. Therefore, in both human and non-human primates the medial and lateral OFC will be distinguished by the medial orbital sulcus. Similarly, the rostral sulcus will serve to discriminate between mOFC and dorsal cingulate regions.

2.5 Conclusions

This chapter presented evidence for the cytoarchitectural and connective distinctions between multiple neighbouring regions in the macaque orbital and ventromedial cortex, and has established that this region of frontal lobe is not a homogeneous structure. It also discussed how the connective patterns of this region imply two connective networks within the human and non-human primate OFC. Finally, this chapter detailed how differences in connective inputs might underlie specialized functional roles, and suggested that anatomical similarities between different species makes it possible to draw on both macaque and human studies when attempting to describe OFC function. Subsequent chapters will draw upon these principles in order to investigate the premise that the anatomical foci for R-O learning, S-O learning and value comparison are the ACC, lOFC and mOFC respectively.

CHAPTER 3: THE MEDIAL ORBITOFRONTAL CORTEX IN EMOTIONAL AND SOCIAL PROCESSING

Socially guided behavior alters after damage to the ventromedial prefrontal cortex (vmPFC). However, interpretations of impairments based on patients with vmPFC lesions are complicated as damage is rarely restricted to a well-defined cortical area. Patients' lesions usually include medial orbitofrontal cortex (mOFC) as well as anterior cingulate cortex (ACC). The purpose of the current study was to investigate the contribution of the mOFC to social valuation and decision-making. Macaque monkeys were tested on a species-specific task measuring animals' valuation of emotional and social stimuli, prior to, and after focal lesions of mOFC. MOFC-lesioned animals were compared to previously collected data with animals with anterior cingulate gyrus (ACCg) and lateral orbital and ventral prefrontal cortex (PFv+o) lesions. The results revealed that, unlike lesions of the PFv+o, mOFC lesions did not induce alterations in emotional processes. Similarly, mOFC lesions did not affect social valuation, unlike the ACCg lesioned animals. MOFC lesions did, however, produce mild impairments in a probabilistic 2-choice decision task, which were not seen after ACCg lesions. The distinct patterns of impairment after ACCg, PFv+o and mOFC lesions suggest that different subregions of the vmPFC contribute differentially to social, emotional and decision-making.

3.1 Introduction

As discussed in Chapter 1 the mOFC as part of the vmPFC has been implicated in controlling social behaviours. Normal human social interactions are disrupted after damage to the vmPFC

(Bechara et al., 1997; Camille et al., 2004; Damasio, 2005; Clark et al., 2008). Patients are seen to become disinhibited in their behaviour, have impaired abilities in recognising emotional faces and voices, and become socially inappropriate: as rated by their friends or families (Hornak et al., 1996). VMPFC patients also struggle in personal moral judgements (Young et al., 2010).

The region of cortex that the vmPFC label is often used to refer to includes both ventral ACC and mOFC (Bechara et al., 1997; Camille et al., 2004; Damasio, 2005; Clark et al., 2008). It was the accidental actions of the infamous American Midwestern railway worker, Phineas Gage, who exploded a tamping iron rod through his prefrontal cortex, and the diligence of his doctor, John Martyn Harlow, which sparked theories of the frontal lobes being a critical region for controlling social aspects of behaviour. Gage was described by his doctor as having altered from a "shrewd, smart businessman, very energetic and persistent in executing all his plans of operation" to a "fitful, irreverent, indulging at times in the grossest profanity [], manifesting but little deference for his fellows, [and] impatient of restraint or advice when it conflicts with his desires." To his friends he was "No longer Gage". These descriptions imply that Gage's social competence had changed dramatically after his brain injury. Reconstructions of the lesion suggest that damage to the vmPFC had occurred (Damasio et al., 1994), although more recent reconstructions have emphasised the likelihood that surrounding cortex, including the ACC, was also damaged. Whilst debate has focused on the nature of the deficit, the precise anatomical position of the critical lesion has received less attention. VMPFC lesions in human patients usually encompass both mOFC (Broadman Area 14) and the subgenual/perigenual anterior cingulate gyrus (Broadman Areas 25, 32) while the OFC lesions in monkeys associated with changes in emotional responsiveness encompass both mOFC and lateral OFC (Izquierdo and Murray, 2004; Izquierdo et al., 2005; Rudebeck et al., 2006a; Machado et al., 2009). The animals

in these studies tend to demonstrate diminished fearful responses to naturally fear inducing stimuli, such as snakes and unfamiliar humans, as well as exhibiting increased aggression towards these stimuli. This pattern of increased aggressive behaviour has also been observed in OFC-lesioned rats interacting with other rats (Rudebeck et al., 2007). In addition to these impairments (Meunier et al., 1997), OFC-lesioned animals also show deficits in decision-making, tested in the context of visual discrimination reversal tasks (Meunier et al., 1997; Izquierdo et al., 2004, 2005; Rudebeck et al., 2008b; Rudebeck and Murray, 2008). This deficit has been proposed to reflect an inability to predict the reinforcement consequences of a stimulus. The modification of associations between stimuli and primary reinforcers, assumed to be impaired in visual discrimination reversal learning (Izquierdo et al., 2004), has been suggested to underlie emotion and social mechanisms (Rolls, 1999, 2005).

This hypothesis has been directly tested in animals with lesions to either the lateral orbital and ventral prefrontal cortex (PFv+o) or the anterior cingulate gyrus (ACCg). Rudebeck and colleagues measured animals' latencies in retrieving food items placed in front of fear-inducing stimuli (toy snakes) or while videos of interesting social stimuli were presented (Rudebeck et al., 2006a). The latencies indexed the macaques' assessment of the relative value of obtaining further information about the stimulus before reaching, in contrast to the incentive value of the food. Normal macaques responded fearfully in the presence of the snake and demonstrated differential interest in the different types of social stimuli, suggesting differential social value estimations (see figure 1.2). However macaques with PFv+o lesions were significantly different to control animals in how they reacted to the fearful stimuli. This group of animals retrieved the food very quickly; indicating they did not find this stimulus threatening. In contrast, PFv+o lesioned animals maintained control-like differential reaching latencies in the presence of the social

stimuli. The authors therefore concluded the valuation of social information was not the responsibility of this region of the orbitofrontal cortex (OFC). Instead, Rudebeck and colleagues argued that the ACCg was a more likely candidate in social valuation as the animals who received lesions to this region were uninterested in any of the videos of the other macaques and the pattern of differential interest seen in control animals was absent. ACCg animals also exhibited significantly fewer affiliative or aggressive behavioural responses to any of the stimuli. Notably, only the PFv+o-lesioned animals were impaired in visual discrimination reversal learning, suggesting perhaps that just emotional processing is supported by adaptive stimulus-outcome learning mechanisms.

A number of human neuroimaging studies also implicate the vmPFC in aspects of social behaviour. We conducted a meta-analysis of functional magnetic resonance imaging (fMRI) investigations of social judgment that identified a cluster of activation in the mOFC and adjacent ACC (Figure 3.1 and Appendix II: Cluster analysis). The meta-analysis focussed on papers listed on Pubmed, and published between 2007 and February 2010. The keywords used were "fmri" and "social". To compare social and non-social related activities in the OFC, we conducted another analysis using the following keywords: "orbitofrontal", "decision", "feedback". We disregarded studies on patients, elders (> 60years old) or children/teenagers (< 20years old). We also removed from our analysis PET studies and fMRI experiments focussing on regions of interest. Finally, we did not take into account articles published in the social neuroscience journals because of a lack of access. Where necessary coordinates were transformed from Talairach coordinates to MNI coordinates. The meta-analysis highlighted the importance of reward-guided decision-making; activation in the same general area as found during decision-making and feedback evaluation. It is not; however, always clear whether involvement of either

mOFC or adjacent ACC in social judgment can be explained by a more fundamental role in decision-making.

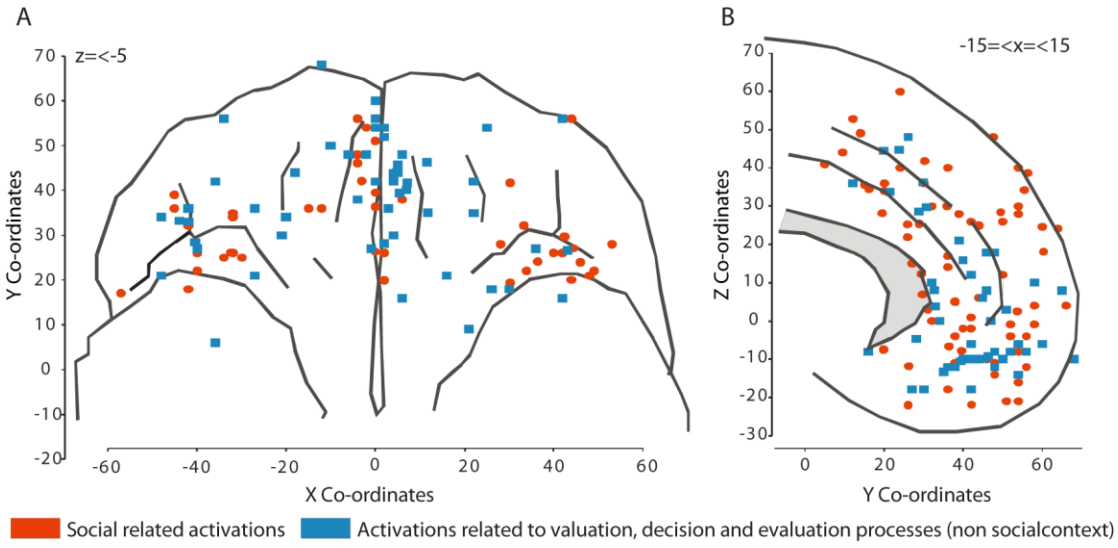

Figure 3.1. Meta-analysis of fMRI activities for social related processes. **A**. Activities are reported on a schematic representation of a ventral view of the prefrontal cortex (adapted from Kringelbach and Rolls, 2004(115)(51)(50)). **B**. Activities are reported on a schematic representation of a medial view of the prefrontal cortex (adapted from Paus et al. 1996(241)(95)(94)). Activations were reported in the mOFC and lateral OFC (A) as well as in the adjacent anterior cingulate, and medial prefrontal cortices (B).

The orbital and medial frontal region in human and non-human primates is composed of multiple cytoarchitectonic areas with different anatomical connections (Petrides and Pandya, 1994; Carmichael and Price, 1995b, a; Ongur et al., 2003; Haber et al., 2006). It is therefore likely that different component regions are involved in different processes. To assess the specific role of one part of the vmPFC, the mOFC, to social valuation and decision-related processes, we conducted a lesion study in monkeys. Notable, the mOFC was a region not included in the PFv+o lesions in the Rudebeck and colleagues (2006a) study, so it was hoped that this investigation would further isolate the contribution of different frontal lobe regions in social and

emotional processing. We used an identical paradigm to Rudebeck and colleagues (2006a) and tested social valuation in four macaques before and after mOFC lesions. Furthermore, utilization of the same behavioural protocol allowed us to compare the mOFC lesion results with the PFv+o and ACCg lesion results obtained by Rudebeck and colleagues (2006a).

To ascertain whether any potential impairment in social valuation was associated with impairment in fundamental aspects of reward-guided decision-making we also tested both mOFC and ACCg animals, pre- and post-operatively, on identical probabilistic 2-choice decision tasks with visual stimuli. Unfortunately, the PFv+o data on the decision-making tasks was not available for analysis. The effects of ACCg lesions on social valuation have previously been published (Rudebeck et al., 2006a) but the effect of ACCg lesions on the probabilistic decision-making tasks has not been reported.

3.2 Methods

Animals

Four male rhesus macaque monkeys (*Macaca mulatta*) aged between 7 and 10 years old and weighing between 9 and 13.5kg received mOFC lesions. All animals were maintained on a 12hr light/dark cycle and had 24hr ad-lib access to water, apart from when they were testing. All experiments were conducted in accordance with the United Kingdom Scientific Procedures Act (1986).

Surgery & anesthetic procedures

At least 12hrs before surgery, macaques were treated with an antibiotic (8.75 mg/kg amoxicillin, i.m.) and a steroidal anti-inflammatory (20 mg/kg methylprednisolone, i.m.) to

reduce the risk of postoperative infection, edema, and inflammation. Additional supplements of steroids were given at 4–6hrs intervals during surgery. On the morning of surgery, animals were sedated with ketamine (10 mg/kg, i.m.) and xylazine (0.5 mg/kg, i.m.) and given injections of atropine (0.05 mg/kg), an opioid (0.01 mg/kg buprenorphine), and a non-steroidal anti-inflammatory (0.2 mg/kg meloxicam) to reduce secretions and provide analgesia, respectively. They were also treated with anH2 receptor antagonist (1 mg/kg ranitidine) to protect against gastric ulceration, which might have occurred as a result of administering both a steroid and non-steroidal anti-inflammatory treatments. Macaques were then moved to the operating theatre where they were intubated, switched onto isoflurane anaesthesia (1–2%, to effect in 100% oxygen), and placed in a head holder. The head was shaved and cleaned using antimicrobial scrub and alcohol. A midline incision was made, the tissue retracted in anatomical layers, and a bilateral bone flap removed. All lesions were made by aspiration with a fine gauge sucker. Throughout the surgery, heart rate, respiration rate, blood pressure, expired CO2, and body temperature were continuously monitored. At the completion of the lesion, the wound was closed in anatomical layers. Non-steroidal anti-inflammatory analgesic (0.2 mg/kg meloxicam, orally) and antibiotic (8.75 mg/kg amoxicillin, orally) treatment were administered for at least 5 days postoperatively. All surgery was carried out under sterile conditions with the aid of a binocular microscope. At least two weeks were allowed for recovery before testing resumed.

The mOFC lesion was made by removing the cortex from the medial orbitofrontal sulcus to the rostral sulcus and included mainly Walker's area 14 (Walker, 1940) but in addition some parts of area 10. Procedures specific to the lesions made in the comparison groups in the PFv+o and ACCg have been published previously (Rudebeck et al., 2006a).

Postmortem lesion analysis

When the animals had completed their testing they were anesthetized with sodium pentobarbitone and perfused with 90% saline and 10% formalin. The brains were then removed, and placed in 10% sucrose formalin until they sank. The brains were blocked in the coronal plane at the level of the most medial part of the central sulcus. Each brain was cut in 50μm coronal sections. Every tenth section was retained for analysis and stained with cresyl violet.

Experiment 1

Apparatus

All training and testing was conducted while the animals were in a transport cage inside a modified Wisconsin General Testing Apparatus (WGTA; figure 3.2a). A Plexiglas box measuring 70 x 11 x 11cm with a hinged back was fixed to the WGTA 20cm in front of the transport cage. In addition behind the box, 50cm from the front of the transport cage was a PC monitor for presenting visual stimuli. On each trial stimuli could be presented either in the box or on the PC monitor. The stimuli presented in the box could be one of the following: 20 neutral control 'junk' objects, one of two fear inducting stimuli (a static rubber snake or a moving wooden snake). Stimuli presented on the screen were video clips 30s in length and were one of two human stimuli: (one of two unknown staring human faces), or one of five social stimuli including a large (11kg) monkey staring, a monkey (8kg) exhibiting affiliative behaviours – lip-smacking, a monkey (9kg) inspecting a transport cage or a monkey (5kg) with food, a female macaque (5kg) with prominent perineal swelling). Alternatively, a moving, neutral control stimulus (a moving randomly changing coloured object) was presented on screen (Figure 3.2b). The video clips were chosen because it made it possible to compare the effects of mOFC lesions

with the effects of ACCg and PFv+o lesions; the stimuli had previously been used in an investigation of the effects of ACCg and PFv+o lesions (Rudebeck et al., 2006). The social stimuli were chosen because they were expected to elicit varying degrees of interest from control monkeys (and indeed this proved to be the case as explained below). Video stimuli were clips taken from longer videos of other monkeys in the colony; recorded while they were either in transport cages or primate chairs. At the time of testing all the monkeys in the video social stimuli were novel to the subjects. All videos were taken using a Panasonic EZ35 mini-DV camera, and edited using Adobe Premier Pro 1.5 software. Videos were played using Windows media player version 9.0.

A camera mounted on top of the PC monitor recorded each monkey's behaviour. The camera faced the whole cage and allowed monkeys' latencies to take food rewards placed at the back of the Perspex box to be measured, and general behaviour and/or facial expressions to be recorded for later analysis.

Procedure

Briefly, animals were tested in the WGTA (Figure 3.2a) and on every trial the monkey retrieved a small food item that was placed in a fixed central position on the top of a transparent plastic box. Two different emotive toy snakes (static and moving) were used to investigate fearfulness (experiment 1a). The five short films of other macaques (detailed above) were used to investigate social valuation in experiment 1b. Responsiveness to videos of humans staring was assessed in experiment 1c. Finally responsiveness to neutral control objects was assessed in order to provide a baseline against which to compare any changes in fearfulness and social valuation (experiment 1d). On each trial, stimuli were placed in the Perspex box or displayed on a screen

behind the box. The animal had 30s to retrieve the food item or else an opaque moveable screen was lowered in-between the animal and the box for the duration of a 30s inter-trial interval. The latency to reach for the piece of food indexed the macaques' assessments of the value of obtaining additional information about the stimulus before reaching, and reflected their relative valuation of the stimulus in contrast to the incentive value of the food. Every other day, animals were exposed to ten different stimuli of possible social or emotional importance and 20 neutral objects. The test was repeated over four sessions (with a day of rest in between each session), and the median reaching latency for each stimulus per animal was calculated. Each stimulus, either in the box or on the screen, was presented once per day. Objects in the box and images on the screen were presented in a pseudorandom order. The constraints enforced on order were that neutral object trials always followed trials in which potentially fear-inducing/social stimuli (snake/monitor stimuli) were presented. In Experiment 1 two animals (mO1 and mO2) had acted as un-operated controls in a previous experiment (Rudebeck et al., 2006a). The other two animals (mO3 and mO4) were tested only in this study; pre- and post-operatively. The data from all four animals were considered together because there was no discernable difference between animals' performances in relation to the time of testing.

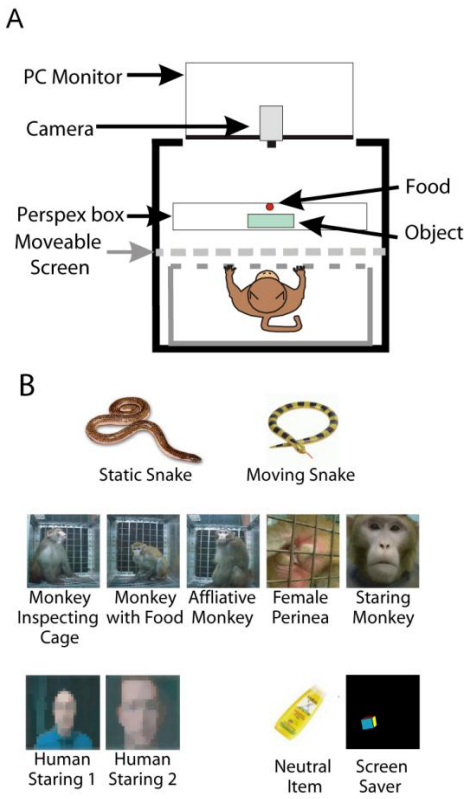

Figure 3.2: WGTA testing apparatus and representations of stimuli. **A**. Monkeys sat in a transport cage facing the perspex box and PC monitor. On each trial the moveable screen was raised and animals could take the valued food item (peanut or quarter date) placed at the far edge of the perspex box. After 30s the screen was lowered regardless of whether the animal had taken the food or not. Represented below are the stimuli (**B**) used including snakes and individual frames of the 5 videos of macaque social stimuli. From left to right: monkey inspecting cage, monkey with food, monkey making affiliative gestures, female monkey perineum and staring monkey. Additional stimuli used included the human social stimuli and neutral stimuli.

Habituation and reward preference test

Animals were first habituated to the testing environment and then trained to take food from the top of the Perspex box while it was empty. The food reward was located at the centre of the back edge of the box nearest the PC monitor so that during the actual test the animal would have to

reach over anything in the box, or as close as possible to the monitor. A small mark on the back of the box meant that the food reward was always put in the same place. Each trial began with the movable screen being raised. The monkey then had 30secs to retrieve the food reward located on the box. The screen stayed up regardless of whether or not the monkey took food reward within the 30s. At the end of the trial the screen was lowered for 30s before the next trial. During this period, the experimenter could change the object in the box or image on the monitor and replace the food item. Before the screen was raised for the next trial, a curtain that obstructed the animal's view of the experimenter was fixed to the back of the WGTA. The curtain was used to ensure that monkeys could not see the experimenter during the trial as the presence of a human could have affected later trials involving human or monkey stimuli presented on the screen.

For the test to assess emotional and social value of the different stimuli the food rewards had to be motivationally significant. We therefore sought a food highly valued by each individual animal. All animals were initially trained to take a single peanut food reward. A food reward was judged as motivational significant if the animal took the food item from the back of the box in under 5s for 20 consecutive trials. Animals who did not reach this criterion with peanut food reward were trained to criterion with a quarter piece of date. This food object was then used throughout the rest of training and testing. Over a further 3 days they were then trained to take their preferred food reward from the top of the box while any one of 9 novel 'junk' object were presented inside, or a moving, changing coloured object was presented on the computer screen positioned behind the box. Objects were presented in sets of 5 per day, with each object being presented twice (10 trials). These junk objects were not used subsequently during testing, and instead further sets of novel junk object were used in the interleaved control trials in the tests of emotion and social behaviour.

Data acquisition

Each trial was recorded on VHS video and analyzed independently by two raters (MPN and JS). Reaching latencies were measured from the beginning of the trial, as defined by the raising of the screen, to the time the animals first grasped the piece of food. Despite high inter-rater reliability (Pearson correlation r=0.986), all trials, in which there was a discrepancy of more than 40ms between the two raters scores, were re-evaluated. 46/960 trials were identified in this manner and re-analysed by both raters.

Data analysis

The start of each trial was initiated when the screen was raised above a fixed point marked on the side of the cage at approximately the same height as the top of the Perspex box. For the reaching latency measurement, the response was considered finished at the point just before the animal moved the food object from its initial position. If the animals did not retrieve the food reward within the 30s, a score of 30s was given. Latency measurements were scored to the nearest frame/0.04s.

The data from Experiment 1a was subjected to a 3-way repeated measures ANOVA with factors of Surgery (2 levels; pre and post-operative), Session (4 levels; 1-4 days), and Stimuli (2 levels; moving and rubber snake). The first two factors were also used in the 3-way repeated measures ANOVAs used to analyze the data from all the other experiments but then the third factor either reflected the 5 levels of social Stimuli (monkey inspecting cage, monkey with food, monkey making affiliative gestures, female monkey perineum and staring monkey) in experiment 1b, the two different human video stimuli (experiment 1c), or the two different

classes of neutral stimuli (moving or static objects). Reaching latencies were log-transformed, when necessary, to minimize the impact of positive skewing, and to reduce between-group differences in reaching latency variance.

In addition to measuring reaching latencies to the food, two experimenters (JS, MPN) scored animals' behaviour in response to each stimulus using an adapted form of the checklist employed by Aggleton and Passingham (Aggleton and Passingham, 1981; Izquierdo and Murray, 2004; Izquierdo et al., 2005; Rudebeck et al., 2006a). The behavioural responses were categorized into *affiliative behaviour* (lip-smacking) and *aggressive/conflict behaviour* (ears flat, open mouth threat, piloerection and cage shaking). Each instance of a behaviour, in each relevant behavioural category, during the 30s trial period, was recorded and the mean frequency was compared pre- and post-operatively. Because the stimuli in the present experiment, as in the study of Rudebeck and colleagues (2006a), were never used to directly threaten the animal they were far less effective in eliciting strong behavioural responses than those used by Aggleton and Passingham. A three way within-subjects ANOVA compared the responses of the animals pre- and post-operatively (Lesion) with respect to the two behavioural Categories (social/affiliative and aggressive/conflict) to the five social stimuli (Stimuli: staring human, female monkey perineum, staring monkey, moving snake and moving pattern).

Subsequent analyses compared the effects of mOFC lesions with those induced by lesions to other regions of the frontal lobe. Previously collected data from animals with PFv+o lesions were compared to the mOFC post-operative testing sessions. Four independent 2 way-repeated measures ANOVAs mirrored the analyses described above. Emotional Stimuli were compared in a 3-way ANOVA of Stimulus, Session and the between-subjects factor of Lesion position (mOFC; PFv+o). Social stimulus effects were compared in a 3-way ANOVA of social Stimuli,

Session and the between-subjects factor of Lesion position. Responses to human video stimuli were compared in a 3-way ANOVA of social human Stimuli, Session and the between-subjects factor of Lesion position. Finally, responses to neutral stimuli were compared in a 3-way ANOVA of neutral Stimuli, Session and the between-subjects factor of Lesion position. Similarly, post-operative latency data from mOFC-lesioned animals were compared with previously collected data from animals with ACCg lesions. The same four independent 2 way-repeated measures ANOVAs, described for the PFv+o comparison were performed for the ACCg comparison. Emotional, Social, human Social and Neutral stimuli were compared in a four independent 3-way ANOVA of Stimulus, Session and the between-subjects factor of Lesion position (mOFC; ACCg).

Experiment 2

Apparatus

Each monkey sat in a testing room, unrestrained in a wheeled transport cage placed 20cm from a touch-sensitive monitor (38cm wide x 28cm high) on which visual stimuli could be presented (8 bit color clipart bitmap images, 128 x 128 pixels) and responses recorded. The clipart stimuli presented to the animals varied location from trial to trial (Figure 3.3). Rewards (190mg Noyes pellets) were delivered from a dispenser (MED Associates) into a food well immediately to the right of the touch screen. A large metal food box, situated to the left below the touch screen, contained each individual's daily food allowance (given in addition to the reward pellets), consisting of proprietary monkey food, fruit, peanuts and seeds, delivered immediately after testing each day. This was supplemented by a forage mix of seeds and grains given ~6 hours

prior to testing in the home cage. Stimulus presentation, experimental contingencies, reward delivery and food box opening was controlled by a computer using in-house software.

Procedure

The mOFC animals were tested pre- and post-operatively on a simple 2-choice task. Before the start of testing, all macaques had received extensive training with touch screens and knew that touching a stimulus on the screen could lead to food reward. Each day, macaques were presented with two novel stimuli on the touch screen at the same time in a left/right configuration. Each stimulus' side of presentation varied from trial to trial. On each trial, selecting one stimulus caused the other to extinguish, and reward to be delivered according to the reward schedule. Auditory tones were used to cue the animal to the presentation of the stimuli, to the selection of a stimulus and to the potential delivery of a reward. Each stimulus was associated with a different outcome probability, one stimulus always being rewarded more than the other. At the start of testing, each stimulus was randomly assigned one of two reward probabilities. The ratios of reward associated with the two stimuli were either 75:25 (in other words one stimulus had a 0.75 probability of reward while the other had a 0.25 probability of reward) and 50:18. Each schedule was performed twice and in an interleaved manner. Monkeys' touches registered their stimulus selections. Upon a decision being made, rewards were delivered according to a specific schedule (75:25 and 50:18) with a fixed probability with a reward matching contingency in place (Herrnstein, 1997; Sugrue et al., 2004; Kennerley et al., 2006; Rudebeck et al., 2008b). This meant that rewards once allocated to a stimulus, remained available until that stimulus was chosen. Further details can be in Rudebeck and colleagues (2008b).

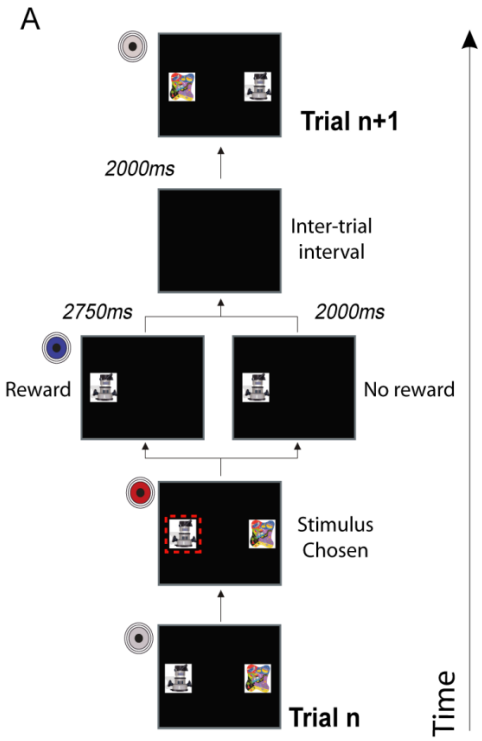

Figure 3.3. Schematic representation of the decision-making task. On each trial, monkeys were presented with 2 clipart stimuli in a left/right configuration on a touch-screen. Each stimulus' side of location varied from trial to trial. Each was associated with a different outcome probability, one stimulus always being rewarded probabilistically more than the other. On each trial, selecting one stimulus caused the other to extinguish and reward to be delivered according to the reward schedule. Grey, blue and red circles represent different 250ms tones. Tones were used to cue the animal to the presentation of the stimuli, to the selection of a stimulus and to the potential delivery of a reward. The animals experienced two reward schedules a 50:18 and a 75:25.

Data Analysis

The performance of each macaque was assessed by calculating the number of trials to reach the ratio of responses (high-probability stimulus choices to low-probability stimulus choices) that yielded 97% of the maximum rate of reward (r_{opt}) (Kennerley et al., 2006). Briefly, r_{opt} was calculated by plotting the expected value (EV) given each rate, r, of high stimulus choice, EV(r),

for the different probability ratios (75:25, 50:18), where p and q represent the probability of reward associated with the high and low stimuli (Eq.1). r_{opt} was then determined for each probability ratio by taking the maximum point on each of the curves plotted. The number of trials that macaques took to achieve 97% of the r_{opt} was determined using a 20 trial moving window (–10/+10) of the subjects choices for the high reward probability stimulus.

$$\mathrm{EV}(r) = 2r\left[1 - \frac{r - rp}{p + r - rp}\right] + 4(1 - r)\left[1 - \frac{1 - r - q + rq}{1 - r + rq}\right]. \quad \textit{Equation 1}$$

If criterion was not reached by the end of the 100 trial session, a score of 100 was allocated to that animal on that session. The results were subjected to a repeated measure ANOVA of Lesion (pre- and post-operative) x Reward Ratio (50:18 and 75:25) x Session.

The ACCg animals were tested and analyzed in a similar way although they were compared to a group of un-operated control animals (N=6) in a three-way ANOVA with a two level factor of Reward Ratio (50:18 and 75:25) x two level factor of Session x the between subjects factor of Group (ACCg; un-operated controls). It is difficult to make direct comparisons between the post-operative performances of the mOFC and ACCg animals as three of the un-operated control animals that were used in the ACCg experiment were subsequently tested as part of the mOFC group. This means that at the final mOFC post-operative test these animals had been tested 3 times on this paradigm whereas the post-operative ACCg animals had never previously been tested on a reward matching task, although they had had experience of other reward-guided visual discrimination tasks.

3.3 Results

Histology

The histology of the mOFC-lesioned animals is shown in Figure 3.4 (and appendix I-Histology) and shows that mOFC lesions were made as intended. The cortex from the medial orbitofrontal sulcus to the rostral sulcus, including mainly Walker's area 14 (Walker, 1940) but also some parts of area 10 were removed. For full details of the ACCg and PFv+o lesions please refer to Rudebeck et al. (2006a). However, the ACCg lesions were largely confined to area 32 and the anterior ventral tiers of area 24, while the PFv+o lesions covered areas 11, 13, 12, 9 and 46.

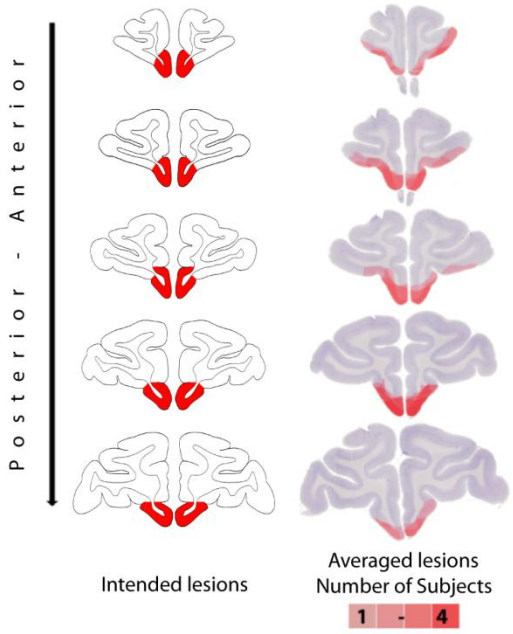

Figure 3.4. Diagram of mOFC intended (left) and actual (right) lesions (mOFC: 1-4 animals). The intensity of redness indicates the extent of the lesion overlap in the four animals.

Experiment 1

Reaching Latencies

MOFC lesions produced no significant effects on reaching latencies for any fear-inducing stimuli in Experiment 1a (Figure 3.5a; neither main effect of mOFC lesion; $F_{1,3}$=0.014, p=0.912, nor interaction of lesion with stimulus type; $F_{1,3}$=0.045, P=0.845). There was, however, a main effect of stimulus type ($F_{1,3=}$27.84, p=0.013); with the animals being slower to reach for the moving snake than the rubber snake.

There was also no effect of lesion ($F_{1,3}$=0.41, p=0.568), or interaction of lesion with stimulus type ($F_{4,12}$=1.30, p=0.327) for reaching times to the social stimuli in experiment 1b (Figure 3.5b). However, a linear main effect of social stimulus type was revealed ($F_{1,3}$=3.48, p=0.040) suggesting that animals, regardless of the presence of an mOFC lesion, agree which images of other macaques are the most interesting (Deaner et al., 2005, Rudebeck et al., 2006, Klein et al., ,2008, 2009). All animals were slower to retrieve food in the presence of a large staring male, a female macaque with visible sexual perineal swellings and a midsized macaque making affiliative lip-smacking gestures, than was the case with the other less socially salient images. As can been seen in figure 3.5c, there was also no effect of mOFC lesion on reaching latencies for the social human stimuli in experiment 1c ($F_{1,3}$=2.53, p=0.210) or interaction between the mOFC lesion and human stimulus type ($F_{1,3}$=0.91, p=0.410).

Finally there was no effect of mOFC lesion on reaching latency in the presence of neutral stimuli (figure 3.5d; main effect: $F_{1,3}$=1.25, p=0.345; interaction of mOFC lesion and neutral stimulus category: $F_{1,3}$=2.332, p=0.0.224). In contrast, there was a three-way interaction between lesion, neutral stimuli and session ($F_{3,9}$=4.21, p=0.041), and a main effect of neutral stimuli ($F_{1,3}$=22.56, p=0.018). Inspection of the data suggests that this three-way interaction can be

attributed to longer reaching latencies in the first testing session pre-operatively towards moving stimuli only. The main effect is due to longer reaching latencies towards the moving stimuli: regardless of the presence of lesion (paired samples t-test pre-op t_3,=-3.06, p=0.055, post-op t_3=-3.15, p=0.051).

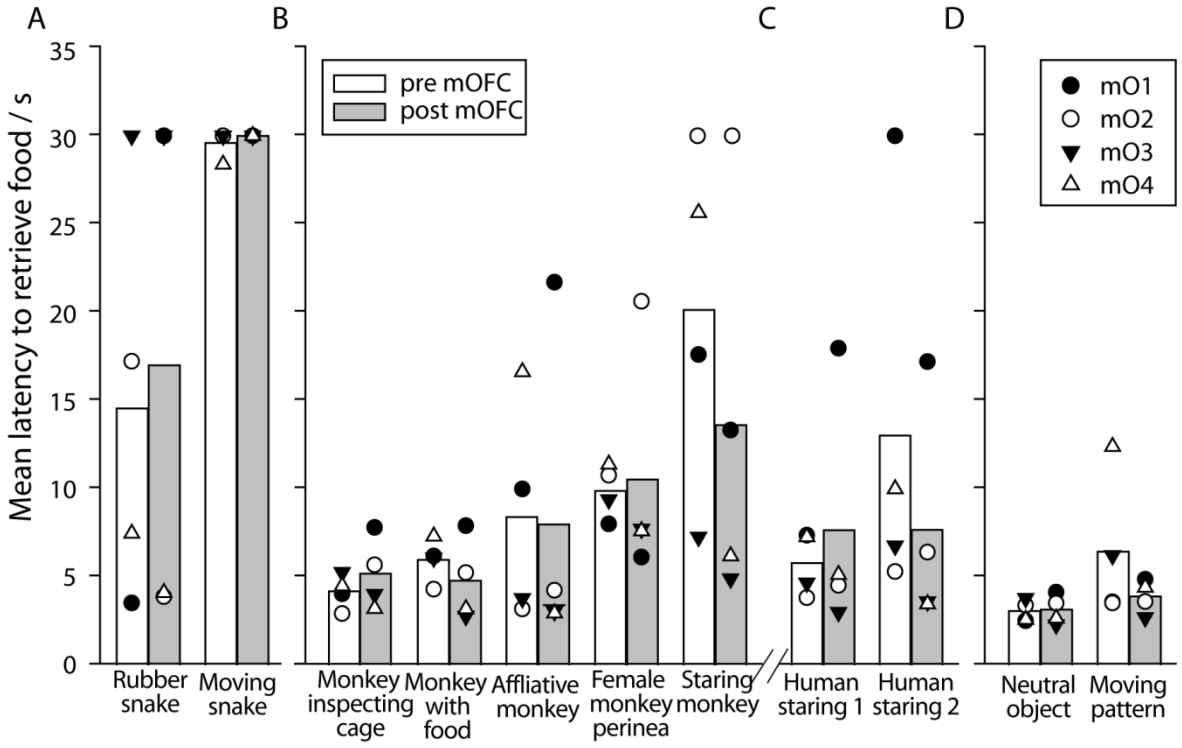

Figure 3.5. Response to mild fear and social stimuli in Experiment 1. Median latency to retrieve food in the presence of a mild fear-inducing stimulus (a, static or moving snake), social stimuli, either unknown macaques (b) or human actors (b) and neutral control stimuli (d). Symbols indicate scores for each individual. No changes in the mean latency to retrieve the food placed in front of any different stimulus types were seem after mOFC lesion effects were seen.

To note, we observed effects of habituation in the responses to all 4 stimuli types. One-way ANOVAs of Session (4 levels; 4 testing days) and fear Stimulus (2 levels; Moving and

Static snake) revealed a near main effect of Session ($F_{3,9}$=4.77, p=0.068), which individual one-way ANOVAs attributed to habituation to the static snake only ($F_{3,9}$=4.89, p=0.028), the moving snake did not show habituation effects over testing session ($F_{3,9}$=0.77, p=0.536). Analyses of the other stimulus types revealed a main effect of Session for the social monkey Stimuli ($F_{3,9}$=11.92, p=0.005) and social human Stimuli ($F_{3,9}$=11.53, p=0.002). Effects of Session to the neutral Stimuli on tended to significance ($F_{3,9}$=4.19, p0.091).

Behavioural responses to stimuli

Not only did the mOFC lesion fail to alter monkeys' reaching latencies to the various categories of stimuli, but it also did not greatly alter any measure of their social interaction during the test (Figure 3.6). Analysis of the frequency of certain social behaviours revealed very few significant effects. MOFC lesions produced no differences in the frequency with which aggressive or affiliative behaviours were displayed. There was no effect of Lesion ($F_{1,3}$=2.99, p=0.182), behavioural Category ($F_{1,3}$=0.71, p=0.461), or social Stimuli ($F_{4,12}$=0.77, p=0.507). There was, however, a significant interaction of Lesion with Stimuli ($F_{4,12}$=5.67, p=0.008), which appears to be as a result of fewer behavioural responses elicited towards the human staring stimuli after mOFC lesions (two-tailed paired samples t-test: t_3=2.45, p=0.092, t_3=5.00, p=0.015; affiliative and aggressive respectively). These results imply mOFC-lesioned animals do not greatly change their overt behaviour to macaque social or emotional stimuli, even if there is a reduction in the responsiveness towards videos of people.

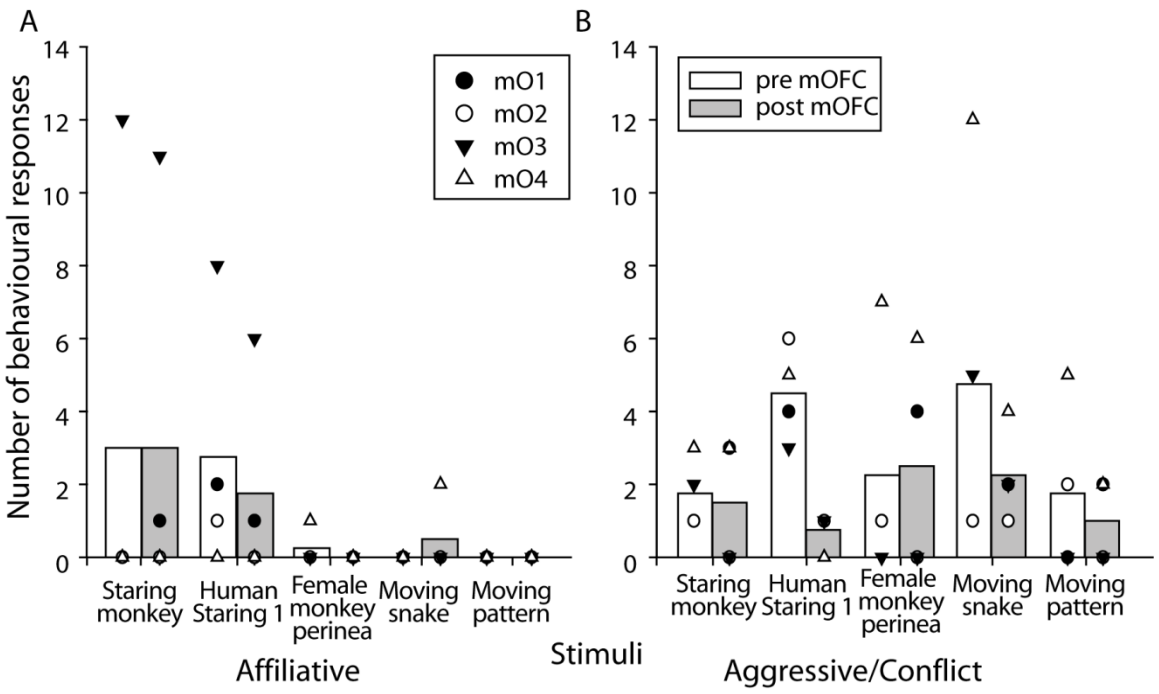

Figure 3.6. Behavioural response to mild fear and social stimuli in Experiment 1. Comparison of the effect of mOFC lesions on the most commonly observed combined measures of affiliative behaviour (a; lip-smacking) and aggression and conflict (b; ear flattening, open mouth threat, cage shaking, and piloerection). Symbols indicate scores for each individual. Overall no differences in the number of affiliative or aggressive responses were observed.

Comparison of mOFC reaching latencies to PFv+o and ACCg-lesioned animals

Rudebeck and colleagues (2006) report that lesions of PFv+o do not alter monkeys reaching latencies in response to social stimuli, but they did affect responsiveness to fear-inducing stimuli (Rudebeck et al., 2006a). In a direct comparison of mOFC and PFv+o lesioned animals' reaching latencies in the context of fear-inducing stimuli it can be seen that the PFv+o-lesioned animals are significantly faster to reach for food placed over emotive stimuli than animals with mOFC lesions (figure 3.7; Fear x Group interaction; $F_{1,5}$=9.29, p0.028 and main effect of Group; $F_{1,5}$=9.59, p=0.027). This suggests that PFv+o animals were less fearful than mOFC animals. In

contrast, no differences were found between the two lesion groups in their responses to the social stimuli (social monkey Stimuli x Session x Group; $F_{12,60}$=1.30, p=0.031).

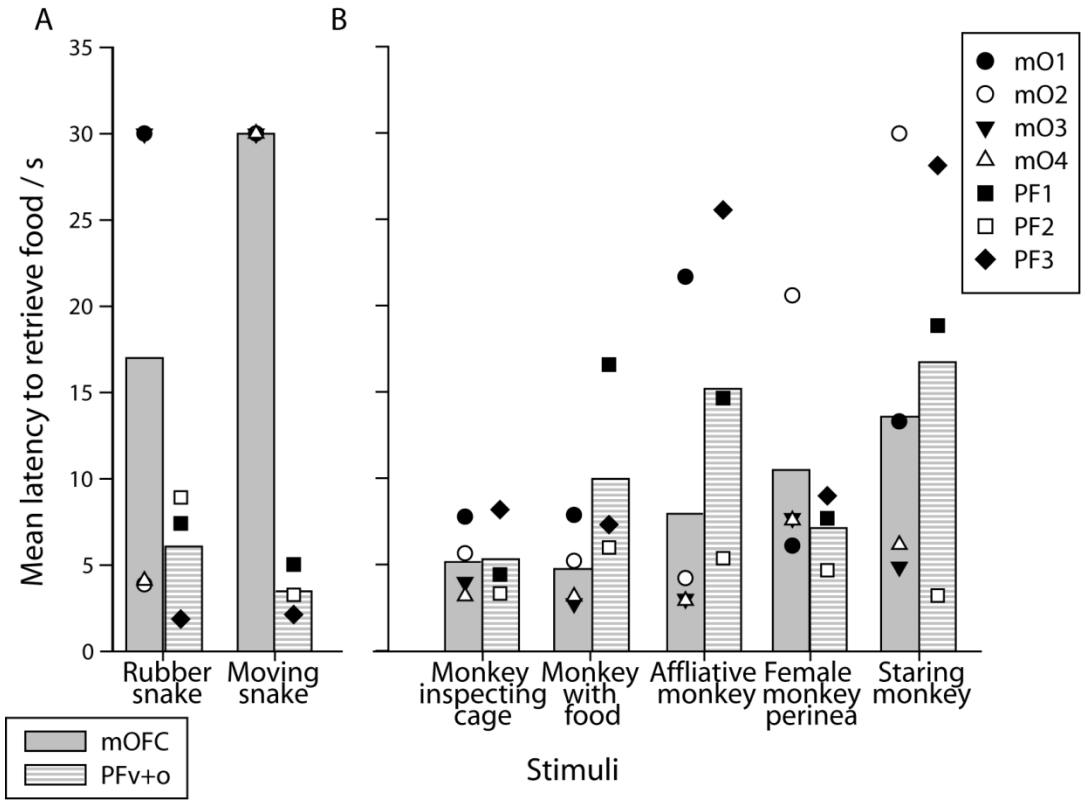

Figure 3.7. A comparison of mOFC and PFv+o lesions in reaching latencies in the presence of mild-fear inducing stimuli (left panel) and the macaque social stimuli (right panel). PFv+o lesion details and effects have been published previously by Rudebeck et al., (2006a). Group differences are demonstrated in reaching latencies towards fear-inducing stimuli with PFv+o lesioned animals being significantly faster in reaching food placed over emotive stimuli than animals mOFC lesions (Fear x Group interaction; $F_{1,5}$=9.29, p0.028 and main effect of Group; $F_{1,5}$=9.59, p=0.027). In contrast, no differences were found between the two lesion groups in their responses to the social stimuli (social monkey Stimuli x Session x Group; $F_{12,60}$=1.30, p=0.0310).

An additional analysis directly compared the effect of mOFC and Rudebeck and colleagues ACCg-lesioned animals on the same social valuation test (Rudebeck et al., 2006a). We compared the two groups in their responses to the fear inducing stimuli and found no

differences between the effects of the two lesions (Figure 3.8). Specifically, there were no interactions involving Group (fear Stimuli x Group $F_{1,5}$=1.04, p=0.355, fear Stimuli x Session x Group $F_{3,15}$=0.72, p=0.513) nor main effects of Group ($F_{1,5}$=4.38, p=0.090). The only main effect of interest related to the identity of the fear Stimuli ($F_{1,5}$=11.70, p=0.019). This implies, neither the mOFC nor the ACCg have fundamentally critical roles in guiding this type of behaviour.

In contrast, a comparison of group responses towards the social stimuli (pictures of other monkeys) revealed that the ACCg was the critical region for social valuation (Figure 3.8bii). There was a significant linear main effect of the identity of the social monkey stimuli on responsiveness ($F_{1,7}$=7.37, p=0.030), confirming that monkeys' behaviour concurred with one another in their valuations of the videos of other monkeys. There was a significant interaction of social monkey Stimulus, Session and Group (ACCg versus mOFC) on the log-transformed reaching latencies ($F_{12,60}$=2.45, p=0.016), in addition to a significant main effect of the identity of the social monkey Stimuli ($F_{4,20}$=3.83, p=0.029).

An analysis that compared both lesion groups' responses to the human Stimuli found no significant group differences ($F_{1,5}$=1.54, p=0.269) or interaction with the stimulus identity ($F_{1,5}$=0.058, p=0.819). Similarly, there were no significant group differences in an analysis of the neutral Stimuli ($F_{1,5}$=0.36, p=0.573), or interactions between group and stimulus identity ($F_{1,5}$=2.10, p=0.207). A main effect of neutral Stimuli was noted ($F_{1,5}$=13.78, p=0.014), which was a result of longer reaching latencies towards the moving pattern stimuli that the neutral static objects (paired samples t-test pre-op t_3,=-3.15, p=0.051, post-op t_3=-3.06, p=0.055).

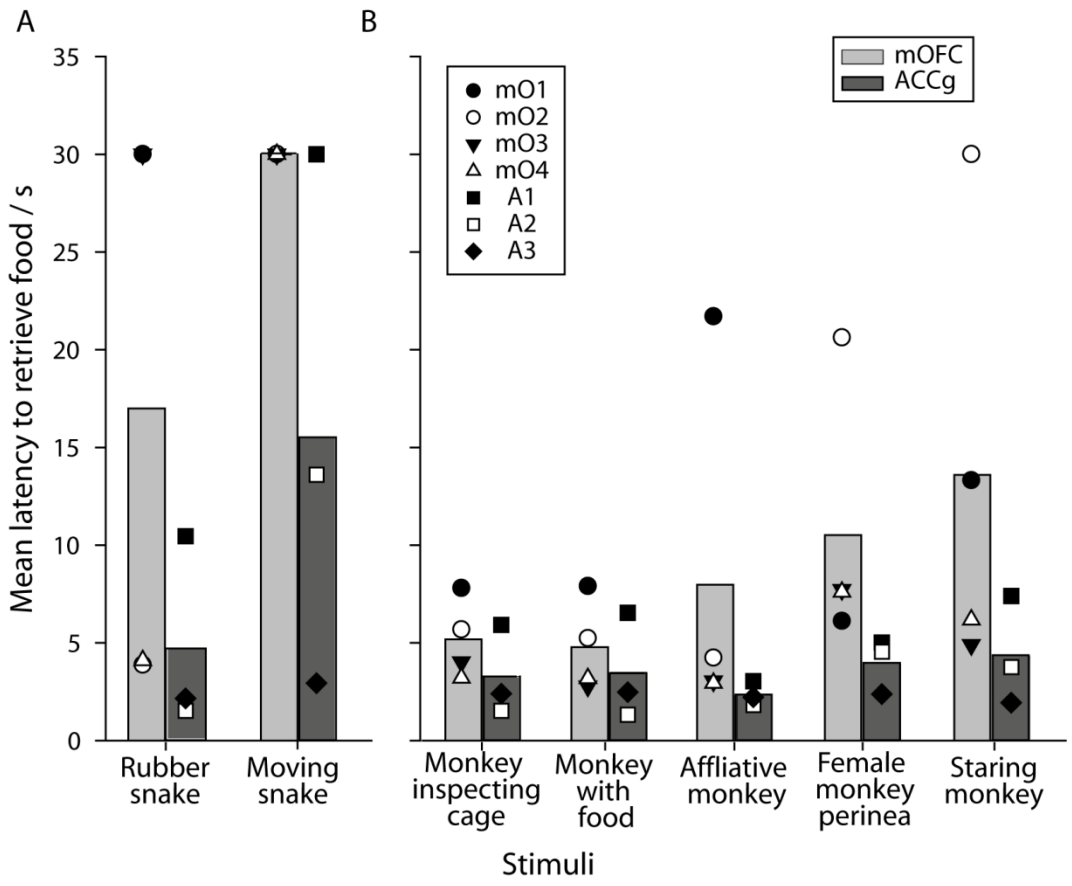

Figure 3.8. A comparison of mOFC and ACCg behaviour elicited towards mild fear and social stimuli MOFC and ACCg lesion groups reaching latencies in the presence of mild-fear inducing stimuli (**A**) and the macaque social stimuli (**B**). There were no group differences in reaching latencies towards fearful stimuli, instead ACCg animals showed a decrease in their reaching latencies in the presence of socially relevant stimuli as compared to mOFC lesioned animals.

Experiment 2

Although the mOFC plays no fundamental role in social valuation or emotional responsiveness it was implicated in the 2-choice decision-making task. Analysis of the data shown in figure 3.9 revealed a main effect of mOFC lesion ($F_{1,3}$=44.17, p=0.007). In contrast, when the ACCg-lesioned animals were compared to their matched controls (Figure 3.9b) no lesion deficit was

apparent; there was neither a main effect of the Lesion (F1,7=2.00, p=0.201) nor any interaction between the effect of the Lesion and the particular type of decision-making Task (F1,7=0.02, p=0.889). This suggests the mOFCs role may be more directed towards decision-making.

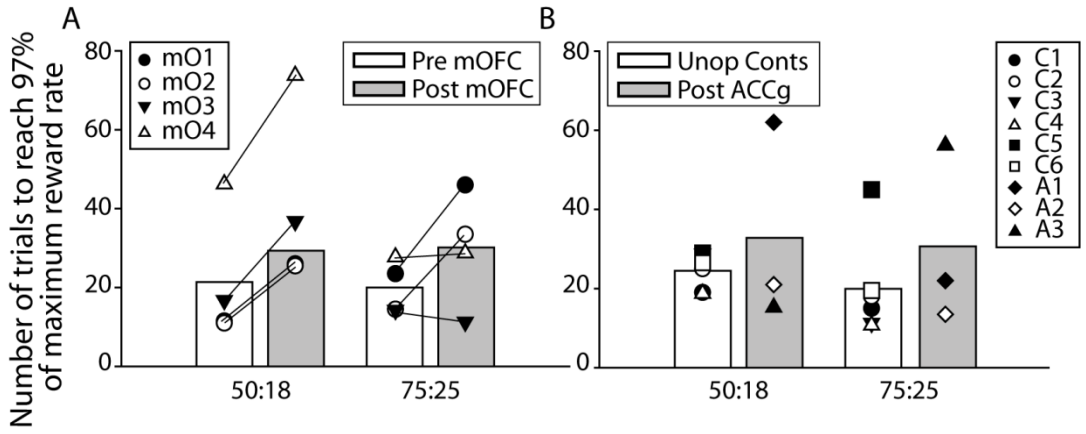

Figure 3.9. Results of the decision-making task and. **A**. and **B**. Performance in experiment 3. Mean number of trials across the two days testing sessions each macaque took to achieve the ratio of responses associated with 97% of the maximum reward rate (r_{opt}) in the stimulus-outcome decision-making task for the two reward schedules. The unfilled bars represent the pre mOFC and CON group (A and B respectively), whereas grey represent mOFC and ACC_g groups (A and B respectively). The performance of individual macaques, within each group, is represented by distinct symbols.

3.4 Discussion

This study examined the effects of mOFC lesions (centred on area 14) on social and emotional valuation, and reinforcement-guided stimulus selection; comparing them with that of PFv+o and ACCg lesions (PFv+o centred on areas 11, 13, 12, 9 and 46, while ACCg centred on 24a, b and 32). MOFC lesions caused no impairments in social valuation or emotional responsiveness. The animals were equally reluctant to reach for food in the presence of fear-inducing stimuli both before and after mOFC lesions. Similarly, there was no change in animals' assessments of how

interesting each social stimulus was: as indexed by reaching latencies, before and after their lesion. Nor did we observe an alteration in other aspects of behaviour in the context of the social stimuli.

The lack of change in social valuation or fearfulness in the mOFC-lesion group cannot be attributed to a lack of sensitivity in the task; the task was sensitive to altered social valuation in animals with ACCg lesions and to altered emotional responsiveness in animals with PFv+o lesions (Rudebeck et al., 2006a). A formal comparison demonstrated that PFv+o-lesioned animals were significantly less fearful of the snake stimuli that mOFC-lesioned animals. Similarly, the ACCg-lesioned animals were significantly less interested in the social stimuli than were the animals with mOFC lesions. Moreover, the null effect of the mOFC lesion on the social and fear tasks cannot be attributed to some deficiency in the surgery; the mOFC-lesioned animals, but not the ACCg-lesioned animals, were impaired in the decision-making task. Experiment 2 showed that mOFC lesions disrupt the ability to choose the better value stimulus option. There is also evidence that the mOFC decision-making deficit becomes more severe when animals choose between more than two different stimuli (Chapter 4 and 5). In summary, there was evidence for a double dissociation between the effects of ACCg and mOFC lesions on social valuation and reward-guided decision-making.

The absence of impairment in social and emotional processing after mOFC lesions initially appears to conflict with the prevalent view that vmPFC lesions cause disinhibited and socially inappropriate behaviour (Damasio, 1994; Rolls et al., 1994; Anderson et al., 2006; Blake and Grafman, 2006). VMPFC and OFC lesions have been implicated in a variety of emotional and decision-making deficits (Bechara et al., 2000; Fellows, 2007; Clark et al., 2008; Heberlein et al., 2008). However, the lesions in patients are often a result of stroke or head trauma and as a

result the damage is often not restricted to one cortical area. In conjunction with the previous study reported by Rudebeck and colleagues (2006a) the present results suggest that it is not damage to the mOFC in patients with vmPFC lesions which causes alterations in social behaviour, but rather damage to the subgenual and perigenual cingulate cortex, and possibly to the medial frontopolar cortex (Bechara et al., 1997; Camille et al., 2004). Furthermore, loss of the white matter tracks underlying damaged cortex may contribute to impairments (Philippi et al., 2009).

It remains a possibility that while mOFC is not essential for simple social valuation, it is important for more complex judgments involving regret or guilt (Saver and Damasio, 1991; Camille et al., 2004; Koenigs and Tranel, 2007; Koenigs et al., 2007; Krajbich et al., 2009). However, judgments about regret do not just reflect broader social considerations, but they also require consideration of counterfactual outcomes that are then compared with actual outcomes. It has recently become clear that information about counterfactual outcomes is represented in parts of frontopolar cortex (Boorman et al., 2009) that may also be damaged in patients with vmPFC lesions. Judgments about guilt may also require knowledge of one's own or another person's intentions and therefore depend on paracingulate areas implicated in theory of mind (Amodio and Frith, 2006; Frith and Frith, 2006; Behrens et al., 2008; Hampton et al., 2008).

It is also possible that the mOFC is more important in complex social situations in which choices have to be made between many different possible courses of action. Chapter 4 and 5 describe evidence that the macaque mOFC is especially important when decisions have to be made between multiple options that are all associated with different levels of reward. This suggests that mOFC might be more important in complex social decision-making settings that require consideration of the benefits of several different possible choices.

Previous investigations of large OFC lesions have reported reduced fearfulness and increased aggressiveness (Izquierdo et al., 2005; Machado and Bachevalier, 2006, 2008). The work of Machado and Bachevalier (2006) suggests that the lesion in the lateral part of the OFC (area 11 and 13) may have been critical for causing these deficits. Rudebeck and colleagues (2006a) previously show that animals with PFv+o lesions, which included lateral OFC, were significantly less fearful than control animals and animals with ACCg lesions. Here we show that the same animals with PFv+o lesions were also significantly less fearful than animals with mOFC lesions; PFv+o lesion animals were significantly faster to reach for food placed over emotive stimuli than animals with mOFC lesions. Neither mOFC lesions in the present study nor lesions that included lateral OFC (Rudebeck et al., 2006a) altered social valuation. Furthermore mOFC-lesioned animals did not display any other changes in their general emotional responsiveness to the various stimuli (Figure 3.6).

The lack of importance of the mOFC in the analysis of social stimuli can perhaps be understood in the context of its anatomical connections. Unlike the lateral OFC, the mOFC receives few direct inputs from temporal areas involved in processing macaque vocalizations (i.e. temporal auditory areas; see Ghazanfar et al., (2005) and Romanski and Averbeck (2009) or faces; areas TE, TEO see Webster et al., (1994) and Carmichael and Price (1995b). FMRI studies conducted with macaques demonstrate lateral OFC responsiveness to images of faces (Tsao et al., 2008), while the ACCg is particularly responsive to the vocalizations of conspecifics (Gil-da-Costa et al., 2004).

Valuation of social information is also an important determinant of activation in the human ACC. Behrens and colleagues (Behrens et al., 2008; Behrens et al., 2009) found that ACCg activation to the delivery of feedback after decision-making, increased in proportion to the

importance of the feedback for finding out about another person. The subjects studied by Behrens and colleagues, played an interactive decision-making game with another player. Feedback was more important for finding out about the other player in phases of the game when the other player's behaviour was changing more rapidly; it was at these points in the game that outcome-related ACCg activity was highest. Predictions and prediction errors concerning the other player's intentions were associated with changes in activation in the paracingulate cortex. Such information about the other player was then used, in conjunction with the subject's own choice-reward history, to estimate the probability of obtaining a reward on each trial of the game and this estimate was associated with mOFC activation. The dissociation between ACCg activation during the valuation of social information and mOFC activation in relation to reward-guided decision-making, mirrors the dissociation between the impairments found after lesions to the two areas in the current experiment. The studies suggest that while mOFC may be active in social decision-making contexts, its activation reflects expectations about the rewards or other benefits that the subjects hope to obtain from the decisions that are made.

Because the mOFC is active in social situations, albeit in a manner that reflects the benefits for the subject that might be obtained from the social situation (Behrens et al., 2008, 2009), it is to be expected that lesions that affect the mOFC are likely to alter the decisions that people and animals make in complex social situations. There is certainly evidence for changes in behaviour in monkeys with OFC lesions in naturalistic and complex social situations (Machado and Bachevalier, 2006, 2008). Such changes may partly reflect the consequences of more primary alterations in animals' fearfulness and aggression that occur as a result of damage to lateral parts of the OFC (Rudebeck et al., 2006). In addition, alterations in behaviour in complex

social situations after OFC lesions, may partly reflect the role that the mOFC has in making reward-based decisions in situations where there are many possible choices (Chapter 4 and 5).

In summary, the mOFC appears to have no critical role in social valuation or in mediating emotional responsiveness. Instead the mOFC seems more involved in comparing the values of choices. This possibility is explored more fully in the following two chapters. Socially inappropriate behaviour, described after vmPFC damage in humans, may be due to the damage which has extended into the ACCg, as this region appears to be far more critical for social valuation. Perhaps what underlies the changes in behaviour exhibited by vmPFC patients is an inability to evaluate the outcome of their socially orientated actions or the potential reaction of the other person.

CHAPTER 4: CONTRASTING ROLES FOR MACAQUE LATERAL AND MEDIAL ORBITOFRONTAL CORTEX IN VALUE ASSIGNMENT AND COMPARISON

Uncertainty about the function of orbitofrontal cortex (OFC) in guiding decisions may be due to its medial and lateral divisions (mOFC, lOFC) having distinct functions. Here we test the hypothesis that the mOFC is more concerned with reward-guided decision-making; in contrast with the lOFCs role in reward-guided learning. Macaques performed 3-armed bandit tasks designed to probe different aspects of learning and choice behavior, and the effects of selective mOFC lesions were contrasted against lOFC lesions. We found that, while lOFC was required for "credit assignment" – the correct assignment of values to visual cues – mOFC was critical for comparison of the cues' values during decision-making. In unchanging probabilistic environments, mOFC lesions induced decision-making impairments when value comparison was difficult without affecting credit assignment and associative learning. By contrast, lOFC lesions caused the opposite pattern of impairment.

4.1 Introduction

Choice is something we are confronted with countless times in our everyday lives. Choices can range from trivial to the profound, and are often based on what we expect to occur following the selection of each option. Some choices present no dilemma, having what we subjectively perceive as an immediately obvious best option, but for most decisions there is not a single option that is more advantageous in every respect. A distributed network of brain regions,

including the amygdala (Morrison and Salzman; Pratt and Mizumori, 1998; Ghods-Sharifi et al., 2009), ventral striatum (Apicella et al., 1991; Roesch et al., 2009) and the OFC (Murray et al., 2007; Rushworth et al., 2007a; Simmons et al., 2007; Platt and Huettel, 2008; Rangel et al., 2008; Schoenbaum et al., 2009) is implicated in representing reward and in decision-making. Whilst many of these areas show a relative degree of specialization of function the contribution of the frontal lobes, and the OFC in particular, remain unclear. It is possible that determining the precise contribution of the OFC may be hampered by an under-appreciation of the profound anatomical segregation between mOFC and lOFC (Ongur and Price, 2000). As detailed in Chapter 2, Ongur and Price dissociate the medial and lateral subdivisions of the OFC into the orbital and medial prefrontal networks. The orbital network receives input from all sensory modalities and is characterized by strong connections with the amygdala, thalamus, insula, temporal pole and dosolateral PFC (Mesulam and Mufson, 1982; Goldman-Rakic, 1987a; Yeterian and Pandya, 1988; Barbas and De Olmos, 1990; Morecraft et al., 1992; Fuster, 1997). In contrast, the medial network has extensive visceromotor outputs, with strong connections with the hippocampus and associated areas of the cingulate, retrosplenial and entorhinal cortices, anterior thalamus and septal diagonal band (Pandya (Pandya et al., 1981; Mesulam et al., 1983; Vogt and Pandya, 1987; Morecraft et al., 1992) .

However, very few lesion experiments have sought to account for these anatomical differences in terms of functional specialisation. One of the few exceptions to date is the study by Iversen and Mishkin (1970) who show evidence for a distinction between medial and lateral orbitofrontal function in terms of visual discrimination reversal learning. This study shows that mOFC lesions impair animals' ability to associate a previously non-rewarded stimulus with reward; while lesions to the lOFC result in a failure to inhibit a response to previously rewarded

stimuli. According to an influential proposal, mOFC and lOFC differ in the degree to which they are concerned with reward and error processing respectively (Kringelbach and Rolls, 2004). The account is based on fMRI data and is untested by any other method. In the following report we examine this hypothesis by investigating whether lesions of mOFC and lOFC in macaques (*Macaca mulatta*) selectively affect animals' responses to positive reinforcement and the absence of reinforcement respectively.

Despite anatomical segregation within the OFC, animal studies typically encompass all of the orbital surface or, for technical reasons, focus on lateral regions. Some of these experiments emphasize the OFCs role in decision-making, particularly when stimulus-outcome relationships are changing, for example in "reversal" tasks (Schoenbaum et al., 2003b; Izquierdo et al., 2004; Clarke et al., 2008; Rudebeck and Murray, 2008) and consistency of choice preferences (Baylis and Gaffan, 1991). Neuronal activity, recorded in the macaque OFC, encodes a number of decision-making signals such as relative reward expectations (Tremblay and Schultz, 1999; Padoa-Schioppa and Assad, 2008). These results are complemented by human patients, whose large and extensive OFC lesions impair aspects of decision-making such as consistency of preference judgments (Fellows and Farah, 2007), and by human neuroimaging studies, which also identify signals reflecting relative reward expectations in the OFC (Plassmann et al., 2007; Elliott et al., 2008; Boorman et al., 2009; FitzGerald et al., 2009).

Kable and Glimcher (2009) recently proposed a two-stage "standard model" of decision-making in which "options under consideration are learned, stored and represented in ventromedial frontal cortex and striatum" at the first stage and then "implemented in lateral prefrontal and parietal areas", as "a choice stage at which a single highly valued action is chosen from amongst the options under consideration". In contrast, recent neuroimaging experiments

suggest ventromedial frontal cortex is part of the circuit for deciding between options on the basis of their value (Boorman et al., 2009; FitzGerald et al., 2009). Moreover, De Martino and colleagues (2006) report that ventromedial frontal activity is correlated with the degree to which subjects' decisions are rational and uninfluenced by irrelevant features of the context in which they are made.

Here we focus on one part of the complex of areas that comprise ventromedial frontal cortex, the mOFC, and test which view of its function – that it learns the values of potential choices, or that it makes decisions between options on the basis of their values – is correct. We examined the effect of lesions of mOFC in four macaques. A lesion that disrupts part a circuit for deciding and discriminating between choice options of differing value should impair decision-making as a function of the proximity between the options' values. By analogy, lesions of visual feature discrimination mechanisms disrupt discrimination as a function of the similarity of the visual features (Buckley et al., 1997). In experiments reported below, macaques were trained to choose between three stimuli associated with differing probabilities of reward. The probabilities of reward therefore determined the options' values and the proximity of the best (V1) and second best (V2) options' values was manipulated.

We therefore first tested the hypothesis that the lOFC and mOFC are relatively more concerned with "credit assignment" – the process by which visual stimuli are associated with reward values during associative learning – and reward-guided decision-making respectively. Recent experiments have shown that OFC lesions which, upon histological examination were found to be centered on lOFC disrupt credit assignment (Walton et al., 2010). Normally, monkeys learn to attribute value to a stimulus as a function of the precise history of reward received in association with the choice of that particular stimulus. Animals with lOFC lesions

instead value a particular stimulus as a proximity-weighted function of the history of all rewards received approximately at the time of stimulus choice, even when the rewards were actually caused by choices of the alternative stimuli on preceding and subsequent trials. This leads to the very counterintuitive, and to date untested prediction, that animals with lOFC lesions should actually be more impaired than controls in "easy" decisions when the reward values of the possible stimulus choices are very different from one another. While normal animals credit such stimuli with each stimulus' own distinct value, in contrast, animals with lOFC lesions should credit both stimuli with approximately their mean value. The first aim of the study was to test this prediction.

By contrast, if the OFC, or a sub-region of the OFC, is important for reward-guided decision-making then lesions might be expected to impair "difficult" decisions where the reward values of potential choices are similar to one another; it is in just such situations that it is more difficult to discern which option is the better one and to choose it. Reward expectation related activity is prominent in the OFC (Tremblay and Schultz, 1999; Plassmann et al., 2007; Simmons et al., 2007; Padoa-Schioppa and Assad, 2008). One interpretation of its presence in the OFC is that it functions to guide reward prediction error-based learning (Schoenbaum et al., 2009). An alternative possibility, however, is that it guides reward-based decisions (Boorman et al., 2009; FitzGerald et al., 2009). The second aim of the study was to assess the contributions made by lOFC and mOFC to reward-guided decision-making. The experiment therefore, examined the effect of mOFC and lOFC lesions on "easy" or "difficult" decisions in which the reward values associated with the different possible choices were either far apart or close together.

By contrasting the roles of lOFC and mOFC in the macaque monkey using a stimulus-guided 3-armed bandit task, the current study found that in line with our hypothesis the areas

made distinct contributions to fundamental aspects of value learning and value comparison respectively.

4.2 Method

Animals

10 male rhesus macaque monkeys (*Macaca mulatta*) aged between 4 and 10 years old and weighing between 7 and 13.5kg were used. 3 animals acted as un-operated controls whereas the other 7 received bilateral aspiration orbitofrontal cortex (OFC), either medial (n=4) or lateral (n=3) lesions following training and pre-surgical testing. The lesions made in the lateral OFC group were initially intended as complete OFC lesions. Only upon histological examination for the publications of Walton et al. (2010)were the lesions discovered to be incomplete and centred on lateral regions. All animals were maintained on a 12hr light/dark cycle and had 24hr ad-lib access to water, apart from when they were being tested. All experiments were conducted in accordance with the United Kingdom Scientific Procedures Act (1986).

Habituation & Pre-training

All animals had extensive experience of three choice touch-screen tasks and, prior to surgery were trained to a criterion of choosing the best, V1, option on 80% of trials in several varying reward probability conditions (Figure 4.2, discussed below).

Apparatus

The apparatus used in this experiment was identical to that used in Chapter 3, Experiment 2.

Surgery and Histology

The details of the surgery, anaesthesia and histological protocols for the mOFC-lesioned animals have been described in Chapter 3. In contrast the lOFC lesion was made by removing cortex between the medial and lateral orbitofrontal sulci (predominantly Walker's areas 11 and 13). For specific details of lOFC lesions see Rudebeck et al. (2008b) and Walton et al. (2010).

Training Histories

Three lOFC-lesion animals were trained, tested and compared with three animals that acted as un-operated controls for the varying schedules for a study recently published by Walton et al. (2010). For this study all animals had extensive training on varying reward schedules prior to testing. With the addition of another animal, three of the un-operated control animals from this experiment went on to become part of the current mOFC-lesion group. Approximately 18 months separated testing in the Walton et al. (2010) experiment and training in the present study. Prior to testing in the current experiment all animals in the mOFC-lesion group were brought to a criterion of 80% correct on 3-choice reversal schedules. We ensured they were at roughly the same pre-operative performance level as they were when they acted as un-operated controls. Critically, the two lesion groups did not differ in terms of their pre-operative performances. This suggests that any differences in post-operative performance between the two groups cannot be attributed to differences in training histories.

Reward Schedules

In all 3-choice experiments, animals made choices between 3 novel stimuli, each associated with different probabilities of reward controlled by pre-determined schedules (Figure 4.2 and 4.3).

The only information available about which stimulus to choose in each session came from trial-by-trial experience of reinforcement. Each schedule was used five times, but the stimuli were novel in each session.

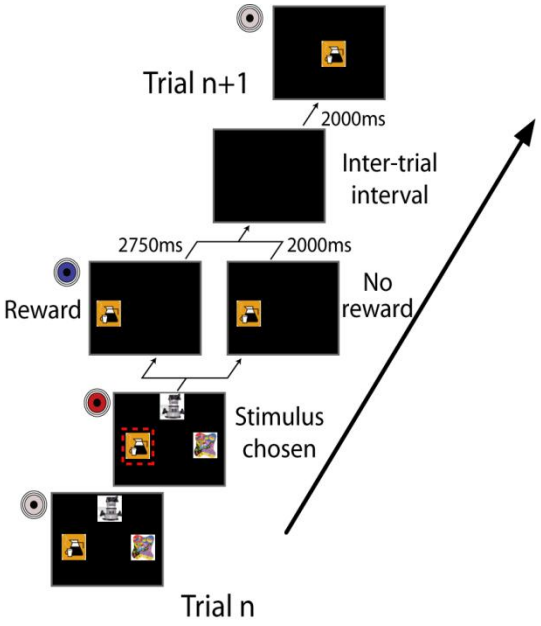

Figure 4.1. Schematic of Task. On each trial, monkeys were presented with 3 clipart stimuli in 3 of 4 possible locations on a touch-screen. Each stimulus' location varied from trial to trial. Each was associated with a different outcome probability. On each trial, selecting one stimulus caused the other two to extinguish and reward to be delivered according to the reward schedule. Grey, blue and red circles represent different 250ms tones.

Variable

Four animals completed four 3-choice tasks, in which the reward probability associated with each stimulus varied over the course of the session, pre and post-operatively. The schedules were presented in an interleaved manner across testing days. Each stimulus was associated with a different probability of receiving a reward, but, as shown in Figure 4.2, the expected reward values changed across the course of the session. This meant that the identity of the best, mid and worst stimulus changed from trial-to-trial. Therefore, in order for the animals to maximize its

reward it had to track these changing probabilities for all three stimuli. The lOFC-lesioned animals had previously completed these varying reward schedules and their data has been published in Walton et al. (2010). This meant that direct comparisons could be made between lesion groups.

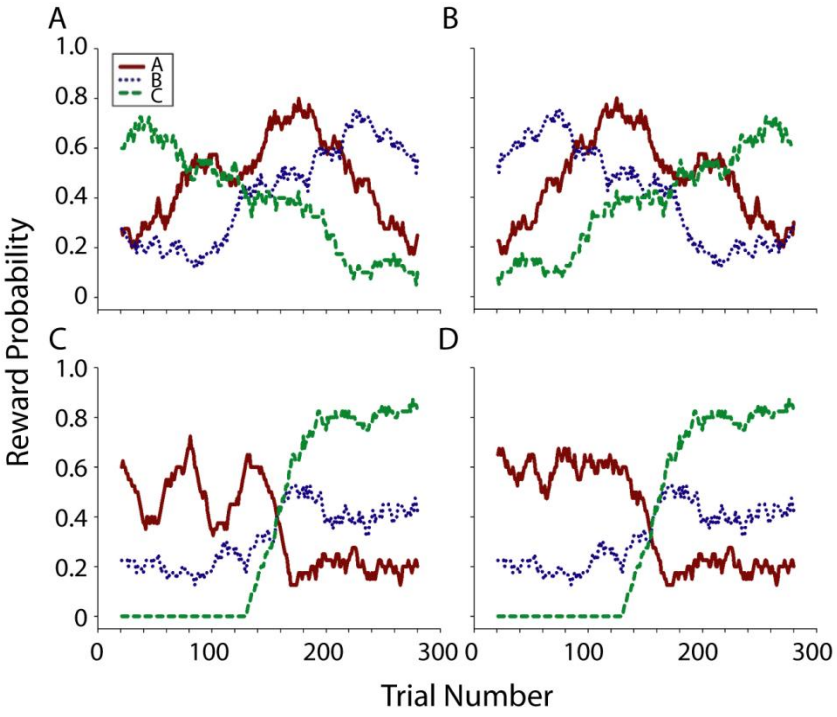

Figure 4.2. Schematic representation of the reward probability associated with each stimulus in the varying schedules averaged over 20 running trials. In these schedules assignment of V1, V2, and V3 identities to each stimulus (S1, S2, S3) was determined by a reinforcement learning algorithm on each trial.

Fixed

We next investigated how differences between the options' values affected learning and decision-making in fixed reward probability schedules. The reward probability of the stimuli with best (V1) and worst (V3) values were the same in all three fixed schedules (0.6 and 0 respectively), but the value of the second best stimulus (V2) was systematically varied between

0.375 (V2_HIGH), 0.2 (V2_MID) or 0 (V2_LOW) (Figures 4.1a-c respectively). We reasoned that a lesion to a brain structure critical for making fine-grained value-guided decisions should impair performance to a greater extent when the difference in value between the best and second best options was small. By contrast, if the lesioned structure is important for value assignment then impairments should be greatest when value differences are large. This hypothesis is derived from the observations by Walton and colleagues (2010) that lOFC lesioned animals' value stimuli as a proximity-weighted average of all outcomes experienced recently, before and after choices are made. While normal animals credit stimuli with each stimulus' own distinct value, making particular use of Thorndike's (1933) "law of effect", in contrast, animals with lOFC lesions credit both stimuli with approximately their mean value, having to rely on intact "spread of effect" mechanisms. This means that lOFC-lesioned animals' stimulus value estimates will be more accurate when value differences are close together than when the value differences are further apart. It is just in these latter situations that the Thorndike's "law of effect", contributes so noticeably to the speed of value learning. The first aim of the study was to test these predictions.

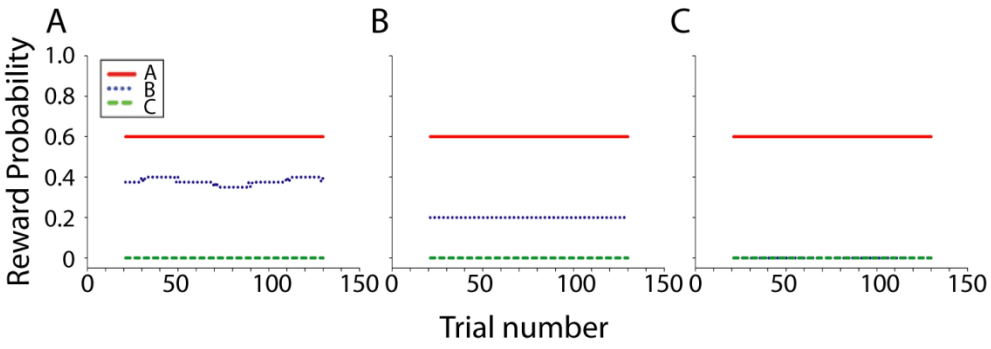

Figure 4.3. Schematic of Fixed reward schedules. The value of best (V1) and worst (V3) options were constant in all three fixed schedules but the value of the second best option (V2) varied from close to V1 to equal to V3 across V2_HIGH (B), V2_MID (C), and V2_LOW (D).

Data analysis - Varying reward schedules and credit assignment

In general all analyses were conducted with standard parametric ANOVAs, that used the Huynh-Feldt correction where appropriate, and standard t-tests.

Gross lesion deficit analysis

The data from the varying reward schedules were analyzed as a function of the subjective expected values of all three different stimuli which were derived using a standard Rescorla-Wagner learning model. The reward learning rate (α) was fitted individually to each animal's pre- and post-operative data using standard non-linear minimization procedures. This was used to estimate the expected value of each of the three stimuli on every trial (the same learning rate was used for all three stimuli). The aim was to identify V1, V2 and V3 stimulus for every trial and determine the probability that the animals chose the best option. The log transformed proportion of V1 choices as function of the total choices was calculated and averaged across monkeys for each third of a testing session. These values were subjected to a repeated measures ANOVA of Lesion (2 levels; pre and post) x Split (3 levels; trial 1-100, 101-200, 201-300).

The effect of past reward history and past choice history on the assignment of reward to stimulus choices

The data from the varying schedules were pooled into two condition schedules and reported using parametric repeated measures analyses, with within-subjects factors of Surgery (2 levels: Pre- or Post-Surgery), Condition (2 levels), and Reward (2 levels; rewarded and un-rewarded). When choice history was considered, this additional factor had 3 levels (Figure 4.6; AB, $A^{2-3}B$, and $A^{4-7}B$). Alternatively, when comparing across different reward histories (Figure 4.7) a fourth factor of Reward history was included (4 levels; $A^{?}AAAB$, $AA^{?}AAB$, $AAA^{?}AB$ $AAAA^{?}B$) where the "?" refers to the presence or absence of reward at the point in the history. Comparison

between mOFC and lOFC-lesion groups required an additional between-subjects factor of Group (2 levels; mOFC and lOFC). Note that options "A", "B" and "C" do not necessarily directly refer to stimuli A, B and C, as depicted in Figure 4.3, but instead to sequences of similar choices; i.e., an "AAB" history could be made up of choice sequences of stimuli AAB, AAC, BBA, CCB, BBC or CCA. Also note that in order to correct for positive skew in the data, values were log transformed prior to analysis.

Fixed reward schedules and reward-guided decision-making

Best Choice analysis

The data from the fixed reward schedules were analyzed as a function of the objective value for all three stimuli, and on that basis stimuli were defined as V1, V2 and V3 for the best, mid and worst option respectively (Figure 4.3). The number of trials to reach a criterion of 70% of V1 stimulus choices was calculated for each session, for each animal, pre and post-operatively. These totals were averaged across the five sessions, and subjected to a two-way repeated measures ANOVA, with factors of Testing Session (pre and post-operative) and Condition (V2_HIGH, V2_MID and V2_LOW). Animals with mOFC and lOFC lesions were compared post-operatively on the same measure in a two-way ANOVA of Condition (V2_HIGH, V2_MID and V2_LOW) and the between-subjects factor of Group (mOFC and lOFC).

Learning Rates

The reward learning rate (α), was fitted individually to each animal's pre and post-operative data on each day using standard non-linear minimization procedures. For the analysis shown in Figure 4.9 data was pooled over the 5 testing days for each animal and then comparisons were made between groups

Re-analysis of the varying reward schedules and reward guided decision-making

Interval Value Difference Analysis

Trials across all *varying* schedules in which the subjective difference in value between V1 and V2 and between V2 and V3 resembled the value differences in the three *fixed* schedules used and described above were extracted (figure 4.8G-L). The *fixed* V2_high schedule was approximately equivalent to trials drawn from the *varying* schedules with a small V1V2 value difference (0.1-0.3 difference in reward probability) and a large V2V3 value difference (0.2-0.5 difference in reward probability). *Fixed* V2_mid was approximated by trials from *varying* schedules with V1V2 and V2V3 value differences of 0.3-0.5 and 0.0499-0.2 respectively while *fixed* V2_low was approximated by trials in which V1V2 and V2V3 value differences were 0.5-0.7 and 0-0.0499 respectively. Trials were binned according to these divisions in value differences and the probability of choosing V1 was compared across the three value difference bins in a two-way repeated measure ANOVA of Testing Session (pre and post-operative) and Value Difference (3 levels; 3 Value Bin (V1V2 small/V2V3 large, V1V2 mid/V2V3 mid and V1V2 large/V2V3 small). The percentage of trials included in this analysis for the mOFC group was 26% and 23% for pre and post respectively and 32% and 19% for the lOFC group.

Error and Correct Switching Analysis

Percentages switching after trials on which a reward was not delivered (an error; ErSw) and percentage of switching on the stimulus choice after a reward (CrSw) was calculated for all three groups in the four variable reinforcement schedules. Groups were compared in two-way ANOVA of Surgery (2 levels; pre and post) and Trial type (2 levels; ErSw and CrSw) with the between subjects factor of Group (2 levels; lOFC and mOFC).

4.3 Results

Histology

Schematics of the actual (Figure 4.4a) alongside the averaged actual (Figure 4.4b) lesions, merged onto a single normal control macaque brain, show the extent of the lesions for animals with mOFC and lOFC lesions. The intensity of redness indicates the extent of the lesion overlap of the respective animal groups. Coronal sections through the frontal lobes, for each individual animal are shown in Appendix I: Histology. As can be observed, the mOFC lesions were made as intended and there was no consistent common area of damage between the two animal groups' lesions. In the mOFC group the cortex from the medial orbitofrontal sulcus to the rostral sulcus, including mainly Walker's area 14 (Walker, 1940) but also some parts of area 10 were removed. In contrast, the lOFC lesion removed cortex between the medial and lateral orbitofrontal sulci including predominantly Walker's areas 11 and 13.

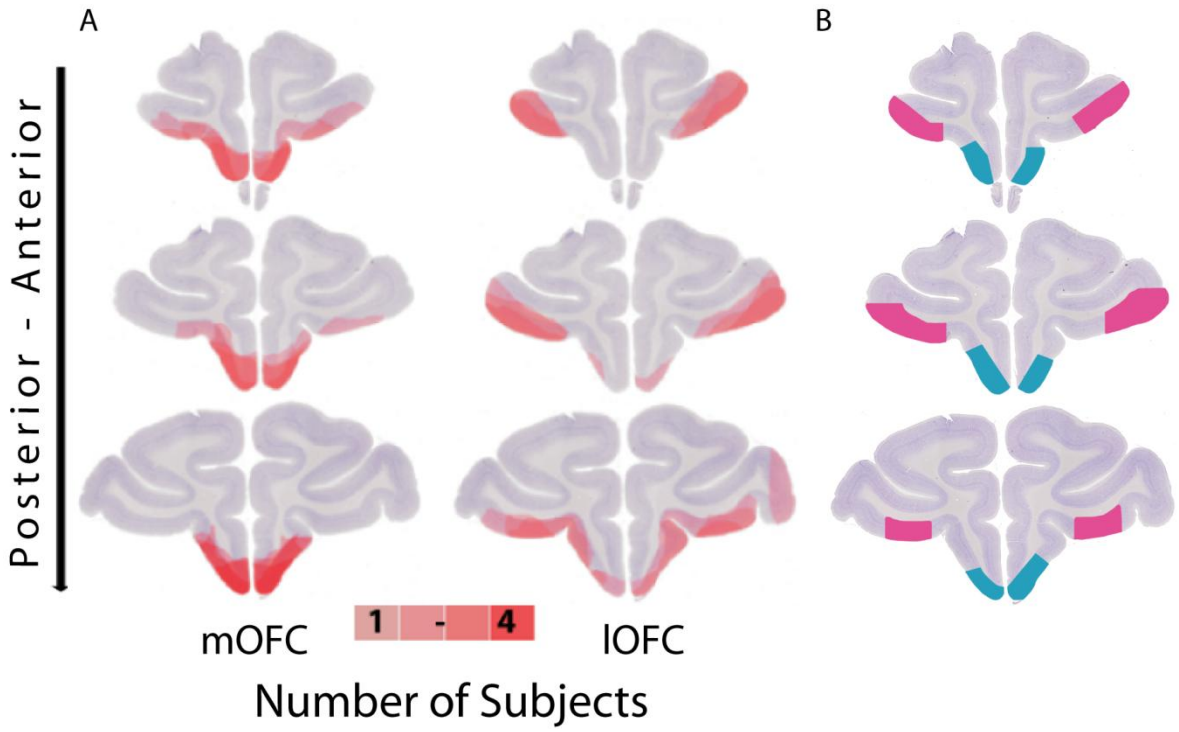

Figure 4.4. Schematics of the actual (A) lesions merged onto a single normal control macaque brain show the extent of the lesions for animals with mOFC and lOFC lesions. The intensity of redness indicates the extent of the lesion overlap of the respective animal groups. B. Lesion overlap for mOFC (blue) and lOFC (pink) represented single normal control macaque brain show there was no consistent common area of the two animal group's lesion.

Varying reward schedules and credit assignment

Using schedules that were identical to ones employed to identify impairments in credit assignment after lOFC lesions (Walton et al., 2010), and together with the absence of group differences in pre-operative performance, meant direct comparisons could be made between mOFC lesions in the current experiment (figure 4.6 and 4.7) and lOFC lesions (Walton et al., 2010).

We first looked for a general deficit in performance similar to that seen after lOFC lesions. LOFC lesions impair performance on such schedules particularly in the second half of

each day's testing session after the options' values have changed (Rudebeck et al., 2008b). We performed a complementary analysis on the pre and post-operative data from the mOFC. Values were assigned to stimuli A, B, and C on each trial on the basis of a Rescorla-Wagner learning algorithm. The proportions of trials on which monkeys took the best value option (V1), as opposed to the second best (V2) or worst (V3) value options, for the first, second and last thirds of the different testing sessions were calculated. As similarly reported for lOFC lesions, mOFC lesions lead to a decrement in the proportion of V1 choices particularly in the later periods of testing sessions (Surgery x Session period interaction: $F_{1,6}$=8.41, p=0.0430). The effects of the two lesions on these measures are very similar.

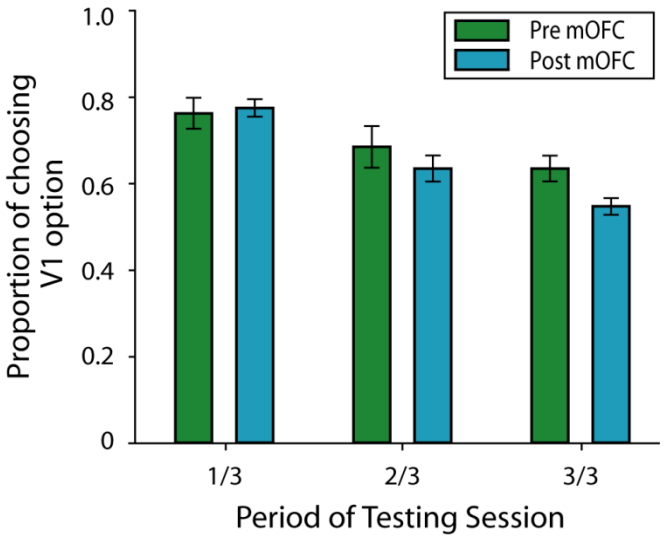

Figure 4.5. Gross mOFC lesion deficit on V1 choices as a function of total choice. As similarly reported for lOFC lesions, mOFC lesions lead to a decrement in the proportion of V1 choices particularly in the later periods of testing sessions (Surgery x Session period interaction: $F_{1,6}$=8.41, p=0.0430).

The next two analyses examined whether mOFC lesions induced poor performance in the same manner as lOFC lesions – by disrupting the assignment of the correct credit for an outcome to the particular stimulus that was chosen. Recent experiments have shown that OFC lesions

centred on lOFC, disrupt credit assignment (Walton et al., 2010). An animal with such a pattern of impaired learning mechanisms will struggle to learn when each option's value is very different from the others; if the animal alternates between choices it will erroneously estimate the value of each as close to the mean. By contrast, in control animals, the ability to learn precise conjoint relationships between choices and outcomes will confer a learning *advantage* when outcomes associated with each stimulus are very different. While choice history and reward history are represented in several brain areas, conjoint representations of reward and choice may be restricted to particular brain regions, and updating the value of a particular choice may depend on an OFC sub-region (Seo and Lee, 2007, 2008; Sul et al., in press).

Subsequent analysis, directly investigated how the valuation of stimuli reflected the recent history of choices and rewards. In this challenging, varying, learning environment, the mOFC-lesioned monkeys performed 3-armed bandit tasks under 4 *varying* schedules of reward assignment (Figure 4.1) pre and post-operatively. The schedules were identical to those employed previously to identify impairments in credit assignment after lOFC lesion (Walton et al., 2010) and so direct comparisons could be made between experiments (Methods). The lOFC-lesioned animals' deficit in apportioning credit, leads to a predictable pattern of errors. Reinforcement was not assigned to the specific choice that led to its delivery, but rather was distributed between preceding and subsequent choices. After a long history of one choice (for example, option A), a new choice (i.e., option B) becomes *less* likely to be reselected by lOFC-lesioned animals, if rewarded than if not, because reinforcement for the B choice was erroneously assigned to the preceding choices of A (choice history effect: Figure 4.6Aii).

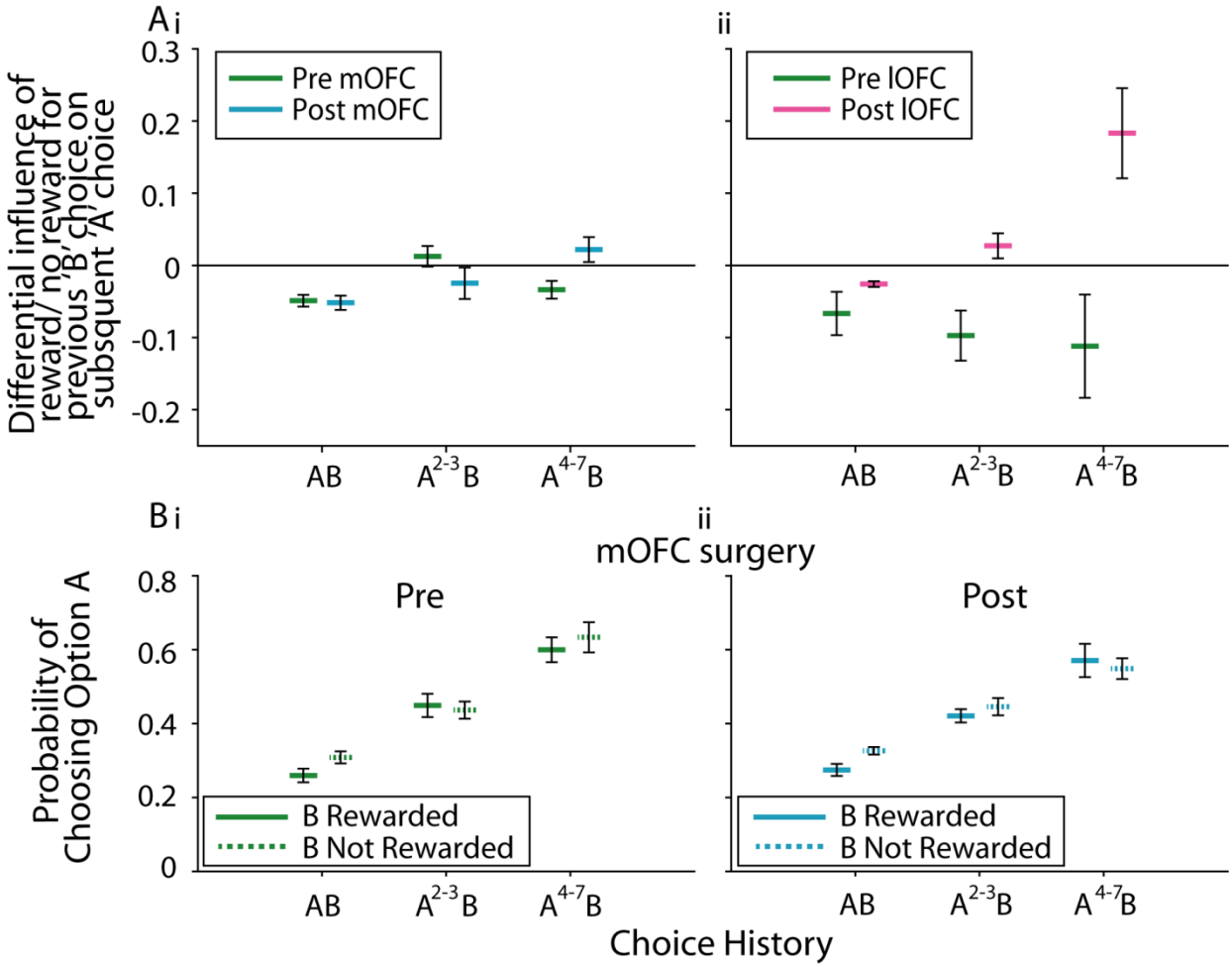

Figure 4.6. Likelihood of choosing a particular option on the current trial (n) after having chosen option A on 4 past trials (n-2 to n-5) and then option B on the previous trial (n-1), plotted as a function of reinforcement on one particular A option in the past (A?). Top row = likelihood of choosing option B on trial n when previous A choice (A?) was either rewarded (filled line) or not rewarded (dashed line). B. Figure A is prepared by comparing the difference in probability of choosing option B for rewarded and unrewarded trials, plotted here independently. Pre (green) and post-operative (blue) results are plotted separately (left and right panels respectively). MOFC and lOFC groups were compared directly in a 5-way repeated measure ANOVA but only mOFC results are presented here, lOFC-lesioned data are published elsewhere (Walton et al., 2010)

However, option B would be *more* likely to be reselected if the preceding A was rewarded than if not, because the reward for the preceding A was erroneously assigned to B (reward proximity effect: Figure 4.7Bii (Walton et al., 2010)). The mOFC group displayed neither pattern of choices (choice history: Figure 4.6B $F_{2,6}$=2.41, p=0.175; reward proximity: Figure 4.7B $F_{1,3}$=0.67, p=0.465). Moreover, direct comparison between the two lesion groups demonstrated a significant difference between the size of the effects (choice history: interaction between Lesion Location x Pre/post-surgery x Choice History, $F_{2,10}$=3.974, p=0.020; reward proximity: interaction between Lesion Location x Pre/post-surgery x Past Reward Trial, $F_{1,5}$=6.726, p=0.049).

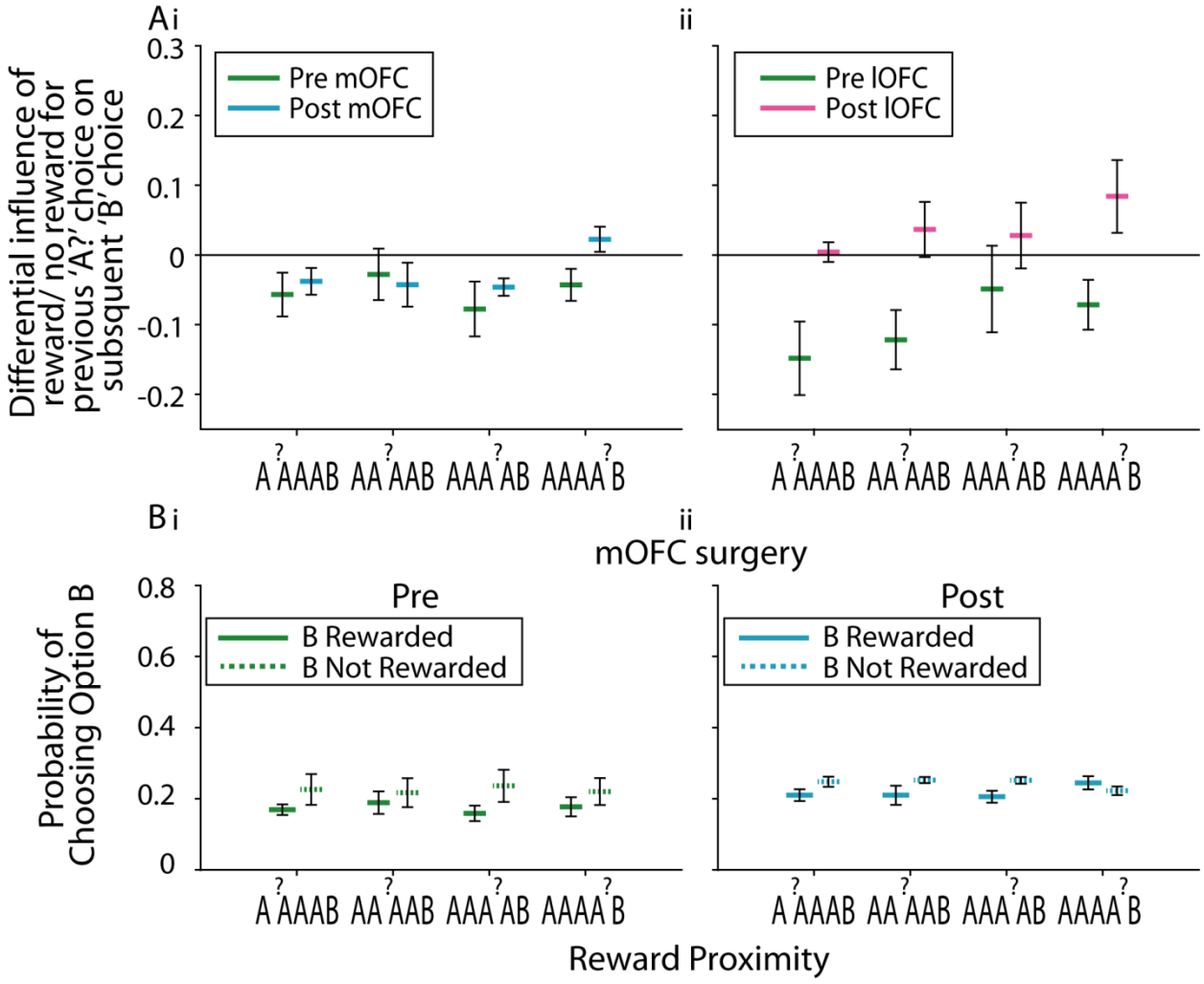

Figure 4.7. Value assignment during learning: Influence of past rewards on valuation of current choice. The difference in likelihood of choosing option B on trial n after previously selecting option A on trials n-2 to n-5 and option B on the previous trial (n-1), as a function of whether the A choices were or were not rewarded ("?" on axis labels indicates presence or absence of reward at that point in the history). After lOFC lesions (inset panel: redrawn from Walton et al. (2010), but not mOFC lesions (main panel), credit for rewards received for earlier choices of A is partly assigned to the subsequent choice of B. Pre-operative control, post mOFC lesion, and post lOFC lesion data are shown in green, blue, and pink respectively. B. Figure A is prepared by comparing the difference in probability of choosing option B for rewarded and unrewarded trials, plotted here independently. Pre (green) and Post-operative (blue) results are plotted separately (left and right panels respectively).

Fixed reward schedules and reward-guided decision-making

In order to test the hypothesis that the mOFC acts as a critical structure for making fine-grained value-guided decisions, macaques made choices between 3 novel stimuli, each associated with *fixed* reward probabilities controlled by pre-determined schedules. We investigated how differences between the options' values affected learning and decision-making by manipulating the reward likelihood of the middle value option across three testing schedules. If the mOFC was involved in a value comparison process we reasoned that a lesion to it should impair performance to a greater extent when the difference in value between the V1 and V2 options was small. By contrast, as detailed above, if the lesioned structure is important for value assignment then impairments should be greatest when value differences are large. As reported below, value learning in control animals is usually fastest in such situations when Thorndike's (1933) "law of effect" can assign value to the appropriate stimulus choice.

Post-operatively, the mOFC group was profoundly impaired when V1 and V2 values were proximate (figure 4.8; blue bars). Choice behaviour was quantified as a function of the number of trials it took animals to reach a criterion of 70% best (V1) choices across 10 trials (Walton et al., 2010). Analysis of mOFC group results revealed a significant interaction between testing Session (Session: pre- and post-surgery) and Condition ($F_{2,6}$=5.63, P=0.042) due to poorer post-operative performance with more proximate option values (t_3=-4.05, P=0.027). Such a pattern of performance suggests the mOFC lesions compromise the process by which options' values are compared so that proximate values can no longer be distinguished.

By contrast lOFC lesions affected performance in the opposite manner (figure 4.8; pink bars). A comparison of the lOFC and mOFC groups' post-operative performance revealed a double dissociation in impairments (Group*Condition: $F_{2,10}$=11.38, P=0.003). The mOFC-lesion

group was worse than the lOFC group in the V2_HIGH condition (t_5=2.87, P=0.035), whereas the lOFC group was worse than the mOFC group in the V2_MID and V2_lOW conditions (t_5=-4.71, P=0.005; t_5=-2.79, P=0.039 respectively). Note that the lOFC impairment pattern is the one predicted for a region primarily concerned with credit assignment during learning. Also consistent with the lOFC impairment being one of learning, rather than decision-making, was the finding that when the deficit was prominent (figure 4.8F) it was only present at the beginning of the session but absent in the second half of the session (t_5=- 1.76, P>0.05) at a time when the animals had learned which option to choose. By contrast, the mOFC deficit was apparent even in the second half of the session (t_5=5.04, P=0.004) as might be expected if it reflected a persistent failure of value-guided decision-making (Figure 4.8A).

Prior to fixed schedules testing, animals with mOFC and lOFC lesions had received identical training on the varying schedules and performed similarly (figure 4.2). Both considerations suggest it is appropriate to compare the groups' post-operative fixed schedule performances. Although animals with lOFC lesions had not received pre-operative testing on the fixed schedules it is difficult to see how this could account for the double dissociation observed. We nevertheless carried out four additional tests to establish whether value guided decision-making was impaired after mOFC, but not lOFC, lesions.

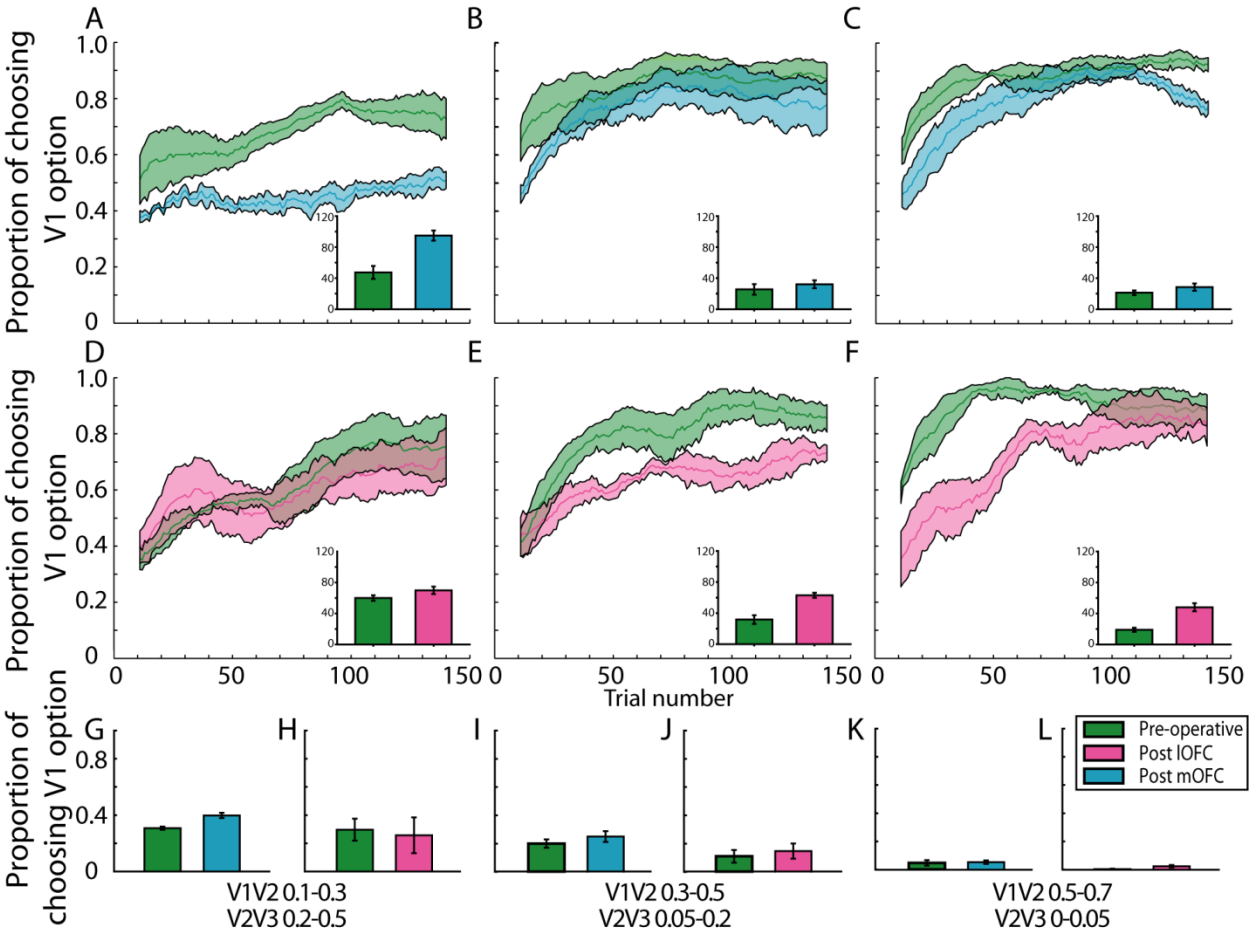

Figure 4.8. Value comparison during decision-making: probability of choosing V1, in the fixed reward schedules, V2_HIGH (A,D), V2_MID(B,E) and V2_LOW (C,F). A-C show pre- (green) and post-operative (blue) performance of mOFC animals, D-F show post-operative performane of the lOFC group (pink) and their un-operated controls (green) (D-F). Mean scores and SEMs are indicated by darker and lighter colours in each case. insets represent the number of trials to reach 70% V1 choices for unoperated or control animals (dark green bars) and mOFC and lOFC lesioned animals (dark blue and pink bars respectively). Controls became slower to choose V1 predominantly as the difference in value between V1 and V2 decreased (right to left of figure) and mOFC lesion animals appeared most impaired when decision-making was most difficult (A). LOFC-lesioned monkeys were, however, no different to controls in this situation (D). By contrast, lOFC-lesioned monkes failed to identify V1 as fast as controls when the V1V2 value difference was high (F, G) but mOFC-lesioned monkeys performed similarly to controls in these situations (B, C).

First, to confirm that lOFC lesions impaired performance on easy decision-making trials, when the V1V2 difference was large, lOFC performance was compared with that of a control group of three macaques with no lesions. The control macaques had training and testing histories that were *identical* in every respect to that of the lOFC animals (methods (Walton et al., 2010)). Just as in the comparison with the mOFC lesion it was found that the lOFC group was more impaired than controls when V1 and V2 option values were disparate (V2_MID: t_4=-4.82, p=0.009; V2_low: t_4=-4.97, p=0.008) but not when they were proximate (V2_High: t_4=-1.65, p=0.174).

Before moving to the next two tests of value-guided decision-making we carried out one further search for value-learning impairments in the fixed schedules to check that we had not confounded them with decision-making impairments. A learning rate, a parameter describing the extent to which feedback changed stimulus value estimates, was fitted to each animal's performance using standard non-linear minimization procedures on each testing day. While the learning rate increased with increasing V1-V2 value differences in controls and mOFC-lesioned animals (both $p<0.05$), this effect was significantly reduced in the lOFC group (linear interaction Group*Condition; lOFCs vs controls: F1,4=27.92, p=0.006; lOFCs vs mOFCs: $F_{1,5}$=17.82, p=0.008 and no effect in lOFC group alone – $p>0.1$).

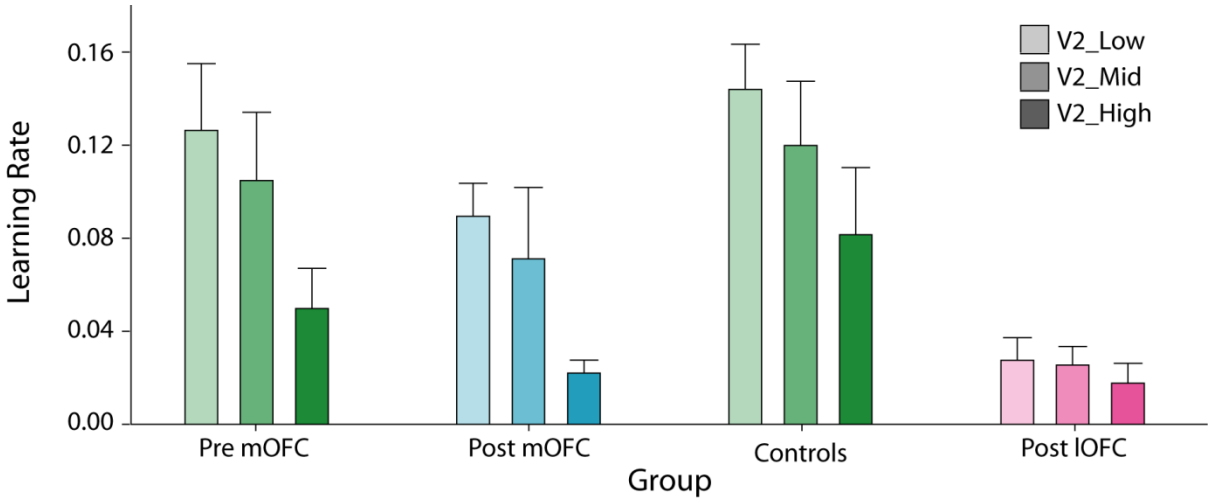

Figure 4.9. A. Influence of multiple option context on learning: The reward learning rate (α) was fitted individually to each animal's pre- and post-operative fixed data using standard non-linear minimization procedures. While the learning rate increased with increasing V1-V2 value differences in the controls and mOFC-lesioned animals, this effect was significantly reduced in the lOFC group.

Re-analysis of the varying reward schedules and reward guided decision-making

The second analysis of value-guided decision-making, sought to confirm that mOFC lesions caused a greater impairment than lOFC lesions when values of choice options were proximate. To conduct this analysis we once again focused on the varying reward schedule data (Figure 4.2) that was collected from both lesion groups under identical pre- and post-operative conditions (methods). Trials were identified across all *varying* schedules in which V1V2 and V2V3 value differences resembled those in the three *fixed* schedules. Despite the dynamic trial-by-trial changes in choice values that characterized *varying* schedules, the same pattern of impairment was seen again after mOFC lesions (Figure 4.8g, i, k; main effects of lesion: $F_{1,3}$=19.43, P=0.022; value difference: $F_{2,6}$=73.84, P<0.001; linear interaction of lesion across three levels of value difference:$F_{1,3}$=48.59, P=0.006) but not after lOFC lesions (figure 4.8h, j, l; $F_{1,2}$=1.96, P=0.296).

Moreover there was once again a significant difference between the patterns of impairment seen after mOFC and lOFC lesions (3-way interaction of Lesion, value difference and Group $F_{1,10}$=6.51, P=0.015;). The dynamic nature of the varying environment means that this analysis was less sensitive to the nature of the lOFC lesion impairment than the analyses presented in figures 4.6 and 4.7.

MOFC and lOFC are not specialized for processing rewards and errors

Previous attempts to characterize mOFC/lOFC differences have focused on specialization for reward and error processing respectively (Kringelbach and Rolls, 2004). If lOFC is specialized for error processing then a lesion should hamper the ability to switch to an alternative after one choice has been unrewarded. By contrast, if mOFC is critical for detecting occurrence of reward then mOFC lesions should have the complementary effect and diminish the rate at which animals stay with the same option after a reward is received. Although both groups, unsurprisingly, switched more after errors both before and after surgery (main effect of trial type: $F_{1,5}$=198.17, p<0.001) there was no evidence for relative insensitivity to rewards and errors after mOFC and lOFC lesions respectively. Instead both lesions caused a general increase in switching (Figure 4.10; main effect of surgery $F_{1,5=}$13.09, p=0.015). Although there was a non-significant trend for mOFC lesion animals to switch more frequently than lOFC lesion animals they did so even prior to surgery.

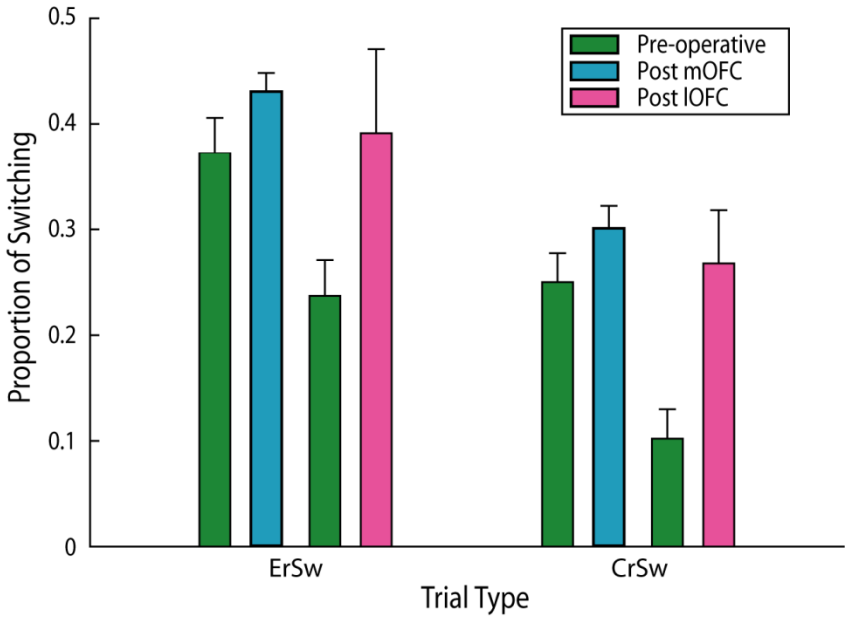

Figure 4.10. Error and Reward sensitivity in pre-operated control animals (green), mOFC (blue) and lOFC (pink) lesioned animals. Proportion of switching after trials on which a reward was not delivered (an error; ErSw) and percentage of switching on the stimulus choice after a reward (CrSw) was calculated for all three groups in the four variable reinforcement schedules. Groups were compared in two-way ANOVA of Surgery (2 levels; pre and post) and Trial type (2 levels; ErSw and CrSw) with the between subjects factor of Group (2 levels; lOFC and mOFC). This analysis showed that both lesions caused a general increase in switching (main effect of surgery $F_{1,5=}13.09$, p=0.015).

4.4 Discussion

The mOFC and lOFC have distinct roles in reward-guided decision-making and learning. There is a double dissociation between the effects of lesions to the two areas. Unlike lOFC, the mOFC does not play a central role in credit assignment during value learning (figure 4.6 and 4.7). Instead mOFC plays a central role in reward-guided multiple option decision-making (figure 4.8).

Although the focus of the current report is on mOFC we will first discuss the results pertaining to the lOFC. The lOFC is critical for credit assignment (Walton et al., 2010). In its absence the values of stimuli no longer reflect the precise history of reward experienced in conjunction with choices of that stimulus; in other words Thorndike's "law of effect" (Thorndike, 1911) is no longer in operation. Instead stimulus values reflect a proximity-weighted average of all outcomes experienced recently, before and after choices are made; in other words the "spread of effect" of reward identified by Thorndike (Thorndike, 1933) still operates. Such an account makes the counterintuitive, and previously untested, prediction that lOFC lesions should make animals relatively worse than control animals on "easy" decision-making tasks when the value of one choice is much better than the values of the alternatives. Under these conditions, control animals learn quickly which choice to make. The expected but counterintuitive pattern of impairment was indeed found after lOFC lesions (figure 4.8F). Moreover it was shown that the impairment was associated with a failure to increase learning rate when the values of choice options were very distinct from one another (figure 4.9). An lOFC role in credit assignment and stimulus reward association learning, accords with recent demonstrations that the representations of the choices that have just been made are activated in lOFC at the time of reward feedback (Tsujimoto et al., 2009). Other accounts of OFC function have also emphasized its importance for learning stimulus-reward associations (Schoenbaum et al., 2009). Although representations of choice history and reward history might be relatively widely distributed throughout the brain (Seo and Lee, 2007, 2008) only a limited number of regions may represent the conjoint history of choices and rewards; parts of the OFC might be unusual in updating the value associated with particular choices (Sul et al., 2010).

While value learning is the first stage of the proposed "standard model" of decision-making, value comparison is the second stage (Kable and Glimcher, 2009). Contrary to the suggestion made by Kable and Glimcher (2009) the lOFC rather than a ventromedial area such as mOFC was essential for value learning in the present study. Moreover Kable and Glimcher's claim that the second stage is "implemented in lateral prefrontal and parietal areas" rather than a ventromedial area such as the mOFC must be qualified. Although small in size mOFC lesions in the current study impaired value-guided decision-making in a number of different analyses. The analyses (figure 4.8) demonstrated that, after mOFC lesions, value comparison was particularly susceptible to errors when the options' values were close. There was, however, no evidence that mOFC lesions impaired credit assignment or other aspects of value learning.

We suggest the "standard model" must be revised in recognition of the finding that ventromedial prefrontal frontal areas such as mOFC affect a comparison between the values of potential choice options. It is for this reason that fMRI studies have reported that activity here, but not lOFC, not only reflects the value of the option that will be chosen, but the difference between its value and the value of the option that will go unchosen (Boorman et al., 2009; FitzGerald et al., 2009). We suggest mOFC is critical for selecting one option's value, rather than the another's, as the goal of behaviour. This would be consistent with the finding that the region is more active when behaviour is under the guidance of goal values and responses are not being made in a "habitual" fashion (de Wit et al., 2009). As the goal value that will guide behaviour is selected, the saliency of representations of locations in the environment and of responses that bring the animal's eye or hand to that location are enhanced in lateral parietal and frontal cortex (Sugrue et al., 2005).

Although fMRI studies of value expectation-related activations in mOFC and adjacent ventromedial prefrontal cortex (vmPFC) are numerous (Murray et al., 2007; Rangel et al., 2008) little is known of this region in other species. While reward expectation-related activation is most prominent in vmPFC/mOFC in such human fMRI studies most neurophysiological recordings made in the OFCs of other primate species have focused on lOFC (Wallis and Kennerley). MOFC lesions have usually only be made in the context of lOFC lesions in the monkey (Izquierdo et al., 2004; Murray et al., 2007; Rudebeck et al., 2008a). The effects of such lesions have been interpreted in terms of impairments of both value learning and decision-making (Murray and Wise; Izquierdo et al., 2004). A number of studies have reported single neuron activity within the region included in the lOFC lesion that is correlated with the values of choices that are taken, as well as with the rewards or errors that follow (Wallis and Kennerley; Wallis, 2007; Kable and Glimcher, 2009).

Prediction errors may guide reward learning (Sutton and Barto, 1998). A representation of expected value must be maintained by the brain to calculate value prediction errors when outcomes do not match prior expectations. The mOFC lesion-induced impairment in decision-making suggests how value expectation-related activity changes in vmPFC/mOFC (Murray et al., 2007; Rangel et al., 2008) might best be interpreted. A representation of expected value must be maintained by the brain to calculate value prediction errors, when outcomes do not match prior expectations (Schoenbaum et al., 2009). Such prediction errors are widely thought to be critical for learning to occur (Rangel et al., 2008; Schoenbaum et al., 2009). If mOFC carried a representation of reward expectation critical for reward prediction error learning, then mOFC lesions, like lOFC lesions, should have altered learning but that was not the case (figure 4.9). MOFC value signals, even if automatically generated (Lebreton et al., 2009), instead appear to

be critical for guiding decisions (Boorman et al., 2009; FitzGerald et al., 2009) then the decision-making impairments that were found after mOFC lesion would be predicted. Although small in size mOFC lesions also impaired aspects of task performance in the present study. There was no evidence that mOFC lesions impaired credit assignment (figure 4.6 and 5.7), but instead the mOFC lesion-induced failure was more easily interpreted in terms of an impairment in value-guided decision-making (figure 4.3).

Some neuroimaging studies (O'Doherty et al., 2001b), and meta-analyses of neuroimaging data (Kringelbach and Rolls, 2004), have been use to support the argument for the relative specialization of the processing of reward and error outcomes in the mOFC and lOFC respectively. No support, however, was found for this hypothesis in the current study (Figure 4.10). The hypothesis that mOFC is concerned with value-guided decision-making can account for the neuroimaging data; it predicts mOFC signals should correlate with the reward expectations associated with choices during and after the comparison process. In addition however, it also predicts that mOFC signals should correlate with the difference in value between choice options (Boorman et al., 2009; FitzGerald et al., 2009) during the comparison process. Moreover, an account of lOFC that focuses on value assignment and learning, predicts lOFC activation to errors if the errors occasion the reassignment of values to options. In addition, however, it predicts an lOFC response to positive outcomes if they also occasion the revaluation of an option. MOFC involvement in value comparison accords with its connections with brain regions implicated in other aspects of reward-guided behavior (Ongur and Price, 2000). By contrast, lOFC involvement in assignment of value to stimuli is consistent with its connections with higher order sensory areas, such as anterior temporal and perirhinal cortex, that represent those stimuli (Kondo et al., 2005), and the finding that the primate lOFC is a prerequisite for

stimulus-reward association learning but not action-reward association learning (Rudebeck et al., 2008b).

We have presented and discussed findings which imply a double dissociation between the function of medial and lateral regions of the OFC. The following chapter will present some further analyses that explore the precise nature of the mOFC animals' deficits in value-guided decision-making. Specifically, it will focus on how the context of a decision influences normal choices and how after mOFC damage the influence of context on the rationality of the decision changes.

CHAPTER 5: DISTORTIONS IN DECISION SPACE - THE ROLE OF THE MACAQUE MEDIAL ORBITOFRONTAL CORTEX IN DECISION-MAKING

The human medial orbitofrontal cortex (mOFC) is implicated in relative reward processing and in macaques we have shown this sub-region has a critical role in comparing expected reward values in multi-option environments. By subsequently investigating animal choice behaviour in dynamically-changing environments we intended to clarify the impairments experienced by mOFC-lesioned macaques relative to their control performances. The results suggest that contrary to axiomatic assumptions of decision theory, the mOFC-lesioned animals' value comparisons became no longer independent of context, or the presence of alternative options. MOFC-lesioned animals are beguiled into choosing the second best option partly as a function of there being a large difference in value between it and the worst option. The pattern of impairment suggests mOFC is critical for maintaining a uniformly scaled "decision-making space" for rational decision-making.

5.1 Introduction

The previous chapter described a double dissociation between the functions of the medial and lateral orbitofrontal cortex. We presented evidence that the lateral regions (lOFC) are relatively more concerned with credit assignment; the process by which expected value is assigned to the appropriate stimuli. In contrast, we show that the medial regions are involved in comparing multiple values in order to make a decision and to select the best option. Whilst still

controversial, if it is indeed the mOFC that makes the decision, then it is possible that the rationality of decisions might be challenged by lesions to this region.

Economic theories argue that a central tenant of rational decision-making is logical consistency across decisions, regardless of the manner in which available choices are presented. It is generally accepted that many human decisions fall outside the economic definition of rational, appearing to be influenced by factors such as risk and context (De Martino et al., 2006; Boorman et al., 2009). Very few animal lesion studies have directly investigated the neurobiological basis of context dependent rational decision-making (Baylis and Gaffan, 1991), however, a number of electrophysiological recording experiments in monkeys have identified neurons in areas 11 and 13 of the orbitofrontal cortex (OFC) which encode relative expectation about the values of choices being made (Tremblay and Schultz, 1999). Cynomolgus monkeys were presented with pairs of stimuli each associated with a different food type. Tremblay and Schultz used three food rewards but presented only two of them in a given trial block. Behaviourally, animals showed clear food preferences, preferring A over B and B over C. Interestingly, when investigating neuronal firing patterns, the authors found that a high proportion of OFC neurons were activated by the reward, or the discriminative instruction cue that was relatively more preferred than the available alternative. For example, a neuron would be more active to A in the presence of B but show stronger activity to B if it was paired with C. The reverse pattern could be seen in relative encoding of the non-preferred rewards and stimuli. More recently, related findings have suggested that the OFC encodes relative expectations about choice values (Padoa-Schioppa and Assad, 2008) implying that context is shaping the neurons' firing patterns.

Context dependency and relative reward effects are also apparent in the OFC in humans (Plassmann et al., 2007; Elliott et al., 2008). Elliott and colleagues (2008) used a human analogue of the Tremblay and Schultz (1999) task comparing BOLD responses to the presentation of abstract patterns which were associated with a particular expectation of a financial reward. The preceding context in which this pattern was presented was manipulated and could either have been simultaneously presented with a pattern associated with a lower reward expectation or a higher expectation of reward. The authors observed that mOFC activity to the same perceptual stimulus was greater when the stimulus predicted the more valuable of the two rewards than when it predicted the less valuable. In contrast, BOLD response in right lOFC was enhanced for the less valuable stimulus. Elliott and colleagues (2008) argued that relative financial reward value is coded in distinct subregions of an extended reward and decision-making network.

It could be argued that a loss of the relative reward expectations might lead to inconsistency in choice preferences. This is just what is seen in monkeys with lesions to the ventromedial prefrontal cortex. Monkeys with lesions in this region show inconsistency in decision-making preferences among pieces of unfamiliar food (Baylis and Gaffan, 1991). These results are complemented by studies of human patients with extensive ventromedial prefrontal cortical lesions who show impairments in decision-making. These patients are inconsistent in their preference judgments among pairs of choices of both primary and abstract concepts (Fellows and Farah, 2007).

Neuroimaging experiments also implicate the ventromedial prefrontal cortex (vmPFC) in decision-making. This region of cortex in humans is thought to be equivalent to more medial regions of macaque mOFC. It has been argued that the ventromedial prefrontal cortex is part of

the circuit for deciding between options on the basis of their expected value; with evidence that it encodes the relative value difference of the current decision (Boorman et al., 2009) for gains as well as losses (FitzGerald et al., 2009). Moreover, De Martino and colleagues (2006) report that vmPFC activity is correlated with the degree to which subjects' decisions are rational and uninfluenced by irrelevant features of the context in which they are made. Increased activation in the OFC and vmPFC was associated with a decreased susceptibility to the framing effect: a manipulation of the context of the decision, which has been shown to influence choices.

The current experiment used the data acquired and discussed in the previous chapter from four macaque monkeys to examine the rationality of decision-making under different reward contexts. The animals were tested on a number of 3-choice tasks, during which the reward probability associated with each stimulus varied across a day's testing session, before and after lesions to the mOFC. We performed additional statistical analyses to quantify the effects of the lesion and to test our interpretations. Specifically, we examined animals' performance as a function of where a decision lay in the "decision-space" defined by the context. We investigated the influence of two contexts. First, we determined how the value difference between the best and second best option, and the value difference between the second best and the worst option would affect selection of the best option. We then investigated how the value of an irrelevant alternative third option in the environment influenced the decision between the other two options. We found that animals with mOFC lesions were negatively influenced by increased value differences between the different options and by high values of an alternative option.

5.2 Method

Four male rhesus macaque monkeys (*Macaca mulatta*) aged between 7 and 10 years old and weighing between 9 and 13.5kg performed a number of 3-choice probabilistic decision-making tasks in which the reward probability varied throughout the course of the session before and after receiving mOFC lesions. The methodological details of the task-specific habituation and pre-training, experimental apparatus and the precise surgical and anesthetic procedures used are described in chapter 3 and specifically chapter 4.

Reward Schedule

Three monkeys completed 5 variable three choice tasks in which the reward probability associated with each stimulus varied over the course of the session, pre and post-operatively (Figure 4.2). As a result of an experimental oversight a fourth monkey only completed four varying schedules. All trials completed are included in the regression analysis and softmax analysis. All other analyses are based only on the four schedules that all monkeys completed. The schedules were presented in an interleaved manner across testing days. The varying schedules were described in the previous chapter however, in short, expected reward values associated with the three different stimuli changed across the course of the session. This meant that the identity of the best (V1), mid (V2) and worst (V3) stimulus changed from trial-to-trial. Therefore, in order for the animals to maximize its reward it now had to track these changing probabilities for all three stimuli. Direct comparisons could be made between the mOFC and lOFC lesioned animals in the softmax analyses (Figure 5.4 and 5.5) because the lOFC-lesioned animals had previously completed these varying reward schedules (Walton et al., 2010).

Data analysis

The data from the varying reward schedules were analyzed as a function of the subjective expected values of all three different stimuli which were derived using a standard Rescorla-Wagner learning model and for analyses making use of softmax regression a Boltzmann action selection rule was applied. The reward learning rate (α) was fitted individually to each animal's pre- and post-operative data using standard non-linear minimization procedures. Boltzmann action selection rules allow you to model choices based on the stimulus value estimations calculated by RL models. Specifically, Boltzmann softmax rules assume that alternative options are ranked and weighted according to their value estimates. Alternative, E-greedy action selection rules do not make this assumption.

V1 choices as a function V1V2 and V2V3

To investigate whether the context of the decision differentially affects choice after mOFC surgery we investigated the impact of increasing V2V3 differences on V1 choices. The data were binned as a function of increasing log V1V2 difference (indexed by the different colours) and log V2V3 difference (on the x-axis), pre and post-operatively. The probability of choosing the V1 was then calculated for each of these bins for every animal and averaged (shown on y-axis).

Logistic regression analyses

To quantify the effects suggested by the analysis above we performed two parallel analyses that examined animal performance as a function of where a decision lies in the "decision-space" defined by V1V2 and V2V3. In each case we used regression analyses to predict various aspects of performance using linear factors of V1V2, V2V3 and the (V1V2)*(V2V3) interaction. By including the (V1V2)*(V2V3) interaction in the analyses allows performance, and deficits, to be measured in particular corners of the decision-space (as opposed to assuming V1V2 and V2V3

act independently). The regression assigns coefficients that indicate the weight of influence of each of the factors on the measure of performance investigated. The first analyses examined whether each of these factors predicted which option, V1, V2 or V3 would be taken. We also included three additional regression terms in this analysis. Specifically, we included the factors of the absolute value V3 and its interaction with the V1V2 or V2V3 value differences; (V1V2)*V3 and (V2V3)*V3 respectively. Pre and post-operative beta weights for each regression were subjected to paired-sampled t-tests.

Decision space analysis and regression

The second analysis fitted the choice data with softmax functions whose inverse temperatures (β) were allowed to vary throughout this same decision space. In this way we hoped to investigate the how animals' choices were influenced by changing contexts. Such softmax functions illustrate how the probability of choosing an option varies as a function of differences between its value and those of other options.

$$P(i) = \frac{\exp(\beta V_i)}{\sum_{i=1}^{3} \exp(\beta V_i)}, \qquad \beta = \beta_0 + K_{12}(V_{\max} - V_{mid}) + K_{23}(V_{mid} - V_{\min}) + K_{\text{int}}(V_{\max} - V_{mid})(V_{mid} - V_{\min})$$

Equation 1

Logistic Softmax Function

In order to determine whether the value comparisons the mOFC animals were making were influenced by the context in which they were made, logistic softmax functions were fitted to each animal's choice data (Figure 5.4 and 5.5). This tested whether the animals were choosing optimally in their environment. We defined three positions in the decision context and allowed each of the three stimuli to act in each role. Stimuli could either be the "chosen option", referred to as X, the 'unchosen' option, as Y, or as the "alternative" option, Z. The data were processed

twice, with each stimulus on every trial acting as each option where possible. The proportions of trials on which a subject chose as a function of the value difference with respect to another option (this could either be positive or negative) were plotted separately for situations when Z was high (top 33% of Z values) and low (bottom 33% of Z values) in value. These distributions were then fitted with a logistic sigmoid function. The function of the logistic curves for when the other option, Z, was high and low value were compared independently in paired sample t-tests for the pre and post-operative data.

In a separate analysis we compared the susceptibility to the influence of context between the medial and lateral OFC lesioned animals (described in the previous chapter). The approach was difficult to apply to the second halves of each day's testing session in the lOFC lesion animals because no learning tended to occur. In general, however, animals with lOFC lesions exhibited learning in the first halves of each session. We therefore applied the same analysis to the first halves of each day's testing session to both groups of animals independently. The function of the logistic curves when the other option, Z, was high, mid or low in value was compared in repeated measures ANOVA of Lesion (2 levels; pre- and post-surgery) and Z value (3 levels; low, mid, high). In a direct comparison of the two lesion groups the additional between-subjects factor of Group (2 levels; mOFC and lOFC) was introduced. The behavioral analysis was performed using Matlab 6.5 (MathWorks).

Average value and response vigor analysis

Pre and post-operative trials were divided into ten value bins on the basis of the mean value of all three stimuli on that trial and as estimated by the reinforcement learning model described above. Average stimulus value increased by 0.05 from one bin to the next. We compared the median

RTs on trials in the ten average value bins before and after surgery in a repeated measures ANOVA of Lesion (2 levels; pre and post surgery) and Value (10 levels).

5.3 Results

Histology

The histological details of these animals have been described in detail in chapters 3 and 4 (figures 3.4, 4.4a and b) and full coronal sections through the frontal lobes, for each individual animal, are also shown in Appendix I: Histology. Briefly however, the lesions were made as intended with the cortex from the medial orbitofrontal sulcus to the rostral sulcus, including mainly Walker's area 14 (Walker, 1940), but also some parts of area 10 being removed.

Contextual effects on reward-guided decision-making

We explored the nature of the mOFC-lesioned animals' decision-making deficits, described in the previous chapter and investigated whether they were related to the context defined by the value of the alternative choices. Re-plotting the data shown in Chapter 4, figure 4.8G-L as a function of the proportion of trials in which the best choice was made as a function of *both* V1V2 and V2V3 value differences shows that control animals were more likely to take the best option as the V1V2 *and* the V2V3 difference increased (solid lines, figure 5.1a). By contrast, in comparison with pre-operative performance, a large V2V3 difference made it more difficult for mOFC-lesioned animals to choose effectively, especially when the V1V2 difference was large (solid lines, figure 5.1b). This may be due to the V2 option appearing distractingly attractive if it is much better than V3. This would suggest that in such situation it becomes more difficult for mOFC- lesioned animals to ignore V2.

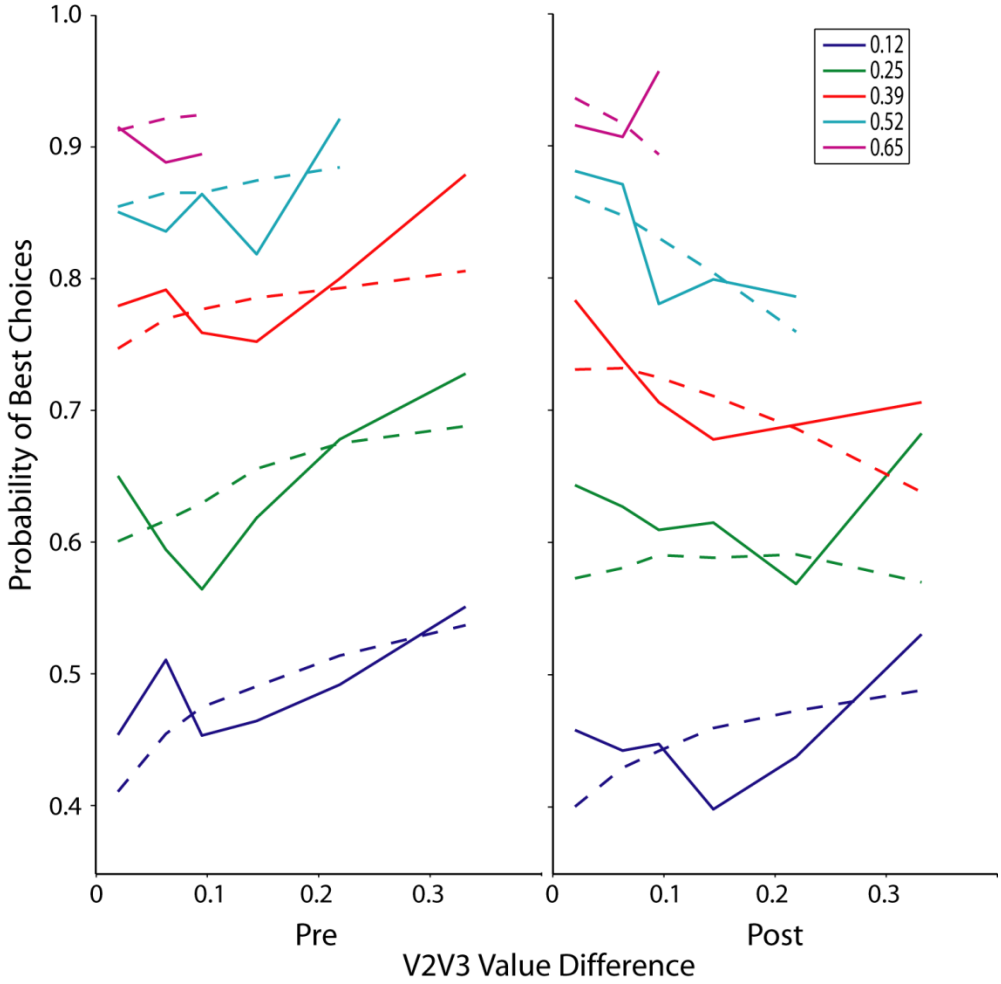

Figure 5.1. Influence of multiple option context on value comparison. **A**. Preoperatively (left) choices of V1 increased with increasing V1V2 (color key) and V2V3 (abscissa) differences. **B**. After mOFC lesion (right) larger V1V2 and V2V3 differences were associated with relatively fewer V1 choices. Solid and dashed lines indicate actual choices and choices predicted by the fitting of a softmax decision rule (figure 5.3).

This effect was quantified by carrying out a regression analysis which tested whether the proportion of V1 choices was predicted by linear factors, not just of the V1V2 difference but terms representing the (V1V2)*(V2V3), the (V1V2)*V3 and the (V2V3)*V3 interaction terms. To estimate these interaction effects the regression included main effects of the V1V2 difference, the V2V3 difference and magnitude of V3. Inspection of figure 5.2 suggests that increasing

V1V2 value differences have a positive impact on V1 choices pre and post-operatively, this result is not inconsistent with the results from Chapter 4, as discussed in the previous chapter mOFC lesion deficits are only apparent when the V1V2 value difference is small. As such the current analysis is not investigating those types of contexts. The analysis showed that the regression coefficients all became significantly more negative after the mOFC lesion (Figure 5.2; $F_{1,3}=75.79$, $p=0.003$). This result suggests the post-operative decline in performance after mOFC lesion was not just a function of small V1V2 value differences as suggested by Chapter 4 but also of the value of V2 being much better than that of V3; V3 value itself being large, and the interaction of these effects, as if such contexts distracted monkeys with mOFC lesions from identifying the best options. What slight decline in this positive influence of increasing V1V2 value differences there is (which while is significantly more negative in the context of all 6 regression terms a one sample t-test suggests the effect is not exceptionally strong for the V1V2 value difference factor independently, $t_3=1.49$, $p=0.234$), has to be considered in the context of the increasing V2V3 value differences and indicated by the V1V2*V2V3 interaction term ($t_3=3.13$, $p=0.052$).

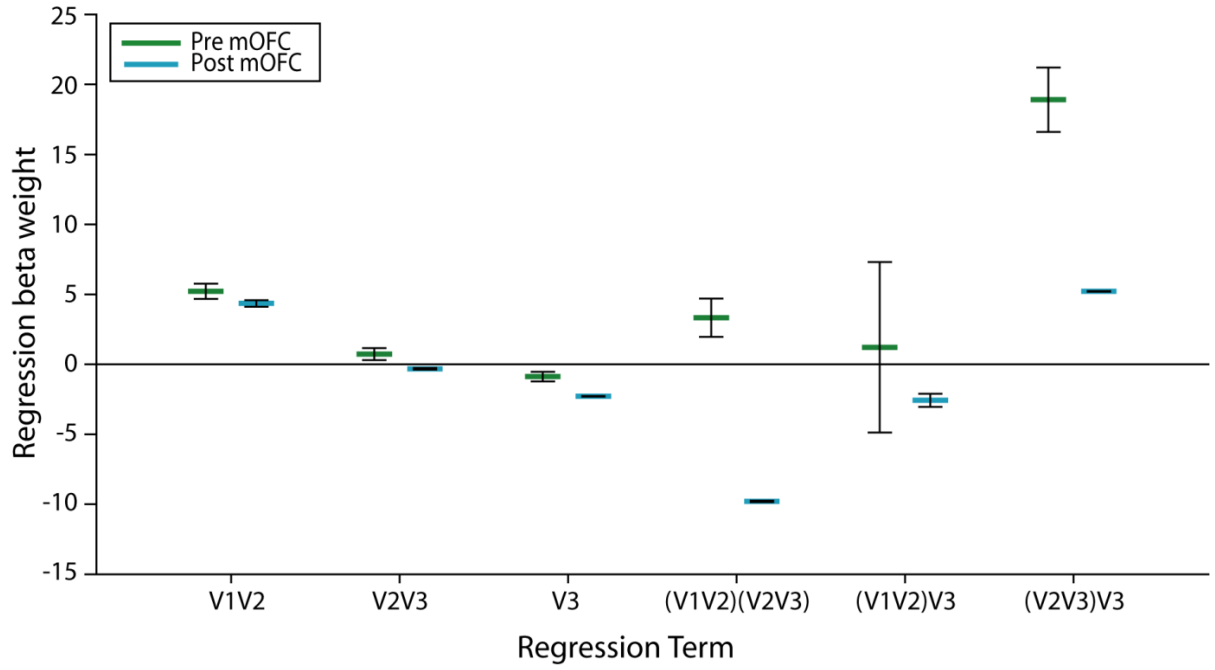

Figure 5.2. Weights of influence of stimulus value differences on choices of V1 before (green) and after (blue) mOFC lesion. The interactions between the stimulus value differences, for example the interaction between the V1V2 and V2V3 difference ((V1V2)(V2V3)), and (V1V2)V3 and (V2V3)V3, are shown on the right of the figure. While the interaction terms are positive prior to surgery, indicating that such combinations of value difference were conducive to good performance, they are all significantly more negative after mOFC lesion.

Distortion of "decision space" during value comparison after mOFC lesion

The analysis described above suggests that the context, or the decision space, of the reward environment influences choice behaviour differentially after mOFC lesions. Another way of illustrating this is to fit the choice data with softmax functions whose inverse temperatures (β) are allowed to vary throughout the decision space. Such softmax functions illustrate how the probability of choosing an option varies as a function of differences between its value and those of other options. If a softmax function has a high β then choices are deterministic functions of value differences, rather than random, and the slopes of the sigmoid functions depicting the decision rule are steep (figure 5.3a). Such a logistic function decision rule predicted V1 choices

well, both pre and post-operatively (proximity between dashed and solid lines in figure 5.1). Animals that are choosing equally effectively throughout the space should, however, have constant values of β. i.e. the linear terms, K, in equation 1 should not differ from zero. The results are summarized in figure 5.3a which shows the change in softmax function through the space described by equation 1 (methods). Equivalent 2-choice functions are shown for illustrative purposes (figure 5.3b). Steep, rather than shallow, slopes indicate that decisions are predictable functions of value differences rather than random. Whilst, preoperatively, almost identical logistic slopes were fitted to the decision functions throughout the decision-space, post-operatively, the slopes become increasingly shallow towards the top right of decision-space where both V1V2 and V2V3 value differences are large. Specifically, prior to mOFC lesion the weights, K, assigned to each term were indeed not significantly different from zero (all Ps> 0.1, figure 5.3b). The mOFC lesion induced a significant negative change in K_{int} ($t_3=5.121$, $p=0.014$, figure 5.3b); i.e. decisions became increasingly random with increasing (V1V2)*(V2V3) interaction (top right hand corner of the decision space). Whilst three out of 4 animals' deficits were in this top right-hand corner, the fourth's spanned the entire right-hand side of decision-space (K_{23}). The sum of the two terms, K_{int} and K_{23}, was significantly less than zero after mOFC lesions; indicating irrational decision-making ($t_3=6.189$, $p=0.008$).

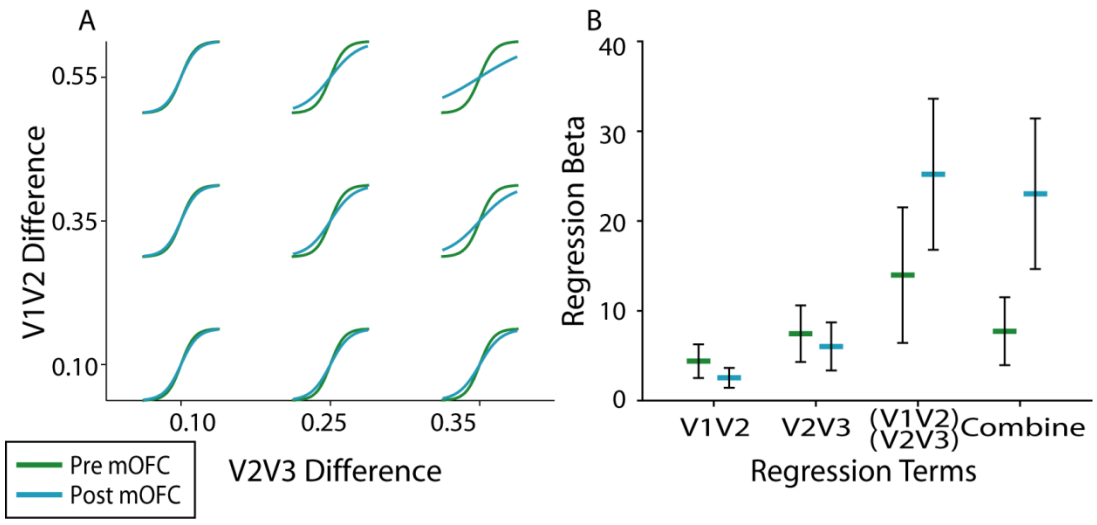

Figure 5.3. Influence of multiple option context on value comparison. A. Logistic functions for softmax decision rules, relating probability of choosing one option rather than another (inset ordinates) to their difference in value (inset abscissas). Similar functions were fitted throughout the "decision space" defined by V1V2 and V2V3 differences before (green) but not after mOFC lesion (blue). B. Weight of influence of V1V2 and V2V3 value differences and their interaction, (V1V2)(V2V3) on the inverse temperature parameter, β; when β is high then choices become deterministic functions of value differences between options and the slopes of the softmax functions in panel A are steep. In control animals β remains constant and is unaffected by the factors (all regression weights are close to zero); decisions are made in a similar way throughout the decision space. After mOFC lesion the influence of the factors, particularly V2V3 and the (V1V2)(V2V3) interaction term (the sum of the influences of these two terms is shown in the right hand column labeled "combine"), increase. After mOFC lesion decisions are irrational in that they are influenced by position in decision space.

The mOFC and the contextual dependence of value comparison

The final assessment of value-guided decision-making also tested whether or not value-guided comparisons were influenced by the context in which they were made. Rationale value-guided decisions between a given pair of options should be made in the same manner regardless of context (von Neumann and Morgenstern, 1947). Logistic functions were constructed to describe each animal's choices between possible pairs of options under two conditions (Figure 5.4). The

gradient of the slope reflects the degree to which decisions are deterministic functions of value as opposed to random. Note however, that a reduction in sigmoid slope after a lesion could reflect impaired value-guided decision-making or impairments in the learning and assignment of values to options prior to comparison during decision-making. Our analysis therefore did not focus simply on the change in sigmoid slope describing value comparison between possible pairs of options in pre and post-operative tests, but on its dependence on the value of the third option. In the first condition the value of the alterative option was high (top 33 percentiles) and in the second condition the value of the alternative option was low (bottom 33 percentiles). It is possible that a faulty learning mechanism might estimate the values of the two options being compared incorrectly but it should do so in the same way in both conditions. It is possible that our modeling and estimation of the options' values was inaccurate but the inaccuracy should be the same in each condition. What is at stake then, is whether the sigmoid curves describing decision-making in the two conditions are identical or different to one another. The two curves were identical pre-operatively (t_3=0.342, p=0.755, figure 5.4a) showing that the distribution of monkeys' choices between any two options does not normally depend on context, as defined in this case by the value of the third, alterative option. After mOFC lesions, however, value comparisons between each pair of options depended significantly on what alternative option was available at the same time (t_3=5.44, p=0.012; figure 5.4b).

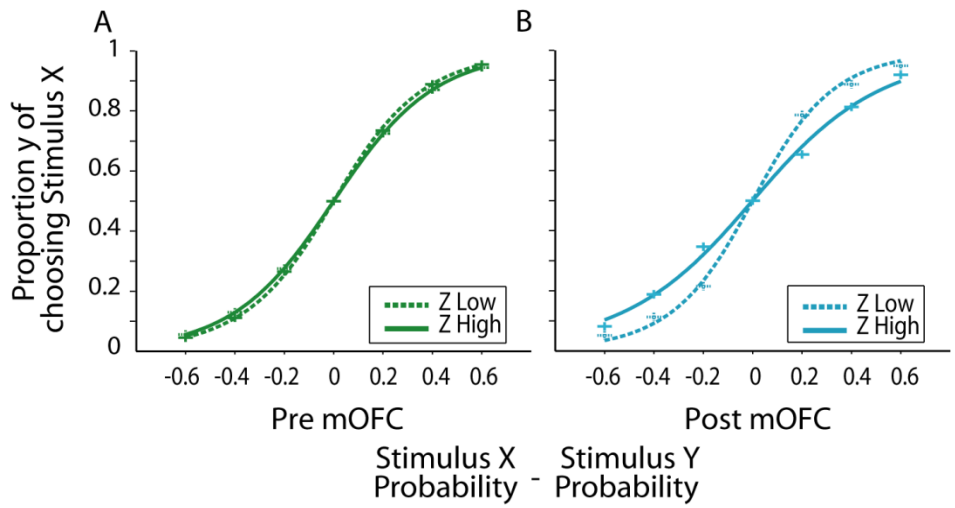

Figure 5.4. Proportion of trials on which monkeys chose options as a function of the relative value difference with respect to one other option in the context of a high (solid line) or low (dashed line) value third option before (i) and after (ii) mOFC lesion (fitted with logistic functions). Normally monkeys' comparisons of two values are uninfluenced by the context of the other available option. This is no longer true after mOFC lesions.

To investigate whether this effect was regionally specific within the OFC, we applied the same analysis principles to the lOFC lesioned animals that had completed the same varying schedules included in the current analysis (see Chapter 4 for details on these animals). The approach was difficult to apply to the second halves of each day's testing session in the lOFC lesion animals because no learning occurred. In general, however, animals with lOFC lesions exhibited learning in the first halves of each session. We therefore applied the same analysis to first halves of each day's testing session and revealed no lOFC impairment (Figure 5.5b, i-ii, $F_{2, 4}$=1.222, p=0.386). By contrast, an increase in the contextual dependency of decision-making was still apparent in the first halves of each day's testing sessions after mOFC lesions (figure 5.5a, i-ii, $F_{2, 6}$=10.092, p=0.039). This was true even though the mOFC impairment was at its least apparent in the first halves of the testing sessions. Finally a direct comparison of the two

lesion groups confirmed that the contextual dependency became significantly greater after mOFC lesion, than it did after lOFC lesions ($F_{2, 10}$=6.76, p=0.019).

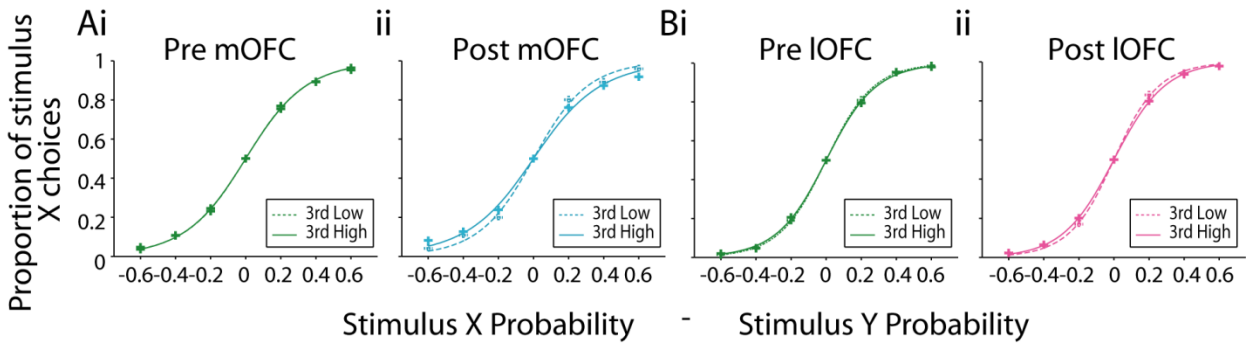

Figure 5.5. Weights of influence of stimulus value differences on choices of V1 before (green) and after (blue) mOFC and (pink) lOFC lesion. The displacement of the softmax function remained statistically significant in the mOFC lesion group, even if small in absolute terms, when the analysis focused just on the first halves of each testing session when performance tended to be strong even post-operatively (Ai-ii) but no such effect was seen after lOFC lesions (CBi-ii); In summary, both pre-operative and lOFC lesion monkeys' comparisons of two values are uninfluenced by the context of the other available option but this is not true after mOFC lesions.

The mOFC and the representation of value

Niv and colleagues have shown that response vigor, as indexed by decreased average reaction time (RT), increases with the average value of an environment (Niv et al., 2007). Slower RTs constitute greater opportunity costs in higher value environments. If mOFC lesions deprive macaques of any sense of value then this relationship should be abolished or at least compromised. Pre and post-operative trials were divided into ten bins on the basis of the mean value of all three stimuli on that trial, as estimated by the reinforcement learning model. This analysis revealed a main effect of average Value ($F_{9, 27}$=26.779 p=0.000), but no effect of the lesion ($F_{1, 3}$=0.670, p=0.473) or interaction between Lesion and average Value ($F_{9, 27}$=0.972,

p=0.455). Essentially the same results were obtained even if the first two bins, when RTs were longest, were excluded from the analysis ($F_{7,\ 21}$=10.25 p=0.001). We therefore argue that macaques with mOFC lesions have not lost their estimate of value but instead are no longer able to use it to compare between different options in certain contexts.

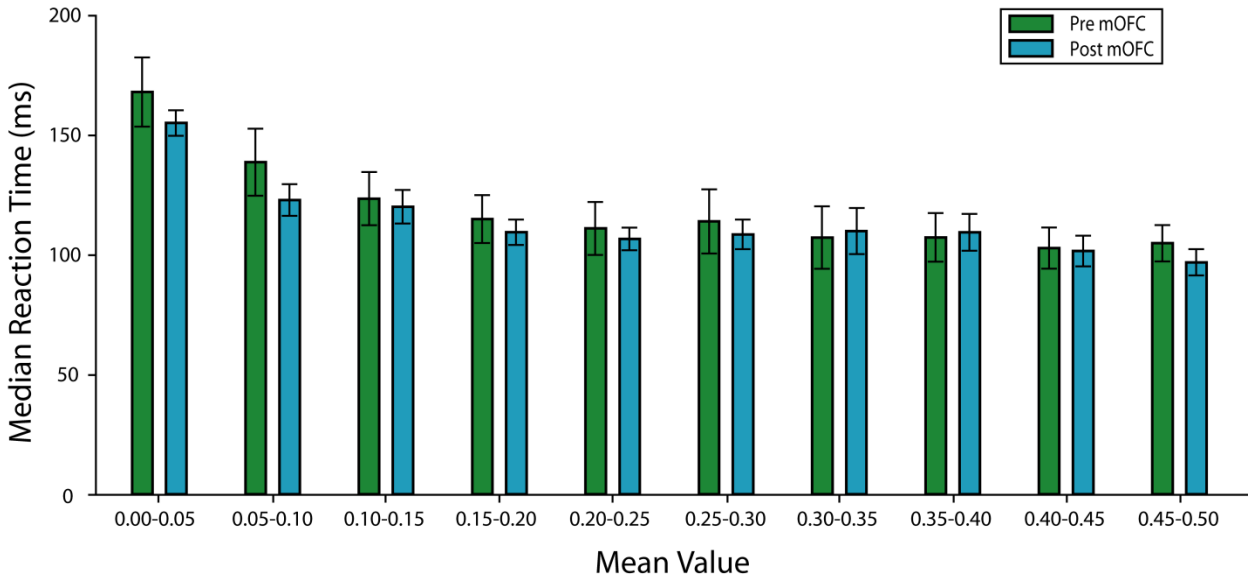

Figure 5.6. mOFC choice reaction times in different mean reward value environments. Pre-and post-operative trials were divided into ten bins on the basis of the mean value of all three stimuli on each trial as estimated by the reinforcement learning model described above. We compared the median RTs on trials in the ten average value bins before and after surgery. Average stimulus value increased by 0.05 from one bin to the next. Normal controls showed faster RTs to higher mean reward value trials and mOFC lesions did not significantly influence this pattern.

5.4 Discussion

The previous chapter suggested that mOFC-lesioned animals struggled to make value comparison judgments particularly when the difference between the best and second best option was small. The current chapter presents data which extends and clarifies the nature of this impairment. We have shown that normal monkeys' choices are positively influenced by increasing differences between the best and mid value and the mid value and worst option, such

that when values are separated, the decision is easy and animals successfully chose the best option. In contrast, mOFC-lesioned animals are negatively influenced by this type of context and seem unable to use these differences to facilitate optimal choice. Moreover, we demonstrate that the mOFC-lesion deficit was not just a function of V1V2 difference but also of the value of V2 being much better than that of V3, V3 value itself being large, and the interaction of these effects, as if such contexts distracted monkeys with mOFC lesions from identifying the best option.

The multiple-option context may have been useful for revealing the mOFC deficit. In a three choice decision, animals with mOFC lesions were sometimes distracted into choosing the worse of any two options partly as a function of the third option's value (Figure 5.5b). In certain combinations a large difference between V2 and V3 values or a high V3 value distracted the mOFC-lesioned animals from identifying V1 (Figure 5.4). Human subjects with lower vmPFC/mOFC BOLD signals are more likely to make irrational decisions that are no longer a function of value differences between options, but which are influenced by context (De Martino et al., 2006). Human patients with vmPFC/mOFC lesions make unusual decisions (Fellows and Farah, 2005), and these changes may stem from failure to attend to the relevant aspects of the decision-making context, or "decision-making space" (Damasio, 1994; Fellows, 2006). The current results demonstrate how certain combinations of value difference, in a quantitatively defined decision-making space, may beguile those with mOFC lesions into making sub-optimal choices. Propensity to make sub-optimal choices varies partly as a function of how much better one sub-optimal choice is than another. This means that people with mOFC lesions might appear to act as *satisficers* rather than *optimizers* (Simon, 1957). The current analysis, however, suggests that impairment is a consequence of disruption of a value comparison mechanism, and

need not reflect motivational change. The decisions made after mOFC lesions may reflect the compromised operation of other brain areas that remained intact. For example, the striatum and anterior cingulate cortex (ACC) also carry choice value signals and are implicated in decision-making (Shidara and Richmond, 2002; Samejima et al., 2005; Amiez et al., 2006; Kennerley et al., 2006; Hayden et al., 2008; Quilodran et al., 2008; Rudebeck et al., 2008b; FitzGerald et al., 2009; Kennerley and Wallis, 2009b). The different functions of reward representations in areas such as OFC and ACC are currently debated (Wallis and Kennerley; Rushworth et al., 2007b; Rudebeck et al., 2008b; Kennerley et al., 2009). Such differences suggest the areas can only partially compensate for one another.

The finding, that after mOFC lesions, decisions are influenced by the context in which they are made has neuroeconomic and computational implications. After practice, under normal circumstances, monkeys' choices abide by decision theory's independence of the irrelevance alternative axiom (Luce, 1959; Ray, 1973) – the distribution of choices made between two options is independent of the value of any third option (figure 5.4a); this is no longer the case after mOFC lesion (figure 5.5b). The same principle is a corollary of many decision rules, such as softmax or probability matching, used in the computational modeling of value-guided choice (Dayan and Abbott, 1999). The present results suggest that such rules only poorly describe how decisions are made in the absence of mOFC.

Neuroimaging experiments have identified value-related activity changes in mOFC and vmPFC in decision-making tasks (Murray et al., 2007) but interpretation has focused on the possibility that it encodes the expected value of the choice taken (O'Doherty et al., 2002). A representation of expected value must be maintained to calculate value prediction errors, when outcomes do not match expectations, and for learning to occur. Two recent studies, however,

suggested that vmPFC/mOFC activity may encode the difference in value between choice options, and that activity correlated with the expected value of a choice actually reflects the output of a competitive interaction between neuronal populations representing the best and second best values (Boorman et al., 2009; FitzGerald et al., 2009). The current results are most easily interpreted in line with this latter notion of an mOFC role in comparing the conditioned values of stimuli. If instead mOFC carried a representation of reward expectation critical for reward prediction error learning, then mOFC lesions should have altered learning rates, but this was not what was found.

Recently, it has been shown that the vmPFC encodes attention-dependent relative value signals between two alternative food items (Lark et al., in press). Whilst this signal was not found to reflect a subsequent decision choice, its existence may be interpreted in the context of the mOFC lesion deficits. We show that choices in contexts in which alternative options have high values are sub-optimal. It is possible that after the mOFC lesion animals are less able to focus or attend exclusively on the stimuli most critical to the decision. Relative value signals, dependent on the focus of attention, may support optimal choices in an intact network, but may lead to the wrong choice being made if the focus of attention is misplaced and the wrong options are considered.

It could be argued that the impairment experienced by the mOFC-lesioned animals reflected only a deficit in representing value per se rather than an impairment of comparison and decision-making. The counter argument is that the animals still appear to have some representation of value as its influence on behaviour remain intact after mOFC lesions (Figure 5.6). The average value of the environment influences response vigour, as well as the speed with which responses are made (Niv et al., 2007) and this also remains the case after mOFC lesions.

We therefore suggest that the mOFC encodes value in a multi-dimensional manner. As a critical region in a decision-making network, one of its roles might be to represent the values of outcome goals under consideration. This process might influence the decision process, potentially through interactions with the amygdala (De Martino et al., 2006), so as to discard distracting values from consideration in order to confine the decision-space to the most relevant options. The mOFCs connections to the ACC might then serve to convey the decision to the action selection network and so to bias subsequent behaviour (Cavada et al., 2000).

CHAPTER 6: THE CONTRIBUTION OF PREDICTABLE REWARDS TO HUMAN VISUOMOTOR ASSOCIATIVE LEARNING

Anticipating the outcome of your choice is critical for guiding behaviour. The formation and maintenance of these learned expectations has been investigated in macaque and rat studies and their acquisition has been associated with improved behavioural accuracy. However, studies in humans are rare as it has often been difficult to prove that outcome consistency facilitates learning. The current study sought to investigate learned expectations, acquired through a goal-directed learning mechanism, using a novel version of the Differential Outcomes Procedure adapted for humans. We combined pre-conditioning stimulus-outcome and response-outcome exposure phases with final stimulus-response learning. During each phase we manipulated the consistency of the outcomes which followed individual stimuli and actions. Predicable outcomes were found to significantly improve learning and recall of visuomotor associations. These results imply that a specific expected outcome can act to guide a selective human behavioural response.

6.1 Introduction

Learned expectations are the basis for many higher order cognitive functions. They can be the result of a number of associations (stimulus–outcome [S-O], stimulus–response [S-R], response–outcome [R-O]) that collectively become the building blocks for trial-and error learning and memory foundation. Once established, they are instrumental in the planning of a choice or an

action and in multi-option environments. Indeed, knowing which option is associated with a desired reward is fundamental for optimal decision-making.

Classic learning theories emphasise the S-R system originally advanced in Thorndike's (1911) 'Law of Effect'. Central to this idea is that the presentation of a reward shortly after the performance of an instrumental action strengthens or reinforces an association between the stimuli present when the response was performed and the response production mechanism. The result is that these stimuli become capable of eliciting the response. However, in response to a number of limitations of this theory, not least the inability of this model to encode the causal relationship between an action and a reward, an additional learning mechanism was proposed. This additional learning mechanism explained a number of early experimental results, namely from devaluation studies, which had emphasized the importance of the outcome in guiding choices and actions (Adams and Dickinson, 1981; Colwill and Rescorla, 1985; Rescorla, 1990; Balleine and Dickinson, 1991; Rescorla, 1992; Balleine and Dickinson, 1998).

One particularly interesting finding is that learning and memory recall are improved when distinct outcomes are available after particular contingent responses. This was first demonstrated in rats that had to learn to press either a right or left lever, inserted into an operant chamber: in the presence of either an auditory tone or clicker. If the animal made the left response in the presence of the clicker it received sucrose solution. If, however, the rat made the right lever response in the presence of the tone solid food was delivered. This paradigm is commonly referred to as the Differential Outcomes Procedure (DOP). The rat's ability to learn the S-R associations in this condition is compared to a condition in which the same food type is delivered (Non-differential Outcomes Procedure; NOP). Typical findings show that animals in the differential-outcomes condition have more rapid learning curves than animals in control

conditions, where the outcome of the event provides no cue to the appropriate action (Trapold and Overmier, 1972; Urcuioli, 2005). This procedure has been shown to facilitate both the initial learning of conditional relationships (as trained in the manner described above) and memory for the conditional stimuli in delayed matching-to-sample tasks (Brodigan and Peterson, 1976). Across species, this finding has been replicated in a number of additional studies with rats (Carlson and Wielkiewicz, 1972; Jones and White, 1994), pigeons (Schmidtke et al.; Kelly and Grant, 2001), horses (Miyashita et al., 2000) and monkeys (Easton and Gaffan, 2002). This effect has become known as the differential outcomes effect (DOE).

The nature of the DOEs mechanism is thought to act by allowing subjects to learn to predict which outcome will be delivered when a correct choice response is made, in order to develop a distinct expectation of each unique reward event, upon the presentation of a stimulus (Savage, 2001). When a sample stimulus is presented, a "representation" of the unique reward associated with it is activated, and serves as an expectation of the forthcoming reward. As learning progresses, each sample stimulus in the set comes to activate an outcome expectancy that is unique to that stimulus. These differential expectancies thus provide an additional source of information for choosing the correct response. Manipulating reward contingences in this manner therefore serves to dramatically facilitate learning and memory.

Given the power of the DOE to facilitate learning in so many species it is curious that the effect has been so rarely reproduced in humans. Match-to-sample studies in young children have shown that differential outcomes, such as tokens of different colours which represent rewards of either toys or food, facilitate learning (Maki et al., 1995; Estevez et al., 2001). Interestingly, older children and adults, when tested under easy match-to-sample conditions, do not demonstrate the DOE (Estevez et al., 2007; Lopez-Crespo et al., 2009). Increasing task difficulty

has however shown to produce a DOE accuracy advantages in older children and adults (Estevez et al., 2003; Estevez et al., 2007).

Easton (2004) used a biconditional discrimination task, adapted from the task used by Easton and Gaffan (2002), which reported differential reinforcement effects in monkeys. Briefly, this task had two sets of instruction cues: immediate and delayed correct feedback. During the task, two stimuli from the same set were presented simultaneously, and one stimulus was arbitrarily deemed correct and one incorrect. If the stimulus came from the immediate set, and the subject selected the correct stimulus, they were immediately reinforced by an auditory tone indicating a correct choice had been selected. In contrast, if the incorrect choice object was selected no feedback was delivered. If an instruction cue was presented from the delayed reinforcement set, and the subject chose the correct choice object, the tone was sounded after 1.5secs. Similarly, incorrect feedback was the same as the immediate cue sets. Subjects were required to learn six independent instruction cue-choice object associations in a successive manner, interspersed with recall test stages where subjects were assessed while they responded to all six of these choice problems. There were also two successive transfer stages, in which half of the choice problems were presented concurrently with a new instruction pair (one delayed and one immediate reinforcement). Learning was compared to a control conditional discrimination task, in which correct feedback was always an immediate tone and incorrect feedback was no auditory tone. Easton found, in this version of the task for humans, the only effect of differential outcomes on learning was during the second transfer phase of the experiment. The re-learning of associations between instruction cue and choice object was improved in the differential outcome condition compared to non-differential conditional learning.

There are a number of caveats to be borne in mind when considering this experiment which may have contributed to the limited DOE. Firstly, the results may be subject to a floor effect, due to the very few numbers of associative learning problems, and as mentioned above, latency or accuracy improvements are only found in humans in particularly challenging tasks (Estevez et al., 2007). Secondly, whilst studies in animals have shown that delayed and immediate outcomes can serve as differential outcomes (Astley and Wasserman, 1999; Astley et al., 2001), in humans this may not be the case. Finally, the outcomes given to subjects were only auditory tones which did not translate to any meaningful reward. It is therefore possible subjects were not motivated to utilize the differential outcomes.

The current study sought to investigate differential reward expectations and their effect on human learning, in a challenging conditional discrimination task. To do so, two groups of subjects were given twelve S-R associations to learn. In one group of *Consistent* subjects S-R associations were differentially rewarded with one of four outcomes which took the form of distinct gift vouchers. In the other group, a control group of *Inconsistent* subjects, rewards for correct S-R selections were randomly selected from one of the four potential outcomes. Two pre-conditioning phases were included in the design in order to enforce the outcome expectations of the two groups. These phases involved exposing subjects, sequentially, to the stimuli in a choice based problem with distinct S-O associations for the Consistent subjects and random S-O associations in the Inconsistent subjects. Similarly, subjects explored response buttons, where the R-O relationships were differential in the Consistent condition and random in the Inconsistent condition. The paradigm was designed in such a way to allow us to investigate whether subjects in the Consistent condition made use of outcome-specific reward expectations to guide their

behaviour, and if by doing so their speed, or accuracy of learning was improved when compared to subjects who could not form learned expectations.

6.2 Methods

Subjects

All subjects gave informed consent to participate in the investigation, which had been approved by the Central Office for Research Ethics Committee (COREC reference number: 05/Q1606/96). 36 right-handed subjects, 16 of whom were men completed the experiment. Collectively subjects had a mean age (and standard deviation) of 25.14yr (4.20). All had normal or corrected-to-normal vision and indicated no family history of psychiatric or neurological disease.

Task and procedure

Reinforcement outcomes took the form of visually presented pictures of gift tokens that were converted into a payment at the end of the experiment. Each subject was asked to rate and choose four distinct gift vouchers to collect from a set of twelve. For each subject we aimed to select gift vouchers which were associated with very different classes of consumables; food, beverages, books or music. Therefore the four most preferred tokens, which fitted within these constraints, were then used as rewards for correct choices in all the subsequent behavioural sessions performed by that subject.

Stage 1: Stimulus-outcome learning task

The first stage of the experiment for all subjects was a concurrent visual discrimination learning task consisting of 12 pairs of visual stimuli. One stimulus in each pair was designated the correct one and choices of it were rewarded with presentation of a reward token. Correct choices of a

given stimulus were always rewarded with a given token outcome for subjects assigned to the Consistent group. In the Inconsistent group, however, correct choices were rewarded with one of the four tokens selected at random (Figure 6.1a, A, S-O phase). On completion of stage 1 subjects in both the Consistent and the Inconsistent groups had learned 12 visual discrimination problems and had learned that 12 visual stimuli were associated with reward. Only subjects in the Consistent group, however, would have been able to form an association between each stimulus and one of four types of reward.

Stage 2: Response-outcome learning task

In the second stage of the experiment subjects explored four button press responses, which were either paired consistently with specific token reward outcomes (Consistent), or random token reward outcomes (Inconsistent; Figure 6.1b, B, R-O). On completion of stage 2 subjects in both the Consistent and Inconsistent groups had learned that all four actions were rewarded when made but only subjects in the Consistent mapping group would have been able to form an association between each response and one of the four types of reward.

Stage 3: Stimulus-outcome repetition task

Subjects then completed an additional 24 trials of the S-O part of the experiment. This was incorporated because of the fixed order of experimental events and allowed us to assess how well the subjects had learned the initial discrimination.

Stage 4. Stimulus-response learning task

Subjects were then required to learn S-R associations as they learned to pair together the stimuli they had seen in stage 1 with the buttons they had explored in stage 2 (Figure 6.1c). Choice of the correct response, for a given S-R pairing was either consistently rewarded with a given reward token outcome (Consistent condition), or randomly rewarded with any of the four

possible reward token outcomes (Inconsistent condition). For subjects in the Consistent condition a given stimulus was always rewarded with given token outcome both at stage 1, 3 and at stage 4 and a given response was always rewarded with a given token outcome both at stage 2 and stage 4. In other words, the component parts of a correct S-R pair rewarded by, for example, a Starbuck's token, at stage 4, would have also both been rewarded by a Starbuck's token in stages 1, 2 and 3. The S-R learning task ended when a criterion of 95% correct performance was reached. For subjects in the Inconsistent group response selection could only be achieved via a direct S-R association. For subjects in the Consistent group response selection could also be based on an indirect link mediated by an S-O association and an O-R association.

The following day, subjects returned to the laboratory and were given sufficient trials in order to reach the same criterion level of performance using the same S-R associations that had been learned on the previous day. They were then also asked to complete the first three parts of the experiment with a new stimulus set, the same reward outcome tokens, and the same response buttons. Response-reward token associations remained consistent across the two sets of tasks for subjects in the Consistent group. The final S-R association learning tasks was performed in a Siemens 3T scanner, and the neural mechanisms mediating reward-guided action selection will be presented and discussed in Chapter 7. Blocks of the previously learned S-R associations (*Old* learning task) were interspersed pseudo-randomly with blocks of the novel stimuli, when subjects were learning, by trial-and-error, the new S-R associations (*New* learning task), and blocks of rest (Figure 6.1d). During the final S-R learning phase, as before, rewards were either given in a consistent manner for a given S-R association (Consistent condition) or randomly (Inconsistent condition). Each experimental block consisted of nine stimuli and lasted in total 40.5secs. Before each experimental block began it was cued for two seconds with "Today's

pictures" (New learning task), "Yesterday's pictures" (Old learning task). There were a total of 216 trials per experimental condition. Rest blocks were 30s in length. At the end of the experiment the total reward tokens were converted into the appropriate monetary payment and rounded to the nearest whole number.

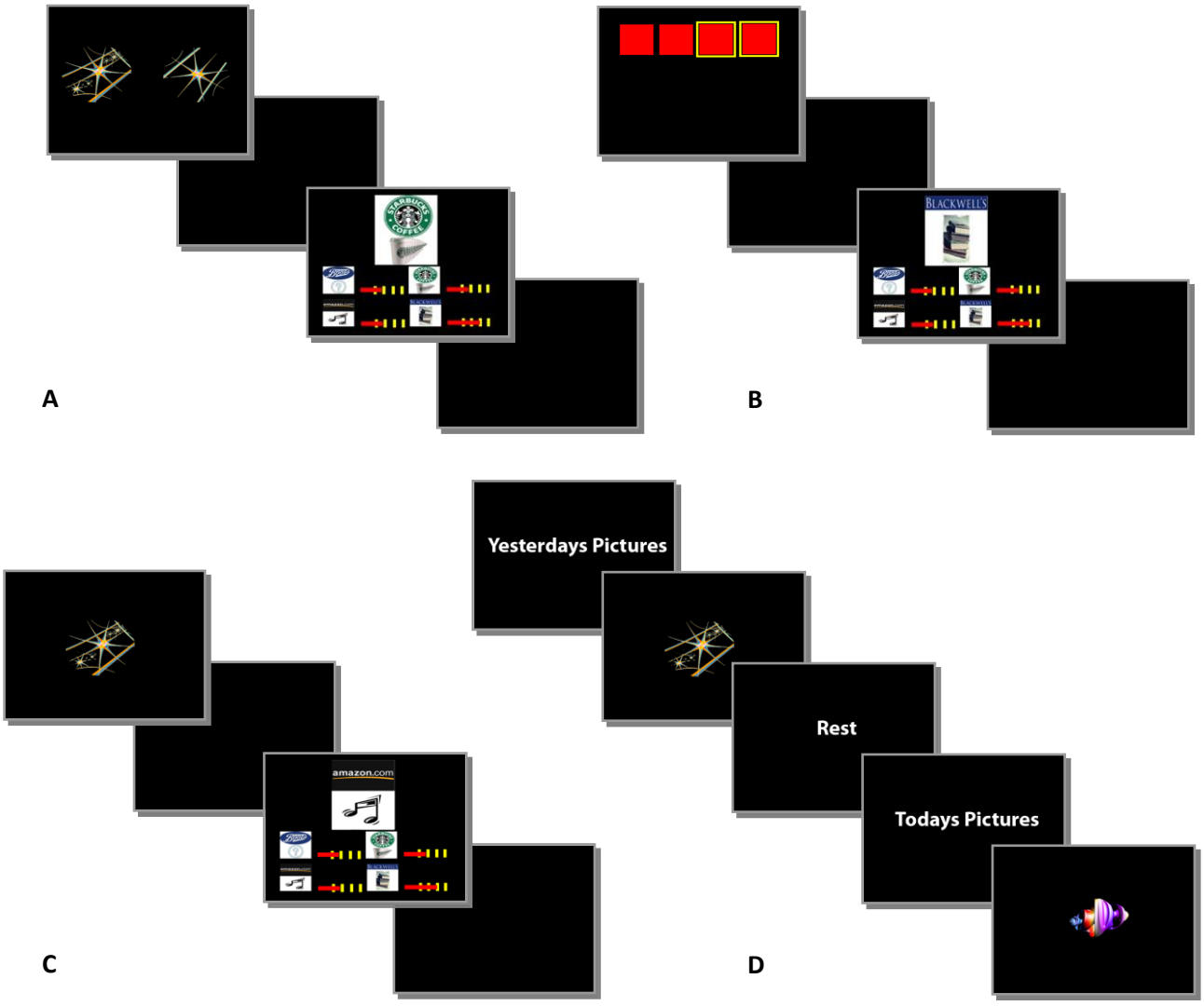

Figure 6.1. (A-C) Schematic representation of the trial events for each phase of Experiment 2. A-C, Timing of stimulus events was the same for all phases of the experiment. Either a pair of stimuli (Stage 1 and 3: Stimulus-outcome: A), four red squares corresponding to the four possible button responses subjects could make, (Stage 2:

Response-outcome: B) or a single stimuli (stage 4: Stimulus-response learning: C) was presented on screen for 1000ms.Subjects were required to either identify which stimulus was rewarded and indicating the side of the screen it was presented on with a corresponding button press (A), or select one of the response buttons that corresponded to one of the high-lighted red squares (B). In stage 4, the Stimulus-response learning phase (C) subjects had to identify which of the four possible responses was rewarded after presentation of each stimulus. Subjects always had the duration of the stimulus presentation and an additional 500ms in which to respond. Feedback was the same regardless of experimental phase. The outcome of the subject's choice was presented. Four money bars reflected the cumulative total of earnings of each token type up until that point in the task. The feedback screen was visible for 1500ms and then immediately replaced by an inter-trial interval (ITI) of 1000ms long. D, Schematic representation of the order of events in the fMRI phase of the experiment. Blocks of trials were presented in a pseudorandom order each consisting of either nine trials of old stimuli (already learned on the previous day) or nine trials of new stimuli (learned during the course of scanning). Each block lasted 45 seconds and was cued for 2 seconds with 'Yesterdays pictures' or 'Todays Pictures' for old and new stimuli respectively. Trial events within these blocks were the same as C. 30 second rest blocks were interspersed within the experiment.

Data acquisition

Stimuli were presented using Presentation (Neurobehavioral Systems, Inc. Albany, CA. Version 0.53 Build 12.05.02) on a Windows 2007 operating system on a MacBook computer (Apple Cupertino, CA).

Data Analysis

Accuracy data were analysed using Excel (Microsoft Office Excel 2003), Matlab 6.5 (MathWorks) and SPSS software (SPSS inc. version 14.0). In general all analyses were conducted with standard parametric ANOVAs, that used the Huynh-Feldt correction where appropriate, and standard two-sample t-tests.

Day 1

The number of correct trials in stage 1, the S-O learning phase, was compared in a two-sample t-test. Response choice was analysed for stage 2, the R-O phases, using a repeated measures 1-way ANOVA with Response (4 levels; 4 responses) and the between subjects factor of Group (2 levels; Consistent and Inconsistent).

The size of the outcome-specific learning effect was calculated for day 1. The percentage of trials performed correctly during the first 3 blocks, each consisting of 36 trials, were calculated and compared between the Consistent and Inconsistent conditions with 2-tailed independent samples t-tests.

Day 2

Accuracy in the S-O phase and response choice in the R-O phases was calculated in the same manner as described above for day 1.

The retention of S-R associations learned on day 1 was measured by calculating the percentage of trials performed correctly for the first 24 trials of the pre-scanning recall session 24 hours after the initial training. One-tailed independent samples t-tests were used to compare the two groups of subjects in the Consistent and Inconsistent conditions.

The accuracy of subjects on day 2 was calculated independently for the New and Old stimulus sets by determining the percentage of correct trials in 6 larger blocks consisting now of 36 trials. The log-transformed scores for the Old and New tasks for both groups of subjects were subjected to a 3-way ANOVA of Task (Old; New), by Time (six blocks of 36 trials) and with the between-subjects factor of Group (Consistent; Inconsistent). Independent samples t-tests were used to further investigate the effects.

6.3 Results

Day 1

Subjects in the Consistent and Inconsistent groups were equally accurate in selecting the rewarded stimulus of a pair in the primary S-O learning phase (t_{34}=0.71, p=0.482), and during the stage 3 S-O repetition phase (t_{34}=0.25, p=0.640), regardless of their group. Investigation of the distribution of response choices in the R-O learning phase also did not suggest a group difference ($F_{1,34}$=0.12, p=0.746) or an interaction with a particular choice of response ($F_{1,34}$=102=0.661, p=0.422). However, there was a significant effect of Response ($F_{3,102}$=6.89,p=0.000).

	R1	R2	R3	R4
Consistent	0.32(0.03)	0.28(0.02)	0.21(0.02)	0.19(0.03)
Inconsistent	0.28(0.02)	0.28(0.02)	0.24(0.02)	0.20(0.02)

Table 6.1. Means (and standard deviations) of the distribution of responses across the four response options on day 1 of R-O learning. Whilst there is no main effect of Group there is a significant main effect of Response with both groups preferring option 1 to option 4 in a linear manner. (N=36)

Figure 6.2 shows the size of the outcome-specific learning effect; comparing percentage accuracy within the first three blocks of pre-scanning training. Comparing the blocks with independent samples t-tests revealed a significant difference in the first block indicating that subjects in the Consistent condition were more accurate over the first 36 trials than those in the Inconsistent condition (t_{34}=2.07, p=0.046). By the second and third block the groups were equally accurate (Block 2; t_{34}=-0.033, p=0.0974, Block3; t_{34}=0.681, p=0.501).

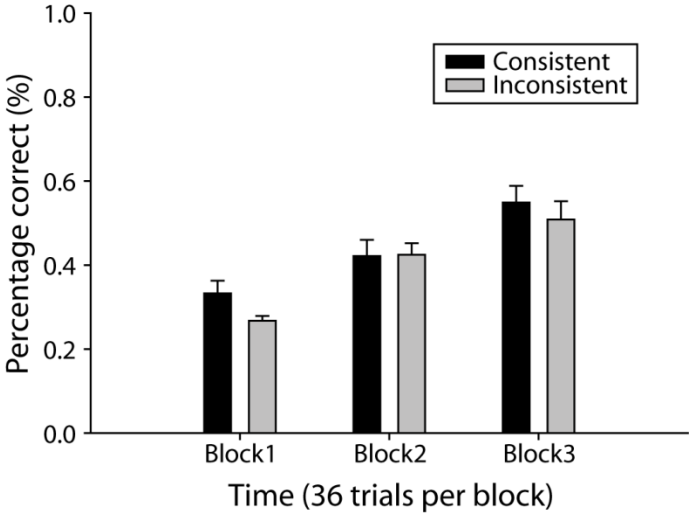

Figure 6.2. Mean percent correct of trials over the first 3 blocks (36 trials per block) of S-R associative learning on day 1. Subjects in the Consistent and Inconsistent Groups are represented by the black and grey bars respectively (n=36).

Day2

If learning of S-R associations was initially facilitated by knowledge of specific S-O and O-R associations it might be hypothesised that memory recall would also be improved. Figure 6.3 shows the accuracy of S-R retention in the first 24 trials, 24hrs after the initial training. An independent t-test confirmed that accuracy was significantly higher in the Consistent group (1-tailed t_{34}=1.74, p=0.046).

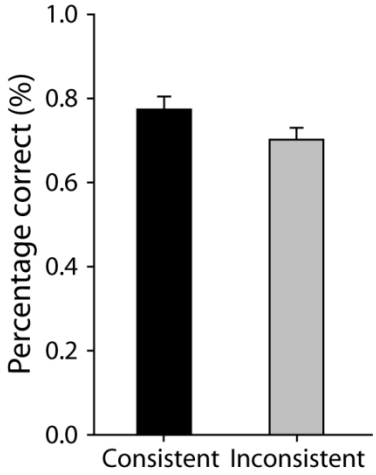

Figure 6.3. Mean percent correct for the first 24 trials of S-R associative recall on day 2. Subjects in the Consistent and Inconsistent Groups are represented by the black and grey bars respectively (n=36)

There were no differences between the groups in their learning of the new stimulus discriminations on day 2. Similar to the results acquired on day 1 there were no group differences in the percentage of trials performed correctly in the initial S-O learning phase (t_{34}=0.25, p=0.640) or stage 3 repetition S-O phase (t_{34}=0.30, p=0.898). The distribution of response choices in the R-O learning phase, again, did not suggest a group difference ($F_{3,102}$=0.20, p=0.656), or an interaction with a particular choice of response ($F_{1,34}$=0.69, p=0.539). There was however, again, a significant effect of Response ($F_{3,102}$=7.05,p=0.001).

	R1	R2	R3	R4
Consistent	0.34 (0.03)	0.26 (0.02)	0.22 (0.02)	0.19 (0.02)
Inconsistent	0.30 (0.04)	0.27 (0.02)	0.25 (0.02)	0.19 (0.02)

Table 6.2. Means (and standard deviations) of the distribution of responses across the four response options on the second day of R-O learning. Whilst there is no main effect of Group there is a significant main effect of Response with both groups preferring option 1 to option 4 in a linear manner. (N=36)

Percentage accuracy scores for the S-R associative learning task acquired on the second day resembled those from day 1 and are shown in figure 6.4. There was a significant advantage of having been trained with Consistent reward outcome mappings as opposed to Inconsistent reward outcome mappings as a repeated measures ANOVA revealed a 3-way interaction of the three factors ($F_{5,34}$=2.67, p=0.043). This was significant for the New stimulus task in a two-way ANOVA, revealing a Time by Group interaction ($F_{5,34}$=2.67, p=0.039). There was no such interaction in the Old stimulus task (Time x Group $F_{5,34}$=0.41, p=0.803). The first block of the New stimulus task was tested with a one-tailed independent samples t-test, which showed that subjects in the Consistent condition were more accurate than those in the Inconsistent condition (t_{34}=1.80, p=0.040).

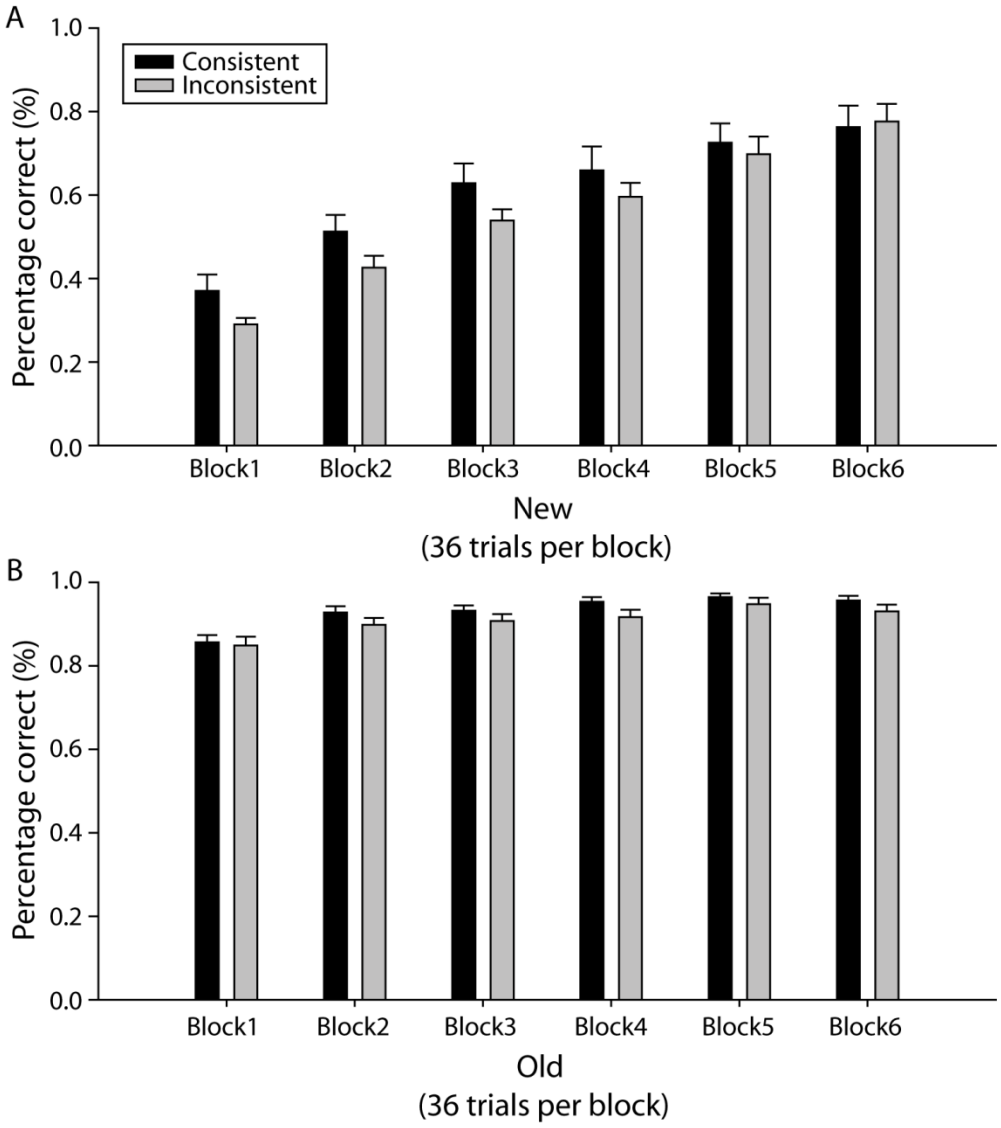

Figure 6.4. Mean percentage correct on day 2 for the 6 blocks (36 trials per block) of S-R associative learning of the New (A) and old (B) stimuli for the Consistent and Inconsistent Group (black and grey bars respectively), (n=36).

6.4 Discussion

The present study has shown a facilitation in the speed of learning and the accuracy of memory recall when subjects have access to outcome-specific reward expectations during S-R learning.

We developed a novel version of the DOP by introducing preconditioning phases which allowed subjects to initially learn S-O and R-O associations prior to learning the S-R associations. We compared subjects trained under this schedule with subjects trained in environments where outcomes were random after choices. A number of species of animals (Schmidtke et al.; Carlson and Wielkiewicz, 1972; Jones and White, 1994; Miyashita et al., 2000; Kelly and Grant, 2001; Easton and Gaffan, 2002) and human under certain match-to-sample conditions (Maki et al., 1995; Estevez et al., 2001) have been shown to benefit, in terms of accuracy and speed of learning, when outcome-specific reward expectations are available to guide behaviour, and now we have demonstrated that this effect in humans generalises to other learning paradigms.

We have shown that subjects learned two sets of novel S-R problems faster if there were consistent S-R-O associations. Although the DOE on the second day was stronger than on the first, this cannot be wholly explained by the subjects' previous experience of S-R learning as the same effect is visible even during the very first blocks in the first learning sessions. Similarly, we were also able to demonstrate an advantage on memory recall of S-R associations after 24hrs for subjects trained with outcome-specific reward expectations.

Despite the deviations of the current paradigm from the standard methods of investigating the DOE in animals, in either match-to-sample or training experiments, we believe our results are compatible with animal studies. Indeed, we propose that the paradigm used in the current experiment adopted a number of critical features which allowed our subjects to make use of outcome-specific reward expectations. First, we challenged our subjects with 12 pairs of S-R associations each day. This number is well beyond Millers magic number 7+/- 2 (Miller, 1956). It may be the case that the benefits of outcome-specific expectations are only apparent in more difficult learning environments. Indeed, the DOE in young children only becomes apparent in

older children when match-to-sample tasks are made more challenging by increasing the number of comparison stimuli (Estevez et al., 2001). Similarly, in healthy adults, accuracy advantages with the DOP are only seen after increasing task difficulty in a symbol judgment task (Estevez et al., 2007). Secondly, we introduced preconditioning phases which served to emphasize the different outcomes for each S-R association in the Consistent condition. Whilst this manipulation has not previously been used in standard DOP it is likely that reward expectations, if available, will guide action selection in a similar manner regardless of the precise way in which they were established. Finally, we used monetary gift vouchers instead of primary rewards to differentiate outcomes. We chose gift vouchers which the subjects had themselves rated as highly rewarding. Human subjects may have been more motivated to perform the task well than would have been the case had juice rewards been used. For each subject we also aimed to select gift vouchers which were associated with very different classes of consumables; food, beverages, books or music. We believe that by doing this we made the task more engaging for subjects. The current study showed images of the outcome types to the subject as positive feedback but it should be noted that experiments with human children have shown that even abstract different coloured tokens, each colour associated with a different class of reward, is an effective means of differentiating outcome s (Estevez et al., 2001). It may be important that future work replicates this experiment using primary reinforcers. Doing so would have the added benefit of being able to determine if subsequent devaluation of an outcome led to a predictable pattern of stimulus selection in a choice task in extinction.

A question of particular importance is whether the DOP could be used to enhance the memory performance of brain damaged populations. Amnesic patients have great difficulty laying down new memories; particularly explicit memories. Savage and Laglais (1995)

implemented the DOP in a T-maze matching-to-position task with an amnesic rat model (Pyrithiamine-induced thiamine deficiency; PTD). The authors show that the PTD rats were severely impaired in learning under a NOP schedule relative to controls, but that this deficit was attenuated, and all but disappeared, when differential outcomes were introduced. Similarly, a follow-up study showed attenuated effects of normal memory impairments due to aging when older rats were trained under the DOP as compared to the NOP and to younger rats. This research raises the possibility that amnesic human patients may benefit from rehabilitation protocols that incorporate elements of differential outcomes. Indeed, Lopez-Crespo and colleagues (2009) demonstrated this very age dependent DOE in humans. Whilst younger adults were found not to take advantage, in terms of their accuracy, of the differential outcomes, the older adults' accuracy increased to that of the younger people's under DOP conditions. The DOE is also evident in adults with learning difficulties. Estevez et al (2003) has shown that differential reinforcements can ameliorate discriminative learning deficits in people with Down's Syndrome. As such, the paradigm used in the current experiment could be easily adapted for use in patients and aged populations, and be used to investigate whether the DOE might relieve learning and memory problems in more complex learning environments.

The data presented above adds to the growing evidence that two distinct neural mechanisms mediate response selection when outcome-specific reward expectations are available. One possibility is that a goal-directed component learns the associations between stimuli, responses and the incentive value of outcomes (S-O, R-O or S-R-O), while a habit-based learning component learns the associations between the stimulus (or context) and the response (S-R). It could be that our Consistent subjects trained under the DOP are able to utilize a goal-

directed and habitual learning mechanism to complete the task whereas Inconsistent subjects would only have access to the habitual learning mechanism.

An alternative theory to the goal-directed learning mechanisms proposes that the dual memory system theory of explicit and implicit memory can explain the DOE enhancements in learning and memory performance (Overmier and Linwick, 2001; Savage, 2001). Explicit memory describes the system that processes the intentional recall and recognition of people, places, things and events. In contrast, implicit memory refers to the process of unintentional learning. This perspective assumes that the DOP taps into the implicit memory system, whereas the explicit memory system is used to solve memory problems with the NOP. It has been argued that the DOP produces unique reward expectations, via classical conditioning (S-O), and that these are discriminable and have predictive value. Therefore after multiple learning trials, the presentation of the sample stimulus itself can result in an activation of the representation of the unique reward. Reward-related learning evokes additional neurobiological substrates including the OFC, amygdala and striatum, when added to an operant task (Kesner and Williams, 1995; Pratt and Mizumori, 1998; Schoenbaum et al., 1999; Baxter et al., 2000) and damage to either the OFC or amygdala has been shown to impair performance during S-R learning under DOP, but not NOP (Ramirez and Savage, 2007). This recruitment, it has been claimed contributes to the activation of the alternative implicit memory system used by the DOP, which is different from the system commonly used to solve conditional discrimination tasks.

If explicit and implicit memory systems are mediating NOP and DOP independently then there should be evidence that disruption to each system should impair learning under the two conditions. Indeed, explicit memory is disrupted by challenges to the cholinergic neurotransmitter system (Schliebs and Arendt, 2006) and it has been shown in elderly human

subjects that under these circumstances NOP performance is impaired. However, if subjects are able to utilise differential outcomes to guide learning i.e. DOP conditions, performance is no different to controls. Similarly, there is also evidence in rats that two different neurotransmitters mediate the DOP and NOP learning systems differentially. Savage and Parson (1997) have shown that learning under DOP is disrupted by challenges from glutamatergic antagonists, whereas learning under NOP is disrupted by cholinergic antagonists. The reverse impairments are not seen in these animals.

It may be the case that the two lines of theoretical reasoning, goal-directed and implicit memory, are not mutually exclusive. It is possible that goal-directed learning and subsequent choices relies on an implicit memory system, which itself recruits or receives reward-related information from specialised regions of the brain. The following chapter aims to address the questions into the neural mechanisms mediating outcome-specific learning. We used the behavioural study outlined above and fMRI to investigate cerebral activity during the final S-R learning phase on the second day of testing.

CHAPTER 7: NEURAL MECHANISMS MEDIATING REWARD-GUIDED ACTION SELECTION

The formation and maintenance of learned reward expectations has been investigated in macaque and rat lesion studies. This process appears to rely on a number of cortical and subcortical regions including the orbitofrontal cortex (OFC), temporal cortex and amygdala. However, this network is still not well understood, particularly in humans. We used a novel Differential Outcomes Procedure described in Chapter 6, which combined initial pre-conditioning stimulus-outcome and response-outcome learning phases with a final stimulus-response learning phase. During each phase we manipulated the consistency of the outcomes which followed stimuli and actions. Functional magnetic resonance imaging was used to investigate the neural mechanisms underlying the behavioural accuracy advantage bestowed when outcomes which follow actions are consistent across learning. The results indicated that three areas commonly involved in reward-guided learning, the lateral OFC (lOFC), medial orbitofrontal/ventromedial frontal cortex (mOFC/vmPFC) and anterior cingulate cortex (ACC) were activated by the task. We show that each of area's contribution can be dissociated, with only the lOFC and ACC more active in subjects with knowledge of reward consistency.

7.1 Introduction

Monitoring, learning, and updating the expected value associated with environmental stimuli are essential for optimal decision-making. Three frontal cortical areas are implicated in reward-guided learning and decision-making: ACC, mOFC/vmPFC, and lOFC but how their

contributions differ remains unclear (Rushworth et al., 2007a; Hare et al., 2008; Rushworth and Behrens, 2008; Rangel and Hare, 2010). We attempted to examine their functions in a reward-guided learning task in which type of reward outcome, and not just presence or amount of reward, could influence action selection.

The OFC is thought to be critical for processing negative outcomes (Kringelbach and Rolls, 2004; Fellows, 2007), and inhibiting previously rewarded actions, such as after a reversal or devaluation (Jones and Mishkin, 1972; Dias et al., 1997; Elliott et al., 2000; Chudasama and Robbins, 2003; Clarke et al., 2008). Furthermore, beyond simply encoding an outcome's scalar value, it appears that the OFC is capable of encoding an outcome's identity. Devaluation studies have shown that, under normal circumstances, a stimulus associated with a once valued outcome will be chosen less frequently if that outcome becomes devalued through satiation (Adams and Dickinson, 1981; Colwill and Rescorla, 1985; Rescorla, 1990; Balleine and Dickinson, 1991; Rescorla, 1992; Balleine and Dickinson, 1998). In contrast though, subjects with OFC damage continue to choose equally between the options (Gallagher et al., 1999; Pickens et al., 2003; Izquierdo and Murray, 2004; Pickens et al., 2005). This has been interpreted as suggesting that OFC animals are incapable of representing the causal relationship between a stimulus, response and a specific outcome. Response selection is often thought to be mediated by S-R associations but distinct outcomes, represented in the OFC could provide part of an additional route, involving both S-O and O-R associations, by which responses might be selected.

Recent evidence suggests macaque lOFC and mOFC, which have distinct anatomical connections (Ongur and Price, 2000), have distinct functions (Walton et al., 2010; Noonan et al., in press). LOFC is critical when macaques learn and assign credit for reward occurrence to a specific stimulus. Our first aim was, therefore, to examine whether lOFC might also be

implicated in learning associations between specific stimuli and specific *types* of reward. We used the novel version of the Differential Outcomes Procedure (DOP), described in Chapter 6 which manipulated reward contingencies associated with specific S-R associations (Savage, 2001; Trapold, 1970; Trapold & Overmier, 1972; Urcuioli, 2005). The behavioural results described in the previous chapter demonstrate, that similarly to monkeys and rats trained under the DOP (Schmidtke et al.; Carlson and Wielkiewicz, 1972; Jones and White, 1994; Miyashita et al., 2000; Kelly and Grant, 2001; Easton and Gaffan, 2002), subjects who had the potential to develop and to use outcome-specific reward expectations to guide action selection benefited in terms of S-R learning and memory facilitation (the Differential Outcomes Effect; DOE).

Lesion work in rats suggests that the neural mechanisms which support behavioural advantages include the basolateral amygdala and the OFC. Damage to the amygdala impairs a rat's performance throughout the task, while OFC lesions impair accuracy only in the later maintenance phase (Ramirez and Savage, 2007). To investigate the neural mechanisms underlying the behavioural advantage in our Consistent subjects we collected functional magnetic resonance image (fMRI) scans while the two groups of subjects learned to select responses either in the context of differential or non-differential outcomes. If lOFC is important for learning associations between specific stimuli and outcome types then lOFC activity will be greater in the differential outcome group whenever an outcome is delivered that informs subjects about those associations.

As part of the investigation of the role of the lOFC we also tested whether the functional connectively between this region and the rest of the brain would change as a result of the availability of differential outcomes in learning. We therefore conducted a PPI analysis, and hypothesised that temporal cortex, including perirhinal cortex and the amygdala, regions which

are repeatedly implicated in value-guided learning (Buckley and Gaffan, 1997, 1998; Gaffan et al., 2000; Murray and Richmond, 2001; Lee et al., 2006; Aggleton et al., 2010) and visual object recognition and discrimination (Gaffan et al., 1993; Baxter et al., 2000; Baxter and Murray, 2002; De Martino et al., 2006; Hampton et al., 2007; Ramirez and Savage, 2007), would show increased functional connectivity between this region and the lOFC during feedback.

Comparison studies of the DOE in humans, with either training or matching-to-sample paradigms, are rare (Easton, 2004; Estevez et al., 2007) possibly because tasks have to be particularly challenging to elicit behavioural effects of differential outcomes. As a result, investigations into the neural mechanisms mediating the acquisition of learned expectations in humans are particularly sparse. These human fMRI studies tend to focus on reward-guided processes once learning has taken place or have confounded learning with choice or conflict and typically find outcome-specific value expectation represented in the vmPFC (Valentin et al., 2007; de Wit et al., 2009). The second aim was to examine whether activity in other frontal areas was concerned with other aspects of a reward's influence on behaviour. The differential outcome procedure allowed testing not only of whether mOFC/vmPFC activity reflected how *informative* an outcome was for updating reward-related associations but alternatively whether it reflected the differing *values* assigned to outcomes (Plassmann et al., 2007; Lebreton et al., 2009).

The ability to monitor and compare ongoing actions as well as performance outcomes with internal goals and standards is critical for optimising decision-making. We therefore also compared the mechanisms mediating successful response retrieval by examining brain activity that changed with increasing response accuracy as a function of whether or not subjects had had the opportunity to learn specific O-R associations (because of their membership of the Consistent and Inconsistent mapping groups). The ACC has been shown to have a role in this function. This

region shows increased activation when subjects explore reward environments, and when feedback is received as a consequence of an explorative action (Walton et al., 2004; Daw et al., 2006; Forstmann et al., 2006; Yoshida and Ishii, 2006). Our third aim was to investigate the ACCs role in reward-guided action selection. If ACC is critical for reward-guided action selection (Rudebeck et al., 2008b) then its activity should reflect the changing probability of selecting correct responses during learning in the context of the DOE.

7.2 Methods

Subjects

The same 36 right-handed subjects (16 males) described in chapter 6 also participated in the present fMRI experiment. Collectively, subjects had a mean age (and standard deviation) of 25.14yr (4.20). All had normal or corrected-to-normal vision and indicated no family history of psychiatric or neurological disease. All subjects gave informed consent to participate in the investigation, which had been approved by the Central Office for Research Ethics Committee (COREC reference number: 05/Q1606/96).

Task and procedure

The task and experimental procedure of this experiment has been described in the previous chapter. Briefly, either a pair of stimuli (stimulus-outcome phase: stage 1 and 3), four red squares corresponding to the four possible button responses subjects could make, (response-outcome phase: stage 2) or a single stimuli (S-R phase: stage 4) was presented to a subject (see Table 7.1 for details). Subjects were required to either identify which stimulus was rewarded and respond by indicating which side of the screen it was presented on with a corresponding button press

(stage 1 and 3), or in response to a red square, select one of the response buttons that corresponded to one of the high-lighted red squares (stage 2). In the S-R phase (stage 4) subjects had to identify which of the four possible responses was correctly rewarded after presentation of a specific stimuli.

Day	Stage				
1	1 (S-O OLD)	2 (R-O)	3 (S-O OLD repeat)	4 (S-R OLD)	
2	4 (S-R OLD recall)	1 (S-O NEW)	2 (R-O)	3 (S-O NEW repeat)	4 fMRI (S-R OLD+NEW)

Table 7.1. Representation of the experimental phases. Over two days subjects initially completed a phases of stimulus-outcome learning of 24 stimili. Timing of stimulus events was the same for all phases of the experiment. Either a pair of stimuli (Stimulus-outcome phase: stage 1 and 3), four red squares corresponding to the four possible button responses subjects could make, (Response-outcome phase: stage 1) or a single stimulus (S-R: stage 4) was presented on screen for 1000ms. Subjects were required to either identify which stimulus was rewarded and respond by indicating which side of the screen it was presented on with a corresponding button press (stage 1 and 3), or select one of the response buttons that corresponds to one of the high-lighted red squares (stage 2). In the S-R phase (stage 4) subjects had to identify which of the four possible responses was correctly rewarded after presentation of a specific stimuli. Subjects always had the duration of the stimulus presentation and an additional 500ms in which to respond. Feedback was the same regardless of experimental phase. The outcome of the subject's choice was presented above four money bars that, if a reward was earned, cumulatively added that reward to the corresponding money bar. The feedback screen was visible for 1500ms and then immediately replaced by an inter-trial interval (ITI) of 1000ms long. During the fMRI phase of the experiment (stage 4 fMRI: OLD + NEW) blocks of trials were presented in a pseudorandom order. Each block consisted of either nine trials of old stimuli or new stimuli and lasted 45 seconds. 2 second cues were used to inform subjects which block of trials they could expect, either 'Yesterdays pictures' or 'Todays Pictures' for old and new stimuli respectively. Trial events within these blocks were the same as previous phases. 30 second rest blocks were interspersed within the experiment.

Feedback consisted of tokens representing one of four gift vouchers which the subject had chosen to collect during the course of the experiment, and was the same regardless of experimental phase. As outlined in Table 7.2, the outcome of the subject's choice was dependent on the condition the subject had been placed in. Subjects were assigned to either a "Consistent" or "Inconsistent" condition. In the consistent condition, correct S-O, R-O or S-R selections were rewarded with one of the four distinct gift voucher outcome. In contrast, Inconsistent group subjects were rewarded randomly with any of the outcomes.

	Stage 1 & 3 Stimulus-Outcome	Stage 2 Response-Outcome	Stage 4 Stimulus-Response
CONISTENT	S1-O1	R1-O1	S1-R1-O1
	S2-O2	R2-O2	S2-R2-O2
	S3-O3	R3-O3	S3-R3-O3
	S4-O4	R4-O4	S4-R4-O4
	…		…
	S12-O4		S12-R4-O4
INCONSISTENT	S1-O1/2/3/4	R1-O1/2/3/4	S1-R1-O1/2/3/4
	S2-O1/2/3/4	R2-O1/2/3/4	S2-R2-O1/2/3/4
	S3-O1/2/3/4	R3-O1/2/3/4	S3-R3-O1/2/3/4
	S4-O1/2/3/4	R4-O1/2/3/4	S4-R4-O1/2/3/4
	…		…
	S12-O1/2/3/4		S12-R4-O1/2/3/4

Table 7.2. In each phase of the experiment subjects had the opportunity to earn rewards for correct responses but the identity of reward was manipulated depending on group. In the consistent condition, correct S-O (stage 1 and 3), R-O (stage 2) or S-R (stage 3) selections were rewarded with one of the four distinct gift voucher outcome and subjects were trained under the DOP. In contrast, Inconsistent subjects were rewarded randomly after a correct choice or response with any of the outcomes, much like a NOP.

Subjects completed the task over two days, as illustrated in Table 7.1. All preconditioning phases (stage 1, OLD and NEW; stage 2; stage 3, OLD and NEW repeat), as well as S-R

learning on day 1 (stage 4, OLD) and recall of S-R learning on day 2 (stage 4r, OLD recap) took place in a quiet testing room. The final S-R learning phase (stage 4, NEW+OLD) was performed in a Siemens 3T scanner. Blocks of the previously learned S-R associations (Old learning task) were interspersed pseudo-randomly with blocks of the novel stimuli which required the subjects to learn, by trial-and-error new S-R associations (New learning task) and blocks of rest. As in the previous experimental phases, rewards were either consistent for a given S-R association (Consistent condition) or random (Inconsistent condition). Each experimental block consisted of nine stimuli and took 40.5secs. Before each block subjects were cued for two seconds with "Today's pictures" (New learning task), "Yesterday's pictures" (Old learning task). There were a total of 216 trials per experimental condition. Rest blocks were 30s in length. Whilst there was a fixed order and timing of events, blocks were jittered by the inclusion of the 2secs cue periods.

Image acquisition

Blood oxygenation-level-dependent (BOLD) fMRI images and T1-weighted anatomical images were acquired on a 3T Siemens MR scanner with a maximum gradient strength of 40 mT•m-1 at the Oxford University Centre for Clinical Magnetic Resonance Imaging (OCMR).

BOLD fMRI data were acquired by using echo planar imaging (EPI) (25 x 5 mm thick axial slices positioned from the top of the brain, with a base resolution of 64mm, matrix size 192 x 192, field of view 192 x 192mm^2, giving a voxel size of 3 x 3 x 5mm, repetition time = 1.5s, 620 volumes, echo time = 30 ms, and flip angle = 73°). A T1-weighted anatomical image was acquired for each subject by using a FLASH sequence (repetition time = 3 ms, echo time = 4.71 ms, and flip angle = 80°, giving a voxel size of 1 x 1 x 1 mm). The EPI scanning sequence lasted 50 minutes.

Data Analysis

Pre-processing

Pre-processing was identical for all of the general linear model (GLM)-based analyses described below. fMRI data were analyzed using tools from the FMRIB Software Library (www.fmrib.ox.ac.uk/fsl). At the first level (single-subjects) pre-processing involved several stages. Non-brain structures were removed using BET (Smith, 2002). Motion artefacts were removed using ICA Melodic software (Jenkinson and Smith, 2001), and the data were spatially smoothed using a 5mm Gaussian kernel of full-width at half maximum. Low-frequency drifts were removed with high-pass temporal filtering with a 90 seconds cut-off. The time series data were analysed using a GLM approach. Registration to standard space was carried out using FLIRT (Jenkinson and Smith, 2001). Statistical analysis was carried out in FEAT (version 5.63) using FILM with local autocorrelation correction (Woolrich et al., 2001). The hemodynamic response function was modelled as a γ function, a normalization of the probability density function of the γ distribution with zero phase, standard deviation of three seconds, and a mean lag of six seconds.

Primary General Linear Model

For the primary GLM analysis, the explanatory variables (EVs) were modelled with their temporal derivates. Four EVs, modelled in an event-related manner, were entered into the GLM at the first level. Specifically, *Errors* were modelled from the time of onset of the incorrect feedback for 1.5secs; informative *First Correct* trials, which included any trial in which the subject correctly paired the stimulus and response for the first time, or after at least one Error trial, were also modelled from the time of onset of the feedback for 1.5secs. *Probability of correct response retrieval* was modelled parametrically, as the average accuracy within each 9

trial block, from the time of the trial onset for 1.5 seconds. Every *Response* was also modelled from the time of its onset until the beginning of the feedback epoch. FEAT was used to fit this model to the data in order to generate Parameter estimates (PEs) for each of the EVs, and to contrast these PEs against one another. There were five contrasts of interest at the first level; Errors, Correct, Informative feedback (Errors + Correct), Informative Reward (Correct-Errors), Probability of correct responses and Responses.

Mixed effects analyses (FLAME 1+2) were applied to the whole-brain group data to generate statistical activation maps for each of the EVs, and to test for an effect of condition. Group Z (Gaussianized T) statistic images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster extent significance threshold of $p = 0.05$. Whilst a number of effects were revealed in this manner at the whole-brain level, only uncorrected images are presented for illustrative purposes. There were four contrasts of interest at the second level. These were Consistent, Inconsistent, Consistent – Inconsistent, and Inconsistent – Consistent.

Additional GLM of Consistent group subjects

While the primary analysis allowed examination of the brain areas with activity that were related to how *informative* an outcome was for the updating of reward outcome-related associations it did not examine the *value* of outcomes. Because each token outcomes had a subjective value that the subjects had reported at the beginning of the experiment it was possible to construct a regressor which identified brain activity that was related to the expected value of the outcome. The parametric value expectation related regressor was constructed from the rating (between 0 and10) subjects had assigned to the gift voucher token that would be received for correct response selection on each trial multiplied by the probability that the subject would receive that token – the probability that response selection would be correct (based on the average accuracy

within each 9 trial mini-block). The regressor was modelled from the onset of the stimulus for 1 second. The GLM also included the same EVs as the primary analysis but no data from the Inconsistent Group were included in the analysis. Subjects in the Inconsistent group could not anticipate the identities of reward outcomes. In theory a regressor reflecting the average value of the outcome multiplied by the probability of correct response selection would have reflected the Inconsistent group subjects' outcome value expectations but such a regressor would have been completely correlated with the Probability of Correct Response Selection. Three subjects from the Consistent group were excluded from this analysis: two as a result of an experimental oversight in misplacing their reward ratings sheets; and one because the subject had indicated that all their chosen gift vouchers were equally valuable.

ROI based signal extraction

We anticipated using three regions of interest (ROI) in our analyses that corresponded to the lOFC, ACC and mOFC/vmPFC. These were selected on the basis of activation coordinates reported in previous studies. The lOFC ROI had an 16mm radius and its location was based on the coordinates from the Kringelbach and Rolls (Kringelbach and Rolls, 2004) meta-analysis of error outcome related activation 32, 42, -18. The coordinate from the peak group difference of the voxels which survived this small volume correction was used as a 4mm diameter ROI in order to extract parameter estimate (-32, 48, -20), translated 4mm dorsally to 32, 48, -18 so that it fell within the cortex, rather than outside the brain, of our subjects. The ACC ROI also had an 16mm radius and its location was based on the average co-ordinates from a number of studies (Walton et al., 2004; Croxson et al., 2005; Behrens et al., 2007; Behrens et al., 2008) conducted in this laboratory that have found reward-related activations in the ACC (-9, 21, 37). The coordinate from the peak group difference of the voxels which survived this small volume

correction was used as a 4mm diameter ROI in order to extract parameter estimate (-8, 20, 32). The mOFC/vmPFC ROI was based on Kringelbach and Rolls' (2004) meta-analysis (4, 40, -24). In practice, however, activity was clearly identifiable in each of the three areas of interest, lOFC and ACC for at least one of the key contrasts of interest. The mean for each Group (Consistent and Inconsistent) was calculated and compared against each other for Errors, Correct and Probability of correct responses in independent-samples t-tests. As no Group differences were identified in the contrast of Informative Correct minus Errors we extracted the peak region of activation from the vmPFC/mOFC (0, 48, -10) and the lOFC region (-28, 50, -20), for the Consistent subjects only. As with the previous lOFC ROI it was impossible to place an ROI over the peak activation as it was too close to the edge of the brain. We therefore placed an ROI 4mm dorsally to the peak (-28, 50, -16). We used a 4mm radius ROI to extract PEs associated with the Errors and Informative Correct feedback regressors, and compared the two regions of interest in a repeated measures ANOVA of Regions (lOFC; vmPFC/mOFC) and Feedback (error; correct). Finally, a 4mm mOFC/vmPFC ROI was located at the peak coordinate (6, 26, -14) in a region reported to reflect reward expectation by Smith and colleagues (2009). PEs were extracted from these regions and compared against zero in independent one-sample t-tests, and directly against each region of interest (vmPFC/mOFC and lOFC) in paired sample t-tests.

Psycholophysiological Interaction (PPI) analysis of lOFC-related activity

A BOLD signal related to the informativeness of outcomes for updating reward outcome-related associations that was greater in the Consistent than the Inconsistent group subjects. Because these results suggested a role for lOFC in learning associations between specific stimuli and reward outcomes we hypothesized that the lOFC might have this specialized role because of its interactions with three regions. First, we examined its interactions with temporal cortical regions

known to represent the forms of the types of stimuli used in the experiment (Grill-Spector, 2003). In the macaque the lOFC is more strongly connected with temporal cortical visual form processing regions than the mOFC/vmPFC (Carmichael and Price, 1995c; Kondo et al., 2005; Saleem et al., 2008). Second, we examined its interactions with perirhinal cortex and the amygdala which have been repeatedly implicated in value-guided learning (Gaffan et al., 1993; Baxter et al., 2000; Baxter and Murray, 2002; De Martino et al., 2006; Hampton et al., 2007; Ramirez and Savage, 2007) and visual object recognition and discrimination (Buckley and Gaffan, 1997, 1998; Gaffan et al., 2000; Murray and Richmond, 2001; Lee et al., 2006; Aggleton et al., 2010) and are known to anatomically connect to OFC (Carmichael and Price, 1995a; Kondo et al., 2005). We therefore looked for task related changes in functional connectivity between lOFC and other brain regions using the psychophysiological interaction (PPI) analysis described by Friston et al. (1997). We focused on: 1) 4mm diameter ROIs derived from co-ordinates from the meta-analysis of object recognition in the occipitotemporal cortex from Grill-Spector (2003). The lateral occipital (LO) and mid fusiform area (mFA) were chosen because of their relatively selective activation for novel, abstract objects similar to the ones that were used in the current experiment. The Talairach coordinates reported by Grill-Spector were converted into MNI space using Matthew Brett's (1999) Matlab conversion Tal2MNI.m script (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). The resulting MNI coordinates were 40, -76, -7 for the LO, and 33, -38, -20 for the mFA.: 2) two 4mm bilateral ROIs in perirhinal cortex (36, -16, -24 and -36, 16, -24) as identified by Lee and colleagues (Lee et al., 2006): 3) two 4mm bilateral ROIs in the amygdala (27, -6, -21 and -27, -6, -21) from Hampton and colleagues (2007).

At the single subject level, preprocessing involved the same stages as those described above. The lOFC was chosen as a seed region for this analysis. In standard space, a 4mm diameter ROI was drawn around the peak group difference in activation for the Errors contrast in the lOFC (32, 42, -16). FLIRT was used to register this mask into each individual subject space (Jenkinson and Smith, 2001). For each subject, the Error EV, Correct EV and the mean BOLD time-series of the lOFC region were entered independently, and as interactions, into a first level GLM analysis. Probability (with their temporal derivative) and 6 motion correction EV were also included in this analysis. FEAT was used to fit these models to the data in order to generate PEs for each of the EVs and the PPI. The contrast of interest was the PPI and this was entered into a Mixed effects analyses (FLAME 1+2) which was applied to the whole-brain group data. This analysis generated statistical activation maps for each of the EVs and tested for an effect of condition. Group Z (Gaussianized T) statistic images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster extent significance threshold of $p = 0.05$. As previously described there were four contrasts of interest at the second level. These were Consistent, Inconsistent, Consistent – Inconsistent, Inconsistent – Consistent.

Given our specific a priori hypotheses concerning the LO, mFA, perirhinal cortex and the amygdala and in processing stimulus and outcome related information, we hypothesized that these regions would interact differentially depending on the availability of outcome-specific information during correct feedback. To explore these hypotheses, we compared the differential functional connectivity between Consistent and Inconsistent group subjects by extracting PEs from two bilateral ROIs in each independent region in separate repeated measures ANOVAs of PPI (Errors, Corrects), Hemisphere (left, right) and Group (Consistent, Inconsistent).

As a point of comparison we performed a similar PPI analysis with the Probability of Correct Responses as the psychological regressor and the timeseries of the ACC and extracted PEs for the same four regions: LO, mFA, perirhinal cortex and amygdala. We compared the PEs directly in a three-way ANOVA of Hemisphere, Region and Group. We compared between Probability of Correct Responses and Error regressors and between Probability of Correct Responses and First Correct regressors directly for the individual regions in three-way repeated measures ANOVAs of Regressor, Hemisphere and Group.

Correlational analyses of subject accuracy and BOLD signal

BOLD signal changes in ACC were better correlated with a greater probability of correct response selection in the Consistent group than in the Inconsistent group. The extent to which each ACC BOLD PEs explained between-subject differences in task performance was investigated. At the single subject level, preprocessing involved the same stages as those described above. In this analysis there were 20 EVs at the first level: six corresponded to the blocks (36 trials each); of the new learning task and six to the old learning task blocks; and six for the rest blocks. There were also six blocks of rest. Each block was modelled from the onset of each experimental 9 trial mini block, or the onset of the rest periods. Each block was composed of 4 mini blocks of either new or old stimuli, or rest. Cues and errors were also included in the model; as were 6 motion parameters. FEAT was used to fit these models to the data and to generate PEs for each of the EVs. For the purpose of this correlational analysis, the PEs for the 12 experimental regressors (NEW and OLD stimuli) for each subject were extracted from a 4mm radius ROI based on coordinates from the ACC (-8, 20, 32) and correlated with each individual's corresponding blocked measure of percentage accuracy.

The two groups of subjects (Consistent and Inconsistent) were compared in a fixed analysis of covariate with a time varying covariate. This analysis allowed us to predict subjects' performance by the parameter estimates of their BOLD signal changes, while considering other non-constant factors such as Time (6 blocks) and Task (OLD and NEW stimuli). Whilst in a standard covariate analysis each subject would contribute a single data pair; this analysis allows subjects to contribute multiple covariates from different periods of time across the testing session, or from different learning conditions. We extracted measures of correlation for Group, Task, Time and for the interactions of the factors Group x Parameter Estimates and Group x Task x Time x Parameter Estimates.

7.3 Results

Identifying the neural mechanisms mediating reward-guided action selection

lOFC and error processing

In order to identify the neural mechanisms mediating reward-guided action selection we first looked for BOLD activity which was modulated by error feedback, in both groups of subjects. We then compared this activation in between-group contrast of Consistent subjects minus Inconsistent subjects. This contrast identified error-related activity that was greater in subjects who were able to employ previously learned outcome-specific reward expectations in order to learn and recall responses. Regions more strongly activated in the Consistent group subjects, relative to the Inconsistent group subjects, who had not previously acquired outcome-specific learned expectations, arguably encode outcome-specific error related information which might serve to contribute to the facilitated learning effects described in the previous chapter.

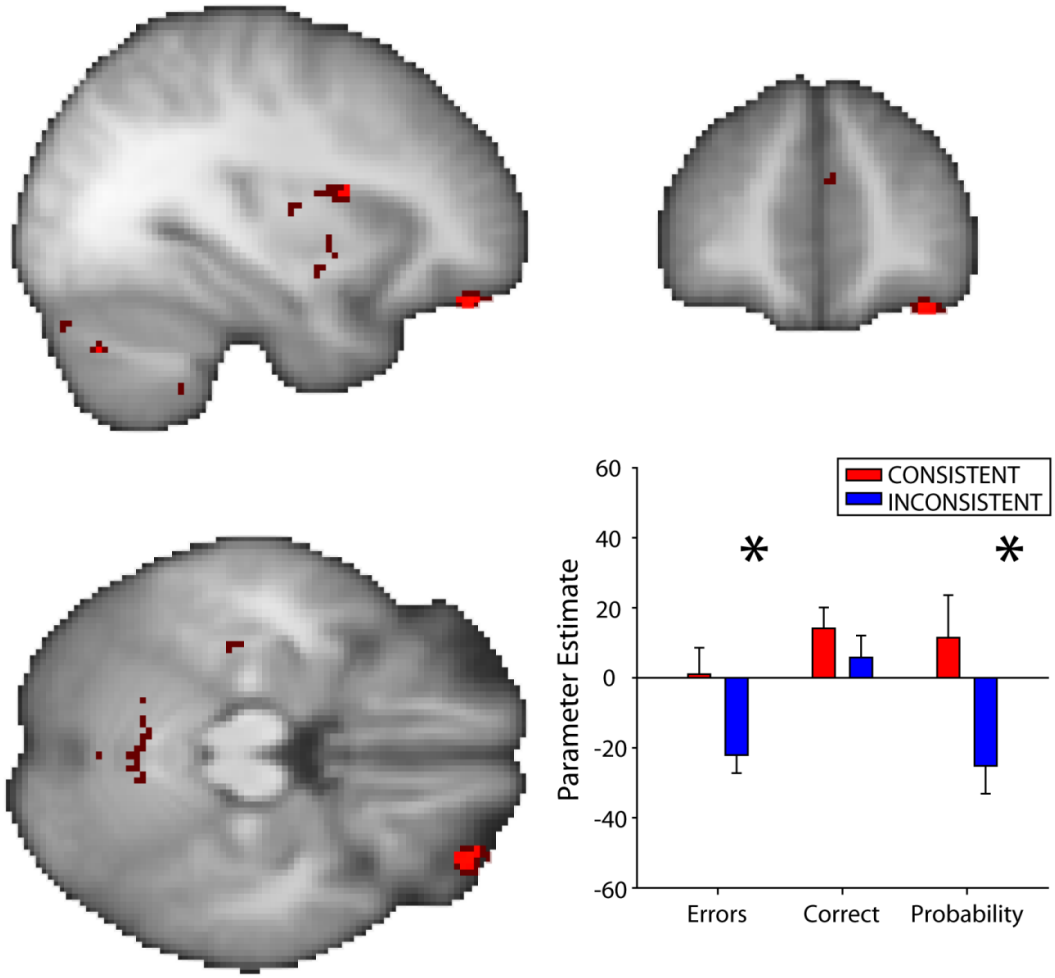

Figure 7.1. Voxels in the lOFC (z=4.15 -32, 48, -20) survived thresholding at p=0.001 (uncorrected) and correction for small volume at p=0.05 with an 8 mm sphere centred on coordinates derived from Kringelbach and Rolls. Areas in the lOFC showing BOLD responses to error feedback in a between-subjects contrast of Consistent-Inconsistent. Images are presented on a mean brain. The threshold is set at p<0.05 (dark red) and p<0.001 (light red) for illustration. A plot of effect sizes from the lOFC from an ROI over the peak difference is shown for each *Errors*, *Informative correct* and *Probability of correct responses*. Significant differences were Errors (p<0.05) and Probability (p<0.05) (n=36).

Activity related to Error feedback was significantly increased in the lOFC of Consistent group subjects. Activity associated with this contrast in the lOFC also survived correction for small volume at p=0.05 with an 8mm radius sphere centred on coordinates derived from Kringelbach and Rolls meta-analysis of fMRI activations classified as "punishers leading to a behavioural change" (-32, 42, -18). This contrast, shown in Figure 7.1, revealed brain activity in the lOFC (z=4.15 -32, 48, -20) whose voxels survived thresholding at p=0.001 (uncorrected). However, this region does not appear to be selective for punishers leading to a behavioural changes as PEs extracted for the Informative Correct regressor revealed significant activation in this region in the Consistent subjects (one sample t-test; t_{17}=2.98, p=0.008). There was also no significant difference between Error and Correct feedback related PEs in the adjacent peak activation for the Consistent subjects (paired sample t-test; t_{17}=-0.79, p=0.440).

Outside this large orbitofrontal ROI sphere, the contrast also revealed activation which survived thresholding at p=0.001 (uncorrected) in the left insula (z=4.57, -38, 2, 16), globus paladus (3.17, -20, -6, -4), premotor (2.99, -56, -10, 28) superior temporal gyrus (3.164, -68, -14, 10) and cerebellum (3.55, 8, -56, -16). These regions were found to be more active in Consistent subjects and are therefore potentially contributing to a heightened Error related signal that facilitates overall learning and performance.

To confirm function specificity of the lOFC to Error related activity we examined the role of this region in representing response selection knowledge (Probability of Correct Response contrast). We used the same 16mm sphere centred on coordinates derived from Kringelbach and Rolls and identified voxels in the lOFC that survived small volume correction at p=0.05 for the Probability of correct responses contrast. PEs were extracted for Errors and Probability of correct responses related activity with an ROI centred on the peak activation of the uncorrected image in

the lOFC (-32, 48, -18). This analysis revealed a significant difference between the two groups in the Errors (t_{34}=2.46, p=0.019) and the Probability of correct responses PEs (t_{34}=2.54, p=0.016).

Interpretation of the reverse Errors contrast (Inconsistent – Consistent) is challenging as it is unlikely to reflect activity related to a pure habitual learning mechanism. It is possible this activity reflects the increased resources needed to complete the task in the absence of reward expectations. Exploratory analysis indicated two small clusters of voxels in the dorsolateral prefrontal (dlPFC; z=3.617, 36, 10, 52) and posterior inferior occipitotemporal cortex (z=3.617, 56, -56, -8). This interpretation for the latter, dlPFC activation, is consistent with reports of its correlation with increasing task difficulty in many different cognitive domains (Duncan and Owen, 2000).

lOFC and stimulus-outcome associations

The OFC and particularly its lateral regions are increasingly being thought of as involved in forging associations between stimuli and outcomes (Murray and Wise; Rolls, 1999; Walton et al., 2010). If this is the case then one would expect brain areas encoding stimulus information, such as the occipital and temporal regions, to work with the lOFC during periods of increased activation. We performed a PPI analysis which examined the interaction of a physiological factor, the time series of lOFC activation, with the psychological, or task factors, of error occurrence (indexed by the *Errors* regressor) or informative correct feedback (indexed by the *Correct* regressor). This analysis revealed activity in a number of visual and temporal areas which survived at the whole brain level (corrected p=0.05), and changed significantly in relation to fluctuations in errors (Figure 7.2a) and correct feedback (Figure 7.2b).

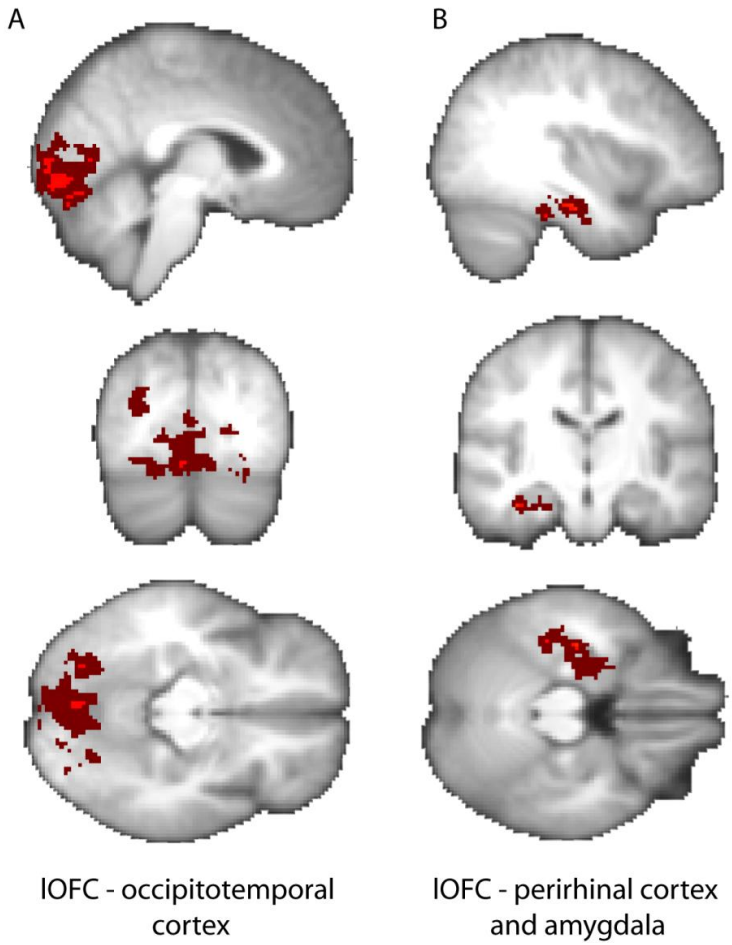

Figure 7.2. The lOFC links stimuli to negative and positive outcomes. Voxels in occipitotemporal cortex during errors (A) and perirhinal cortex and the amygdala during first correct feedback of Consistent subjects which survived whole brain (uncorrected; dark red) and those which survive p=0.001 uncorrected (light red) thresholding from a PPI analyses with seed voxels in the lOFC (n=18)

Several regions of the occipitotemporal cortex are known to represent novel objects similar to the stimuli used in the current task (Grill-Spector, 2003). PEs were therefore extracted from two ROIs derived from regions identified as showing relatively selective enhanced activation to novel abstract objects in the lateral occipital region (LO, 40, -76, -7) and the mid fusiform area (mFA, 40, -51, -21) (Figure 7.3). As a repeated measures ANOVA indicated no

effect of Group or Group interactions with either factors of hemisphere or feedback for either occipitotemporal region the two groups of subjects were pooled and the PEs compared against zero in a number of one-sample t-tests. As hypothesised a number of regions significantly increased in functionally connectivity with the lOFC during errors (right LO; t_{35}=2.60, p=0.014, left mFA; t_{35}=2.03, p=0.050, right mFA; t_{35}=3.73, p=0.001) and correct feedback (right mFA; t_{35}=2.06, p=0.047).

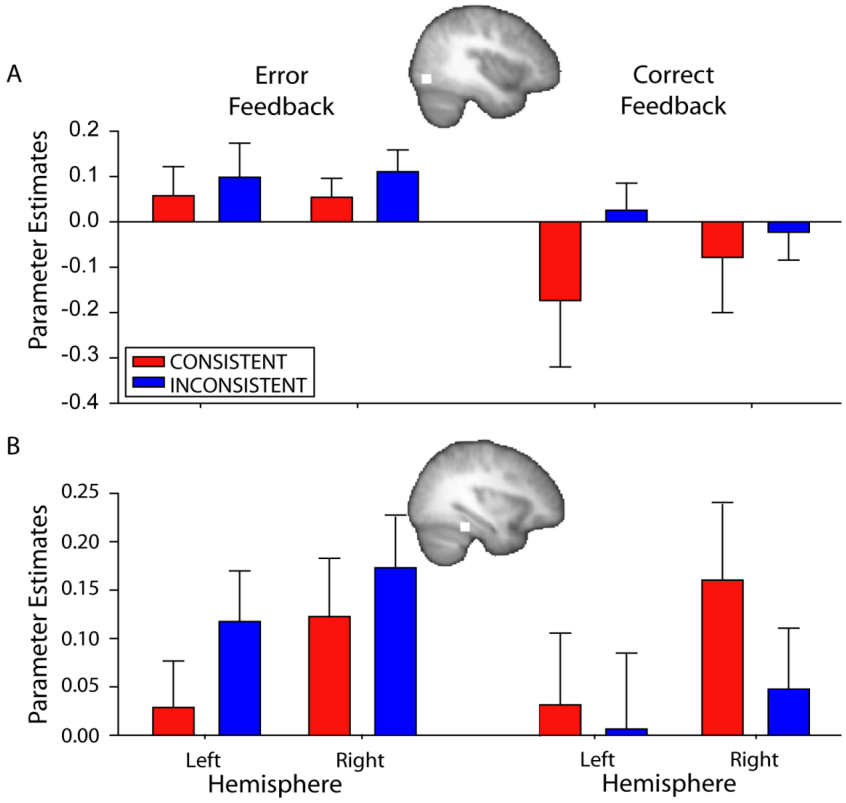

Figure 7.3. Changes in functional connectivity between the lOFC and regions in the occipitotemporal cortex for errors and correct feedback. PEs were extracted from bilateral ROIs in the Lateral Occipital (A) and medial fusiform area (B) from independent PPI analyses with seed voxels in the lOFC for the Consistent (red) and Inconsistent (blue) subjects. Insets show positions of the ROIs for both extracted regions and were based on the meta-analysis from Grill-Spector (2003). As hypothesised a number of regions were significantly more functionally connected with the lOFC during errors (right LO and left and right mFA) and correct feedback (right mFA) (n=36).

The present task required subjects to learn associations between complex objects and rewarding outcomes. The perirhinal cortex is involved in visual object recognition and discrimination (Buckley and Gaffan, 1997, 1998; Gaffan et al., 2000; Murray and Richmond, 2001; Lee et al., 2006; Aggleton et al., 2010), while the amygdala encodes signals which relate to value-guided learning (Gaffan et al., 1993; Baxter et al., 2000; Baxter and Murray, 2002; De Martino et al., 2006; Hampton et al., 2007; Ramirez and Savage, 2007). As such, we hypothesised that these two regions would show changes in functional connectivity with the lOFC during feedback periods in the task. Exploration of the PPI analysis described above for the Consistent group subjects indentified a large cluster of activation in the perirhinal cortex and amygdala which survived whole brain comparisons (Figure 7.2b). We extracted PEs using bilateral 4mm radius ROI in the perirhinal cortex based on coordinates from Lee and colleagues (2006) for the PPI for Error and Correct feedback and compared the activity in a three-way repeated measures ANOVA (Figure 7.4a). The results showed a significant three-way interaction of Feedback, Hemisphere and Group ($F_{1,34}$=8.22, p=0.007), and a main effect of Hemisphere ($F_{1,34}$=5.24, p=0.028). Independent samples t-tests restricted the significant differential group effects to the Correct feedback in the right hemisphere and a trend to significance in the left hemisphere (t_{34}=2.69, p=0.011 and t_{34}=1.84, p=0.074, respectively)

Similarly, in figure 7.4b we extracted PEs using bilateral 4mm radius ROI in the amygdala based on coordinates from Hampton and colleagues (2007) and in the same way identified a significant three-way interaction of Feedback, Hemisphere and Group ($F_{1,34}$=7.22, p=0.011) and a main effect of Hemisphere ($F_{1,34}$=6.20, p=0.018). Independent samples t-tests restricted the significant differential group effects to the Correct feedback in the right hemisphere and a trend to significance in the left hemisphere (t_{34}=2.48, p=0.018 and t_{34}=1.78, p=0.085

respectively). These results suggests that despite the PPI analysis being insensitive to the original group difference at the lOFC seed, the perirhinal cortex and amygdala increase in functional connectivity with the lOFC while processing correct feedback selectively when outcome-specific information is available in the reward environment.

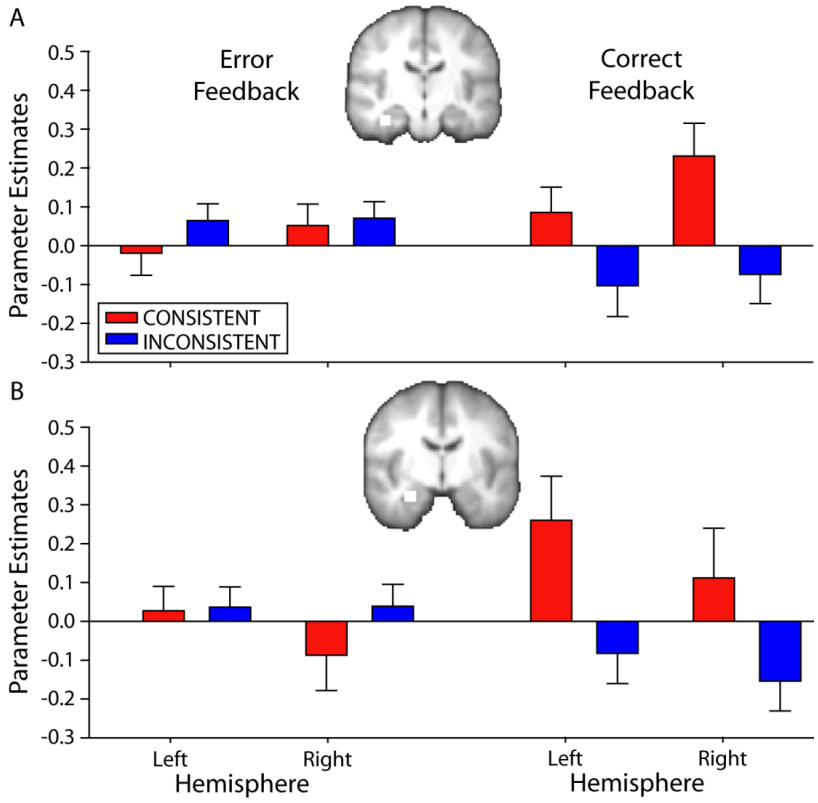

Figure 7.4 Changes in functional connectivity between the lOFC and the anterior temporal cortex for error and correct feedback. PEs extracted from bilateral ROIs in the perirhinal cortex (A) and amygdala (B) based on coordinates from Lee et al. (2006) and Hampton et al. (2007) respectively for Consistent (red) and Inconsistent (blue) subjects. Significant group differences in functional connectivity between Consistent and Inconsistent subjects for the correct feedback were found in both regions. PEs were extracted with a 4mm seed and extraction ROI shown above on the averaged brain (n=36).

mOFC and first-correct outcomes

Recent non-human primate lesion work has suggested that the lOFC plays a critical function in value assignment (Walton et al., 2010). The authors show that damage to the lOFC causes animals to erroneously misattribute the credit for rewards, not just to the stimulus choice that led to its delivery, but to prior and subsequent stimulus choices. This means that values of stimuli no longer reflect the precise history of reward experienced in conjunction with choices of that stimulus. Moreover, this role has been shown to be exclusive to the lateral regions of the OFC; as mOFC-lesioned animals do not show this deficit (Noonan et al., 2010) (details in Chapter 4). In light of this we investigated whether the outcome-specific activity found in the OFC in the present study was specific to the lateral regions, or whether it was also evident, albeit not significant, at a group level analysis in more medial OFC. To do so we extracted the Error feedback related activity in the co-ordinates from an ROI in the medial regions of the OFC based on Kringelbach and Rolls' (2004) meta-analysis (4, 40, -24). This analysis indicated there was no significant difference between the effect identified by this regressor in the two conditions (independent sample t-test, t_{34}=-0.62, p=0.541).

To further explore differences between the lOFC and mOFC we compared activity associated with the experience of positive feedback. A number of experiments find activity in the vmPFC/mOFC that represents positive reinforcement feedback (O'Doherty et al., 2001b; Rolls et al., 2003c) and so we attempted to replicate this in the present study. The comparison of informative Correct minus Error feedback across the whole brain revealed reward-related activation in a network of areas including the vmPFC/mOFC. As in other studies vmPFC/mOFC activity to reward outcomes was a relative activation, from a deactivated state, compared to error feedback. We extracted the PEs for the Errors and Correct regressors from an ROI centred on the

peak vmPFC/mOFC co-ordinates (z=7.52, 0, 48, -10) and compared them to the same regressors extracted from the peak activation of the Errors regressor in the lOFC. To simplify the comparison and because of the lack of evidence for Group differences we chose to compare PEs for the Consistent group subjects only (-28, 50, -16). As illustrated in Figure 7.5 the vmPFC/mOFC shows a striking relative activation in response to correct feedback compared to errors whereas the lOFC does not. A repeated measures ANOVA of Region (vmPFC/mOFC; lOFC) and Feedback (Correct; Errors) confirms the significance of the effect. There was a main effect of Region ($F_{1,17}$=66.52, p=0.000), Feedback ($F_{1,17}$=45.95, p=0.000) and critically an interaction between the two factors ($F_{1,17}$=58.40, p=0.000).

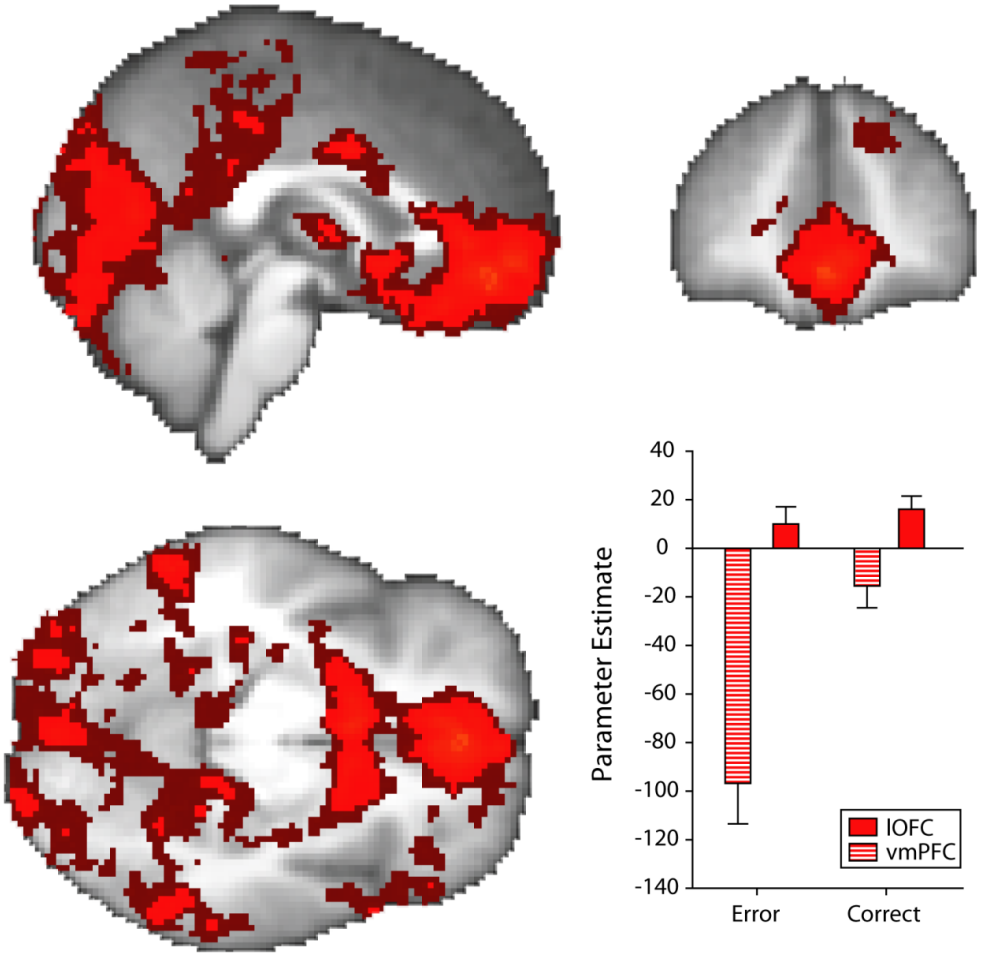

Figure 7.5. The reward network. Voxels surviving thresholding at p=0.05 (corrected) are shown in dark red for the contrast of *Informative Correct* feedback minus *Error* feedback. Shown in light red are those voxels which survive threshold at p=0.001. A plot of effect sizes from and ROI from the peak vmPFC/mOFC co-ordinates (z=7.52, 0, 48, -10) and compared to PEs from the peak activation for the *Errors* in the lOFC for the Consistent subjects only. Analysis confirmed the significant difference between the two frontal regions with the vmPFC/mOFC and not the lOFC showing a heightened activation in response to positive feedback (n=18).

mOFC and reward expectation

Several theories have emphasised the importance of the vmPFC/mOFC for value expectation (Schoenbaum et al., 1999; O'Doherty et al., 2002; Schoenbaum and Roesch, 2005; Smith et al.,

2009). We therefore conducted an analysis to investigate whether there was evidence of this in the present study. We used an additional GLM analysis, which included a regressor designed to capture the expected reward value for each outcome on every trial. This regressor also varied parametrically with the probability that the subject would be correct on that trial and therefore reflected how strong their reward expectations were likely to be. This is only appropriate for the Consistent subjects as only those subjects were able to develop an expectation of a particular reward. We were able to do this with 15 Consistent group subjects whose reward ratings were available and showed differential preferences for at least one of the outcomes. Recently, Smith and colleagues (2009) identified a region within the vmPFC/mOFC which encoded reward expectation (12, 58, 2). We therefore compared activity related to reward expectation in this region with activity related to reward expectation in the lOFC. PEs related to reward expectation were extracted from ROIs from both the left and right vmPFC/mOFC co-ordinates (Figure 7.6). We averaged the signal between the two hemispheres and compared all PEs, drawn from both the vmPFC/mOFC and from the lOFC, against zero in one-sample t-test. We found that the activity in the vmPFC/mOFC was significantly above zero (one-tailed; $t_{15}=1.84$, $p=0.043$) whereas the beta values in our lOFC region were not (two-tailed; $t_{15}=0.004$, $p=0.997$). Moreover in a direct comparison between the vmPFC/mOFC and lOFC a paired samples t-test demonstrated that the two regions were significantly different from each other (one-tailed; $t_{15}=1.84$, $p=0.043$).

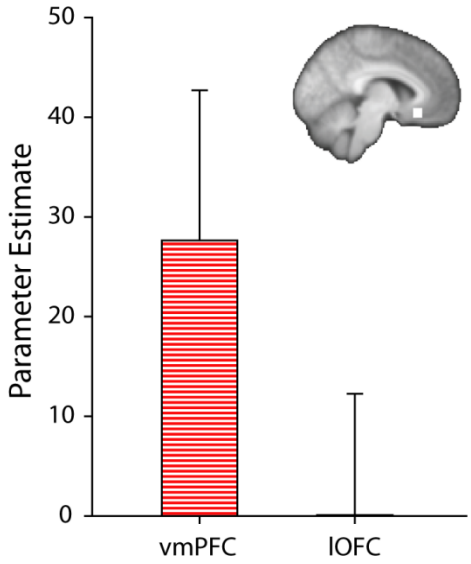

Figure 7.6. PEs from a reward expectation EV from a lateral OFC (peak Consistent co-ordinates -28, 50, -16) and a vmPFC/mOFC reward expectation co-ordinates (averaged both hemispheres) from Smith et al (12, 58, 2 and -12, 58, 2). Comparison between the vmPFC/mOFC and lOFC with an independent samples t-test suggests that the two regions are significantly different from each other (t=1.84, p=0.043) with the vmPFC/mOFC encoding to reward expectation parametrically (n=15).

ACC and task knowledge

Activity that was identified as parametrically modulating with the subjects' probabilities of correct response selection (*Probability of Correct Response* contrast) was compared in the Consistent and Inconsistent group subjects. This variable reflects subjects' knowledge of the task and which response is the correct one to select given each stimulus. Therefore, regions more active in Consistent group subjects arguably reflect the knowledge and deployment of S-O and O-R associations that mediate the superior performance in that group.

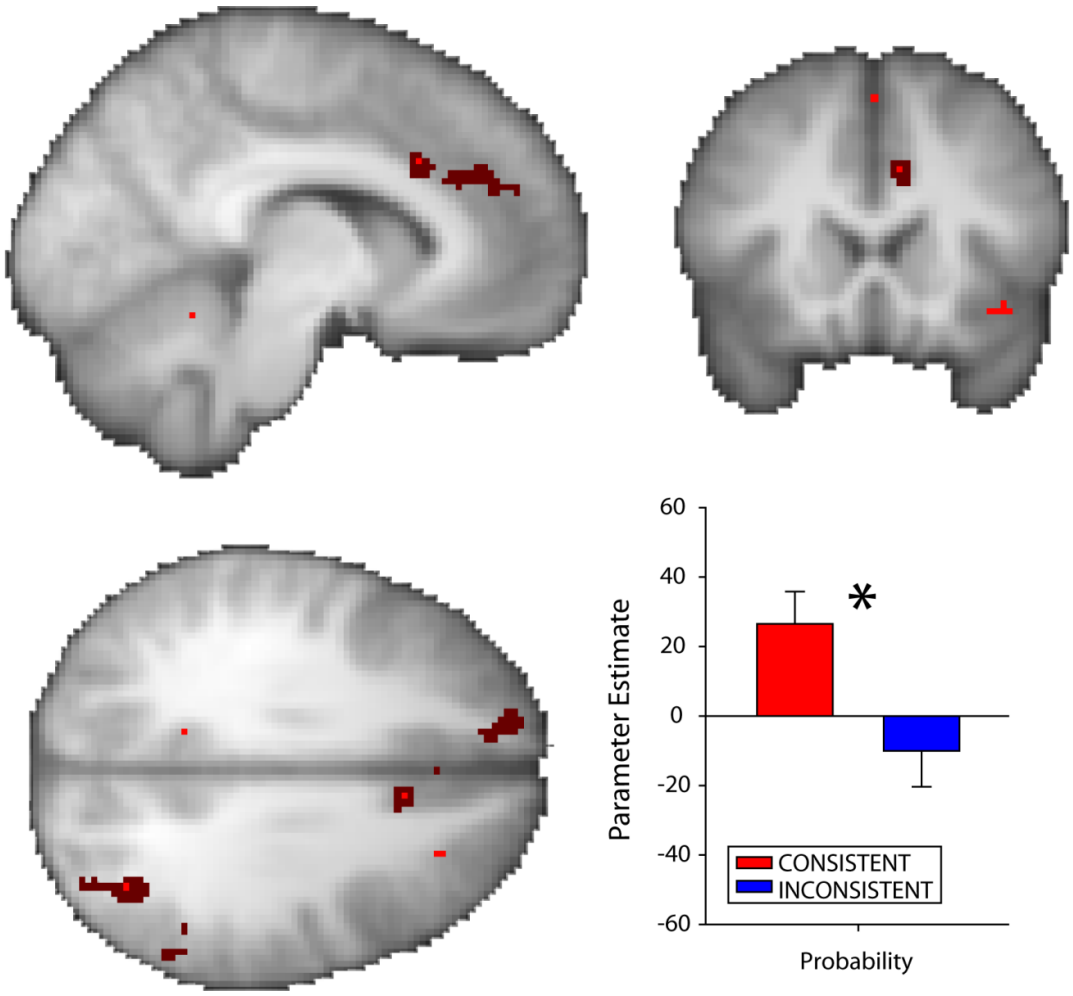

Figure 7.7. Voxels in ACC (z=4.34 -8, 20, 32) survived thresholding at p=0.001 (uncorrected) and correction for small volume at p=0.05 with an 8 mm sphere centred on averaged coordinates from reward-related activations in this laboratory (-9, 21, 37). These voxels show BOLD responses to parametrically varying activation associated with the probability of being correct over each 9 trial block in a between-subjects contrast of Consistent-Inconsistent. Images are presented on a mean brain. Voxels in dark red survive correction at the whole brain (p=0.05) and those which survive uncorrected at p<0.001 are shown in light red. A plot of effect sizes from the ACC from an ROI over the region of peak difference is shown for this regressor. Independent t-tests confirm a significant difference (p<0.05), (n=36)

Figure 7.7 shows voxels in the ACC with enhanced activation in Consistent group subjects (z=4.34, -8, 20, 32), surviving thresholding at p=0.001 (uncorrected), and correction for small volume at p=0.05 with an 8mm radius sphere centred on averaged coordinates from reward-related activations in this laboratory (-9, 21, 37). This activity changes with increasing knowledge of which is the correct response to make. ROI coordinates from the peak activation location for the Consistent-Inconsistent group difference were used to extract PEs for the effect of Probability of Correct Response. Independent sample t-tests confirmed that there were significant differences in PEs of the Probability of Correct Response related activity (t_{34}=2.26, p=0.031). Whilst there was no a priori hypothesis concerning additional regions likely to be more active in this contrast, exploration of the data suggests that bilateral angular gyrus (z=3.49, -54, -50, 36 and z=4.315, -42, -64, 42) also showed differential activation when outcome-specific reward expectations were available to guide behaviour.

Recently, a diffusion weighted imaging and tractography-based parcelation study and meta-analysis suggested that more rostral regions of the ACC are activated in tasks requiring an element of motor function, and often overlap with responses to reward or error detection (Beckmann et al., 2009). The rostral cingulate region is known to interconnect heavily with motor and premotor regions in both the monkey (Dum and Strick, 1991; Morecraft and Van Hoesen, 1992; Dum and Strick, 1993, 1996) and human (Beckmann et al., 2009). This makes it an appropriate candidate for forging links between actions and their resulting consequences (Rushworth et al., 2007a; Rudebeck et al., 2008b). The ACC activation in the present study lies within this rostral region suggesting that it may similarly associate actions with outcomes. However, critically, its activation is dependent on the consistency of the outcome following the choice, which suggests it may be making a unique contribution to action-based outcome-specific

learning. In subjects in the Consistent group, specific reward expectations for each stimulus, the ACC activity may represent outcome-specific knowledge which could be used to facilitate action selection.

The reverse contrast (Inconsistent – Consistent) revealed no substantiated activity.

ACC and reward-guided action selection

Previous studies suggest that the OFC and ACC appear to be relatively more concerned with the association of outcomes with stimuli, or with actions (Walton et al., 2004; Rudebeck et al., 2008b). By extension, if the activation of the ACC in relation to the Probability of Correct Response in the present study is due to its role in mediating O-R associations, as opposed to S-O associations, then the ACC should show no increase in functional connectivity with temporal regions. We performed an equivalent PPI analysis for the ACC timeseries and the psychological regressor of Probability of Correct Response. We extracted PEs from the same bilateral LO, mFA, perirhinal cortex and amygdala ROIs described above. As illustrated in figure 7.8 there was no differential changes in functional connectivity in any of the regions tested. A three-way ANOVA confirmed there was no interactions between Group and Region ($F_{3,102}$=0.93, p=0.383) or Group, Region and Hemisphere ($F_{3,102}$=0.16, p=0.881). In independent repeated measures ANOVAs comparing PEs for the PPI regressors (Errors, Probability or Correct, Probability) with Hemisphere (left, right) and the between-subjects factor of Group (Consistent, Inconsistent) for each temporal ROI we showed that increases in functional connectivity were selective to analyses which were seeded in the lOFC. Of interest, increases in functional connectivity in the LO and mFA were only seen with the error timeseries PPI (main effect of PPI regressor: LO; $F_{1,34}$=12.88, p=0.001, mFA; $F_{1,34}$=14.48, p=0.001). Analysis which focused on correct feedback

compared to the Probability timeseries PPI in the perirhinal cortex and amygdala reveal Regressor by Group interactions (perirhinal; $F_{1,34}$=10.50, p=0.003, amygdala; $F_{1,34}$=11.73, p=0.002). These interactions are due to increases in functional connectivity in the Consistent group subjects during correct feedback (Figure 7.4, correct feedback) but decreases during the Probability regressor (Figure 7.8c and d). The reverse is evident for the Inconsistent group subjects.

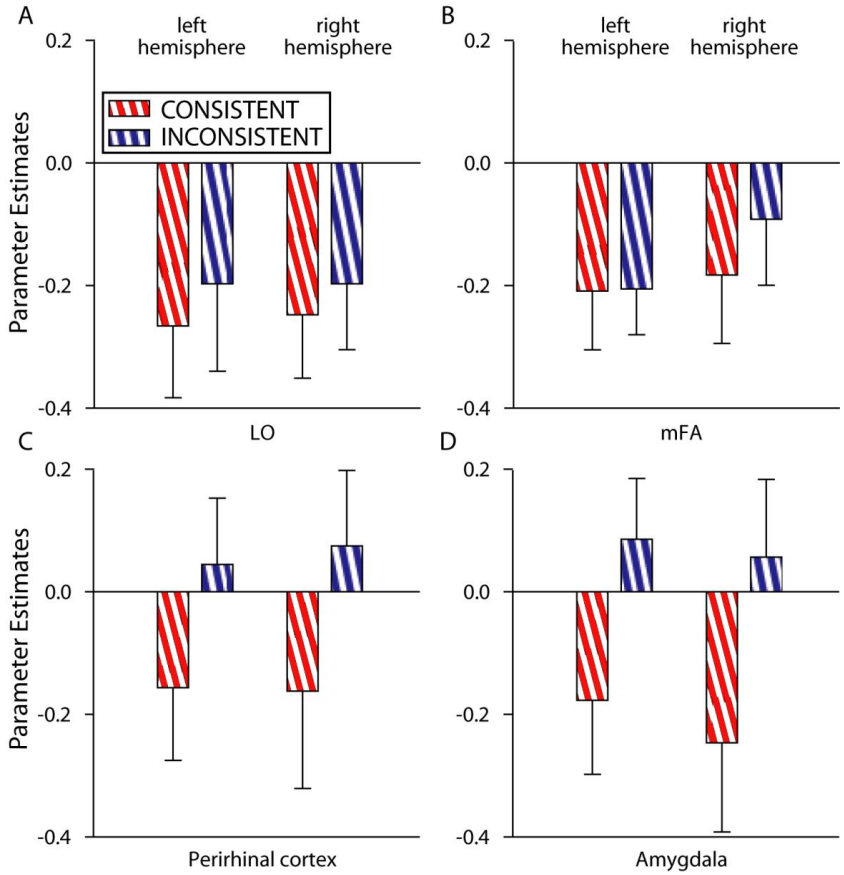

Figure 7.8. PEs from the Probability of Correct Responses contrast from the ROIs in the Lateral Occipital (A) medial fusiform Area (B) perirhinal cortex (C) and amygdala (D) from independent PPI analyses with seed voxels for Consistent (red) and Inconsistent (blue) subjects. PEs extracted from bilateral ROIs in the LO and mFA based on co-ordinates from a meta-analysis by Grill-Spector (2003). PEs extracted from bilateral ROIs in the perirhinal cortex and amygdala based on coordinates from Lee et al. (2006) and Hampton et al. (2007) respectively (n=36).

Finally, if ACC is critical for reward-guided action selection (Rudebeck et al., 2008b) then its activity should reflect the changing probability of selecting correct responses during learning in the context of the DOP. We therefore investigated whether the inter-individual differences in BOLD parameter effects in the ACC would correlate positively with inter-individual differences in measures of behavioural accuracy. In other words we were interested in whether or not subjects with large Probability of Correct Response effects in the ACC were also the same subjects that performed best. A supplementary GLM included Probability of Correct Response regressors for each of the new and old learning blocks, (12 regressors, 6 for new learning blocks, 6 for old learning blocks). The possibility of correlation between the subjects' block specific parameter effects with their behavioural accuracy scores was assessed. Figure 7.9 suggests that accuracy in the Consistent condition is positively correlated with ACC BOLD activity. This is particularly apparent in the new learning blocks (upward slopes of red lines in figure 7.9, A and B). By contrast the same figure suggests that accuracy in the Inconsistent condition is negatively correlated with ACC BOLD activity (downward slopes of blue lines in figure 7.9, A and B). Again this effect is more evident in the new (A and B) rather than old (C and D) learning task, and is more consistent in the later blocks of time (B). The two groups of subjects (Consistent and Inconsistent) were compared in a fixed effects analysis of covariance with a time varying covariate. We investigated the predictability of subject performance (Block by block percentage accuracy) by BOLD activity in the ACC while considering the time varying covariates of Task and Time. This analysis suggested that subjects' performance was predicted by the interaction between Group and Parameter estimates ($F_{1,2}$=4.33, p=0.014), and the interaction between Group, Task, Time and Parameter estimates ($F_{1,22}$=2.56, p=0.000). In this analysis, performance was not predictable by Group assignment alone ($F_{1,1}$=0.22, p=0.640).

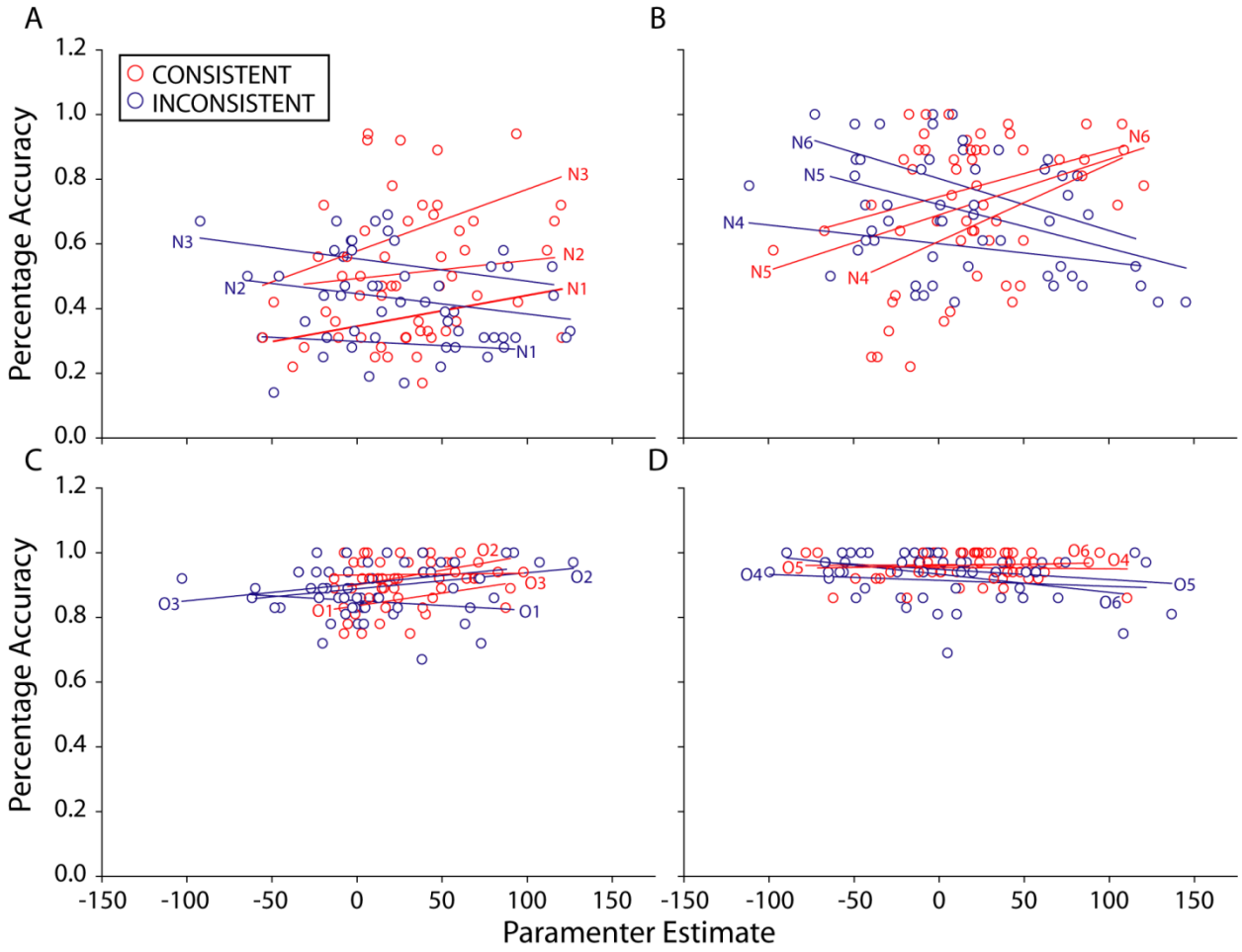

Figure 7.9. Linear correlations of extracted PE (2mm diameter ROI from ACC) for individual blocks (1-6) of S-R learning against its block related average percentage accuracy score during NEW (A and B) and OLD (C and D) stimulus blocks with percentage accuracy score over the same blocks for Consistent (red) and Inconsistent (blue) subjects. Consistent subjects tend to show positive correlations between PE from the ACC and percentage accuracy scores during NEW S-R learning while Inconsistent show a negative correlation between these two factors. No such difference is group difference is observed in the OLD S-R learning task (n=36).

Response

Responses were modelled from the time of the response onset until the onset of the feedback. Whilst no a priori hypothesis was established the same between-group contrasts were performed

on the data. These analyses revealed no significant group differences in BOLD activation that survived uncorrected thresholds (p=0.001) for the Consistent minus Inconsistent contrast. In comparison, the reverse contrast, shown in figure 7.10 (Inconsistent – Consistent), revealed a number of brain regions with higher activity in the Inconsistent subjects than Consistent Subjects (uncorrected p=0.001). These included: the caudate (z=4.00, -16, 12, 6), globus pallidus (z=3.99, p=-10, -8, 14); Supplementary Pre-motor (z=3.85, 4, -8, 58); post central (z=4.53, -24, -30, 64), angular gyrus (z=3.65, -48, -46, 30) and posterior inferior occipitotemporal cortex (z=3.69, -50, -58, 2). This network may reflect the increased difficulty of the task faced by the subjects in the Inconsistent condition.

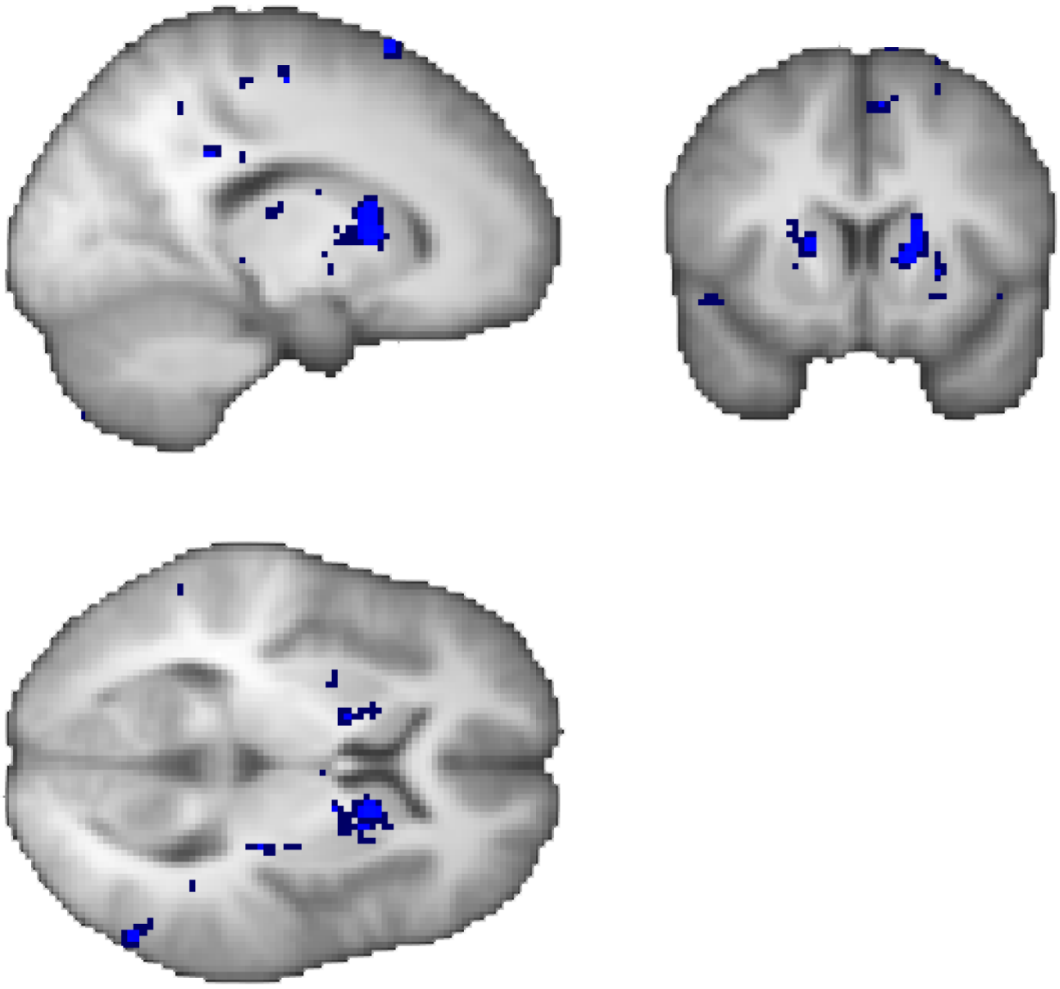

Figure 7.10. Voxels in Caudate, Putamen, SMA, post central sulcus, angular gyrus and inferior occipitotemporal cortex survived thresholding at p=0.001 (uncorrected). Areas showing BOLD responses to associated to a response in a between-subjects contrast of Inconsistent-Consistent. Images are presented on a mean brain and focus on the peak zstat for the caudate nucleus (-16, 12, 6). The threshold is set at p<0.05 (dark blue) and p<0.001 (light blue) for illustration (n=36).

7.4 Discussion

This study used a novel version of the Differential Outcomes Procedure to compare cerebral activity in subjects trained under a consistent reward schedule with subjects trained in

environments where reward outcomes types were random after correct choices. The findings presented above suggest that distinct brain regions, including the OFC and ACC, are specialised for reward-type specific processing and they are recruited when subjects have outcome-specific information to guide choice and behaviour. The improved learning and memory recall in Consistent subjects might be explained by the activation of these brain regions.

The OFC has been repeatedly implicated in flexible behaviour in response to changes in reinforcements. Changes in cerebral activation in this region are seen in response to errors (Thorpe et al., 1983; O'Doherty et al., 2003a; Sul et al., 2010), positive reinforcement (Elliott et al., 2003; O'Doherty et al., 2003a) and rapid changes in S-O contingencies, which suggest a change is needed in behaviour (Tremblay and Schultz, 2000; O'Doherty et al., 2003a; Walton et al., 2004; Stalnaker et al., 2006). However, the OFC is responsible for more than just the binary properties of reward or lack thereof, as devaluation studies in animals suggest the OFC encodes reward identity (Gallagher et al., 1999; Pickens et al., 2003; Izquierdo et al., 2004; Pickens et al., 2005; Ostlund and Balleine, 2007a). The present study localises the representation of reward identity to the lOFC as this area significantly increases in activation in response to error feedback in the Consistent subjects, relative to the Inconsistent subjects. It is therefore possible that the lOFC not only encodes the conjunction of a particular reward value with a particular stimulus choice (Walton et al., 2010), but if distinct outcomes are available in the reward environment, the lOFC encodes the conjunction of a particular reward identity with a particular stimulus choice.

As learning is likely to be dependent on the distributed pattern of activity across brain networks we performed a PPI analysis to investigate changes in functional connectivity between the lOFC and other brain regions during the task. This analysis showed that the lOFC increased in functional connectivity with temporal cortical regions known to represent novel abstract

images of the sort that we used in the current experiment. This implied that the lOFC has access to stimulus representation at the time error feedback is received. We therefore speculate that the lOFC may be relatively more concerned with the S-O, as opposed to O-R associations. Interestingly, while there were no task differences in these posterior temporal regions between Consistent and Inconsistent group subjects, the PPI analysis identified group effects in more anterior temporal cortex. The perirhinal cortex and amygdala increased their functional connectivity with the lOFC more so in the Consistent group subjects than the Inconsistent group subjects during correct feedback. The perirhinal cortex has strong mutual connections with lOFC (Kondo et al., 2005) and is typically engaged in visual object recognition and discrimination (Lee et al., 2006). Damage to perirhinal cortex in both humans and animals produces amnesia and impairs discrimination of complex objects (Buckley and Gaffan, 1997, 1998; Gaffan et al., 2000; Murray and Richmond, 2001; Aggleton et al., 2010). Similarly, the amygdala, has established connections with lOFC (Carmichael and Price, 1995a) and like the OFC encodes value-related signals (De Martino et al., 2006; Hampton et al., 2007). Damage to this region has been shown to selectively impair animals' ability to alter their actions to changes in the value of a reinforcer (Hatfield et al., 1996; Malkova et al., 1997). Notably lesions to the amygdala affect rats' abilities to establish S-R associations under DOP conditions (Ramirez and Savage, 2007). Surgical disconnections between the amygdala and OFC impair monkeys choice behaviour following changes in value of specific outcomes (devaluation) (Baxter et al., 2000). Taken together and in the context of the present findings it appears that the lOFC, perirhinal cortex and amygdala are constructively coordinating in order to facilitate learning of multiple object-reward-specific associations.

Chapter 4 described lesion work in monkeys that suggests a double dissociation between the functions of the lateral and medial regions of the OFC (Noonan et al., 2010). Furthermore, it proposes that while the lOFC assigns value to the immediately chosen stimulus; the mOFC compares between the values of the choice options. The present study also demonstrated differences in the nature of the information encoded in the lOFC and vmPFC/ mOFC, suggesting that these may also reflect different contributions to learning and decision-making. The lOFC is more active in the Consistent group subjects suggesting that its activity reflects knowledge of associations between particular types of outcome. However, consistent with a number of studies (O'Doherty et al., 2001b; Rolls et al., 2003c), the vmPFC/mOFC showed a relatively greater level of activation to informative correct outcomes than to errors. The vmPFC/mOFC activity, therefore, probably does not reflect the informative impact that the reward outcome will have on learning; both informative correct outcomes and errors both provide subjects with information about the types of S, R, and O associations that exist the presence. Instead the vmPFC/mOFC appears to be representing the scalar value of the rewards; its activity was parametrical modulated by the size of the reward expectation. Other studies have emphasised the importance of the vmPFC/mOFC in representing reward expectation (O'Doherty et al., 2002).

The present results conflict with recently published neuroimaging experiments which identify outcome-specific expectations in the vmPFC/mOFC (Valentin et al., 2007; de Wit et al., 2009). The activation of the vmPFC/mOFC in those studies might reflect processes more related to reward-guided decision making that reward-guided learning. The experiment conducted by Valentin and colleagues, asked subjects to choose between different instrumental actions that were associated the subsequent delivery of different food rewards (tomato juice, chocolate milk and orange juice). Subjects were trained on this task and scanned during the last 20 trials of

learning. They were then fed to satiation with one of the specific outcomes before being rescanned while performing the same task in extinction. Not only did the authors find subjects less likely to select the action associated with the high probability of the devalued outcome, but this was reflected in higher activity in the vmPFC/mOFC. Arguably, during the periods when neurophyiological data was acquired the subjects had formed reasonably stable outcome-expectations and so were now using this information to choose between the different options. Such a signal probably reflects choice rather than a learning signal.

The OFC has some of the most well understood anatomical connective patterns in the frontal lobe, and so the functional differences proposed above are consistent with the different anatomical connections of the medial and lateral OFC (Ray and Price, 1993; Carmichael and Price, 1996; Ongur et al., 1998; Ferry et al., 2000). The lateral subdivision of the OFC is most strongly connected with the amygdala, medial thalamic regions, insula, temporal pole, inferior parietal lobule and the dlPFC (Mesulam and Mufson, 1982; Goldman-Rakic, 1987b; Yeterian and Pandya, 1988; Barbas and De Olmos, 1990; Fuster, 1997). In contrast, the medial subdivision has its strongest connections with the hippocampus and associated areas of the cingulate, retrosplenial and entorhinal cortices, anterior thalamus and the septal diagonal band (Pandya et al., 1981; Mesulam et al., 1983; Vogt and Pandya, 1987; Morecraft et al., 1992).

The current work conflicts with alternative theories which have been proposed to account for the anatomical segregation of these two regions of the OFC. Kringelbach and Rolls (2004) conducted a meta-analysis and concluded that the lOFC were involved in evaluating punishers which when detected may lead to a change in the current behaviour. In contrast, they argued, mOFC areas were involved in decoding and monitoring the reward value of reinforcers. The present study argues against this distinction as there were no differences between the encoding of

errors or informative correct feedback in the lOFC. The lOFC, therefore, may not specifically encode errors, per se, but it may act to guide behavioural change by encoding any informative feedback which might serve to suggest a change is necessary.

The ACC has an established role in monitoring ongoing actions. The ACC represents not only the occurrence of an error (Gemba et al., 1986; Ito et al., 2003), and correct responses (Walton et al., 2007b), but it does so whenever an outcome suggests the need to revise the estimate of the value of an action (Matsumoto et al., 2003; Walton et al., 2004; Amiez et al., 2005; Kennerley et al., 2006). The present study contributes to this growing work; demonstrating that a region of the ACC encodes an outcome monitoring signal that is greater when distinct outcome-specific expectations are available to guide action selection. Furthermore, the PPI analysis is consistent with non-human primate work which has demonstrated that the OFC and ACC play distinct and complementary roles in representing S-O and R-O associations, respectively (Rushworth et al., 2007a; Rudebeck et al., 2008b). Given the ACCs role in guiding voluntary choice (Kennerley et al., 2006; Walton et al., 2007b) a representation of outcome identity might serve to facilitate appropriate action selection which would be reflected in improvements in learning and memory. Indeed, the signal in this region correlates positively with block-by-block learning in the Consistent subjects, particularly in the later stages of the new learning task. As well as having access to information regarding goals and internal states of the animal, from neurons originating in prefrontal and limbic regions (Bates and Goldman-Rakic, 1993; Morecraft and Van Hoesen, 1998), parts of the primate dorsal ACC also send efferent projections to both primary motor cortex and the spinal cord, giving it direct influence over motor behaviour (Dum and Strick, 1991).

It is intriguing that the ACC signal correlates negatively with block-by-block learning in the subjects in the Inconsistent group with inconsistent S-O and R-O mappings. This could imply that this sub-region of the ACC is continually attempting to extract information regarding the nature of the reward from the environment, and when it is available it is able to successfully guide selection of the appropriate action. If no outcome-response expectations are established in the system, the ACC may lack appropriate information and could possibly disrupt successful action selection.

Taken together, the evidence presented above supports the emerging dissociation between the ACC and OFC in their respective roles in reinforcement-guided learning. Typically reports of OFC impairment have been investigated using S-O learning tasks (Rolls, 1999; Murray et al., 2007), whereas ACC lesion impairments are identified with R-O learning tasks (Shima and Tanji, 1998; Hadland et al., 2003; Kennerley et al., 2006). Whilst the homologies are more difficult to establish between rats and humans than monkeys and humans, the findings are much the same. Ostlund and Balleine (2007a) neatly demonstrate that lesions to the rat OFC disrupt the tendency of Pavlovian cues to facilitate instrumental performance in a Pavlovian-Instrumental Transfer task, but leave intact the suppressive effects of outcome devaluation. It was therefore argued that its role was limited to encoding predicative S-O relationships that could bias action selection. In contrast, lesions to the rat prelimbic cortex (PL; argued to be representative of the human ACC) abolish the animals' sensitivity to instrumental performance in outcome devaluation but have no effect on pavlovian-instrumental transfer. PL lesions also impair instrumental contingency degradation learning; the selective weakening of the predictive status of a previously trained CS by delivering outcomes with the same probability both in its presence and absence (Ostlund and Balleine, 2005). Combining these findings suggest that while

the PL, or ACC is important for encoding R-O associations (Dickinson and Balleine, 1993; Corbit and Balleine, 2000; Balleine, 2005); the OFC is critical for representing S-O associations.

Despite causality being notoriously difficult to infer in fMRI studies, this pattern is reflected in imaging experiments in humans. As noted above, the OFC shows increased activation in many stimulus based tasks where a choice leads to rewarding and punishing feedback in various sensory modalities (Kahnt et al.; Elliott et al., 1997; Rogers et al., 1999a; Elliott et al., 2000; Breiter et al., 2001; Critchley et al., 2001; Knutson et al., 2001; Gottfried et al., 2003; O'Doherty et al., 2003a; Rolls et al., 2003a; Rolls et al., 2003c), and activity reflects changes in S-O contingencies (O'Doherty et al., 2003a; Walton et al., 2004). In contrast, ACC activity is prominent when subjects explore their environments through trial-and-error learning; when salient feedback is obtained as a consequence of the explorative action, and when revision of expectation was required for the performance of a subsequent action (Walton et al., 2004; Daw et al., 2006; Forstmann et al., 2006; Yoshida and Ishii, 2006).

This experiment has shown that the formation and maintenance of learned expectations appears to rely on a network of cortical and subcortical regions including the lOFC, ACC and the amygdala and perirhinal cortex. The differential signal in the lOFC suggests that if distinct outcomes are available in the reward environment it may encode the conjunction of a particular reward identity with a particular stimulus choice. Furthermore, this work implicates the lateral and medial regions in representing the informativeness of an outcome for guiding learning, regardless of whether or not it is positive or negative, and in representing the scalar value of reward respectively. The ACC also showed increased in proportion to the Probability of correct response retrieval that was greater when specific outcome expectations were available to guide response selection. These signals correlated with behavioural accuracy across individual subjects

during learning, and so may reflect the presence of O-R associations that facilitated task performance in the Consistent group.

CHAPTER 8: GENERAL DISCUSSION

Behavioural choice, guided by accumulated experience, valuation and comparison is critical for an animal to negotiate its economic and social environment. While many aspects of these functions are mediated by the frontal lobes, the precise contribution from particular regions remains debated. Despite evidence showing anatomical and connectional heterogeneity within this structure, the OFC has often been regarded as a uniform region. This thesis aims to resolve some of the uncertainty about OFC function, by assuming that the medial and lateral regions of the OFC contribute differentially to learning and decision-making using two distinct methodologies. The first approach used circumscribed lesions to the mOFC of macaque monkeys and examined the contribution of the mOFC to social and emotional processing. The second set of experiments compared the effects of mOFC and lOFC lesions, investigating the unique contribution these regions in value assignment and comparison. Finally, a human-neuroimaging experiment investigated the differential representation of outcome-specific contingency learning in the vmPFC. Combining the findings from these experiments suggests that specific parts of the OFC make markedly different contributions to different cognitive functions.

8.1 Social and emotional valuation in the vmPFC

Various theories have argued that changes in personality following frontal brain injury are due to specific OFC damage and are supported by this region's role in stimulus-outcome (S-O) learning. However, Rudebeck and colleagues show that only emotional processing relies on the OFC (Rudebeck et al., 2006a). In contrast, social valuation is mediated by the ACC. This thesis

argues that as only lateral regions of the OFC support S-O learning, only damage to lateral areas should contribute to impairments in emotional processing. Chapter 3 supported this argument showing that animals with selective lesions of the mOFC were no different in measures of fearfulness or aggression following surgery. Neither did mOFC-lesioned animals value social stimuli differentially to their pre-operative performance. It therefore appears that the region once thought of as the most likely candidate to account for the changes in personality experienced by Phineas Gage does not actually support these functions. MOFC lesions did however disrupt choice behaviour on simple 2-choice probabilistic tasks and the nature of this impairment was explored in Chapters 4 and 5. Taken together, however, the experiments from this thesis suggest that while the mOFC does not play a direct role in social or emotional processing, its part perhaps becomes more prominent in complex social or emotive environments. Experiments show that OFC damage impairs the subjective feelings of guilt and regret (Saver and Damasio, 1991; Camille et al., 2004; Koenigs and Tranel, 2007; Koenigs et al., 2007; Krajbich et al., 2009). These emotions involve an element of decision-making and of comparisons of counterfactual and actual choice outcomes which may depend on the mOFC. Further experiments might explore these issues in light of the findings from Chapter 3.

8.2 Dissociating learning and decision-making in the OFC

For many years the nature of neural encoding in the prefrontal cortex (PFC) has been debated. Many theorists suggest that higher-order mental processes arise from dynamic and distributed activity across the PFC and cite evidence that ‘executive’ tasks cause activation in a broad expanse of cortex (Carpenter et al., 2000; Duncan and Owen, 2000). Other theories propose a more modular organisation of PFC, drawing from the broad differences between collective

activations from the different portions of the PFC (Fletcher and Henson, 2001; Wagner et al., 2001). In this context, Chapter 4 describes clear evidence for a double dissociation between effects of relatively small and focal OFC lesions. This work found that, in unchanging probabilistic environments, lOFC lesions induced credit assignment and associative learning impairments, but did not affect decision-making impairments when value comparison was difficult. By contrast, mOFC lesions caused the opposite pattern of impairment, and furthermore produced notable deficits in choice behaviour when the value of an irrelevant alternative option was high. These results imply a degree of fractionation of function even with the OFC. Finding a double dissociation within a region, often functionally considered as a homogenous structure, is particularly important as it highlights the significance of the fine-grain anatomical and connective differences. Furthermore, it suggests the necessity of consistent nomenclature across disciplines.

It could be argued that the global deficits experienced by the mOFC and lOFC-lesioned animals are relatively slight compared to memory deficits experienced by temporal lobe lesioned animals. This could be taken as evidence that frontal areas are less regionally specialised than posterior brain regions and represent functions in a more distributed manner. However, while this may be the case, a number of experimental differences can also account for the relatively mild impairments. The animals used in Chapter 4 and 5 had extensive practice on many learning and decision-making tasks before the lesions were made. As such, the network employed to solve these problems was functionally more experienced and therefore may have been better able to compensate after lesions challenged nodes within it. It is also important to remember that whilst the lesion effects appear relatively mild when analysed using global measures, such as percentage of errors, selective impairments are prominent when more detailed and complex

analyses are applied. Indeed, global measures of lesion deficits do not distinguish between lOFC and mOFC lesioned animals (Figure 4.5), it is only when the animals' abilities to solve the tasks are investigated on trial-by-trial basis that the group performance levels become distinct. The many trials performed by animals during these types of experiments not only reduce the impact of noise on estimates of behaviour, but also permit the detailed analyses described in this thesis. Furthermore, sophisticated trial-by-trial analyses allow researchers to make the most use of each experimental animal. This may be particularly relevant when considering the importance of reducing the ethical as well as the financial costs involved animal research.

Another particularly important consideration with animal lesion experiments is the nature of the lesion itself. Traditional aspiration lesions often damage underlying white matter tracts, as well as targeted cortical grey matter. This means that it is often not possible to rule out an interpretation which attributes the deficit to a disconnection between two critical brain regions. It is known that many efferent hippocampal and inferior temporal cortical fibres pass by the ventromedial prefrontal regions through the fornix and uncinate fasicle (Cavada et al., 2000; Croxson et al., 2005; Shamy et al., 2010) en route to the OFC. The hippocampus and interior temporal cortex are particular involved in memory encoding (Lepage et al., 1998; Dolan and Fletcher, 1999) and it is therefore plausible that networked with a region involved in associating stimuli to outcomes a disconnection between those two regions would produce deficits similar to those seen in the lOFC animals. The hippocampus is also involved in memory retrieval. A disconnection between a comparator region, located within the medial prefrontal network, and a region holding stored stimulus-outcome representations would impair decision-making in a manner similar to the mOFC-lesioned animals. Similarly, the OFC receives efferent projections from the amygdala and perhaps relies on the value representations estimated by this region.

Without access to the amygdala through disconnection the lOFC may be unable to associate stimuli and outcomes (Gaffan et al., 1993; Baxter et al., 2000). Finally, local disconnection between the medial prefrontal network of areas 14, 10, 25, 32 and 24 may give rise to the decision-making impairments observed in the current experiments. For example, the frontal polar cortex is involved in representing couterfactoral options, choice switching and explorative behaviour (Daw et al., 2006; Boorman et al., 2009). Potential local disconnections may disrupt local inhibition or cellular competition between neighbouring brain regions resulting in choice being more reliant on FPC representations of second best option causing increased exploratory behaviour, evidenced by the shift in the softmax function in figure 5.4. Similarly, disconnection between mOFC and anterior cingulate regions, 25, 32 and 24, involved in action selection and outcome monitoring (Rushworth et al., 2004; Walton et al., 2004; Walton et al., 2007a), might be responsible for deficits in translating choice into action selection biases. It is therefore necessary to replicate these findings with fibre-sparing excitotoxic lesions in order to confirm the specificity of the interpretation. Future experiments could investigate the nature of the reward network by explicitly using disconnection lesions. Combining unilateral excitotoxic lesions targeting a prefrontal node, with a lesion of a subcortical valuation node, or even a cortical action-selection node, would lead to a greater understanding of critical anatomical pathways mediating the function under investigation here (Gaffan et al., 1993; Baxter et al., 2000). Furthermore, by exploring the BOLD responses of lesioned animals with fMRI during learning and decision-making tasks it would be possible to identify which downstream regions in the decision-making network depend on the information from lOFC or mOFC, and in the absence of this information how these regions compensate. From a clinical perspective, these studies could quantify not only the degradation in anatomical connectivity following damage, such as that seen

in patients who have suffered strokes, but also the potential connective plasticity and functional compensatory mechanisms which may contribution to recovery over time. Anatomical and functional reorganisations after brain damage, which if related to behavioural task-specific improvement, are particularly relevant for human stroke patients under clinical rehabilitation programs.

A final consideration is that of the neuropharmacological contribution to learning and decision-making. Numerous studies show that chronic drug abusers have altered decision-making (Rogers et al., 1999b; Grant et al., 2000; Hanson et al., 2008). One class of drugs, the opiates, when chronically abused, produce deficits in decision-making very similar to those experienced by patients with orbital damage (Rogers et al., 1999b). Indeed, both functional and structural changes have been identified in the OFC of substance dependent individuals relative to controls (Tanabe et al., 2007; Bjork et al., 2008; Tanabe et al., 2009). Dopamine and serotonin are two neurotransmitters which have been implicated in the neuromodulation of aspects of learning and decision-making. Reductions in dopamine levels in Parkinson patients are associated with lower than normal learning rates (Rutledge et al., 2009), impaired use of positive reward prediction errors (Rutledge et al., 2009) and in switching choice selection (Rutledge et al., 2009). In contrast, enhanced dopamine is associated with increased impulsivity and increasing temporal discounting on reward value (Pine et al., 2010). Similarly, administration of the antagonist haloperidol in healthy control subjects is associated with enhanced Go-learning from positive reinforcement during a Go and No-go task, whereas the dopamine agonist caberoline diminished just this type of learning. Depletions of serotonin, through tryptophan administration, also implicate this neurotransmitter in aspects of learning and decision-making. Specifically, challenges to serotonin levels alter discrimination between magnitudes of expected

gain (Rogers et al., 2003), although this does not affect decisions between losses of different magnitudes or relative probabilities (Anderson et al., 2003; Rogers et al., 2003). Low levels of serotonin are also associated with increased selection of a low rewarding stimuli and increases in the rate of temporal discounting (Schweighofer et al., 2008), as well as slower associative learning when actions are followed by a delayed punishment (Tanaka et al., 2009). Taken together, it would therefore be valuable to explore the specific role of dopamine and serotonin in the modulation of value assignment and comparison in the tasks described in this thesis.

8.3 Processing differential reinforcement in the brain

Many studies demonstrate that unique outcome-specific expectations can facilitate animal learning and memory recall of S-R associations in animals (Schmidtke et al.; Carlson and Wielkiewicz, 1972; Trapold and Overmier, 1972; Jones and White, 1994; Miyashita et al., 2000; Kelly and Grant, 2001; Easton and Gaffan, 2002; Urcuioli, 2005; Ramirez and Savage, 2007). Chapter 6 showed that these effects were also evident in human learners, and the following chapter described the neural basis of the improved performance. This study showed that the lOFC and ACC increased in regional BOLD responses in subjects with access to outcomes-specific representations. However, while differential activity was identified in the lOFC at the time of an error feedback, the ACC distinguished between the different groups of subjects at the stimulus onset, in a contrast that reflected the probability that a subject would be correct in their choice. Chapter 7 argued that because the lOFC increased in functional connectivity with occipito-temporal regions of cortex it was involved in learning S-O specific associations. Selective lesions of OFC impair S-O learning (Rudebeck et al., 2008b; Rudebeck and Murray, 2008) and selective damage to lateral parts specifically impairs credit-assignment (Walton et al.,

2010). Combining these results suggests that the lOFC may be involved in assigning a particular outcome to a specific stimulus. The results of the experiment described in Chapter 7 conflict with many studies which argue that the mOFC (or vmPFC in humans) is more involved in outcome-specific or goal-directed learning (Valentin et al., 2007; de Wit et al., 2009). However, as these studies tend to use devaluation experiments, which as discussed confound learning and decision-making, they could be misidentifying the mOFCs activation in stimulus selection with the process of monitoring and updating the changes in outcome value. Therefore these experiments raise the question whether multiple brain regions have the ability to represent outcome-specific information, but may only do so in the context of specific types of task. If the present experiment had been designed to separate choice from learning, one could hypothesise that the mOFC and not the lOFC would show enhanced activation. Similarly, the ACC, a region which has not previously been implicated in goal-directed learning, may only be evident in tasks which emphasise the importance of response selection. In this experiment ACC activity is less likely to be associated with S-O learning as, unlike lOFC and temporal cortex, there was no increase in functional connectivity between ACC and the temporal cortex. Instead the peak ACC activation was centred in a region known to be connected with motor and premotor cortex. Damage to the ACC impairs R-O learning (Rudebeck et al., 2008b) and so the findings from the present study further support the suggestion that the ACC is important for this function, as well as suggesting that it may represent outcome-specific aspects of R-O learning. It therefore may be important to explore the role of the ACC in R-O devaluation experiments to confirm its involvement in goal-directed behaviour.

Whilst this was a challenging experiment, the paradigm was designed to accommodate a number of additional conditions, which may also serve to dissociate the prefrontal regional

contributions to S-O and R-O learning. The current experiment only compared subjects who had access to both consistent S-O and R-O associations (Consistent) with subjects who did not have established outcome-specific representations (Inconsistent). However, it would be interesting to compare between groups of subjects who were exposed to consistent S-O and inconsistent R-O associations during the preconditioning phases, with the groups of subjects exposed to the alternative mappings of consistent R-O and inconsistent S-O. It would be anticipated that at the presentation of the stimulus consistent S-O only subjects would hold an outcome-specific representation, which could be regionally localised, as the consistent R-O only subjects would lack this representation. Similarly, at the time of the response consistent R-O subjects would be expecting a specific outcome from that response, whereas consistent S-O subjects would not. Modelling the specific state-action values across learning might be expected to identify areas associated with updating and assigning outcome-specific credit to a particular stimulus or action.

An alternative experiment would involve using multivariate decoding techniques (Haynes and Rees, 2006; Haynes et al., 2007). Such an analysis would distinguish patterns of BOLD activation across the brain induced by either one stimulus or another. If applied to an event-related version of this paradigm, multivariate decoding might indentify brain regions whose overall activation distinguish between each outcome during the feedback epoch. If this activation overlapped with activation that distinguished outcome-specific expectations at the time of the stimulus presentation, it would provide particularly strong evidence that this brain region represents both outcome-specific reward expectation, as well as outcome-specific reward receipt. From the results of the present experiment, the lOFC is a likely candidate to mediate these functions.

REFERENCES

Abler B, Walter H, Erk S, Kammerer H, Spitzer M (2006) Prediction error as a linear function of reward probability is coded in human nucleus accumbens. Neuroimage 31:790-795.

Adams CD, Dickinson A (1981) Instrumental Responding Following Reinforcer Devaluation. Quarterly Journal of Experimental Psychology Section B-Comparative and Physiological Psychology 33:109-121.

Aggleton JP, Passingham RE (1981) Syndrome produced by lesions of the amygdala in monkeys (Macaca mulatta). J Comp Physiol Psychol 95:961-977.

Aggleton JP, Albasser MM, Aggleton DJ, Poirier GL, Pearce JM (2010) Lesions of the rat perirhinal cortex spare the acquisition of a complex configural visual discrimination yet impair object recognition. Behav Neurosci 124:55-68.

Alexander GE, Crutcher MD, DeLong MR (1990) Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog Brain Res 85:119-146.

Amiez C, Joseph JP, Procyk E (2005) Anterior cingulate error-related activity is modulated by predicted reward. Eur J Neurosci 21:3447-3452.

Amiez C, Joseph JP, Procyk E (2006) Reward encoding in the monkey anterior cingulate cortex. Cereb Cortex 16:1040-1055.

Amodio DM, Frith CD (2006) Meeting of minds: the medial frontal cortex and social cognition. Nat Rev Neurosci 7:268-277.

An X, Bandler R, Ongur D, Price JL (1998) Prefrontal cortical projections to longitudinal columns in the midbrain periaqueductal gray in macaque monkeys. J Comp Neurol 401:455-479.

Anderson IM, Richell RA, Bradshaw CM (2003) The effect of acute tryptophan depletion on probabilistic choice. J Psychopharmacol 17:3-7.

Anderson SW, Barrash J, Bechara A, Tranel D (2006) Impairments of emotion and real-world complex behavior following childhood- or adult-onset damage to ventromedial prefrontal cortex. J Int Neuropsychol Soc 12:224-235.

Apicella P, Ljungberg T, Scarnati E, Schultz W (1991) Responses to reward in monkey dorsal and ventral striatum. Exp Brain Res 85:491-500.

Arana FS, Parkinson JA, Hinton E, Holland AJ, Owen AM, Roberts AC (2003) Dissociable contributions of the human amygdala and orbitofrontal cortex to incentive motivation and goal selection. J Neurosci 23:9632-9638.

Astley SL, Wasserman EA (1999) Superordinate category formation in pigeons: association with a common delay or probability of food reinforcement makes perceptually dissimilar stimuli functionally equivalent. J Exp Psychol Anim Behav Process 25:415-432.

Astley SL, Peissig JJ, Wasserman EA (2001) Superordinate categorization via learned stimulus equivalence: quantity of reinforcement, hedonic value, and the nature of the mediator. J Exp Psychol Anim Behav Process 27:252-268.

Bailey P, Bonin G (1951) The isocortex of Man. Urbana: University of Illinois Press.

Balleine B, Dickinson A (1991) Instrumental performance following reinforcement devaluation depends upon incentive learning. Quarterly Journal of Experimental Psychology 43B:279-296.

Balleine B, Dickinson A (1998) The role of incentive learning in instrumental outcome revaluation by sensory-specific satiety. Animal Learning & Behavior 26:46-59.

Balleine BW (2005) Neural bases of food-seeking: affect, arousal and reward in corticostriatolimbic circuits. Physiol Behav 86:717-730.

Barbas H (1988) Anatomic organization of basoventral and mediodorsal visual recipient prefrontal regions in the rhesus monkey. J Comp Neurol 276:313-342.
Barbas H (1993) Organization of cortical afferent input to orbitofrontal areas in the rhesus monkey. Neuroscience 56:841-864.
Barbas H, Pandya DN (1989) Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. J Comp Neurol 286:353-375.
Barbas H, De Olmos J (1990) Projections from the amygdala to basoventral and mediodorsal prefrontal regions in the rhesus monkey. J Comp Neurol 300:549-571.
Barbas H, Blatt GJ (1995) Topographically specific hippocampal projections target functionally distinct prefrontal areas in the rhesus monkey. Hippocampus 5:511-533.
Bates JF, Goldman-Rakic PS (1993) Prefrontal connections of medial motor areas in the rhesus monkey. J Comp Neurol 336:211-228.
Baxter MG, Murray EA (2002) The amygdala and reward. Nat Rev Neurosci 3:563-573.
Baxter MG, Parker A, Lindner CC, Izquierdo AD, Murray EA (2000) Control of response selection by reinforcer value requires interaction of amygdala and orbital prefrontal cortex. J Neurosci 20:4311-4319.
Baylis LL, Gaffan D (1991) Amygdalectomy and ventromedial prefrontal ablation produce similar deficits in food choice and in simple object discrimination learning for an unseen reward. Exp Brain Res 86:617-622.
Bechara A, Damasio H, Damasio AR (2000) Emotion, decision making and the orbitofrontal cortex. Cereb Cortex 10:295-307.
Bechara A, Damasio AR, Damasio H, Anderson SW (1994) Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 50:7-15.
Bechara A, Damasio H, Tranel D, Damasio AR (1997) Deciding advantageously before knowing the advantageous strategy. Science 275:1293-1295.
Bechara A, Damasio H, Damasio AR, Lee GP (1999) Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. J Neurosci 19:5473-5481.
Beckmann M, Johansen-Berg H, Rushworth MF (2009) Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. J Neurosci 29:1175-1190.
Behrens TE, Hunt LT, Rushworth MF (2009) The computation of social behavior. Science 324:1160-1164.
Behrens TE, Woolrich MW, Walton ME, Rushworth MF (2007) Learning the value of information in an uncertain world. Nat Neurosci 10:1214-1221.
Behrens TE, Hunt LT, Woolrich MW, Rushworth MF (2008) Associative learning of social value. Nature 456:245-249.
Behrens TE, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, Matthews PM, Brady JM, Smith SM (2003) Characterization and propagation of uncertainty in diffusion-weighted MR imaging. Magn Reson Med 50:1077-1088.
Berlin HA, Rolls ET, Kischka U (2004) Impulsivity, time perception, emotion and reinforcement sensitivity in patients with orbitofrontal cortex lesions. Brain 127:1108-1126.
Bjork JM, Momenan R, Smith AR, Hommer DW (2008) Reduced posterior mesofrontal cortex activation by risky rewards in substance-dependent patients. Drug Alcohol Depend 95:115-128.
Blake P, Grafman J (2006) Effect of orbitofrontal lesion on mood and aggression. In: The Orbitofrontal Cortex (Zald DH, Rauch SL, eds). Oxford: Oxford University Press.
Boorman ED, Behrens TE, Woolrich MW, Rushworth MF (2009) How green is the grass on the other side? Frontopolar cortex and the evidence in favor of alternative courses of action. Neuron 62:733-743.
Boorman ED, Behrens TE, Woolrich MW, Rushworth MF (unpublished observations).

Bray S, O'Doherty J (2007) Neural coding of reward-prediction error signals during classical conditioning with attractive faces. J Neurophysiol 97:3036-3045.
Bray S, Shimojo S, O'Doherty JP (2010) Human medial orbitofrontal cortex is recruited during experience of imagined and real rewards. J Neurophysiol 103:2506-2512.
Breiter HC, Aharon I, Kahneman D, Dale A, Shizgal P (2001) Functional imaging of neural responses to expectancy and experience of monetary gains and losses. Neuron 30:619-639.
Brett M (1999) The MNI brain and the Talairach atlas. In. Cambridge.
Brodigan DL, Peterson GB (1976) Two-choice conditional discrimination performance of pigeons as a function of reward expectancy, prechoice delay and domesticity. Animal Learning & Behavior 4:121-124.
Brodmann K (1905) Beitraege zur histologischen Lokalisation der Grosshirnrinde. III Mitteilung. Die Rindenfelder der niederen Affen. Journal Psychological Neurology 4.
Brodmann K (1909) Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues. Leipzig: J.A. Barth.
Bruce C, Desimone R, Gross CG (1981) Visual properties of neurons in a polysensory area in superior temporal sulcus of the macaque. J Neurophysiol 46:369-384.
Buckley MJ, Gaffan D (1997) Impairment of visual object-discrimination learning after perirhinal cortex ablation. Behav Neurosci 111:467-475.
Buckley MJ, Gaffan D (1998) Perirhinal cortex ablation impairs visual object identification. J Neurosci 18:2268-2275.
Buckley MJ, Gaffan D (2006) Perirhinal cortical contributions to object perception. Trends Cogn Sci 10:100-107.
Buckley MJ, Gaffan D, Murray EA (1997) Functional double dissociation between two inferior temporal cortical areas: perirhinal cortex versus middle temporal gyrus. J Neurophysiol 77:587-598.
Butter CM, Snyder DR, McDonald JA (1970) Effects of orbital frontal lesions on aversive and aggressive behaviors in rhesus monkeys. J Comp Physiol Psychol 72:132-144.
Camille N, Coricelli G, Sallet J, Pradat-Diehl P, Duhamel JR, Sirigu A (2004) The involvement of the orbitofrontal cortex in the experience of regret. Science 304:1167-1170.
Carlson JG, Wielkiewicz RM (1972) Delay of reinforcement in instrumental discrimination learning of rats. J Comp Physiol Psychol 81:365-370.
Carmichael ST, Price JL (1994) Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. J Comp Neurol 346:366-402.
Carmichael ST, Price JL (1995a) Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. J Comp Neurol 363:615-641.
Carmichael ST, Price JL (1995b) Sensory and premotor connections of the orbital and medial prefrontal cortex of macaque monkeys. J Comp Neurol 363:642-664.
Carmichael ST, Price JL (1995c) Sensory and premotor connections of the orbital and medial prefrontal cortex of macaque monkeys. The Journal of Comparative Neurology 363:642-664.
Carmichael ST, Price JL (1996) Connectional networks within the orbital and medial prefrontal cortex of macaque monkeys. J Comp Neurol 371:179-207.
Carmichael ST, Clugnet MC, Price JL (1994) Central olfactory connections in the macaque monkey. J Comp Neurol 346:403-434.
Carpenter PA, Just MA, Reichle ED (2000) Working memory and executive function: evidence from neuroimaging. Curr Opin Neurobiol 10:195-199.
Cavada C, Company T, Tejedor J, Cruz-Rizzolo RJ, Reinoso-Suarez F (2000) The anatomical connections of the macaque monkey orbitofrontal cortex. A review. Cereb Cortex 10:220-242.
Chavis DA, Pandya DN (1976) Further observations on corticofrontal connections in the rhesus monkey. Brain Res 117:369-386.

Chiavaras MM, Petrides M (2000) Orbitofrontal sulci of the human and macaque monkey brain. J Comp Neurol 422:35-54.
Chiavaras MM, LeGoualher G, Evans A, Petrides M (2001) Three-dimensional probabilistic atlas of the human orbitofrontal sulci in standardized stereotaxic space. Neuroimage 13:479-496.
Chudasama Y, Robbins TW (2003) Dissociable contributions of the orbitofrontal and infralimbic cortex to pavlovian autoshaping and discrimination reversal learning: further evidence for the functional heterogeneity of the rodent frontal cortex. J Neurosci 23:8771-8780.
Ciaramelli E, Muccioli M, Ladavas E, di Pellegrino G (2007) Selective deficit in personal moral judgment following damage to ventromedial prefrontal cortex. Soc Cogn Affect Neurosci 2:84-92.
Clark L, Bechara A, Damasio H, Aitken MR, Sahakian BJ, Robbins TW (2008) Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. Brain 131:1311-1322.
Clarke HF, Robbins TW, Roberts AC (2008) Lesions of the medial striatum in monkeys produce perseverative impairments during reversal learning similar to those produced by lesions of the orbitofrontal cortex. J Neurosci 28:10972-10982.
Colwill RC, Rescorla RA (1985) Postconditioning devalutation of a reinforcer affects and incentive responding. Journal of Experimental Psychology: Animal Behavior Processes 11:120-132.
Corbit LH, Balleine BW (2000) The role of the hippocampus in instrumental conditioning. J Neurosci 20:4233-4239.
Corbit LH, Balleine BW (2003) The role of prelimbic cortex in instrumental conditioning. Behav Brain Res 146:145-157.
Critchley HD, Mathias CJ, Dolan RJ (2001) Neural activity in the human brain relating to uncertainty and arousal during anticipation. Neuron 29:537-545.
Croxson PL, Johansen-Berg H, Behrens TE, Robson MD, Pinsk MA, Gross CG, Richter W, Richter MC, Kastner S, Rushworth MF (2005) Quantitative investigation of connections of the prefrontal cortex in the human and macaque using probabilistic diffusion tractography. J Neurosci 25:8854-8866.
D'Ardenne K, McClure SM, Nystrom LE, Cohen JD (2008) BOLD responses reflecting dopaminergic signals in the human ventral tegmental area. Science 319:1264-1267.
Dade LA, Jones-Gotman M, Zatorre RJ, Evans AC (1998) Human brain function during odor encoding and recognition. A PET activation study. Ann N Y Acad Sci 855:572-574.
Damasio AR (1994) Descartes' Error: Emotiom, Reason, and the Human Brain. Putman Publishing.
Damasio AR, Tranel D, Damasio H (1990) Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. Behav Brain Res 41:81-94.
Damasio H (2005) Disorders of Social Conduct Following Damage to Prefrontal Cortices. In: Neurobiology of Human Values (Changeux JP, Damasio A, Singer W, Christen Y, eds). Berlin Heidelberg: Springer-Verlag.
Damasio H, Grabowski T, Frank R, Galaburda AM, Damasio AR (1994) The return of Phineas Gage: clues about the brain from the skull of a famous patient. Science 264:1102-1105.
Daw ND, O'Doherty JP, Dayan P, Seymour B, Dolan RJ (2006) Cortical substrates for exploratory decisions in humans. Nature 441:876-879.
Dayan P, Abbott LF (1999) Theoretical Neuroscience: Computational and Mathematical Modeling of Neural Systems. MIT Press.
de Bruin JP, van Oyen HG, Van de Poll N (1983) Behavioural changes following lesions of the orbital prefrontal cortex in male rats. Behav Brain Res 10:209-232.
De Martino B, Kumaran D, Seymour B, Dolan RJ (2006) Frames, biases, and rational decision-making in the human brain. Science 313:684-687.
De Martino B, Kumaran D, Holt B, Dolan RJ (2009) The neurobiology of reference-dependent value computation. J Neurosci 29:3833-3842.

de Wit S, Corlett PR, Aitken MR, Dickinson A, Fletcher PC (2009) Differential engagement of the ventromedial prefrontal cortex by goal-directed and habitual behavior toward food pictures in humans. J Neurosci 29:11330-11338.
den Ouden HE, Friston KJ, Daw ND, McIntosh AR, Stephan KE (2009) A dual role for prediction error in associative learning. Cereb Cortex 19:1175-1185.
Dias R, Robbins TW, Roberts AC (1997) Dissociable forms of inhibitory control within prefrontal cortex with an analog of the Wisconsin Card Sort Test: restriction to novel situations and independence from "on-line" processing. J Neurosci 17:9285-9297.
Dickinson A, Balleine B, eds (1993) Actions and responses: the dual psychology of behaviour. Malden, MA: Blackwell.
Dolan RJ, Fletcher PE (1999) Encoding and retrival in human medial trmporal lobes: An emporical investigation using functional magnetic resonance imaging (fMRI). Hippocampus 9:25-34.
Dum RP, Strick PL (1991) The origin of corticospinal projections from the premotor areas in the frontal lobe. J Neurosci 11:667-689.
Dum RP, Strick PL, eds (1993) Cingulate motor areas. . Boston: Birkhauser.
Dum RP, Strick PL (1996) Spinal cord terminations of the medial wall motor areas in macaque monkeys. J Neurosci 16:6513-6525.
Duncan J, Owen AM (2000) Common regions of the human frontal lobe recruited by diverse cognitive demands. Trends Neurosci 23:475-483.
Dunn BD, Dalgleish T, Lawrence AD (2006) The somatic marker hypothesis: a critical evaluation. Neurosci Biobehav Rev 30:239-271.
Easton A (2004) Differential reward outcome learning in adult humans. Behav Brain Res 154:165-169.
Easton A, Gaffan D (2002) Insights into the nature of fronto-temporal interactions from a biconditional discrimination task in the monkey. Behav Brain Res 136:217-226.
Economo C, Koskinas GN (1925) Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen. Wein, Austria: Spinger.
Eichenbaum H, Stewart C, Morris RG (1990) Hippocampal representation in place learning. J Neurosci 10:3531-3542.
Elliott R, Frith CD, Dolan RJ (1997) Differential neural response to positive and negative feedback in planning and guessing tasks. Neuropsychologia 35:1395-1404.
Elliott R, Dolan RJ, Frith CD (2000) Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. Cereb Cortex 10:308-317.
Elliott R, Agnew Z, Deakin JF (2008) Medial orbitofrontal cortex codes relative rather than absolute value of financial rewards in humans. Eur J Neurosci 27:2213-2218.
Elliott R, Newman JL, Longe OA, Deakin JF (2003) Differential response patterns in the striatum and orbitofrontal cortex to financial reward in humans: a parametric functional magnetic resonance imaging study. J Neurosci 23:303-307.
Eslinger PJ, Damasio AR (1985) Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. Neurology 35:1731-1741.
Estevez AF, Fuentes LJ, Overmier JB, Gonzalez C (2003) Differential outcomes effect in children and adults with down syndrome. Am J Ment Retard 108:108-116.
Estevez AF, Fuentes LJ, Mari-Beffa P, Gonzalez C, Alvarez D (2001) The Differential Outcome Effect as a Useful Tool to Improve Conditional Discrimination Learning in Children. Learning and Motivation 32:48-64.
Estevez AF, Vivas AB, Alonso D, Mari-Beffa P, Fuentes LJ, Overmier JB (2007) Enhancing challenged students' recognition of mathematical relations through differential outcomes training. Q J Exp Psychol (Colchester) 60:571-580.

Fellows LK (2006) Deciding how to decide: ventromedial frontal lobe damage affects information acquisition in multi-attribute decision making. Brain 129:944-952.
Fellows LK (2007) The role of orbitofrontal cortex in decision making: a component process account. Ann N Y Acad Sci 1121:421-430.
Fellows LK, Farah MJ (2003) Ventromedial frontal cortex mediates affective shifting in humans: evidence from a reversal learning paradigm. Brain 126:1830-1837.
Fellows LK, Farah MJ (2005) Different underlying impairments in decision-making following ventromedial and dorsolateral frontal lobe damage in humans. Cereb Cortex 15:58-63.
Fellows LK, Farah MJ (2007) The role of ventromedial prefrontal cortex in decision making: judgment under uncertainty or judgment per se? Cereb Cortex 17:2669-2674.
Ferry AT, Ongur D, An X, Price JL (2000) Prefrontal cortical projections to the striatum in macaque monkeys: evidence for an organization related to prefrontal networks. J Comp Neurol 425:447-470.
FitzGerald TH, Seymour B, Dolan RJ (2009) The role of human orbitofrontal cortex in value comparison for incommensurable objects. J Neurosci 29:8388-8395.
Fletcher PC, Henson RN (2001) Frontal lobes and human memory: insights from functional neuroimaging. Brain 124:849-881.
Forstmann BU, Brass M, Koch I, von Cramon DY (2006) Voluntary selection of task sets revealed by functional magnetic resonance imaging. J Cogn Neurosci 18:388-398.
Fox AS, Shelton SE, Oakes TR, Converse AK, Davidson RJ, Kalin NH (2010) Orbitofrontal cortex lesions alter anxiety-related activity in the primate bed nucleus of stria terminalis. J Neurosci 30:7023-7027.
Frey S, Kostopoulos P, Petrides M (2000) Orbitofrontal involvement in the processing of unpleasant auditory information. Eur J Neurosci 12:3709-3712.
Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ (1997) Psychophysiological and modulatory interactions in neuroimaging. Neuroimage 6:218-229.
Frith CD, Frith U (2006) The neural basis of mentalizing. Neuron 50:531-534.
Fuster JM (1997) The prefrontal cortex. Anatomy, physiology and neuropsychology of the frontal lobe, 3rd Edition. New York: Raven.
Gaffan D, Murray EA, Fabre-Thorpe M (1993) Interaction of the amygdala with the frontal lobe in reward memory. Eur J Neurosci 5:968-975.
Gaffan EA, Eacott MJ, Simpson EL (2000) Perirhinal cortex ablation in rats selectively impairs object identification in a simultaneous visual comparison task. Behav Neurosci 114:18-31.
Gallagher M, McMahan RW, Schoenbaum G (1999) Orbitofrontal cortex and representation of incentive value in associative learning. J Neurosci 19:6610-6614.
Galvan A, Hare TA, Davidson M, Spicer J, Glover G, Casey BJ (2005) The role of ventral frontostriatal circuitry in reward-based learning in humans. J Neurosci 25:8650-8656.
Gemba H, Sasaki K, Brooks VB (1986) 'Error' potentials in limbic cortex (anterior cingulate area 24) of monkeys during motor learning. Neurosci Lett 70:223-227.
Ghashghaei HT, Hilgetag CC, Barbas H (2007) Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. Neuroimage 34:905-923.
Ghazanfar AA, Maier JX, Hoffman KL, Logothetis NK (2005) Multisensory integration of dynamic faces and voices in rhesus monkey auditory cortex. J Neurosci 25:5004-5012.
Ghods-Sharifi S, St Onge JR, Floresco SB (2009) Fundamental contribution by the basolateral amygdala to different forms of decision making. J Neurosci 29:5251-5259.
Glascher J, Hampton AN, O'Doherty JP (2009) Determining a role for ventromedial prefrontal cortex in encoding action-based value signals during reward-related decision making. Cereb Cortex 19:483-495.

Godschalk M, Lemon RN, Kuypers HG, Ronday HK (1984) Cortical afferents and efferents of monkey postarcuate area: an anatomical and electrophysiological study. Exp Brain Res 56:410-424.
Goldman-Rakic PS (1987a) Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: Handbook of physiology (Mountcastle VB, Plum F, eds), pp 373-417. Bethesda, MD: American Physiological Society.
Goldman-Rakic PS (1987b) Circuitry of the frontal association cortex and its relevance to dementia. Arch Gerontol Geriatr 6:299-309.
Gonzalez LE, Rujano M, Tucci S, Paredes D, Silva E, Alba G, Hernandez L (2000) Medial prefrontal transection enhances social interaction. I: behavioral studies. Brain Res 887:7-15.
Gottfried JA, O'Doherty J, Dolan RJ (2002) Appetitive and aversive olfactory learning in humans studied using event-related functional magnetic resonance imaging. J Neurosci 22:10829-10837.
Gottfried JA, O'Doherty J, Dolan RJ (2003) Encoding predictive reward value in human amygdala and orbitofrontal cortex. Science 301:1104-1107.
Grant S, Contoreggi C, London ED (2000) Drug abusers show impaired performance in a laboratory test of decision making. Neuropsychologia 38:1180-1187.
Grill-Spector K (2003) The neural basis of object perception. Curr Opin Neurobiol 13:159-166.
Haber SN, Knutson B (2010) The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology 35:4-26.
Haber SN, Kim KS, Mailly P, Calzavara R (2006) Reward-related cortical inputs define a large striatal region in primates that interface with associative cortical connections, providing a substrate for incentive-based learning. J Neurosci 26:8368-8376.
Hadland KA, Rushworth MF, Gaffan D, Passingham RE (2003) The anterior cingulate and reward-guided selection of actions. J Neurophysiol 89:1161-1164.
Hampton AN, Bossaerts P, O'Doherty JP (2008) Neural correlates of mentalizing-related computations during strategic interactions in humans. Proc Natl Acad Sci U S A 105:6741-6746.
Hampton AN, Adolphs R, Tyszka MJ, O'Doherty JP (2007) Contributions of the amygdala to reward expectancy and choice signals in human prefrontal cortex. Neuron 55:545-555.
Hanson KL, Luciana M, Sullwold K (2008) Reward-related decision-making deficits and elevated impulsivity among MDMA and other drug users. Drug Alcohol Depend 96:99-110.
Hare TA, Camerer CF, Rangel A (2009) Self-control in decision-making involves modulation of the vmPFC valuation system. Science 324:646-648.
Hare TA, O'Doherty J, Camerer CF, Schultz W, Rangel A (2008) Dissociating the role of the orbitofrontal cortex and the striatum in the computation of goal values and prediction errors. J Neurosci 28:5623-5630.
Hatfield T, Han JS, Conley M, Gallagher M, Holland P (1996) Neurotoxic lesions of basolateral, but not central, amygdala interfere with Pavlovian second-order conditioning and reinforcer devaluation effects. J Neurosci 16:5256-5265.
Hayden BY, Nair AC, McCoy AN, Platt ML (2008) Posterior cingulate cortex mediates outcome-contingent allocation of behavior. Neuron 60:19-25.
Haynes JD, Rees G (2006) Decoding mental states from brain activity in humans. Nat Rev Neurosci 7:523-534.
Haynes JD, Sakai K, Rees G, Gilbert S, Frith C, Passingham RE (2007) Reading hidden intentions in the human brain. Curr Biol 17:323-328.
Heberlein AS, Padon AA, Gillihan SJ, Farah MJ, Fellows LK (2008) Ventromedial frontal lobe plays a critical role in facial emotion recognition. J Cogn Neurosci 20:721-733.
Herrnstein R (1997) The Matching Law. In: A posthumous collection of papers of R.J. Herrnstein (Rachlin H, Laibson DI, eds). Cambridge, MA.: Harvard University Press.

Hornak J, Rolls ET, Wade D (1996) Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. Neuropsychologia 34:247-261.
Hornak J, Bramham J, Rolls ET, Morris RG, O'Doherty J, Bullock PR, Polkey CE (2003) Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. Brain 126:1691-1712.
Hornak J, O'Doherty J, Bramham J, Rolls ET, Morris RG, Bullock PR, Polkey CE (2004) Reward-related reversal learning after surgical excisions in orbito-frontal or dorsolateral prefrontal cortex in humans. J Cogn Neurosci 16:463-478.
Hosokawa T, Kato K, Inoue M, Mikami A (2004) Neurons in the orbitofrontal cortex code both visual shapes and reward types. Neuroreport 15:1493-1496.
Hosokawa T, Kato K, Inoue M, Mikami A (2007) Neurons in the macaque orbitofrontal cortex code relative preference of both rewarding and aversive outcomes. Neurosci Res 57:434-445.
Hsu DT, Price JL (2007) Midline and intralaminar thalamic connections with the orbital and medial prefrontal networks in macaque monkeys. J Comp Neurol 504:89-111.
Huerta MF, Kaas JH (1990) Supplementary eye field as defined by intracortical microstimulation: connections in macaques. J Comp Neurol 293:299-330.
Ito S, Stuphorn V, Brown JW, Schall JD (2003) Performance monitoring by the anterior cingulate cortex during saccade countermanding. Science 302:120-122.
Iversen SD, Mishkin M (1970) Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. Exp Brain Res 11:376-386.
Izquierdo A, Murray EA (2004) Combined unilateral lesions of the amygdala and orbital prefrontal cortex impair affective processing in rhesus monkeys. J Neurophysiol 91:2023-2039.
Izquierdo A, Suda RK, Murray EA (2004) Bilateral orbital prefrontal cortex lesions in rhesus monkeys disrupt choices guided by both reward value and reward contingency. J Neurosci 24:7540-7548.
Izquierdo A, Suda RK, Murray EA (2005) Comparison of the effects of bilateral orbital prefrontal cortex lesions and amygdala lesions on emotional responses in rhesus monkeys. J Neurosci 25:8534-8542.
Jenkinson M, Smith S (2001) A global optimisation method for robust affine registration of brain images. Med Image Anal 5:143-156.
Jones B, Mishkin M (1972) Limbic Lesions and Problem of Stimulus-Reinforcement Associations. Experimental Neurology 36:362-&.
Jones EG, Powell TP (1970) An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. Brain 93:793-820.
Jones M, White KG (1994) An Investigation of the Differential - Outcomes Effect within Sessions. Journal of the Experimental Analysis of Behavior 61:389-406.
Kable JW, Glimcher PW (2007) The neural correlates of subjective value during intertemporal choice. Nat Neurosci 10:1625-1633.
Kable JW, Glimcher PW (2009) The neurobiology of decision: consensus and controversy. Neuron 63:733-745.
Kahneman D, Tversky A (1979) Prospect theory: An analysis of decisions under risk. Econometrica 47:263-291.
Kahnt T, Heinzle J, Park SQ, Haynes JD The neural code of reward anticipation in human orbitofrontal cortex. Proc Natl Acad Sci U S A 107:6010-6015.
Kalin NH (2003) Nonhuman primate studies of fear, anxiety, and temperament and the role of benzodiazepine receptors and GABA systems. J Clin Psychiatry 64 Suppl 3:41-44.
Kelly R, Grant DS (2001) A differential outcomes effect using biologically neutral outcomes in delayed matching-to-sample with pigeons. Quarterly Journal of Experimental Psychology Section B-Comparative and Physiological Psychology 54:69-79.

Kennerley SW, Wallis JD (2009a) Evaluating choices by single neurons in the frontal lobe: outcome value encoded across multiple decision variables. Eur J Neurosci 29:2061-2073.
Kennerley SW, Wallis JD (2009b) Encoding of reward and space during a working memory task in the orbitofrontal cortex and anterior cingulate sulcus. J Neurophysiol 102:3352-3364.
Kennerley SW, Dahmubed AF, Lara AH, Wallis JD (2009) Neurons in the frontal lobe encode the value of multiple decision variables. J Cogn Neurosci 21:1162-1178.
Kennerley SW, Walton ME, Behrens TE, Buckley MJ, Rushworth MF (2006) Optimal decision making and the anterior cingulate cortex. Nat Neurosci 9:940-947.
Kepecs A, Uchida N, Zariwala HA, Mainen ZF (2008) Neural correlates, computation and behavioural impact of decision confidence. Nature 455:227-231.
Kesner RP, Williams JM (1995) Memory for magnitude of reinforcement: dissociation between the amygdala and hippocampus. Neurobiol Learn Mem 64:237-244.
Killcross S, Coutureau E (2003) Coordination of actions and habits in the medial prefrontal cortex of rats. Cereb Cortex 13:400-408.
Kim H, Shimojo S, O'Doherty JP (2006) Is avoiding an aversive outcome rewarding? Neural substrates of avoidance learning in the human brain. PLoS Biol 4:e233.
Knutson B, Cooper JC (2005) Functional magnetic resonance imaging of reward prediction. Curr Opin Neurol 18:411-417.
Knutson B, Fong GW, Adams CM, Varner JL, Hommer D (2001) Dissociation of reward anticipation and outcome with event-related fMRI. Neuroreport 12:3683-3687.
Knutson B, Taylor J, Kaufman M, Peterson R, Glover G (2005) Distributed neural representation of expected value. J Neurosci 25:4806-4812.
Kobayashi S, Pinto de Carvalho O, Schultz W (2010) Adaptation of reward sensitivity in orbitofrontal neurons. J Neurosci 30:534-544.
Koenigs M, Tranel D (2007) Irrational economic decision-making after ventromedial prefrontal damage: evidence from the Ultimatum Game. J Neurosci 27:951-956.
Koenigs M, Young L, Adolphs R, Tranel D, Cushman F, Hauser M, Damasio A (2007) Damage to the prefrontal cortex increases utilitarian moral judgements. Nature 446:908-911.
Kolb B (1974) Social behavior of rats with chronic prefrontal lesions. J Comp Physiol Psychol 87:466-474.
Kondo H, Saleem KS, Price JL (2003) Differential connections of the temporal pole with the orbital and medial prefrontal networks in macaque monkeys. J Comp Neurol 465:499-523.
Kondo H, Saleem KS, Price JL (2005) Differential connections of the perirhinal and parahippocampal cortex with the orbital and medial prefrontal networks in macaque monkeys. J Comp Neurol 493:479-509.
Krajbich I, Adolphs R, Tranel D, Denburg NL, Camerer CF (2009) Economic games quantify diminished sense of guilt in patients with damage to the prefrontal cortex. J Neurosci 29:2188-2192.
Kringelbach ML, Rolls ET (2004) The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog Neurobiol 72:341-372.
Kringelbach ML, O'Doherty J, Rolls ET, Andrews C (2003) Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. Cereb Cortex 13:1064-1071.
Lacroix L, Spinelli S, Heidbreder CA, Feldon J (2000) Differential role of the medial and lateral prefrontal cortices in fear and anxiety. Behav Neurosci 114:1119-1130.
Lebreton M, Jorge S, Michel V, Thirion B, Pessiglione M (2009) An automatic valuation system in the human brain: evidence from functional neuroimaging. Neuron 64:431-439.
Lee AC, Bandelow S, Schwarzbauer C, Henson RN, Graham KS (2006) Perirhinal cortex activity during visual object discrimination: an event-related fMRI study. Neuroimage 33:362-373.
Lepage M, Habib R, Tulving E (1998) Hippocampal PET activations of memory encoding and retrieval: the HIPER model. Hippocampus 8:313-322.

Lopez-Crespo G, Plaza V, Fuentes LJ, Estevez AF (2009) Improvement of age-related memory deficits by differential outcomes. Int Psychogeriatr 21:503-510.
Luce RD (1959) Individual Choice Behaviour: A Theoretical Analysis. New York: Wiley.
Machado CJ, Bachevalier J (2006) The impact of selective amygdala, orbital frontal cortex, or hippocampal formation lesions on established social relationships in rhesus monkeys (Macaca mulatta). Behav Neurosci 120:761-786.
Machado CJ, Bachevalier J (2007) The effects of selective amygdala, orbital frontal cortex or hippocampal formation lesions on reward assessment in nonhuman primates. Eur J Neurosci 25:2885-2904.
Machado CJ, Bachevalier J (2008) Behavioral and hormonal reactivity to threat: effects of selective amygdala, hippocampal or orbital frontal lesions in monkeys. Psychoneuroendocrinology 33:926-941.
Machado CJ, Kazama AM, Bachevalier J (2009) Impact of amygdala, orbital frontal, or hippocampal lesions on threat avoidance and emotional reactivity in nonhuman primates. Emotion 9:147-163.
Mah L, Arnold MC, Grafman J (2004) Impairment of social perception associated with lesions of the prefrontal cortex. Am J Psychiatry 161:1247-1255.
Mah LW, Arnold MC, Grafman J (2005) Deficits in social knowledge following damage to ventromedial prefrontal cortex. J Neuropsychiatry Clin Neurosci 17:66-74.
Maia TV, McClelland JL (2004) A reexamination of the evidence for the somatic marker hypothesis: what participants really know in the Iowa gambling task. Proc Natl Acad Sci U S A 101:16075-16080.
Maki P, Overmier JB, Delos S, Gutman AJ (1995) Expectancies as factors influencing conditional discrimination performance of children. The Psychological Record 45:45-71.
Malkova L, Gaffan D, Murray EA (1997) Excitotoxic lesions of the amygdala fail to produce impairment in visual learning for auditory secondary reinforcement but interfere with reinforcer devaluation effects in rhesus monkeys. J Neurosci 17:6011-6020.
Matelli M, Camarda R, Glickstein M, Rizzolatti G (1986) Afferent and efferent projections of the inferior area 6 in the macaque monkey. J Comp Neurol 251:281-298.
Matsumoto K, Suzuki W, Tanaka K (2003) Neuronal correlates of goal-based motor selection in the prefrontal cortex. Science 301:229-232.
McClure SM, Laibson DI, Loewenstein G, Cohen JD (2004) Separate neural systems value immediate and delayed monetary rewards. Science 306:503-507.
McClure SM, Ericson KM, Laibson DI, Loewenstein G, Cohen JD (2007) Time discounting for primary rewards. J Neurosci 27:5796-5804.
McDannald MA, Saddoris MP, Gallagher M, Holland PC (2005) Lesions of orbitofrontal cortex impair rats' differential outcome expectancy learning but not conditioned stimulus-potentiated feeding. J Neurosci 25:4626-4632.
Mesulam MM, Mufson EJ (1982) Insula of the old world monkey. I. Architectonics in the insulo-orbito-temporal component of the paralimbic brain. J Comp Neurol 212:1-22.
Mesulam MM, Mufson EJ, Levey AI, Wainer BH (1983) Cholinergic innervation of cortex by the basal forebrain: cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey. J Comp Neurol 214:170-197.
Meunier M, Bachevalier J, Mishkin M (1997) Effects of orbital frontal and anterior cingulate lesions on object and spatial memory in rhesus monkeys. Neuropsychologia 35:999-1015.
Milad MR, Wright CI, Orr SP, Pitman RK, Quirk GJ, Rauch SL (2007) Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. Biol Psychiatry 62:446-454.

Miller GA (1956) The magical number seven plus or minus two: some limits on our capacity for processing information. Psychol Rev 63:81-97.
Mineka S, Keir R, Price V (1980) Fear of snakes in wild- and laboratory-reared rhesus monkeys (Macaca mulatta). Animal Learning & Behavior 8:653-663.
Mink JW (1996) The basal ganglia: focused selection and inhibition of competing motor programs. Prog Neurobiol 50:381-425.
Mishkin M, Suzuki WA, Gadian DG, Vargha-Khadem F (1997) Hierarchical organization of cognitive memory. Philos Trans R Soc Lond B Biol Sci 352:1461-1467.
Miyashita Y, Nakajima S, Imada H (2000) Differential outcome effect in the horse. Journal of the Experimental Analysis of Behavior 74:245-254.
Morecraft RJ, Van Hoesen GW (1992) Cingulate input to the primary and supplementary motor cortices in the rhesus monkey: evidence for somatotopy in areas 24c and 23c. J Comp Neurol 322:471-489.
Morecraft RJ, Van Hoesen GW (1998) Convergence of limbic input to the cingulate motor cortex in the rhesus monkey. Brain Res Bull 45:209-232.
Morecraft RJ, Geula C, Mesulam MM (1992) Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. J Comp Neurol 323:341-358.
Morris JS, Dolan RJ (2004) Dissociable amygdala and orbitofrontal responses during reversal fear conditioning. Neuroimage 22:372-380.
Morrison SE, Salzman CD Re-valuing the amygdala. Curr Opin Neurobiol.
Morrison SE, Salzman CD (2009) The convergence of information about rewarding and aversive stimuli in single neurons. J Neurosci 29:11471-11483.
Muakkassa KF, Strick PL (1979) Frontal lobe inputs to primate motor cortex: evidence for four somatotopically organized 'premotor' areas. Brain Res 177:176-182.
Murphy FC, Nimmo-Smith I, Lawrence AD (2003) Functional neuroanatomy of emotions: a meta-analysis. Cogn Affect Behav Neurosci 3:207-233.
Murray EA, Wise SP Interactions between orbital prefrontal cortex and amygdala: advanced cognition, learned responses and instinctive behaviors. Curr Opin Neurobiol 20:212-220.
Murray EA, Wise SP Interactions between orbital prefrontal cortex and amygdala: advanced cognition, learning responses and instinctive behaviours. Current Opinion in Neurobiology.
Murray EA, Richmond BJ (2001) Role of perirhinal cortex in object perception, memory, and associations. Curr Opin Neurobiol 11:188-193.
Murray EA, O'Doherty JP, Schoenbaum G (2007) What we know and do not know about the functions of the orbitofrontal cortex after 20 years of cross-species studies. J Neurosci 27:8166-8169.
Niv Y, Daw ND, Joel D, Dayan P (2007) Tonic dopamine: opportunity costs and the control of response vigor. Psychopharmacology (Berl) 191:507-520.
Noonan MP, Walton ME, Behrens TE, Sallet J, Buckley MJ, Rushworth MF (2010) Separate value comparison and learning mechanisms in macaque medial and lateral orbitofrontal cortex. Proc Natl Acad Sci U S A.
Noonan MP, Walton ME, Behrens T, Sallet J, Buckley MJ, Rushworth MFS (in press) Contrasting roles for macaque lateral and medial orbitofrontal cortex in value assignment and comparison. Proc Natl Acad Sci U S A.
O'Doherty J, Critchley H, Deichmann R, Dolan RJ (2003a) Dissociating valence of outcome from behavioral control in human orbital and ventral prefrontal cortices. J Neurosci 23:7931-7939.
O'Doherty J, Rolls ET, Francis S, Bowtell R, McGlone F (2001a) Representation of pleasant and aversive taste in the human brain. J Neurophysiol 85:1315-1321.
O'Doherty J, Kringelbach ML, Rolls ET, Hornak J, Andrews C (2001b) Abstract reward and punishment representations in the human orbitofrontal cortex. Nat Neurosci 4:95-102.

O'Doherty J, Winston J, Critchley H, Perrett D, Burt DM, Dolan RJ (2003b) Beauty in a smile: the role of medial orbitofrontal cortex in facial attractiveness. Neuropsychologia 41:147-155.
O'Doherty J, Rolls ET, Francis S, Bowtell R, McGlone F, Kobal G, Renner B, Ahne G (2000) Sensory-specific satiety-related olfactory activation of the human orbitofrontal cortex. Neuroreport 11:893-897.
O'Doherty JP (2007) Lights, camembert, action! The role of human orbitofrontal cortex in encoding stimuli, rewards, and choices. Ann N Y Acad Sci 1121:254-272.
O'Doherty JP, Deichmann R, Critchley HD, Dolan RJ (2002) Neural responses during anticipation of a primary taste reward. Neuron 33:815-826.
Obayashi S, Nagai Y, Suhara T, Okauchi T, Inaji M, Iriki A, Maeda J (2009) Monkey brain activity modulated by reward preferences: a positron emission tomography study. Neurosci Res 64:421-428.
Ongur D, Price JL (2000) The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb Cortex 10:206-219.
Ongur D, An X, Price JL (1998) Prefrontal cortical projections to the hypothalamus in macaque monkeys. J Comp Neurol 401:480-505.
Ongur D, Ferry AT, Price JL (2003) Architectonic subdivision of the human orbital and medial prefrontal cortex. J Comp Neurol 460:425-449.
Ostlund SB, Balleine BW (2005) Lesions of medial prefrontal cortex disrupt the acquisition but not the expression of goal-directed learning. J Neurosci 25:7763-7770.
Ostlund SB, Balleine BW (2007a) Orbitofrontal cortex mediates outcome encoding in Pavlovian but not instrumental conditioning. J Neurosci 27:4819-4825.
Ostlund SB, Balleine BW (2007b) The contribution of orbitofrontal cortex to action selection. Ann N Y Acad Sci 1121:174-192.
Overmier BJ, Linwick D (2001) Conditional choice - unique outcomes establish expectancies that mediate choice behaviour. Integrative Physiological and Behavioural Science 36:173-181.
Padoa-Schioppa C (2009) Range-adapting representation of economic value in the orbitofrontal cortex. J Neurosci 29:14004-14014.
Padoa-Schioppa C, Assad JA (2006) Neurons in the orbitofrontal cortex encode economic value. Nature 441:223-226.
Padoa-Schioppa C, Assad JA (2008) The representation of economic value in the orbitofrontal cortex is invariant for changes of menu. Nat Neurosci 11:95-102.
Pandya DN, Kuypers HG (1969) Cortico-cortical connections in the rhesus monkey. Brain Res 13:13-36.
Pandya DN, Van Hoesen GW, Mesulam MM (1981) Efferent connections of the cingulate gyrus in the rhesus monkey. Exp Brain Res 42:319-330.
Parkinson JK, Murray EA, Mishkin M (1988) A selective mnemonic role for the hippocampus in monkeys: memory for the location of objects. J Neurosci 8:4159-4167.
Passingham RE, Stephan KE, Kotter R (2002) The anatomical basis of functional localization in the cortex. Nat Rev Neurosci 3:606-616.
Paton JJ, Belova MA, Morrison SE, Salzman CD (2006) The primate amygdala represents the positive and negative value of visual stimuli during learning. Nature 439:865-870.
Paus T, Tomaiuolo F, Otaky N, MacDonald D, Petrides M, Atlas J, Morris R, Evans AC (1996) Human cingulate and paracingulate sulci: pattern, variability, asymmetry, and probabilistic map. Cereb Cortex 6:207-214.
Petrides JS, Pandya A (1994) Comparative architectonic analysis of the human and the macaque frontal cortex. In: Handbook of neuropsychology (Boller F, Grafman J, eds), pp 17-58: Elsevier Science.
Petrides M, ed (2006) The orbitofrontal cortex: sulcal and gyral morphology and architecture. New York: Oxford University Press.

Petrides M (2007) The orbitofrontal cortex: novelty, deviation from expectation, and memory. Ann N Y Acad Sci 1121:33-53.
Phelps EA, Delgado MR, Nearing KI, LeDoux JE (2004) Extinction learning in humans: role of the amygdala and vmPFC. Neuron 43:897-905.
Philippi CL, Mehta S, Grabowski T, Adolphs R, Rudrauf D (2009) Damage to association fiber tracts impairs recognition of the facial expression of emotion. J Neurosci 29:15089-15099.
Pickens CL, Saddoris MP, Gallagher M, Holland PC (2005) Orbitofrontal lesions impair use of cue-outcome associations in a devaluation task. Behav Neurosci 119:317-322.
Pickens CL, Saddoris MP, Setlow B, Gallagher M, Holland PC, Schoenbaum G (2003) Different roles for orbitofrontal cortex and basolateral amygdala in a reinforcer devaluation task. J Neurosci 23:11078-11084.
Pine A, Shiner T, Seymour B, Dolan RJ (2010) Dopamine, time, and impulsivity in humans. J Neurosci 30:8888-8896.
Plassmann H, O'Doherty J, Rangel A (2007) Orbitofrontal cortex encodes willingness to pay in everyday economic transactions. J Neurosci 27:9984-9988.
Plassmann H, O'Doherty JP, Rangel A (2010) Appetitive and aversive goal values are encoded in the medial orbitofrontal cortex at the time of decision making. J Neurosci 30:10799-10808.
Plassmann H, O'Doherty J, Shiv B, Rangel A (2008) Marketing actions can modulate neural representations of experienced pleasantness. Proc Natl Acad Sci U S A 105:1050-1054.
Platt ML, Huettel SA (2008) Risky business: the neuroeconomics of decision making under uncertainty. Nat Neurosci 11:398-403.
Poremba A, Malloy M, Saunders RC, Carson RE, Herscovitch P, Mishkin M (2004) Species-specific calls evoke asymmetric activity in the monkey's temporal poles. Nature 427:448-451.
Pratt WE, Mizumori SJ (1998) Characteristics of basolateral amygdala neuronal firing on a spatial memory task involving differential reward. Behav Neurosci 112:554-570.
Preuschoff K, Quartz SR, Bossaerts P (2008) Human insula activation reflects risk prediction errors as well as risk. J Neurosci 28:2745-2752.
Quilodran R, Rothe M, Procyk E (2008) Behavioral shifts and action valuation in the anterior cingulate cortex. Neuron 57:314-325.
Ramirez DR, Savage LM (2007) Differential involvement of the basolateral amygdala, orbitofrontal cortex, and nucleus accumbens core in the acquisition and use of reward expectancies. Behav Neurosci 121:896-906.
Rangel A, Hare T (2010) Neural computations associated with goal-directed choice. Curr Opin Neurobiol 20:262-270.
Rangel A, Camerer C, Montague PR (2008) A framework for studying the neurobiology of value-based decision making. Nat Rev Neurosci 9:545-556.
Ray JP, Price JL (1993) The organization of projections from the mediodorsal nucleus of the thalamus to orbital and medial prefrontal cortex in macaque monkeys. J Comp Neurol 337:1-31.
Ray P (1973) Independence of Irrelevant Alternatives. Econometrica 41:987-991.
Rescorla RA (1990) Instrumental responses become associated with reinforcers that differ in one feature. Animal Learning and Behaviour 18:206-211.
Rescorla RA (1992) Depression of an instrumental response by a single devaluation of its outcome. Q J Exp Psychol B 44:123-136.
Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S (2004) The role of the medial frontal cortex in cognitive control. Science 306:443-447.
Roesch MR, Olson CR (2004) Neuronal activity related to reward value and motivation in primate frontal cortex. Science 304:307-310.

Roesch MR, Olson CR (2005a) Neuronal activity dependent on anticipated and elapsed delay in macaque prefrontal cortex, frontal and supplementary eye fields, and premotor cortex. J Neurophysiol 94:1469-1497.
Roesch MR, Olson CR (2005b) Neuronal activity in primate orbitofrontal cortex reflects the value of time. J Neurophysiol 94:2457-2471.
Roesch MR, Singh T, Brown PL, Mullins SE, Schoenbaum G (2009) Ventral striatal neurons encode the value of the chosen action in rats deciding between differently delayed or sized rewards. J Neurosci 29:13365-13376.
Rogers RD, Tunbridge EM, Bhagwagar Z, Drevets WC, Sahakian BJ, Carter CS (2003) Tryptophan depletion alters the decision-making of healthy volunteers through altered processing of reward cues. Neuropsychopharmacology 28:153-162.
Rogers RD, Owen AM, Middleton HC, Williams EJ, Pickard JD, Sahakian BJ, Robbins TW (1999a) Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex. J Neurosci 19:9029-9038.
Rogers RD, Everitt BJ, Baldacchino A, Blackshaw AJ, Swainson R, Wynne K, Baker NB, Hunter J, Carthy T, Booker E, London M, Deakin JF, Sahakian BJ, Robbins TW (1999b) Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. Neuropsychopharmacology 20:322-339.
Rolls ET (1999) The Brain and Emotion. Oxford: Oxford University Press.
Rolls ET (2000) The orbitofrontal cortex and reward. Cereb Cortex 10:284-294.
Rolls ET (2005) Emotion Explained. New York: Oxford University Press.
Rolls ET, Baylis LL (1994) Gustatory, olfactory, and visual convergence within the primate orbitofrontal cortex. J Neurosci 14:5437-5452.
Rolls ET, Kringelbach ML, de Araujo IE (2003a) Different representations of pleasant and unpleasant odours in the human brain. Eur J Neurosci 18:695-703.
Rolls ET, Verhagen JV, Kadohisa M (2003b) Representations of the texture of food in the primate orbitofrontal cortex: neurons responding to viscosity, grittiness, and capsaicin. J Neurophysiol 90:3711-3724.
Rolls ET, McCabe C, Redoute J (2008) Expected value, reward outcome, and temporal difference error representations in a probabilistic decision task. Cereb Cortex 18:652-663.
Rolls ET, Hornak J, Wade D, McGrath J (1994) Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. J Neurol Neurosurg Psychiatry 57:1518-1524.
Rolls ET, Critchley HD, Mason R, Wakeman EA (1996) Orbitofrontal cortex neurons: role in olfactory and visual association learning. J Neurophysiol 75:1970-1981.
Rolls ET, O'Doherty J, Kringelbach ML, Francis S, Bowtell R, McGlone F (2003c) Representations of pleasant and painful touch in the human orbitofrontal and cingulate cortices. Cereb Cortex 13:308-317.
Romanski LM, Averbeck BB (2009) The primate cortical auditory system and neural representation of conspecific vocalizations. Annu Rev Neurosci 32:315-346.
Rosene DL, Van Hoesen GW (1977) Hippocampal efferents reach widespread areas of cerebral cortex and amygdala in the rhesus monkey. Science 198:315-317.
Rudebeck PH, Murray EA (2008) Amygdala and orbitofrontal cortex lesions differentially influence choices during object reversal learning. J Neurosci 28:8338-8343.
Rudebeck PH, Bannerman DM, Rushworth MF (2008a) The contribution of distinct subregions of the ventromedial frontal cortex to emotion, social behavior, and decision making. Cogn Affect Behav Neurosci 8:485-497.

Rudebeck PH, Buckley MJ, Walton ME, Rushworth MF (2006a) A role for the macaque anterior cingulate gyrus in social valuation. Science 313:1310-1312.
Rudebeck PH, Walton ME, Smyth AN, Bannerman DM, Rushworth MF (2006b) Separate neural pathways process different decision costs. Nat Neurosci 9:1161-1168.
Rudebeck PH, Walton ME, Millette BH, Shirley E, Rushworth MF, Bannerman DM (2007) Distinct contributions of frontal areas to emotion and social behaviour in the rat. Eur J Neurosci 26:2315-2326.
Rudebeck PH, Behrens TE, Kennerley SW, Baxter MG, Buckley MJ, Walton ME, Rushworth MF (2008b) Frontal cortex subregions play distinct roles in choices between actions and stimuli. J Neurosci 28:13775-13785.
Rushworth MF, Behrens TE (2008) Choice, uncertainty and value in prefrontal and cingulate cortex. Nat Neurosci 11:389-397.
Rushworth MF, Walton ME, Kennerley SW, Bannerman DM (2004) Action sets and decisions in the medial frontal cortex. Trends Cogn Sci 8:410-417.
Rushworth MF, Behrens TE, Rudebeck PH, Walton ME (2007a) Contrasting roles for cingulate and orbitofrontal cortex in decisions and social behaviour. Trends Cogn Sci 11:168-176.
Rushworth MF, Buckley MJ, Behrens TE, Walton ME, Bannerman DM (2007b) Functional organization of the medial frontal cortex. Curr Opin Neurobiol 17:220-227.
Rutledge RB, Lazzaro SC, Lau B, Myers CE, Gluck MA, Glimcher PW (2009) Dopaminergic drugs modulate learning rates and perseveration in Parkinson's patients in a dynamic foraging task. J Neurosci 29:15104-15114.
Saleem KS, Kondo H, Price JL (2008) Complementary circuits connecting the orbital and medial prefrontal networks with the temporal, insular, and opercular cortex in the macaque monkey. J Comp Neurol 506:659-693.
Salzmann E, Vidyasagar TR, Creutzfeldt OD (1993) Functional comparison of neuronal properties in the primate posterior hippocampus and parahippocampus (area TF/TH) during different behavioural paradigms involving memory and selective attention. Behav Brain Res 53:133-149.
Samejima K, Ueda Y, Doya K, Kimura M (2005) Representation of action-specific reward values in the striatum. Science 310:1337-1340.
Savage LM (2001) In search of the neurobiological underpinnings of the differential outcomes effect. Integr Physiol Behav Sci 36:182-195.
Savage LM, Langlais PJ (1995) Differential outcomes attenuate memory impairments on matching-to-position following pyrithiamine-induced thaimine deficiency in rats. Psychiobiology 23:153-160.
Savage LM, Parsons JP (1997) The Effects of delay-Interval, Inter-trial-Interval, Amnestic Drugs, and Differential Outcomes on Matching-to-Position in Rats. Psychobiology 25:303-312.
Saver JL, Damasio AR (1991) Preserved access and processing of social knowledge in a patient with acquired sociopathy due to ventromedial frontal damage. Neuropsychologia 29:1241-1249.
Schafer A, Leutgeb V, Reishofer G, Ebner F, Schienle A (2009) Propensity and sensitivity measures of fear and disgust are differentially related to emotion-specific brain activation. Neurosci Lett 465:262-266.
Schienle A, Schafer A, Hermann A, Walter B, Stark R, Vaitl D (2006) fMRI responses to pictures of mutilation and contamination. Neurosci Lett 393:174-178.
Schliebs R, Arendt T (2006) The significance of the cholinergic system in the brain during aging and in Alzheimer's disease. J Neural Transm 113:1625-1644.
Schmidtke KA, Katz JS, Wright AA Differential outcomes facilitate same/different concept learning. Anim Cogn 13:583-589.
Schoenbaum G, Roesch M (2005) Orbitofrontal cortex, associative learning, and expectancies. Neuron 47:633-636.

Schoenbaum G, Chiba AA, Gallagher M (1998) Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning. Nat Neurosci 1:155-159.
Schoenbaum G, Chiba AA, Gallagher M (1999) Neural encoding in orbitofrontal cortex and basolateral amygdala during olfactory discrimination learning. J Neurosci 19:1876-1884.
Schoenbaum G, Setlow B, Saddoris MP, Gallagher M (2003a) Encoding predicted outcome and acquired value in orbitofrontal cortex during cue sampling depends upon input from basolateral amygdala. Neuron 39:855-867.
Schoenbaum G, Roesch MR, Stalnaker TA, Takahashi YK (2009) A new perspective on the role of the orbitofrontal cortex in adaptive behaviour. Nat Rev Neurosci 10:885-892.
Schoenbaum G, Setlow B, Nugent SL, Saddoris MP, Gallagher M (2003b) Lesions of orbitofrontal cortex and basolateral amygdala complex disrupt acquisition of odor-guided discriminations and reversals. Learn Mem 10:129-140.
Schoenemann PT, Sheehan MJ, Glotzer LD (2005) Prefrontal white matter volume is disproportionately larger in humans than in other primates. Nat Neurosci 8:242-252.
Schonberg T, Daw ND, Joel D, O'Doherty JP (2007) Reinforcement learning signals in the human striatum distinguish learners from nonlearners during reward-based decision making. J Neurosci 27:12860-12867.
Schultz W (2000) Multiple reward signals in the brain. Nat Rev Neurosci 1:199-207.
Schultz W, Tremblay L, Hollerman JR (1998) Reward prediction in primate basal ganglia and frontal cortex. Neuropharmacology 37:421-429.
Schultz W, Tremblay L, Hollerman JR (2000) Reward processing in primate orbitofrontal cortex and basal ganglia. Cereb Cortex 10:272-284.
Schweighofer N, Bertin M, Shishida K, Okamoto Y, Tanaka SC, Yamawaki S, Doya K (2008) Low-serotonin levels increase delayed reward discounting in humans. J Neurosci 28:4528-4532.
Seltzer B, Pandya DN (1989) Frontal lobe connections of the superior temporal sulcus in the rhesus monkey. J Comp Neurol 281:97-113.
Seo H, Lee D (2007) Temporal filtering of reward signals in the dorsal anterior cingulate cortex during a mixed-strategy game. J Neurosci 27:8366-8377.
Seo H, Lee D (2008) Cortical mechanisms for reinforcement learning in competitive games. Philos Trans R Soc Lond B Biol Sci 363:3845-3857.
Shah AP, Treit D (2003) Excitotoxic lesions of the medial prefrontal cortex attenuate fear responses in the elevated-plus maze, social interaction and shock probe burying tests. Brain Research 969:183-194.
Shamy JL, Carpenter DM, Fong SG, Murray EA, Tang CY, Hof PR, Rapp PR (2010) Alterations of white matter tracts following neurotoxic hippocampal lesions in macaque monkeys: a diffusion tensor imaging study. Hippocampus 20:906-910.
Shidara M, Richmond BJ (2002) Anterior cingulate: single neuronal signals related to degree of reward expectancy. Science 296:1709-1711.
Shima K, Tanji J (1998) Role for cingulate motor area cells in voluntary movement selection based on reward. Science 282:1335-1338.
Simmons JM, Ravel S, Shidara M, Richmond BJ (2007) A comparison of reward-contingent neuronal activity in monkey orbitofrontal cortex and ventral striatum: guiding actions toward rewards. Ann N Y Acad Sci 1121:376-394.
Simon HA (1957) Models of Man. New York: Wiley.
Small DM, Jones-Gotman M, Zatorre RJ, Petrides M, Evans AC (1997a) Flavor processing: more than the sum of its parts. Neuroreport 8:3913-3917.
Small DM, Jones-Gotman M, Zatorre RJ, Petrides M, Evans AC (1997b) A role for the right anterior temporal lobe in taste quality recognition. J Neurosci 17:5136-5142.

Small DM, Zatorre RJ, Dagher A, Evans AC, Jones-Gotman M (2001) Changes in brain activity related to eating chocolate: from pleasure to aversion. Brain 124:1720-1733.
Small DM, Zald DH, Jones-Gotman M, Zatorre RJ, Pardo JV, Frey S, Petrides M (1999) Human cortical gustatory areas: a review of functional neuroimaging data. Neuroreport 10:7-14.
Smith BW, Mitchell DG, Hardin MG, Jazbec S, Fridberg D, Blair RJ, Ernst M (2009) Neural substrates of reward magnitude, probability, and risk during a wheel of fortune decision-making task. Neuroimage 44:600-609.
Smith DV, Hayden BY, Truong TK, Song AW, Platt ML, Huettel SA (2010) Distinct value signals in anterior and posterior ventromedial prefrontal cortex. J Neurosci 30:2490-2495.
Smith ML, Milner B (1989) Right hippocampal impairment in the recall of spatial location: encoding deficit or rapid forgetting? Neuropsychologia 27:71-81.
Smith SM (2002) Fast robust automated brain extraction. Hum Brain Mapp 17:143-155.
Stalnaker TA, Roesch MR, Franz TM, Burke KA, Schoenbaum G (2006) Abnormal associative encoding in orbitofrontal neurons in cocaine-experienced rats during decision-making. Eur J Neurosci 24:2643-2653.
Sugrue LP, Corrado GS, Newsome WT (2004) Matching behavior and the representation of value in the parietal cortex. Science 304:1782-1787.
Sugrue LP, Corrado GS, Newsome WT (2005) Choosing the greater of two goods: neural currencies for valuation and decision making. Nat Rev Neurosci 6:363-375.
Sul JH, Kim H, Huh N, Lee D, Jung MW (2010) Distinct roles of rodent orbitofrontal and medial prefrontal cortex in decision making. Neuron 66:449-460.
Sul JH, Kim H, Huh N, Lee D, Jung MW (in press) Distinct roles of rodent orbitofrontal and medial prefrontal cortex in decision making. Neuron.
Sutton R, Barto AG (1998) Reinforcement Learning. Cambridge, Massachusetts: MIT Press.
Takahashi YK, Roesch MR, Stalnaker TA, Haney RZ, Calu DJ, Taylor AR, Burke KA, Schoenbaum G (2009) The orbitofrontal cortex and ventral tegmental area are necessary for learning from unexpected outcomes. Neuron 62:269-280.
Tanabe J, Thompson L, Claus E, Dalwani M, Hutchison K, Banich MT (2007) Prefrontal cortex activity is reduced in gambling and nongambling substance users during decision-making. Hum Brain Mapp 28:1276-1286.
Tanabe J, Tregellas JR, Dalwani M, Thompson L, Owens E, Crowley T, Banich M (2009) Medial orbitofrontal cortex gray matter is reduced in abstinent substance-dependent individuals. Biol Psychiatry 65:160-164.
Tanaka SC, Balleine BW, O'Doherty JP (2008) Calculating consequences: brain systems that encode the causal effects of actions. J Neurosci 28:6750-6755.
Tanaka SC, Doya K, Okada G, Ueda K, Okamoto Y, Yamawaki S (2004) Prediction of immediate and future rewards differentially recruits cortico-basal ganglia loops. Nat Neurosci 7:887-893.
Tanaka SC, Shishida K, Schweighofer N, Okamoto Y, Yamawaki S, Doya K (2009) Serotonin affects association of aversive outcomes to past actions. J Neurosci 29:15669-15674.
Thorndike EL (1911) Animal Intelligence: Experimental Studies. New York: Macmillan.
Thorndike EL (1933) A Proof of the Law of Effect. Science 77:173-175.
Thorpe SJ, Rolls ET, Maddison S (1983) The orbitofrontal cortex: neuronal activity in the behaving monkey. Exp Brain Res 49:93-115.
Tobler PN, O'Doherty J P, Dolan RJ, Schultz W (2006) Human neural learning depends on reward prediction errors in the blocking paradigm. J Neurophysiol 95:301-310.
Tobler PN, O'Doherty JP, Dolan RJ, Schultz W (2007) Reward value coding distinct from risk attitude-related uncertainty coding in human reward systems. J Neurophysiol 97:1621-1632.

Toni I, Rowe J, Stephan KE, Passingham RE (2002) Changes of cortico-striatal effective connectivity during visuomotor learning. Cereb Cortex 12:1040-1047.
Toni I, Ramnani N, Josephs O, Ashburner J, Passingham RE (2001) Learning arbitrary visuomotor associations: temporal dynamic of brain activity. Neuroimage 14:1048-1057.
Tranel D, Hathaway-Nepple J, Anderson SW (2007) Impaired behavior on real-world tasks following damage to the ventromedial prefrontal cortex. J Clin Exp Neuropsychol 29:319-332.
Trapold MA, Overmier JB, eds (1972) The second learning process in instrumental learning. New York: Appleton-Century-Crafts.
Tremblay L, Schultz W (1999) Relative reward preference in primate orbitofrontal cortex. Nature 398:704-708.
Tremblay L, Schultz W (2000) Modifications of reward expectation-related neuronal activity during learning in primate orbitofrontal cortex. J Neurophysiol 83:1877-1885.
Tsao DY, Schweers N, Moeller S, Freiwald WA (2008) Patches of face-selective cortex in the macaque frontal lobe. Nat Neurosci 11:877-879.
Tsujimoto S, Genovesio A, Wise SP (2009) Monkey orbitofrontal cortex encodes response choices near feedback time. J Neurosci 29:2569-2574.
Tversky A, Kahneman D (1981) The framing of decisions and the psychology of choice. Science 211:453-458.
Urcuioli PJ (2005) Behavioral and associative effects of differential outcomes in discrimination learning. Learning & Behavior 33:1-21.
Ursu S, Carter CS (2005) Outcome representations, counterfactual comparisons and the human orbitofrontal cortex: implications for neuroimaging studies of decision-making. Brain Res Cogn Brain Res 23:51-60.
Valentin VV, O'Doherty JP (2009) Overlapping prediction errors in dorsal striatum during instrumental learning with juice and money reward in the human brain. J Neurophysiol 102:3384-3391.
Valentin VV, Dickinson A, O'Doherty JP (2007) Determining the neural substrates of goal-directed learning in the human brain. J Neurosci 27:4019-4026.
van Duuren E, Lankelma J, Pennartz CM (2008) Population coding of reward magnitude in the orbitofrontal cortex of the rat. J Neurosci 28:8590-8603.
Van Hoesen G, Pandya DN, Butters N (1975) Some connections of the entorhinal (area 28) and perirhinal (area 35) cortices of the rhesus monkey. II. Frontal lobe afferents. Brain Res 95:25-38.
Van Hoesen GW, Pandya DN, Butters N (1972) Cortical afferents to the entorhinal cortex of the Rhesus monkey. Science 175:1471-1473.
Verhagen JV, Rolls ET, Kadohisa M (2003) Neurons in the primate orbitofrontal cortex respond to fat texture independently of viscosity. J Neurophysiol 90:1514-1525.
Vidyasagar TR, Salzmann E, Creutzfeldt OD (1991) Unit activity in the hippocampus and the parahippocampal temporobasal association cortex related to memory and complex behaviour in the awake monkey. Brain Res 544:269-278.
Vogt BA, Pandya DN (1987) Cingulate cortex of the rhesus monkey: II. Cortical afferents. J Comp Neurol 262:271-289.
von Neumann J, Morgenstern O (1947) Theory of games and economic behaviour. 2nd ed Princeton University Press.
Wagner AD, Maril A, Bjork RA, Schacter DL (2001) Prefrontal contributions to executive control: fMRI evidence for functional distinctions within lateral Prefrontal cortex. Neuroimage 14:1337-1347.
Walker EA (1940) A cytoarchitectural study of the prefrontal area of the macaque monkey. . The Journal of Comparative Neurology 73:59-86.
Wallis JD (2007) Orbitofrontal cortex and its contribution to decision-making. Annu Rev Neurosci 30:31-56.

Wallis JD, Kennerley SW Heterogeneous reward signals in prefrontal cortex. Curr Opin Neurobiol 20:191-198.
Wallis JD, Miller EK (2003) Neuronal activity in primate dorsolateral and orbital prefrontal cortex during performance of a reward preference task. Eur J Neurosci 18:2069-2081.
Walton ME, Devlin JT, Rushworth MF (2004) Interactions between decision making and performance monitoring within prefrontal cortex. Nat Neurosci 7:1259-1265.
Walton ME, Bannerman DM, Alterescu K, Rushworth MF (2003) Functional specialization within medial frontal cortex of the anterior cingulate for evaluating effort-related decisions. J Neurosci 23:6475-6479.
Walton ME, Rudebeck PH, Bannerman DM, Rushworth MF (2007a) Calculating the cost of acting in frontal cortex. Ann N Y Acad Sci 1104:340-356.
Walton ME, Croxson PL, Behrens TE, Kennerley SW, Rushworth MF (2007b) Adaptive decision making and value in the anterior cingulate cortex. Neuroimage 36 Suppl 2:T142-154.
Walton ME, Behrens TE, Buckley MJ, Rudebeck PH, Rushworth MF (2010) Separable learning systems in the macaque brain and the role of orbitofrontal cortex in contingent learning. Neuron 65:927-939.
Wang XJ, Tegner J, Constantinidis C, Goldman-Rakic PS (2004) Division of labor among distinct subtypes of inhibitory neurons in a cortical microcircuit of working memory. Proc Natl Acad Sci U S A 101:1368-1373.
Webster MJ, Bachevalier J, Ungerleider LG (1994) Connections of inferior temporal areas TEO and TE with parietal and frontal cortex in macaque monkeys. Cereb Cortex 4:470-483.
Weller JA, Levin IP, Shiv B, Bechara A (2007) Neural correlates of adaptive decision making for risky gains and losses. Psychol Sci 18:958-964.
Woolrich MW, Ripley BD, Brady M, Smith SM (2001) Temporal autocorrelation in univariate linear modeling of FMRI data. Neuroimage 14:1370-1386.
Yeterian EH, Pandya DN (1988) Corticothalamic connections of paralimbic regions in the rhesus monkey. J Comp Neurol 269:130-146.
Yoshida W, Ishii S (2006) Resolution of uncertainty in prefrontal cortex. Neuron 50:781-789.
Young L, Bechara A, Tranel D, Damasio H, Hauser M, Damasio A (2010) Damage to ventromedial prefrontal cortex impairs judgment of harmful intent. Neuron 65:845-851.
Zald DH, Pardo JV (1997) Emotion, olfaction, and the human amygdala: amygdala activation during aversive olfactory stimulation. Proc Natl Acad Sci U S A 94:4119-4124.
Zald DH, Lee JT, Fluegel KW, Pardo JV (1998) Aversive gustatory stimulation activates limbic circuits in humans. Brain 121 (Pt 6):1143-1154.
Zatorre RJ, Jones-Gotman M, Evans AC, Meyer E (1992) Functional localization and lateralization of human olfactory cortex. Nature 360:339-340.

APPENDIX

I: Histology

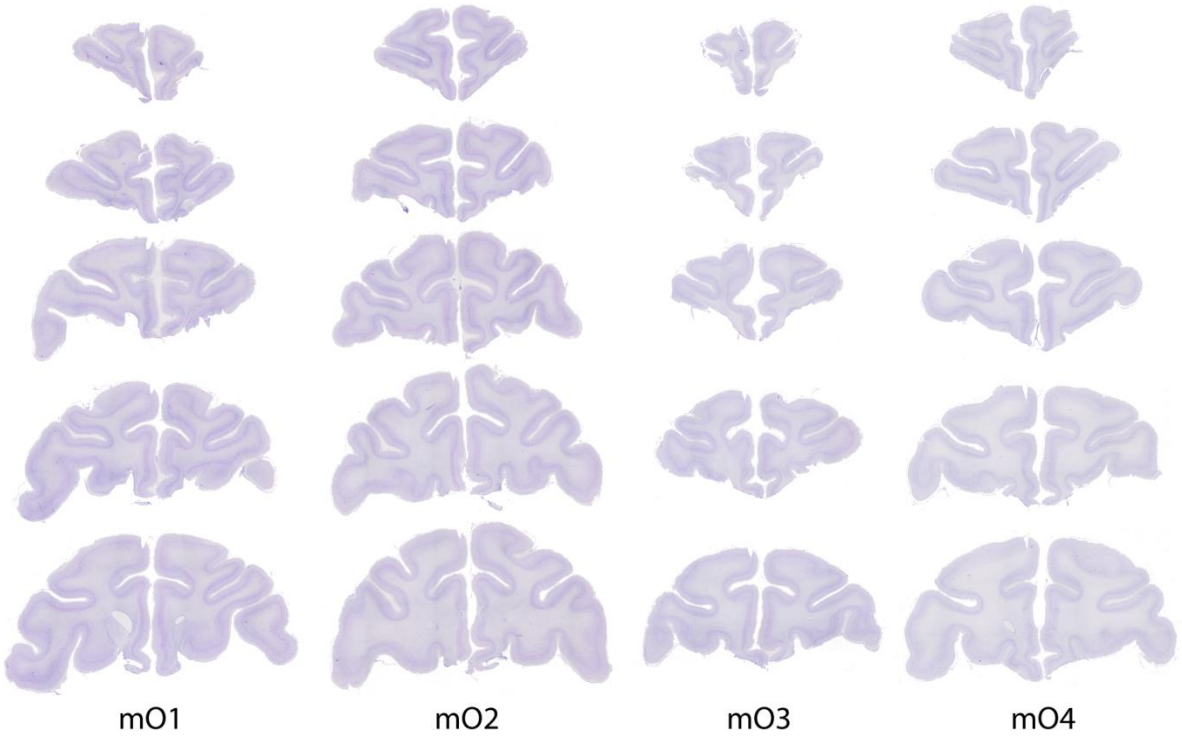

Figure AI.1. Coronal sections through the frontal lobes, for each individual animal of the mOFC-lesioned group (mo1, mo2, mo3, mo4). The lesions were made as intended, from the medial orbitofrontal sulcus to the rostral sulcus, including mainly Walker's area 14 (1940) but also some parts of area 10 were removed.

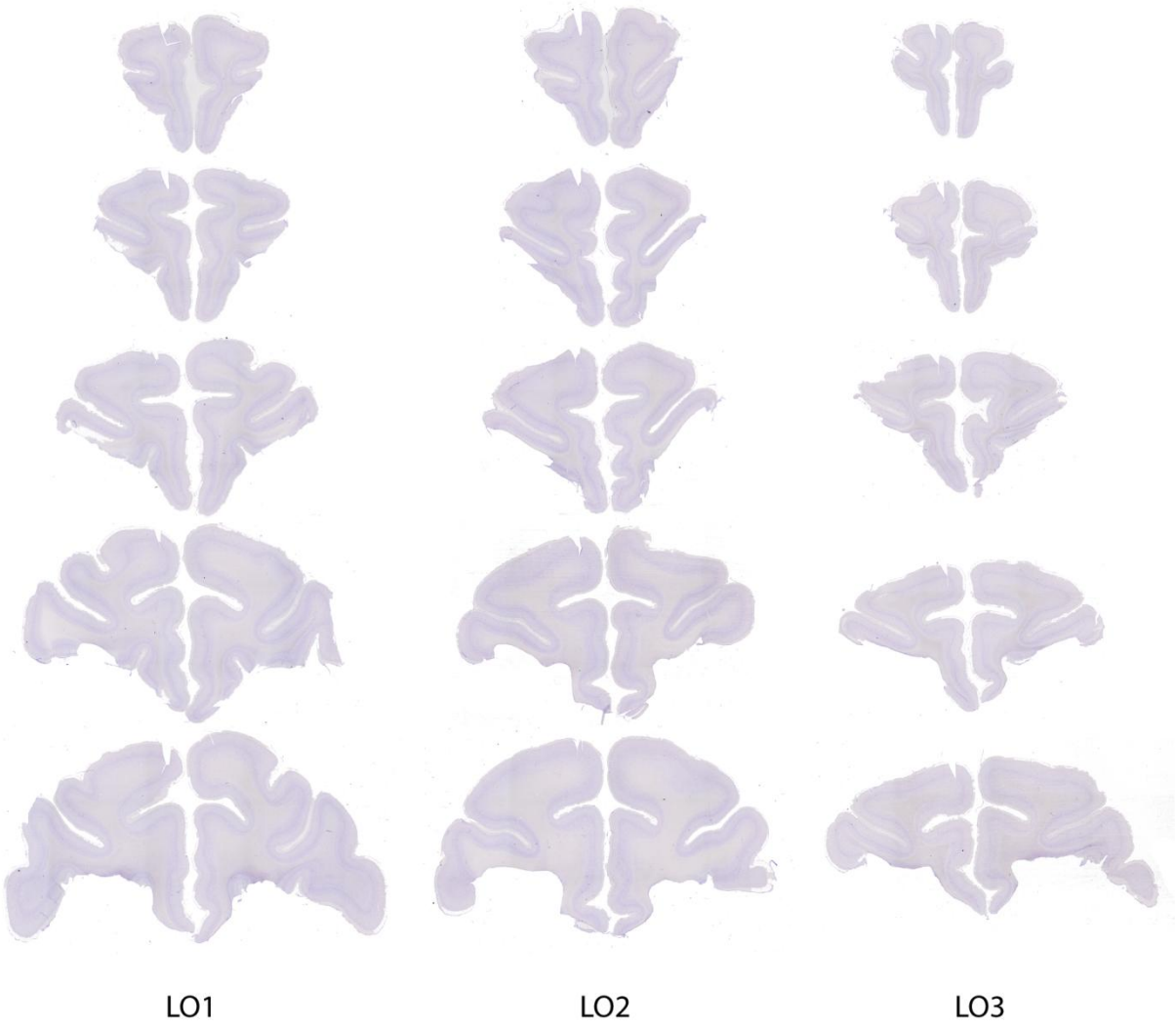

Figure AI.2. Coronal sections through the frontal lobes, for each individual animal of the lOFC-lesioned group (mo1, mo2, mo3, mo4). The lOFC lesions removed cortex between the medial and lateral orbitofrontal sulci including predominantly Walker's (1940) areas 11 and 13.

II: Cluster Analysis

Coordinates for the social related activations were taken from the following studies:

Left Hemisphere [MNI Coordinates]				Right Hemisphere [MNI Coordinates]			References
x	y	z		x	y	z	
-2	66	4		2	54	-8	
-42	32	-14		-	-	-	Akitsuki Y, Decety J (2009) Social context and perceived agency affects empathy for pain: an event-related fMRI investigation. Neuroimage 47:722-734.
-26	47	12		8	42	-2	
-	-	-		35	29	1	
-	-	-		26	35	5	Amting JM, Miller JE, Chow M, Mitchell DG (2009) Getting mixed messages: the impact of conflicting social signals on the brain's target emotional response. Neuroimage 47:1950-1959.
-2	54	-16		14	38	-4	
-4	46	-10		8	64	24	
-32	34	-14		28	28	-20	Beer JS, Hughes BL (2010) Neural systems of social comparison and the "above-average" effect. Neuroimage 49:2671-2679.
-34	25	-14		52	12	18	
-45	16	22		49	22	-5	
-30	25	-14		52	12	18	
-45	12	22		34	22	-10	
-34	52	16		8	24	40	Blasi G, Hariri AR, Alce G, Taurisano P, Sambataro F, Das S, Bertolino A, Weinberger DR, Mattay VS (2009) Preferential Amygdala Reactivity to the Negative Assessment of Neutral Faces. Biol Psychiatry.
-	-	-		49	9	32	
-3	49	28		-	-	-	Buckholtz JW, Asplund CL, Dux PE, Zald DH, Gore JC, Jones OD, Marois R (2008) The neural correlates of third-party punishment. Neuron 60:930-940.
-	-	-		1	5	41	
-	-	-		1	42	1	Chatterjee A, Thomas A, Smith SE, Aguirre GK (2009) The neural response to facial attractiveness. Neuropsychology 23:135-143.

-33	21	0		36	24	-4	
-36	21	0		36	24	-4	
-36	2	-1		36	24	-7	
-45	54	3		0	30	42	
0	30	42		12	54	3	
-3	42	-22		0	36	-7	
0	36	-7		-	-	-	Chiao JY, Harada T, Oby ER, Li Z, Parrish T, Bridge DJ (2009) Neural representations of social status hierarchy in human inferior parietal cortex. Neuropsychologia 47:354-363.
-48	7	25		53	5	33	
-6	14	49		6	39	28	
-56	10	16		-	-	-	
-48	38	12		-	-	-	
-12	44	6		-	-	-	Chiao JY, Mathur VA, Harada T, Lipke T (2009) Neural basis of preference for human social hierarchy versus egalitarianism. Ann N Y Acad Sci 1167:174-181.
-14	54	40		-	-	-	
-2	24	60		-	-	-	
-52	20	-2		-	-	-	
-4	56	-12		2	26	-22	Falk EB, Rameson L, Berkman ET, Liao B, Kang Y, Inagaki TK, Lieberman MD (2009) The Neural Correlates of Persuasion: A Common Network across Cultures and Media. J Cogn Neurosci.
-14	52	-1		-	-	-	Freeman JB, Rule NO, Adams RB, Jr., Ambady N (2009) Culture shapes a mesolimbic response to signals of dominance and subordination that associates with behavior. Neuroimage 47:353-359.
-8	54	30		-	-	-	Gilbert SJ, Williamson ID, Dumontheil I, Simons JS, Frith CD, Burgess PW (2007) Distinct regions of medial rostral prefrontal cortex supporting social and nonsocial functions. Soc Cogn Affect Neurosci 2:217-226.
-8	42	-2		10	40	-2	
-6	36	14		-	-	-	Gutchess AH, Kensinger EA, Schacter DL (2009) Functional neuroimaging of self-referential encoding with age. Neuropsychologia.
-40	22	-14		46	24	-16	Hall J, Whalley HC, McKirdy JW, Sprengelmeyer R, Santos IM, Donaldson DI, McGonigle DJ, Young AW, McIntosh AM, Johnstone EC, Lawrie SM (2009) A common neural system mediating two different forms of social judgement. Psychol Med:1-10.

-3	19	28	6	16	35	
-3	26	25	-	-	-	
-	29	25	-	29	25	
-6	10	44	-	-	-	
-6	29	12	3	26	22	Immordino-Yang MH, McColl A, Damasio H, Damasio A (2009) Neural correlates of admiration and compassion. Proc Natl Acad Sci U S A 106:8021-8026.
-15	27	15	-	-	-	
-15	36	-18	-	-	-	Kim H, Adolphs R, O'Doherty JP, Shimojo S (2007) Temporal isolation of neural processes underlying face preference decisions. Proc Natl Acad Sci U S A 104:18253-18258.
-3	12	53	-	-	-	Klucharev V, Hytonen K, Rijpkema M, Smidts A, Fernandez G (2009) Reinforcement learning signal predicts social conformity. Neuron 61:140-151.
-4	48	-11	6	38	-11	
-	-	-	4	36	17	Kuzmanovic B, Georgescu AL, Eickhoff SB, Shah NJ, Bente G, Fink GR, Vogeley K (2009) Duration matters: dissociating neural correlates of detection and evaluation of social gaze.
-	-	-	6	38	5	Neuroimage 46:1154-1163.
-32	26	-10	44	20	-16	Lamm C, Batson CD, Decety J (2007) The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. J Cogn Neurosci 19:42-58.
-	-	-	4	56	-4	
-	-	-	32	52	-4	Li J, Xiao E, Houser D, Montague PR (2009) Neural responses to sanction threats in two-party economic exchange. Proc Natl Acad Sci U S A 106:16835-16840.
-11	30	7	0	40	-8	
-12	48	48	2	58	-1	
-13	56	39	6	60	25	
0	40	-8	19	33	51	
-3	60	18	17	45	51	
-32	26	-10	-	-	-	Lindner M, Hundhammer T, Ciaramidaro A, Linden DE, Mussweiler T (2008) The neural substrates of person comparison--an fMRI study. Neuroimage 40:963-971.
-41	30	22	-	-	-	Ortigue S, Thompson JC, Parasuraman R, Grafton ST (2009) Spatio-temporal dynamics of human intention understanding in temporo-parietal cortex: a combined EEG/fMRI repetition suppression paradigm. PLoS One 4:e6962.
-46	22	-4	42	26	-8	
-56	22	8	40	26	-8	Pfeifer JH, Masten CL, Borofsky LA, Dapretto M, Fuligni AJ, Lieberman MD (2009) Neural correlates of direct and reflected self-appraisals in adolescents and adults: when social perspective-taking informs self-perception. Child Dev 80:1016-1038.

-54	10	10	48	22	-2	
-46	18	-4	14	50	12	
-54	26	10	2	54	110	
-54	18	12	4	20	36	
-46	24	0	4	20	34	
-56	20	6	-	-	-	
-56	26	6	-	-	-	
-42	26	0	-	-	-	
-56	26	6	-	-	-	
-50	18	4	-	-	-	
-2	58	10	-	-	-	
-6	54	28	-	-	-	
-10	50	26	-	-	-	
-10	42	26	-	-	-	
-6	54	28	-	-	-	
-2	32	30	-	-	-	
-24	32	26	-	-	-	
-34	34	14	-	-	-	Platek SM, Kemp SM (2009) Is family special to the brain? An event-related fMRI study of familiar, familial, and self-face recognition. Neuropsychologia 47:849-858.
-39	24	3	30	42	-12	Pochon JB, Riis J, Sanfey AG, Nystrom LE, Cohen JD (2008) Functional imaging of decision conflict. J Neurosci 28:3468-3473.
-	-	-	9	36	30	
-48	-14	-8	44	56	-12	Satterthwaite TD, Wolf DH, Gur RC, Ruparel K, Valdez JN, Gur RE, Loughead J (2009) Frontolimbic responses to emotional face memory: the neural correlates of first impressions. Hum Brain Mapp 30:3748-3758.

-46	11	14	4	32	0	
-46	7	14	42	25	18	
-32	35	-11	49	42	4	
-10	44	25	53	28	-7	
-55	18	6	56	25	0	
-57	17	-6	63	9	16	
-59	22	12	-	-	-	
-46	27	2	-	-	-	
-46	24	17	-	-	-	
-53	30	21	-	-	-	
-4	52	-4	-	-	-	Trautmann SA, Fehr T, Herrmann M (2009) Emotions in motion: dynamic compared to static facial expressions of disgust and happiness reveal more widespread emotion-specific activations. Brain Res 1284:100-115.
-2	48	-14	-	-	-	
-	55	34	2	20	-7	
-	-	-	2	15	36	
-	-	-	-	55	34	van den Bos W, McClure SM, Harris LT, Fiske ST, Cohen JD (2007) Dissociating affective evaluation and social cognitive processes in the ventral medial prefrontal cortex. Cogn Affect Behav Neurosci 7:337-346.
-	-	-	2	20	-7	
0	31	3	0	31	3	Wager TD, Waugh CE, Lindquist M, Noll DC, Fredrickson BL, Taylor SF (2009) Brain mediators of cardiovascular responses to social threat: part I: Reciprocal dorsal and ventral sub-regions of the medial prefrontal cortex and heart-rate reactivity. Neuroimage 47:821-835.
-54	20	-4	16	8	44	
-40	26	-16	4	26	48	Wittfoth M, Schroder C, Schardt DM, Dengler R, Heinze HJ, Kotz SA (2009) On Emotional Conflict: Interference Resolution of Happy and Angry Prosody Reveals Valence-Specific Effects. Cereb Cortex.
-	-	-	42	16	-10	
-16	58	24	48	18	28	Wolf I, Dziobek I, Heekeren HR (2009) Neural correlates of social cognition in naturalistic settings: A model-free analysis approach. Neuroimage.
-	-	-	54	26	8	

-	-	-		48	21	-9	Zahn, R. et al. Social concepts are represented in the superior anterior temporal cortex. Proc Natl Acad Sci U S A 104, 6430-5 (2007).

Coordinates for the non social related activations were taken from the following studies:

Left Hemisphere [MNI Coordinates]				Right Hemisphere [MNI Coordinates]			References
x	y	z		x	y	z	
-	-	-		-6	48	-8	Boorman ED, Behrens TE, Woolrich MW, Rushworth MF (2009) How green is the grass on the other side? Frontopolar cortex and the evidence in favor of alternative courses of action. Neuron 62:733-743.
0	42	-6		-	-	-	Chib VS, Rangel A, Shimojo S, O'Doherty JP (2009) Evidence for a common representation of decision values for dissimilar goods in human ventromedial prefrontal cortex. J Neurosci 29:12315-12320.
0	54	-6		0	54	-6	Chua HF, Gonzalez R, Taylor SF, Welsh RC, Liberzon I (2009) Decision-related loss: regret and disappointment. Neuroimage 47:2031-2040.
-	-	-		25	54	-12	
-36	19	-4		6	21	34	Clark L, Lawrence AJ, Astley-Jones F, Gray N (2009) Gambling near-misses enhance motivation to gamble and recruit win-related brain circuitry. Neuron 61:481-490.
-4	33	8		4	33	4	
-21	30	-12		-	-	-	Cunningham WA, Kesek A, Mowrer SM (2009) Distinct orbitofrontal regions encode stimulus and choice valuation. J Cogn Neurosci 21:1956-1966.
-4	40	16		-	-	-	De Martino B, Kumaran D, Holt B, Dolan RJ (2009) The neurobiology of reference-dependent value computation. J Neurosci 29:3833-3842.
-36	42	-10		-	-	-	
-	-	-		6	48	-12	Elliott R, Agnew Z, Deakin JF (2008) Medial orbitofrontal cortex codes relative rather than absolute value of financial rewards in humans. Eur J Neurosci 27:2213-2218.
-44	33	-7		12	35	-13	Engelmann JB, Tamir D (2009) Individual differences in risk preference predict neural responses during financial decision-making. Brain Res 1290:28-51.
-3	30	36		12	46	-9	
-	-	-		5	39	-11	
-	-	-		43	27	-7	
-	-	-		9	31	30	
-15	30	-6					FitzGerald TH, Seymour B, Dolan RJ (2009) The role of human orbitofrontal cortex in value comparison for incommensurable objects. J Neurosci 29:8388-8395.
-1	24	45		4	44	-10	Graham S, Phua E, Soon CS, Oh T, Au C, Shuter B, Wang SC, Yeh IB (2009) Role of medial cortical, hippocampal and striatal interactions during cognitive set-shifting. Neuroimage 45:1359-
-35	51	6		38	34	23	

-40	14	13	38	50	17	1367.
-32	53	9	0	0	0	
-40	28	-14	5	46	-10	
-35	50	3	3	20	45	
-32	52	6	8	29	29	
-40	27	-13	41	34	28	
-	-	-	31	54	5	
-	-	-	5	46	-10	
			2	28	-5	
-	-	-	7	42	-10	
-	-	-	38	34	20	
			4	42	-10	
-	-	-	41	34	24	
-	-	-	31	52	5	
			5	44	-10	
-	-	-	7	40	-10	
-	-	-	38	49	13	
			5	44	-10	
-3	45	6	3	51	3	Hare TA, Camerer CF, Rangel A (2009) Self-control in decision-making involves modulation of the vmPFC valuation system. Science 324:646-648.
-3	39	21	3	36	-12	
-1	27	-18	21	9	-21	Hare TA, O'Doherty J, Camerer CF, Schultz W, Rangel A (2008) Dissociating the role of the orbitofrontal cortex and the striatum in the computation of goal values and prediction errors. J Neurosci 28:5623-5630.
-27	36	-6	24	36	-3	
0	26	-12	42	30	-20	Kato J, Ide H, Kabashima I, Kadota H, Takano K, Kansaku K (2009) Neural correlates of attitude change following positive and negative advertisements. Front Behav Neurosci 3:6.
-48	22	-3	0	26	-12	
-	-	-	16	63	9	
-	-	-	30	19	-22	
-3	42	12	0	60	-6	Lawrence NS, Jollant F, O'Daly O, Zelaya F, Phillips ML (2009) Distinct roles of prefrontal cortical subregions in the Iowa Gambling Task. Cereb Cortex 19:1134-1143.
-3	51	3	-	-	-	
-9	48	18	-	-	-	
-48	21	-9	-	-	-	

-27	21	-18	-	-	-	
-36	6	-6	-	-	-	
0	60	-6	-	-	-	
-4	38	-12	6	16	-8	
-48	34	-6	42	56	-8	
-20	34	-16	22	42	-14	
-34	56	-12	24	56	-2	
-18	44	-18	0	56	-8	Liu X, Powell DK, Wang H, Gold BT, Corbly CR, Joseph JE (2007) Functional dissociation in frontal and striatal areas for processing of positive and negative reward information. J Neurosci 27:4587-4597.
0	56	-8	-	-	-	
-	-	-	26	18	-16	
-	-	-	46	6	28	
-	-	-	46	14	30	
-	-	-	36	4	30	
-	-	-	8	46	8	
-	-	-	30	18	-14	Peters J, Buchel C (2009) Overlapping and distinct neural systems code for subjective value during intertemporal and risky decision making. J Neurosci 29:15727-15734.
-	-	-	4	30	-18	Plassmann H, O'Doherty J, Rangel A (2007) Orbitofrontal cortex encodes willingness to pay in everyday economic transactions. J Neurosci 27:9984-9988.
-54	34	2	2	54	-14	
-12	68	-10	20	22	38	Sailer U, Robinson S, Fischmeister FP, Moser E, Kryspin-Exner I, Bauer H (2007) Imaging the changing role of feedback during learning in decision-making. Neuroimage 37:1474-1486.
-10	50	-10	-	-	-	Tanaka SC, Balleine BW, O'Doherty JP (2008) Calculating consequences: brain systems that encode the causal effects of actions. J Neurosci 28:6750-6755.
-2	48	-12	12	12	36	
-4	65	8	50	16	6	
-34	48	10	8	58	10	
-30	34	0	52	26	-2	
-	-	-	28	42	26	
-	-	-	14	46	18	
-	-	-	52	28	8	Tobler PN, O'Doherty JP, Dolan RJ, Schultz W (2007) Reward value coding distinct from risk attitude-related uncertainty coding in human reward systems. J Neurophysiol 97:1621-1632.
-	-	-	16	21	-23	Venkatraman V, Payne JW, Bettman JR, Luce MF, Huettel SA (2009) Separate neural mechanisms underlie choices and strategic preferences in risky decision making. Neuron 62:593-602.
-	-	-	12	47	0	Weber B, Rangel A, Wibral M, Falk A (2009) The medial prefrontal cortex exhibits money illusion. Proc Natl Acad Sci U S A 106:5025-5028.

-	-	-	22	35	-23	
-	-	-	49	8	25	
-	-	-	2	32	10	
-	-	-	2	34	0	
-	-	-	58	38	0	Weber BJ, Huettel SA (2008) The neural substrates of probabilistic and intertemporal decision making. Brain Res 1234:104-115.
-42	33	-6	51	30	0	
-	-	-	30	45	-3	Wrase J, Kahnt T, Schlagenhauf F, Beck A, Cohen MX, Knutson B, Heinz A (2007) Different neural systems adjust motor behavior in response to reward and punishment. Neuroimage.
-34	14	24	46	32	26	Xue G, Ghahremani DG, Poldrack RA (2008) Neural substrates for reversing stimulus-outcome and stimulus-response associations. J Neurosci 28:11196-11204.