

**NEURAL REPRESENTATION OF SOCIAL, MONETARY AND CHOCOLATE  
REINFORCER PROCESSING**

JINGYI ZHU

Doctor of Philosophy

ASTON UNIVERSITY

May 2016

© Jingyi Zhu, 2016

Jingyi Zhu asserts her moral right to be identified as the author of this thesis

This copy of the thesis has been supplied on condition that anyone who consults it is understood to recognise that its copyright rests with its author and that no quotation from the thesis and no information derived from it may be published without appropriate permission or acknowledgement.

Neural Representation of Social, Monetary and Chocolate Reinforcer Processing

JINGYI ZHU

PhD in Neuroscience

05-2016

Little attention has been paid to social reinforcer processing compared with food and monetary reinforcers, in the reward-related functional magnetic resonance imaging (fMRI) literature. This is surprising as social reinforcers pervade our daily lives and are often experienced more frequently than food or monetary reinforcers. The question of whether social reinforcers are processed in the same or different brain regions as other reinforcer types remains poorly understood. In this thesis, three fMRI studies were employed to investigate this question, in healthy individuals. The experimental paradigms focused on two main aspects of reward processing: neural patterns of activation associated with different reward types and valence, and also correlations between neural activation to rewards and participants' hedonic level. The studies reported in this thesis revealed that amygdala and a subregion of the OFC responded more sensitively to social reinforcers than monetary, or food reinforcers, indicating social reinforcers modulate the affective response more strongly in the brain reward network. The results also provide evidence for a medial-lateral functional dissociation in the OFC to rewards and punishment, so that medial OFC responded more strongly to rewards and lateral OFC to punishments. Moreover, fMRI study-1 revealed a crossover interaction between reinforcement valence and reward type in the lateral OFC, indicating this region may be involved in the functional integration of both reward type and valence. This is consistent with the theory of a common neural currency, for valuing different rewards in the OFC. As activation in the reward network may also be attributed to the hedonic experience of gaining rewards, fMRI study-2 and study-3 also explored the relationship between BOLD activity in response to rewards and participants' hedonic scores. These two studies demonstrated highly significant correlations between BOLD activity in the OFC (positive correlation) and insula (negative correlation) and self-reported levels of hedonic response. The findings of the correlations between reward and hedonic level could have important implications for understanding how human hedonic levels affect responses to various reinforcements.

Keywords: OFC, amygdala, insula, common currency, reward

## **Acknowledgements**

Over the course of the PhD I have received help from some people, both in academic and personal matters. I would like to take this opportunity to thank as many of them as possible.

First and foremost, I would like to take this opportunity to thank my supervisors, Dr. Olivia Longe, Dr. Jade Ngoc Thai and Prof. Adrian Burgess for their continuous encouragement and enthusiasm shown towards this study. Dr. Olivia Longe and Jade Thai were present during most of the fMRI scans to make sure everything went smoothly. I would like to thank Olivia in particular for helping me to do the E-Prime programming and thank both Dr. Olivia Longe and Dr. Jade Thai for teaching me the basics of fMRI analysis.

I would like to thank Dr. Olivia Longe and Prof. Adrian Burgess further for reading my numerous drafts of each experiment and each chapter of the thesis. Also, I would like to thank Prof. Adrian Burgess for guiding me to do the statistical analysis for the behavioural experiments.

I would also like to thank my office colleagues who have been helpful and supportive during my PhD. I would also like to thank all volunteers who participated in my studies. Last but not the least, I would like to thank my parents for being very supportive and encouraging throughout my PhD.

## List of Contents

<b>CHAPTER 1 INTRODUCTION</b> .....	<b>10</b>
1.1. REWARD AND PUNISHMENT – REINFORCER VALENCE .....	11
1.2. REINFORCEMENT LEARNING .....	12
1.2.1. <i>Classical Conditioning</i> .....	13
1.2.2. <i>Instrumental Conditioning</i> .....	13
1.3. PRIMARY AND SECONDARY REINFORCERS .....	15
1.3.1. <i>Neuroimaging studies of Reinforcement Processing</i> .....	15
1.4. THE BRAIN REWARD NETWORK.....	17
1.5. FUNCTION OF THE BRAIN REWARD NETWORK AS REVEALED WITH FMRI .....	18
1.5.1. <i>DA Systems - DA Neurons and pathways</i> .....	19
1.5.2. <i>Amygdala</i> .....	21
1.5.2.1. <i>Amygdala contributes to stimulus-valence association</i> .....	22
1.5.2.2. <i>Stimulus-value association versus stimulus-reward association</i> .....	23
1.5.3. <i>Striatum – dorsal and ventral striatum</i> .....	24
1.5.4. <i>Orbitofrontal Cortex – OFC</i> .....	26
1.5.4.1. <i>Coding reward value at receipt</i> .....	27
1.5.4.2. <i>OFC medial-lateral trend: rewards versus punishments</i> .....	28
1.5.4.3. <i>Posterior-to-anterior trend: increasing complexity</i> .....	29
1.5.4.4. <i>Functional integration of OFC</i> .....	30
1.5.4.5. <i>Medial OFC codes context-dependent relative value</i> .....	32
1.5.5. <i>Insula</i> .....	32
1.5.6. <i>Multi-types reward processing – social versus monetary reinforcement</i> ...	33
1.5.6.1. <i>Findings and limitations of past fMRI studies on employing social and monetary reward processing</i> .....	34
1.5.7. <i>The Brain Reward Network works as a system rather than separate entities</i> 35	
1.5.8. <i>Implications for investigating neural substrates of social reinforcement</i> ....	38
1.6. AIMS, OBJECTIVES AND HYPOTHESIS OF THESIS.....	39
1.6.1. <i>Aims and hypothesis of fMRI study-1</i> .....	40
1.6.2. <i>Aims and hypothesis of fMRI study-2</i> .....	40
1.6.3. <i>Aims and hypothesis of fMRI study-3</i> .....	41
<b>CHAPTER 2 GENERAL METHODS</b> .....	<b>42</b>
2.1. INTRODUCTION .....	42
2.2. PARTICIPATION .....	42
2.2.1. <i>Recruitment of Participants</i> .....	42
2.2.2. <i>Inclusion and Exclusion Criteria</i> .....	43
2.3. RATING SCALES .....	43
2.3.1. <i>Hospital Anxiety and Depression Scale (HADS)</i> .....	44
2.3.2. <i>Beck Depression Inventory (BDI)</i> .....	44
2.3.3. <i>Snaith-Hamilton Pleasure Scale (SHAPS)</i> .....	44
2.4. MAGNETIC RESONANCE IMAGING (MRI) .....	46
2.4.1. <i>Physical principles of MRI</i> .....	46
2.5. FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI).....	50
2.5.1. <i>Principles of BOLD signal</i> .....	50
2.5.2. <i>Physiology of BOLD response</i> .....	51
2.5.3. <i>Advantage and disadvantages of fMRI</i> .....	52
2.6. FMRI DATA ACQUISITION AND ANALYSIS .....	54
2.6.1. <i>Pre-Processing</i> .....	54
2.6.1.1. <i>Slice Timing</i> .....	54
2.6.1.2. <i>Realignment</i> .....	55
2.6.1.3. <i>Smoothing</i> .....	56

2.6.2.	<i>Statistical Analysis</i> .....	56
2.6.3.	<i>Haemodynamic Response Function</i> .....	58
2.6.4.	<i>Random and Fixed Effects Analyses</i> .....	59
2.6.5.	<i>Small Volume Correction analysis</i> .....	60
2.7.	GENERAL PROCEDURE FOR THE FMRI STUDIES.....	60
2.8.	SAFETY ASPECTS AND ETHICAL CONSIDERATIONS.....	61
2.9.	EXPERIMENT DESIGN.....	62
2.10.	TARGET DETECTION TASK.....	63
<b>CHAPTER 3 BEHAVIOURAL STUDIES</b> .....		<b>65</b>
3.1.	INTRODUCTION OF BEHAVIOURAL EXPERIMENTS.....	65
3.2.	METHODS OF BEHAVIOURAL EXPERIMENTS.....	66
3.2.1.	<i>Participants</i> .....	66
3.2.2.	<i>Task paradigm – Reward based reversal-learning task</i> .....	66
3.2.3.	<i>Data analysis – traditional ANOVA method</i> .....	68
3.2.4.	<i>Data analysis – test for equivalence</i> .....	68
3.3.	ANOVA RESULTS OF BEHAVIOURAL EXPERIMENT 1.....	69
3.3.1.	<i>Acquisition Phase Performance – Mean Percentage Correct Scores</i> .....	70
3.3.2.	<i>Reversal Phase Performance – Mean Percentage Correct Scores</i> .....	70
3.4.	ANOVA RESULTS OF BEHAVIOURAL EXPERIMENT 2.....	70
3.4.1.	<i>Acquisition Phase Performance – Mean Percentage Correct Scores</i> .....	71
3.4.2.	<i>Reversal Phase Performance – Mean Percentage Correct Scores</i> .....	71
3.5.	TEST FOR EQUIVALENCE RESULTS – EXPERIMENT 1.....	72
3.6.	TEST FOR EQUIVALENCE RESULTS – EXPERIMENT 2.....	74
3.7.	TEST FOR EQUIVALENCE RESULTS – COMBINED EXPERIMENT 1 AND 2.....	76
3.8.	DISCUSSION OF BEHAVIOURAL EXPERIMENTS.....	79
<b>CHAPTER 4: FMRI STUDY-1</b> .....		<b>81</b>
4.1.	INTRODUCTION.....	81
4.2.	METHODS.....	85
4.2.1.	<i>Participants</i> .....	85
4.2.2.	<i>Stimuli and task</i> .....	86
4.2.3.	<i>Image Acquisition and Analysis</i> .....	87
4.3.	BEHAVIOURAL RESULTS.....	88
4.4.	FMRI RESULTS.....	89
4.4.1.	<i>Main effect of valance irrespective of reinforcer type</i> .....	89
4.4.2.	<i>Main effect of reinforcer type irrespective of valance</i> .....	90
4.4.3.	<i>Interaction contrast</i> .....	91
4.4.4.	<i>Activations in other brain regions</i> .....	93
4.4.5.	<i>Pairwise contrasts within the reinforcer type and valence</i> .....	94
4.5.	DISCUSSION.....	94
4.5.1.	<i>Activations in the Brain Reward Network to Reinforcer Valence</i> .....	95
4.5.2.	<i>Activations in the Brain Reward Network to Reinforcer Type</i> .....	96
4.5.3.	<i>Interaction of reward type and valence in the OFC</i> .....	98
<b>CHAPTER 5 FMRI STUDY-2</b> .....		<b>101</b>
5.1.	INTRODUCTION.....	101
5.2.	METHODS.....	103
5.2.1.	<i>Participants</i> .....	103
5.2.2.	<i>Stimuli and task</i> .....	103
5.2.3.	<i>Image Analysis</i> .....	104
5.3.	BEHAVIOURAL RESULTS.....	106
5.4.	IMAGING RESULTS.....	106
5.4.1.	<i>Main effects of valence</i> .....	107
5.4.2.	<i>Main effects of reward type</i> .....	107
5.4.3.	<i>ROI analysis on Amygdala</i> .....	108

5.4.4	<i>Interaction of reward type and ‘valence’</i> .....	108
5.4.5	<i>Pairwise contrasts within the reinforcer type and valence</i> .....	109
5.4.6.	<i>Correlation between SHAPS and brain activity in response to MR</i> .....	111
5.4.6.1.	Positive Correlation.....	111
5.4.6.2.	Negative Correlation .....	111
5.4.7.	<i>Correlation between SHAPS and brain activity in response to SR</i> .....	111
5.4.7.1.	Positive Correlation.....	111
5.4.7.2.	Negative Correlation .....	111
5.5	DISCUSSION.....	113
5.5.1.	<i>Main effects contrasts of reward type</i> .....	114
5.5.2.	<i>Main effects contrasts of valence</i> .....	115
5.5.2.1.	Medial-lateral functional specialization in OFC to valence processing..	115
5.5.2.2.	Subgenual cingulate activation to rewards .....	115
5.5.2.3.	Dorsal striatum activation to rewards .....	115
5.5.2.4.	Insula activation to control stimuli .....	116
5.5.3.	<i>Interaction Contrast</i> .....	117
5.5.4.	<i>Regression with SHAPS scores</i> .....	118
5.5.4.1.	Positive regression .....	118
5.5.4.2.	Negative regression.....	119
<b>CHAPTER 6 FMRI STUDY-3 .....</b>		<b>122</b>
6.1.	INTRODUCTION .....	122
6.2.	METHODS .....	123
6.2.1.	<i>Participants</i> .....	123
6.2.2.	<i>Stimuli and task</i> .....	124
6.2.3.	<i>Image Analysis</i> .....	125
6.3.	BEHAVIOURAL RESULTS .....	126
6.4.	IMAGING RESULTS .....	127
6.4.1	<i>Main effects of valence</i> .....	127
6.4.2	<i>Main effects of reward type</i> .....	127
6.4.3	<i>Pairwise contrasts of reward types within each polarity of valence</i> .....	129
6.4.4	<i>Pairwise contrasts of valence within each reward type</i> .....	130
6.4.5	<i>Correlation between SHAPS and brain activity in response to MR</i> .....	130
6.4.6	<i>Correlation between SHAPS and brain activity in response to SR</i> .....	130
6.4.7	<i>Correlation between SHAPS and brain activity in response to CR</i> .....	132
6.5	DISCUSSION.....	135
6.5.1.	<i>Subtractive Analyses - Main effects contrasts of valence</i> .....	135
6.5.1.1.	Role of striatum in rewarding events .....	135
6.5.1.2.	Role of OFC in rewarding events .....	136
6.5.1.3.	Role of Insula related to perception of control events as ‘punishing’ ...	136
6.5.2.	<i>Subtractive Analyses - Main effects contrasts between the reward types</i>	137
6.5.3.	<i>Pairwise comparison of the reward events</i> .....	137
6.5.3.1.	Social versus monetary reward.....	137
6.5.3.2.	Monetary reward versus chocolate and social reward versus chocolate	138
6.5.3.3.	Social reward versus control .....	139
6.5.4.	<i>Regression Analyses</i> .....	139
6.6.	CONCLUSION.....	142
<b>CHAPTER 7 FINAL DISCUSSION.....</b>		<b>143</b>
7.1.	SUMMARY OF THE MAIN FINDINGS .....	143
7.2.	MAIN THEMES .....	145
7.2.1.	<i>OFC represents different reinforcer values</i> .....	146
7.2.1.1.	Medial-lateral dissociation in the OFC to rewards and punishments ...	146
7.2.1.2.	Greater OFC activation to social reinforcers .....	146
7.2.1.3.	The OFC role for integration of different kinds of reward information ..	146

7.2.2.	<i>The amygdala responds to affective value of social reinforcers</i> .....	147
7.2.3.	<i>The dorsal striatum acts to maintain rewards</i> .....	149
7.2.4.	<i>Role of the insula in processing negative reinforcement</i> .....	149
7.2.5.	<i>The correlation between BOLD activity and SHAPS hedonic level</i> .....	150
7.2.5.1.	OFC activation is positively correlated with hedonic tone.....	151
7.2.5.2.	<b>Subgenual cingulate and putamen activations are negatively correlated with hedonic level</b> .....	151
7.2.6.	<i>Evidence for the Context Dependent Theory of Reward processing</i> .....	152
7.2.7.	<i>Evidence for the OFC-amygdala-striatum circuit</i> .....	153
7.3.	LIMITATIONS .....	154
7.3.1.	<i>Limitations for the pilot behavioural tests</i> .....	154
7.3.2.	<i>Possible limitation for sample size</i> .....	154
7.3.3.	<i>Possible limitation for sample representation</i> .....	155
7.4.	FUTURE RESEARCH .....	155
7.5.	CONCLUSION.....	157
	<b>LIST OF REFERENCES</b> .....	<b>158</b>
	<b>WEB REFERENCES</b> .....	<b>176</b>

## List of Tables

Table 3.1.....	70
Table 3.2.....	74
Table 3.3.....	75
Table 3.4.....	77
Table 4.1.....	90
Table 4.2.....	93
Table 5.1.....	105
Table 5.2.....	110
Table 5.3.....	113
Table 6.1.....	126
Table 6.2.....	129
Table 6.3.....	131
Table 6.4.....	131
Table 6.5.....	134

## List of Figures

Figure 1.1.....	21
Figure 1.2.....	38
Figure 2.1.....	49
Figure 3.1.....	67
Figure 3.2.....	72
Figure 3.3.....	73
Figure 3.4.....	75
Figure 3.5.....	76
Figure 3.6.....	77
Figure 3.7.....	78
Figure 3.8.....	78
Figure 4.1.....	87
Figure 4.2.....	91
Figure 4.3.....	92
Figure 5.1.....	104
Figure 5.2.....	107
Figure 5.3.....	109
Figure 5.4.....	112
Figure 5.5.....	112
Figure 6.1.....	125
Figure 6.2.....	128
Figure 6.3.....	132
Figure 6.4.....	133

## Chapter 1 Introduction

Reinforcement is a central concept in behaviorism and is viewed as an essential mechanism in the shaping and control of behavior (Skinner, 1953; Ferster and Skinner, 1957). Human behaviour is usually driven by various types of reinforcement, such as primary (e.g. food, water, and sex), monetary and social (e.g. praise and reputation) reinforcement. Skinner (1953; Ferster and Skinner, 1957) proposed a reinforcement theory of motivation, which suggested that an event (occurring after a behaviour) can be referred to as a reinforcer, only if it results in an increase in the frequency of the behaviour in a similar context in the future. As an example, if a child is taken to visit a local park, where he/she receives an ice-cream when they ask for one; if the frequency of "asking for ice-cream" behavior increases whenever the child visits the park again in the future, the ice-cream can be considered as reinforcing. On the other hand, If the "asking for ice-cream" behavior does not increase on future park visits; the ice-cream cannot be called a reinforcer. In other words, the reinforcement theory of motivation suggests that reinforced behaviour is likely to be repeated (Ferster and Skinner, 1957).

Reinforcement can be positive or negative. Behaviour that results in positive consequences tends to be repeated, whereas a behaviour that results in negative consequences tends to be avoided. Reinforcers thus include both rewards and punishments, and are important influences driving human behaviour. Animal learning theories have suggested that rewards can elicit learning, approach, and consummatory behaviour, and positive emotions, whereas punishments can elicit avoidance and withdrawal behaviour and negative emotions (Schultz, 2004).

Human behaviour is driven by social reinforcers just as much as by monetary and food reinforcers in daily life. For instance, children often work hard on something in anticipation of their mother's praise or employees may toil over a piece of work in anticipation of their managers' affirmation. For many individuals, social reinforcement may be even more important than monetary. An example of this is the finding that appreciation for work carried out has been reported to be more motivating than monetary rewards by business employees (Graham and Unruh, 1990; Koch, 1990; Stuart, 1992; Steele, 1992).

Human neuroimaging studies exploring the neural basis of reinforcer processing, have tended to overlook social reinforcers compared with primary and monetary reinforcers. There have been many functional magnetic resonance imaging (fMRI) studies which have investigated primary reward processing, especially food stimuli (including food, water, taste and smell), and also many have focussed on abstract rewards such as money (Thut

et al., 1997; O'Doherty et al., 2001, 2003; Knutson et al., 2001). Relatively little attention has been paid to social reinforcer processing, which is surprising given its pervasive role in daily life compared with monetary reinforcers. Furthermore, whether the same neural representation exists for different types of reinforcers (social, monetary, and food remains an unanswered question (Kim et al., 2010; Lin et al., 2011). This is mainly because most studies have focused on neural activations to a single reinforcer type or have had methodological limitations (e.g. compared different reinforcer types in separate tasks) which have meant comparisons among reinforcers can only be interpreted qualitatively (Kim et al., 2010).

The primary interest of this thesis is to compare social with monetary reinforcer processing (reward and punishment) by using fMRI. Also, to study whether different reinforcer types (social, monetary and food) have distinct or overlapping regions of neural activation. In the section below, it will describe in more detail rewards and punishments, and then a brief literature of associative learning theory will be discussed, followed by a review of the literature on functional imaging of reward processing. Following this review, there will be an outline of the aims of the subsequent chapters.

### **1.1. Reward and punishment – reinforcer valence**

Reward processes do not have dedicated receptors like the primary sensory systems do, whereby the brain can accept information about the body and the environment around it via visual, auditory, touch or taste receptors. Information from sensory receptors is then translated into neural signals and passed on to other brain regions for higher level processes (Schultz, 2007). Rewards, therefore, cannot be directly and fully investigated from the physical and chemical information of their input stimuli, but are defined primarily by their influence on behaviour (Schultz, 2007).

According to animal learning theory, rewards are any events or stimuli that increase the frequency, intensity and probability of behaviour which leads to such objects. In other words, rewards elicit learning, as they induce a “come back for more” reaction (positive reinforcement) (Schultz, 2004). Also, rewards can be any object or stimulus that serves as an incentive or goal for action (Wise, 2002). Moreover, rewards induce positive emotions such as pleasure and hedonia.

In contrast, punishments have the opposite valence to rewards and include any event or stimulus that induces withdrawal behaviour and avoidance learning. During avoidance

learning, punishments serve as negative reinforcers by either increasing refrain or withdrawal behaviour that is associated with an aversive outcome (a Punisher), or by increasing behaviour that leads to a decrease of an aversive outcome (Schultz, 2007). The former is called passive avoidance while the latter is an active avoidance which involves an active instrumental response to reduce the impact of an aversive outcome (Schultz, 2007). Finally, punishments induce negative emotions such as anger, fear and panic (Schultz, 2007).

Both rewards and punishments can, therefore, be seen as important influences driving human behaviour. Below, the following section describes how reinforcers are thought to induce learning in animals and humans, and following this section, how they have traditionally been classified as either primary or secondary reinforcers.

## **1.2. Reinforcement Learning**

Learning is associated with changes in behaviour that are direct consequences of experience or training, and which cannot be attributed to other processes such as maturation or temporary physiological changes in an organism. Such changes or modifications of behaviour are relatively "permanent" (i.e. not transitory) (Sutton and Barto, 1998). Animals can learn to perform appropriate actions in response to particular stimuli, which are associated with rewards or punishments. This learning ability forms the basis of a branch of behavioural psychology called reinforcement learning (RL). RL is learning what to do, i.e. how to map stimuli to actions, so as to obtain the most reward or minimum punishment (Sutton and Barto, 1998). Rewards and punishments are defined by any stimuli that an animal or human will work to receive or avoid respectively (Rolls, 1999).

Associative learning, a form of reinforcement learning, is categorized into Pavlovian (classical) and operant (instrumental) conditioning. Both categories concern the way in which animals and humans learn to predict and respond to important events in their environments, such as delivery of appetitive or aversive stimuli (e.g. food/water when hungry/thirsty and mild electric shock, respectively). All the experiments that were demonstrated in this thesis adopted instrumental conditioning, as participants were asked to give button press responding to task stimuli to receive rewards. Therefore, instrumental conditioning will be explained in more detail.

### **1.2.1. Classical Conditioning**

Pavlovian reinforcement (1927, 1960), or classical conditioning involves presenting a neutral stimulus (i.e. any event that does not result in an overt behavioural response from the organism under investigation, also called conditioned stimulus; CS) along with a significant stimulus (e.g. food), also called the unconditioned stimulus (US) which elicits an innate, often reflexive response (unconditioned response; UR). When the CS and US are repeatedly paired, they become associated, and the CS will start eliciting a behavioural response even without the US, this response is called the conditioned response (CR). For example, repeatedly presenting a bell sound (CS) along with food (US) to an animal, results a few trials later with the bell sound becoming associated with the food, and the animal begins to salivate once it hears the bell sound even without the presence of food. Classical conditioning is therefore considered to involve reward prediction (Schultz, 2007). During the classical conditioning, the stimuli delivered are not contingent on the animal's behaviour (Dorf and Bishop, 2005). An animal receives input signals which correspond to the CS and the US. Its output is represented by the unconditioned response which slowly becomes replaced by the conditioned response. The animal obtains a US or reward which is not dependent on the responses it makes.

### **1.2.2. Instrumental Conditioning**

While classical conditioning results in the formation of an association between two stimuli, and involves outcome predictions (Schultz, 2007), instrumental conditioning (Skinner, 1957) forms an association between an action (behavioural response) and a consequence (the stimulus/outcomes that follows). Therefore, instrumental conditioning is also called response-stimulus (RS) conditioning and uses outcomes (rewards or punishments) to modify the occurrence of behaviour. For example, rats can learn to press a lever to get a meatball, and can also learn to press a button to avoid an electric shock. Regarding reward receipt, the rats have to launch a behavioural response (operant response) to get a reward, and without such a response, no reward will occur.

During the instrumental conditioning, the stimuli obtained by the animal depends on its actions (Klopf et al., 1993). The feedback during instrumental conditioning indicates that the US or reward obtained by the animal is dependent on the response it elicits. This was originally demonstrated by Edward Thorndike, who built puzzle boxes in which cats were placed and had to learn how to operate a lever to exit the box (Thorndike, 1911). By doing so, the cats obtained a reward located outside the box but which had been visible from inside the box. Although the cats initially struggled to learn, with repetition, they required less time to make exits and get the reward. Thorndike, therefore, proposed that animals

learn from “trial and error” and associations between the stimulus and response are “strengthened” by the reward and “weakened” otherwise. Rewards and punishers were defined as the consequences that “strengthen” or “weaken” behaviours respectively. Although Bandura (1977) later described reinforcement as a principally informative and motivational operation, rather than a physical response strengthener, reinforcement learning today is still based on Thorndike’s ideas of the law of effect.

During instrumental conditioning, rewards serve as goals of behaviour, which therefore increase the frequency of operant behaviours. Instrumental conditioning also produces reward predictions, as Pavlovian learning does. When a discrepancy occurs between the reward prediction and the reward outcome, a prediction error occurs, which can advance learning. This was stressed in Kamin’s blocking effect (1969) and the associative Rescorla-Wagner learning rules (1972), which conceptualized the learning effect, and suggested that learning of a stimulus or behaviour occurs only after an unpredicted reinforcer or a prediction error happened, and would slow progressively as the reinforcer became more and more easily predicted. Furthermore, a reward prediction error can reduce the strength of the CS and the attention to the CS or reward, and result in the extinction of the already learned behaviour. Therefore, the associative Rescorla-Wagner learning rules could also be called attentional learning rules (Mackintosh, 1975; Pearce and Hall, 1980), as the associative learning was related to the degree of attention elicited by the CS and reward.

Both forms of conditioning (Pavlovian and Instrumental) concern the ways in which animals or humans learn to predict and respond to important events in their environments, such as delivery of appetitive and aversive stimuli. Reinforcement learning is based on learning how to maximize a reward by mapping situations to actions. Reinforcement learning is considered to be “minimally supervised,” because the animals and humans are not explicitly told which actions lead to a maximum reward, but must work out for themselves by the reinforcements they receive (Sutton and Barto, 1990; 1998).

The ability of an animal or human to make predictions and adapt according to changing conditions in the environment is a necessity for survival. They need to be able to predict future events, such as the presence of food or danger. Predictions help animals and humans to decide on their behavioural actions, such as whether to approach a target food or to avoid approaching dangerous objects. For example, if a bird finds apples on a tree, it learns to associate the tree with apples and always goes to the tree when it searches for apples. At some point, there are no more apples on the tree. How does the bird stop going to that tree to look for apples, while still maintaining the association between the

tree and the apples, so that in the future when the tree again starts producing apples, the bird returns to find the same happy outcome? This is an example of reversal learning. When a stimulus-reward (seeing the tree - getting apples) contingency changes, an animal's or human's behaviour towards the stimulus which once predicted the reward changes accordingly. The bird has learned the tree-getting apple association, then learned the 'changes' in this association. Animals and humans can demonstrate such behavioural flexibility by inhibiting appetitive behaviour when the incentive value of the conditioned stimulus (CS) that predicts the reward changes.

### **1.3. Primary and secondary reinforcers**

Reinforcers can be classified as either primary or secondary (Skinner, 1974). Primary reinforcers are unconditioned reinforcers which can reinforce behaviour without requiring any learning, such as sleep, food, water and sexual stimuli. These reinforcers have obtained their reinforcement function because of the survival and evolution needs of a species (Skinner, 1974).

Secondary reinforcers or conditioned reinforcers that are common in daily human life include money, beauty, and praise and gain their reinforcement function by learned association with primary reinforcers (Hermstein, 1964). For instance, most of us would be delighted to find a twenty-pounds note on the pavement, as we could imagine the goods we might buy with it, but the same twenty-pound note has no meaning or value to a person who has never used the money. All the reinforcers (social, monetary and chocolate) that were used in this thesis belonged to secondary reinforcers, also called abstract reinforcers. The reinforcer of chocolate that was used in this thesis was delivered after the task event; participants could only receive a picture of chocolate during the task presentation. The following section will introduce the previous neuroimaging studies, especially fMRI studies that have employed abstract reinforcers. Also, the literature of neuroimaging studies that have employed primary reinforcers will be briefly reviewed, as primary reinforcers were the most widely studied reinforcers in the past.

#### **1.3.1. Neuroimaging studies of Reinforcement Processing**

Primary reinforcers used in a number of human fMRI studies include juice and water (Berns et al., 2001; O'Doherty et al., 2001; 2002; 2003; Pagnoni et al., 2002; McClure et al., 2003; De Araujo and Rolls., 2004; Valentin et al., 2007; 2009; Kim et al., 2010; Levy and Glimcher., 2011), appetitive/aversive smells (Gottfried et al., 2002; Anderson et al.,

2003), sexual stimuli – erotic movies (Arnow et al., 2002), and sexual behaviour (Komisaruk et al., 2002). Only a few social stimuli have been employed as reinforcers directly in fMRI experiments (Izuma et al., 2008; Spreckelmeyer et al., 2009; Rademacher et al., 2010; Lin et al., 2011; Scott-Van Zeeland, 2010), however, many social stimuli have been identified to have reward values and activate reward circuitry, such as beautiful faces (Aharon et al., 2001), social interaction (Rilling et al., 2002), affect-laden words (Hamann and Mao, 2002), and social reputation (Izuma, Saito and Sdatao, 2008; good reputation was used as a social reward). Human neuroimaging studies employing primary reinforcers draw close links to animal work, with regard to the reported brain regions activated, as the findings derived from human studies are similar and complementary to animal studies (Berridge and Kringelbach, 2008).

There have been a growing number of neuroimaging studies (mostly fMRI) employing abstract reinforcers, especially money (Thut, et al., 1997; O'Doherty et al., 2001, 2003; Knutson et al., 2001), over the past decade which strengthens and enhances understanding of the human brain reward network. More recently, there have been a small number of fMRI studies which have started to compare reward processing of monetary reinforcers with another reinforcer type, such as monetary versus a primary food reinforcer (juice; Kim et al., 2010; Beck et al., 2010), monetary versus abstract food reinforcer (picture of food/water; Levy and Glimcher, 2011), monetary versus a social reinforcer (smiling face; Spreckelmeyer et al., 2009; Rademacher et al., 2010), and even compare monetary reinforcer with more than one incommensurable consumer goods – monetary versus snacks versus trinkets (Chib et al., 2009; FitzGerald et al., 2009). A comparison of neural activity between different types of reinforcers such as social and monetary, can test directly where in the human brain the values of different types of rewards are represented, anticipated, and compared in order to make decisions and generate approach or avoidance behaviour (FitzGerald et al., 2009; Lin et al., 2011; Rademacher et al., 2010). Comparative studies of reward type have frequently focused on different cognitive functions, including reward anticipation, receipt, and consumption, and more complex reward related decision-making (Levy and Glimcher, 2012). Dissociable as well as shared neural activations have been found when comparing two reward types (Levy and Glimcher, 2012; Kim et al., 2010; Valentin et al., 2009; Izuma et al., 2008; Lin et al., 2011; Smith et al., 2010).

On the other hand, fMRI studies employ reinforcer valence (positive and negative reinforcers; or reward versus punishment) have also found some dissociable as well as common neural activation (Breiter et al., 1997; O'Doherty et al., 2001; 2003; O'Doherty, 2007; Tom et al., 2007; Basten et al., 2010). Previous reward processing fMRI studies

have focused on rewards more than negative reinforcers, and in most cases, a negative reinforcer has been employed in studies that compared reinforcer valence rather than employed as a reinforcer by itself (O'Doherty et al., 2003; Paulus and Stein 2006). One of the most established findings concerning the reinforcer valence, is the medial-lateral OFC dissociation in human OFC activation to rewards (e.g. monetary gain) and punishments (monetary loss), that medial OFC responds to rewards, whereas the lateral OFC responds to punishments (O'Doherty et al., 2001; Small et al., 2001; Ursu and Carter, 2005; Anderson et al., 2003; Gottfried et al., 2002; Rolls, Kringelbach, and Araujo, 2003). This will be discussed in more detail in section 1.5.4.

The following section includes a discussion on reward-related brain structures (OFC, amygdala, striatum and insula) and their functions, regarding reward and punishment processing that has been revealed by fMRI studies.

#### **1.4. The brain reward network**

As stated in McClure et al (2004), it is unlikely that the brain responds to diverse types of reward equivalently. In order to make economic exchanges, an individual has to compare the values of different goods and spend money to obtain goods. Therefore, in principle, the brain has to code the different values of goods and make comparisons, in order to decide if a good is worth to buy. Based on the neuroeconomic theory (Samuelson, 1947; Von Neumann and Morgenstern, 1944; Montague and Berns, 2002), McClure et al (2004) proposes the brain may first encode the subjective values of different types of reward in order to make comparisons on a common valuation scale, and then make decision on an appropriate action, such as exchange one outcome for another outcome (Levy and Glimcher, 2012). There has been substantial progress toward employing fMRI to investigate the neural mechanisms of reward processing. Although, the brain regions activated by rewards vary with respect to the behavioural tasks (involving various cognitive functions), both primary and abstract rewarding stimuli have been reported to increase blood-oxygen-level-dependent (BOLD) activity very consistently, across a common set of brain structures when they are perceived, anticipated or approached, which includes the OFC, ventral striatum, and amygdala (referred to as reward circuitry, reviewed in McClure et al., 2004).

Additionally, O'Doherty (2004) reviewed existing literature on human reward processing and uncovered a similar brain network which contributes to reward-related learning in humans, and includes the vmPFC that covers orbital and medial PFC, amygdala, striatum

and dopaminergic midbrain. More recently, Levy and Glimcher (2012) reviewed the fMRI literature with regard to processing monetary magnitude, that is, on studies examining the receipt and choice of monetary rewards with differing amounts, during an fMRI scan. Increased BOLD activation in some brain regions is highly associated with processing monetary reward magnitudes, which includes the medial PFC (especially the subregion of OFC) and ventral striatum (Delgado et al., 2000; Elliot et al., 2000; 2003; Knutson et al., 2001; 2003; 2005; Breiter et al., 2001; Glascher et al., 2009; Peters and Buchel, 2009; Levy et al., 2010; Tom et al., 2007; Basten et al., 2010). Other brain regions including the amygdala (Grabenhorst and Rolls, 2011) and insula (Platt and Huettel, 2008; Rushworth, 2008; Wallis, 2011), have also been associated with an increased BOLD response to choice making on the basis of monetary magnitudes (reviewed Levy and Glimcher 2012), but the evidence is not as strong as for medial PFC/OFC and ventral striatum. Relatively few fMRI findings stress the amygdala or insula's role in choice making with different monetary amounts, in comparison with the enormous number in evidence for the medial PFC/OFC and ventral striatum. More importantly, Levy and Glimcher (2012) assert that BOLD activation in the vmPFC/OFC is correlated with the representation of subjective reward value and choice for reward related actions. In other words, this region plays a role as a neural common currency that different values can be compared. Thus, an appropriate choice can be made.

To sum up, the brain regions of the OFC/vmPFC, striatum, and amygdala (maybe insula as well), could be referred to as the brain reward network with regard to the representation of the anticipation, expectation, approach and consumption of rewards, and reward-based decision making. These regions are also the primary regions of interest (ROIs) in this thesis. In order to understand these brain regions and their functions in reward processing, the following section will demonstrate the anatomical connections and functions (revealed by fMRI studies) of each region that form the Dopamine (DA) pathways, as DA is a neurotransmitter that commonly associated with rewarding experiences. Therefore, DA pathways that are associated with reward processing will be reviewed first.

### **1.5. Function of the brain reward network as revealed with fMRI**

fMRI allows for the observation of neural activity changes in relation with applied functionally relevant time scales (Rosen et al., 1998), and event-related fMRI enables researchers to explore separate functions of different regions in the brain reward network. Although fMRI has successfully identified the reward related neural structures, that is, the brain reward network, less attention has been paid to the functions each of these different

structures have in reward processing. The following section will discuss the functions of these different structures, by introducing the dopamine pathways (especially the mesolimbic and mesocortical pathways) and associated brain regions, which include the amygdala, dorsal and ventral striatum, and OFC. Furthermore, region of insula and its functions will also be discussed, as it has unique connections directly with the amygdala, ventral striatum, and OFC, and has been reported to play a role in reward processing and decision making, respond to many negative reinforcers such as monetary loss (O'Doherty, Critchley et al. 2003; Paulus and Stein 2006), and reviewed to be involved in all subjective feelings and contributes to salience, awareness, and consciousness (Craig, 2009).

### **1.5.1. DA Systems - DA Neurons and pathways**

Dopamine (DA) is a neurotransmitter commonly associated with the brain reward system, as DA is released in reward related brain structures such as nucleus accumbens and PFC, and is associated with rewarding experiences. DA is involved in rewarded learning (Pessiglioni et al., 2006; 2007), in the hedonic response to reward (Arias-Carrion and Poppel, 2007; Phillips et al., 2003; Wise, 2008), the anticipation and receipt of reward, especially when encoding reward prediction error – where a reward is better than expected (Arias-Carrion, 2010) and in reward-seeking behaviours such as approach, consumption and addiction (Arias-Carrion and Poppel, 2007). Moreover, DA is necessary to evaluate the salience of important rewarding stimuli (Schultz, 2002), and in the production of movements (Smith and Villalba, 2008).

DA neurons are located in the ventral tegmental area (VTA) and substantia nigra pars compacta of the midbrain (Arias-Carrion and Poppel, 2007). These neurons project axons to large areas of the forebrain to release DA through 4 major pathways (Figure 1.1), which include the mesocortical pathway, mesolimbic pathway, nigrostriatal pathway and tuberoinfundibular pathway (Hynes and Rosenthal, 1999; Wise, 2004; Arias-Carrion and Poppel, 2007).

The nigrostriatal pathway begins in the substantia nigra and connects to the dorsal striatum (caudate and putamen), and is involved in the control of voluntary movements. Evidence that the death of dopamine neurons in this pathway can result in Parkinson's Disease has been reported in multiple studies (e.g. Diaz and Jaime, 1996; Smith and Villalba, 2008). The tuberoinfundibular pathway begins in the hypothalamus and projects to the pituitary gland (the median eminence, or the infundibular region), and is associated with hormonal regulation and maternal behaviour like nurturing, and pregnancy. As these

areas of human functioning and behaviour are not the focus of this thesis, it will not discuss these pathways any further.

Both, the mesocortical and mesolimbic pathways begin in the VTA, the former connects to the PFC, cingulate, and perirhinal cortex, while the latter connects both to the limbic system (includes amygdala and hippocampus) via the ventral striatum (nucleus accumbens) and to the medial PFC (Arias, Carrion and Poppel, 2007). The mesolimbic and mesocortical DA systems have been collectively called the mesocorticolimbic system because of the overlap between them (Wise, 2004; 2005).

The mesocorticolimbic system is suggested to be associated with motivation, reward and emotion-related behaviour (Mogenson et al., 1980). DA is released in the nucleus accumbens and PFC when motivation is augmented by naturally rewarding stimuli such as water, food, sex and drives such as hunger and thirst, and also neutral stimuli (or CS) that become associated with naturally rewarding ones (Cornish and Kallivas, 2000).

There are three main explanations for the role of the mesocorticolimbic system in reward processing: hedonia, incentive salience, and reinforcement learning (Berridge, 2007; Arias-Carrion and Poppel, 2007; Di Chiara and Bassareo, 2007). Rewards are wanted, liked and pursued (Berridge and Robinson, 1998; Di Chiara and Bassareo, 2007). Therefore, the reward consumption induces feelings of pleasure and hedonia, which consequently initiate learning. Incentive salience (wanting) shows a possible role for DA, as DA is released when a stimulus is highly desired and results in actions to receive it. Drivers such as hunger, thirst, and sexual arousal will raise the incentive salience of the reward and rewarding cues (Kelley and Berridge, 2002).

Reinforcement-learning theory assumes that animals learn appropriate actions that can maximize future rewards by the following processes (Montague et al., 2004; Sutton and Barto, 1998): The brain compares the value of each past action by comparing the amount of received reward or punishment and saves this in memory, then uses this stored information to predict the value of possible future actions (Hyman et al., 2006). The prediction is then compared with the actual reward obtained from an action; reward prediction error occurs when a difference between the reward prediction and the actual reward received happens (Schultz, 1998). The firing of DA neurons is suggested as a consequence of reward-anticipation, and the DA neurons encode such reward prediction errors (Schultz, 1998, 2001, Arias, Carrion and Poppel, 2007). This hypothesis is based on the evidence provided by Schultz and colleagues (1998). They recorded VTA and SNc DA neural activities in awake-behaving monkeys during classical conditioning, in which

monkeys were trained to expect a juice reward after a sensory cue. The results showed an increase in the firing of certain DA neurons when the monkey received a reward greater than expected, which resulted in increased desire or motivation for the reward. On the other hand, the firing rate of DA neurons is decreased when the received reward is worse than expected. The firing rate of DA neurons remains at baseline level when the received reward is just as expected (Schultz, 2001; Montague et al., 1996; 2004). Therefore, the DA system is believed to be essential for learning from feedback, as it codes prediction errors which advance learning (Schultz, 2001; 2007).

The following sections will discuss the anatomical connections and functions (revealed by fMRI studies) of each reward related structures that form the DA mesocorticolimbic and nigrostriatal pathways, starting with the amygdala, then the ventral and dorsal striatum, followed by the OFC and PFC.



**Figure 1.1: DA projection pathways** (illustration from Davis's Drug Guide for Nurses, 11<sup>th</sup> Edition, 2006).

### 1.5.2. Amygdala

The amygdala has two distinct sections – the basolateral amygdala (BLA) and the central nucleus (CeA) of the amygdala (Cardinal et al., 2002; Baxter and Murray, 2002). The amygdala receives and returns projections from most cortical and subcortical structures, such as the nucleus accumbens, the DA system (VTA and SNc), the basal forebrain cholinergic system and the PFC, especially medial PFC and the OFC (Baxter and Murray, 2002). Therefore, it is not surprising that the amygdala may be involved in many cognitive and emotional processes as it interacts with such a broad number of brain areas (Murray,

2007). The amygdala has been considered to play a vital role in the neural processing of emotion, motivation, learning, memory, attention and reward (Murray, 2007).

#### **1.5.2.1. Amygdala contributes to stimulus-valence association**

The amygdala has been revealed to have an involvement in processing primarily negative affect for decades, which results from the dominance of fear conditioning (emotional learning) studies (LeDoux, 2003; Fanselow and Gale 2003). However, contrary findings have been reported from both human fMRI studies and animal (monkeys and rats) single cell recording studies (Nishijo, 1988; Sugase-Miyamoto and Richmond's, 2005; Paton et al., 2006; Schoenbaum et al., 1998; 1999), that is, the amygdala has also been found to contribute to positive affect and positive reinforcement (Hamman and Mao, 2002; Anderson et al., 2003; Hommer et al., 2003; Small et al., 2003; Somerville et al., 2006; reviewed in Murray, 2007).

For instance, Paton et al (2006) recorded single cell neural activity in the amygdala of monkeys (*Macaca mulatta*), in an experiment where visual stimuli led to a positive or negative reinforcement or non-reinforcement, through classical conditioning. Monkeys in their study saw pictures associated with either a liquid reward, or an air puff directed at the face (punishment), or nothing (non-reinforcement). Learning was demonstrated by either the monkeys licking after viewing positive pictures, or blinking after the air puff. Paton et al (2006) recorded from the amygdala neurons during picture presentation, before the delivery of the reinforcement stimuli, and found that a group of neurons encoded positive valence while another separate group of neurons encoded negative valence. These neurons are not spatially segregated. Moreover, Paton et al (2006) found that amygdala neurons began to change activity within a few trials after reinforcer reassignment (reversal – change in picture value), but the rate of change was identical in licking and blinking responses, suggesting that amygdala neurons might contribute to learning. Their results support Nishijo (1988) and Sugase-Miyamoto and Richmond's (2005) findings that amygdala contributes to positive reinforcement. Evidence supporting the amygdala's role in positive affect has also been reported in rat studies (Schoenbaum et al., 1998; 1999). Human fMRI studies also provide evidence supporting the contribution of the amygdala to positive affect (reviewed in Murray, 2007). In Somerville et al.'s (2006) fMRI study, they found stimulus-valence associations, where the right amygdala responded to both positive and negative faces, compared to neutral faces.

Furthermore, the amygdala has been reported to respond to reinforcer intensity (how

arousing a stimulus is) rather than reinforcer valence when BOLD activity in response to rewarding and aversive stimuli are compared directly (Sanghera, 1979; Hommer et al., 2003; Small et al., 2003; reviewed in McClure et al., 2004; Wilson and Rolls, 2005). The valence here is referred to as either the positive or negative value of reinforcement or reward, and the neural processes related to it, which include both stimuli valuation and emotional/affective representation. Therefore, the predominance of findings on the amygdala's strong role in responding negative emotional stimuli can be explained, as aversive stimuli are usually more salient and have more behavioural relevance than positive stimuli (Anderson et al., 2003).

#### **1.5.2.2. Stimulus-value association versus stimulus-reward association**

Stimulus-reward association is the basic model for investigating reward processing, which involves associative learning through classical conditioning. Two tasks traditionally used to investigate this process are reward based reversal learning and 'win-stay, lose-shift' tasks (Murray, 2007). Early amygdala lesion studies in monkeys (Aggleton and Passingham, 1981; Barrett, 1969; Jones and Mishkin, 1972; Schwartzbaum and Poulos, 1965; Spiegler and Mishkin, 1981) reported profound impairments on these tasks, suggesting a contribution of the amygdala in stimulus-reward associations or more generally, reward processing. However, more recent lesions studies that adopted selective lesions of the amygdala have overturned these earlier findings (Baxter and Murray, 2000). For example, Stefanacci (2003) adopted selective amygdala lesions (excitotoxic) on macaque monkeys on a win-stay, lose-shift task, and reported only a mild and transient disruptive effect. Additionally, Izquierdo and Murray (2007) used selective bilateral amygdala lesions on rhesus monkeys on an objective reversal learning task and reported no disruptive effect. Therefore, the two tasks used to study stimulus-reward association are independent of amygdala function (Baxter and Murray, 2002).

On the other hand, there have been arguments that posit the amygdala contributes to stimulus-value rather than stimulus-reward valuation. This is primarily because the food rewards used in the reversal learning and 'win-stay, lose-shift' tasks have limited reward (or affective) value, and the processing of this limited reward information may not involve amygdala. In both tasks, monkeys always receive a food reward, so that they do not need to assign any particular value to the food, as there is no need to distinguish between different foods and update the object representation. In contrast, a reinforcer-devaluation task that involves stimulus-value associations requires rapid updating of the reinforcer value to support instrumental behaviour and goal-directed action and has been revealed

to be mediated by the BLA (Murray, 2007). For example, pairing malaise (caused by injections of lithium chloride) with a food reward in rats reduces responding to the CS that is paired with the food (Holland and Rescorla, 1975). This devaluation of the food reward results in a decrease of responding to the CS (Holland, 1990; 1998). This effect has also been reported following an amygdala-OFC disconnection (Baxter et al., 2000). Supporting evidence for the amygdala's role in the stimulus-value association has also been reported in lesion studies, only in lesions of BLA, not CeA (Hatfield et al., 1996). A dissociation between BLA and the CeA was further demonstrated by Blundell et al (2001) and Corbit and Balleine (2005), who demonstrated that BLA plays a role in processing reward-specific value such as the taste of food, whereas the CeA plays a role in reward-general value such as general positive emotion or arousal that caused by receiving food reward. Lesions studies support this view by showing that BLA lesions disrupt reward-specific affect but leave general affect processes intact. By contrast, CeA lesions disrupt general affect while leave the reward-specific affect unimpaired (reviewed in Murray, 2007).

To sum up, the amygdala plays a role in processing both positive and negative affective value of rewards and processing reward intensity. The amygdala is also involved in the processing of the value of rewards (affective value and reinforcement) during instrumental learning (Murray, 2007). Moreover, the amygdala has connectivity with sensory areas (e.g. the inferior temporal and perirhinal cortex) and the OFC to help guide decisions or select responses. Some amygdala functions are binding with the OFC (Schoenbaum and Roesch, 2005; Baxter et al., 2000) such as updating the expected reward values. The amygdala is assumed to update current values first, then the OFC merges and stores all the values for updating the expected reward outcomes (Holland and Gallagher, 2004).

### **1.5.3. Striatum – dorsal and ventral striatum**

The striatum is the largest nucleus of the basal ganglia (BG), and it is subdivided into dorsal and ventral striatum on the basis of external connectivity (Voorn et al. 2004). The ventral striatum (nucleus accumbens) is densely innervated by midbrain DA neurons which originate from the VTA (as discussed in section 1.4.2), and interacts with both the limbic structures and the medial PFC, and has efferent projects to the subcortical and limbic regions (Day and Carelli, 2007) such as the lateral hypothalamus, VTA and the ventromedial regions of the ventral pallidum (Kelley, 1999). Whilst, the dorsal striatum (Caudate and putamen) is innervated by midbrain DA neurons that begin from the substantia nigra, and interact with many cortical regions including PFC, cingulate, and perirhinal cortex. The efferent connectivity of the dorsal striatum resembles some of the efferent connectivity of nucleus accumbens so that it projects to the basal ganglia regions

such as the ventral pallidum and the substantia nigra (Robbins and Everitt, 1996; Kelley, 1999). In addition, the whole striatum interacts with the sensorimotor and motivational regions of the brainstem via the thalamus (Kelley, 1999).

Therefore, according to its external connectivity, the nucleus accumbens may integrate information associated with motivation, drive, and emotion and translate this into action (Mogenson et al., 1980). The striatum can be a region of “limbic-motor” interface (Mogenson et al., 1980; Kelley, 1999) and a region where “motivational-emotional determinants of behaviour become transformed into actions” (Mogenson et al., 1980; Kelley, 1999).

Previous fMRI studies investigating reward processing have reported that BOLD activation in ventral striatum is related directly to prediction errors (unexpected outcomes) of rewards and the anticipation of rewards (Montague et al., 1996; Schultz et al., 1997; Berns et al., 2001; Pagnoni et al., 2002; McClure, et al., 2003; O’Doherty et al., 2003; reviewed in McClure et al., 2004). For instance, stronger BOLD responses were found when subjects expected greater amounts of reward compared with lesser amounts, which were also paired with faster reaction times (RT) to the rewarding cues (Knutson et al., 2001b). FMRI studies have indicated that anticipation of monetary gains results in increased activation of the nucleus accumbens. Also, the nucleus accumbens has been suggested as having a vital role in recognising environmental stimuli as cues for rewarding events (Spreckelmeyer et al., 2009; Kalivas and Volkow, 2005; Knutson and Cooper, 2005).

There have been many fMRI studies which have revealed neural activity in the striatum during reinforcement learning and proposed this activity reflect dopaminergic input to some extent (Pessiglione et al., 2006; McClure et al., 2003; O’Doherty et al., 2003). The dorsal and ventral striatum have a different specialized function regarding reinforcement learning. O’Doherty et al (2004) investigated changes in striatal BOLD activations during the learning of stimuli-reward outcome associations in both instrumental and classical conditioning, in which the former required an active response while the latter did not. They reported increased ventral striatal activations in both conditioning contexts, but dorsal striatal activity was only present to the instrumental conditioning. Thus, they suggested that the dorsal striatal region might contribute more to action-reward associations (O’Doherty et al., 2004; Tricomi et al., 2004; 2006). In other words, the ventral striatum is correlated with prediction errors occurred (unexpected outcome occurred) during both classical and instrumental learning, whereas the dorsal striatum is specifically correlated with instrumental learning, where individuals must learn instrumental actions-rewards

associations (O'Doherty et al., 2004; Delgado, 2007; Tricomi et al., 2004). Therefore, the ventral striatum could mediate learning of stimulus-reward associations whereas the dorsal striatum focuses on action performance by learning of action-reward outcome associations and especially learning of instrumental action values (Suri and Schultz, 1999; Sutton and Barto, 1998; O'Doherty, 2004).

Generally, the dorsal striatum has been revealed by many reward processing fMRI studies to play a role in different aspects of motivational and learning processes which support goal-directed actions (Brovelli et al., 2011). As described above, the dorsal striatum plays a role in reinforcement learning of stimulus-action-reward associations, and enables the maintenance of information about the rewarding outcome of an action in order to enable the better/greater ones to be selected more frequently in future (O'Doherty et al., 2004; Tricomi et al., 2004; Bellebaum et al., 2008). Therefore, it is not surprising that this region has been revealed to contribute to reward anticipation, expectation and delivery (O'Doherty et al., 2002; Knutson et al., 2001; Delgado, Locke, Stenger, and Fiez, 2003; Elliott et al., 2003; Berns, McClure et al., 2001; Knutson et al., 2001; Delgado et al., 2000) as well as to process salient stimuli (Lauwereyns et al., 2002). The function of striatum could be explained by the prediction error occurred during action-reward association learning and may be mediated by afferent DA input, so that DA nerve cells project onto the "critic" – nucleus accumbens to alert an individual that a potential rewarding event is within reach (Schultz, 1998). Then a response action results in a better/greater than predicted reward in a given context become reinforced, and the "actor" – dorsal striatum enables it to be selected more frequently in future (Montague et al., 1996).

#### **1.5.4. Orbitofrontal Cortex – OFC**

The OFC has a unique anatomical location and connectivity in relation with reward processing (Montague, 2004), as it receives signals directly from visual, olfactory, taste and somatosensory areas (Elliott et al., 2000; Rolls, 2000) and closely interacts with the amygdala and ventral striatum, which contribute to reward and affective processing (Carmichael and Price, 1995). The OFC is also a part of the PFC and therefore directly interacts with other areas of the PFC (Carmichael and Price, 1996). As a result, the OFC is thought to be involved in storing the reward value of sensory stimuli, and in reward and affect related processing in addition to sharing many of the functions of other PFC areas (Montague and Berns, 2002).

On the basis of the findings from previous fMRI studies examining human reward processing, the OFC is believed to play a role in a number of rewards related functions,

such as the representation of reward value when perceived, reward expectation/prediction, and updating expectations based on the prediction error signals generated in the midbrain. The OFC also uses abstract knowledge, to guide reward predictions and make decisions (Wallis, Anderson and Miller, 2001; as reviewed in O'Doherty, 2007). Among all these functions, the neural pattern of activation in the OFC to reward value during the receipt of reinforcement is of particular interest in the current thesis, and the task paradigms were deliberately simplified to focus on the receipt of rewarding stimuli and exclude any decision-making components (will be discussed in section 1.5.5.1).

#### **1.5.4.1. Coding reward value at receipt**

Coding the reward value of a stimulus is one of the most established findings with regard to the OFC function (O'Doherty, 2007). Experiments in monkeys have reported that OFC neurons increase activity in response to preferential tastes (Rolls, 2008), and the increased rate of neuronal activity is associated with the relative rather than absolute stimulus reward value. For instance, OFC neuronal activation is increased in the case of hunger to fruit juice but significantly decreased in the case of satiety when the corresponding food is thus no longer rewarding (Rolls, 2008). Similarly, Tremblay and Schultz's (1999) experiments in macaques have shown that the amplitude of neuronal activity in the OFC is associated with the relative value of rewards in comparison with other available rewards (Tremblay and Schultz, 1999). These findings from the animal neurophysiology literature are supported by fMRI studies on humans which have reported the OFC (and some have shown striatum as well) plays a role in encoding the reward value of various primary rewards, received via diverse sensory modalities, such as visual, auditory, olfactory/gustatory and somatosensory stimuli (Rolls, et al., 2003; Small, et al., 2003; O'Doherty et al., 2003). Also, the OFC is involved in encoding the reward value of abstract rewards, such as money and social praise (Breiter et al., 2001; Elliott et al., 1997; Knutson et al., 2001). Furthermore, the OFC responds to both rewards and punishments (Breiter et al., 1997; O'Doherty et al., 2001; 2003; Montague and Berns 2002; O'Doherty, 2007).

Different regions of the OFC appear to be functionally specialised, in relation to coding reward value and the regulation of approach or avoidance behaviour (Elliott et al., 2000; O'Doherty, 2007). Below, the section will discuss in greater detail the functional specialisation of the OFC in relation to processing different types of reward information.

#### **1.5.4.2. OFC medial-lateral trend: rewards versus punishments**

O'Doherty et al (2001) reported a medial-lateral dissociation in human OFC activation to rewards (monetary gain) and punishments (monetary loss), during a monetary reward based reversal-learning task. They found medial areas of the OFC responded to monetary rewards, whereas the lateral areas of the OFC responded to monetary loss. In the meantime, a similar medial-lateral functional dissociation within the OFC was reported by Small et al (2001) during the consumption of a chocolate meal. They found that medial OFC activation was elicited during the early stages of chocolate consumption, whereas lateral OFC activation was elicited after satiety. Small et al., (2001) extrapolated from their findings that the chocolate had a high reward value during early feeding but became aversive after satiety. Later in 2005, in Ursu and Carter's fMRI study of facial attractiveness, where subjects were presented with faces which had high and low attractiveness while they performed an unrelated gender judgement task. They found medial OFC responded to faces high in attractiveness whereas lateral OFC responded to faces low in attractiveness. Furthermore, similar results have been reported by a number of imaging studies of olfaction, where the medial OFC responded to pleasant odours, whereas lateral OFC responded to aversive odours (Anderson, et al., 2003; Gottfried et al., 2002; Rolls, Kringelbach, and Araujo, 2003).

Not all neuroimaging studies of reward processing are in agreement with the above findings and some contradictory findings add uncertainty to a medial-lateral distinction in the OFC. For example, an fMRI study conducted by Elliott and colleagues (2003) examined monetary gain and loss, found both the medial and lateral OFC responded to both monetary gain and loss. A similar finding was also reported by Breiter et al (2001), that the medial and lateral OFC responded equally to rewarding and punishing feedback.

A possible explanation for the discrepancy among studies was suggested by O'Doherty (2007), that studies who failed to report a medial-lateral functional dissociation within the OFC (Elliott et al., 2003; Breiter et al., 2001; Kim et al., 2006) employed complicated task paradigms (compared to those studies that report a dissociation) that involving several different cognitive processes besides coding reinforcer value. One example of such task is the gambling task, which involves processes such as reward anticipation or expectation, response selection, and detecting change and applying behavioural strategies (O'Doherty, 2007). These various cognitive processes might not be controlled or disambiguated in a given task, and therefore, may contribute to such differences between studies. Kim et al's (2006) fMRI study employed an instrumental decision-making task, supported O'Doherty's

(2001; 2007) view by showing that both medial and lateral OFC were activated during reward anticipation, but only medial OFC was elicited after receiving a rewarding outcome and following successful avoidance of an aversive outcome. Their results additionally suggested that there should be a functional dissociation between the receipt and the expectation of a reward. Thus, it is worth to employ simple task paradigms that focus on one main cognitive process (e.g. coding reward value at the receipt), in order to investigate the function of the OFC in reward processing. This was an aim within the present thesis (see section 1.5.5.1 and chapter 2).

#### **1.5.4.3. Posterior-to-anterior trend: increasing complexity**

O'Doherty et al's (2003) fMRI study of probabilistic reversal learning, reported another OFC functional dissociation. Here participants had to choose between two actions that would lead to rewards (monetary gain) and punishers (monetary loss) with different probabilities. One action was associated with a 70% probability of getting a reward and a 30% probability of getting a punishment, whereas the other action was associated with a 30% probability of receiving a reward and 70% probability of getting a punishment. The contingencies reversed on a trial by trial basis, where participants could either maintain the on-going response to the current stimulus or change their choice of stimulus (stay versus switch). Their results indicated that stay behaviours were related with activity in the anterior medial OFC regardless of the outcome valence (i.e. it does not matter if it was a reward or punisher), whereas switch behaviours were associated with activity in the posterior lateral OFC when the outcome was a monetary loss. This study led O'Doherty et al (2003) to propose that the OFC could contribute to behavioral choice and that different areas of the OFC responds to different behavioral strategies, such as the anterior medial OFC responds to "maintained" on-going behaviour, whereas the posterior lateral OFC responds to "changed" behaviour. Therefore, they suggest that OFC could play a role in reporting consequences of decisions and computing the decision of which action would be appropriate to take next.

In addition, Kringelbach and Rolls (2004) reviewed the neuroimaging literature by using meta-analysis and showed a significant increase in the complexity of the processes with regard to reward representation and processing from the posterior part of OFC to the anterior part of OFC. For instance, monetary reinforcers are represented much more anteriorly in the OFC (O'Doherty et al., 2001) than posterior areas which representing simpler reinforcers such as taste (De Araujo et al., 2003a,b,c; Kringelbach et al., 2003;

Rolls et al., 2003a,b; Small et al., 1997). Moreover, BOLD responses to taste-olfactory combined stimulus were revealed in more anterior parts of the OFC than the unimodal version of the same reinforcers (i.e. taste alone or smell alone; De Araujo et al., 2003). Kringelbach and Rolls (2004) suggested these findings may reflect a hierarchy of processing within the OFC, so that higher level processing occurs more anteriorly.

To sum up, the OFC responds to various rewards and punishments, and there is some degree of functional specialization within the OFC with regards to coding the reward/affect valence, stay/switch action choices on the basis of reward prediction, or the complexity of the reward nature. Therefore, the OFC may play a role in coding different reward types, valence and other reward information.

#### **1.5.4.4. Functional integration of OFC**

Contrary to functional specialization in the OFC, there have thus also been theories suggesting that the OFC is a candidate region where different outcomes or rewarding events are evaluated and compared on a common valuation scale or a common currency, in order to choose an appropriate action. Take for example, a situation where an individual has to make a choice between receiving an appetising food and a small amount of money, the brain has to compare the values of the two different outcomes (maybe together with subjective affective state) by representing and converting them on a common neural currency, before computing the decision about what action to take (Montague and Berns, 2002; Rolls, 1999; Rolls and Grabenhorst, 2008). The OFC is a candidate region in this situation as it has a unique anatomical connectivity which allows it respond to different types of rewards (primary and abstract) and punishment, and plays a role in the representation of reward value at the receipt, reward anticipation, reward prediction, and even decision making. However, only a few fMRI reward processing studies provided direct evidence for a convergence and merging function of the OFC. The direct evidence here means an fMRI study that has employed multiple reward types, magnitudes, and valence in a single task.

Levy and Glimcher (2012) have reviewed previous fMRI studies which employed a single task to compare reward magnitudes and suggested a small number of brain regions encode different reward magnitudes (usually monetary reward magnitudes) during reward expectancy and decision making. For example, the ventral striatum activity is associated with the magnitude of monetary rewards in evaluation (Delgado et al., 2000; Elliot et al., 2000), anticipation (Knutson et al., 2001), expectation (Breiter et al., 2001), and receipt

(Elliott et al., 2003), etc. Similarly, the medial PFC especially the OFC has also been revealed to encode the amount of money an action will yield (Knutson et al., 2001; 2003; Glascher et al., 2009), and is correlated with the expected values of monetary lotteries (Knutson et al., 2005; Peters and Buchel, 2009; Levy et al., 2010), and the subjective valuations of gains and losses (Tom et al., 2007; Basten et al., 2010), etc.

Compared to the substantial number of fMRI studies investigating reward magnitude in a single task, a limited number of fMRI studies have made direct comparisons of multiple reward types in a single task. A direct comparison of neural activity between different abstract reinforcers such as social and monetary, as well as among different primary reinforcers, within a single task, can test directly where in the brain the values of different types of rewards are represented and compared by a common currency (to make economic decisions). Both dissociable and overlapping findings of BOLD activity have been reported by previous reward-related fMRI studies involving multiple reward types. For example, a recent fMRI study has revealed that primary (juice) and monetary rewards elicited differed neural activity in the right-lateralized control regions, including anterior prefrontal cortex (PFC), and dorsolateral PFC, during a reward-based working memory task (Beck et al., 2010). Another recent fMRI study by Kim et al (2010) found partially overlapping activity in the vmPFC and the anterior insula to the anticipation of both juice and monetary rewards, and the anterior insula also showed a negative correlation with increasing expected reward for both reward types.

Are the values of different types of rewards represented in distinct or overlapping brain areas? Are the representations merged and converged into a single common scale for comparison in order to guide actions? Does the OFC or striatum also contribute to the representation of different reward types, in addition to reward magnitude? Recently, in Levy and Glimcher's (2012) meta-analysis of ten fMRI studies on decision making (i.e. action needs to be made between different choices) using multi-types of reinforcers, they revealed a strongly consistent result for a subregion in the vmPFC – the medial OFC (bilateral), which played the role of a common currency/substrate to represent subjective values of different types of reinforcer. All these studies compared reward processing of monetary reinforcers with another reinforcer type (as already mentioned in section 1.3.1), such as money versus a primary reward like juice (Kim et al., 2010; Valentin et al., 2009), money versus food/water picture (Levy and Glimcher, 2011), money versus incommensurable goods (FitzGerald et al., 2009), and money versus social stimulus – reputation, smiling/angry faces, attractive faces (Izuma et al., 2008; Lin et al., 2011; Smith et al., 2010), money versus pain (Talmi et al., 2009), and even compared 3 types of reinforcers – money versus snacks food versus trinkets (hat) (Chib et al., 2009). Levy and

Glimcher (2012) reports a similar finding across the ten multi-types reward processing fMRI studies that the OFC/vmPFC acts as a common currency/substrate which allows for comparisons of different reward values in order to make an appropriate choice. Also, these findings to some extent fit with the Montague and Berns' (2002) theory that OFC-striatum works as a common neural substrate.

#### **1.5.4.5. Medial OFC codes context-dependent relative value**

The OFC has been reported to code relative value of financial rewards (Elliott et al., 2008) rather than absolute value. According to the context-dependent theory (Nieuwenhuis et al., 2005; Elliott et al., 2008), the reward processing system determines whether an outcome is favorable or unfavorable on the basis of the range of possible outcomes encountered in a particular setting—judging the best possible outcome to be favorable and the worst possible outcome to be unfavorable, regardless of the absolute magnitudes of these outcomes (Nieuwenhuis et al., 2005). Previous fMRI studies have reported that BOLD responses to rewarding stimuli are influenced by the context in which the outcomes are experienced (O'Doherty et al., 2000; Small et al., 2001; Gottfried et al., 2003; Akitsuki et al., 2003; Elliott et al., 2000, 2008; Nakahara et al., 2004; Nieuwenhuis et al., 2005). Those previous fMRI studies suggesting the context-dependent theory, employ only single type of reward but with different magnitude, such as Nieuwenhuis et al (2005) and Elliott et al (2008) used different amounts of money, while Tremblay and Schultz's (1999) animal study used food with 3 favorable levels (raisins, apple and cereal).

#### **1.5.5. Insula**

The insula has unique connectivity with the cognitive, affective and homeostatic brain systems (Menon and Uddin, 2010). It has bi-directional connections (both efferent and afferent projections) with the OFC, anterior cingulate, nucleus accumbens, and the amygdala (Reynolds and Zahm, 2005; Menon and Uddin, 2010).

The insula has been proposed to play a role in integrating emotion related and interoceptive information, and send this information to the OFC and anterior cingulate, to influence decision making (Levy and Glimcher, 2012). The insula has also been reported to receive homeostatic sensory inputs via the thalamus, and forward outputs to the amygdala, ventral striatum and OFC (Menon and Uddin, 2010), and is well placed for combining information relating internal bodily states (such as pain, temperature and

arousal) into higher-order cognitive and emotional/affective processes (Craig, 2002; 2009). This region has been reviewed to be involved in all subjective feelings and contributes to salience, awareness, and consciousness (Craig, 2009).

The insula, especially the anterior insula has been suggested to have an important role in the processing of a number of basic emotions and feelings, mostly negative feelings such as pain, disgust (Singer, 2006; Wicker et al., 2003), anger, fear, and evaluation of 'distressing cognitions' (Reiman et al., 1997). Also, Kim et al (2010) have suggested in an fMRI study that the insula has a general role in indicating when a negative consequence is expected in relation to aversive outcomes. They reported that right anterior insula activation was negatively correlated with an expected reward, that is, the less the magnitude of the expected reward, the greater the anterior insula activation. Indeed, the insula has previously been reported to respond to many different types of negative reinforcers, such as the receipt of monetary loss (O'Doherty, Critchley, et al. 2003; Paulus and Stein 2006), during the anticipation and also receipt of painful stimuli (Seymour et al. 2004) and when risk averse individuals made risky gambles (Huettel et al. 2006; Preuschoff et al. 2006). Additionally, the insula has been implicated in responding to disgusting odours (Wicker et al., 2003) and aversive tastes (Small et al. 1999) as well as in the evaluation of 'distressing cognitions' (Reiman et al., 1997). In addition, the anterior insula is involved in the processing of many social experiences such as norm violations (Sanfey et al., 2003), social-emotional processing (Phan et al., 2002) and empathy (Singer, 2006).

The anterior insula also has been suggested to play an important role in "regulation" of salience, and selective attention (Eckert et al., 2009; Menon and Uddin, 2010). For example, 'during a challenging task, this 'regulation of salience' function would be involved where attention is waning and results in careless mistakes (error monitoring/awareness), but once there is too much arousal it may lead to risks creating poor performance by becoming anxious (Eckert et al., 2009).

#### **1.5.6. Multi-types reward processing – social versus monetary reinforcement**

Other fMRI studies have also investigated the neural pattern of action to multi-types of reward, but these involved no decision-making components in their tasks (Rademacher et al., 2010; Spreckelmeyer et al., 2009), or have focused on other cognitive functions like working memory (Beck et al., 2010), or have employed a patient group (Scott-Van Zeeland, 2010). Scott-Van Zeeland (2010) revealed that children with autism showed a

diminished frontostriatal BOLD response to social rewards, but not monetary rewards during rewarded learning, which may relate to social learning impairments evident in these children.

fMRI studies involving comparisons between social and monetary reward processing in healthy adults is of particular interest, as the current thesis is primarily focused on comparing the neural representations of these two types of reinforcement. The following section will focus on previous fMRI studies which have specifically compared social with monetary reward processing, outlining their main findings and also limitations.

#### **1.5.6.1. Findings and limitations of past fMRI studies on employing social and monetary reward processing**

Among the few fMRI studies involving multi-types of reward processing in healthy individuals, only a handful of them (there have been five studies of this kind) have compared monetary with social reinforcement (Izuma et al., 2008; Lin et al., 2011; Rademacher et al., 2010; Spreckelmeyer et al., 2009; Smith et al., 2010). The findings are rather mixed, as both distinct and overlapping neural representations have been reported, for these two reinforcers (Izuma et al., 2008; Lin et al., 2011; Rademacher et al., 2010; Spreckelmeyer et al., 2009; Smith et al., 2010). Three of the previous fMRI studies have reported social and monetary rewards have overlapping neural representation (Izuma et al., 2008; Lin et al., 2011; Smith et al., 2010), in which Izuma et al (2008) reported the dorsal striatum responded to the receipt of both reward types, while Lin et al (2011) revealed the vmPFC/OFC is a common area correlated with the stimulus value at the time of choice for both social and monetary rewards, and Smith et al (2010) reported the anterior vmPFC/OFC responded to the experienced value of both reward types (receipt value via passive viewing), and the posterior vmPFC/OFC responded to the decision value (decide whether to exchange money for attractive faces) of both rewards.

On the other hand, two fMRI studies reported distinct neural representations between social and monetary reinforcers (Rademacher et al., 2010; Spreckelmeyer et al., 2009), in which Rademacher et al (2010) found differences in the amygdala and thalamus, so that the amygdala was more sensitive to social reward whereas the thalamus was more sensitive to monetary reward during reward consumption (but not during reward anticipation). Spreckelmeyer et al (2009) found increased BOLD activation in a range of mesocorticolimbic brain regions (anterior cingulate, caudate, amygdala and nucleus accumbens) to the anticipation of monetary reward, but not social reward (smiling face).

One of the main limitations of the above studies is that none of them included a direct contrast between the two reward types within a single task. For example, Izuma et al (2008) conducted two separate and different tasks for the two reward types. Lin et al (2011) compared where BOLD activity was parametrically related with two versions of a rewarded instrumental learning task, one with monetary rewards/punishments and the other with social. Spreckelmeyer et al (2009) presented the two types of rewards in two separate task sessions. Thus, the reward types were not directly contrasted in these studies, which make the interpretation of these results difficult, as it is unclear if any differences found were due to the type of reward or to task differences (e.g., a difference in action contingency). Furthermore, the fMRI studies involving social and monetary reward processing employed different task paradigms and focused on different cognitive functions, including reward anticipation (Spreckelmeyer et al., 2009), receipt/consumption (Rademacher et al., 2010; Smith et al's), and more complex reward related decision-making (Izuma et al., 2008; Lin et al., 2011; Smith et al., 2010) and associative learning (Scott-Van Zeeland, 2010).

This thesis aimed to improve on the above studies by employing social and monetary reinforcers within a single simple task paradigm, to narrow down the cognitive functions and focus purely on the receipt of reinforcement. Both overlapping and distinct neural activations in response to social and monetary reinforcers were expected to be found in the OFC, striatum, amygdala and maybe insula as well (Levy and Glimcher, 2012), on the basis of their functions in reward processing as discussed above. Moreover, these reward-related brain regions would be expected to work together as a system to represent the subjective reward values and guide action choices rather than as separate entities (Levy and Glimcher, 2012). The following section would discuss this assumption in more detail.

#### **1.5.7. The Brain Reward Network works as a system rather than separate entities**

While the various types of information about rewarding stimuli (e.g. nature of the stimulus, emotional response, stimulus relative value in context it appears, internal state, etc) could be represented separately in one or more regions of the brain reward network. It is more probable that the OFC works in cooperation with the other reward related regions (i.e. striatum, amygdala, and insula) to represent subjective reward values of different types of reward (Levy and Glimcher, 2012).

The vmPFC/OFC is a strong candidate to represent the subject-specific subjective value

of every kind of reward that has ever been investigated in fMRI studies (Levy and Glimcher 2012) and may act as a common neural currency to allow comparisons across different values. Levy and Glimcher (2012) also suggested that the neural common currency of value representation and comparison may arise not only on the vmPFC/OFC but also on the striatum and insula (Levy and Glimcher, 2012). The robust anatomical and functional connections among these regions support this possibility.

The OFC lies in the inferior part of PFC and receives direct inputs from taste, olfactory, visual and somatosensory areas (Elliott et al., 2000; Rolls, 2000). It interacts closely with the amygdala and ventral striatum, which contribute to reward and affective processing (Carmichael and Price, 1995), as well as interacts other areas within the PFC (Carmichael and Price, 1996). The OFC, therefore, could play a role in coding the reward and affective value of sensory stimuli and share functions with other parts of the prefrontal cortex (Montague, 2004).

The amygdala is also a key hub for processing rewards as it has bi-directional connections with most cortical and subcortical structures, including the nucleus accumbens, the DA system (VTA and SNc), the basal forebrain cholinergic system and the medial PFC and OFC (Baxter and Murray, 2002). Some amygdala functions with regard to reward processing (e.g. coding and updating of reward values) are binding with the OFC (Schoenbaum and Roesch, 2005; Baxter et al., 2000; Holland and Gallagher, 2004). Previous studies have suggested the OFC–amygdala circuit contributes to the adaptation of changes in stimulus–reward and action–reward mappings (Cools et al., 2004; Goto and Grace, 2005; Kesner and Rogers, 2004; Kringelbach, 2005). In Camara et al's (2008; 2009) functional connectivity study of reward processing, they suggested that such adaptation processes were more crucial after a monetary loss than gain, as the loss indicated the need for a change in behavior. In another functional connectivity fMRI study using a feedback-guided reversal learning task (Cohen et al., 2008), amygdala–OFC connections were found to predict participants' learning behavior following rule reversals, stressing the OFC-amygdala circuit's role in learning from negative events.

The insular cortex also has bi-directional connections with many regions important for reward processing and decision making, including the OFC, anterior cingulate, nucleus accumbens, and the amygdala (Reynolds and Zahm, 2005). Furthermore, it has been proposed that the insular cortex play a role in integrating emotion related and interoceptive information, and forwards this information to the OFC and anterior cingulate, to influence decision making (Levy and Glimcher, 2012). The insula, therefore, could also directly influence other reward-related limbic regions like the amygdala and NAcc.

The striatum receives direct input from most regions of the cerebral cortex and limbic structures including the amygdala and hippocampus, and receives additional input indirectly from sensorimotor and motivational regions of the brainstem via the thalamus, and also receives input from the SNc (dopamine) and the raphe nuclei (serotonin) in the midbrain. Camara et al's (2009) functional connectivity study of reward processing used the ventral striatum as a seed region to test the functional connectivity with several other regions, including the OFC, insula, amygdala and hippocampus. They revealed that all these regions correlated with the ventral striatum in the processing of monetary gain and losses. Some previous experiments have also revealed a number of frontal-basal ganglia circuits which modulate cortical processing during learning, motivation and motor preparation (Kelley, 2004; Lisman and Grace, 2005; Münte et al., 2008). Camara et al (2009) have pointed out that these functional circuits overlap and share some important processing stations, and highlighted a network (ventral striatum, OFC, amygdala, insula, and hippocampus) which plays a role in processing reward gains and losses.

Levy and Glimcher (2012) proposed a possible schema for understanding how various reward information converges towards a single common value representation, before passing on to the motor control circuitry to make appropriate choices (Figure 1.2). The vmPFC/OFC appears to be the centre for the common value representation of subjective reward values that may be comprised of assorted reward-related information such as the internal state (satiety, thirst, hormonal levels, etc.), sensory nature of the rewarding stimuli, motivation, stimulus relative value in context it appears, emotional intensity and arousal, etc. Levy and Glimcher (2012) has also suggested that the subcortical regions (striatum and insula) represent the subjective value of different rewards, and pass the information onto the vmPFC/OFC. Here, the final comparisons are made between the various sources of information about the rewarding stimuli before the decision signals are sent to the motor control system in order to apply appropriate actions. The role of the insula and striatum in common value representation is not as certain as the vmPFC/OFC (Levy and Glimcher, 2012) and future studies of these regions with regard to their functions in this role are needed.



**Figure 1.2: The brain reward network for representation of subjective values of rewarding stimuli** (illustration from Levy and Glimcher, 2012). Information about sensory reward stimuli (e.g. visual stimuli) is passed on to both subcortical and cortical structures. The OFC/vmPFC is the main region that works like a neural common currency to represent the subjective value of the different rewards. Other possible candidates include striatum and insula.

To sum up, the vmPFC/OFC, striatum, amygdala and insula may work together as a reward system, in which the vmPFC/OFC, striatum, and insula represent subjective values of different types of reward which, together with other information relating to the reward characteristics of the stimuli are merged and converged in the vmPFC/OFC to make a final comparison to guide actions. In order to make this kind comparison, the vmPFC/OFC (maybe also the striatum and insula) must first be able to distinguish between different values. Therefore, in the fMRI studies that are included in this thesis, social and monetary reinforcers are expected to elicit the same reward network, while the reward values of them may be represented differently within each of these regions (especially within the vmPFC/OFC).

#### **1.5.8. Implications for investigating neural substrates of social reinforcement**

Since Skinner (1953) proposed that social praise and reprimand could play a vital role in education, and subsequent studies investigating the effect of social feedback on education revealed an amelioration of performance due to anticipated positive social feedback in young children (Sorce et al., 1985; Kohls et al., in press), positive social feedback such as praise has been widely accepted and applied in daily school and home

education.

Investigation of the neural substrates of social reinforcement could, therefore, help improve our understanding of the vital role social reinforcement's play in daily life. Moreover, such work could add weight to the current brain imaging literature on reward processing, as the number of social reward studies is relatively small (Hare et al., 2010; Zink et al., 2008) compared with primary and monetary reward studies.

More importantly perhaps, investigation of the neural substrates of social reinforcement may have clinical implications for patients with dysfunctional emotional and social behaviour such as autism, social phobia, depression and anxiety (Britton, 2006). For example, autistic patients commonly have decreased motivation to attend to social stimuli (Hobson and Lee, 1998), such as they are having reduced attention to the faces of others (Osterling and Dawson, 1994; Hobson, 1986; Hobson et al., 1988a, b; Pierce et al., 2001). Patients with autism also have less cortical face specialization (Grelotti et al., 2002; Pelphrey et al., 2004) and reduced speech (Klin, 1991; Pelphrey et al., 2004). The reduced motivation to attend to social stimuli may be due to social stimuli having decreased reward value in autistic individuals (Dawson et al. 1998; 2005). Moreover, autistic patients have also been found to have diminished frontostriatal BOLD responses to social rewards during reward-related learning, which may be due to social learning impairments (Scott-Van Zeeland et al., 2010). On the other hand, patients with depression show a pervasive loss of motivation and pleasure, in all forms of reward, including a loss of interest in socialization, work, food, and sex (Drevets, 2001). Additionally, the depressed mood has been found to be related to specific abnormalities in the identification of facial expressions (Cooley and Nowicki, 1989; Wexler, Levenson, Warrenburg and Price, 1994), which is a basic process for social interaction (Darwin, 1872/1965). Therefore, a better understanding of the neural basis of social reinforcement, and comparisons of social reinforces with other types of reinforcement may have important implications for understanding a wide range of clinical disorders with social-emotional deficits.

## **1.6. Aims, Objectives and hypothesis of thesis**

Although the findings summarized above have been replicated across species, techniques, and experimental designs, the vast majority of studies have used only non-social rewards such as juice, food or money, and only a handful have directly compared social and non-social rewards. This raises a fundamental question: do the same brain regions implement value representation for social and non-social rewards? This thesis,

therefore, focused on the question – do the representations of values for social and non-social reinforcers involve distinct or overlapping brain regions?

### **1.6.1. Aims and hypothesis of fMRI study-1**

The first aim of the thesis was to overcome the limitations of previous studies examining different reward types, by directly comparing the neural substrates of both social and monetary reinforcers (reward and punishment) in a single fMRI task paradigm. In addition, and unlike previous studies, the social reinforcers were chosen to be of direct relevance to participants in their natural environment (described in detail in chapter 4). Furthermore, this study also aimed to extend previous studies by examining the neural effects of both reward and punishment for both monetary and social reinforcers. Given the well-defined reward network outlined above, the current study hypothesized that both reinforcer types would elicit responses in the OFC, striatum, and amygdala but that dissociation would also be evident between reinforcer types within these regions. In particular, given the amygdala's key role in recognizing emotion from faces (Adolphs, 2010), the study expected to find greater activation in this area for social reward and punishment compared to monetary. It also sought to examine the conjoint effects of reward type and valence within the OFC and test the hypothesis that the OFC is a site of integration (Montague et al., 2002; Levy and Glimcher, 2012) for different forms of reward information.

### **1.6.2. Aims and hypothesis of fMRI study-2**

The second aim of this thesis was to further investigate the differences and similarities between social and monetary reward processing. Also, in order to overcome a limitation of the fMRI study-1 (no neutral/control stimuli) to include neutral control conditions in the fMRI study-2, as it could then further explore the amygdala activation to social reinforcers by comparing an emotional face with a neutral face and by comparing a neutral monetary control condition with a neutral face.

An almost inevitable confound of the first fMRI study was that activation in the OFC, striatum and amygdala may not only be related to reward value but also to the hedonic experience of gaining social or monetary rewards. Some studies suggest that the relative value of rewards and hedonic experience are intimately linked (Kringelbach 2005, Elliott et al., 2008), with the higher reward value of an event being a critical factor for an increase in subjective pleasure. Therefore, the second fMRI study also interested in exploring the

relationship between neural activity in response to rewards and participants' hedonic scores as measured by The Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995). This study assumed that the pleasure level an individual claimed they normally derived from pleasurable daily events (as measured by SHAPS) would be correlated with their BOLD activations in response to rewards (or to a specific reward). Some previous fMRI studies have revealed that the BOLD response in the OFC is robustly correlated (positively or negatively) with a state of subjective pleasantness in response to specific reward information (e.g. Grabenhorst et al., 2010; Rolls et al. 2003; de Araujo et al. 2003; Kringelbach et al. 2003). Thus, study-2 expected to find those with high scores on SHAPS to have high medial OFC activation to rewards (both social and monetary rewards), not only as the medial OFC has been associated with reward receipt (O'Doherty et al. 2001; Small et al. 2001; Ursu and Carter, 2005), but also because the Kringelbach (2005) model of OFC function proposes that reward values of different reinforcers are coded by distinct OFC subregions which are then made available for subjective hedonic experience. It also expected the SHAPS score to be correlated with dorsal striatal activation either positively or negatively, as the fMRI study-1 found a clear association between reward receipt and increased activation in the dorsal striatum.

### **1.6.3. Aims and hypothesis of fMRI study-3**

A final objective of this thesis was to compare three different types of reward (social praise, money, and chocolate) in a single task. Similar to the previous two fMRI studies, study-3 aimed to find if the values of social, monetary and food rewards would be represented in a distinct or similar neural network. Also, this study wished to further examine the interesting findings of the regression analysis between BOLD activity and self-reported pleasure responses from the fMRI study-2. Therefore, it explored again the relationship between BOLD response to rewards (social, monetary and chocolate) and the SHAPS pleasure score (Snaith-Hamilton et al., 1995) to see if it would find consistent findings with study-2: the higher hedonic level the stronger OFC activation, while the lower hedonic level the stronger insula activation.

## Chapter 2 General Methods

### 2.1. Introduction

The next chapter details the methods used to perform the fMRI experiments reported in this thesis. Firstly, the procedures for the recruitment of participants including the exclusion criteria are described. This is followed by a section outlining the behavioural assessment tools used to assess participants mood state. In addition, the chapter discusses the procedures used to perform the experiments, and the safety and ethical considerations of fMRI scanning. Towards that end, there is a detailed section on the fMRI data analysis, using SPM (<http://www.fil.ion.ucl.ac.uk/spm>), including a section on experiment design in fMRI.

### 2.2. Participation

#### 2.2.1. Recruitment of Participants

Participants for each of the pilot behavioural (computer based reward learning task) and the fMRI studies were recruited through the online Psychology Research Participation System (<http://aston.sona-systems.com>). This system allows researchers to upload their study information, contact details, recruitment criteria, and available experiment time slots that potential participants can book.

20 participants were recruited for the first fMRI study (fMRI study-1) in 2009 via the Aston Psychology Research Participation System. Aston University students and staff who booked the study slots on the system underwent screening (see details in the section 2.2.2 below) on a first-come-first-served basis. 15 participants were recruited for the second fMRI experiment (fMRI study-2) by the same procedure in 2010. Again 15 participants were recruited for the third fMRI experiment (fMRI study-3) in 2011. Each participant was only allowed to partake in one experiment.

To be noted, the 15 participants that were recruited for the third fMRI study-3, were required to be 'chocolate lovers.' This is the only different criteria from study-1 and study-2. All the participants claimed that they love chocolate and eat chocolate or desserts made from chocolate very often (e.g. at least 2-3 times per week). There was no need to do formal screening on this, as the study-3 aimed to make sure that no one 'hate' or 'dislike' chocolate, participants should at least 'like' eating chocolate at some point. Thus, ensure that chocolate would be rewarding to participants during the task.

### **2.2.2. Inclusion and Exclusion Criteria**

Taking part in these studies was on a voluntary basis. All participants were required to be between 18 to 40 years old and able to communicate effectively (oral and reading skills) in English. Eligible participants were also screened for normal, or corrected to normal vision. Colour-blind individuals were excluded from the experiments as they would not have been able to distinguish between targets (blue and green stars) from non-targets (red, yellow, purple), in the target detection task. Moreover, in the third fMRI experiment, due to the nature of the food stimulus presented in the task, participants with any nut, milk or chocolate allergies were excluded from participation.

For the fMRI studies, any participant with a general contraindication to the procedure, such as metal implants, heart pacemaker, cochlear implant, metallic tattoos or problems with thermoregulatory control, was excluded for safety purposes. To ensure all study candidates safety, each participant answered a thorough safety screening questionnaire prior to being scanned.

In line with standard practice in human imaging studies of emotion, participants were also excluded if they had a history of mental illness, neurological illness, head injury, substance abuse within the previous two years, or other medical disorders likely to impact on their cognitive performance.

In both the pilot behavioural and the three fMRI studies, participants were assessed for their current mood state using the Beck Depression Inventory (BDI) and the Hospital Anxiety and Depression Scale (HADS) to screen for depression and anxiety. Participants with a BDI score > 13, indicative of the presence of a possible mood disturbance were excluded from the study (Beck et al., 1988). Participants who had HADs score > 8 were additionally excluded from the study (Zigmond and Snaith., 1983). Moreover, in fMRI study-2 and study-3, participants also completed the Snaith-Hamilton Pleasure Scale (SHAPS, Snaith et al., 1995) to assess their current hedonic level. Participants who had SHAPS score > 4 indicated an abnormal level of hedonic tone (Snaith et al., 1995). All three mood scales are described in greater detail below.

### **2.3. Rating scales**

### **2.3.1. Hospital Anxiety and Depression Scale (HADS)**

The first assessment of mood, the Hospital Anxiety and Depression Scale (HADS) comprises a self-assessment scale, which is reliable in detecting depression and anxiety states in hospital and outpatient clinic settings (Sagen, 2009). This scale has 14 items, 7 of which are related to anxiety (anxiety subscale) while the other 7 are related to depression (Zigmond and Snaith, 1983). Even numbered questions assess depression whereas odd-numbered questions assess anxiety. Each of the items has 4 statements that reflect the level of severity of depression or anxiety on a scale of 0 to 3. Individuals are requested to circle the statement that best describes their feelings and experiences over the past week, including 'today'. The scores of the anxiety items are added together, and the scores of the depression items are summed. The highest possible score is 21 while the lowest is 0 for both depression and anxiety subscales. Scores ranging from 0-7 are considered to indicate normal mood states meaning there is no depression or anxiety (Sagen, 2009). Those who score between 8-10 on the HADS are considered to have a borderline mood state, indicating mild depression or anxiety, while scores between 11-21 are considered abnormal (Zigmond and Snaith 1983). The participants in these studies, all scored less than 7 on this scale and were therefore considered to have a normal healthy mood.

### **2.3.2. Beck Depression Inventory (BDI)**

The Beck Depression Inventory (BDI) was the second mood scale given to study participants. The BDI consists of a self-rating inventory of 21 items to measure a heterogeneous cluster of depressive cognitions and symptoms (Beck, 1961). Each item on the BDI has 4 statements that reflect the extent of severity of symptoms, on a scale of 0 to 3. Individuals completing the BDI are requested to circle the statement that best describes their feelings and experiences over the previous week. It is possible for more than one alternative, for each variable to be chosen, but only the statement with the highest score was considered when calculating the total BDI score. The lowest possible score for this test is 0, and the highest is 63. According to Beck et al (1996), scores of 0-13 are interpreted to indicate minimal depression, scores between 14-19 indicate mild depression, scores ranging from 20-28 show moderate depression, and finally scores of 29-62 indicate severe depression. For each of the experiments carried out, none of the participants had a score exceeding 13.

### **2.3.3. Snaith-Hamilton Pleasure Scale (SHAPS)**

All the participants also completed the Snaith-Hamilton Pleasure Scale (SHAPS), which is a self-report measure with 14 questions designed to assess hedonic capacity (Snaith et al., 1995). For each question, a Likert scale of 1-4 is provided, where 1 is strongly disagree, 2 is disagree, 3 is agree and 4 is strongly agree. Both disagree and strongly disagree options are scored as 0 (Snaith et al. 1995), whereas both agree and strongly agree choices are scored as 1, making the total possible SHAPS score range from 0 to 14 (the higher score the higher hedonic level). There are two cut-off scores provided to discriminate between normal and abnormal levels of hedonic tone. The first cut-off is 2/3, that is, a rating over 2, indicates a perceptible hedonic tone. The second cut-off score is 4/5, in other words, rating over 4, indicates a clinically significant hedonic tone.

The SHAPS scores of the participants that have been included in the fMRI data analysis (N=11 for fMRI–study 1; N=12 for fMRI–study 2) are almost the same, i.e. almost all of the participants (10 out of 11 participants in fMRI-study 2; all of the participants in fMRI-study 3) have the maximum score of 14, as they have answered either ‘agree’ or ‘strongly agree’ to the 14 questions. None of these participants has answered ‘strongly disagree’ to any of these questions. This results in that all participants have the same SHAPS score, however, it does not mean that all participants have the same hedonic level. It is reasonable to assume that a participant who has answered ‘strongly agree’ to the 14 questions could have a higher hedonic level (stronger hedonic intensity) than a participant who has answered ‘agree’ to the 14 questions, although they both have the same SHAPS score of 14.

As discussed in chapter 1, one aim of this thesis is to study the correlation between the hedonic level and the BOLD activation in response to specific reward stimuli in the fMRI studies. In these fMRI studies, the SHAPS hedonic score will be used as a factor in the fMRI regression analysis. Therefore, the neural responses to rewards for each participant will be correlated with his/her hedonic score. If the SHAPS is scored according to Snaith et al (1995), there would not have been enough variation within participants’ scores to carry out the regression analyses. Thus, the SHAPS has to be re-scored to enlarge the variation in each individual’s scores, so that participants who have answered ‘strongly agree’ will not be scored as the same as the participants who have answered ‘agree’, but will be scored higher. The SHAPS scores, therefore, have been re-scored as disagree = 0, agree = 2, strongly agree = 4. The scale points are equally spaced, and it is linearly correlated with the hedonic intensity, i.e. the higher score the higher hedonic intensity (answered strongly agree).

All mood scales were completed on the day of the fMRI scan. Participants were briefed prior to completing the BDI, HADS, and SHAPS, as to the purpose and nature of the mood scales.

The next section below will introduce the physics of MRI and fMRI, the procedure for my imaging studies, safety and ethics considerations, fMRI data analysis and also experimental design.

## **2.4. Magnetic Resonance Imaging (MRI)**

MRI is based on a computerized tomographic imaging technique, which utilizes the inherent magnetic properties of human tissue to produce a digital, grayscale image of the Nuclear Magnetic Resonance (NMR) signal in a thin slice through the human body. It was first developed in the early 1950's as a spectroscopic technique, used to detect the microscopic chemical and physical composition of molecules. Damadian (1971) first discovered that nuclear magnetic relaxation times of tissues and tumours were different, which therefore resulted in the interest of using this technique to detect disease. Later on, the combination of computer tomography and NMR signal resulted in a powerful tool that provided very detailed soft tissue contrast. Therefore, MRI can distinguish different body tissues as different body tissues have different chemical compositions (Damadian, 1977). In health facilities worldwide, use of MRI has tremendously grown. There are no health threats since it does not use ionising radiation. Doctors have adopted this technology which helps them to diagnose different diseases, which include, for example, scanning for strokes, cancer, tendonitis, torn ligaments, brain tumours and multiple sclerosis. MRI has also been extensively used in neurosciences to examine the structure and function of the human brain.

### **2.4.1. Physical principles of MRI**

MRI produces sliced images of the NMR signal through the human body. Each slice of the image has a thickness (Thk), which is usually 2 or 3 mm Thk, and is composed of many voxels. The volume of each voxel is approximately  $2 \text{ mm}^3$  and contains one or more tissues. Within any one tissue, there are many cells, each of which is composed of many water molecules. Each water molecule ( $\text{H}_2\text{O}$ ) is composed of one oxygen and two hydrogen atoms (Pauling and Coryell, 1936).

An atom consists of a central nucleus surrounded by a cloud of negatively charged

electrons. The central nucleus contains a number of positively charged protons and electrically neutral neutrons. Electrons are particles which have an electric charge, and a magnetic field is produced whenever an electric charge moves. Electrons orbit around the nucleus, which is referred to as the orbital angular momentum. Meanwhile, electrons spin around their own axis, which is referred to as a spin angular momentum. An atom has a magnetic moment which is a result of the electrons spin and orbital angular momentum (together referred to as total angular momentum of electrons), as well as the protons and neutrons spin.

It is noteworthy that not all nuclei have nuclear spin, which creates a magnetic moment and can interact with MRI external magnets to produce NMR signals. Whether an atomic nucleus has an NMR signal depends on the spin quantum number of protons and neutrons within that nucleus (spin angular momentum). When the number of protons and neutrons in an atomic nucleus, are both even (e.g.  $^{12}\text{C}$  and  $^{16}\text{O}$ ) or both odd (e.g.  $^{14}\text{N}$  and  $^2\text{H}$ ), then it has 0 nuclear spin number. Thus, it is an NMR inactive nucleus. On the other hand, if the spin quantum number of protons is even whilst the number of neutrons is odd, or the number of the proton is odd whilst the number of neutrons is even, then the atomic nucleus has nuclear spin which can produce an NMR signal. Hydrogen nuclei ( $^1\text{H}$ ) and some other nuclei in human tissue such as  $^{13}\text{C}$ ,  $^{19}\text{F}$ ,  $^{23}\text{Na}$  and  $^{31}\text{P}$  are examples of the NMR active nuclei.

In most atoms, electrons act in pairs, which have opposite spins that result in their magnetic fields cancelling each other so that no net magnetic field exists. However, there are materials which have some unpaired electrons which can lead to a net magnetic field to react with an external magnetic field more strongly. This reaction depends on the structure of the atom and molecule as well as the net magnetic field of the atoms. Materials are commonly classified as diamagnetic and paramagnetic (also ferromagnetic) with regard to MRI.

Diamagnetic materials have all the electrons spin in pairs (paired spin), which results in no permanent net magnetic moment per atom. When placed in a magnetic field, they are slightly repelled by the magnetic field, which causes a weak, negative magnetic susceptibility. Most materials in the periodic table are diamagnetic such as water, copper, silver, gold, nitrogen, and barium sulphate and most body tissues. On the other hand, some materials have some unpaired electrons, which result in a net magnetic moment per atom, such as paramagnetic and ferromagnetic materials. When placed in a magnetic field, paramagnetic materials (e.g. aluminium) are slightly attracted by the field, which results in a small, positive susceptibility to magnetic fields. Similarly, ferromagnetic

materials (e.g. iron) also have some unpaired electrons, and are strongly attracted by magnetic fields and can even retain their magnetic properties after the external field has been removed. Therefore, ferromagnetic materials have large, positive magnetic susceptibility. Examples of these kind materials include oxygen and ions of various metals like iron (Fe), magnesium (Mg), and gadolinium (Gd). These ions mean atoms or molecules which have an unequal total number of protons and electrons, therefore, result in a net positive (more protons than electrons) or negative (more electrons than protons) electrical charge.

The composition of the human body is mainly water and fat. These components have numerous hydrogen atoms that make the composition of the human body to consist of 63% hydrogen nuclei. Thus, the hydrogen nucleus is used most readily in MRI. Although the other nuclei ( $^{13}\text{C}$ ,  $^{19}\text{F}$ ,  $^{23}\text{Na}$ , and  $^{31}\text{P}$ ) mentioned above are also NMR active, these nuclei have very low signal yield, therefore, are more suitable for use with the magnetic resonance spectroscopy (MRS) technique which can read low signal-to-noise ratios better than MRI.

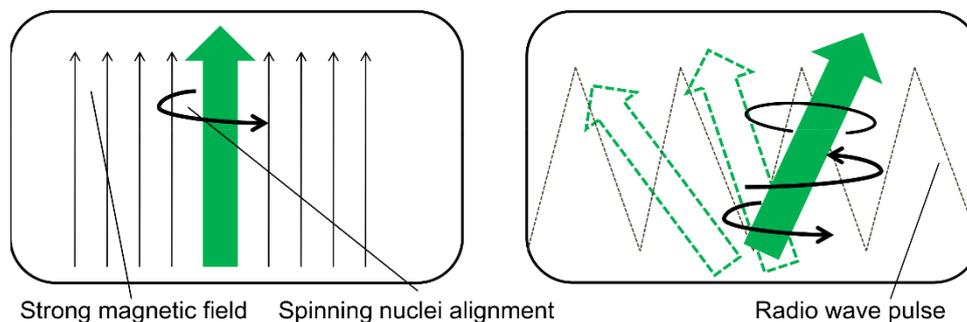
Magnets of atoms can interact with the magnets of the environment so that atoms can be influenced by external magnetic fields. A major component of the MR scanner is an extensive, superconductive electrical coil, cooled by liquid helium that produces a very strong static magnetic field. Strengths of magnetic fields are measured in gauss (G) and Tesla (T). One Tesla equates to 10000 gauss. As a point of reference, the earth's magnetic field is about 0.5 gauss. MR scanners currently used in humans for fMRI studies have static fields ranging from 1.5 to 15 Tesla.

When nuclei with an uneven number of protons or neutrons, i.e. have a non-zero nuclear spin number, such as hydrogen nuclei are exposed to a strong static homogeneous magnetic field, the nuclei align their spinning axes along with the direction of the applied magnetic field. However, some of the protons align with the field whilst some others actually align against the field, which results in cancelling out of the effects of the opposing spins, but there will always be a slight majority of protons that align with the field, thus, a net result of an alignment with the external field is received.

The MRI scanner can send a brief pulse of radio waves in order to tip the aligned spinning nuclei away from their parallel orientation with the magnetic field (Figure 2.1), and provide energy for the nuclei to do a “wobbling” motion, called precession. The rate of precession is known as the resonance (or Larmor frequency). After the brief pulse of radio waves is stopped, the wobbling nuclei return their spinning axes to the original orientation that

parallel with the magnetic field, i.e. realign with the magnetic field. The radio frequency (RF) energy is absorbed by the nuclei when it receives the RF pulse, and the emission process of RF occurs with the changing of spins from the wobbling precession (a high-energy state) to the realignment of the nuclei with the external magnetic field (a low-energy state). This emission process is called nuclear magnetic resonance, which forms the basis for contrasting the tissue properties in MRI. Together with the adding of time-varying gradients following the RF pulses, full MR images of proton signals can be produced and encoded in a three-dimensional way (Hennig, 1999).

Figure 2.1.



**Figure 2.1: Spinning atomic nuclei aligned with the applied external magnetic field.**

When a brief pulse of radio waves is sent by the MRI scanner, the spinning nuclei were tipped away from the original parallel orientation with the magnetic field and perform a wobbling motion called precession.

If an MR signal is encoded by a tissue contrast arising from a time course whereby the system returns to thermal equilibrium or the proton alignment recovers along the direction of the initial applied magnetic field, then the image is referred to as T1-weighted (Hashemi et al., 2004). The second relaxation time, T2, occurs after a RF pulse is turned off, which tips the magnetization into the transverse plane perpendicular to the direction of the initial magnetic field, during which coherence of proton spins is lost, so that some protons start to spin a little bit faster to get out of this phase than others do, due to the random interactions between the spins. Therefore, T2 time measures the rate of the exponential decay of the RF signal emitted.

Both T1 and T2 range from 10-1000ms for MRI and are inherent physical relaxation parameters that are unique to human tissue and have little association to the strength of the magnetic field. This is because different tissues have different magnetic susceptibilities depending on the microstructure of tissue, i.e. chemical surroundings. T1 time enables MRI to distinguish between different types of tissue and is mainly used in

structural imaging. T1 relaxation time is the time taken after the excitation RF pulse to allow for 63% of the magnetization to return its alignment. Higher magnetic fields cause longer persistence of T1 times. T2 relaxation time is the time taken after the event of excitation (after the turning off of RF pulse), during which the signal amplitude has been reduced to 36.8% of its original value (Hashemi et al., 2004).

However, T2 relaxation time lacks the assumption of inhomogeneity of external magnetic field as well as a local field within a voxel. For example, each hydrogen atom has a slightly different magnetic field strength. There are many factors that affect the homogeneity of the magnetic field. Therefore, the NMR signal could decay faster than T2 would predict. Also, different tissues have different magnetic susceptibilities which can distort the field of tissue borders, such as the field of air and tissue interfaces. Greater inhomogeneity results in decreased image intensity. Therefore, a third relaxation time defined as T2\* combines the function of T2, i.e. the decay of the signal in relation to random proton-proton interactions, and also of these external factors (Chavhan et al., 2009). A T2\* contrast could vary across tissue types as well as across physiological states. T2\* contrasts form the basis of the fMRI technique that is most commonly used in imaging studies of the human brain.

## **2.5. Functional Magnetic Resonance Imaging (fMRI)**

fMRI is a non-invasive technique used to assess the association between functional brain activity and changes in MRI signals. The changes in MRI signal are reflected by the different magnetic properties of haemoglobin in blood flow, in terms of its oxygenated and deoxygenated state. This is called "Blood Oxygenation Level Dependent (BOLD) signal change in neural regions of the brain are activated. Ogawa et al (1990) were the first to reveal that changes in T2\* weighted MRI images were associated directly with the presence of deoxygenated haemoglobin in the blood. BOLD-based fMRI has progressed fast and substantially since then, in many areas of neuroscience research (Jezzard and Buxton, 2006) because people do not need any surgery, ingest or inject any substances, or be exposed to radiation like some past neuroimaging techniques such as positron emission tomography (PET).

### **2.5.1. Principles of BOLD signal**

The time series of the BOLD signal to a brief task stimulus reflects changes in blood flow and the oxygenation state of haemoglobin. When neural regions of the brain become

active, the capillaries dilate automatically to increase the local blood flow to these regions in order to bring more oxygen to neural cells (Huettel et al., 2009; p. 6-7). The oxygen is carried by haemoglobin, which is a protein molecule within red blood cells. Once the haemoglobin releases the oxygen to cells in an active region, it is called deoxyhaemoglobin.

The haemoglobin molecule contains iron atoms, and have a strong magnetic susceptibility, thus, it is an ideal intravascular contrast agent to produce fMRI contrasts. The difference between oxygenated and deoxygenated haemoglobin in terms of their magnetic properties is used as a local indicator of brain functional activation.

The deoxygenated haemoglobin has a magnetic property (paramagnetism or a paramagnetic molecule) and is more magnetic than oxygenated haemoglobin (diamagnetism). Deoxyhaemoglobin causes a slight disturbance in the magnetic field of its surroundings, which results in a large magnetic susceptibility effect. These disturbances are used in fMRI to detect the concentration of deoxyhemoglobin in the blood flow. The paramagnetism of deoxyhaemoglobin results in a shortening of the T2\* and thus leads to a decrease in the MRI signal. The increase in blood flow due to neural activation leads to a decrease in deoxyhemoglobin, which in turn results in an overall increase in T2\* signal (Huettel et al., 2009, p. 194). The diamagnetic oxyhaemoglobin, on the other hand, interferes with the magnetic MR signal less and so does not significantly disturb the regional magnetic field, nor affect T2\*.

In reality, the increase in blood flow to the more active regions of the brain is always greater than the oxygen demand of these regions, and as a result, there is a net increase in oxyhaemoglobin and a decrease in the concentration of deoxyhemoglobin (it becomes diluted in a large volume of blood). This decrease in the concentration of deoxyhemoglobin is measured using fMRI and inferred as increased brain activity (Attwell and Iadecola 2002; Attwell and Laughlin, 2001; Bonvento et al. 2002; Harrison et al. 2002).

### **2.5.2. Physiology of BOLD response**

fMRI indirectly measures neural activity; it shows an association between neural activity and the hemodynamic BOLD responses in active brain regions. This technique reflects the hemodynamic response which relates to an increase in the local blood flow in order to meet the metabolic demand for glucose and oxygen of an active brain region. The theory to explain this process posits that biological signaling exists between neurons and local vasculature, so that increased blood flow follows directly from increased synaptic

activity (Attwell and Iadecola 2002; Bonvento et al. 2002; Harrison et al. 2002).

Astrocytes in the brain (glial cells, not neurons) surround both synapses and capillaries and are responsible for a neurotransmitter (e.g. glutamate) recycling among synaptic cells, in order to transmit a neural signal. These glial cells take excitatory neurotransmitters released from the pre-synaptic cell quickly and are then detected at the post-synaptic cell, to stop its action on the post-synaptic membrane. This results in a chemical change in the neurotransmitter molecules which deactivates them, and delivers them back to nearby neurons for reuse (Zonta et al., 2003). The actions of glial cells, at both the pre and postsynaptic sites, take a lot of energy (MacIntosh, 2007).

To elaborate further, BOLD response in an active brain region may reflect its input and local processing which place demands on energy metabolism, rather than its output. Evidences have been provided by simultaneous fMRI and electrophysiological studies (Logothetis et al., 2001; Logothetis and Wandell, 2004) which have revealed that BOLD signal is more correlated with pre-synaptic rather than the output spiking activity signals of a neuron population (i.e. the actual neuron firing output or the action potentials) which transmit the information to downstream processing areas. In addition, the density of vasculature is correlated with the number of synapses, not the number of neurons in the active brain region (Logothetis et al., 2004). Therefore, BOLD response may reflect different aspects (i.e. increased synaptic activity) of neuronal activity from the single neuron recording of action potentials. However, there has been another study using simultaneous fMRI and electrophysiological recording which reported a tight relationship between a negative BOLD response and neuronal activity decreases in the stimulated region of monkey visual area V1 (Shmuel et al., 2006).

Although it is still not clearly understood how the BOLD response reflects neuronal electrical activity, there is no doubt that there are relationships between the BOLD response and the neural activity in active brain regions. Therefore, the non-invasive fMRI is an ideal technique to study the neural substrates of sensory-cognitive processes in humans. The following section will discuss the advantages and disadvantages of fMRI.

### **2.5.3. Advantage and Disadvantages of fMRI**

The non-invasive nature and high spatial resolution of fMRI make it an ideal technique to study sensory and cognitive processes in humans. Firstly, among the few non-invasive electrophysiological (e.g. EEG and MEG) and hemodynamic brain mapping techniques (e.g. PET and fMRI), fMRI does not use radiation unlike PET and have obviously better

spatial resolution than MEG. If fMRI is applied correctly, it has almost no risks. Also, fMRI can produce whole-brain images with very high resolution up to 1 mm compare with MEG and EEG, which can only localize neural sources to 8-10 mm (Ganis and Kosslyn, 2002) and cannot localize the activity on the cortical surface very well (on the order of 10 mm) and in the neural structures located deep beneath the surface.

Limitations include that the inherent spatial and temporal resolution of fMRI depends on the brain ROI so that regions with a higher vascular density such as the primary motor and auditory cortex produce better hemodynamic signals on the smallest functional unit. Therefore, differences in vascular density cause the variation in spatial sensitivity during a whole-brain imaging. Moreover, fMRI provide a relatively poor temporal resolution (a few seconds) compared with MEG and EEG (measured in milliseconds). After stimulus onset, the onset of detectable BOLD signal changes relative to the putative onset of neural activity is about 2 sec, and the BOLD signal peaks at 6 – 9 sec, then returns to baseline after the neural activation stops (Ganis and Kosslyn, 2002). Differences in the onset latency of the BOLD response exist between different brain regions, such as variations in the onset latency of BOLD response are usually between 4 – 8 sec in visual and motor cortex (Ganis and Kosslyn, 2002). Therefore, it is unable to detect the temporal order of activation of two regions (less than 1 sec for most cognitive tasks) depends on the absolute BOLD onset latencies, as there are large variations in BOLD response latencies (several seconds) over space (Ganis and Kosslyn, 2002). However, it is able to observe the relative timing of BOLD activation stages within an ROI in response to different experimental manipulations, and obtain subsecond temporal resolution. Previous fMRI studies had reported that BOLD response images could be obtained with presented stimuli as rapid as 2 per second when the stimuli interval was randomized (Ganis and Kosslyn, 2002). Thus, fMRI is able to use rapid presentation paradigms as MEG and EEG, which is good as it allows direct comparisons between the results obtained from fMRI and MEG and EEG.

Furthermore, it is not very suitable for auditory studies because of the considerable noise generated during imaging which may make it difficult for subjects to hear the stimuli (headphones overcome this problem to some extent). Also, fMRI is not very suitable for motor studies, because head movement (as small as 2mm) can generate large artefacts and ruin an entire fMRI scan (Seto et al., 2001), as well as reduce the signal-to-noise ratio in activated regions. Moreover, there will be susceptibility artefacts and signal drop-out in medial temporal lobe and orbitofrontal cortex regions as these areas yield a smaller signal to noise ratio compared to other cortical regions. The application of a multi-shot echo-planar imaging (EPI) sequence with interleaved slices could help to overcome such

susceptibility artefacts. In addition, the commonly used fast imaging EPI method does not work well for the tissue-air adjacent areas.

In the fMRI experiments in this thesis, each volume contained 40 axial slices, angled at 25-30 degrees away from the eyes (nasal area, which can result in distortion artefacts in the ventral PFC), which could also help to overcome susceptibility artefacts. Previous studies have provided evidence that activations in these regions could be well observed without a doubt (Beauregard et al., 1998; Lidaka et al., 2001), helping to resolve any concerns of fMRI's usefulness as an imaging tool to investigate any cognitive functions with regard to these regions.

## **2.6. fMRI data acquisition and analysis**

fMRI was performed on a 3 Tesla (3T) Siemens Trio scanner at Aston University, using a T2\* weighted gradient echo planar imaging sequence with the following parameters; Time of Echo (TE) = 30 ms, Time of Repetition (TR) = 2.8 sec, matrix size = 64x64, 3mm slice thickness and 3x3mm in-plane resolution. Each volume contained 40 axial slices, angled at 25-30 degrees away from the eyes (due to the nasal area, which can result in distortion artefacts in the ventral PFC). The task presentation was projected on a screen behind the participant's head and was viewed through a mirror mounted on the head coil. The participant's responses to the target detection paradigm were collected using an MRI compatible Lumina button response pad.

In all fMRI scans, sets of images were collected sequentially in time while participants performed the tasks. Thus, the fMRI data had four dimensions: x, y, z, and time, which showed both spatial and temporal features in the data which were correlated with the experimental design.

Image analysis was performed in SPM (SPM2 for fMRI experiment 1 and SPM8 for fMRI experiment 2 and 3 (<http://www.fil.ion.ucl.ac.uk/spm>)). All images were first pre-processed before analyzing.

### **2.6.1. Pre-Processing**

#### **2.6.1.1. Slice Timing**

Whether to perform slice-timing before or after realignment is dependent on the following elements. If there is significant head movement, there will be large signal differences

across nearby voxels (especially the edge regions of the brain), to perform slice-timing first can interpolate signals from different brain regions. Slice time correction after realignment may shift voxels to adjacent slices (and hence different time points), which is especially problematic for interleaved slice acquisition, where the time difference between adjacent slices may be  $\frac{1}{2}$  TR. Thus, slice time correction should be applied first for interleaved sequences, which is what the fMRI study 1-3 did. This is less relevant for sequential (ascending/descending) slice acquisition, where the time difference between adjacent slices is very small, so that realignment first may be better, to allow for movement effects. Finally, slice timing correction is necessary for an event-related design, but not a block design study. This is because, SPM applies the same model for all voxels, so although the acquisition of the slices is several seconds apart, the same signal that is predicted for voxels in the first slice is also predicted for voxels in the last slice (Henson et al., 1999). A block design, on the other hand, is where several scans are averaged together during analysis. As slice-timing involves interpolating the signal to a time rather than when it was acquired, any gain in accuracy from interpolating the data from slices within one scan may be lost in the process of averaging across scans.

A slice-timing correction was applied in the first place because my fMRI images were acquired in slices from the bottom up in an interleaved fashion. The interleaved sequence means to acquire slice numbers 2, 4, 6... then 1, 3, 5..., as it had an even number of slices. If there were an odd number of slices, then it acquires 1, 3, 5... then 2, 4, 6... The interleaved order can minimize "cross-talk" effects between slices. For example, slice 2 is partially excited when acquiring slice 1 so with the interleaved order; this does not measure slice 2 immediately after. Thus, slice timing corrections shift each voxel's time course so that just like all the slices were acquired at the same time (at  $\frac{1}{2}$  TR).

#### **2.6.1.2. Realignment**

The realignment procedure is performed as a pre-processing step, to move each image volume in each scan session to line up spatially with each other and with the preceding session. This procedure can minimize the effects of a participant's head movements during the scan as the movements can be a major source of artefact. Firstly, it realigns each volume within the scan to the first scan selected (reference scan) in each session. The parameters of an affine 'rigid-body' transformation are estimated to minimise the sum of square differences between each successive scan and the reference scan (Friston et al., 1996). A rigid body transformation can be defined in 3 dimensions by 6 parameters, which include 3 translations  $x$ ,  $y$ ,  $z$  in mm and 3 rotations  $x$ ,  $y$ ,  $z$  (degrees).

The spatial normalization step is followed by the realignment, it moves or 'warps' the brains of each participant (functional or structural T1) to fit with the shape of a standard template brain, in order to compare the signal across different brains. This is referred to as inter-subject averaging. Also, this step allows for comparison across studies. The template used in SPM is a single subject T1 image template which is a standard Montreal Neurological Institute (MNI) echo-planar imaging template. Normalisation is a data transformation that reduces differences in brain position, size, and shape via translation, rotation, skewing, scaling or zooming (affine movement). The previous step of realignment produces a mean image of the time series, which is used here to estimate the warping parameters that map the brain image onto a template. Mathematical algorithms are then used to minimize the sum of squares differences between the brain image and the template (Ashburner and Friston, 1999).

### **2.6.1.3. Smoothing**

Finally, it is necessary to spatially smooth fMRI data prior to analysis. The fMRI data were smoothed by convolving the images with a Gaussian kernel filter of 8mm, which is often described by the full width of the kernel at half its maximum height (FWHM). Common values for the kernel widths vary between 4–12 mm FWHM, the kernel width is suggested to be 3 times the voxel size, so that an FWHM 9mm is suitable for 3mm voxels. In the experiments, as it tested for within-subject effects and looked for relatively smaller cortical activations in areas like OFC, striatum, and amygdala, it applied a filter of 8mm. The wider the kernel, the greater the smoothing effect and the larger impact on nearby voxels have on each other. Smoothing increases sensitivity by averaging out uncorrelated noise across voxels but reduces spatial resolution by blurring the activity images across the smoothed areas. Furthermore, if the spatial extent of an ROI is larger than the spatial resolution, smoothing can reduce random noise in individual voxels and increase the signal-to-noise ratio within the region. A benefit of blurring is that it improves the cross subject averaging, make it less affected by inter-subject anatomical differences.

### **2.6.2. Statistical Analysis**

The analysis of the fMRI data can be either hypothesis led/testing or data driven. Most fMRI studies (including those in my thesis) adopt hypothesis testing, which assumes BOLD responses will occur at pre-determined time periods, which are based on the experimental paradigm (Bandettini et al. 1993). Data-driven methods, on the other hand,

attempt to extract features in the fMRI data without any a priori assumptions. Examples include Principal Component Analysis (PCA) and Independent Component Analysis (ICA). Data-driven methods are useful when features in the fMRI data are not predictable, such as in the presence of transient effects (Nangini et al. 2005).

After the pre-processing procedures, the fMRI data were analyzed statistically in SPM, which models the pre-processed data on a voxel-by-voxel basis application of a subset of a multivariate regression analysis. This is defined as the general linear model (GLM) and is used to specify a matrix for systematic analysis. The GLM assumes that the data are composed of the linear combination of difference model factors. The design matrix of the GLM can be thought as how the model factors change with time.

The composition of the design matrix is a series of columns, each of which has a unique time course that corresponds to some experimental effect. Generally, each of the columns represents a different type of stimulus. For example, in the fMRI study-1 presented in chapter 4, all experimental feedback categories were modelled as event types which were: social reward (SR), social punishment (SP), monetary reward (MR), monetary punishment (MP). The first column of the matrix contains the time course associated with SR while the second column has a different time course associated with SP. The third column and the fourth column represent MP and MR respectively. When this model of statistical analysis is fit to the fMRI data, an approach of generalized least squares is applied in estimating the parameter estimates or 'goodness of fit' for every voxel. These estimates are for each column in the model in relation to the corresponding voxel time course, and the parameter estimates retrieved from each voxel are used to make statistical inferences regarding the hypotheses generated for single subjects or groups.

Even more particularly, statistical analysis of fMRI data by use of SPM tests the null hypothesis, which states that there is no relationship between the effect induced by the experiment and the data contained in the voxel. In this case, SPM can undertake two types of statistical test, either an 'F' or a 'T' test, from the outcomes of the analysis of variance performed on each voxel. On the contrary, the null hypothesis holds that all experimental effects are zero and can be evaluated through the F statistic to generate SPM {F} or, alternatively, that some particular linear combinations in the experiment or a 'contrast' observed in the estimates of the parameter are zero in the case of SPM {T}.

The principal difference between a T-test and an F-test is that a T-test is unidirectional while an F test is bidirectional. This means that T-tests focus on either positive or negative differences between the estimates of tested parameters, whereas F tests focus simply on

the differences between the estimates of the parameters. With that in mind, it is worth noting that after calculation of the estimates of T and F, SPM converts these statistics to scores of Z (the time series for voxels in the fMRI). Considering that the authors of SPM hold the argument that only T-tests can be used in models of random effects, Z-scores can be utilized in the same way as SPM is used to display and analyze the values of P from the statistics of T or F experiments.

To ensure that there is control over the possibility of false positives in the experiments, the significance of the statistics is corrected according to the random field theory (Worsley, 2003). This prevents recording of larger than expected Z scores. Spatial correlation is evident in functional imaging data. This is because data coming from one voxel contains signals from the tissue surrounding the voxel. The effect that causes this spatial correlation is the spatial re-slicing and smoothing done during pre-processing of the fMRI data. The Z scores recorded at each voxel are, for that reason, not independent of each other. This makes it impossible to use the standard method of applying a Bonferroni correction because the correction is bound to be too conservative (Brett et al., 1996). For this reason, random field theory is the appropriate method for application of data analysis in this thesis.

This thesis had a priori hypothesis of expected regions of activation for each experiment. In this situation, it is reasonable to use the uncorrected statistics to reject the null hypothesis. However, as the a priori hypothesis is regional, and not voxel-specific, some form of correction is necessary. This can be done by specifying an appropriate minimum cluster size which is the number of voxels in a cluster that are needed for the cluster to be considered “real” (Forman et al., 1995). In the experiments described later, the extent threshold for cluster size was set at 7 voxels.

### **2.6.3. Haemodynamic Response Function**

During the performance of the statistical analysis described above, it is important to make an assumption about the shape of the hemodynamic response, in addition to approximating the temporal profile of the response. In the process of analyzing the shape of the approximated hemodynamic response function, there are several measures that are taken as potential measures of the magnitude, duration, and latency of the neuronal activity involved in delivering the hemodynamic reaction. These measures include an estimated response amplitude/height (H), full-width at half-max (W), and time-to-peak aspects of the hemodynamic response function.

In order to estimate the BOLD signal in an experimental paradigm, SPM utilizes a canonical hemodynamic response function (HRF). In this case, this function is assumed to originate from the system as indicated by the magnetic resonance signal when an individual is subjected to a brief period of intense neuronal stimulation. The benefit of using a canonical response function is that t-tests on the data can be interpreted in terms of response magnitude, latency or duration (Henson et al., 1999), while a possible limitation is that response that differs a lot from the canonical form may not be detected (Henson et al., 2001).

Ideally, the parameters of the hemodynamic response function should be interpreted directly in terms of the alterations that occur in neuronal activity. These measures should also be estimated in such a way that the statistical power of the collected data gets maximized for optimal statistical relevance. This will allow for broad generalization of the research findings to the population from where the subjects were recruited. Additionally, accurate estimation of the hemodynamic response function is useful in preventing both false negative and positive results from coming up. These false results that arise from ill-fitting and constrained statistical models because even small extents of wrong modelling have high chances of causing severe loss in the validity and power of the data (Lindquist and Wager, 2007; Loh, Lindquist and Wager 2008).

#### **2.6.4. Random and Fixed Effects Analyses**

There are two types of inferences that can be retrieved from an fMRI time series. A fixed event analysis applies a within-subject variation of data and gives a statistical inference that can be generalized only to the subject group under investigation. Analytical methods of fixed effects can generate results that are highly significant due to the extensive degrees of freedom that are available. However, the inferences that can be drawn from such analysis are considerably limited (Friston et al., 1999; Beckmann et al., 2003).

Considering that the analysis does not model the variation existing between subjects, a few subjects who may not demonstrate the desired representation of the study sample may fundamentally drive the effect size. This means that if only a small number of subjects activate a single area, many fixed effects analyses may detect this significant finding of limited generalization. Fixed effects analysis, therefore, cannot be applied in making inferences concerning the study population as a whole (Friston et al., 1999; Beckmann et al., 2003).

Random effects analysis comprises of both within the subject and between the subjects variance (Worsley et al., 2002). This allows for generalization of the experimental findings to the entire population from which the study participants came. It follows that more participants are needed in order to achieve a notable result with random effects analyses. This necessity is brought about by the fact that the degrees of freedom are dependent on the number of participants who undergo fMRI. Typically, an experimental sample that exceeds 10 participants is used for fMRI studies if random effects analysis is the method of analysis (Holmes and Friston, 1999). Random effects analysis methodology was applied in analyzing data from all 3 fMRI experiments in this thesis.

#### **2.6.5. Small Volume Correction analysis**

Small volume correction (SVC) is an ROI analysis that is implemented in SPM. It is simply a correction that can be applied when the study has an apriori hypothesis about some localized brain regions being activated, but no particular interest in other brain regions, i.e. the apriori hypothesis does not apply to the entire brain. The standard Family-Wise Error (FEW) or False Discovery Rate correction (FDR) procedures would by default be applied to the whole brain, which means it would be looking for effects (i.e. significant voxels) all around the brain. This resulted in that Type I error correction would be much more stringent than it was needed if testing was applied only the small volume of particular interest, meaning that the Type II error rate would go up (risk of not detecting an effect actually present), thus reducing the sensitivity of the analysis.

In the case that the fMRI studies in this thesis have some apriori hypothesis about some brain regions (e.g. OFC, amygdala, striatum), SVC would be applied to these pre-defined volumes (see details in Chapter 4 – 6), thus allow a more sensitive test for the brain region of particular interest.

#### **2.7. General Procedure for the fMRI studies**

Firstly, participants came into the MRI unit and undertook the preliminary steps of the study which included signing consent forms and filling out the safety screening forms (Appendix 1) for the scanning environment to ascertain they had no metal implants, metallic tattoos, etc. and removed any clothing or personal belongings (jewellery) with metal before they entered the MRI control room. After these steps, participants were taken to the MRI control room and were weighed for an accurate body weight. Subsequently, participants read an information sheet on what they were required to do in the scanner

and were then shown a brief demonstration of the target detection task on the experimenter's laptop, including the different reinforcers they could receive and how they were required to respond. Study participants were then given time to ask any questions that they had concerning the MRI environment or the task involved.

Participants were then taken to the scanner room and asked to lie on the scanning table ready to undergo the fMRI scan. For protection from the noise of the scanner, subjects received foam earplugs, which they were asked to insert into their ear canal. An alarm button, which was in the form of a squeeze bulb, was taped to the participants' stomach, and they were told they could press this to stop the scanning session at any point if they were not happy, or uncomfortable. A two-button hand-held response box was placed in the participants' right hand (unless they were left-handed), and they were told to press one specific button with their index finger, to give a response during the task.

The fMRI scanning session, for each of the three studies, comprised of a functional scan and an anatomical scan. All the fMRI studies applied the same simple target detection task paradigm (event-related design), which was presented during the functional scanning session. Very shortly before the functional scan began, participants were informed that the task was about to begin, and they were also briefed on the targets they were to respond to. During the functional scan, participants viewed the task via a three-way mirror placed over their head, which reflected a projection screen (which had the task displayed).

Although all the fMRI experiments utilised the same target detection paradigm, the stimuli (target cue) and reinforcers varied between the experiments. The task details provided for each of the 3 experiments are presented in chapters 4, 5 and 6 respectively.

## **2.8. Safety Aspects and Ethical Considerations**

Although MRI is a relatively safe technique and has no known health effects, there are a number of safety concerns related with the scanning of human volunteers that had to be considered when carrying out the studies described within this thesis. First and most importantly, the presence of metal anywhere in the human body can be hazardous because of the strong magnetic field, which can result in heating up effects, of the metal. Therefore, all participants were screened carefully to be metal free through the use of two screening checklists. The initial screen listed possible metal objects that could be contained in a human body. Also, the screening excluded anyone who was pregnant or thought they could be pregnant. The second screening then was used to remove any

metal objects on a person, such as keys, coins, jewellery, underwire bra, etc. and to confirm participants' well-being, i.e. no colds, etc.

In addition, the noise of the MRI machine when scanning is very loud and can result in discomfort or even harm to participants' hearing. Therefore, individuals were provided with earplugs or headphones to protect them from the noisy scanning environment. Furthermore, it is possible that the inner core of the MRI magnet where participants lie down could make some of them feel very trapped or claustrophobic and anxious. Potential study participants who suffered from claustrophobia were excluded from the study. Also, an alarm button was provided to participants to minimize any sense of panic they may have had, and they were advised they could press the alarm at any point to stop the scan if they were not happy.

Ethical approval of the protocol for each study presented in this thesis was approved by the Aston University Ethics Committee.

## **2.9. Experiment Design**

There are two main methods used to present stimuli in fMRI studies, which include an event-related design and a block design. During task presentation in a block-design, trials are alternated into two (or more) different blocks/conditions in order to compare the differences between them or can have a control condition between two experimental conditions.

On the other hand, during an event-design task presentation, trials are not presented in a set sequence but presented randomly. The randomized trials do not need to model the hemodynamic response function (HFR) to return to baseline after every trial, as the HFR is deconvolved afterwards. More importantly, the inter-trial intervals can also be randomized, which can eliminate confounds such as habituation, anticipation and the subjects cognitive set (Rosen et al., 1998). During each trial of presentation in an event-related study, there are usually a number of different events such as the presentation of fixation, a task stimulus (e.g. a word or picture), delay period, and response (e.g. motor response).

One advantage of employing an event-related design in fMRI is that it can allow observations of neural activity associated with each trial and each event within the trial, rather than blocks of trials. In other words, the ability to randomize and mix different types

of events can allow isolation of each event, as well as the cognitive state of an individual, so that one cannot predict what event will appear next. Furthermore, events or trials can be categorized after the experiment according to a participant's performance. Thus, although event-related designs give lower statistical power compared to block designs because of a smaller ratio of task period to baseline period (i.e. the MR signal is small), for certain fMRI experiments involving cognitive tasks (Buckner et al., 1996), event-related designs could reflect the underlying neuronal activation more accurately than blocked designs.

All the fMRI experiments presented in this thesis employed a randomized event-related design, with the application of randomized stimuli presentation, as well as having randomized fixation periods. Randomized event-related fMRI designs allow for the rapid presentation of stimuli (Burock et al., 1998), and detect transient haemodynamic responses to the stimuli (Josephs and Henson, 1999). For example, event stimuli presented as rapid as 34ms, are able to produce detectable BOLD responses (Rosen et al., 1998). The experiments presented the visual target stimulus as well as the feedback stimulus for 2 sec, which has been demonstrated to robustly produce a detectable BOLD response (Blamire et al., 1992).

## **2.10. Target detection task**

The target detection task was designed to narrow down cognitive functions that may underlie the signaling for perceived reinforcement and to exclude complex decision making and reversal-learning components, which are the most common task components used in reward processing studies. Simple task paradigms that can isolate component reward processes and focus on one specific cognitive function have been recommended by previous studies (O'Doherty, 2007; Elliott et al., 2008; 2002). There have been dearth reward processing studies which have focused on one specific cognitive function (Elliott et al., 2008), as the most widely applied task paradigms are the learning tasks and decision-making tasks which always include more than one cognitive function, such as guessing, anticipation, receipt, error prediction, and decision-making. One example of the simple task paradigm that focused on one specific function is the Elliott et al (2008) fMRI study of relative reward value. They adopted a simple task paradigm to exclude any value-dependent behavioural choice or decision-making component. Similar to the target detection task that was used in this thesis, Elliott et al (2008) used 3 abstract black-and-white patterns, each was associated with an amount of money (10p, 50p and £1). Participants were pre-trained to learn the associations between patterns and money.

During the fMRI task sessions, two patterns were paired and presented on the screen, then one of them would disappear, leaving a single pattern on either the left or right of the screen. Participants were asked to give the left or right button responses as appropriate in order to obtain the amount of money associated with the single remaining pattern. It is obvious that participants in their experiment only need to give button responses to the 'target' they see, i.e. the single remaining stimulus, no choice has to be made to get the reward.

The target detection task paradigm that has employed in this thesis also designed to exclude behavioural choices. Participants will only need to give button responses to pre-defined 'targets' (blue or green stars), which are associated with specific rewards. There will be one target presented on the screen on each trial, and participants only need to press one button to give a response. The task presentation sequence was an event-related design and remained the same for all the fMRI studies. Generally, in each trial, participants first saw a fixation cross "+" in the middle of the screen, followed by a star which could be 1 of 5 possible colours, red, orange, purple, blue or green. Blue and green colour stars were targets while others were non-targets. Participants had to respond to the targets, by pressing a button on a response button box as fast as possible to get an associated reward, and ignore non-targets. However, if they did not respond fast enough to targets, they would receive punishment or a neutral control feedback. The task descriptions and instructions provided for each version of the experiment are presented in chapters 4 to 6.

## Chapter 3 Behavioural studies

### 3.1. Introduction of behavioural experiments

How did previous reward processing fMRI studies (especially those compared neural processing of multi-types of reinforcers) choose their 'rewards' or 'task stimuli' in the tasks? For example, in a study aimed to compare reward processing of a monetary reward with a primary reward (e.g. juice) during a learning task, how to choose the rewarding stimulus among different amounts of monetary reward and different amounts of juice intake during the task? Can we just randomly pick up a rewarding stimulus from 20p, 50p or £1 to compare with winning a specific amount of juice intake (e.g. 20ml, 50ml, 100ml) during the task? There had been no previous multi-types (or multi-magnitude) reward processing fMRI studies that provided their rationale for choosing rewarding stimuli. However, it was reasonable to assume that winning a larger amount of money (e.g. £1) in each trial would be more rewarding than winning a smaller amount of juice intake (e.g. 20ml) during a reward based learning task. Therefore, one would be less confident with any differences found in the neural responses to winning £1 and winning 20ml juice intake during the task, as any differences were possibly due to variances in the behavioural effects or due to the absolute value of the rewarding stimuli.

A test of equivalence between different types of reinforcers behaviourally could increase the reliability of the task paradigm and improve confidence in the neural findings in the later fMRI experiments. Classical or standard statistical tests (e.g. t-test or ANOVA) were usually used to find group differences, but the results of "no significant difference" also had been used the most widely to conclude that groups were comparable or similar (Rusticus and Lovato, 2011). However, the finding of no significant difference was not enough to prove that two groups were equivalent. In other words, no significant difference was found was not the same as saying that the two outcomes were similar or equivalent, might be because a sample size was too small to find a difference. Therefore, classical statistical tests were not suitable to be used to test for equivalence or similarity. Alternatively, a confidence interval approach would be more recommended for the test for equivalence (Rusticus and Lovato, 2011, Blackwelder, 2004, Rogers, Howard and Vessey, 1993). This approach had been suggested as easy to use and interpret (Rusticus and Lovato, 2011) and involves calculating the confidence interval around the mean difference between two groups, and defining a region of equivalence (equivalence interval), if this confidence interval is within the region of equivalence, then one could say that two measures are equivalent (Rusticus and Lovato, 2011). It is important to note that there are no set standards for defining the equivalence interval which depends on upon the scientific or clinical context of the experiment and requires a strong rationale (Lewis, Watson, and White, 2009).

The aim of current behavioural experiments in this thesis was to find a monetary reward that would have an equivalent behavioural effect (have similar effects on learning performance) to the selected social reward in two reversal learning tasks. Stated briefly, the current studies aimed to assess the equivalence between the reward value of winning differing amounts of money and being presented with a smile (using the experimenters face and accompanying voice saying 'well done'). This chapter will use the confidence interval approach to testing the equivalence between the two types of rewards. Before this, classical ANOVA test will also be demonstrated to provide a comparison to the equivalence test results, as the analysis of variance methods has been the most widely used approach in the past. By making the assumption that the selected social and monetary rewards have equivalent value, any neural differences found between processing of social and monetary rewards in the later fMRI experiments can be interpreted as not being due to the absolute value of the rewarding stimuli.

## **3.2. Methods of behavioural experiments**

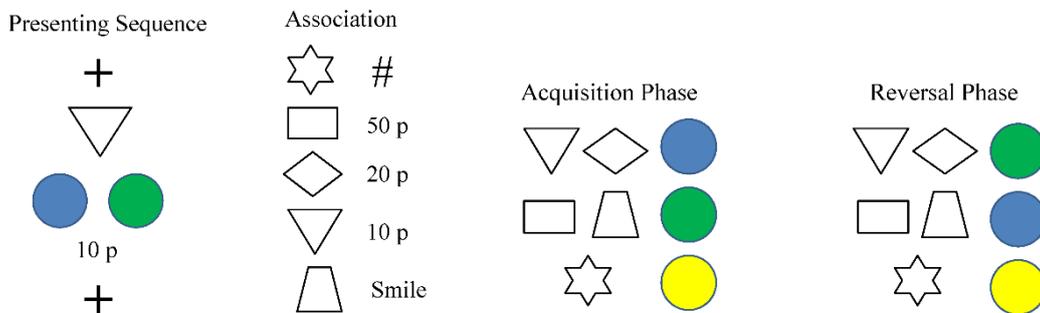
### **3.2.1. Participants**

I recruited 12 staff and student volunteers (Mean age 25; SD  $\pm 1.4$ ; 6 male and 6 female) from Aston University for the behavioural experiment 1, then I recruited a different 12 volunteers, also from Aston University, for my second behavioural experiment (Mean age 24; SD  $\pm 1.12$ ; 6 male and 6 female). All had normal or corrected to normal vision. All participants gave informed consent, and all procedures were approved by the Aston University ethics committee. All participants filled out the HAD scale (anxiety mean = 5.4; SD  $\pm 2.1$ ; depression mean = 4; SD  $\pm 2.12$ ; Zigmond et al., 1983). These volunteers would be excluded from participation if they had clinically significant depressive or anxiety symptoms as determined by the HADS with sub-scores of greater than 10.

### **3.2.2. Task paradigm – Reward based reversal-learning task**

Both behavioural experiment 1 and 2 employed the same reward based reversal-learning task. Participants were asked to learn the associations between 5 abstract shapes and 3 colours (blue, green or yellow) with the help of monetary and social feedback. On each trial (as shown in Figure 3.1), participants first saw a fixation cross "+" in the middle of the screen (1.5s), then one of 5 shapes was presented in the middle of a computer screen for 2 seconds, followed by 2 coloured circles, in the left and right-hand positions of the screen (2s). During the presentation, participants were asked to select one of the 2 colours by pressing a left or right response button. Following the button press, if a correct response was made, this would lead to either a monetary reward—indicated by a coin picture (accompanied by a sound "single

penny falling on desk”), or to a social reward—indicated by a smiling face picture plus thumb up gesture (a photograph of the researcher) accompanied by her voice saying “well done”. If an incorrect response was made, or the shape was not associated with a reward an image of a grey background with “#” symbol would appear. Each stimulus shape was associated with a specific reward and was paired with a correct response (green, blue or yellow colour circle).



**Figure 3.1:** The first column from the left shows the presenting sequence which starts with a fixation cross, followed by a shape and then two colours, one of which the participants needed to choose in order to get a reward. The second column shows the stimuli shapes and their associated reward. The third column shows the associations used during the acquisition-learning phase. The triangle and diamond were associated with blue, whereas the square and pentagon were associated with green. The fourth column shows the associations used during the reversal learning phase. The triangle and diamond were associated with green whereas square and pentagon were associated with blue. Therefore, in the acquisition phase, the correct responses are blue when the triangle or diamond is presented, whilst the correct responses are green when the square or pentagon is presented. In the reversal phase, the correct responses are green when the triangle or diamond is presented, whilst the correct responses are blue when the square or pentagon is presented. In both learning phases, the star was associated with yellow and no reward.

In the acquisition phase, participants learned that there were two shapes associated with blue and two associated with green that could lead to a reward, and that the shape associated with yellow always led to no reward (Figure 3.1). In the reversal learning phase, the two shapes that were originally associated with blue would be the reverse and were now associated with green to get a reward and vice versa for the other two rewarded shapes. The shape associated with yellow would remain unrewarding and have the same association as in the acquisition phase (Figure 3.1). There were 180 trials in total, split into 90 trials in the acquisition phase and 90 trials in the reversal phase. Each learning phase was comprised of 3 blocks with 30 trials per block. The colour presentation on the screen was counterbalanced across participants so that half the participants saw blue always on the left and the other half saw the

blue colour always on the right side, to reduce the effect of visual lateralization.

The monetary rewards used in experiment 1 were 10p, 20p and 50p, and as the results showed the smile and 20p were the most similar in terms of participants responses, then, a further experiment 2 was conducted to test whether 20p would have the most similar learning curve with a smile, due to its absolute value as opposed to its relative position between 10p and 50p, by using 5p instead of 50p. Therefore, experiment 2 had an identical procedure to experiment 1 with the only difference being that 50p was replaced by 5p, and thus 20p was now the highest monetary value reward and 10p replaced 20p as the middle value.

### 3.2.3. Data analysis – traditional ANOVA method

Standard statistical analyses were performed using SPSS 15. Data were analyzed by using a repeated measures ANOVA. For each learning phase, the factors in the ANOVA were reward type or magnitude (smile, 5p, 10p, 20p) and blocks (1 to 3) and the interaction between them. Learning curves were drawn on the basis of the block and group effect on learning performance (percentage of correct). Thus, different rewards could be compared by their learning curves (e.g. shape, peak, and bottom) across blocks. The ANOVA results for experiment 1 and 2 were presented in section 3.3 and 3.4 respectively.

### 3.2.4. Data analysis – test for equivalence

The confidence interval approach was used to show that the difference between social and monetary rewards (smile, 5p, 10p, 20p) was unlikely to be greater than the specified value (region of equivalence). If this specified value is sufficiently small, one could say the two were equivalent. The analysis process was stated in the following 5 steps.

Step 1, identify a measure of the reward value,  $M_{monetary}$ , of the stimuli that wish to show to be equivalent to the standard (in this case, the reward value of a smile,  $M_{smile}$ ).

Step 2, identify the largest value on this measure which can be considered insignificant,  $\delta M_{smile}$ .

Step 3, define the region of equivalence which is the region where values of  $M_{monetary}$  could be deemed, for all practical purposes, to be identical with  $M_{smile}$ . This is defined as mean  $(M_{smile}) \pm \delta M_{smile}$ .

Step 4, calculate the mean value of  $M_{monetary}$  and its confidence intervals: mean ( $M_{monetary}$ )

$\pm$  C.I. ( $M_{monetary}$ ).

Step 5, if the confidence intervals, mean ( $M_{monetary}$ )  $\pm$  C.I. ( $M_{monetary}$ ), lie within the region of equivalence, mean( $M_{smile}$ )  $\pm$   $\delta M_{smile}$ , one can say that two measures are equivalent.

To consider each of these steps in more detail, the first question was how to measure the reward value of each of the stimuli. For example, in experiment 1, 3 monetary rewards (10p, 20p & 50p) were compared to a social reward (smile) which was the standard on acquisition and reversal learning task. Because the number of trials was low, it would make sense to combine the data from both the reversal and acquisition trials. Theoretically, learning would be more effective to a more rewarding stimulus and the simplest way to measure this was to look at the total number of rewarded trials. However, a better measure would also include the rate of learning, and this can be obtained from the area under the curve (AUC) of the cumulative number of rewarded trials by trial number.

The second question was how to define  $\delta M$ . This value was critical because if we define it large enough, then any value of  $M_{monetary}$  could be considered equivalent to  $M_{smile}$ . There was no objective solution to this, but it was reasonable to define  $\delta M$  as some proportion of the standard deviation (S.D.) of the observed values of  $M_{smile}$ . It was commonly used either  $z=0.675$  which means that 1/2 of the sample would be seen in the equivalence zone or  $z=0.967$  which means that 2/3 of the sample would be seen in the equivalence zone. The former  $z=0.675$  was used in the analysis. Steps 3 to 5 calculations followed automatically from the definitions in 1 and 2. The region of equivalence would be the mean ( $M_{smile}$ )  $\pm$  0.675 and 95% C. I. was used for the difference between the means of two groups. The results of experiment 1 and 2 were shown in section 3.5 and 3.6 respectively.

### **3.3. ANOVA results of behavioural experiment 1**

Task performance in both acquisition and reversal learning phases was calculated on the mean percentage of correct responses. The effects of time on task and reward magnitude were analyzed by using the mixed design ANOVA with 3 time blocks and 4 rewards: 10p, 20p, 50p, and smile. The mean percentage of correct responses were the dependent variables for ANOVA. The ANOVA was performed firstly for the acquisition phase and secondly for the reversal phase. The descriptive statistics were shown in Table 3.1. The plots of mean percentage correct scores (learning curves) in both learning phases were shown in Figure 3.2.

### 3.3.1. Acquisition Phase Performance – Mean Percentage Correct Scores

During the acquisition phase, results of the mean percentage correct scores showed that participants performed best (73.6%; SD ± 25.3) during 50p trials. On the other hand, participants made their worst performance on smile trials (61.1%; SD ± 30.7) and 20p trials (61.8%; SD±29.6). Meanwhile, the mean percentage correct score was 67.36% (SD ± 31.5) on the 10p trials. The smile and the 20p trials had the most similar scores. However, there were no significant main effects,  $F(3, 99) = 1.647, p > 0.05$  or interactions with mean correct scores across reward values and blocks,  $F(6, 99) = 1.453, p > 0.05$ .

### 3.3.2. Reversal Phase Performance – Mean Percentage Correct Scores

During the reversal learning phase, participants performed best for both 50p (77.1%; SD ± 29.5) and 10p (77.1%; SD ± 27.6) trials. Participants made their worst performance on smile trials (65%; SD ± 30.6). Again, the results showed that smile (65%; SD ± 30.6) and the 20p (67.4%; SD ± 33.7) had the most similar mean. However, ANOVA reported no significant main effects,  $F(3, 99) = 2.72, p > 0.05$ , or interactions with mean correct scores across reward values and blocks,  $p > 0.05$ .

<b>Table 3.1. Descriptive statistics of the mean performance for experiment 1 and 2</b>					
<b>Mean % Correct</b>					
	<b>Experiment 1</b>			<b>Experiment 2</b>	
Reward	Acquisition	Reversal		Acquisition	Reversal
10p	67.4	77.1		76.5	74.2
20p	61.8	67.4		61.4	72.0
50p	73.6	77.1		63.6	79.6
Smile	61.1	65.2		60.6	71.2

**Table 3.1:** The first column shows reward type and magnitude: social reward – smile; monetary reward – ten pence, twenty pence, and fifty pence. Column 2 and 3 shows the mean performance during the acquisition and reversal learning phases in experiment 1. Column 4 and 6 shows the mean performance during the two learning phases in experiment 2.

### 3.4. ANOVA results of behavioural experiment 2

The task performance (mean percentage correct scores) was analyzed using ANOVA in exactly the same way as in experiment 1. Experiment 2 used 5p instead of 50p in this

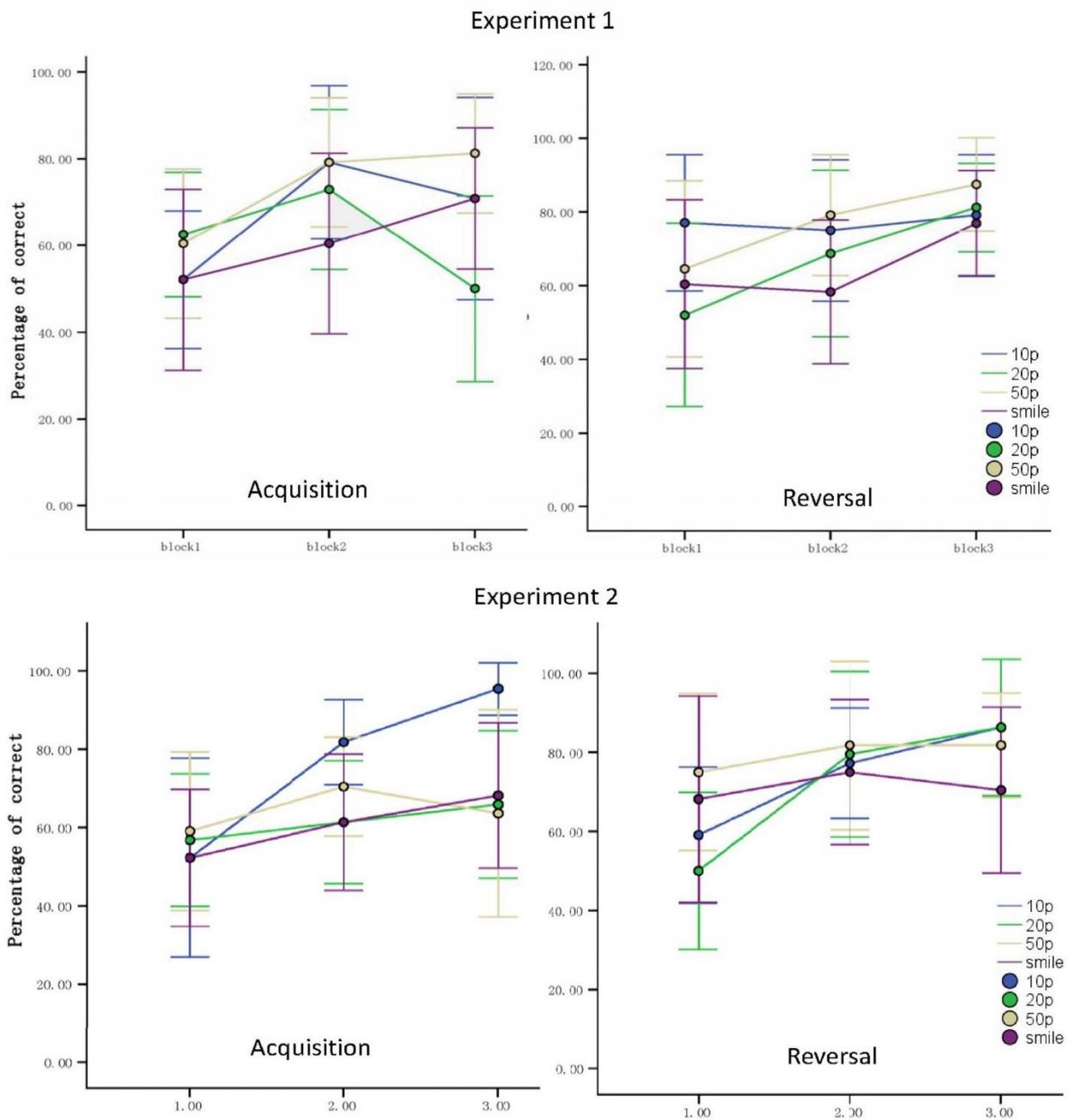
experiment. The descriptive statistics are shown in Table 3.1, and the plots of mean percentage correct scores in both learning phases are presented in figure 3.2.

#### **3.4.1. Acquisition Phase Performance – Mean Percentage Correct Scores**

In the acquisition-learning phases: participants performed best in 10p trials (76.5% of correct; SD  $\pm$  29.9) and worst on the smile trials (60.6%; SD  $\pm$  26.5). The smile (60.6%; SD  $\pm$  26.5) and 20p (61.3%; SD  $\pm$  25.1) were the two reward types with the most similar performance profile. 5p (63.6%; SD  $\pm$  29.5) showed the second similar performance with the smile. The ANOVA reported no significant effect of reward on performance made in the task,  $F(3, 90) = 1.84, p > 0.05$ , and no interaction of reward with a block. Also, no significant difference between blocks,  $F(6, 90) = 1.219, p > 0.05$ .

#### **3.4.2. Reversal Phase Performance – Mean Percentage Correct Scores**

In the reversal learning phase: participants performed best in 5p trials (79.5%; SD  $\pm$  26.8) and worst on the smile trials (71.21%; SD  $\pm$  31.9). The most similar scores were found in the Smile and 20p trials (72%; SD  $\pm$  32.3). The ANOVA reported no significant main effect of reward on performance  $F(3, 90) = 2.16, p > 0.05$ , and no interaction of reward with the block. Also, there was no significant difference between blocks  $F(6, 90) = 1.56, p > 0.05$ .

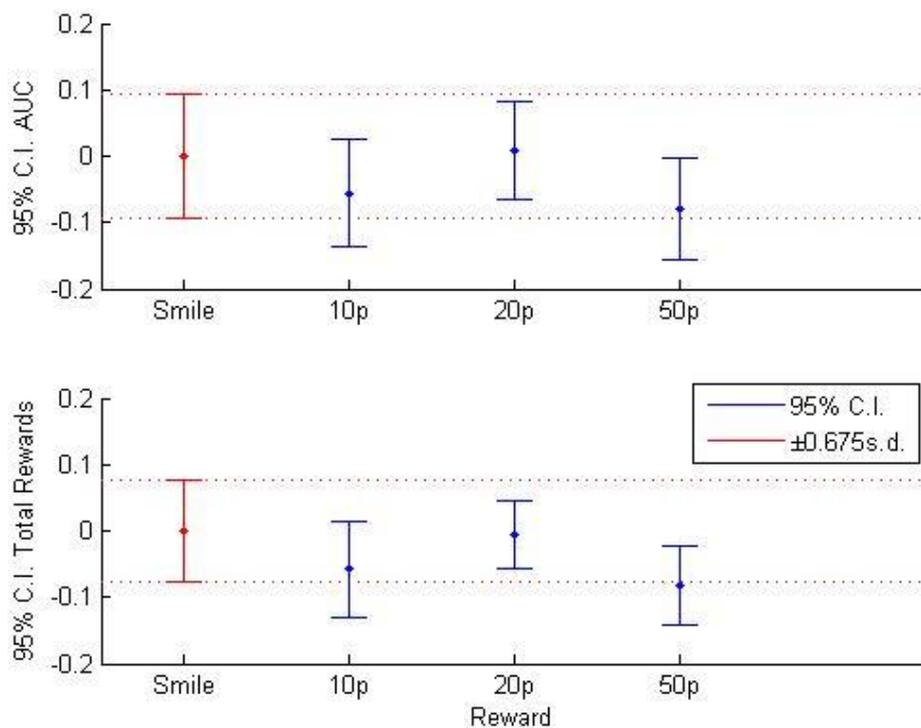


**Figure 3.2:** Means plots for percentage correct scores in behavioural experiment 1 and 2, shown with standard error bars at a 0.05 confidence interval. Each reward is represented with a colour: smile – purple; 10p – blue; 20p – green; 50p – yellow.

### 3.5. Test for equivalence results – experiment 1

The results combined all of the acquisition and reversal learning trials data, which were showed in figure 3.3 and table 3.2. The mean Learning curve for experiment 1 was showed in figure 3.6. This learning curve was drawn according to the mean proportion of the maximum possible score (rewarded trials) as the trial number went on. The figure

showed the learning curve for the smile with the best-fit regression line and 95% C. I. The results showed that 20p was the best fit to the smile in this experiment.

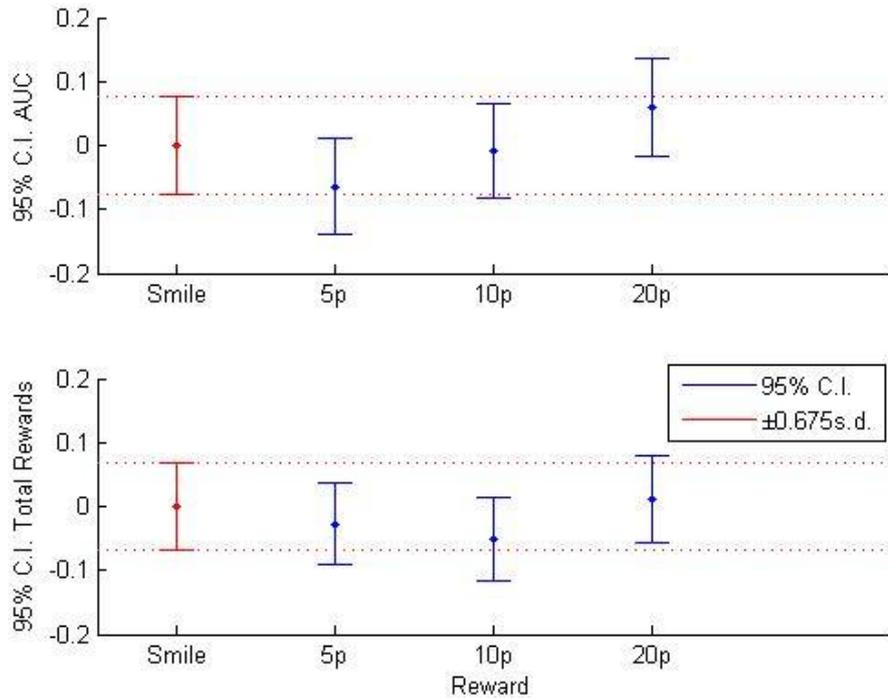


**Figure 3.3:** Equivalence Values for Experiment 1, it shows the equivalence results from experiment 1 for 10, 20 and 50p with the smile as the reference reward. The upper panel indicates the area under the curve (AUC) and the lower panel indicates the total proportion of trials that were rewarded. In the upper panel, the red bars indicate the region of equivalence and the blue bars indicate the 95% C.I. for the difference between the AUC for 10p, 20p and 50p respectively. The lower panel shows the same for the proportion of trials that were rewarded. It is clear that only the error-bars for the 20p reward fell within the zone of equivalence. Therefore, 20p can be considered to have a reward value equivalent to a smile.

Table 3.2: Equivalence results – Experiment 1								
	Money	Mean	Standard error	Lower C.I.	Upper C.I.	Smile S.D.	Equivalence zone	
							Lower bound	Upper bound
95% C.I. AUC	10P	-0.056	0.041	-0.137	0.026	0.137	-0.103	0.103
	20P	0.009	0.037	-0.064	0.082			
	50P	-0.080	0.039	-0.157	-0.002			
95% C.I. Total proportion of trials rewarded	10P	-0.058	0.037	-0.130	0.014	0.115	-0.086	0.086
	20P	-0.005	0.026	-0.056	0.046			
	50P	-0.083	0.030	-0.143	-0.024			

### 3.6. Test for equivalence results – experiment 2

The results were showed in figure 3.4 and table 3.3. Learning curve for experiment 2 was showed in figure 3.7. The results showed that 10p was the best fit to the smile for the first half of the trials but by the end, 20p is the closest match to the smile.

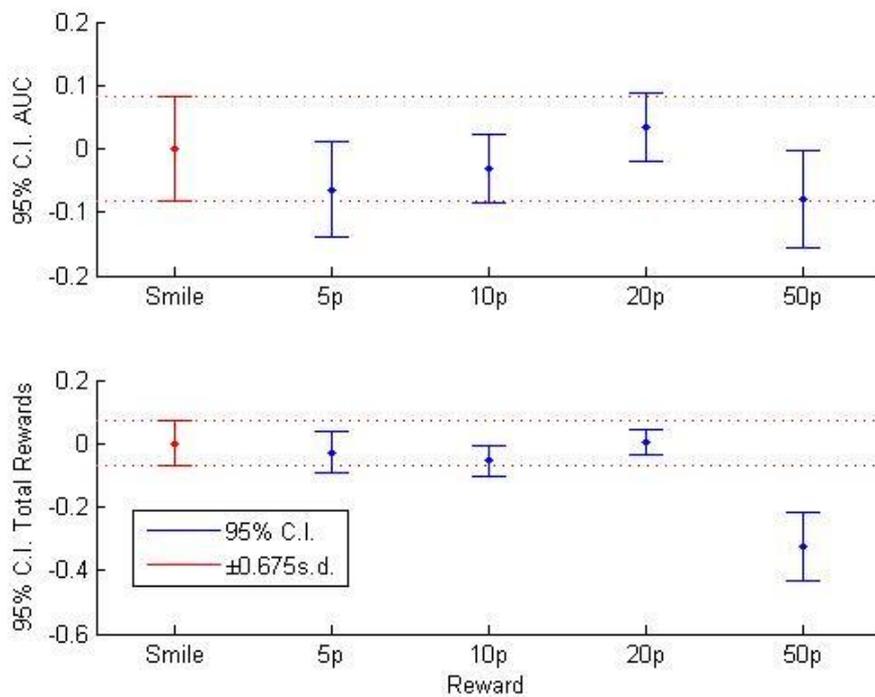


**Figure 3.4:** Equivalence Values for Experiment 2, it shows the equivalence results from experiment 2 for 5p, 10p, and 20p with the smile as the reference reward. The results suggest that for this experiment, 10p was equivalent to a smile for AUC and 20p was close to the equivalent for the total proportion of rewards.

Table 3.3: Equivalence results – Experiment 2									
	Money	Mean	Standard error	Lower C.I.	Upper C.I.		Smile S.D.	Equivalence zone	
								Lower bound	Upper bound
95% C.I. AUC	5P	-0.064	0.038	-0.139	0.010		0.113	-0.085	0.085
	10P	0.008	0.037	-0.082	0.065				
	20P	-0.059	0.039	-0.017	-0.136				
95% C.I. Total proportion of trials rewarded	5P	-0.028	0.032	-0.091	0.036		0.100	-0.075	0.075
	10P	-0.051	0.033	-0.115	0.013				
	20P	-0.012	0.035	-0.056	-0.079				

### 3.7. Test for equivalence results – combined experiment 1 and 2

The results also showed the combined data from experiment 1 and 2 (Figure 3.5 and Table 3.4). Both 10p and 20p were equivalent to the smile for AUC, but only 20p was equivalent in terms of the proportion of trials rewarded. Experiments 1 and 2 were not entirely consistent but combining the data suggested that 20p was the closest match. Note that there was no ordinal relationship for either AUC or proportion of results rewarded. The learning curve for experiment 1 and 2 combined was showed in figure 3.8. The results showed that 20p was the best fit to the smile.



**Figure 3.5:** Equivalence Values for Experiments 1 and 2, it shows the equivalence results from experiment 1 and 2 combined for 5p, 10p, 20p and 50p with the smile as the reference reward. The results suggest that both 10p and 20p were equivalent to the smile for AUC, but only 20p was equivalent in terms of the proportion of the total trials rewarded.

Table 3.4: Equivalence results – Experiment 1 and 2 combined									
	Money	Mean	Standard error	Lower C.I.	Upper C.I.		Smile S.D.	Equivalence Interval	
								Lower bound	Upper bound
95% C.I. AUC	5P	-0.064	0.038	-0.139	0.010		0.123	-0.092	0.092
	10P	-0.032	0.028	-0.086	0.023				
	20P	0.034	0.027	-0.019	0.087				
	50P	-0.080	0.039	-0.157	-0.002				
95% C.I. Total proportion of trials rewarded	5P	-0.028	0.032	-0.091	0.036		0.106	-0.079	0.079
	10P	-0.054	0.024	-0.102	-0.007				
	20P	0.003	0.021	-0.038	0.045				
	50P	-0.325	0.054	-0.432	-0.219				

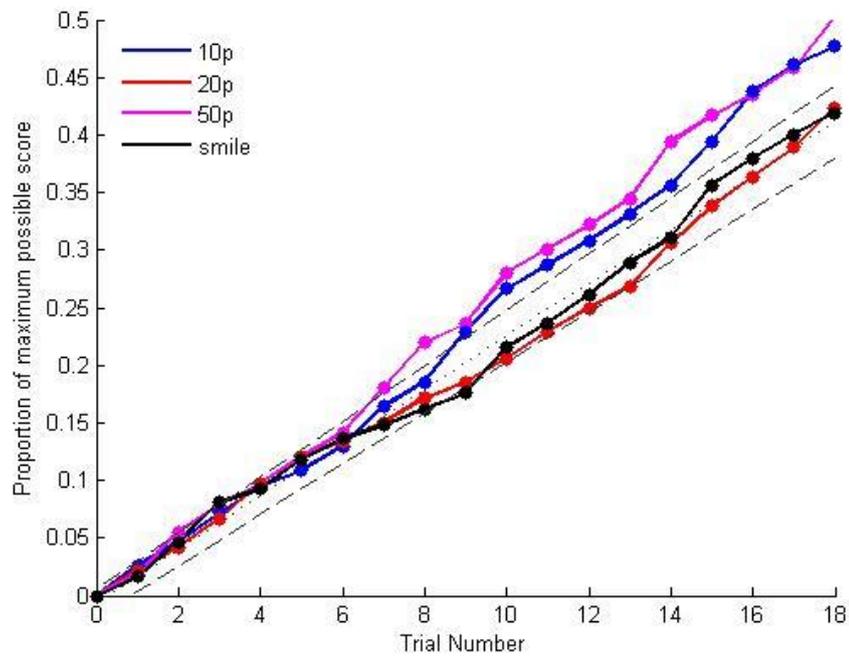
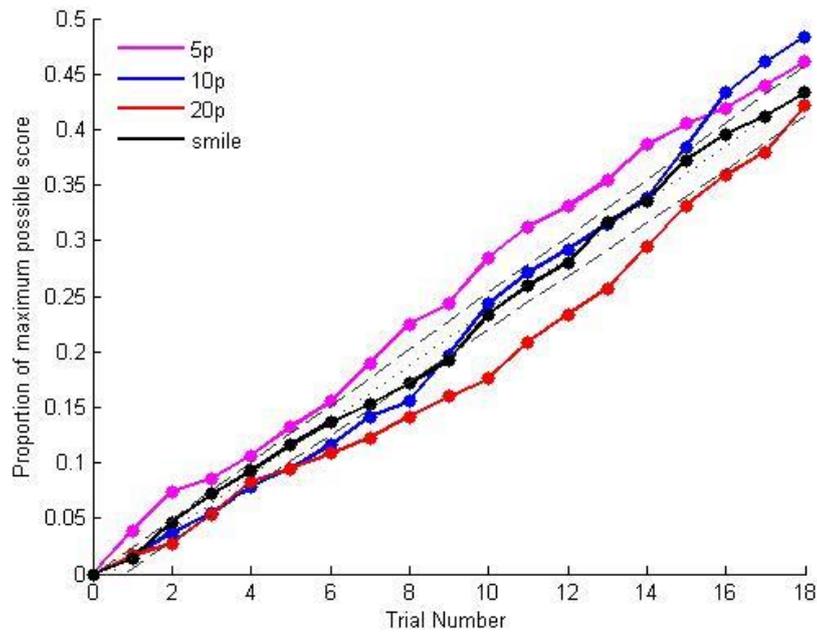
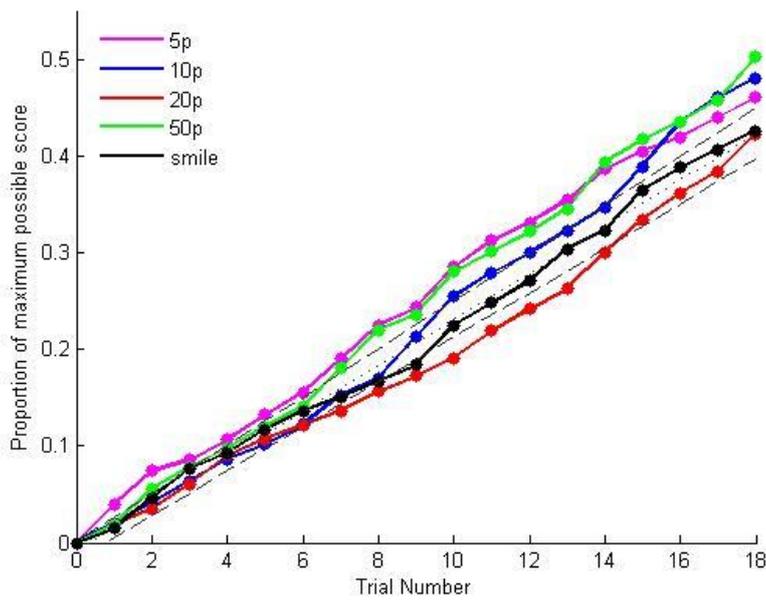


Figure 3.6: Learning curve for experiment 1. 20p is the closest match to the smile.



**Figure 3.7:** Learning curve for experiment 2. 10p is the best fit for the first half of the trails but by the end, 20p is nearest to the smile.



**Figure 3.8:** Learning curve for experiment 1 and 2 combined. 20p is the closest fit to the smile.

### **3.8. Discussion of Behavioural experiments**

Though the ANOVA analysis of both behavioural experiments did not reveal any significant differences on mean percentage correct scores between any pair of the reward comparisons, the descriptive statistics could give a suggestion on choosing one monetary reward which has the closest value to the social reward to be used in the later fMRI experiments. The behavioural experiment 1 compared one social reward (a smiling face saying well done) and three monetary rewards (10p, 20p, and 50p) and revealed that a smile and 20p may have the most similar task performance on the mean percentage correct scores. The plots of the learning curves supported this view. The experiment 2 further tested whether 20p would have the most similar effects on task performance with the smile, due to its absolute value as opposed to its relative position between 10p and 50p, by using 5p instead of 50p. The results of Experiment 2 also showed the rewarding value of a smile and 20p were the most similar based on the mean percentage correct scores.

The current studies reported the results only on the basis of mean percentage of correct response. Many previous studies conducted reversal learning tasks draw their learning curves on the basis of mean percentage of correct answers, but not mean reaction time (RT; Bellebaum et al., 2008; Izquierdo et al., 2006). This was due to more individual differences on RT, as it was sensitive to attention, mood, and motivational level and even environmental conditions. Therefore, the mean percentage correct responses was a more accurate measure of learning performance than RT.

As stated in section 3.1, traditional ANOVA test was not suitable to look for equivalence or similarity between different reward values. No significant difference had been found was not the same as saying that the two outcomes were similar or equivalent, might be because of a small sample size. Instead, if the confidence intervals of a tested reward value (i.e. one of the monetary rewards) could lie within the defined region of equivalence (equivalence interval, or proper value of the smile), it would be reasonable to conclude equivalence between the two values. The current studies, therefore, conducted the test for equivalence, using this confidence interval approach. The results were supportive to the descriptive statistics of the ANOVA test. The 20p reward was consistently contained within the zone of equivalence in terms of the total proportion of trials that were rewarded, in both experiment 1 and 2 as well as this two experiments combined. The mean learning curves (calculated on the basis of the mean proportion of maximum possible score, or total proportion of rewarded trials) also showed that 20p was the closest match to the smile across experiment 1 and 2 as well as this two experiments combined. The smiling face and 20p were therefore decided to be used as incentives in the following fMRI experiments. Any neural differences found in the fMRI experiments could be interpreted as not being due to differences in the absolute value of the rewarding stimuli.

In summary, if one study were aimed to demonstrate that two or more groups were equivalent, similar or comparable, then equivalence testing would be recommended. Also, the equivalence interval selected should be relevant to the research context and with strong rationale. Equivalence testing had not been used to select matched/similar rewarding stimuli in any of the previous reward processing studies. The current two pilot studies had a try to use the equivalence testing to choose two behaviourally matched rewarding stimuli. It would increase the confidence of any neural findings in the fMRI reward processing experiments and improve the reliability of the task paradigm. Furthermore, this two pilot studies could be improved by increase the sample size, thus to increase the confidence in results.

## Chapter 4: fMRI study-1

### 4.1. Introduction

There have been many human neuroimaging studies which have investigated the nature of primary reward processing, especially reward processing in relation to food stimuli (including food, water, taste and smell), and also many have focussed on abstract rewards such as money (Thut, et al., 1997; O'Doherty et al., 2001, 2003; Knutson et al., 2001). To date, however, relatively little attention has been paid to social reinforcers, which is surprising given the pervasive role of social reinforcers in everyday life and their relative strength compared to monetary rewards. Appreciation for work done, for example, has been reported to be more motivating than monetary rewards by business employees (Graham and Unruh, 1990; Koch, 1990; Stuart, 1992; Knippen and Green, 1990; Steele, 1992).

Previous neuroimaging studies have revealed that although there is some variation in the brain areas that respond to rewards with respect to the behavioural task and type of stimuli used (primary and monetary), there is also a common set of brain structures that respond to all rewards, often referred to as the brain reward network, that includes the striatum, amygdala, medial PFC and OFC (reviewed in McClure, et al. 2004 and O'Doherty, 2004). The same network is activated by punishments as well (Dreher, 2007; Gottfried et al. 2003; Marco-Pallares et al. 2007; Nieuwenhuis et al. 2005; O'Doherty et al., 2001; Small et al., 2001; Tom et al. 2007; van Veen et al. 2004). The current study was aimed to examine the neural effects of both reward and punishment for both monetary and social reinforcers, as well as to examine the conjoint effects of reward type and valence within the brain reward network, especially the OFC which had been revealed as a site of integration (Montague et al., 2002; Levy and Glimcher, 2012) for different forms of reward information. Therefore, the primary region of interests (ROIs) in this thesis include the OFC (and the medial PFC), amygdala and the striatum.

The OFC is of particular interest to the current study, due to its well-established function in encoding the perceived value (affective value) of rewarding stimuli (O'Doherty, 2007). Certain regions of the OFC are thought to be functionally dissociated in relation to coding reinforcement value, such that the medial areas of the OFC respond to reward while more lateral areas respond to punishment (O'Doherty et al. 2001; Small et al. 2001; Ursu and Carter, 2005), although this medial-lateral functional dissociation has not consistently been observed (Elliott et al. 2003; Breiter et al. 2001). One explanation for those studies failing to find functional dissociations within the OFC used complex tasks such as

gambling tasks, involving a number of distinct processes besides coding reinforcer value, such as reward anticipation, response selection, and applying behavioural strategies (O'Doherty et al. 2007). My current study employed a simple target detection task to probe the function of 'coding reinforcer value, upon consumption', thus, I expected to find the medial-lateral dissociation within the OFC.

On the other hand, the OFC has been suggested to be involved in the convergence and merging of the valuation of different rewards and punishments into a common valuation scale or common neural currency in order to make an appropriate action (Montague and Berns 2002; Levy and Glimcher, 2012). This region is, therefore, the hypothesised candidate of the integration effects of reward types (social and monetary) and valence (reward and punishment) in the current study. Although there has been a lot of work on reward processing, few studies have examined directly whether the processing of different segments of reward information, such as reward type and valence, are integrated into the OFC. This functional integration would enable a common valuation scale as hypothesised by Montague et al. (2002) and reviewed by Levy and Glimcher (2012), thus allowing goal-directed control of behaviour to depend on the current environmental (comparison of different outcomes) and/or related emotional context.

Only the human neuroimaging studies which had met the minimum experimental design requirements could provide direct evidence for such integration. As Levy and Glimcher (2012) suggested that only the fMRI studies involve processing of multiple reward types in a single task and show that different reward values were represented in the same brain areas, could provide such direct evidence. To date, only few fMRI studies have involved multi-types of reward comparison (Levy and Glimcher, 2012), and among these studies, only five of them have included social reinforcers in the comparison (Izuma et al., 2008; Lin et al., 2011; Smith et al., 2010; Rademacher et al., 2010; Spreckelmeyer et al., 2009). Only a handful of these studies compared different reward types within a single task (Kim et al., 2010; Valentin et al., 2009; Smith et al., 2010), as most of them have employed separate tasks or sessions for different reward types.

Take Kim et al's (2010) fMRI study as an example of comparing multiple reward types within in a single task. They compared the anticipation/receipt of the primary (juice) with abstract (money) reinforcers within a reward-related action selection task (Kim et al., 2010), and found partially overlapping activity in the vmPFC/OFC and the anterior insula to the anticipation of both juice and monetary rewards, which may add weight to the theory of a common neural currency. Moreover, Kim et al's (2010) study examined reward anticipation as opposed to reward receipt and suggested that reward anticipation and

receipt may have dissociable neural processes. Rademacher et al's (2010) findings support Kim et al's idea by showing that the neural mechanisms underlying reward consumption are more modality specific than those for reward anticipation. Therefore, a separate evaluation of the neural responses related to different reward processes (i.e. anticipation, receipt/consumption, approach or decision-making) is necessary. One way to do this is to employ task paradigms that focus on one of these processes.

Furthermore, the amygdala was also of particular interest in this fMRI study due to its well-established function in face processing, including both emotional faces (Adolphs, 2010) and neutral faces (Gothard et al., 2007). The amygdala is also thought to be closely associated with both arousing (reinforcer intensity) (Sanghera, 1979; Hommer et al. 2003; reviewed in McClure et al., 2004; Wilson and Rolls, 2005) and emotional (positive and negative) stimuli (Adolphs, 2010). There is also evidence that the amygdala responds to social signals of emotion (Dalglish, 2004). Meanwhile, the amygdala has been suggested to play a role in the consumption of monetary rewards (Hommer et al., 2003; Elliott et al., 2008; Small et al., 2001) and social rewards (Rademacher et al., 2010). Therefore, the current study had hypothesised that it would find amygdala activation in response to all rewards (maybe also to all punishments) and to find the amygdala is preferentially activated to social reinforcers when compared with monetary.

Finally, the striatum is of interest to the current study as the dorsal striatum appears to respond to the perceived 'value' of the reward outcome during action-reward learning, and works as an "actor" (O'Doherty et al. 2004) i.e. maintaining the reward outcome of actions to optimize future choices for continued reward. BOLD activation in the ventral striatum during learning may only play a role in passive forms of appetitive learning that learn to predict future rewards (O'Doherty et al. 2004), and is directly related to signal errors in the prediction of rewards and also to the anticipation of rewards (Montague et al. 1996; Schultz et al. 1998; Berns et al. 2001; Pagnoni et al. 2002; McClure, et al. 2003; O'Doherty et al. 2003; McClure et al., 2004).

Whether social reinforcers have overlapping or distinct neural representation within the reward network from monetary reinforcers is still unclear. Of the few fMRI studies have sought to compare the neural activations of social reinforcers with other reinforcer types, the findings to date are rather mixed. For example, three fMRI studies have revealed social and monetary rewards have a similar neural representation (Izuma et al., 2008; Lin et al., 2011; Smith et al., 2010), while two others report distinct neural representations (Rademacher et al., 2010; Spreckelmeyer et al., 2009). To elaborate further, Izuma et al (2008) found social rewards (a good reputation) were processed similarly to monetary

rewards in the dorsal striatum, though they conducted two separate tasks for the two reward types. This made the interpretation of their results difficult, as it is unclear if any differences found were due to the type of reward or to differences in action contingency. Also, Lin et al (2011) compared where BOLD activity was parametrically related with two versions of a rewarded instrumental learning task, one with monetary rewards/punishments and the other with social. They found a common area between the two reward types in the medial OFC which correlated with stimulus cue value, and another shared region of medial OFC which correlated with reward magnitude (Lin et al., 2011). Additionally, Smith et al (2010) reported the anterior vmPFC/OFC responded to the experienced value of both reward types (receipt value via passive viewing), and the posterior vmPFC/OFC responded to the decision value (decide whether to exchange money for attractive faces) of both rewards.

Contrarily, Rademacher et al (2010) and Spreckelmeyer et al (2009) both found differences in regional brain activations between social and monetary reward types. Rademacher et al., (2010) found differences in the amygdala and thalamus, such that SR was associated with activation in the amygdala whereas MR was associated with activation in the thalamus during reward consumption (but not during reward anticipation). While, Spreckelmeyer et al., (2009) found increased activation in a range of mesolimbic brain regions (anterior cingulate, caudate, amygdala and nucleus accumbens) to the anticipation of monetary rewards, but not social (smiling face) rewards, which was observed in male study participants, but not female (Spreckelmeyer et al., 2009). However, the two types of rewards were presented in two separate task sessions in Spreckelmeyer et al's study, thus, the reward types were not directly contrasted. Actually, this is a task limitation for all these above studies that did not make a direct contrast between the two reward types within a single task. This makes the interpretation of these results difficult, as it is unclear if any differences seen were due to the type of reward or to task differences (e.g., a difference in action contingency).

The focus of this chapter, therefore, was to carry out an fMRI study, aimed to overcome the limitations of previous studies examining different reward types, by directly comparing the neural substrates of both social and monetary reinforcers (reward and punishment) in a single task paradigm. In addition, vivid social reinforcers had been used, which were chosen to be of direct relevance to participants in their natural environment. These were the face and voice of the experimenter. The reward was taken to be an image of the researcher's smiling face with a thumb up gesture plus the experimenter's voice saying 'well done'. The punishment was a frowning face with a thumb down gesture and the experimenter's voice saying 'too slow'. The experimenter was somebody who both

recruited and screened the participants prior to the study, thus, participants were very likely to have built a rapport. Given that study volunteers are usually eager to please experimenters (Milgram, 1974; Ost et al. 2005), we suggest that this made the social stimuli more relevant than simply choosing the face of a complete stranger (Rademacher et al., 2010; Spreckelmeyer et al., 2009). In other words, such unique, ecologically valid and vivid social stimuli were thought to be more salient or have more social value or stronger affective intensity than a stranger's face. Furthermore, this study also extended previous studies by including both reward and punishment for both monetary and social reinforcers. Given the well-defined reward network outlined above, the current study hypothesized that both reinforcer types would elicit responses in the ROIs (OFC, striatum, and amygdala) but that dissociations would also be found between reinforcer types within each of the ROIs. It also hypothesized that the OFC is a site of integration of reward type and valence (Montague and Berns, 2002; Levy and Glimcher, 2012), that is, if the study could find an activation of the OFC in a crossover interaction of type and valence, but not specifically to the main effect of reward valence or type in isolation, this would imply integration at this point of processing (Gray et al., 2002).

In addition, the current study (also the second and third fMRI studies) carried out a post-scan informal questioning of the study participants, to ask about generally which reward or punishment stimuli they liked or disliked the most. The results showed that many (about half of them) claimed to not mind if they lost 20p during the monetary punishment, but stressed "really not liking" the social punishment. Also, the current study reported that slightly majority participants claimed they were more excited about winning money than receiving social praise, although the behavioural results did not reveal any RT differences between monetary and social cues. The post-scan interviews could give a general idea about the subjective value or affective intensity of the social and monetary stimuli, which might be helpful in understanding the brain scanning results. However, the results of the post-scan questioning will not be used as main results as it was from an informal interview.

## **4.2. Methods**

### **4.2.1. Participants**

The current study recruited 20 volunteers (mean age = 23, SD  $\pm$ 1.41; 4 male and 16 female) from the Aston University staff and student population. All participants gave informed consent, and all procedures were approved by Aston University Ethics Committee. A safety screening questionnaire was administered prior to scanning. All participants filled out the HADS (anxiety mean = 5.4; SD  $\pm$  2.1; depression mean = 4.0;

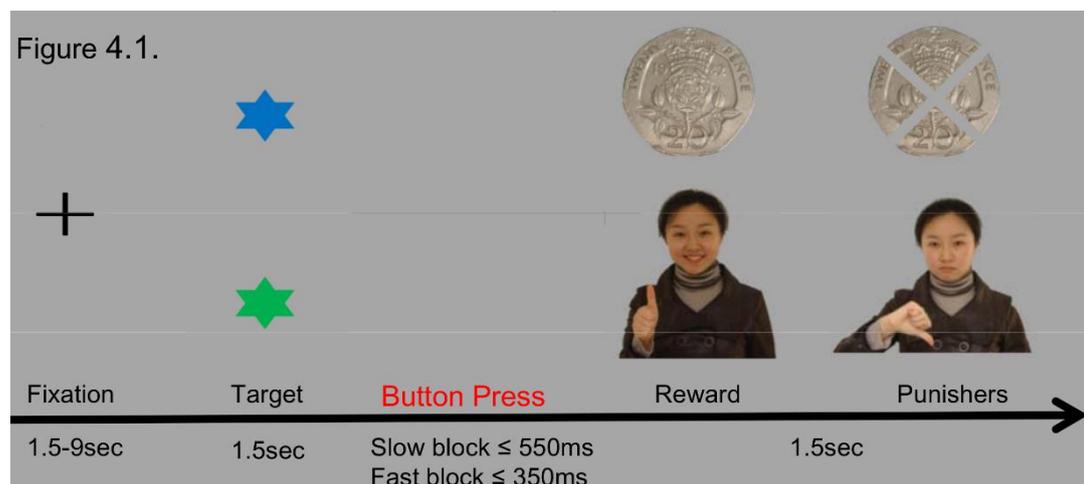
SD  $\pm$  2.12, Zigmond et al., 1983) as well as the BDI scale (mean = 5.0; SD  $\pm$  0.71, Beck, 1978). This study excluded from participation individuals who had a formal contraindication to assessment with MRI, or who had clinically significant depressive or anxiety symptoms as determined by the HADS (score > 10), or by the BDI (score > 9). No participants in the study were found to have scores above the cut-off values on either mood scale.

#### **4.2.2. Stimuli and task**

Prior to the fMRI experiment, the study examined behavioural responses to social and monetary reinforcers using two pilot reversal learning tasks (n = 24) to assess the equivalence between the reward value of winning differing amounts of money (image of coin value presented with a coin sound (coin dropping on wooden surface) and being presented with a smile (experimenters face and accompanying voice saying 'well done'; as described in detail in chapter 2). As my behavioural experiments showed that participants behaved almost equally in terms of the rate of learning or the proportion of trials rewarded for the smiling face and 20p (for both experiments), these two rewards were used as incentives in the following fMRI experiment, plus the corresponding punishments (social: disappointing face with voice saying "too slow"; monetary: image of 20p with a cross drawn through it- signifying a 20p loss, accompanied with an error sound).

In the fMRI task, it used a simple target detection paradigm. In each trial, participants first saw a fixation cross "+" in the middle of the screen (variable length 1.5-9sec), followed by a star (i.e. target, presented for 1.5sec) which could be 1 of 5 possible colours, red, orange, purple, blue or green. The blue and green stars were targets that participants had to respond to, by pressing a button on a response box as fast as possible to get an associated reward, and ignore non-targets (purple, orange or red stars), i.e. no response required. Participants were informed that if they would receive a reward if they responded fast enough to targets, otherwise they would receive a punishment. The green star was associated with social reinforcements whereas the blue star was associated with monetary. After participants made their response to a target, either a reward (20p coin with a coin falling sound or the experimenter's smiling face accompanied by voice saying 'well done') or a punishment (20p loss; image of 20p with a cross through it, presented with an metallic error sound or experimenter's disappointed face accompanied by voice saying 'too slow') was presented (Figure 4.1). Rewards were presented for 1.5sec. The task consisted of 200 trials altogether, which included 120 trials of targets (60 blue and 60 green) plus 80 trials of non-targets (27 purple, 26 red, 27 orange). It was comprised of randomized two block types: fast and slow reaction blocks with 25 trials per block (15

targets and 10 non-targets). In the fast reaction block, participants had to respond to the targets within 350ms; whilst, in the slow reaction block, participants had to respond to the targets within 550ms. Fast and slow blocks were utilized to force participants to vary their reaction times needed to gain a reward, hence leading them to keep their concentration on the task. Participants were told that any money they won in the task they could take home, up to a maximum of £10.00. The scan session ran for approximately 30 minutes.



**Figure 4.1: Task Presenting Sequence.** From left to the right: the fixation cross, a target, then a reward shows up after a button press response. Photos on the bottom right: SR and SP. Photos on the upper right: MR and MP. The photos were taken on the same day and with the same background. SP photo was the experimenter's disappointed face accompanied by a voice saying 'too slow' whereas SR photo was the experimenter's smiling face accompanied by a voice saying 'well done'. MP photo was an image of 20p with a cross through it represents 20p loss, accompanied by a metallic error sound whereas MR photo was a 20p coin with a coin falling sound.

#### 4.2.3. Image Acquisition and Analysis

FMRI was performed on a 3 Tesla (3T) Siemens Trio scanner at Aston University, using a T2\* weighted gradient echo planar imaging sequence with the following parameters; Time of Echo (TE) = 30 ms, Time of Repetition (TR) = 2.8 sec, matrix size = 64x64, 3mm slice thickness and 3x3mm in-plane resolution. Each volume contained 40 axial slices, angled at 25-30 degrees away from the eyes (nasal area, which can result in distortion artefacts in the ventral PFC). The task was projected on a screen behind the participant's head and was viewed through a mirror mounted on the head coil. The participant's responses to the target detection paradigm were collected using an MRI compatible Lumina button response pad.

All fMRI data were analyzed using SPM2 (Wellcome Institute of Neurology, implemented in Matlab; Mathworks, MA). 1 participant aborted the scan before completion, 2 participants data were removed due to technical problems with stimulus presentation and a further 2 participants' data were rejected after pre-processing due to excessive motion ( $> 3.5\text{mm}$ ), and 1 participant was rejected due to a large artefact in the PFC. Statistical analysis was therefore performed on 14 participants.

Prior to model application, brain volumes from each participant were realigned to the first volume to correct for head motion. Functional images were then spatially normalized into a standard single subject T1 image template. Following this, spatial smoothing was applied with an isotropic Gaussian kernel filter of 10-mm full-width half-maximum to facilitate inter-subject averaging. For each participant, all experimental feedback categories were modelled as event types which were: social reward (SR), social punishment (SP), monetary reward (MR) and monetary punishment (MP). A series of t-contrast images were carried out to determine whether the fitted parameter values at each voxel were significantly greater than zero for each participant. These were then entered into a random effects group analysis. The activations were thresholded at a voxel threshold of  $p < 0.001$ , uncorrected, and accepted as significant those clusters that survived at  $p < 0.05$ , corrected for multiple comparisons for the entire brain. For the regions of interest (ROI; medial and lateral OFC, amygdala, striatum), it report activations that survive an uncorrected threshold of  $p < 0.001$ , but are significant at  $p < 0.05$  when a small volume correction (SVC) is applied. The SVC applied to medial OFC, was a sphere of 10mm radius and was based on the coordinates of the peak voxel within the medial OFC (left: -6, 36, -15) reported as the site of overlapping activation for social and monetary reinforcers (Lin et al., 2011). The SVC used for the lateral OFC was also based on a sphere of 10 mm radius defined around the peak activation coordinates that were reported to the anticipation of monetary reward (right: 30, 32, -2; Spreckelmeyer et al., 2009). Analysis also applied SVC on the striatum; for the caudate it used the coordinates of the peak voxel (-18, 12, -1) of left caudate activation to anticipated rewards reported by Rademacher et al., (2010), where social and monetary rewards were used; for the putamen, it used the coordinate of the peak voxel reported in Izuma et al (2008; right: 22, 16, -4) which was commonly activated to social and monetary rewards. As SPM coordinates are given in MNI space; regions were identified by converting the coordinates to Talairach space with a nonlinear transform (Brett et al., 2001).

### **4.3. Behavioural Results**

Mean reaction times were calculated for each condition. Data were analysed in a 2x2 repeated measures ANOVA (reward type: social and monetary; and block type: fast and slow). There was no significant difference between the two reward levels, that is, there was no significant difference between the monetary and social conditions in the fast block,  $F(1, 13) = 0.189, p > 0.05$ . Also, there was no significant differences between the monetary and social conditions in the slow block,  $F(1, 13) = 0.049, p > 0.05$ .

The data were also analysed in ANOVA with two further repeated measures (hit and false alarms, and block type: fast and slow), in order to investigate if the fast and slow blocks would affect participants' reaction time in general. In other words, it would like to examine if the participants would react differently in a fast hit and slow hit conditions, also to investigate if they would react differently in fast false and slow false conditions. The results showed that no significant difference was found between the fast false and slow false trials,  $F(1, 13) = 5.217, p > 0.05$ , or between a fast hit and slow hit trials,  $F(1, 13) = 1.307, p > 0.05$ .

It also calculated the mean percentage hit rates on the task for the social cue targets (green stars) and financial (blue stars). These were virtually the same for both targets, as mean hits for social targets were 64.7% and for financial 64.3%. A repeated ANOVA showed that there was no significant effect associated with cue type,  $F(1, 13) = 0.196, P > 0.05$ . This means of course that the percentage of missed targets for both cues was also virtually the same (35.3% social; 35.7% financial), and thus, there was no difference in the number of social and financial punishments received across reinforcer types.

#### **4.4. FMRI Results**

The results of the subtractive contrasts are outlined first for the main effects of reinforcer type and valence, followed by an interaction contrast.

##### **4.4.1. The main effect of valance irrespective of reinforcer type**

Here, the results found effects of valance type within the OFC, with evidence provided for a functional dissociation between medial and lateral portions. This was supported by the contrast of both punishment types versus both rewards, which revealed significantly greater BOLD activation in the right lateral OFC (BA 47) and also right lateral PFC (BA9). For the reverse contrast (rewards vs. punishments), results found significantly greater left medial OFC (BA10) and left caudate activation to rewards (Table 4.1).

<b>Table 4.1. BOLD activation associated with the main effects contrast of valence irrespective of reward type</b>							
Region	Voxels	P-corrected	Brodmann's Area	Z score	X	Y	Z
<b>(A) Reward vs. Punishment</b>							
L Medial OFC	12	0.035*	BA10	3.8	-7	40	-4
L Caudate	40	0.013*		3.40	-1	6	5
L Caudate	19	0.037*		3.55	-10	19	6
L Subgenual Cingulate	47	0.035	BA25	3.32	-1	12	-4
L Parahippocampal gyrus	41	0.005	BA30	4.0	-14	-41	6
L Lingual gyrus	145	0.017	BA17	3.95	-14	-95	-7
R IOG	171	0.007	BA17	3.78	23	-91	-6
<b>(B) Punishment vs. Reward</b>							
R Lateral OFC	113	< 0.001	BA 47	4.16	40	21	0
	42	0.004		3.3	47	17	2
R SFC	13	0.024	BA 8	3.37	19	46	38
L STG/MTG	1234	< 0.001	BA22	5.77	-55	-28	4
		< 0.001	BA21	5.02	-51	-22	0
R STG/MTG	1203	< 0.001	BA22	5.1	53	-34	6
		< 0.001	BA22	5.0	47	-21	5

Voxels significant at  $p < 0.05$  after correction are reported. \* Significant corrected  $p$  values shown after SVC. Coordinates are presented in Talairach space. L=left; R = right.

#### 4.4.2. The main effect of reinforcer types irrespective of valence

Regions of the reward network that showed significantly greater activation to social reinforcers than to monetary reinforcers (Figure 4.2), were the left lateral OFC (BA 47), bilateral medial OFC (BA 11, 10), bilateral caudate and right medial PFC (BA 9) (significant at a corrected level of  $p < 0.05$ ; Table 4.2). Additionally, greater activation was present to social reinforcer than monetary in the left amygdala and right lateral fusiform gyrus (BA 37; fusiform face area), at the uncorrected threshold of  $p < 0.001$ . The amygdala activation was significant at a corrected level after SVC (Table 4.2).

The inverse contrast of monetary reinforcers contrasted with social (Table 4.2), revealed greater right DLPFC (BA 9) at a threshold of  $p < 0.05$  corrected. The only other region of activation which encompassed my ROIs was in the left frontopolar area (BA 10), although this activation was present at the uncorrected threshold of  $p < 0.001$ .



**Figure 4.2: BOLD activations for the main effects contrast of reward type.** Axial slices showing greater BOLD activation to social than monetary reinforcers, in the left amygdala, lateral OFC (BA47) and bilateral medial OFC (BA11) and bilateral caudate. Activations were overlaid on a canonical high-resolution structural image in MNI space (MRICRON, <http://www.sph.sc.edu/comd/rorden/mricron>).

#### 4.4.3. Interaction contrast

A 'valance x reinforcer type' interaction was performed, to test for regions that may integrate both types of reward information. It took as evidence for an area of integration, where activity was present in a region for the interaction contrast, but where there was no main effect for either factor (reward type or valance) (Gray et al., 2002). The interaction contrast [(monetary reward vs. monetary punishment) vs. (social reward vs. social punishment)], showed just such a pattern in the right lateral OFC (BA 11; Table 4.2). Here the results observed that neural activity was greatest in the SP and MR conditions and lowest in the SR and MP conditions (Figure 4.3). No main effect was found for either factor; i.e. there was no activation found in the right lateral OFC (BA 11) in the contrast of all social vs. all monetary reinforcement, nor in the contrast of all rewards vs. all punishments. Therefore, this region may contribute to the integration of both functions. The same interaction contrast [(monetary; reward vs. punishment) vs. (social; reward vs. punishment)] also revealed significant activation in striatal regions including the right NACS, caudate and bilateral putamen. However, when it plotted the parameter estimates for each individual condition, at the peak voxel for each of the striatal clusters, the activation pattern did not show a true crossover interaction (Figure 4.3). Rather activation was significantly lower for MP than MR, while activation associated with SR and SP was almost equal across all the striatal clusters. It also performed the inverse contrast [(social; reward vs. punishment) vs. (monetary; reward vs. punishment)], but did not find any significant activation in the ROIs.



**Figure 4.3: BOLD activations present in the reward network in the interaction contrast.** Axial slices showing increased BOLD activation to the interaction of reward type and valence [(monetary reward vs. monetary punishment) vs. (social reward vs. social punishment)] in the OFC and striatum. The bar plots shows the strength of activation (beta values) for each individual condition for the crossover interaction at the right OFC (26, 37, -5) and the interaction in the right nucleus accumbens (14, 7, -10), caudate (12, 15, -6) and putamen (20, 11, -7). Activations were overlaid on a canonical high-resolution structural image in MNI space (MRICRON, <http://www.sph.sc.edu/comd/rorden/mricron>).

<b>Table 4.2. BOLD activation associated with the main effects contrast of reward type irrespective of valence</b>							
Region	Voxels	P-corrected	Brodmann's Area	Z score	X	Y	Z
<b>(A) Social vs. Monetary Reward</b>							
L Amygdala	9	0.041*	BA28	3.45	-16	-10	-11
L Caudate	14	0.040*		3.47	-16	9	10
R Caudate	24	0.034*		3.52	18	17	8
L Medial OFC	461	0	BA11	5.09	-3	39	-10
R Medial FC		0	BA10	3.68	3	48	14
R Medial FC		0	BA9	4.25	1	50	36
L Lateral OFC	223	0.001	BA47	4.15	-38	22	-10
L Lateral PFC		0.001	BA46	3.4	-47	32	10
R STG	3240	0	BA22	6.11	51	-34	6
L STG	3442	0	BA22	5.03	-60	-26	6
R Cuneus	558	0	BA18	4.93	6	-81	26
L Cuneus	558	0	BA18	4.7	-11	-75	20
R Fusiform gyrus	63	0.004	BA37	3.83	38	-45	-16
<b>(B) Monetary vs. Social Reward</b>							
L Frontopolar Gyrus	19	0.962	BA10	4.03	-23	58	10
R Lateral PFC	193	0.003	BA8	3.95	49	19	41
L Lingual Gyrus	7716	< 0.001	BA18	6.2	-11	-98	-7
R Lingual Gyrus	7716	< 0.001	BA18	6.02	8	-78	-8
R MOG/Cuneus	7716	< 0.001	BA17	5.54	24	-84	13
R Fusiform Gyrus	56	0.029	BA37	3.86	49	-53	-11
L Fusiform Gyrus	50	0.026	BA37	3.67	-48	-54	-10
R IPL	302	< 0.001	BA40	4.56	39	-50	49
L IPL	253	< 0.001	BA40	3.19	-39	-49	49
<b>(C) Interaction Contrast (Monetary reward vs. punishment) vs. (social reward vs. punishment)</b>							
R OFC	9	0.025*	BA11	3.33	26	37	-5
R NACS	202	< 0.001		4.85	14	7	-10
L NACS	116	< 0.001		4.12	-18	7	-10
R Putamen	167	< 0.001		4.28	20	11	-7
R Caudate	98	< 0.001		3.67	12	15	-6
R Putamen	22	< 0.001		3.79	28	-12	8

Voxels significant at  $p < 0.05$  after correction are reported. \* Significant corrected  $p$  values shown after SVC. Coordinates are presented in Talairach space. L=left; R = right.

#### 4.4.4. Activations in other brain regions

In addition, this study tested for areas showing significant effects in the group analyses, in areas outside the brain reward network. As the study did not have any a-priori hypothesis about these areas, it does not make any inferences about them but merely report them for completeness (Table 4.1 and Table 4.2).

The contrast of valence i.e. both punishments versus both rewards revealed significant temporal (BA22/21; STG/MTG) and right superior frontal cortex (BA 8; SFC) activation. In

the reverse contrast of both rewards versus punishments, the results found a number of clusters of activation in the left lingual gyrus and right inferior occipital gyrus (BA17; IOG), as well as left subgenual cingulate (BA25).

Additionally, this study found increased activation in the bilateral superior temporal gyrus (BA 22), right fusiform gyrus (BA 37) and bilateral occipital gyrus (cuneus; BA 18) to social vs. monetary reinforcers. The results also found increased bilateral occipital gyrus (lingual gyrus; BA 18, 19) and bilateral inferior parietal lobe (BA 40) activation to monetary reinforcers compared to social.

#### **4.4.5. Pairwise contrasts within the reinforcer type and valence**

The current study additionally examined the pairwise contrasts within each of the statistical factors (reinforcer type and valence). As each factor had two levels, it contrasted positive versus negative valence within each reward type and contrasted social versus monetary type within each polarity of valence. For example, it contrasted SR versus MR within the reward polarity as well as contrasted SP versus MP within the punishment polarity. Also, it contrasted SR versus SP within the social reinforcer type as well as contrasted MR versus MP within the monetary reinforcer type. The results corresponded well with the findings of the main effects contrasts of both reinforcer type and valence. However, no additional knowledge was gained on the differences in encoding varying types and valence of reward within reward processing regions. Thus, the results of pairwise contrasts did not report for the current study.

#### **4.5. Discussion**

The current fMRI study (study-1) used a simple target detection task to investigate whether the receipt of social and monetary reinforcers are mediated by different neural substrates within the brain reward network. The target detection task was designed to narrow down cognitive functions that may underlie signalling for perceived reinforcement and to exclude complex decision making and reversal-learning components, which are the most common task components used in reward processing studies. One of the main findings was that social and monetary reinforcers are indeed processed differently in the brain reward network, as the study found greater medial PFC (BA9), medial and lateral OFC (BA10, 11, 47) and amygdala activation to social reinforcers, whereas greater DLPFC (BA9) and frontopolar (BA10) activation to monetary reinforcers. However, the current findings also reveal the lateral part of the OFC (BA 11) has a role in integrating

information about both reward type and valence, which supports the view the OFC is a site of integration for different segments of reward information which may relate to coding the salience of a particular stimulus, thus could compare different possible outcomes' values in the context of a common valuation scale (Montague and Berns, 2002).

#### **4.5.1. Activations in the Brain Reward Network to Reinforcer Valence**

The current finding of a medial-lateral functional dissociation between reward and punishment within the OFC, where the left medial OFC (BA10/11) responded more to reward, while the right lateral OFC (BA47) responded more to punishment, is supported by many previous neuroimaging studies (O'Doherty et al., 2001; Small et al., 2001; Ursu and Carter, 2005). However, some past studies, have not observed this medial-lateral functional distinction (Elliott et al., 2003; Breiter et al., 2001). One explanation for this inconsistency is attributed to the fact that some studies employed complex tasks such as gambling tasks, involving a number of distinct cognitive processes besides coding reinforcer value, such as reward anticipation, and decision making which may have contributed to the inconsistency between studies (O'Doherty, 2007; Kim et al., 2010). The finding, therefore, adds weight to the view of a medial-lateral functional dissociation between the coding of receipt of reward and punishment within the OFC (O'Doherty, 2007; Kim et al. 2006).

Additionally, the study found greater dorsal striatal activation for rewards than punishment, as greater caudate activation was observed in both reward types contrasted with punishment. The dorsal striatum (caudate and putamen) has been demonstrated to act as an integral part of a neural circuit which contributes to different aspects of motivational and learning processes that support goal-directed action (Brovelli et al., 2011). For example, many previous fMRI studies have revealed increased dorsal striatal activation during the anticipation of rewards (O'Doherty et al., 2002; Knutson et al., 2001), the processing of salient stimuli (Lauwereyns et al., 2002), and during reward expectation and delivery (Delgado et al., 2000; 2003; Elliott et al., 2003; 2004; Berns, McClure et al., 2001; Knutson et al., 2001). The current results of greater BOLD activation in the caudate to rewards minus punishments may be explained by the caudate function in action-reward learning (O'Doherty et al., 2004; Tricomi et al., 2004). This learning is needed to maintain the information of rewarding outcomes of actions, thus enabling better ones to be chosen more frequently (O'Doherty et al., 2004). Such learning processes could be mediated by afferent dopamine input, so that actions associated with better outcomes (such as greater predicted reward) in a given context, are learned and become reinforced and are thus more likely to be selected in future (Montague et al., 1996). O'Doherty et al (2004) referred

to the dorsal striatum as an “actor” that acts to maintain favorable rewards whereas the ventral striatum is a “critic” which only plays a role in passive forms of learning of stimulus-reward associations, which learns to predict future rewards (O’Doherty et al. 2004), and is directly related to signal errors in the prediction of rewards and also to the anticipation of rewards (Montague et al. 1996; Schultz et al. 1998; Berns et al. 2001; Pagnoni et al. 2002; McClure, et al. 2003; O’Doherty et al. 2003; McClure et al., 2004).

#### **4.5.2. Activations in the Brain Reward Network to Reinforcer Type**

The finding of distinct BOLD activation in the medial and lateral OFC (BA10, 11, 47), PFC (BA9) and amygdala between the two types of reinforcers (social and monetary), suggests that different rewards may be represented and valued in a distinct manner in the brain (Kringelbach and Rolls, 2004; Kim et al., 2010). This process of encoding divergent reward types is necessary, as depending on the immediate physiological needs of an animal and their current motivational state, a distinct representation of the value of each reinforcer type must be represented in the brain (Kim et al., 2010).

The greater medial PFC (BA9) activation observed to social reinforcers compared to monetary, is consistent with Izuma et al (2008) study which also reported greater medial PFC activation to social reinforcers compared to financial. This finding supports theories that the medial PFC plays a specific role in human social interactions (Adolphs, 2010), as the region is associated with making inferences about the content of others’ minds (Amodio and Frith, 2006; Saxe et al., 2004). Making inferences about others minds is necessary for most social exchanges, as the representation of reward values associated with a particular outcome may be dependent on the behaviour of other individuals.

The OFC and especially the medial sector of the OFC are also frequently associated with social interactions. However, the current finding of greater activation in the left medial and lateral OFC (BA10, 11, 47) observed to social reinforcers may not be due to social cognition per se, but more likely, be attributable to its other established function – modulation of the affective evaluative processes due to the intrinsically rewarding/aversive nature of the perceived reinforcers. (McClure and Montague, 2004).

Differences in activation between social and financial reinforcement in the medial PFC and OFC may have important clinical implications for many psychiatric illnesses, especially for patients with dysfunctional emotional and social behaviour such as autism, social phobia, depression and anxiety (Britton, 2006). For instance, common symptoms of autism include a decreased motivation to attend to social stimuli (Hobson and Lee,

1998), reduced attention to the faces of others (Dawson et al., 1998; Osterling and Dawson, 1994; Hobson, 1986; Hobson et al., 1988a, b; Pierce et al., 2001), less cortical face specialisation (Grelotti, Gauthier, and Schultz, 2002; Pelphrey, Adolphs, and Morris, 2004) and reduced speech (Klin, 1991; Kuhl, Coffey-Corina, Padden, and Dawson, 2005; Pelphrey et al., 2004). The social motivation hypothesis of autism (Dawson et al. 1998; 2005) suggests a lack of social motivation is due to social stimuli having decreased reward value. On the other hand, patients with depression generally show a pervasive loss of motivation and pleasure, in all forms of reward, including a loss of interest in socialization, work, food, and sex (Drevets, 2001). Additionally, the depressed mood has been associated with specific abnormalities in the identification of facial expressions (Cooley and Nowicki, 1989; Wexler, Levenson, Warrenburg and Price, 1994), which is a basic process for social interaction (Darwin, 1872/1965). It is possible to expect that patients with autism or depression could have reduced medial PFC and OFC activation to social stimuli. Therefore, a better understanding of the neural basis of social reinforcement, and differences in activation between social rewards/punishments and other reinforcer types such as financial or primary reinforcers may have important implications for our understanding a wide range of clinical disorders with social-emotional deficits.

In agreement with the priori hypothesis, the BOLD signal in the amygdala was found to be significantly greater to social reinforcers than monetary. Although, the amygdala has been suggested to be a central component of the brain reward network (Baxter et al., 2002), and has been revealed to play a role in the consumption of a range of different reward types such as monetary rewards (Homer et al., 2003; Elliott et al., 2008; Small et al., 2001) and social rewards (Rademacher et al., 2010), it is not certain that the greater amygdala activation in the current study, was due to the affective value of social reinforcers. This is because the amygdala is also associated with facial processing (e.g. Whalen et al., 2001, Benussi et al., 2007, N'Diaye et al., 2009, Mattavelli et al., 2012), including both emotional faces (Adolphs, 2010) and neutral faces (Gothard et al 2007). Hence, the current finding may either be due to the stronger affective value of the social reward or punishment, or due to a general sensitivity of the amygdala to facial stimuli. The current study does not include a neutral face stimulus, which may be a limitation as it cannot be certain if the amygdala activation is due to the positive/negative emotion elicited by a social reward/punishment or just due to the face itself. A neutral face stimulus is included in my second fMRI study (see next chapter 5) in order to compare amygdala activation elicited by neutral and smiling faces (SR).

In addition, the study revealed greater bilateral caudate activation in response to social reinforcers compared with monetary. As already discussed in the above section, the dorsal

striatum may act as an “actor” to maintain favorable rewards (O’Doherty et al., 2004) and play a role in the processing of salience of reward and delivery of reward. The current result may be attributed to the stronger emotional intensity of social reinforcers (especially social punishments), given my post-scan informal questioning of the participants (see more details in the following section 4.5.3) that social punishment was claimed to be the most “don’t like” while “lose 20p” was reported to be “don’t mind”. Thus, social punishment could have stronger salience to participants, so that participants might work harder to respond faster to avoid social punishment.

Finally, the results also found the right DLPFC (BA9) was more sensitive to monetary reinforcers than social, as it found significantly greater right DLPFC (BA 9) activation to monetary reinforcers compared to social. This may indicate that participants were more motivated by monetary reinforcers. Longe et al (2009) have suggested that motivational context influences lateral PFC activity and that higher financial rewards in a rewarded memory task resulted in both better task performance and greater activation of the DLPFC than lower financial rewards (Longe et al., 2009). The post-scan informal interview results in the current study reported that slightly majority participants claimed they were more excited about monetary rewards than social, although the behavioural results did not reveal any RT differences between monetary and social cues.

#### **4.5.3. Interaction of reward type and valence in the OFC**

Although the current finding revealed a medial-lateral functional specialisation within the OFC when responding to rewards and punishments, it also expected to test the hypothesis of the conjoint function of the OFC that could integrate both reward type and valence information (Montague and Berns, 2002). Previous imaging studies have demonstrated that the OFC plays a role in processing different types of reward, including primary (Rolls, 2000; 2004), monetary and social (reviewed in O’Doherty et al., 2007) rewards, and also different valences (O’Doherty et al., 2007). However, there has been no direct evidence for interaction between these two functions within the OFC to date. The observation of an integration of the neural responses to both valence and type of reinforcer (crossover interaction) in the right lateral OFC (BA11), provides direct evidence for this hypothesis. The plots of the interaction (Figure 4.3) showed clearly that task-related brain activation was selectively influenced by affective value (emotion induced by valence), so that neural activity was greatest in the MR and SP conditions, whereas lowest in the SR and MP conditions. Furthermore, the main effects contrasts of both rewards versus punishments as well as social reinforcers versus monetary did not reveal any significant activation in the right lateral OFC, and thus the interaction meets the primary requirements

for a true crossover interaction. To sum up, the current results provide strong evidence that the right lateral OFC is involved in the convergence and merging of the valuation of different types of rewards and punishments into a common valuation scale as hypothesised by Montague and Berns (2002), which enables the goal-directed control of behaviour to depend on the current environment and/or emotional context. This common currency function of the OFC and the functional specialization findings within the OFC, need not be mutually exclusive. For instance, as Elliott et al (2008) suggested, different types of reward could be valued separately, and a common valuation scale may pool these independent valuations together with motivational state information, to influence decision making.

Besides the OFC, the current results of the interaction contrast of [(monetary; reward vs. punishment) vs. (social; reward vs. punishment)] also revealed a significantly increased striatal activation (both dorsal and ventral striatum – caudate, putamen and NACs). However, when the beta values for the individual parameters were plotted for each region, a crossover pattern of activation was not revealed, and instead, it observed less activation in all three striatal areas to MP than to any of the other reinforcers – MR, SR and SP (figure 3). Past neuroimaging studies suggest the striatum and especially the dorsal striatum is part of brain reward circuitry which contributes to the control of motivated behaviour, where the striatum codes the valence of feedback and ranks it on the basis of preference or magnitude (Delgado et al., 2003). Furthermore, Zink et al (2004) demonstrate that the function of the striatum in reward processing is dependent on the saliency of a reinforcer, rather than pure hedonic value. The post-scan informal questioning of the study participants found that many (not all) claimed to not mind if they lost 20p during the monetary punishment, but stressed “really not liking” the social punishment. This may due to the fact that the social punishment, i.e. the experimenter’s angry face was the face of the experimenter that the participants knew who was in the control room watching their performance. Thus this punishment had more salience to them than the loss of a small amount of money. Participants also claimed to enjoy receiving both the financial and social rewards, but more participants claimed to feel excited about monetary reward than social reward. To sum up, this finding could be interpreted as that participant were less responsive to MP, or it seemed to be of less consequence to them than the other types of reinforcers, according to my participants’ reports and past research findings (Delgado et al., 2003, Zink et al., 2004).

In conclusion, the current study used vivid social reinforcer stimuli (experimenter’s face, voice, and gestures) that may have had more relevance to participants than previous studies that employed faces as social reinforcers, given the significant differences in the

reward network it observed between reinforcer types. As no other previous study has compared social and monetary reinforcers within a single task, the study provides direct evidence rather than assumptions on the existence of neural differences between these two types of the reinforcer. Finally, right lateral OFC was found to be involved in integrating the coding of different reward types and valence, which provides tangible support for the internal common currencies theory (Montague and Berns, 2002).

## Chapter 5 fMRI study-2

### 5.1. Introduction

In chapter 4 presented above (study-1), it compared social with monetary reinforcement and found that while both reinforcers elicited increased BOLD activation in some common brain regions, there was also evidence of stronger amygdala and OFC (lateral and medial) activation for social reinforcement than monetary. Notably, study-1 also found a crossover interaction between reinforcement valence and reward type in the right lateral OFC (BA 11), indicating that the OFC is involved in the functional integration of both reward type and valence, and hence may act as a type of common currency scale for comparing different reward types and values (Montague and Berns, 2002).

In chapter 5, it planned to carry out another fMRI study that was aimed to further compare and contrast the similarities and differences between social and monetary reward processing. The task paradigm was very similar to that used in study-1, but it employed neutral control stimuli – a social control stimulus (SC) and a monetary control stimulus (MC) instead of the previous punishment conditions (SP and MP). Study-2 was interested in further exploring amygdala activation to social reward by comparing a smiling face with a control face (neutral face). The rationale for the change in task parameters was because the amygdala has been suggested to respond to all faces including neutral faces (Gothard et al., 2007), therefore, it was uncertain if the stronger amygdala activation that had been elicited by social reward (smiling face) in the fMRI study-1 was due to the reward value (or positive emotion) elicited by the smiling face or just due to the face itself. Therefore, in this fMRI study-2, by adopting the neutral face and monetary control stimulus would answer this questions better. Besides, this study would also do an ROI analysis on amygdala with pairwise comparisons between SR and SC, SR and MR, as well as SR and MC, which would show a clearer picture of the amygdala activation in response to social reward compared to the monetary reward. Study-2 was hypothesized to find some differences between the two reward types, for example that social reward would elicit stronger BOLD activations in the amygdala and OFC (both lateral BA47 and medial BA11) than monetary reward. On the other hand, it was hypothesized in this study that both social and monetary rewards would elicit BOLD activations in the same regions of the common brain reward network (OFC, striatum), which are for the purposes of this experiment my ROIs.

The findings of the BOLD responses in the OFC, striatum, and amygdala in response to social and monetary rewards (in fMRI study-1), may not only be related to the relative reward value but also, be related to the hedonic experience of gaining such rewards. It

has been revealed that gaining favoured rewards (with higher relative reward value) may be binding with an increase in subjective pleasure (Kringelbach, 2005, Elliott et al., 2008). The reward stimuli used in the current study were expected to elicit feelings of pleasure and motivation (Treméau et al., 2009; Steenbergen, 2011). Therefore, it was of interest in this chapter to additionally explore the relationship between the neural encoding of rewards and the level of self-reported hedonic levels, as measured by the SHAPS (Snaith et al., 1995).

A better understanding of hedonic processing has been suggested to be helpful to develop effective treatments to deal with many emotional disorders, such as depression, eating disorders and obesity (Kringelbach, 2005; Kringelbach et al., 2003; Grabenhorst et al., 2010). These disorders are often present with pronounced anhedonia. The OFC has been revealed as the strongest candidate for relating different types of reward to hedonic experience (Kringelbach, 2005). Generally, several brain regions have been found to be related to the hedonic impact of rewards, such as OFC, insula, amygdala, nucleus accumbens, cingulate cortex, and brainstem ventral tegmental area (Kringelbach, 2005; Kringelbach and Berridge, 2009). To date, the subjective hedonic level has received little attention in studies of reward processing, and its relationship with brain activation in responses to rewards remain enigmatic.

The current study aimed to use the measure of hedonia/anhedonia as a factor in the fMRI regression analysis (see section 5.2), to see if the pleasure level an individual claimed they currently derived from pleasurable daily events (as measured by SHAPS) would be correlated with their BOLD activations to a specific reward stimulus. High levels of self-reported anticipated pleasure can enhance motivation and preparation for a future event (Treméau et al., 2009). Furthermore, previous fMRI studies that explored the relationship between subjective pleasantness ratings and brain activity in response to reward encoding have revealed that OFC (medial and lateral) activation is robustly correlated with a state of subjective pleasantness (positively or negatively) in response to specific reward information (Kringelbach et al., 2003; Grabenhorst et al., 2010). Small et al (2001) in a PET study, also found significant regional cerebral blood flow decreases in the bilateral medial OFC, caudate, putamen, insula and thalamus as the subjective pleasantness ratings to milk chocolate decreases.

Based on the findings of past imaging studies (O'Doherty et al., 2001; Small et al., 2001), including the findings from the fMRI study-1, that demonstrated a strong association between reward receipt and increased activation in the medial OFC, it expected those with high scores on the SHAPS (high SHAPS scores indicate a robust hedonic response to rewards) to have strong medial OFC activation to rewards (social and monetary

rewards). The current study also expected the SHAPS score to be correlated with striatal activation (mainly dorsal striatum) either positively or negatively, as dorsal striatum has been revealed to be related to reward anticipation, expectation and delivery (O'Doherty et al., 2002; Knutson et al., 2001; Delgado et al., 2003; Elliott et al., 2003; Berns et al., 2001; Knutson et al., 2001; Delgado et al., 2000).

## **5.2. Methods**

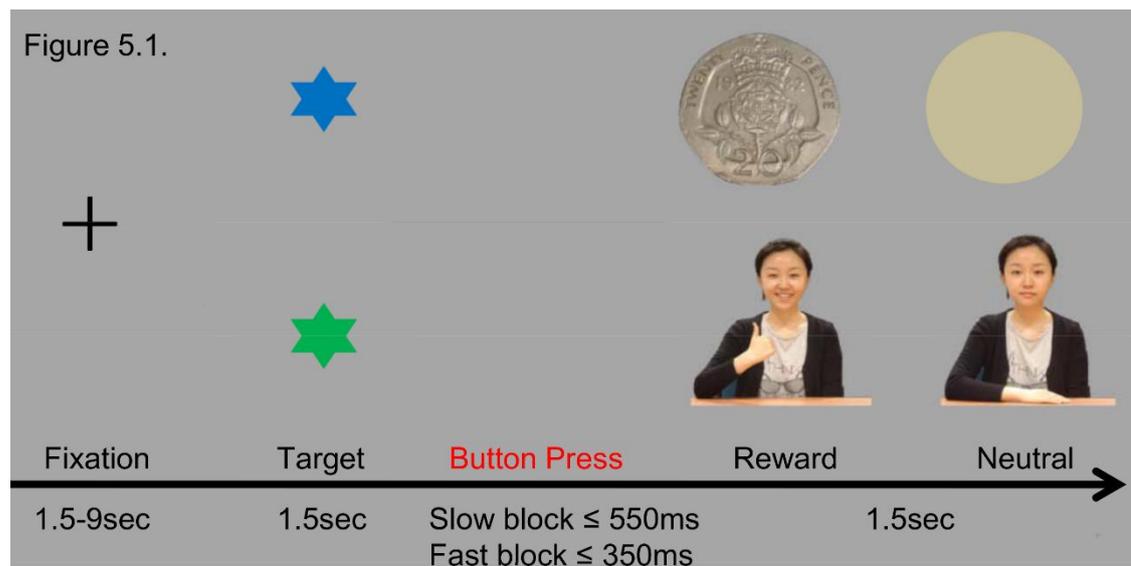
### **5.2.1. Participants**

15 staff and student volunteers (mean age = 21, SD  $\pm$  2.03; 4 male and 11 female) were recruited from Aston University. All participants gave informed consent, and all procedures were approved by Aston University Ethics Committee. A safety screening questionnaire was administered prior to scanning. All participants filled out the HADS (anxiety mean = 5; SD  $\pm$  3.01; depression mean = 3; SD  $\pm$  2.7; Zigmond et al., 1983), the BDI (mean = 6; SD  $\pm$  0.8; Beck, 1978) and the SHAPS scale (mean = 41; SD  $\pm$  7.07; Snaith et al., 1995) on the date of the functional neuroimaging scan. No participants were found to have scores on either the BDI or HADS, which indicated a clinically abnormal mood (further details in Chapter 2). The SHAPS scores were used as regressors in a regression analysis, to examine the correlation between participants' current hedonic responsiveness to pleasurable stimuli and BOLD activity in response to rewards.

### **5.2.2. Stimuli and task**

In the fMRI task, it used the same target detection paradigm as the fMRI study presented in chapter 4. In each trial, participants first saw a fixation cross "+" in the middle of the screen (randomized inter-trial interval 1.5-9sec), followed by a star (presented for 1.5sec), which could be 1 of 5 possible colours, red, orange, purple, blue or green. The blue and green stars were targets that participants had to respond to, by pressing a button on a response box as fast as possible to get an associated reward, and ignore non-targets (purple, orange or red stars). Participants were informed that they would receive a reward if they responded fast enough to targets, otherwise they would receive a control feedback. The task consisted of 200 trials altogether (exactly the same as in chapter 4), which was comprised of randomized slow (response within 550ms) and fast (response within 350ms) trial types. Fast and slow blocks were utilized to force participants to keep their concentration on the task. The green star was associated with social reinforcements whereas the blue star was associated with monetary (Figure 5.1). After participants made

their response to a target, either a reward (monetary or social; see chapters 3 and 4 for details), or control feedback (monetary control; solid-filled circle, same dimensions as a 20p coin accompanied by a short metal sound or social control; experimenter's neutral face accompanied by their voice saying 'neutral') was presented. Rewards were presented for 1.5sec. Participants were told that any money they won in the task they could take home, up to a maximum of £10.00. The scan session ran for approximately 30 minutes.



**Figure 5.1: Task Presenting Sequence.** From left to the right: the fixation cross, followed by a target/non-target. Participants made a button press response here which was followed by the reinforcer feedback (reward or control). Photos on the bottom right: SR and SC. Photos on the upper right: MR and MC. The photos were taken on the same day and with the same background. The SC photo was the experimenter's neutral face presented simultaneously with the experimenter's voice saying 'neutral', whereas the SR photo was the experimenter's smiling face accompanied by her voice saying 'well done'. The MC photo was a solid-filled circle in a 20p coin size accompanied by a short metal sound whereas the MR photo was a 20p coin accompanied by the sound of a coin falling.

### 5.2.3. Image Analysis

All fMRI data were analyzed using SPM8 (Wellcome Institute of Neurology, implemented in Matlab; Mathworks, MA). 2 participants' data were removed due to technical problems with stimulus presentation and a further participants' data was rejected after pre-processing due to excessive motion ( $> 5\text{mm}$ ), and 1 participant was rejected due to a large artefact in the PFC. Statistical analysis was therefore performed on 11 participants.

Prior to model application, brain volumes from each participant were realigned to the first volume to correct for head motion. Functional images were then spatially normalized into a standard single subject T1 image template. Following this, spatial smoothing was applied with an isotropic Gaussian kernel filter of 10-mm FWHM to facilitate inter-subject averaging. For each participant, all experimental feedback categories were modelled as event types which were: SR, SC, MR, and MC. In addition, following the contrast analysis of the condition-specific experimental effects (reward events) that was obtained via GLM in a voxel-wise way for each subject, the SHAPS hedonic scores rated by subjects was additionally modelled as separate subject-specific regressors, which were entered as parametric modulators for the regressors of the reward events. A series of t-contrast images were carried out to determine whether the fitted parameters values at each voxel were significantly greater than zero for each participant. These were then entered into a random effects group analysis. The regression analysis of the BOLD response with given parameters of interest (i.e. hedonic scores and reward events) was performed at the second stage, after applying one sample t-tests to the first stage subject-specific parameter estimates by performing linear parametric modulation as implemented in SPM8.

It thresholded the activations at a voxel threshold of  $p < 0.001$ , uncorrected, and accepted as significant those clusters that survived at  $p < 0.05$ , corrected for multiple comparisons for the entire brain. For the regions of interest (ROI; OFC, amygdala, striatum), I reported activations that survive an uncorrected threshold of  $p < 0.001$  but were significant at  $p < 0.05$  when a small volume correction (SVC) was applied. The SVC applied to the OFC, striatum, amygdala, caudate and putamen were based on a sphere of 10mm radius and was based on the peak coordinates in these regions reported in past reward processing studies (see Table 5.1). As SPM coordinates are given in MNI space; regions were identified by converting the coordinates to Talairach space with a nonlinear transform (Brett et al. 2001).

Region	Coordinate	Study	Reward Function
OFC (BA11)	30, 32, -2	Spreckelmeyer et al., 2009	Anticipation of monetary reward
OFC (BA10)	-6, 36, -15	Lin et al., 2011	Overlapping activation for social and monetary reinforcers
Caudate	12, 9, 4	Robinson et al., 2010	Respond to unexpected reward and punishment
Caudate	-18, 18, 4	Redcay et al., 2010	A combination of reward and live social interaction
Putamen	-18, 4, 14	Grabenhorst et al., 2010	A common scale for subject pleasantness of different primary reward

Putamen	22, 16, -4	Izuma et al., 2008	Commonly activated to social and monetary rewards
Amygdala	-21, -6, -21	Britton et al., 2006	Negative emotions relative to neural conditions
Amygdala	20, -2, -18	Redcay et al., 2010	A combination of reward and live social interaction

### 5.3. Behavioural Results

Mean reaction times for each condition were analyzed in a 2x2 repeated measures ANOVA (reward type: social and monetary; and block type: fast and slow). There was no significant difference between the social and monetary conditions in the slow block,  $F(1, 10) = 3.27$ ,  $p > 0.05$ . Also, there was no significant differences between the monetary and social conditions in the fast block,  $F(1, 10) = 2.1$ ,  $p > 0.05$ .

The mean percentage hit rates on the task were also calculated for both social cue targets (green stars) and monetary (blue stars). These were similar for both targets, as mean hits for social targets were 67.3% and for monetary 70.2%. A repeated measures ANOVA showed that there was no significant difference in the number of social and monetary rewards received across reinforcer types,  $F(1, 10) = 3.14$ ,  $p > 0.05$ . The total number of social cue targets were the same as monetary cue targets, which means the percentage of missed targets for both cues was also very close (32.7% social; 29.8% monetary). In other words, there was no significant effect associated with cue type.

Another repeated ANOVA test with hit and false alarms, and fast and slow block type was used to examine if the fast and slow blocks would affect participants' reaction time in general. Results showed that no significant difference was found between the fast false and slow false trials,  $F(1, 10) = 6.07$ ,  $p > 0.05$ , or between a fast hit and slow hit trials,  $F(1, 10) = 2.32$ ,  $p > 0.05$ .

### 5.4. Imaging results

The results of the subtractive contrasts (contrast analysis) are outlined first for the main effects of reward type and valence, and the contrast between SR versus MR, followed by an interaction contrast and then the regression analyses.

#### 5.4.1 Main effects of valence

The contrast of all rewards versus all control stimuli (Table 5.2) revealed significant BOLD responses in the striatum (right caudate, left putamen) and right-sided OFC/VMPFC; specifically right medial OFC (BA10 extending to dorsal anterior cingulate (BA32), right subgenual cingulate (BA25). The results also observed activations in the right STG (BA42) and left middle temporal gyrus (MTG; BA21).

The reverse contrast revealed greater BOLD activation for all control stimuli than for rewards, in the right frontopolar OFC (BA10) and right anterior insula (BA13).

#### 5.4.2 Main effects of reward type

The contrast of all monetary stimuli (reward and control) versus all social (reward and control) revealed significant BOLD responses in the right lateral OFC (BA10), bilateral IPL (BA40) and left lateral parahippocampal gyrus (BA19; Table 5.2).

The reverse contrast of all social compared to monetary (Figure 5.2) stimuli showed greater BOLD activation for social reinforcement in several regions of the reward network – lateral OFC (BA47; bilaterally), left medial OFC (BA11), and bilateral amygdala (Table 5.2). Additionally, greater right anterior (BA13), left mid-insula (BA13) and lateral PFC (BA9; BA45) was observed to social reinforcers. Finally, significantly greater clusters of activation were observed to social reinforcers than monetary in temporal, parietal and occipital gyrus locations (Table 5.2). These clusters were (Table 5.2) bilateral MTG/IOG (BA37/BA19), bilateral STG (BA22), left lateral STG (BA38) and bilateral fusiform gyrus (BA37).



**Figure 5.2: BOLD activations for the main effects contrast of reward type.** Axial slices

showing greater BOLD activation to social than monetary reinforcers, in the right amygdala, left and right lateral OFC (BA47) and left medial OFC (BA11). Activations were overlaid on a canonical high-resolution structural image in MNI space (MRICRON, <http://www.sph.sc.edu/comd/rorden/mricron>).

#### **5.4.3 ROI analysis on Amygdala**

Significant bilateral amygdala activation was found in the contrast of all social reinforcement (reward and control) versus all monetary reinforcement. However, the simple pair-wise comparison of SR vs. MR did not reveal amygdala activation. It therefore, performed an ROI analysis using a mask for the right and left amygdala on the simple pair-wise comparisons of SR vs. MR and SR vs. SN. The contrast of SR vs. MR revealed significant right-sided amygdala activation (21, -8, -9) and the contrast of SR vs. SN also demonstrated greater right amygdala activation (31, -8, -14).

#### **5.4.4 Interaction of reward type and 'valence'**

The interaction contrast [(SR vs. SC) vs. (MR vs. MC)] showed that SR compared to SC elicited greater BOLD responses in the left mid-insula (BA13) as well as right anterior insula (BA13), than MR compared to MC. The reverse interaction contrast of [(MR vs. MC) vs. (SR vs. SC)] revealed that MR compared to MC elicits greater BOLD responses in the left lateral OFC (BA47) than SR versus SC (Figure 5.3).



**Figure 5.3: BOLD activations present in the reward network in the interaction contrast.** Axial slices showing increased BOLD activation to the interaction of reward type and valence [(MR vs. MC) vs. (SR vs. SC)] in the OFC, and to the interaction of [(SR vs. SC) vs. (MR vs. MC)] in the insula. The bar plots shows the strength of activation (beta values) for each individual condition for the crossover interaction at the right OFC (-34, 33, -6), left insula (-42, 0, -11) and right insula (32, 18, 8). Activations were overlaid on a canonical high-resolution structural image in MNI space (MRICRON, <http://www.sph.sc.edu/comd/rorden/mricron>).

#### 5.4.5 Pairwise contrasts within the reinforcer type and valence

Similar to my fMRI study-1, the current study showed that the results of the pairwise contrasts (SR versus MR; SR versus SP; MR versus MP) were found to compliment the findings of the main effects contrasts of both reinforcer type and valence, however no significant additional information was provided from what the main effects findings already

showed in terms of neural activation differences in response to different types and valence of reward. Thus, the current section did not report the pairwise contrasts results for the current study.

<b>Table 5.2. BOLD activation associated with the main effects contrasts of reward type and valence.</b>							
Region	Brodmann's Area	Voxels	P corrected	Z score	X	Y	Z
<b>Monetary vs. Social</b>							
R Frontopolar Gyrus	BA10	12	0.040	3.5	42	44	10
R IPL	BA40	75	< 0.001	4.15	34	-45	40
L IPL	BA40	12	0.042	3.41	-37	-48	39
L Parahippocampal Gyrus	BA19	17	0.037	3.59	-31	-50	1
<b>Social vs. Monetary</b>							
L OFC	BA 47	1141	< 0.001	6.85	-27	15	-11
L OFC	BA 47	117	< 0.001	4.41	-36	28	-6
L OFC	BA 11	9	0.042*	3.25	-1	37	-12
R OFC	BA47	2057	< 0.001	4.83	40	13	-12
L Insula	BA13	1141	< 0.001	4.56	-43	2	-11
R Insula	BA13	52	< 0.001	4.27	42	26	4
R Amygdala		74	0.021*	3.77	23	-3	-19
R Amygdala		74	0.009*	5.49	18	-8	-14
L MTG	BA19	620	< 0.001	4.41	-46	-63	12
R MTG	BA37	2057	< 0.001	8.9	45	-64	6
L Fusiform Gyrus	BA37	160	< 0.001	4.38	-36	-47	-15
R Fusiform Gyrus	BA37	12	0.041	3.39	38	-60	-13
R STG	BA22	2056	< 0.001	7.61	58	-34	7
L STG	BA38	1141	< 0.001	8.69	-38	10	-21
<b>(C) Rewards vs. Control stimuli</b>							
R Caudate		23	0.032*	3.64	8	14	-1
R Caudate		22	0.041*	3.56	14	22	16
L Putamen		46	0.029*	3.62	-29	-13	6
R OFC/Anterior Cingulate	BA10/32	29	0.041	3.47	2	46	-8
R Anterior Cingulate	BA25	572	< 0.001	4.36	1	20	-8
R STG	BA42	7	0.047	3.38	64	-23	12
L MTG	BA21	7	0.045	3.3	-58	-14	-7
<b>(D) Controls stimuli vs. Rewards</b>							
R Frontopolar Gyrus	BA 10	61	0.027	4.11	34	52	18
R Insula	BA13	18	0.039	3.48	31	23	0
<b>(E) Interaction contrast (social reward vs. control) vs. (monetary reward vs. control)</b>							
L Insula	BA 13	15	0.034	4.06	-42	0	-11
R Insula		19	0.042	3.47	32	18	8
<b>(F) Interaction contrast (monetary reward vs. control) vs. (social reward vs. control)</b>							
L OFC	BA 47	14	0.022*	3.96	-34	33	-6

Voxels significant at  $p < 0.05$  after correction are reported. \* Significant corrected  $p$  values shown after SVC. Coordinates are presented in Talairach space. L=left; R = right.

#### **5.4.6. Correlation between SHAPS and brain activity in response to MR**

##### **5.4.6.1. Positive Correlation**

The regression analyses showed a positive association between the SHAPS pleasure score and extensive OFC activation (right lateral and medial OFC; BA47, BA10 and left medial; BA11), right frontopolar gyrus (BA10), and also left hippocampus activation (Table 5.3; Figure 5.4).

##### **5.4.6.2. Negative Correlation**

A negative correlation was also found between the SHAPS pleasure score and increased bilateral posterior insula (BA13) and left anterior insula (BA13) activation. Also, a negative correlation was found between SHAPS pleasure score and increased bilateral putamen, left subthalamic nucleus and subgenual cingulate (BA25) activation in response to MR (Table 5.3; Figure 5.5).

#### **5.4.7. Correlation between SHAPS and brain activity in response to SR**

##### **5.4.7.1. Positive Correlation**

The regression analyses in the context of SR revealed a positive association between the SHAPS pleasure score and increased caudate (bilateral) activation. Also, a positive correlation was found between SHAPS pleasure score and increased right dorsolateral PFC (BA46; extending to right lateral OFC BA47), and increased right medial OFC (BA10) and frontopolar gyrus (BA10) activation when participants were in receipt of SR (Table 5.3; Figure 5.4).

##### **5.4.7.2. Negative Correlation**

A negative correlation was found between SHAPS pleasure score and increased bilateral anterior insula (BA13) and left posterior insula (BA13) activation in response to SR. Finally, a negative correlation was observed between SHAPS pleasure score and increased putamen (bilateral) and subthalamic nucleus activation, in addition to the right subgenual cingulate (BA25) activation (Table 5.3; Figure 5.5).



**Figure 5.4: Positive regression between BOLD activations in the OFC and SHAPS hedonic score in response to each type of rewards.** Axial slices are showing increased BOLD activation to social (orange) and monetary (green) reinforcers, in the left and right OFC (BA47; BA11; BA10). Activations were overlaid on a canonical high-resolution structural image in MNI space (MRICRON, <http://www.sph.sc.edu/comd/rorden/mricron>).



**Figure 5.5: Negative regression between BOLD activations in the insula and SHAPS hedonic score in response to each type of rewards.** Axial slices showing increased BOLD activation to social (red) and monetary (blue) reinforcers, in the left and right insula. Activations were overlaid on a canonical high-resolution structural image in MNI space (MRICRON, <http://www.sph.sc.edu/comd/rorden/mricron>).

<b>Table 5.3. Bold activation associated with regression of SHAPS score.</b>							
Region	Brodmann's Area	Voxels	P corrected	Z Score	X	Y	Z
<b>Positive Regression in response to MR</b>							
R OFC	BA47	34	< 0.001	4.19	44	21	-4
	BA10	29	0.038	3.75	14	37	-8
L OFC	BA11	9	0.026*	3.76	-21	42	-5
Hippocampus		11	0.047	3.29	-31	-23	-7
<b>Negative Regression in response to MR</b>							
L Insula	BA13	428	< 0.001	5.5	-38	11	14
	BA13	340	< 0.001	5.02	-38	-33	20
R Insula	BA13	822	< 0.001	4.67	38	-34	22
L Subthalamic Nucleus		359	< 0.001	4.89	-7	-12	-4
L Putamen		34	0.042	3.92	-18	1	-1
R Putamen		35	0.044	3.84	18	-2	3
L Subgenual cortex	BA25	21	0.021	4.35	-8	16	-9
<b>Positive Regression in response to SR</b>							
R OFC	BA10	13	0.044	3.51	18	35	-8
	BA10	11	0.017*	3.34	42	50	10
R OFC	BA46/47	45	0.039	3.52	44	42	-4
R Caudate		24	0.014*	4.07	21	-31	18
L Caudate		57	0.009*	4.12	-20	10	18
<b>Negative Regression in response to SR</b>							
L Insula	BA13	261	< 0.001	4.56	-35	-33	19
	BA13	19	0.040*	3.67	-38	5	10
R Insula	BA13	29	0.033*	3.89	32	20	12
L Subthalamic Nucleus		248	< 0.001	4.17	-7	-14	-3
L Putamen		26	0.031*	3.83	-16	0	2
R Putamen		15	0.039*	3.56	14	-2	1
L Subgenual cortex	BA25	10	0.042	3.57	1	9	-9

Voxels significant at  $p < 0.05$  after correction are reported. \* Significant corrected  $p$  values shown after SVC. Coordinates are presented in Talairach space. L=left; R = right.

## 5.5 Discussion

The fMRI study (study-2) presented in this chapter, compared and contrasted social and monetary reinforcer processing – i.e. reward valuation when perceived. The task paradigm was very similar to study-1 (chapter 4), in that participants were rewarded for their speed of response to targets, with social and monetary rewards, but instead of using punishments, the task utilised neutral control stimuli as reinforcers.

To summarise the results, the main effects contrasts revealed many consistent findings with study-1, in that a similar pattern of neural activation was observed to both the contrasts of reward type and the contrast of valence. However, the interaction contrast did not reveal the same crossover interaction in the OFC between reward type and valence observed in study-1. Lastly, the regression analysis findings strengthen the importance of

the role of the OFC in reward processing, with a strong positive association observed between OFC activation and increasing SHAPS scores in the context of both MR and SR. These regression analyses, together with the main effects results are discussed in detail below.

### **5.5.1. Main effects contrast of reward type**

Consistent with the hypothesis, the current results revealed that some regions of the brain reward network are more sensitive to social than monetary reinforcers, with greater activation found in the lateral OFC (BA 47), medial OFC (BA 11) and amygdala to social reinforcers. The medial PFC and medial portion of the OFC have frequently been associated with human social interactions (Adolph, 2010). Moreover, Izuma et al's (2008) fMRI study of reward processing found greater medial PFC activation to social reinforcers than monetary. However, as discussed in chapter 4, the greater activation of the medial and lateral OFC observed to social reinforcers in my studies, may not necessarily be attributable to social cognition. Rather, in accordance with theories of the OFC's role in reward processing (O'Doherty, 2007), the OFC activation observed in the current study is most likely a result of the modulation of affective evaluative processes, due to the intrinsically rewarding/aversive value of the social stimuli.

A further finding of differences in functional activation between reward types was found in the amygdala, with greater right amygdala activation to social reinforcers (reward and control) than monetary. Additionally, it carried out an ROI analysis on the amygdala, which also revealed significantly greater right amygdala activation in the contrast of SR vs. MR and SR vs. SC. Thus, consistent with study-1, social reward elicited greater amygdala activation, suggesting SR has a stronger affective intensity than the other reinforcer types. This result also supports the view amygdala activation is closely related to how arousing (reinforcer intensity) stimuli are (Sanghera, 1979; Hommer et al. 2003; Small et al. 2001; reviewed in McClure et al., 2004; Wilson and Rolls, 2005). Furthermore, the greater right amygdala activation observed to SR than SC, supports the many studies suggesting that the amygdala is more responsive to an emotional face (Adolphs, 2010) than a neutral face. This is important, as it aimed for SR to have a stronger affective intensity than SC in the current task paradigm.

## **5.5.2. Main effects contrast of valence**

### **5.5.2.1. Medial-lateral functional specialization in OFC to valence processing**

Coherent with theories of a medial/lateral functional dissociation in the OFC in relation to reward processing, this study revealed rewards elicited greater medial OFC (BA10) activation than control stimuli while control stimuli elicited greater right lateral frontopolar gyrus (BA10) activation. This results could suggest that the control stimuli (not receiving rewards) were having some punishing effects. This result adds weight to the view the medial-lateral functional dissociation within the OFC to reward valence, is especially apparent in imaging studies examining neural activation purely to the receipt of reinforcers (O'Doherty, 2007; Kim et al. 2006).

### **5.5.2.2. Subgenual cingulate activation to rewards**

Furthermore, the results showed that rewards elicited greater subgenual cingulate cortex (BA25) activation than control stimuli. The subgenual area (BA25) lies in the ventral and posterior part of the vmPFC, and the finding is in line with data from single-cell recording studies in primates. For instance, one single-cell neuron study in monkeys revealed that neurons in the ventral portion of the vmPFC were persistently more active to appetitive reward conditions, whereas neurons in a more dorsal section were persistently active in the aversive punishment conditions (Monosov and Hikosaka, 2012). Moreover, Smith et al (2010) in an fMRI study revealed that the more posterior region of the vmPFC (which is where the subgenual cingulate lies) encodes the relative decision value between different reward categories (attractive faces versus money), and is associated with the combined representation of expected value and reward magnitude (Smith et al., 2010; Rolls et al., 2008). In addition, Katharina et al (2011) have suggested that vmPFC BOLD activation is associated with the consumption of reliably predictable rewards and facilitates long-term memory formation. Therefore, the current result of increased subgenual cingulate activation may be related to the vmPFC role in encoding the expected reward value, remembering the reward and comparing the received reward value with previous rewards (encoding relative value).

### **5.5.2.3. Dorsal striatum activation to rewards**

A clear difference between reward and control stimuli was also evident in the striatum, with significantly greater BOLD activation in the left putamen and right caudate (dorsal

striatum) to rewards compared with control stimuli. The caudate and putamen works as an integral part of the neural circuitry involved in different aspects of motivational and learning processes, that support goal-directed action (Brovelli et al., 2011). For instance, the dorsal striatum responds to reward anticipation (O'Doherty et al., 2002; Knutson et al., 2001), to salient stimuli (Lauwereyns et al., 2002), and to reward expectation and delivery (Delgado, Locke, Stenger, and Fiez, 2003; Elliott et al., 2003; Berns, McClure et al., 2001; Knutson et al., 2001; Delgado et al., 2000). The current results may be attributable to its function in action-reward learning (O'Doherty et al., 2004; Tricomi et al., 2004), during which the dorsal striatum act to maintain information about the rewarding outcomes of actions to enable better outcomes or rewards to be chosen more frequently (O'Doherty et al., 2004). Montague et al (1996) suggested that such learning could be mediated by afferent dopamine input so that actions associated with greater predicted rewards in a given context become reinforced and are thus more likely to be selected in future (Montague et al., 1996).

#### **5.5.2.4. Insula activation to control stimuli**

One finding that had not been hypothesized prior to this study, was of significantly increased right anterior insula activation to control stimuli compared to rewards. There was also evidence of greater left mid-insula (BA 13) and right anterior activation to social reinforcement than monetary. The insula, especially the anterior insula has been suggested to have an important role in the processing of a number of basic emotions and feelings, mostly negative feelings such as pain, disgust (Singer, 2006; Wicker et al., 2003), anger, fear, and evaluation of 'distressing cognitions' (Reiman et al., 1997). The anterior insula is also involved in the processing of many social experiences such as norm violations (Sanfey et al., 2003), social-emotional processing (Phan et al., 2002) and empathy (Singer, 2006). The current findings support the view the insula is involved in the processing of social cognitions and negative emotions and suggests the control stimuli in the current study were viewed by participants as having a negative valence. This would also fit with the finding discussed above of greater lateral OFC activation to control stimuli (section 5.5.2), and indicates that not receiving a reward, even if it is just a control stimulus may be experienced as a punishing event.

Alternatively, the finding of greater activation to control stimuli in the right anterior insula may be attributable to the "regulation" of salience when control stimuli are received (Eckert et al., 2009), as the right anterior insula has been revealed to play a role in the interaction between salience of the selective attention created to achieve a task and the salience of

arousal created to keep focused upon the relevant part of the environment (Eckert et al., 2009). During a challenging task, this regulation of salience might be involved where attention is waning and results in careless mistakes, but once there is too much arousal it may lead to risks creating a poor performance by becoming anxious (Eckert et al., 2009).

To expand this view further, it is reasonable to assume that the increased anterior insula activation to control stimuli could be associated with mistakes monitoring, as the control stimuli were only ever presented when participants erred. Errors resulted in participants' arousal. The concept of "error awareness" had been established as the ability to consciously perceive people's own mistakes or unwanted outcomes (Klein, Ullsperger, and Danielmeier, 2013; Wessel et al., 2012). The current finding could reflect that the right anterior insula activation increased when receiving and processing information on surprising and unexpected errors (Wessel et al., 2012), and even involved in the increased necessity of effort (Croxson et al., 2009; Prevost et al., 2010).

### **5.5.3. Interaction Contrast**

The interaction contrast [(SR vs. SC) vs. (MR vs. MC)] revealed significant BOLD activation in the left mid-insula (BA13) and right anterior insula (BA13). According to the plots of interaction (Figure 5.3), the task-related BOLD activation in the left mid-insula did not show a crossover interaction pattern, but appeared to be selectively influenced by affective value (emotion induced by valence) so that BOLD activity was greatest to SR within the 'social conditions', and was greatest to MC within the "monetary conditions". Also, the task-related BOLD activity in the right anterior insula did not show a crossover interaction pattern, and the activation here was driven by MC.

The reverse interaction contrast [(MR vs. MC) vs. (SR vs. SC)] revealed significant BOLD activation in the left lateral OFC. The plots of interaction (Figure 5.3) showed that task-related BOLD activity in this region was lowest to MC, but was similar across the other conditions. Obviously, the interaction plots did not show a crossover interaction pattern in the OFC, which may be due to the valence was not as polarised as in study-1. The current task paradigm was designed to exclude punishments (negative valence) and use neutral control stimuli in order to explore the hypothesis optimally (i.e. explore amygdala activation in response to a smiling face compared with a neutral face). BOLD responses to reward stimuli are influenced by the context in which outcomes are experienced (Tremblay and Schultz 1999; Akitsuki et al., 2003; Elliott et al., 2000; Nakahara et al., 2004; Nieuwenhuis et al., 2005; Elliott et al., 2008). Therefore, as the context of the presentation of rewards is different in study-2, it is reasonable to assume that the reward

value of the social and monetary stimuli is different from study-1. The context-dependent theory will be discussed in detail in chapter 6, in which my results provide further evidence to support this theory.

#### **5.5.4. Regression with SHAPS scores**

##### **5.5.4.1. Positive regression**

Of note, it found that high scores on the SHAPS were positively correlated with right medial and lateral OFC (BA47; BA10) and frontopolar gyrus activation in the context of rewards, regardless of reward type. Put simply, this means that the more pleasure a person claimed to obtain from everyday rewarding events (refer to it as a 'subjective enjoyment' state) the stronger the BOLD activation observed in the OFC to the consumption of social and monetary rewards.

Previous fMRI studies have investigated the relationship between subjective pleasantness ratings of reward stimuli made by participants, during task presentation and BOLD activity to rewards (e.g. Grabenhorst et al., 2010; Rolls et al. 2003; de Araujo et al. 2003; Kringelbach et al., 2003). For instance, Grabenhorst et al (2010) found BOLD activity in the ventral PFC (include the OFC BA47) positively correlated with the subjective pleasantness of two fundamentally different rewards, taste in the mouth or warmth on the hand. This suggests that the BOLD response in the OFC is robustly correlated with a state of subjective pleasantness, however whether this is positively or negatively depends on specific reward information (Kringelbach et al., 2003). The subjective pleasantness in these studies can be conceptualized as measuring a 'liking' state.

A 'liking' state is similar in some degree to the 'subjective enjoyment' described in the current study, whereby a higher SHAPS score meant participants might be more responsive to rewards during the task. The findings, therefore, suggest that how responsive an individual is to the experience of pleasure from rewards in their everyday lives, such as enjoying a favourite television programme or being with close friends, correlates well with increased OFC activation to rewards in the task. This is important as it implies that there is a direct correlation between an individual's current hedonic levels and activation in the OFC to rewarding stimuli, which could be useful in mood disorders such as depression where anhedonia is a common symptom. In other words, patients with mood disorders who were experiencing anhedonia might have decreased OFC activation to rewards in a reward related experimental task.

#### 5.5.4.2. Negative regression

On the other hand, the negative correlation between SHAPS scores and neural activation in the context of rewards, revealed activation in the insula (anterior and posterior), putamen, subgenual cingulate (BA25) and subthalamic nucleus, i.e. the lower the score on SHAPS or the less pleasure participants reported they derived from rewarding events the greater the activation in these areas.

The finding of a negative correlation between insula activation and reduced pleasure to rewarding events, is similar in some aspects to Kim et al (2010), who in an fMRI study, reported that right anterior insula activation was negatively correlated with an expected reward, that is, the less the magnitude of the expected reward, the greater the anterior insula activation. Kim et al (2010) interpreted their findings to suggest that the insula has a general role in indicating when a negative consequence is expected in relation to aversive outcomes. Indeed, the insula has previously been reported to respond to many different types of negative reinforcers, such as the receipt of monetary loss (O'Doherty, Critchley et al., 2003; Paulus and Stein 2006), during the anticipation and also receipt of painful stimuli (Seymour et al., 2004) and when risk aversive individuals made risky gambles (Huettel et al., 2006; Preuschoff et al., 2006). Additionally, the insula has been implicated in responding to disgusting odours (Wicker et al., 2003) and aversive tastes (Small et al., 1999) as well as in the evaluation of 'distressing cognitions' (Reiman et al., 1997).

The insula receives afferent information from sensory pathways via the thalamus and sends projections to the amygdala, ventral striatum, and OFC, and is well placed for combining information relating internal bodily states (such as pain, temperature, and arousal) into higher-order cognitive and emotional/affective processes (Craig, 2002; 2009). This region has been reviewed to be involved in all subjective feelings and contributes to salience, awareness, and consciousness (Craig, 2009).

The finding of a negative correlation between levels of hedonic experience and insula activation in response to reward in the current study extends previous findings. Rather than reporting that the insula is signalling a negative event, here it shows that the lack of pleasure derived from a positive rewarding event is related to an increased insula response. However, whether this is due to inappropriate signalling of the insula region that these rewarding events are negative, or whether this activation relates to an inability to 'switch-off' negative feelings, that then interfere with the conscious experience of pleasure to rewards that may be signalled by other regions in the reward network it can

only speculate. It would, therefore, suggest this may be a fruitful area for future researchers to examine.

In many ways, the subgenual cingulate region, where it also observed a negative correlation between SHAPS scores and BOLD activation, is similar to the insula in its proposed role in modulating negative emotions. However, the subgenual cingulate has also been suggested to play an important role in major depression and has been the target of deep brain stimulation to treat the disorder, as the hyperactivation of the region is thought to allow negative emotions to overwhelm thinking and mood (Hamani et al., 2011). McNeely et al (2008) have suggested that the subgenual cingulate (BA25) is involved in both acute sadness and antidepressant treatment effects, indicating a critical role for this region in modulating negative mood states (Mayberg et al., 1999; Seminowicz et al., 2004). Clinical data supports this view by showing that a decrease in subgenual cingulate activity is reported with a clinical response to different antidepressant treatments including specific serotonin reuptake inhibitor (SSRI) antidepressant medications, electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and ablative surgery (Dougherty et al., 2003; Goldapple et al., 2004; Malizia, 1997; Mayberg et al., 2000; Mottaghy et al., 2002; Nobler et al., 2001). The current finding of a negative correlation between a measure of hedonic response and BOLD activations in subgenual cingulate could be attributed to its function in modulating negative emotions and an impaired response to rewarding stimuli.

In addition, the current study revealed that a decreasing SHAPS pleasure score was correlated with greater bilateral putamen activation in response to both rewards. The negative correlation between SHAPS scores and BOLD activation in putamen may be similar to the negative correlation finding in the insula, as these two regions have been proposed to play a role in “hate circuit” of the brain, as suggested by Zeki and Romaya (2008) in an fMRI study. Putamen was reported to play a role in processing perception of contempt and disgust, and could be part of the motor system mobilize individuals to take action (Zeki and Romaya, 2008). Moreover, the BOLD activity level in the hate circuit directly correlates with the level of hate an individual claims, which may have legal implications concerning malicious crimes (Zeki and Romaya, 2008). It could be assumed that putamen, just like the insula, which played a role in modulating negative emotions generally. Alternatively, it could be assumed that participants with low hedonic level (low responsiveness to everyday rewards) hate or dislike the rewards. In other words, the less pleasure, the higher putamen and insula responses, and the more dislike of the rewarding stimuli.

In conclusion, the current study adds weight to the findings of the fMRI study-1 by showing strongly consistent results between the two studies, such as some brain regions (OFC and right amygdala) in the reward network respond to social reinforcers more sensitively than to monetary, provide further evidence for the existence of neural differences between these two types of reinforcer. Also, the current study reports the insula is closely associated with reward processing, suggesting future investigation on its function in reward and emotion. The regression findings of direct correlations between BOLD response in some brain regions (OFC and insula) and hedonic score, are especially of interest as it believe that investigation of the neural patterns of activation, evident in the relationship between rewards and feelings of pleasure, could have important implications for understanding the role of hedonic response in both healthy and mood disordered individuals. For example, the findings showed that the higher hedonic level the stronger OFC activation while the lower hedonic level the stronger insula activation. It could be assumed that patients with a mood disorder who were experiencing anhedonia, would have decreased OFC activation or increased insula activation when they were doing a reward related fMRI task.

## Chapter 6 fMRI study-3

### 6.1. Introduction

In Chapter 5 presented above, the fMRI study-2 compared social with monetary rewards and revealed some consistent results with the fMRI study-1 (chapter 4) in that some brain regions of the reward network were more sensitive to social reinforcers than monetary reinforcers, such as the lateral OFC (BA47), medial OFC (BA11) and bilateral amygdala. In addition, the fMRI study-2 revealed significant BOLD activation in the left OFC (BA47) in the interaction contrast [(MR vs. MC) vs. (SR vs. SC)], which however did not show a true crossover interaction when plotted, and was therefore inconsistent with study-1. This could be due to the fact that the valence of the stimuli in study-2 was not as polarised as in study-1, as neutral control stimuli were employed instead of punishments. In the current chapter, the fMRI study-3 will use the same task paradigm as used for study-2 which employed reward conditions and neutral control conditions. This study was designed to explore further the question of whether encoding different types of reinforcers engage distinct or overlapping brain regions by comparing three types of reward processing (social, monetary and food – chocolate) in a single target detection task.

Food reward is the most frequently used reward in neurophysiological recording studies of nonhuman primates and rodents (Schultz, 1998; Mirenowicz and Schultz, 1994; Morris et al., 1999; Roesch et al., 2007). Also, many human neuroimaging studies have been conducted to investigate the neural representation of reward for food reinforcers such as juice (O'Doherty et al., 2002; De Araujo and Rolls, 2004; Valentin et al., 2007; 2009; Kim et al., 2010; Levy and Glimcher 2011). The results of these studies commonly show that a primary food reward elicits significant BOLD activation in brain regions within the reward circuit (OFC and striatum). There have been very few human fMRI studies that compared monetary and food reward processing (Valentin et al., 2009; Kim et al., 2010; Levy and Glimcher, 2011), whilst even less fMRI studies compared social with monetary rewards (Izuma et al., 2008; Sprekelmeyer et al., 2009; Rademacher, 2010; Lin et al., 2011), and there have been no fMRI studies to date that have compared a range of common human reinforcers, monetary, social and food within a single task, as I aimed to in the current study.

The primary hypothesis was that all three types of reward would elicit BOLD activation in the OFC and striatal regions in the brain reward network, but it also expected to find some differences within the reward network between the three types of reward encoding. In addition, it aimed to explore further the relationship between BOLD activations and the

level of SHAPS hedonic score recorded in this experiment. The fMRI study-2 revealed a positive correlation between SHAPS hedonic score and the BOLD activations in the right OFC (BA47; BA10) and right frontopolar gyrus (BA10), whilst a negative correlation between SHAPS hedonic score and BOLD activations in the anterior and posterior insula, bilateral putamen, and subgenual cingulate (BA25) in response to both social and monetary rewards regardless of reward type. That is, the more pleasure a person claimed to obtain from daily rewarding events (subjective enjoyment), the stronger the BOLD activation observed in the medial and lateral OFC to the consumption of social and monetary rewards. The less subjective enjoyment, the stronger the BOLD activation observed in the insula, putamen and subgenual cingulate to the consumption of social and monetary rewards. This regression result is important as it implies a direct correlation between an individual's current hedonic levels and BOLD activation in the OFC, striatum, insula and BA25, which is useful in understanding the neural activations of patients with mood disorders such as depression where anhedonia is the main issue. In the current fMRI experiment, it will further investigate the correlation between the subjective enjoyment level and the BOLD activations to a specific reward stimulus. It expected to find similar results with chapter 5, that is, to find a positive correlation between BOLD activations in the OFC and SHAPS score in response to all types of rewards, whilst a negative correlation between BOLD activations in the insula, putamen, BA25 and SHAPS score in response to all types of rewards.

In addition, this study also had informal post-scan interviews, just like the previous fMRI studies. Participants were asked which type of reward stimulus they liked or disliked the most. Most of the participants in the current study said they were more excited about the money and chocolate reward. However, many of them even said they disliked receiving the social reward (examiner's smiling face with sounds). This is very different from the study-1 and study-2, in which many participants reported they liked the social reward more than monetary rewards. The interview results might be supportive to interpret neural activities and relative to behavioural results.

## **6.2. Methods**

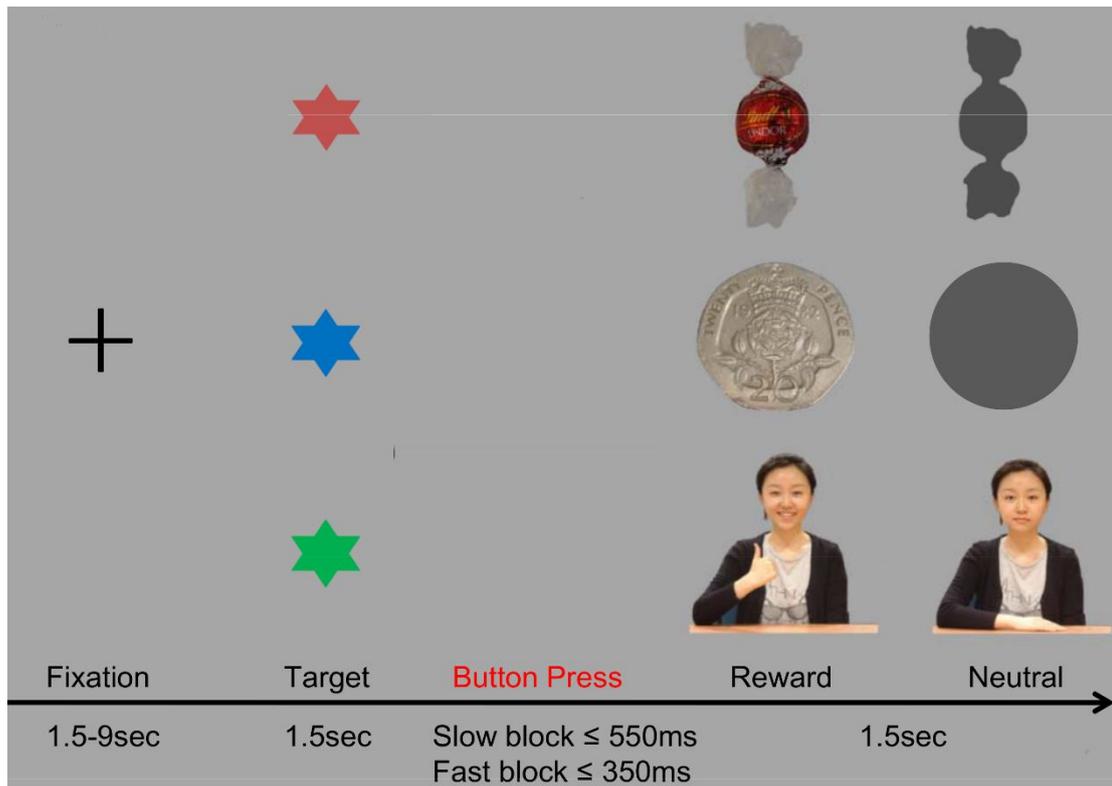
### **6.2.1. Participants**

This study recruited 15 staff and student volunteers (mean age = 23, SD  $\pm$ 1.41; 3 male and 12 female) from Aston University. All participants gave informed consent, and all procedures were approved by Aston University Ethics Committee. A safety screening questionnaire was administered prior to scanning. All participants filled out the Hospital

Anxiety and Depression Scale (anxiety mean = 4.7; SD  $\pm$  2; depression mean = 3; SD  $\pm$  2.1; Zigmond et al., 1983), the Beck Depression Inventory (mean = 4; SD  $\pm$  0.51; Beck, 1978) and the SHAPS (mean = 43; SD  $\pm$  6.7; Snaith et al., 1995). No participants were found to have 'abnormal' scores in these mood scales (see details in Chapter 2).

### **6.2.2. Stimuli and task**

In the fMRI task, it used the same format of the target detection paradigm as the fMRI study-1 and study-2. In each trial, participants first saw a fixation cross "+" in the middle of the screen (randomized inter-trial interval 1.5-9sec), followed by a star (presented for 1.5sec) which could be 1 of 5 possible colours, red, orange, purple, blue or green. Rather than two targets as used in the previous studies, this time, there were three targets – blue, green and red stars that participants had to respond to, by pressing a button on a response box as fast as possible to get an associated reward, and ignore non-targets (purple and orange stars). Participants were informed that if they could not respond fast enough to targets, they would receive a neutral feedback. The green star was associated with social reinforcements whereas the blue star was associated with monetary, and the red star was associated with chocolate. After participants made their response to a target, either a reward (picture of 20p coin with sound of a coin falling, or the experimenter's smiling face accompanied by voice saying 'well done', or picture of a Lindor chocolate with a happy jingle musical sound) or neutral feedback (a solid-filled 20p shape accompanied by short metallic sound or experimenter's neutral face accompanied with her voice saying 'neutral' or a solid-filled chocolate shape accompanied by a neutral musical sound) was presented. The reward stimulus was presented for 1.5 seconds. Participants were told that any money they won in the task they could take home, up to a maximum of £10.00. Also, the chocolate reward presented in the task was associated with a box of Lindor chocolate which worth £7, and participants were told that they could take home after the experiment. The scan session ran for approximately 30 minutes.



**Figure 6.1: Task Presenting Sequence.** From left to the right: the fixation cross, a target, then a reward shows up after a button press response. Photos on the bottom right: SR and SC. Photos on the middle right: CR and CC. Photos on the upper right: MR and MC. SC photo was the experimenter’s neutral face presented with the experimenter’s voice saying ‘neutral’ whereas SR photo was the experimenter’s smiling face accompanied by her voice saying ‘well done’. MC photo was a solid-filled circle in a 20p coin size accompanied by a short metallic sound whereas MR photo was a 20p coin with a coin falling sound. CC photo was a solid-filled chocolate shape accompanied by a neutral musical sound whereas CR photo was a Lindor chocolate with a happy jingle musical sound.

### 6.2.3. Image Analysis

All fMRI data were analyzed using SPM8 (Wellcome Institute of Neurology, implemented in Matlab; Mathworks, MA). 1 participants’ data was removed due to technical problems with the button box not working properly, and a further participants’ data was rejected after pre-processing due to excessive motion (> 5mm), and 1 participant stopped the experiment (by pressing the alarm button) due to discomfort, and 1 participant was rejected due to a large artefact in the PFC. Statistical analysis was therefore performed on 11 participants. Prior to model application, brain volumes from each participant were realigned to the first volume to correct for head motion. Functional images were then spatially normalized into a standard single subject T1 image template. Following this, it

applied spatial smoothing with an isotropic Gaussian kernel filter of 10-mm full-width half maximum to facilitate inter-subject averaging. For each participant, all experimental feedback categories were modelled as event types which were: SR, SC, MR, MC, CR (chocolate reward) and CC (chocolate control stimulus). In addition, following the contrast analysis of the condition-specific experimental effects (reward events) that was obtained via GLM in a voxel-wise way for each subject, the SHAPS hedonic scores rated by subjects was additionally modelled as separate subject-specific regressors, which were entered as parametric modulators for the regressors of the reward events. A series of t-contrast images were carried out to determine whether the fitted parameter values at each voxel were significantly greater than zero for each participant. These were then entered into a random effects group analysis.

It thresholded the activations at a voxel threshold of  $p < 0.001$ , uncorrected, and accepted as significant those clusters that survived at  $p < 0.05$ , corrected for multiple comparisons for the entire brain. For the regions of interest (ROI; OFC, amygdala, striatum), it reported activations that survive an uncorrected threshold of  $p < 0.001$  but were significant at  $p < 0.05$  when a small volume correction (SVC) was applied. The SVC applied was based on a sphere of 10 mm diameter based on peak co-ordinates in the OFC, striatum, and amygdala reported in past reward processing studies (see Table 6.1). As SPM coordinates are given in MNI space; regions were identified by converting the coordinates to Talairach space with a nonlinear transform (Brett et al., 2001).

<b>Table 6.1. Coordinates chose for the SVC analysis.</b>			
Region	Coordinate	Study	Reward Function
OFC (BA11)	30, 32, -2	Spreckelmeyer et al., 2009	Anticipation of monetary reward
Putamen	-18, 4, 14	Grabenhorst et al., 2010	A common scale for subject pleasantness of different primary reward
Putamen	22, 16, -4	Izuma et al., 2008	Commonly activated to social and monetary rewards
Amygdala	-21, -6, -21	Britton et al., 2006	Negative emotions relative to neural conditions
Amygdala	20, -2, -18	Redcay et al., 2010	A combination of reward and live social interaction

### 6.3. Behavioural Results

Mean reaction times for each condition were analyzed in a 2x2 repeated measures ANOVA. There was no significant difference between the three reward levels,  $F(1, 12) = 1.69$ ,  $p > 0.05$ . There was also no interaction between reward type and block type  $F(1, 12) = 2.31$ ,  $p > 0.05$ .

The mean percentage hit rates on the task were also calculated for social cue targets (green stars) and monetary (blue stars) and chocolate targets (red stars). These were similar for monetary and chocolate targets, as mean hits for MR were 64% and for CR were 63%, both were significantly higher than the mean hits for SR (51%). The mean missed-hits for MR were 36% which was similar to the missed-hits for CR (37%), and both had significantly lower missed-hits rate than SR (49%). A repeated ANOVA showed that there was a significant difference in the number of social and monetary rewards (or controls) received across reinforcer types,  $F(1, 12) = 12.38, p < 0.05$ . Also, there was a significant difference in the number of social and chocolate rewards (or controls) received across reinforcer types,  $F(1, 12) = 17.89, p < 0.05$ . There was no significant difference in the number of monetary and chocolate rewards received across reinforcer types,  $F(1, 12) = 1.82, P > 0.05$ .

#### **6.4. Imaging results**

Below, the results of the subtractive contrasts are outlined first, for the main effects of reward type and valence, followed by the results of the pairwise comparisons for the three rewards. It reports the results of the pairwise contrasts because unlike the previous studies 1 and 2, the current findings of pairwise contrasts provide supplementary information for understanding the results of the main effect contrasts. Lastly the results of the regression analyses are presented.

##### **6.4.1 Main effects of valence**

The contrast of all rewards versus all control stimuli (Table 6.2) revealed significant BOLD responses in the left medial frontopolar gyrus extending to OFC (BA10), left medial anterior cingulate (BA24), right medial globus pallidus (10, -1, -1), left hippocampus, left and right putamen, and left caudate.

The reverse contrast (Table 6.2) revealed greater BOLD activation for all control stimuli than for rewards, in the right lateral OFC (BA47), the right lateral frontopolar gyrus (BA10), right DLPFC (BA46) and right anterior insula (BA13).

##### **6.4.2 Main effects of reward type**

The contrast of all social versus all monetary stimuli (includes both rewards and control

stimuli) revealed significant BOLD responses, in the left OFC (BA47), left amygdala and right thalamus (Table 6.2). The reverse contrast of all monetary versus all social stimuli revealed no significant BOLD activation in our ROIs (Figure 6.2).

The contrast of all social versus all chocolate stimuli (Table 6.2) revealed significant BOLD responses in right DLPFC (BA46), right substantia nigra, right amygdala, right insula (BA13) and left hippocampus. The reverse contrast revealed greater BOLD responses for all chocolate feedback than all social feedback in the right hippocampus and left anterior cingulate (BA32; Figure 6.2).

The contrast of all monetary versus all chocolate feedback (Table 6.2) revealed significant BOLD responses in right parahippocampal gyrus (BA28). The reverse contrast did not reveal any significant BOLD activation in our ROIs.



**Figure 6.2: BOLD activations for the main effects contrast of reward type.** Axial slices (left and middle slice) showing greater BOLD activation to social than monetary reinforcers in the left amygdala, left lateral OFC (BA47). Axial slices (right slice) showing greater BOLD activation to social than chocolate reinforcers in the left amygdala. Activations were overlaid on a canonical high-resolution structural image in MNI space (MRICRON, <http://www.sph.sc.edu/comd/rorden/mricron>).

<b>Table 6.2. BOLD activation associated with the main effects contrasts of reward type and valence</b>							
Region	Brodman's Area	Voxels	P corrected	Z score	X	Y	Z
<b>(A) Social vs. Monetary</b>							
L OFC	BA 47	47	0.008	3.47	-42	25	-1
L Amygdala		39	0.018	3.79	-17	-5	-16
R Thalamus		15	0.024	3.59	12	-29	-5
<b>(B) Monetary vs. Social</b>							
No significant activation found in the ROIs							
<b>(C) Social vs. Chocolate</b>							
R Amygdala		7	0.012	3.24	20	-8	-14
R Substantia Nigra		18	0.007	3.54	16	-25	-10
R Insula	BA 13	26	0.032	3.53	42	26	6
R DLPFC	BA 46	76	0.014	4.03	49	25	15
L Hippocampus		80	0.012	4.08	-27	-14	-10
<b>(D) Chocolate vs. Social</b>							
R Hippocampus		35	0.019	4.19	30	-45	2
L Anterior Cingulate	BA 32	9	0.009	3.77	-17	36	-2
<b>(E) Monetary vs. Chocolate</b>							
R Parahippocampal Gyrus	BA 28	24	0.023	3.85	27	-23	-8
<b>(F) Chocolate vs. Monetary</b>							
No significant BOLD activations found in our ROIs							
<b>(G) Rewards vs. Control stimuli</b>							
L Medial FG	BA 10	74	0.008	3.72	-3	56	13
L Caudate		378	<0.001	4.19	-12	13	4
R Putamen		663	<0.001	4.9	18	14	-1
L Putamen		378	<0.001	4.08	-16	12	-6
L Anterior Cingulate	BA 24	8	0.037	3.38	-7	30	9
L Hippocampus		447	<0.001	5.37	-30	-13	-14
<b>(H) Control stimuli vs. Rewards</b>							
R Frontopolar Gyrus	BA 10	17	0.016	3.51	21	48	13
R OFC	BA 47	12	0.031	3.48	34	18	-6
R DLPFC	BA 46	19	0.004	3.85	45	41	7
R Insula	BA 13	21	0.037	3.35	42	13	3

Voxels significant at  $p < 0.05$  after correction are reported. \* Significant corrected  $p$  values shown after SVC. Coordinates are presented in Talairach space. L=left; R = right.

### 6.4.3 Pairwise contrasts of reward types within each polarity of valence

No significant BOLD activation was found in the ROIs (OFC, striatum, and amygdala) in any of the pairwise contrasts of reward types. Some findings were found in the limbic and DLPFC area (Table 6.3), with greater right DLPFC activation found in the contrast of SR versus CR, and greater right hippocampus activation was found in the contrast of CR versus SR, and greater left hippocampus activation found in the contrast of SR versus

MR.

#### **6.4.4 Pairwise contrasts of valence within each reward type**

The contrast of MR versus MC (Table 6.4) revealed greater BOLD activation in the left lateral globus pallidus and right medial subgenual cingulate (BA25). No significant results found in the reverse contrast of MC versus MR in our ROIs.

The contrast of CR versus CC (Table 6.4) revealed greater BOLD activation in the left medial frontopolar gyrus (BA10), left caudate, right putamen, right medial globus pallidus, left and right parahippocampal gyrus. No significant results found in the reverse contrast of CC versus CR in our ROIs.

The contrast of SR versus SC (Table 6.4) revealed greater BOLD activation in the left lateral anterior cingulate (BA32) and left hippocampus and right medial subgenual cingulate (BA25). The reverse contrast of SC versus SR revealed greater BOLD activation in the right lateral OFC (BA47), right lateral frontopolar gyrus (BA10) and right DLPFC (BA46).

#### **6.4.5 Correlation between SHAPS and brain activity in response to MR**

Regression analyses showed a positive association between SHAPS pleasure score and increased right OFC (BA47), right frontopolar gyrus (BA10) and right thalamus activation in response to MR (Table 6.5; Figure 6.3).

A negative correlation was found between SHAPS pleasure score and increased right anterior insula (BA13) activation in response to MR (Table 6.5; Figure 6.4).

#### **6.4.6 Correlation between SHAPS and brain activity in response to SR**

The Regression analyses showed a positive association between SHAPS pleasure score and increased left OFC (BA47), right DLPFC (BA46), left mid-insula (BA13), right amygdala and left anterior cingulate/subgenual cortex (BA25) activation in response to SR (Table 6.5; Figure 6.3).

A negative correlation was found between SHAPS pleasure score and increased right anterior insula (BA13) and bilateral red nucleus activation in response to SR (Table 6.5;

Figure 6.4).

<b>Table 6.3. BOLD activation associated with the contrasts of reward type.</b>							
Region	Brodmann's Area	Voxels	P corrected	Z Score	X	Y	Z
<b>CR vs. SR</b>							
R Hippocampus		14	0.001	3.61	32	-43	1
<b>SR vs. MR</b>							
L Hippocampus		14	0.013	3.69	-36	-11	-15
<b>SR vs. CR</b>							
R DLPFC	BA 46	57	0.027	3.84	53	25	15
R DLPFC	BA 46	57	0.027	3.28	45	29	10
No significant BOLD activation found in ROIs in any other pair of contrasts.							

Voxels significant at  $p < 0.05$  after correction are reported. \* Significant corrected  $p$  values shown after SVC. Coordinates are presented in Talairach space. L=left; R = right.

<b>Table 6.4. BOLD activation associated with the contrasts of reward valence.</b>							
Region	Brodmann's Area	Voxels	P corrected	Z Score	X	Y	Z
<b>MR vs. MC</b>							
L Lateral Globus Pallidus		85	0.026	3.63	-14	5	-5
R Anterior Cingulate	BA 25	30	0.036	3.52	5	-1	-7
<b>CR vs. CC</b>							
L Frontopolar gyrus	BA 10	26	0.02	3.51	-3	54	9
L Caudate		55	0.019	3.98	-10	13	4
R Putamen		128	0.001	4.48	23	8	-2
R Medial Globus Pallidus		8	0.004	3.58	10	1	-6
L Parahippocampal Gyrus	BA 35	95	0.003	3.88	-23	-22	-14
	BA 36	95	0.013	3.6	-27	-30	-15
R Parahippocampal Gyrus	BA 28	21	0.024	3.64	19	-29	-9
<b>SR vs. SC</b>							
L Hippocampus		38	0.023	4.43	-36	-13	-14
R Subgenual Cingulate	BA 25	11	0.006	4.26	5	22	-13
L Anterior Cingulate	BA 32	7	0.019	3.47	-16	38	6
<b>SC vs. SR</b>							
R DLPFC	BA 46	46	0.015	3.8	47	41	4
R Frontopolar gyrus	BA 10	46	0.032	3.47	40	42	13
R OFC	BA 47	76	0.008	3.64	42	14	-8
			0.009	3.56	38	20	-13
			0.009	3.55	34	16	-6
No significant BOLD activation found in ROIs any other pair of contrasts.							

Voxels significant at  $p < 0.05$  after correction are reported. \* Significant corrected  $p$  values shown after SVC. Coordinates are presented in Talairach space. L=left; R = right.

#### 6.4.7 Correlation between SHAPS and brain activity in response to CR

Regression analyses showed a positive association between SHAPS pleasure score and increased right OFC (BA47), right frontopolar gyrus (BA10) and right DLPFC (BA46) activation in response to CR (Table 6.5; Figure 6.3).

A negative correlation was found between SHAPS pleasure score and increased right anterior insula (BA13) and bilateral red nucleus activation when participants were in receipt of the CR (Table 6.5; Figure 6.4).



**Figure 6.3: Positive regression between BOLD activations in the OFC and SHAPS hedonic score in response to each type of rewards.** Axial slices showing increased BOLD activation to social (red) and monetary (blue) and chocolate (green) reinforcers, in the right OFC (BA47). Activations were overlaid on a canonical high-resolution structural image in MNI space (MRICRON, <http://www.sph.sc.edu/comd/rorden/mricron>).



**Figure 6.4: Negative regression between BOLD activations in the insula and SHAPS hedonic score in response to each type of rewards.** Axial slices showing increased BOLD activation to social (red) and monetary (blue) reinforcers and chocolate (green), in the right anterior insula. Activations were overlaid on a canonical high-resolution structural image in MNI space (MRICRON, <http://www.sph.sc.edu/comd/rorden/mricron>).

Table 6.5. BOLD activation associated with regression of SHAPS score.							
Region	Brodmann's Area	Voxels	P corrected	Z Score	X	Y	Z
Positive regression to MR							
R OFC	BA 47	289	<0.001	4.53	45	32	-1
R OFC	BA 47	48	0.026	4.19	42	20	-11
R OFC	BA 47	11	0.006	3.69	22	19	-13
R Frontopolar	BA 10	289	<0.001	3.81	40	44	16
R Frontopolar	BA 10	289	<0.001	3.75	29	50	10
R Thalamus		144	0.002	3.62	10	-31	0
Negative regression to MR							
R Insula	BA 13	10	0.033	3.61	34	18	12
Positive regression to SR							
L OFC	BA 47	11	0.003	3.41	-49	23	0
R Amygdala	Amygdala	27	0.034	3.68	18	-6	-16
R DLPFC/Frontopolar	BA 46/10	64	0.031	3.64	47	39	11
Negative regression to SR							
R Red Nucleus		82	0.017	4.69	5	-22	-3
L Red Nucleus		82	0.017	4.44	-3	-20	-3
R Insula	BA 13	44	0.028	3.45	29	22	10
R Insula	BA 13	44	0.014	3.39	36	15	8
Positive regression to CR							
R OFC	BA 47	140	0.004	4.56	27	14	-19
R OFC	BA 47	140	0.004	4.56	36	20	-13
R DLPFC	BA 46	245	<0.001	4.53	47	38	0
R Frontopolar Gyrus	BA 10	245	<0.001	4.53	31	43	5
Negative regression to CR							
R Red Nucleus		136	0.005	4.44	5	-24	-3
L Red Nucleus		136	0.005	4.44	-3	-25	-5
R Insula	BA 13	56	0.022	3.85	38	14	12
R Insula	BA 13	56	0.014	3.85	40	11	4
R Insula	BA 13	56	0.011	3.85	32	24	12

Voxels significant at  $p < 0.05$  after correction are reported. \* Significant corrected  $p$  values shown after SVC. Coordinates are presented in Talairach space. L=left; R = right

## **6.5 Discussion**

The current fMRI study compared and contrasted the encoding in the brain reward network of social, monetary and chocolate rewards. The task paradigm was the same as the previous study-2 but added in a new reward stimulus – i.e. chocolate. The main effects of valence showed mostly consistent results with the findings of the fMRI study-1 and 2, such as the region of medial frontopolar (BA10) gyrus and dorsal striatum that responded significantly more to rewards whereas right lateral frontopolar gyrus and OFC (BA47) responded more to the control conditions. However, the main effects contrast between the social and monetary reinforcers did not reveal strong dissociation within the regions of reward network, bar the social versus monetary contrast which demonstrated greater left amygdala and OFC (BA47) activation for social reinforcers. The social versus chocolate contrast reported greater right amygdala, insula and substantia nigra activation for social reinforcers. Finally, the regression analysis revealed consistent results with the findings observed in study-2, which was a positive correlation between SHAPS pleasure score and right OFC (BA47) and right frontopolar gyrus (BA10) activation, and a negative correlation between SHAPS pleasure score and right anterior insula (BA13) activation in response to rewards regardless of reward type.

Below, it will first discuss those main effects contrasts results that were consistent with the fMRI study-1 and study-2, together with the new findings regarding the chocolate reinforcer, followed by a discussion of the findings of the pairwise comparisons. Finally, it will discuss the results of the positive and negative regressions between BOLD activation to rewards and SHAPS hedonic scores.

### **6.5.1. Subtractive Analyses - Main effects contrasts of valence**

#### **6.5.1.1. Role of striatum in rewarding events**

The current study revealed greater BOLD activation in the caudate and putamen to all rewards (chocolate, social and monetary) compared with the control stimuli. As previously discussed, dorsal striatum is involved in reward-based learning (Brovelli et al., 2011), reward anticipation, expectation and delivery (O'Doherty et al., 2002; Knutson et al., 2001; Delgado, Locke, Stenger, and Fiez, 2003; Elliott et al., 2003; Berns, McClure et al., 2001; Knutson et al., 2001; Delgado et al., 2000), and in the processing of salient stimuli (Lauwereyns et al., 2002). The current results of greater BOLD activation in the dorsal striatum to rewards compared with control stimuli may be attributable to its function in learning about actions and reward consequences (O'Doherty et al., 2004; Tricomi et al.,

2004), as the dorsal striatum maintains information about the rewarding outcomes of actions, in order to choose actions that enable better outcomes more frequently (O'Doherty et al., 2004). O'Doherty et al (2004) therefore, called dorsal striatum an “actor” that act to maintain rewards.

#### **6.5.1.2. Role of OFC in rewarding events**

In addition, the current results showed that rewards elicited greater activations in the medial frontopolar gyrus extending to OFC (BA 10) activation than control conditions, whilst the reverse contrast of control conditions versus rewards elicited greater activations in the right lateral frontopolar gyrus (BA10) and right lateral OFC (BA47). This result is consistent with both fMRI study-1 and study-2 and provides further evidence to the view of a medial-lateral functional dissociation within the OFC in response to reward valence and the receipt of reinforcers (O'Doherty, 2007; Kim et al., 2006). Furthermore, the contrast of control conditions versus rewards elicited greater activation in the right lateral OFC (BA47). The lateral OFC was prominently activated to punishment in study-1 and its activation in the current study would suggest that the control stimuli were perceived as having a punishing component.

#### **6.5.1.3. Role of Insula related to perception of control events as ‘punishing’**

Finally, it revealed greater BOLD activation for all control stimuli than for rewards, in the right anterior insula (BA13). As already discussed in chapter 5, a finding of greater insula activation to control stimuli than rewards, suggests that control events, when presented in a task with reward events, are perceived by participants as ‘punishing’, so that insula was processing ‘negative’ emotions or feelings elicited by the control events (Singer, 2006; Wicker et al., 2003; Reiman et al., 1997). An alternative perspective to this finding of greater activation to control conditions in the right anterior insula is that it may be due to the “regulation” of salience when control stimuli are received (Eckert et al., 2009). The right anterior insula has been revealed to contribute to the interaction between salience of the selective attention created to achieve a task and the salience of arousal created to keep focused upon the relevant part of the environment (Eckert et al., 2009). During a challenging task, this regulation of salience might be involved where attention is waning and results in careless errors, but once there is too much arousal it may lead to risks creating a poor performance by becoming overly anxious (Eckert et al., 2009). This view could be explained further that the increased right anterior insula activation reflected self-monitoring of errors (error awareness), as the control stimuli were only presented when

participants erred.

### **6.5.2. Subtractive Analyses - Main effects contrasts between the reward types**

The current results revealed greater BOLD activation in the lateral OFC (BA47) and amygdala to social rather than monetary reinforcers. This result was consistent with the findings from the study-1 and 2. As already discussed in chapter 5, coding of the perceived value (affective value) is the most established function of the OFC in reward processing (O'Doherty, 2007). Therefore, the greater activation of OFC observed to social stimuli was more likely due to the valuation of the rewarding/aversive value of the social stimuli, rather than due to social cognitions.

Also, the stronger amygdala activation observed to social stimuli compared with monetary and compared with chocolate stimuli may be attributable to the stronger affective intensity of the social stimuli – both smiling and neutral faces. As discussed in chapter 5, the amygdala activation is related closely to how arousing (reinforcer intensity) stimuli are (Sanghera, 1979; Hommer et al., 2003; Small et al., 2001; reviewed in McClure et al., 2004; Wilson and Rolls, 2005).

### **6.5.3. Pairwise comparison of the reward events**

#### **6.5.3.1. Social versus monetary reward**

Somewhat surprisingly, the current study did not show clear dissociable neural responses in the OFC and PFC in the contrast of MR versus SR or the reverse of SR versus MR as the previous fMRI studies showed, which may be due to a 'de-valued' SR or the changed 'relative value' of the stimuli. This may be because participants changed the perception of the value of the SR, in the context of the additional CR presents. The 'de-valued' SR can be explained by the context-dependent theory (Nieuwenhuis et al., 2005; Elliott et al., 2008).

According to the context-dependent theory (Nieuwenhuis et al., 2005; Elliott et al., 2008), the reward processing system determines whether an outcome is favorable or unfavorable on the basis of the range of possible outcomes encountered in a particular setting—judging the best possible outcome to be favorable and the worst possible outcome to be unfavorable, regardless of the absolute magnitudes of these outcomes (Nieuwenhuis et al., 2005). The scaling of the reward by the range of possible outcomes is consistent with reward prediction error theory, according to which brain areas are sensitive to deviations

from expected reward rather than to absolute magnitude of reward (Holroyd and Coles, 2002; Montague and Berns, 2002; Schultz, 2002). Previous fMRI studies have reported that BOLD responses to rewarding stimuli are influenced by the context in which the outcomes are experienced (O'Doherty et al., 2000; Small et al., 2001; Gottfried et al., 2003; Akitsuki et al., 2003; Elliott et al., 2000, 2008; Nakahara et al., 2004; Nieuwenhuis et al., 2005). Those previous fMRI studies suggesting the context-dependent theory, employ only single type of reward but with different magnitude, such as Nieuwenhuis et al (2005) and Elliott et al (2008) used different amounts of money, while Tremblay and Schultz's (1999) animal study used food with 3 favorable levels (raisins, apple and cereal). Thus, there is a strong possibility in the current study that the reward value of social and monetary stimuli was affected by the newly added chocolate reward. The chocolate reward here is not an immediate reward, but as the monetary reward is given after the experiment. According to my behavioural results, the target detection rate for monetary/chocolate reward was very similar and significantly higher than for SR, and the target detection rate for SR and SC were almost the same. This may suggest that in the current task context, participants are not very motivated by SR, in other words, SR reward strength is not as strong as the previous experiments. According to the informal post-scan interview results, most of the participants in the current study said they were more excited about the money and chocolate rewards, however, many of them said they disliked receiving the social reward. This is very different from the study-1 and study-2, in which many participants reported they liked the social reward more than monetary rewards. Therefore, the behavioural and interview results are supportive to the explanation of the 'de-valued' SR, and similar valued MR and CR (discussed in below).

#### **6.5.3.2. Monetary reward versus chocolate and social reward versus chocolate**

Neither the contrast of MR versus CR nor SR versus CR revealed dissociable neural response in the brain reward network. This may be explained as the affective value, or emotional intensity of the three rewards is encoded somehow similarly in the current task paradigm. The behavioural results show MR and CR have very similar target detection accuracy rates, and both were significantly higher than SR. One explanation of the similar valuation of MR and CR may be that all participants were told that the money and chocolate they won during the task would be paid after the experiment, and participants knew the value of the chocolate (worth £7) before the experiment. Knowing the high street value of the chocolate may have inflated the value of the reward (or affective value), but may also have de-valued SR. Furthermore, chocolate stimuli could be more rewarding as all the participants were claimed to be chocolate lovers. In other words, in the context of

receiving a chocolate, money or social reward, being given a social reward feels like a loss.

The SR is not rewarding as strongly compared to the previous study-1 and study-2 so that it did not find any dissociable neural responses between SR and MR as before. Also, the MR and CR were similarly valued, so that there were no dissociable neural responses found in the reward network. In other words, the SR in my fMRI study-1 and study-2 has stronger reward/affective value than MR, whereas it is devalued somehow and no longer perceived as a reward in the current task paradigm.

### **6.5.3.3. Social reward versus control**

The contrast of SR versus SC did not reveal any significant activation in the reward network while the reverse contrast of SC versus SR showed significant right lateral OFC (BA47/10) activation, which is the same as my fMRI study-1 finding (chapter 4) of the contrast of SP versus SR. These findings were the neural evidence of 'de-valued' SR and 'punishing' SC. Taking together of this finding and the above finding of stronger amygdala activation in response to social stimuli compared with monetary and chocolate stimuli, it may, therefore, suggest that although SR is not rewarding as previous studies, and it has punishing effect instead, it still has strong affective salience.

### **6.5.4. Regression Analyses**

The current study employed a regression analysis of the SHAPS hedonic score and BOLD activity to rewards. Firstly, this revealed a positive correlation between SHAPS pleasure score and increased right OFC (BA47) and right frontopolar gyrus (BA10) activation in response to each of the reward types. There was an additional positive correlation between the SHAPS scores and increased amygdala activation, which was only in the context of SR. A negative correlation was observed between SHAPS scores and increased right anterior insula (BA13) activation in response to all three types of reward. These regression results (except the amygdala finding) were consistent with the fMRI study-2 and below it would discuss them in greater detail.

There have been some neuroimaging studies suggesting that the OFC is generally correlated with a state of subjective pleasantness, such as Kringelbach et al (2003), who have revealed a negative correlation between the subjective pleasantness rating of a liquid food when it is eaten to satiety and the BOLD activation in the OFC (BA47 and

BA11). In chapter 5, it has already discussed Kringelbach et al's findings in greater detail, together with findings from Grabenhorst et al (2010) and Small et al (2001) whose studies suggest a positive correlation between BOLD activity in the OFC and a state of subjective pleasantness. Kringelbach et al (2003) have suggested that whether the BOLD responses in the OFC is positively or negatively correlated with a state of subjective pleasantness rating, may depend on specific reward information, for example, sensory specific. Both the current study and study-2 showed that a high SHAPS pleasure score was correlated with increased OFC (right BA10 and BA47) activation when participants received social, monetary and chocolate rewards. That is, the greater the self-reported hedonic response to everyday rewarding events the stronger the BOLD activation observed in the OFC to the consumption of a variety of abstract and primary rewards. As already argued in chapter 5, the OFC may play a key role in reward valuation and expectation (O'Doherty, 2003; Gottfried et al., 2003) and representing subjective pleasantness of reinforcers (Kringelbach, 2005). The current findings suggest that how responsive an individual is to the experience of pleasure to rewards in their daily lives (e.g. enjoying a favourite TV programme) correlates well with increased OFC activation to rewards in our task. This implies a direct correlation between an individual's current hedonic levels and activation in the OFC to rewarding stimuli, which could be useful in understanding mood disorders such as depression where anhedonia is a common symptom. It would be reasonable to assume that patients who are experiencing anhedonia, may have decreased OFC activation in response to rewarding stimuli during any reward related fMRI tasks.

A positive correlation between the hedonic score and BOLD responses in the right amygdala was observed in response to SR only. The amygdala has been suggested to respond to reward intensity (or encode reward value which is an interaction between valence and intensity) rather than just valence, as previous evidence has shown the amygdala responds to pleasant as well as aversive stimuli (O'Doherty et al., 2001; Canli et al., 2002; Small et al., 2003; Anderson et al., 2003; O'Doherty et al., 2004). Therefore, the positive correlation of self-reported hedonic levels with increased BOLD activation in the amygdala may not necessarily be attributable to positive emotions, but more likely due to the specific reward intensity of SR. If it reflects on the main effects contrasts results across all three of my fMRI studies, increased amygdala activation was related more strongly with social reinforcers than monetary or chocolate reinforcers, and suggests social reinforcers have a stronger affective intensity than the other two types of reinforcers in the current task paradigm. More importantly however, this finding also leads it to the conclusion that the amygdala activation to SR is not solely due to face processing, but also incorporates an arousal/affective response (reinforcer intensity; Sanghera, 1979; Hommer et al., 2003; Small et al., 2001; reviewed in McClure et al., 2004; Wilson and

Rolls, 2005).

At the opposite end of the hedonic scale, and strongly in keeping with the findings in study-2, it observed a negative correlation between SHAPS scores and increased insula activation (BA 13) to all three reward types, i.e. the less subjective enjoyment reported by participants on the SHAPS scale, the stronger the BOLD activation observed in the insula to the consumption of social, monetary and chocolate rewards. One explanation of this negative correlation could be attributed to the insula's function in processing negative feelings (Singer, 2006; Wicker et al., 2003; Reiman et al., 1997). The main effects contrasts of all control events versus all rewards could provide more evidence of this explanation as the control stimuli may have negative effects which may suggest this region plays a role in processing some negative affective value of the reward stimuli. Also, this finding adds weight to the idea that insula is involved in the representation of the subjective value of different reward stimuli in a negative manner (Levy and Glimcher, 2012). Furthermore, the current finding stresses the anterior insula's role in emotional salience, awareness and consciousness (Craig, 2002; 2008; 2009) especially negative emotion and implies a direct negative correlation between an individual's current hedonic levels and activation in the anterior insula to rewarding stimuli, which is useful in understanding depression where abnormal activation of anterior insula has been established well in depression (Giesecke et al., 2005; Sprengelmeyer et al., 2011; Strigo et al., 2008; Herwig et al., 2009; Johnstone et al., 2007).

A role for the insula in reward processing has not been well established in the human neuroimaging literature, and it is primarily not a region of interest in many reward processing studies. Past reward related neuroimaging studies have revealed that anterior insula plays a role in risk prediction in gambles, such as encoding reward-related uncertainty (Elliott et al., 2000; Critchley et al., 2001; Ernst et al., 2002; Huettel et al., 2005; Paulus et al., 2003; Singer et al., 2009). Also, a recent fMRI study has revealed a positive correlation between increasing activation in the anterior insula and increasing risk prediction errors (Preuschoff et al., 2008). Furthermore, as discussed above in chapter 5, the right anterior insula activation could play a role in self-monitoring of errors (error awareness) as it increased when receiving and processing information on surprising and unexpected errors (Wessel et al., 2012), and even involved in increased necessity of effort (Croxson et al., 2009; Prevost et al., 2010). The current findings of the right anterior insula (both the main effects contrasts and the regression results) seem more likely to suggest it has a role in processing affective value (negatively) when to perceive of reward stimuli.

Alternatively, it may suggest that the insula is involved in processing unexpected errors during the task.

## **6.6. Conclusion**

The central finding of the current study was a demonstration of dissociable neural responses within the reward network to the different abstract reinforcers which included social, monetary and chocolate reinforcers. Crucially, the introduction of a chocolate reward into the task paradigm, resulted in a change of the relative value of the rewards (social and monetary) to each other, so that SR appeared to be 'devalued' compared with the previous fMRI study-1 and study-2, providing evidence for the 'context-dependent' theory (Nieuwenhuis et al., 2005) of reward. Furthermore, the current study has revealed consistent results in the regression analysis with the fMRI study presented in chapter 5, i.e. levels of pleasure obtained from everyday rewarding events were positively correlated with BOLD activation in the OFC during the consumption of social, monetary and chocolate rewards. Whilst, a negative correlation was found with self-reported pleasure to rewarding events, and BOLD activation observed in the insula during the consumption of social, monetary and chocolate rewards. Investigation of the neural pathways and activation patterns engaged in the correlation between reward and hedonic level would have important implications for understanding how human daily hedonic levels respond to various types of reinforcement. This investigation may help further down the line understanding disorders with anhedonia, such as depression. It could assume that patients who are experiencing anhedonia, may have decreased OFC and increased insula activation in response to rewards during reward related fMRI tasks.

## Chapter 7 Final Discussion

This thesis examined the behavioural and neural correlates of reward-related processing in healthy human volunteers. Different aspects of reward were considered, including different types of reinforcer and valence. This chapter will briefly summarise the main findings of this thesis and discuss the main themes with the implications for understanding the human brain reward system, followed by a discussion of the methodological limitations and future research plans.

### 7.1. Summary of the main findings

This thesis began with the question of whether the receipt of social and monetary reinforcers, is mediated by different neural substrates within the brain reward network. However, before the first fMRI study was conducted, a social reinforcer and also different magnitudes of monetary reinforcer were carefully chosen and tested for equivalence in two pilot behavioural studies (chapter 3). Both pilot tasks revealed that the social reinforcer (a smiling face) and a monetary reinforcer (20p win) had the most equivalent behavioural effects on learning. As a result, the smiling face and 20p were used in the fMRI studies as task stimuli.

For the first experiment, described in chapter 4, it had hypothesised that neural activation to reinforcers may be affected by the reinforcer type, with social reinforcers resulting in differential activation to financial reinforcers in regions important for emotional processing, including the OFC. The first fMRI experiment did indeed reveal evidence consistent with this hypothesis, as social and monetary reinforcers were represented differently and separately in regions of OFC and amygdala within the brain reward network. In addition, the results also provided evidence to support theories of a medial-lateral functional dissociation within the OFC in terms of receipt of reward valence (Elliott et al., 2000; O'Doherty et al; 2001; 2007). Furthermore, this thesis provided direct evidence that the OFC plays a role as a common valuation scale which compares the values of social and monetary rewards and punishments in order to prepare for an appropriate action. This was demonstrated by a crossover interaction that was detected in the right lateral OFC (chapter 4) between reinforcer types and valence and provides direct evidence for Montague and Bern's (2002) theory that the OFC contributes to coding the salience of a particular stimulus, by comparing different possible values of reward outcomes.

In chapter 5, the second fMRI experiment further investigated the hypothesis and findings tested in study-1, but concentrated on comparing two types of rewards, and used two neutral control stimuli, instead of punishments in the task. The results revealed consistent findings with study-1, which the lateral OFC (BA 47), medial OFC (BA 11) and amygdala were more sensitive to social than monetary reinforcers. Also, the second experiment provided further support for the theory of a medial-lateral functional dissociation within the OFC for reward valence (Elliott et al., 2000; O'Doherty et al.; 2001; 2007; Kim et al., 2006). Finally, fMRI study-2 included a regression analysis of the SHAPS hedonic score and BOLD activity to rewards. The results revealed a positive correlation between SHAPS hedonic score and the right OFC (BA47; BA10) activation in response to rewards. In other words, the more pleasure a person claimed to obtain from everyday rewarding events the stronger the BOLD activation observed in the OFC to the consumption of social and monetary rewards. The finding, therefore, suggests that how responsive an individual is to the experience of pleasure from rewards in their daily lives, such as enjoying a favourite television programme, correlates well with increased OFC activation to rewards in our task. This finding fits with the view that medial OFC is not only of primary importance in coding reward value but also responsible for hedonic experience (Kringelbach et al., 2005).

A negative correlation was additionally found between the SHAPS hedonic score and BOLD activations in the insula (anterior and posterior), putamen, and subgenual cingulate (BA25) in response to rewards, regardless of reward type. This means the less pleasure a person claimed to obtain from everyday rewarding events, the stronger the BOLD activation in the insula (and putamen and subgenual cingulate) to the consumption of social and monetary rewards. The negative correlation between self-reported levels of hedonia and BOLD activations in the insula could be attributed to the insula's known role in modulating negative events and emotions (Singer, 2006; Wicker et al., 2003; Reiman et al., 1997), or in the "regulation" of salience when control stimuli are received (Eckert et al., 2009), or in error awareness (Klein, Ullsperger and Danielmeirer, 2013; Wessel et al., 2012). Similarly, the negative correlation between self-reported levels of hedonia and BOLD activations in the subgenual cingulate could be due to its function in modulating negative mood states (Mayberg et al., 1999; Seminowicz et al., 2004) and impaired responses to rewarding stimuli, which is in agreement with the view that hyperactivation of the subgenual cingulate area is linked with poor emotional regulation, as evident in mood disorders such as depression (Mayberg et al., 2008). The negative correlation between SHAPS scores and BOLD activation in the putamen may be similar to the negative correlation finding in the insula, as these two regions have been proposed to play a role in strong negative emotions such as hate, as increased BOLD activity in these regions directly correlates with the level of hate an individual claims to feel for other

individuals (Zeki and Romaya, 2008). It could suggest that the stronger BOLD activation in insula and putamen, the less pleasure of perceiving rewarding stimuli, and it may be possible that the rewarding stimuli could have a negative affective effect rather than be rewarding.

The final experiment (study-3, chapter 6) utilised an additional reward (chocolate) to the previous experiments, and here it compared and contrasted the receipt of social, monetary and chocolate rewards in the brain reward network. The social versus monetary main effects contrast demonstrated consistent results with study-1 and study-2, in that the amygdala and left OFC (BA47) were more sensitive to social reinforcers than monetary: indicating social reinforcers had greater reward value and generated a stronger emotional response. Social reinforcers also appeared to generate a greater affective response than chocolate reinforcers, as the significantly greater amygdala, hippocampal and insula activation was observed to social reinforcement. However, unlike the other two experiments, the pairwise contrasts in study-3 provided additional information for understanding the findings of the main effects contrast, by showing that the newly added chocolate reward appeared to influence the relative value of the social and monetary rewards to each other, so that SR appeared to be 'devalued' compared with the previous fMRI study-1 and study-2, and it did not find a significant difference in the neural activations between social and monetary rewards within the reward network. This finding provides evidence for the 'context-dependent' theory (Nieuwenhuis et al., 2005) of reward. Furthermore, study-3 also included a regression analysis of the SHAPS hedonic score and BOLD activity to rewards, and revealed very consistent results with the findings observed in study-2, which was a positive correlation between SHAPS pleasure score and right OFC (BA47) activation, and a negative correlation between SHAPS pleasure score and right anterior insula (BA13) activation in response to rewards regardless of reward type. These regression findings add weight to the findings of the fMRI study-2.

The seven main themes that emerged from these findings are discussed below, together with their implications for our understanding of human reward systems and the possible pathophysiology of mood disorders.

## **7.2. Main themes**

## **7.2.1. OFC represents different reinforcer values**

### **7.2.1.1. Medial-lateral dissociation in the OFC to rewards and punishments**

The first theme is derived from a strongly consistent finding across all the fMRI studies, which showed a medial-lateral functional dissociation between reward and punishment (or control stimuli) within the OFC, where the medial OFC responded more to rewards, while the lateral OFC responded more to punishment, and is supportive of the view that medial-lateral functional dissociation within the OFC to reward valence, is especially apparent in fMRI studies focusing on neural activation to the receipt of reinforcers that are uncomplicated by higher order cognitive processes such as decision-making (O'Doherty, 2007; Kim et al., 2006).

### **7.2.1.2. Greater OFC activation to social reinforcers**

The first theme is further supported by another consistent finding across the three fMRI studies, which was greater activation to social reinforcers in the OFC, compared to monetary reinforcer types. This finding could be attributed to the OFC function in modulation of affective evaluative processes due to the intrinsically rewarding/aversive value of the social stimuli (McClure and Montague, 2004) rather than due to social cognitions, as the coding of the perceived value (affective value) is the most established function of the OFC in reward processing (O'Doherty, 2007). This finding implies that social reinforcers generally have stronger emotional intensity than monetary or chocolate rewards, in the current task paradigm. Therefore, the finding adds weight to the view that the OFC is involved in coding different types of reward (Levy and Glimcher, 2012).

### **7.2.1.3. The OFC role for integration of different kinds of reward information**

Although the OFC responded more to social than monetary reinforcers and had a medial-lateral functional dissociation to rewards and punishments, it also revealed the right lateral OFC contributes to an integration of the neural responses to both valence and type of reinforcer in fMRI study-1. This was shown by the crossover interaction between valence and type, which demonstrated that task-related brain activation was selectively influenced by affective value (emotion induced by valence) so that neural activity was greatest in the MR and SP conditions, and lowest in the SR and MP conditions. Therefore, another theme emerged from the current results providing robust evidence that the lateral OFC is involved in the convergence and merging of the valuation of different types of rewards and

punishments into a common valuation scale, as hypothesised by Montague and Berns (2002), which enables the comparison of different values and goal-directed control of behaviour to depend on the current environment and/or emotional context.

This common currency function of the OFC and the functional specialization findings within the OFC, need not be mutually exclusive. Different types of reward could be valued separately, and a common valuation scale may pool these independent valuations together with motivational state information, to influence decision making (Elliott et al., 2008). Similarly, Levy and Glimcher (2012) have recently reviewed OFC function in representing subjective values of different rewards, by conducting a meta-analysis of fMRI studies that had researched multi-types of reward processing. The principle finding of the meta-analysis was a sub-region of the vmPFC/OFC appeared to act as a common neural currency to represent different reward values that could be comprised of various reward-related information such as the internal state of the participant (satiety, thirst, hormonal levels, etc.), sensory nature of the rewarding stimuli, stimulus relative value in the context it appears, emotional intensity and arousal. Moreover, Levy and Glimcher (2012) suggested that only studies that have employed multi-types reward processing within a single task can provide direct evidence to the common currency theory. The findings, therefore, can provide such direct evidence as it compared social with monetary rewards and punishments within a single target detection task.

### **7.2.2. The amygdala responds to affective value of social reinforcers**

The third theme to emerge from the findings is that amygdala activation is more responsive to social reinforcers than monetary. When it revealed this result in fMRI study-1, it was not certain whether the greater amygdala activation was due to the affective value of social reinforcers or just due to its function in facial processing (Whalen et al., 2001, Benuzzi et al., 2007, N'Diaye et al., 2009, Mattavelli et al., 2012). This was because the social stimuli were emotional faces with either a positive or negative facial expression, but it did not include a neutral face stimulus without any emotional expressions in the task, to test whether amygdala activation was due to face processing or reward value. The pairwise comparison of SR versus SP did not reveal any significant amygdala activation, which might be because that the SR and SP had similar affective intensity.

To further examine this finding, a neutral face stimulus was included in the fMRI study-2, in which it compared amygdala activation elicited by neutral and smiling faces. The results again showed greater amygdala activation to social reinforcers (reward and neutral control stimulus) than monetary. An ROI analysis on the amygdala additionally revealed

significantly greater amygdala activation in the contrast of SR versus MR and SR versus SC. Therefore, the findings that SR elicited greater amygdala activation than SC implied the greater amygdala activation to social reinforcers was due to the high affective intensity of social rewards, rather than basic face processing per se. This finding also supports the view that amygdala activation is related closely to how arousing (reinforcer intensity) stimuli are (Sanghera, 1979; Hommer et al., 2003; Small et al., 2001; reviewed in McClure et al., 2004; Wilson and Rolls, 2005). The fMRI study-3 provided further evidence for the amygdala role in processing affective intensity, by showing that increased amygdala activation was observed to social stimuli compared with monetary and also compared with chocolate stimuli. Although in the study-3, SR was suggested to be 'devalued' and SC was found to be 'punishing', the greater amygdala activation to social reinforcers observed was explained in this thesis as reflecting affective intensity rather than basic face processing. As discussed in chapter 6, it is possible that the 'punishing' SC and 'de-valued' SR somehow still had strong affective salience.

One supporting evidence was the finding of a positive correlation between scores on the SHAPS hedonic scale and BOLD responses in the right amygdala, in response to SR only, in the study-3. This SR specific activation could be interpreted as due to the specific affective intensity of SR, rather than simply to positive emotions. As discussed above, across all three fMRI studies, greater amygdala activation was related more strongly with social reinforcers than monetary or chocolate reinforcers, and suggests amygdala activation to social reinforcers in the task paradigm were due to reward value (which is an interaction between valence and intensity) rather than just valence (O'Doherty et al., 2001; Canli et al., 2002; Small et al., 2003; Anderson et al., 2003; O'Doherty et al., 2004). Hence, the correlation between amygdala activation to SR and hedonic level provides additional evidence that the amygdala activation to SR in the task paradigm is due to an arousal/affective response (reinforcer intensity, rather than to face processing (Sanghera, 1979; Hommer et al., 2003; Small et al., 2001; reviewed in McClure et al., 2004; Wilson and Rolls, 2005).). In addition, the positive correlation between the SHAPS hedonic scores and BOLD responses in the right amygdala could also simply reflect that happier people having greater amygdala activity, in line with that some researches have demonstrated mood-congruency in amygdala activity. For example, depressed individuals have shown greater amygdala responses on viewing sad than happy faces, whereas healthy individuals have responded more strongly to happy than sad faces (Stuhmann et al., 2013; Gaffrey et al., 2011).

### **7.2.3. The dorsal striatum acts to maintain rewards**

The fourth theme is derived from the consistent finding across all the studies of greater BOLD activation in the dorsal striatum (putamen and caudate) to rewards compared with punishment/control stimuli, which could implicate this region is involved in action-reward learning (Brovelli et al., 2011), during which this region acts to maintain better rewarding outcomes or enable better rewards to be chosen more frequently (O'Doherty et al., 2004). This learning processing could be mediated by afferent dopaminergic input so that actions associated with greater predicted rewards in a given context become reinforced, and thus are maintained (Montague et al., 1996). The current theme supports the view that the dorsal striatum is involved in various motivational and learning processes that support goal-directed action (Brovelli et al., 2011).

### **7.2.4. Role of the insula in processing negative reinforcement**

A further theme came from the findings of the second and third studies which revealed greater BOLD activation in the right anterior insula to control stimuli compared to rewards, which could suggest that control events, when presented in a task with reward events, are perceived by participants as having a negative valence – or 'punishing', so that the insula was processing 'negative' emotions or feelings elicited by the control events (Singer, 2006; Wicker et al., 2003; Reiman et al., 1997). This interpretation is dependent on the important role of the anterior insula in the processing of various types of negative reinforcers and events and feelings, such as the receipt of monetary loss (O'Doherty, Critchley, et al., 2003; Paulus and Stein 2006). This would also fit with the finding discussed above of greater lateral OFC activation to control stimuli, which indicates that a control stimulus (not receiving a reward) may be experienced as a punishing event. This finding additionally supports the view that the insula is involved in the representation of the subjective value of rewards, in a negative manner (Levy and Glimcher, 2012).

Furthermore, evidence that insula activation in the study was linked to the negative perception of control stimuli was provided in study-2 and 3 which found that the lower the scores (less pleasure) participants reported on the SHAPS, the greater the BOLD activation in the insula. This finding of a negative correlation between reduced pleasure to rewarding events and increased insula activation is similar in some aspects to the finding reported by Kim et al (2010) that the less the magnitude of the expected reward, the greater the anterior insula activation. The finding could be interpreted in a similar way, as the insula is involved in processing negative reinforcement and subjective feelings.

However, it is unknown whether this activation is due to the insula is coding the rewarding events as negative, or due to an inability to 'switch-off' negative feelings, which then disturb the conscious experience of pleasure to rewards gained during the task that may be signaled by other regions in the reward network, and it can only speculate the meaning. Therefore, the insula could be a fruitful area for future reward imaging studies to explore further.

In addition, the theme could be interpreted as the right anterior insula is involved in the "regulation" of salience when control stimuli are received (Eckert et al., 2009), rather than in processing negative emotions elicited by the control stimuli. When control stimuli are received during the target detection task, this regulation of salience might be involved where attention is waning as careless mistakes or unexpected errors happen (not receiving rewards – response to the targets too slow), but once there is too much arousal it may lead to risks creating poor performance by becoming anxious (Eckert et al., 2009). To expand this view further, it is reasonable to assume that the increased anterior insula activation to control stimuli could be associated with self-monitoring of mistakes, as the control stimuli were only presented when participants erred. Errors resulted in participants' arousal. This ability to consciously perceive one's own mistakes has been established as "error awareness" (Klein, Ullsperger, and Danielmeirer, 2013; Wessel et al., 2012). The current finding could reflect that the right anterior insula activation increased when receiving and processing information on surprising and unexpected errors (Klein, Ullsperger, and Danielmeirer, 2013; Wessel et al., 2012), and even involved in increased necessity of effort (Croxson et al., 2009; Prevost et al., 2010).

#### **7.2.5. The correlation between BOLD activity and SHAPS hedonic level**

Activation in the OFC and other regions in the reward network to rewards may not only be related to reward value but also to the hedonic experience of gaining rewards, as the relative value of rewards and hedonic experience are intimately linked (Kringelbach 2005, Elliott et al., 2008). The sixth theme to emerge from the findings of this thesis was the direct correlation between BOLD activation in several brain regions and self-reported levels of hedonic tone on the SHAPS. It has already discussed the negative correlation between insula activation and scores on the SHAPS above, in addition to the positive correlation between amygdala and SHAPS. Below it discusses two more of the regions showing significant correlations between activation in the context of reward and hedonic levels.

### **7.2.5.1. OFC activation is positively correlated with hedonic tone**

High scores on the SHAPS, were positively correlated with right medial and lateral OFC activation in response to rewards, regardless of reward type. There have been no previous fMRI studies to have explored this kind of relationship. Only a few experiments have studied the relationship between subjective pleasantness ratings of a specific reward stimulus gained by participants during task presentation and BOLD response to that reward (e.g. Grabenhorst et al., 2010; Rolls et al., 2003; de Araujo et al., 2003; Kringelbach et al., 2003). These have tended to find BOLD activation in the OFC is robustly correlated with a state of subjective pleasantness, (Kringelbach et al., 2003, Grabenhorst et al., 2010). The subjective pleasantness in these previous studies can be conceptualized as measuring a 'liking' state, which is similar in some degree to the "responsiveness to rewards" described in the current study, whereby a higher SHAPS score could mean participants were more responsive to rewards during the task. Therefore, the finding of a positive correlation between the OFC activation and SHAPS score is compatible with the findings of these previous studies to some degree.

### **7.2.5.2. Subgenual cingulate and putamen activations are negatively correlated with hedonic level**

The second study additionally revealed a negative regression between SHAPS scores and BOLD activation in the subgenual cingulate and putamen in response to each reward. The subgenual cingulate has been suggested to play a critical role in modulating negative mood states, as this region is involved in both acute sadness and antidepressant treatment effects (Mayberg et al., 1999; Seminowicz et al., 2004). Importantly this region is the target of deep brain stimulation to treat major depression, as hyperactivation of the subgenual cingulate allows negative emotions to overwhelm thinking and mood (Hamani et al., 2011). Clinical data provides further evidence by showing that a decrease in subgenual cingulate activity is reported with a clinical response to various antidepressant treatments (e.g. SSRI, antidepressant medications, ECT, rTMS and ablative surgery; Dougherty et al., 2003; Goldapple et al., 2004; Malizia, 1997; Mayberg et al., 2000; Mottaghy et al., 2002; Nobler et al., 2001). Therefore, the finding of a negative correlation between a measure of hedonic response and subgenual cingulate activation could be due to its function in modulating negative emotions and an impaired response to rewarding stimuli.

The results of study-2 also revealed a decreasing SHAPS score was correlated with

greater bilateral putamen activation to each type of reward. This finding can be interpreted in a similar way to the regression finding of insula activation, as these two regions have been referred to as the “hate circuit” of the brain (Zeki and Romaya, 2008), and putamen has been reported to be involved in processing the perception of contempt and disgust, and could be part of the motor system to mobilize individuals to take action (Zeki and Romaya, 2008). Therefore, an interesting question could be asked with regard to the negative correlation between BOLD activation (especially in putamen and insula) and hedonic level – did the participants with low hedonic level (low responsiveness to everyday rewards) hate or dislike the rewards? This could be an interesting area for future reward imaging studies to explore, as it might be the case that the less pleasure, the higher putamen and insula responses, and the more dislike of the rewarding stimuli.

The direct correlation observed in the thesis between BOLD activations and SHAPS scores shows how responsive an individual is to the experience of pleasure from rewards in their everyday lives correlates directly with BOLD activation in the brain reward network. Further investigation of the correlation between reward and hedonic level could have important implications for understanding disorders which have symptoms of anhedonia and impaired motivation, such as depression.

#### **7.2.6. Evidence for the Context Dependent Theory of Reward Processing**

The final theme is derived from study-3 which demonstrated that coding the relative value of rewards in the brain reward network is context dependent. The pairwise contrasts in study-3 revealed very different results from the previous two experiments, as no dissociable neural responses were found between SR and MR, which may be attributed to the changed ‘relative value’ of the stimuli, or due to a “de-valued” SR. The reason for this may be that participants changed the perception of the value of the SR, in the context of the additional CR present. This finding supports the context-dependent theory (Nieuwenhuis et al., 2005; Elliott et al., 2008), which suggests the reward processing system judges the best possible outcome in a given context to be favorable and the worst possible outcome to be unfavorable, regardless of the absolute magnitudes of these outcomes (Nieuwenhuis et al., 2005). Evidence has been shown by many previous fMRI studies which have reported that BOLD responses to rewarding stimuli are influenced by the context in which the outcomes are experienced (O’Doherty et al., 2000; Small et al., 2001; Gottfried et al., 2003; Akitsuki et al., 2003; Elliott et al., 2000, 2008; Nakahara et al., 2004; Nieuwenhuis et al., 2005). Thus, the reward values of social and monetary stimuli in study-3 were very likely affected by the added presence of the chocolate reward.

The behavioural results support this view by showing that the target detection rate for monetary and chocolate reward was very similar but significantly higher than for SR. Also the target detection rate for SR and SC were almost the same. This may suggest that in the current task context, participants are not very motivated by SR, or SR was not as rewarding as in the previous experiments. The informal post-scan interview results also support this view as most participants said they were more excited about the money and chocolate, some of them even said they disliked receiving the social reward. This is very different from study-1 and study-2, in which many participants reported they liked the social reward more than monetary rewards.

In addition, neither the pairwise contrast of MR versus CR nor SR versus CR revealed dissociable neural response in the brain reward network. This may be explained, as the affective value or emotional intensity of the three rewards was encoded similarly in the current task paradigm. The behavioural results show MR and CR had very similar target detection accuracy rates. Also, another reason may be that participants knew the high street value of the chocolate (worth £7) before the experiment, which may have inflated the value of the reward (or affective value), but may also have de-valued SR. To sum up, the SR in the fMRI study-1 and study-2 had stronger reward/affective value than MR, whereas it appeared de-valued in study-3 so that it had the same affective intensity to MR and CR.

### **7.2.7. Evidence for the OFC-amygdala-striatum circuit**

Although in the discussion sections of the three experimental chapters it focuses on the role of each of the regions of the brain reward network separately, it strongly believes the OFC-amygdala-striatum circuit exists in the reward processing tasks. Taking into account the strong anatomical and functional connections between the OFC, striatum, amygdala and insula (Camara et al., 2009) as discussed in chapter 1 as well as the consistency of the results of the three fMRI studies provides some basis for this assumption. These regions (OFC, striatum, and amygdala) were reliably activated in the union by the receipt of social, monetary and chocolate reinforcers. The OFC-amygdala-striatum circuit has been reviewed in McClure et al (2004) to be a common reward network. Also, the OFC-striatum circuit has been proposed by Montague and Berns (2002) to be a common currency in a prediction error based model of how reward expectancy should influence decision making. This common currency allows for comparison of different reward values in order to make decisions. This thesis provides evidence to support the existence of the reward network and provides direct evidence to support the OFC function as a common currency.

### **7.3. Limitations**

Some limitations of the experiments presented in this thesis may have become apparent over the course of reading this thesis. The section below draws attention to some of these limitations and discusses these under three main headings. These are limitations regarding the pilot behavioral tests, the sample groups, and the food reward employed.

#### **7.3.1. Limitations of the pilot behavioural tests**

A behavioural test needs to be applied once a new fMRI study is conducted and there are changes in the task stimuli, even if the changes are small. fMRI studies 2 and 3 could have been improved by applying behavioural experiments beforehand to test the equivalence of the task stimuli, just like it did before in the fMRI study-1. As discussed in Chapter 2, a test of equivalence between social and monetary reinforcers behaviourally can increase the reliability of the task paradigm and give confidence to findings in the later fMRI studies. Thus, it could be more confident with the neural responses to the different types of reinforcer, and that any differences were not due to variances in the behavioural effects. Furthermore, in the fMRI study-3, it added a new reward stimulus – chocolate into the task paradigm, which resulted in a context change so that the original social and monetary reward may have changed in their relative value to each other. Therefore, the design and indeed interpretation of the fMRI studies could have been improved by carrying out tests examining reward learning for all of the reinforcers used (rewards and punishments).

#### **7.3.2. Possible limitation for sample size**

Each of the studies presented could have gained greater validity by having a larger sample of participants. According to Friston et al (1999), for group random effects analysis, an experimental sample that exceeds 10 participants in fMRI studies is necessary to achieve 70-80% power at the voxel level for typical activations at a  $p < 0.05$  threshold (Friston et al., 1999). The study-2 and 3 analyzed data on 11 participants, which therefore is a reasonable size for the data analysis. Also, take into consideration the significance of the SPM statistics, which use multiple corrections according to the random field theory (Worsley, 2003), to ensure there is control over the possibility of false positives in the experiments, thus ensuring the reliability of any significant effect revealed. However, the fMRI studies in this thesis could potentially be improved by using larger sample sizes, as

there have been other researchers who have suggested a slightly larger sample size for random effects fMRI analysis. For instance, Desmond and Glover (2002) suggested that having a minimal of 12 subjects was necessary in order to achieve 80% power at the single voxel level for typical activations at a liberal threshold of 0.05, whereas the number of subjects needs to be doubled when a more realistic threshold is applied that approaches those used after correcting for multiple comparisons.

### **7.3.3. Possible limitation for sample representation**

In the study-3, it recruited chocolate lovers in order to make sure the participants employed in this study like this reward, as obviously not everyone likes chocolate. However, this may result in small sample representation as the chocolate lover's brain activity in response to rewards in the current task paradigm may not be entirely representative of the population in general. For example, increased reward value of gaining chocolate would influence the reward value of social and monetary stimuli. In study-3, the chocolate lovers may have coded the chocolate reward as having a greater subjective value or elicited more pleasure from the receipt of chocolate than a more representative sample of the population would have. To recruit participants normally as did in study-1 and 2 would avoid this limitation, however, it would be likely to have the result that chocolate reward was not rewarding enough if more participants did not like chocolate. It would be useful to do a separate behavioural experiment to test the equivalency of the behavioural effects of the three rewards, prior to the fMRI study.

### **7.4. Future research**

This section examines future areas of investigation that were outside the capacity and time-scale of this thesis, but which may be important to conduct in the future.

The results presented provide evidence that distinct patterns of activation in the reward network underlie the receipt of different types of rewards. Information about rewarding stimuli is most likely represented in one or more of these regions depending on the nature, intensity and context of the stimuli, and then merged in the OFC for comparison, in order for an appropriate action to be made. When the OFC acts as a common currency, it does not work on its own, but more likely acts in union with the striatum, amygdala, and insula. Therefore, an obvious direction for future work to take would be to examine functional connectivity of these neural regions (OFC, amygdala, and striatum) in the studies it performed using psychophysiological interaction analyses or structural equation

modelling.

The third experiment would have benefited from comparing an immediate primary food reward (e.g. liquid chocolate receipt, whilst in the scanner) with the other reinforcer types used. This was actually the primary aim of this study – to compare primary food, abstract money, and social reinforcement within a task paradigm. As discussed in Chapter 1, primary and secondary reinforcers are likely to be encoded through different neural circuits, whereby primary reinforcers may be encoded via sensory and subcortical systems, while more complex secondary or abstract reinforcers may be encoded via multi-modal cortical pathways. Moreover, most of the multi-types reward processing studies have employed primary juice and monetary reward (Levy and Glimcher, 2012). Therefore, future studies that compare primary liquid chocolate with money or compare primary liquid chocolate with social reward could provide compatible results to the previous studies. Furthermore, this kind of study could help to test the findings of functional specialization within the reward network and the common currency theory.

This thesis reports evidence consistent with the hypothesis that there is a direct association between self-reported hedonic scores and BOLD activation in the OFC to rewards. Moreover, we found correlations between the insula and subgenual cingulate activation with anhedonia which has important implications for patients with poor emotional regulation and/or motivational responses, especially patients with depression. Future studies on depressed patient groups and comparisons with control groups could examine the above findings further, as anhedonia is the main symptom of depression. Moreover, any future studies that examine reward processing in depressed patients, particularly if examining levels of hedonic response, would benefit from dividing patients into different groups, according to their symptoms. Some researchers theorise that depression is a heterogeneous group of disorders (Chen et al., 2000). Given that patient groups are often very small in imaging studies, results can be confounded by the heterogeneity of symptoms present. Therefore, a better insight into anhedonia might be provided by the correlating severity of anhedonia with impaired neural responses of reward regions in depressed individuals.

Furthermore, similar fMRI studies on social and monetary reward processing could be tested on patients with autism, as Scott-Van Zeeland (2010) revealed that children with autism showed a diminished frontostriatal BOLD response to social rewards, but not monetary rewards during rewarded learning, which may relate to social learning impairments evident in these children. The findings in this thesis reported social and

monetary reinforcers were valued differently in some regions of the reward network (OFC and amygdala), with greater reward value (affective intensity) to social reinforcers than monetary. This finding could be examined further in patients with autism, where social stimuli may have a reduced reward value (Dawson et al., 1998; 2005; Schultz, 2005).

## **7.5. Conclusion**

This thesis generated seven main themes which could be separated into two categories – themes derived from the contrast analyses between different reinforcers, and themes derived from regression analyses between BOLD activity and SHAPS hedonic scores. The finding of distinct BOLD activation in the OFC (medial and lateral) between the social and monetary reinforcers and the two polarities of valence, suggests that different rewards may be represented and valued separately in the brain (Kringelbach and Rolls, 2004; Kim et al., 2010). This process of encoding divergent reward information is the basis of the process of encoding convergent reward information in the OFC – a common neural currency for representation and comparison of different reward values. The finding of a crossover interaction between reinforcer type and valence in the OFC provides direct evidence for this common currency theory. Besides the OFC, the amygdala, also responded to social and monetary reinforcers in a distinct manner, with greater amygdala activation to social than monetary reinforcers. This finding suggested a role for the amygdala in coding the affective value of rewarding stimuli and that social reinforcers have stronger affective intensity than monetary and food in the task paradigm. The themes derived from the regression analyses implicated that how responsive an individual is to the experience of pleasure from daily rewards correlated directly with BOLD activation in the OFC, putamen, and insula in response to rewards in the task. Thus, further investigation of the correlations between reward and hedonic level could have important implications for understanding how human hedonic levels impact on responses to various reinforcements.

## List of References

- ADOLPHS, R., 2010. Conceptual Challenges and Directions for Social Neuroscience. *Neuron*, **65**(6), pp. 752-767.
- AGGLETON, J.P. and PASSINGHAM, R.E., 1981. Stereotaxic surgery under X-ray guidance in the rhesus monkey with special reference to the amygdala. *Exp Brain Res*, **44**(3), pp. 271-276.
- AHARON, I., ETCOFF, N. and OTHERS, 2001. Beautiful faces have variable reward value: fMRI and behavioural evidence. *Neuron*, **32**(3), pp. 537-551.
- AKITSUKI, Y., SUGIURA, M. and OTHERS, 2003. Context-dependent cortical activation in response to financial reward and penalty: an event-related fMRI study. *NeuroImage*, **19**(4), pp. 1674-1685.
- ANDERSON, I.M., RICHELL, R.A. and OTHERS, 2003. The effect of acute tryptophan depletion on probabilistic choice. *J Psychopharmacol*, **17**(1), pp. 3-7.
- ARAUJO, I.E. and ROLLS, E.T., 2003. Representation in the human brain of food texture and oral fat. *J Neuroscience*, **24**(12), pp. 3086-3093.
- Arias-Carrion, O. and Poppel, E., 2007. Dopamine, learning, and reward-seeking behavior. *Acta Neurobiol Exp (Wars)*, **67**(4), pp. 481-488.
- Arias-Carrion, O. and Stamelou, M., 2010. Targeting the orexin system: a new approach for treating insomnia. *CNS Neurol Disord Drug Targets*, **9**(6), pp. 667.
- ARNOW, B.A. and OTHERS, 2002. Brain activation and sexual arousal in healthy, heterosexual males. *Brain*, **125**(5), pp. 1014-1023.
- ASHBURNER, J. and FRISTON, K.L., 1999. Nonlinear spatial normalization using basis functions. *Hum Brain Mapping*, **7**(4), pp. 254-266.
- ATTWELL, D. and IADECOLA, C., 2002. The neural basis of functional brain imaging signals. *Trends Neuroscience* **25**(12), pp. 621-625.
- ATTWELL, D. and LAUGHLIN, S.B., 2001. An energy budget for signaling in the grey matter of the brain. *J Cereb Blood Flow Metab*, **21**(10), pp. 1133-1145.
- BANDETTINI, P., JESMANOWICZ, A., WONG, E.S. and HYDE, J.S., 1993. Processing strategies for time-course data sets in functional MRI of the human brain. *Magn Reson Med*, **30**(2), pp. 161-173.
- BANDURA, A., 1977. Self-efficacy: toward a unifying theory of behavioural change. *Psychol Rev*, **84**(2), pp. 191-215.
- BARRETT, T.W., 1969. Studies of the function of the amygdaloid complex in *Macaca mulatta*. *Neuropsychologia*, **7**, pp. 1-12.

- BASTEN, U., BIELE, G., HEEKEREN, H.R. and FIEBACH, C.J., 2010. How the brain integrates costs and benefits during decision making. *Proc Natl Acad Sci USA*, **107**(50), pp. 21767-21772.
- BAXTER, M.G. and MURRAY, E.M., 2007. Early discrimination reversal learning impairment and preserved spatial learning in a longitudinal study of Tg2576 APPsw mice. *Neurobiol Aging*, **28**(8), pp. 1248-1257.
- BAXTER, M.G. and MURRAY, E.A., 2002. The amygdala and reward. *Nat Rev Neuroscience*, **3**(7), pp. 563-573.
- BAXTER, M.G., PARKER, A. and OTHERS, 2000. Control of response selection by reinforcer value requires the interaction of amygdala and orbital prefrontal cortex. *J Neuroscience*, **20**(11), pp. 4311-4319.
- BEAUREGARD, M.A.O., 1998. The functional neuroanatomy of major depression: an fMRI study using an emotional activation paradigm. *Neuroreport*, **9**(14), pp. 3253-3258.
- BECK, A., WARD, C., MENDELSON, M., MOCK, J. and ERBAUGH, J., 1961. An inventory for measuring depression. *Archives of General Psychiatry*, **4**, pp. 561-571.
- BECK, A.T., STEER, R.A., BALL, R. and RANIERI, W., 1996. Comparison of Beck Depression Inventories-IA and-II in psychiatric outpatients. *Journal of personality assessment*, **67**(3), pp. 588-597.
- BECK, A.T., STEER, R.A. and GARBIN, M.G.J., 1988. Psychometric properties of the Beck Depression Inventory Twenty-five years of evaluation. *Clin.Psych.Review*, **8**, pp. 77-100.
- BECK, S.M., LOCKE, H.S., SAVINE, A.C., JIMURA, K. and BRAVER, T.S., 2010. Primary and secondary rewards differentially modulate neural activity dynamics during working memory. *PLoSOne*, **5**(2).
- BECKMANN, C.F., JENKINSON, M. and SMITH, S.M., 2003. General multilevel linear modelling for group Analysis in fMRI. *NeuroImage*, **20**, pp. 1052-1063.
- BELLEBAUM, C., JOKISCH, D., GIZEWSKI, E.R., FORSTING, M. and DAUM, I., 2012. The neural coding of expected and unexpected monetary performance outcomes: Dissociations between active and observational learning. *Behavioural Brain Research*, **227**(1), pp. 241-251.
- BELLEBAUM, C., KOCH, B. and OTHERS, 2008. Focal basal ganglia lesions are associated with impairments in reward-based reversal learning. *Brain*, **131**(3), pp. 829-841.
- BERNS, G.S., MCCLURE, S.M. and OTHERS, 2001. Predictability modulates human brain response to reward. *J Neuroscience*, **21**(8), pp. 2793-2798.
- BERRIDGE, K.C., 2007. The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology (Berl)*, **191**(3), pp. 391-431.
- BERRIDGE, K.C. and KRINGELBACH, M.L., 2008. Affective Neuroscience of pleasure: reward in humans and animals. *Psychopharmacology (Berl)*, **199**(3), pp. 457-480.

- BERRIDGE, K.C. and ROBINSON, T.E., 1998. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res Brain Res Rev*, **28**(3), pp. 309-369.
- BLACKWELDER, W.C., 2004. Current issues in clinical equivalence test. *Journal of dental research*, **83**, pp. 113-115.
- BLAMIRE, A.A.O., 1992. Dynamic mapping of the human visual cortex by high-speed magnetic resonance imaging. *Proc Natl Acad Sci USA*, **89**(22), pp. 11069-11073.
- BLUNDELL, P., HALL, G. and OTHERS, 2001. Lesions of the basolateral amygdala disrupt selective aspects of reinforcer representation in rats. *J Neuroscience*, **21**(22), pp. 9018-9026.
- BONVENTO, G., N SIBSON and L PELLERIN, 2002. Does glutamate image your thoughts? *Trends Neuroscience*, **25**(7), pp. 359-364.
- BREITER, H.A.O., 1997. Acute effects of cocaine on human brain activity and emotion. *Neuron*, **19**(3), pp. 591-611.
- BREITER, H.C., AHARON, I. and OTHERS, 2001. Functional imaging of neural responses to expectancy and experience of monetary gains and losses. *Neuron*, **30**(2), pp. 619-639.
- BRITTON, J.C. and OTHERS, 2006. Neural correlates of social and nonsocial emotions: An fMRI study. *NeuroImage*, **31**, pp. 397-409.
- BROVELLI, A., NAZARIAN, B., MEUNIER, M. and BOUSSAOU, 2011. Differential roles of caudate nucleus and putamen during instrumental learning. *NeuroImage*, **57**(4), pp. 1580-90.
- BUCKNER, R.L., BANDETTINI, P.A., O' CRAVEN, K.M., SAVOY, R.L., PETERSEN, S.E., RAICHLE, M.E. and ROSEN, B.R., 1996. Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging. *Proc Natl Acad Sci USA*, **93**, pp. 14878-14883.
- BUROCK, M., BUCKNER, R.L., WOLDORFF, M.G., ROSEN B.R. and DALE, A.M., 1998. Randomized event-related experimental designs allow for extremely rapid presentation rates using functional MRI. *Neuroreport*, **9**(16), pp. 3735-3739.
- CAMARA, E., RODRIGUEZ-FORNELLS, A. and MUNTE, T.F., 19. 2008. Functional connectivity of reward processing in the brain. *Frontiers in Human Neuroscience*, **2**, pp. 19.
- CAMARA, E., RODRIGUEZ-FORNELLS, A., YE, Z. and MUNTE, T.F., 2009. Reward networks in the brain as captured by connectivity measures. *Frontiers in Human Neuroscience*, **3**(3), pp. 350-362.
- CARDINAL, R.N., PARKINSON, J.A. and OTHERS, 2002. The role of the anterior cingulate cortex in the control over behavior by Pavlovian conditioned stimuli in rats. *Behav Neuroscience*, **117**(3), pp. 566-587.
- CARMICHAEL, S.T. and PRICE, J.L., 1995. Sensory and premotor connections of the orbital and medial prefrontal cortex. *J Comp Neurol*, **363**, pp. 642-664.

- CARMICHAEL, S.T. and PRICE, J.L., 1996. Connectional networks within the orbital and medial prefrontal cortex of macaque monkeys. *J Comp Neurol*, **371**, pp. 179-207.
- CHAVHAN, G.B., BABYN, P.S., THOMAS, B., SHROFF, M.M. and HAACKE, E.M., 2009. Principles, techniques, and applications of T<sup>2</sup>\*-based MR imaging and its special applications. Radio graphics. *A Review Publication of the Radiological Society of North America*, **9**(5), pp. 1433-1449.
- CHIARA, G. and BASSAREO, V., 2007. Reward system and addiction: what dopamine does and doesn't do. *Curr Opin Pharmacol*, **7**(1), pp. 69-76.
- CHIB, V.S., RANGEL, A., SHIMOJO, S. and O'DOHERTY, J.P., 2009. Evidence for a common representation of decision values for dissimilar goods in the human ventromedial prefrontal cortex. *J Neuroscience*, **29**(39), pp. 12315-12320.
- COHEN, A.L., FAIR, D.A., DOSENBACH, N.U., MIEZIN, F.M., DIERKER, D., VAN ESSEN, D. C. PETERSEN and S. E., 2008. Defining functional areas in individual human brains using resting functional connectivity MRI. *NeuroImage*, **41**(1), pp. 45-57.
- COOLEY, E. and S NOWICKI JR, 1989. Discrimination of facial expressions of emotion by depressed subjects. *Genet Soc Gen Psychol Monogr*, **115**(4), pp. 449-465.
- Cools, R., CLARK, L. and ROBBINS, T.W., 2004. Differential responses in human striatum and prefrontal cortex to changes in object and rule relevance. *J Neuroscience* **24**(5), pp. 1129-1135.
- CORBIT, L.H. and BALLEINE, B.W., 2005. Double dissociation of basolateral and central amygdala lesions on the general and outcome-specific forms of pavlovian instrumental transfer. *J Neuroscience*, **25**(4), pp. 962-970.
- CORNISH, J.L. and KALLIVAS, P.W., 2000. Glutamate transmission in the nucleus accumbens mediates relapse in cocaine addiction. *J Neuroscience*, **20**(15), pp. RC89.
- CRAIG, A.D., 2009. How do you feel now? The anterior insula and human awareness. *Nat rev Neuroscience*, **10**(1), pp. 59-70.
- CRAIG, A.D., 2002. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neuroscience*, **3**(8), pp. 655-666.
- CRIBBIE, R.A., GRUMANN, J. and ARPIN-CRIBBIE, C., 2004. Recommendations for applying tests of equivalence. *Journal of Clinical Psychology*, **60**, pp. 1-10.
- D., D.D. and OTHERS, 2003. Cerebral metabolic correlates as potential predictors of response to anterior cingulotomy for treatment of major depression. *J Neurosurg*, **99**(6), pp. 1010-1017.
- DAMADIAN, R., 1977. Nuclear magnetic resonance: a noninvasive approach to cancer. *Hosp Pract*, **12**, pp. 63-70.
- DAMADIAN, R., 1971. Tumor detection by nuclear magnetic resonance. *Science*, **171**(3976), pp. 1151-1153.
- DARWIN, C., 1872. The expression of the emotions in man and animals. *Chicago, IL, University of Chicago Press*.

- DAY, J.J. and CARELLI, R.M., 2007. The nucleus accumbens and Pavlovian reward learning. *Neuroscientist*, **13**(2), pp. 148-159.
- DELGADO, M.R., 2007. Reward-related responses in the human striatum. *Ann NY Acad Sci*, **1104**, pp. 70-88.
- DELGADO, M.R., LOCKE, H.M. and OTHERS, 2003. Dorsal striatum responses to reward and punishment: effects of valence and magnitude manipulations. *Cogn Affect Behav Neuroscience*, **3**(1), pp. 27-38.
- DELGADO, M.R., NYSTROM, L.E. and OTHERS, 2000. Tracking the hemodynamic responses to reward and punishment in the striatum. *J Neurophysiol*, **84**(6), pp. 3072-3077.
- DIAZ, J., 1996. How Drugs Influence Behaviour. *Englewood Cliffs, Prentice Hall Press*.
- DORF, R.C. and BISHOP, R.H., 2005. Modern Control Systems. *Upper Saddle River, NJ 07458. Pearson Prentice Hall*.
- DREVETS, W.C., 2001. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Current opinion in neurobiology*, **11**, pp. 240-249.
- ECKERT, M.A., MENON, V., WALCZAK, A., AHLSTROM, J., DENSLOW, S., HORWITZ, A. and DUBNO, J.R., 2009. At the heart of the ventral attention system: the right anterior insula. *Hum Brain Mapping*, **30**(8), pp. 2530-2541.
- ELLIOTT, R., AGNEW, Z. and DEAKIN, J.F., 2008. Medial orbitofrontal cortex codes relative rather than absolute value of financial rewards in humans. *Eur J Neuroscience*, **27**, pp. 2213-2218.
- ELLIOTT, R., FRISTON, K.J. and OTHERS, 2000. Dissociable neural responses in human reward systems. *J Neuroscience*, **20**(16), pp. 6159-6165.
- ELLIOTT, R., FRITH, C.D. and DOLAN, R.J., 1997. Differential neural response to positive and negative feedback in planning and guessing tasks. *Neuropsychologia*, **35**, pp. 1395-1404.
- ELLIOTT, R., NEWMAN, J.L., LONGE, O.A. and DEAKIN, J.F., 2004. Instrumental responding for rewards is associated with enhanced neuronal response in subcortical reward systems. *NeuroImage*, **21**(3), pp. 984-990.
- ELLIOTT, R., NEWMAN, J.L., LONGE, O.A. and DEAKIN, J.F., 2003. Differential response patterns in the striatum and orbitofrontal cortex to financial reward in humans: a parametric functional magnetic resonance imaging study. *J Neuroscience*, **1**(23), pp. 303-307.
- FANSELOW, M.S. and GALE, G.D., 2003. The amygdala, fear and memory. *Ann N Y Acad Sci*, **985**, pp. 125-134.
- FERSTER, C.B. and SKINNER, B.F., 1957. Schedules of reinforcement. Office of Naval Research. *New York: Harvard University, and United States. Appleton-Century-Crofts*.
- FITZGERALD, T.H., SEYMOUR, B. and DOLAN, R.J., 2009. The role of human orbitofrontal cortex in value comparison for incommensurable objects. *The Journal of*

*Neuroscience. The Official Journal of the Society for Neuroscience*, **29**(26), pp. 8388-8395.

FORMAN, S.D., COHEN, J.D., FITZGERALD, M., EDDY, W.F., MINTUN, M. and NOLL, D.C., 1995. Improved assessment of significant activation in functional magnetic resonance imaging, fMRI: Use of a cluster size threshold. *Magn Reson. Med*, **33**, pp. 636-647.

FRISTON, K.J., HOLMES, A.P. and WORSLEY, K.J., 1999. How many subjects constitute a study? *NeuroImage*. **10**(1), pp. 1-5.

FRISTON, K., HOLMES, A.P., PRICE, C.J. and BUCHEL, K.W., 1999. Multisubject fMRI studies and conjunction analyses. *NeuroImage*, **10**(4), pp. 385-396.

GANIS, G. and KOSSLYN, S.M., 2002. Neuroimaging. In V.S. Ramachandran, Ed. *Encyclopedia of the Human Brain*, **3**, pp. 493-505. New York Academic Press.

GLASCHER, J., HAMPTON, A.N. and O'DOHERTY, J.P., 2009. Determining a role for ventromedial prefrontal cortex in encoding action-based value signals during reward-related decision making. *Cereb Cortex*, **19**(2), pp. 483-495.

GOTHARD, K.M. and OTHERS, 2007. Neural Responses to Facial Expression and Face Identity in the Monkey Amygdala. *Neurophysiol*, **97**, pp. 1671-1683.

GOTO, Y. and GRACE, A.A., 2005. Dopaminergic modulation of limbic and cortical drive of nucleus accumbens in goal-directed behaviour. *Nat Neuroscience* **8**(6), pp. 805-812.

GOTTFRIED, J.A., O'DOHERTY, J. and DOLAN, R.J., 2002. Appetitive and aversive olfactory learning in humans studied using event-related functional magnetic resonance imaging. *J Neuroscience*, **22**, pp. 10829-10837.

GRABENHORST, F., D'SOUZA, A.A., PARRIS, B.A., ROLLS, E.T. and PASSINGHAM, R.E., 2010. A common neural scale for the subjective pleasantness of different primary rewards. *NeuroImage*, **51**(3), pp. 1265-1274.

GRABENHORST, F. and ROLLS, E.T., 2011. Value, pleasure and choice in the ventral prefrontal cortex. *Trends Cogn Sci*, **15**(2), pp. 56-67.

GRAHAM, G.H. and UNRUH, J., 1990. The motivational impact of nonfinancial employee appreciation practices on medical technologists. *Health Care Superv*, **8**(3), pp. 9-17.

GRELOTTI, D.J., GAUTHIER, I. and SCHULTZ, R.T., 2002. Social interest and the development of cortical face specialization: what autism teaches us about face processing? *Developmental Psychobiology*, **40**, pp. 213.

HAMANI, C. and OTHERS, 2011. The subcallosal cingulate gyrus in the context of major depression. *Biol Psychiatry*, **69**(4), pp. 301-308.

HAMANN, S. and MAO, H., 2002. Positive and negative emotional verbal stimuli elicit activity in the left amygdala. *Neuroreport*, **13**, pp. 15-19.

HARE, T.A., CAMERER, C.F., KNOEPFLE, D.T. and RANGEL, A., 2010. Value computations in ventral medial prefrontal cortex during charitable decision making incorporate input from regions involved in social cognition. *Journal of Neuroscience*, **30**, pp. 583-590.

- HARRISON, R.V., HAREL, N., PANESAR, J. and MOUNT, R.J., 2002. Blood capillary distribution correlates with hemodynamic-based functional imaging in cerebral cortex. *Cerebral Cortex*, **12**(3), pp. 225-233.
- HASHEMI, R.H., BRADLEY, W.G. and LISANTI, C., 2004. MRI. The Basics. Second edition, *Williams and Wilkins*.
- HASHEMI, R.H., BRADLEY, W.G. and LISANTI, C.J., 2010. MRI: The basics. *Lippincott Williams and Wilkins*.
- HATFIELD, T. and OTHERS, 1996. Neurotoxic lesions of basolateral, but not central, amygdala interfere with Pavlovian second-order conditioning and reinforcer devaluation effects. *J Neuroscience* **16**(16), pp. 5256-5265.
- HENNIG, F.J., 1998. Current and future applications of magnetic resonance in cardiovascular disease edited by Charles B. Higgins, Joanne S. Ingwall, and Gerald M. Pohost *Futura Publishing Company, Inc., Armonk, N. Y.*
- HENSON, R.N.A. and RUGG, M.D., 2001. Effects of stimulus repetition on latency of the BOLD impulse response. *NeuroImage*, **13**, pp. 683.
- HENSON, R.N.A., RUGG, M.D. and FRISTON, K.J., 2001. The choice of basis functions in event-related fMRI. *NeuroImage*, **13**, pp. 149.
- HERRNSTEIN, R.J., 1964. Secondary reinforcement and rate of primary reinforcement. *Journal of the Experimental Analysis of Behaviour*, **7**, pp. 27-36.
- HOBSON, R., 1986. The autistic child's appraisal of expressions of emotion: a further study. *J Child Psychol Psychiatry*, **27**(3), pp. 321-342.
- HOBSON, R. and LEE, A., 1998. Hello and goodbye: a study of social engagement in autism. *J Autism Dev Disorder*, **28**(2), pp. 117-127.
- HOBSON, R. and J OUSTON, A.L., 1988. Emotion recognition in autism: coordinating faces and voices. *Psychol Med*, **18**(4), pp. 911-923.
- HOLLAND, P., 1998. Amount of training affects associatively-activated event representation. *Neuropharmacology*, **37**(4-5), pp. 461-469.
- HOLLAND, P.C., 1990. Event representation in Pavlovian conditioning: image and action. *Cognition*, **37**(1-2), pp. 105-31.
- HOLLAND, P.C. and GALLAGHER, M., 2004. Amygdala-frontal interactions and reward expectancy. *Current Opinion in Neurobiology*, **14**, pp. 148-155.
- HOLLAND, P.C. and RESCORLA, R.A., 1975. Second-order conditioning with food unconditioned stimulus. *J Comp Physiol Psychol*, **88**(1), pp. 459-467.
- HOMMER, D.W., KNUTSON, B. and OTHERS, 2003. Amygdala recruitment during anticipation of monetary rewards: an event-related fMRI study. *Ann N Y Acad Sci*, **985**, pp. 476-478.

- HUETTEL, S.A., STOWE, C.J., GORDON, E.M., WARNER, B.T. and PLATT, M.L., 2006. Neural signatures of economic preferences for risk and ambiguity. *EMBO J*, **25**(12), pp. 2828-2836.
- HYMAN, S.E., MALENKA, R.C. and OTHERS, 2006. Neural mechanisms of addiction: the role of reward-related learning and memory. *Annual Rev Neuroscience* **29**, pp. 565-598.
- HYNES, M. and ROSENTHAL, A., 1999. Specification of dopaminergic and serotonergic neurons in the vertebrate CNS. *Curr Opin Neurobiol*, **9**(1), pp. 26-36.
- IIDAKA, T. and OMORI, M., MURATA, T., KOSAKA, H., YONEKURA, Y., OKADA, T., SADATO, N., 2001. Neural interaction of the amygdala with the prefrontal and temporal cortices in the processing of facial expressions as revealed by fMRI. *J Cognitive Neuroscience*, **13**(8), pp. 1035-1047.
- IZQUIERDO, A. and MURRAY, E.A., 2007. Selective bilateral amygdala lesions in rhesus monkeys fail to disrupt object reversal learning. *J Neuroscience* **27**(5), pp. 1054-1062.
- IZUMA, K., SAITO, D.N. and OTHERS, 2008. *Processing of social and monetary rewards in the human striatum*. *Neuron*, **58**(2), pp. 284-294.
- JEZZARD, P. and BUXTON, R.B., 2006. The clinical potential of functional magnetic resonance imaging. *J Magn Reson Imaging*, **23**(6), pp. 787-793.
- JONES, B. and MISHKIN, M., 1972. Limbic lesions and the problem of stimulus-reinforcement associations. *Exp Neurol*, **36**(2), pp. 362-377.
- JOSEPHS, O. and HENSON, R.N.A., 1999. Event-related fMRI: modelling, inference and optimisation. *Phil. Trans Roy Soc London*, **354**, pp. 1215-1228.
- K, G., SEGAL, Z., GARSON, C., LAU, M., BEILING, P., KENNEDY, S. and MAYBERG, H., 2004. Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behaviour therapy. *Arch Gen Psychiatry*, **61**(1), pp. 34-41.
- KALIVAS, P. and VOLKOW, N.D., 2005. The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry*, **162**(8), pp. 1403-1413.
- KATHARINA, A.B., HANS-PETER, S. and OTHERS, 2011. *Ventromedial prefrontal cortex activation is associated with memory formation for predictable rewards*. *PloSOne*, **6**(2), pp. e16695.
- KEEDWELL, P.A., ANDREW, C., WILLIAMS, S.C., BRAMMER, M.J. and PHILLIPS, M.L., 2005. *The neural correlates of anhedonia in major depressive disorder*. *Biological Psychiatry*, **58**(11), pp. 843-853.
- KELLEY, A.E. and BERRIDGE, K.C., 2002. The Neuroscience of natural rewards: relevance to addictive drugs. *J Neuroscience*, **22**(9), pp. 3306-3311.
- KELLEY, A., 2004. Memory and addiction: shared neural circuitry and molecular mechanisms. *Neuron*, **44**(1), pp. 161-79.
- KELLEY, A., 1999. Functional specificity of ventral striatal compartments in appetitive behaviours. *Ann NY Acad Sci*, **29**(877), pp. 1-90.

- KESNER, R. and ROGERS, J., 2004. An analysis of independence and interactions of brain substrates that subserve multiple attributes, memory systems, and underlying processes. *Neurobiol Learn Mem*, **82**(3), pp. 199-215.
- KIM, H., SHIMOJO, S. and O'DOHERTY, J.P., 2010. Overlapping responses for the expectation of juice and money rewards in human ventromedial prefrontal cortex. *Cereb Cortex*, **21**(4), pp. 769-776.
- KIM, H., SHIMOJO, S. and OTHERS, 2006. Is avoiding an aversive outcome rewarding? Neural substrates of avoidance learning in the human brain. *PLoS Biol*, **4**(8), pp. e233.
- KLEIN, T.A., ULLSPERGER, M. and DANIELMEIER, C., 2013. Error awareness and the insula: links to neurological and psychiatric diseases. *Frontiers in Human Neuroscience*, **7**, pp. 14.
- KLIN, A., 1991. Young autistic children's listening preferences in regard to speech: a possible characterization of the symptom of social withdrawal. *Journal of Autism and Developmental Disorders*, **21**, pp. 29-42.
- KLOPF, D., 1993. Diagnosis of right heart stress with one-and two-dimensional echocardiography-sensible normal values, problems and limitations. *Pneumologie*, **47**(1), pp. 14-18.
- KNUTSON, B. and COOPER, J.C., 2005. Functional magnetic resonance imaging of reward prediction. *Curr Opin Neurol*, **18**(4), pp. 411-417.
- KNUTSON, B., FONG, G.W. and OTHERS, 2003. A region of mesial prefrontal cortex tracks monetarily rewarding outcomes: characterization with rapid event-related fMRI. *NeuroImage*, **18**(2), pp. 263-272.
- KNUTSON, B. and OTHERS, 2001. Anticipation of increasing MR selectively recruits nucleus accumbens. *J Neuroscience*, **21**, pp. RC159.
- KOCH, J., 1990. Perpetual thanks: its assets. *Personnel Journal*, **69**(1), pp. 72-3.
- KOHL, G., PELTZER, J. and OTHERS, *In Press*. Differential effects of social and non-social reward on response inhibition in children and adolescents.
- KOMISARUK, B.R. and OTHERS, 2002. Functional localization of brainstem and cervical spinal cord nuclei in humans with fMRI. *AJNR Am J Neuroradiol*, **23**(4), pp. 609-617.
- KRINGELBACH, M. and ET ROLLS, 2004. The functional neuroanatomy of the human orbitofrontal cortex evidence from neuroimaging and neuropsychology. *Prog Neurobiol*, **72**(5), pp. 341-372.
- KRINGELBACK, M. and O'DOHERTY, J., ROLLS, E.T., ANDREWS, C., 2003. Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. *Cereb Cortex*, **13**(10), pp. 1064-1071.
- LAUWEREYNS, J., TAKIKAWA, Y., KAWAGOE, R., KOBAYASHI, S., KOIZUMI, M., COE, B., SAKAGAMI, M. and HIKOSAKA, O., 2002. Feature-based anticipation of cues that predict reward in monkey caudate nucleus. *Neuron*, **33**(3), pp. 463-73.
- LEDOUX, J.E., 2003. The Self: From Soul to Brain. Annals of the New York Academy of Sciences. *New York Academy of Sciences ISBN 978-1573314503*.

- LEVY, D.J. and GLIMCHER, P.W., 2011. Comparing apples and oranges: using reward-specific and reward-general subjective value representation in the brain. *J Neuroscience*, **31**(41), pp. 14693-14707.
- LEVY, D.J. and GLIMCHER, P.W., 2012. The root of all value: a neural common currency for choice. *Curr Opin Neurobiol*, **22**(6), pp. 1027-1038.
- LEWIS, I., WATSON, B. and WHITE, K.M., 2009. *Internet versus paper-and-pencil survey methods in psychological experiments: Equivalence testing of participant responses to health-related messages*. *Australian Journal of Psychology*, **61**, pp. 107-116.
- LIN, A., ADOLPHS, R. and RANGEL, A., 2011. Social and monetary reward learning engage overlapping neural substrates. *Social Cognitive and Affective Neuroscience*, **7**(3), pp. 274-281.
- LINDQUIST, M. and WAGER, T.D., 2007. Validity and power in hemodynamic response modeling: a comparison study and a new approach. *Hum Brain Mapping*, **28**(8), pp. 764-784.
- LISMAN, J. and GRACE, A.A., 2005. The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron*, **46**(5), pp. 703-713.
- LOGOTHETIS, N. and WANDELL, B.A., 2004. Interpreting the BOLD signal. *Annu Rev Physiol*, **66**, pp. 735-769.
- LOGOTHETIS, N. and PAULS, J., AUGATH, M., TRINATH, T., OELTERMANN, A., 2001. Neurophysiological investigation of the basis of the fMRI signal. *Nature*, **412**(6843), pp. 150-157.
- LOGOTHETIS, N. and PFEUFFER, J., 2004. On the nature of the BOLD fMRI contrast mechanism. *Magn Reson Imaging*, **22**(10), pp. 1517-1531.
- LOH, J., LINDQUIST, M.A. and WAGER, T.D., 2008. Residual analysis for detecting mis-modeling in fMRI Statist. *Sinica*, **18** (4), pp. 1421-1448.
- LONGE, O., SENIOR, C and RIPPON, G., 2009. The lateral and ventromedial prefrontal cortex work as a dynamic integrated system: evidence from FMRI connectivity analysis. *Journal of Cognitive Neuroscience*, **21**(1), pp. 141-154.
- MACINTOSH, B.J., 2007. Developing fMRI technology for stroke recovery research. Department of Medical Biophysics, University of Toronto.
- MACKINTOSH, N.J., 1975. Blocking of conditioned suppression: role of the first compound trial. *J Exp Psychol Anim Behav Process*, **1**(4), pp. 335-345.
- MALIZIA, A.L., 1997. The frontal lobes and neurosurgery for psychiatric disorders. *J Psychopharmacol*, **11**(2), pp. 179-187.
- MAYBERG H. S., BRANNAN, S.K., TEKELL, J.L., SILVA, J.A., MAHURIN, R.K., MCGINNIS, S. and JERABEK, P.A., 2000. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. *Biol Psychiatry*, **48**(8), pp. 830-43.

- MAYBERG, H.S. and OTHERS, 1999. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am J Psychiatry*, **156**(5), pp. 675-682.
- MCCLURE, S.M., DAW, N.D. and OTHERS, 2003. A computational substrate for incentive salience. *Trends Neuroscience*, **26**(8), pp. 423-428.
- MCCLURE, S.M., YORK, M.K. and OTHERS, 2004. The neural substrates of reward processing in humans: the modern role of fMRI. *Neuroscientist*, **10**(3), pp. 260-268.
- MCNEELY, H.E., MAYBERG, H.S., LOZANO, A.M. and KENNEDY, S.H., 2008. Neuropsychological impact of Cg 25 deep brain stimulation for treatment-resistant depression: Preliminary results over 12 months. *The Journal of Nervous and Mental Disease*, **196**(5), pp. 405-410.
- MIRENOWICZ, J. and SCHULTZ, W., 1994. Importance of unpredictability for reward responses in primate dopamine neurons. *Institute de Physiology*, **72**(2), pp. 1024-1027.
- ML, K., 2005. The human orbitofrontal cortex: linking reward to hedonic experience. *Nat Rev Neuroscience*, **6**(9), pp. 691-702.
- MOGENSEN, G.J., WU, M. and JONES, D.L., 1980. Locomotor activity elicited by injections of picrotoxin into the ventral tegmental area is attenuated by injections of GABA into the globus pallidus. *Brain Res*, **191**(2), pp. 569-571.
- MONOSOV, I.E. and HIKOSAKA, O., 2012. Regionally distinct processing of rewards and punishments by the primate ventromedial prefrontal cortex. *J Neuroscience*, **32**(30), pp. 10318-30.
- MONTAGUE, P.R., DAYAN, P. AND SEJNOWSKI, T.J., 1996. A framework for mesencephalic dopamine systems based on predictive Hebbian learning. *J Neuroscience*, **16**(5), pp. 1936-47.
- MONTAGUE, P.R. and BERNS, G.S., 2002. Neural economics and the biological substrates of valuation. *Neuron*. **36**(2), pp. 265-284.
- MONTAGUE, P.R. and OTHERS, 2004. Dynamic gain control of dopamine delivery in freely moving animals. *J Neuroscience* **24**(7), pp. 1754-1759.
- MONTANA, P.J. and CHARNOV, B.H., 2000. International Management. *New York: Barron's*, pp. 477-488.
- MORRIS, R., PANDYA, D.N. and PETRIDES, M., 1999. Fibre system linking the middorsolateral frontal cortex with the retrosplenial/presubicular region in the rhesus monkey. *J Comp Neurol*, **407**, pp. 183-192.
- MORRIS, R., PETRIDES, M. and PANDYA, D.N., 1999. Architecture and connections of retrosplenial area 30 in the rhesus monkey, macaca mulatta. *The European Journal of Neuroscience*, **11**(7), pp. 2506-2518.
- MOTTAGHY, F.M. and OTHERS, 2002. Correlation of cerebral blood flow and treatment effects of repetitive transcranial magnetic stimulation in depressed patients. *Psychiatry Res*, **20**(115), pp. 1-14.

- MUNTE, T.A.O., 2008. Contribution of subcortical structures to cognition assessed with invasive electrophysiology in humans. *Frontiers in Human Neuroscience* **2**(1), pp. 72-78.
- MURRAY, E.A., 2007. The amygdala, reward and emotion. *Trends Cogn Sci*, **11**(11), pp. 489-497.
- NAKAHARA, H., ITOH, H., KAWAGOE, R., TAKIKAWA, Y. and HIKOSAKA, O., 2004. Dopamine neurons can represent context-dependent prediction error. *Neuron*, **41**(2), pp. 269-280.
- NANGINI, C., MACINTOSH, B.J. and TAM, F., STAINES, W.R., GRAHAM, S.J., 2005. Assessing linear time-invariance in human primary somatosensory cortex with BOLD fMRI using vibrotactile stimuli. *Magn Reson Med*, **53**(2), pp. 304-311.
- NIEUWENHUIS S., SLAGTER H. A., VON GEUSAU N. J. A., HESLENFELD D. J., HOLROYD C. B., 2005. Knowing good from bad: differential activation of human cortical areas by positive and negative outcomes. *Eur J Neuroscience*, **21**, pp. 3161-3168.
- NISHIJO, H., UWANO, T. and OTHERS, 1998. Gustatory and multimodal neuronal responses in the amygdala during licking and discrimination of sensory stimuli in awake rats. *J Neurophysiol*, **79**(1), pp. 21-36.
- NOBLER, M.S. and OTHERS, 2001. Decreased regional brain metabolism after ECT. *Am J Psychiatry*, **158**(2), pp. 305-308.
- O'DOHERTY, J., KRINGELBACH, M.L. and OTHERS, 2001. Abstract reward and punishment representations in the human orbitofrontal cortex. *Nat Neuroscience*, **4**(1), pp. 95-102.
- O'DOHERTY, J. and P., 2007. Lights. Camembert, Action! The Role of Human Orbitofrontal Cortex in Encoding Stimuli, Rewards, and Choices. *Ann. N. Y. Acad Sci*, **1121**, pp. 254-272.
- O'DOHERTY, J.P., DAYAN, P. and OTHERS, 2003. Temporal difference models and reward-related learning in the human brain. *Neuron*, **38**(2), pp. 329-337.
- O'DOHERTY, J.P., DEICHMANN, R. and OTHERS, 2002. Neural responses during anticipation of a primary taste reward. *Neuron*, **33**(5), pp. 815-826.
- O'DOHERTY, J.P. and OTHERS, 2001. Representation of pleasant and aversive taste in the human brain. *J Neurophysiol*, **85**, pp. 1315-1321.
- O'DOHERTY, J., CRITCHLEY, P. and OTHERS, 2003. Dissociating valence of outcome from behavioral control in human orbital and ventral prefrontal cortices. *J Neuroscience*, **23**(21), pp. 7931-7939.
- O'DOHERTY, J., DAYAN, P. and OTHERS, 2004. *Dissociable roles of ventral and dorsal striatum in instrumental conditioning*. *Science*, **304**(5669), pp. 452-454.
- OGAWA, S., LEE, T.M., KAY, A.R. and TANK, D.W., 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences USA*, **87**, pp. 9868-9872.

- OGAWA, S., LEE, T.M., NAYAK, A.S. and GLYNN, P., 1990. Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magn Reson Med*, **14**(1), pp. 68-78.
- OSTERLING, J. and DAWSON, G., 1994. Early recognition of children with autism: a study of first birthday home videotapes. *J Autism Dev Disord*, **24**(3), pp. 247-257.
- PAGNONI, G., ZINK, C.F. and OTHERS, 2002. Activity in human ventral striatum locked to errors of reward prediction. *Nat Neuroscience*, **5**(2), pp. 97-98.
- PATON, J.J., BELOVA, M.A. and OTHERS, 2006. The primate amygdala represents the positive and negative value of visual stimuli during learning. *Nature*, **439**(7078), pp. 865-870.
- PATRICK, J.M. and BRUCE, H.C., 2008. Management. 4th Edition, Barron's Educational Series, pp.247.
- PAULING, L. and CORYELL, C.D., 1936. The Magnetic Properties and Structure of the Hemochromogens and Related Substances. *Proceedings of the National Academy of Sciences of the United States of America*, **22**(3), pp. 159-163.
- PAULUS, M.P. and STEIN, M.B., 2006. An insular view of anxiety. *Biol Psychiatry*, **60**(4), pp. 383-387.
- PAVLOV, I.P., 1927/1960. *Conditional Reflexes*. New York, Dover Publications, the 1960 edition is not an unaltered republication of the 1927 translation by Oxford University Press. [http, pp. //psychclassics.yorku.ca/Pavlov/](http://psychclassics.yorku.ca/Pavlov/)
- PEARCE, J.M. and HALL, G., 1980. A model for Pavlovian learning: variations in the effectiveness of conditioned but not of unconditioned stimuli. *Psychol Rev*, **87**(6), pp. 532-552.
- PELPHREY, K., ADOLPHS, R. and MORRIS, J.P., 2004. Neuroanatomical substrates of social cognition dysfunction in autism. *Mental Retardation and Developmental Disabilities Research Reviews*, **10**, pp. 259-271.
- PESSIGLIONE, M., SEYMOUR, B. and OTHERS, 2006. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature*, **442**(7106), pp. 1042-1045.
- PETERS, J. and BUCHEL, C., 2009. Overlapping and distinct neural systems code for subjective value during intertemporal and risky decision making. *J Neuroscience*, **29**(50), pp. 15727-347.
- PHAN, K.L., WAGER, T., TAYLOR, S.F. and LIBERZON, I., 2002. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *NeuroImage*, **16**(2), pp. 331-48.
- PHILLIPS, M.L., DREVETS, W.C., RAUCH, S.L. and LANE, R., 2003. Neurobiology of emotion perception: The neural basis of normal emotion perception. *Biological Psychiatry*, **54**(5), pp. 504-514.
- PIERCE, K., MULLER, R.A., AMBROSE, J., ALLEN, G. and COURCHESNE, E., 2001. Face processing occurs outside the fusiform 'face area' in autism: evidence from functional MRI. *Brain*, **54**(5), pp. 504-514.

- PLATT, M.L. and HUETTEL, S.A., 2008. Risky business: the neuroeconomics of decision making under uncertainty. *Nat Neuroscience* **11**(4), pp. 398-403.
- PREUSCHOFF, K., BOSSAERTS, P. and QUARTZ, S.R., 2006. Neural differentiation of expected reward and risk in human subcortical structures. *Neuron*, **51**(3), pp. 381-390.
- RADEMACHER, L., KRACH, S. and OTHERS, 2010. Dissociation of neural networks for anticipation and consumption of monetary and SRs. *NeuroImage*, **49**, pp. 3276-3285.
- RAMNANI, N., ELLIOTT, R., ATHWAL, B.S. and PASSINGHAM, R.E., 2004. Prediction error for free monetary reward in the human prefrontal cortex. *NeuroImage*, **23**(3), pp. 777-786.
- REDCAY, E. and OTHERS, 2010. Live face-to-face interaction during fMRI : a new tool for social cognitive Neuroscience. *NeuroImage*, **50**(4), pp. 1639-1647.
- REIMAN, E.M., LANE, R.D., AHERN, G.L., SCHWARTZ, G.E. and DAVIDSON, R.J., 1997. Neuroanatomical correlates of externally and internally generated human emotion. *Am J Psychiatry*, **154**(7), pp. 918-925.
- REYNOLDS, S. and ZAHM, D.S., 2005. Specificity in the projections of prefrontal and insular cortex to ventral striatopallidum and the extended amygdala. *J Neuroscience* **25**(50), pp. 11757-11767.
- RILLING, J., GUTMAN, D. and OTHERS, 2002. A neural basis for social cooperation. *Neuron*, **35**(2), pp. 395-405.
- ROBINSON, O.J. and OTHERS, 2010. Dissociable responses to punishment in distinct striatal regions during reversal learning. *NeuroImage*, **51**, pp. 1459-1467.
- ROESCH, M.R., CALU, D.J. and SCHOENBAUM, G., 2007. Dopamine neurons encode the better option in rats deciding between differently delayed or sized rewards. *Nat Neuroscience*, **10**(12), pp. 1615-1624.
- ROGERS, J.L., HOWARD, K.I. and VESSEY, J.T., 1993. Using significance tests to evaluate equivalence between two experimental groups. *Psychological Bulletin*, **113**, pp. 553-565.
- ROLLS, E.T. and MCCABE, C. and Redoute, J., 2008. Expected value, reward outcome, and temporal difference error representations in a probabilistic decision task. *Cereb Cortex*, **18**(3), pp. 652-663.
- ROLLS, E.T., 2004. The functions of the orbitofrontal cortex. *Brain Cognition*, **55**(1), pp. 11-29.
- ROLLS, E.T., 2000. The orbitofrontal cortex and reward. *Cereb Cortex*, **10**(3), pp. 284-294.
- ROLLS, E.T., 1999. Spatial view cells and the representation of place in the primate hippocampus. *Hippocampus*, **9**(4), pp. 467-480.
- ROLLS, E.T., AGGELOPOULOS, N.C. and ZHENG, F., 2003. The receptive fields of inferior temporal cortex neurons in natural scenes. *J Neuroscience*, **23**(1), pp. 339-348.

- ROLLS, E. and GRABENHORST, F., 2008. The orbitofrontal cortex and beyond: from affect to decision-making. *Prog Neurobiol*, **86**(3), pp. 216-244.
- ROLLS, E., KRINGELBACH, M.L. and DE ARAUJO, I.E., 2003. Different representations of pleasant and unpleasant odours in the human brain. *Eur J Neuroscience*, **18**(3), pp. 695-703.
- ROSEN, B.R., BUCKNER, R.L. and DALE, A.M., 1998. Event-related functional MRI: Past present, and future. *Proceedings of the National Academy of Sciences U.S.A.*, **95**, pp. 773-780.
- RUSHWORTH, M.F., 2008. Intention, choice, and the medial frontal cortex. *Ann NY Acad Sci*, **1124**, pp. 181-207.
- RUSTICUS, S.A. and LOVATO, C.Y., 2011. Applying test of equivalence for multiple group comparisons: Demonstration of the confidence interval approach. *Practical Assessment Research and Evaluation*, **16**(7).
- SAGEN, U., VIK, T.G., MOUM, T., MORLAND, T., FINSET, A., DAMMEN, T., 2009. Screening for anxiety and depression after stroke: comparison of the hospital anxiety and depression scale and the Montgomery and Asberg depression rating scale. *J Psychosom Res*, **67**(4), pp. 325-332.
- SAMUELSON, P., 1972. *Foundations of Economic Analysis*. Cambridge, MA, Harvard University Press.
- SANFREY, A.G., HASTIE, R., COLVIN, M.K. and GRAFMAN, J., 2003. Phineas gauged: decision-making and the human prefrontal cortex. *Neuropsychologia*, **41**(9), pp. 1218-1229.
- SANGHERA, M.K., ROLLS, E.T. and OTHERS, 1979. Visual responses of neurons in the dorsolateral amygdala of the alert monkey. *Exp Neurol*, **63**(3), pp. 610-626.
- SCHOENBAUM, G., CHIBA, A.A. and GALLAGHER, M., 1998. Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning. *Nat Neuroscience*, **1**(2), pp. 155-159.
- SCHOENBAUM, G. and ROESCH, M., Orbitofrontal cortex, associative learning, and expectancies. *Neuron*, **47**(1), pp. 633-636.
- SCHULTZ, W., 2007. Multiple dopamine functions at different time courses. *Annu Rev Neuroscience*, **30**, pp. 259-288.
- SCHULTZ, W., 2004. Neural coding of basic reward terms of animal learning theory, *game theory, microeconomics and behavioural ecology*. *Curr Opin Neurobiol*, **14**(2), pp. 139-147.
- SCHULTZ, W., 2002. Getting formal with dopamine and reward. *Neuron*, **36**(2), pp. 241-263.
- SCHULTZ, W., 2001. Reward signalling by dopamine neurons. *Neuroscientist*, **7**(40), pp. 293-302.
- SCHULTZ, W., 1998. Predictive reward signal of dopamine neurons. *J Neurophysiol*, **80**(1), pp. 1-27.

- SCHULTZ, W. and P DAYAN, P.M., 1997. A neural substrate of prediction and reward. *Science*, **275**(5306), pp. 1593-1599.
- SCHWARTZBAUM, J.S. and POULOS, D.A., 1965. Discrimination behaviour after amygdectomy in monkeys: learning set and discrimination reversals. *J Comp Physiol Psychol*, **60**(3), pp. 320-328.
- SCOTT-VAN ZEELAND, A.A. and OTHERS, 2010. *Reward processing in autism. Autism Res*, **3**(2), pp. 53-67.
- SEMINOWICZ, D.A. and OTHERS, 2004. Limbic-frontal circuitry in major depression at a path modelling metanalysis. *NeuroImage*, **22**(1), pp. 409-418.
- SETO, E., SELA, G., MCILROY, W.E., BLACK, S.E., STAINES, W.R., BRONSKILL, M.J., MCINTOSH, A.R. and GRAHAM, S.J., 2001. Quantifying head motion associated with motor tasks used in fMRI. *NeuroImage*, **14**(2), pp. 284-297.
- SEYMOUR, B., DAW, N. and OTHERS, 2007. Differential encoding of losses and gains in the human striatum. *J Neuroscience*, **27**(18), pp. 4826-4831.
- SEYMOUR, B. and OTHERS, 2004. *Temporal difference models describe higher-order learning in humans. Nature*, **429**(6992), pp. 664-7.
- SHMUEL, A. and AUGATH, M., OELTERMANN, A., LOGOTHETIS, N.K., 2006. Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1. *Nat Neuroscience*, **9**(4), pp. 569-577.
- SINGER, A.R. and DOBSON, K.S., 2006. An experimental investigation of the cognitive vulnerability to depression. *Behav Res Ther*, **45**(3), pp. 563-575.
- SKINNER, B.F., 1974. Behaviour modification. *Science*, **185**(4154), pp. 813.
- SKINNER, B.F., 1953. *Science and Human Behaviour*. NY. The Free Press.
- SKINNER, B.F. and MORSE, W.H., 1957. Concurrent activity under fixed-interval reinforcement. *J Comp Physiol Psychol*, **50**(3), pp. 279-281.
- SMALL, D.M., 1997. Flavour processing: more than the sum of its parts. *Neuroreport*, **8**(18), pp. 3913-3917.
- SMALL, D.M., 1999. Human cortical gustatory areas: a review of functional neuroimaging data. *Neuroreport*, **10**(1), pp. 7-14.
- SMALL, D.M., JONES-GOTMAN, M. and DAGHER, A., 2003. Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. *NeuroImage*, **19**(4), pp. 1709-1715.
- SMALL, D.M. and ZATORRE, R.J., 2001. *Changes in brain activity related to eating chocolate. Brain*, **124**(9), pp. 1720-1733.
- SMITH, D.V., HAYDEN, B.Y., TRUONG, T.K., SONG, A.W., PLATT, M.L. and HUETTEL, S.A., 2010. Distinct value signals in anterior and posterior ventromedial prefrontal cortex. *J Neuroscience*, **30**, pp. 2490-2495.

- SMITH, Y. and VILLALBA, R., 2008. Striatal and extrastriatal dopamine in the basal ganglia: an overview of its anatomical organization in normal and Parkinsonian brains. *Mov Disord*, **23** (3), pp. 534-547.
- SNAITH, R.P., HAMILTON, M.S., HUMAYAN, D. and HARGREAVES, P.T., 1995. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. *Br J Psychiatry*, **167**(1), pp. 99-103.
- SORCE, J.F., EMDE, R.N. and OTHERS, 1985. Maternal emotional signalling: its effects on the visual cliff behaviour of 1-year-olds. *Developmental Psychology*, **21**, pp. 195-200.
- SPIEGLER, B.J. and MISHKIN, M., 1981. Evidence for the sequential participation of inferior temporal cortex and amygdala in the acquisition of stimulus-reward associations. *Behavioural Brain Res*, **3**(3), pp. 303-317.
- SPRECKELMEYER, K.N., KRACH, S., KOHLS, G., RADEMACHER, L., IRMAK, A., KONRAD, K., KIRCHER, T. and GRUNDER, G., 2009. Anticipation of monetary and SR differently activates mesolimbic brain structures in men and women. *Soc Cogn Affect Neuroscience*, **4**, pp. 158-165.
- STEELE, R.A., 1992. Awards energize a suggestion programme. *Personnel Journal*, **71**(10), pp. 96-99.
- STEENBERGEN, B., 2011. Motor preparation in unilateral cerebral palsy. *Dev Med Child Neurol*, **53**(10), pp. 877-878.
- STEFANACCI, L., CLARK, R.E. and OTHERS, 2003. Selective neurotoxic amygdala lesions in monkeys disrupt reactivity to food and object stimuli and have limited effects on memory. *Behavioural Neuroscience*, **117**(5), pp. 1029-1043.
- STUART, P., 1992. Fresh ideas energize reward programmes. *Personnel Journal*, **71**, pp. 102.
- SUGASE-MIYAMOTO, Y. and RICHMOND, B.J., 2005. Neuronal signals in the monkey basolateral amygdala during reward schedules. *J Neuroscience*, **25**(48), pp. 11071-11083.
- SURI, R. and SCHULTZ, W., 1999. A neural network model with dopamine-like reinforcement signal that learns a spatial delayed response task. *Neuroscience* **91**(3), pp. 871-890.
- SUTTON, R.S. and BARTO, A.G., 1998. Reinforcement learning: An introduction, adaptive computation and machine learning. The MIT Press.
- TALMI, D.A.O., 2009. How humans integrate the prospects of pain and reward during choice. *J Neuroscience*, **29**(46), pp. 14617-14626.
- THORNDIKE, E.L., 1911. A scale for measuring the merit of English writing. *Science*, **33**(859), pp. 935-938.
- THUT, G., SCULTZ, W., ROELCKE, U. and OTHERS, 1997. Activation of the human brain by monetary reward. *Neuroreport*, **8**(5), pp. 1225-1228.
- TOM, S.M., FOX, C.R., TREPEL, C. and POLDRACK, R.A., 2007. The neural basis of loss aversion in decision-making under risk. *Science*, **315**(5811), pp. 515-518.

- TREMBLAY, L. and SCHULTZ, W., 1999. Relative reward preference in primate orbitofrontal cortex. *Nature*, **398**(6729), pp. 704-708.
- TREMEAU, F. and OTHERS, 2009. *Emotion antecedents in schizophrenia*. *Psychiatry Res*, **169**(1), pp. 43-50.
- TRICOMI, E.M., DELGADO, M.R. and FIEZ, J.A., 2004. Modulation of caudate activity by action contingency. *Neuron*, **41**, pp. 281-292.
- URSU, S. and CARTER, C.S., 2005. Outcome representations, counterfactual comparisons and the human orbitofrontal cortex: implications for neuroimaging studies of decision-making. *Cognitive Brain Research*, **23**(1), pp. 51-60.
- VALENTIN, V.V., DICKINSON, A. and O'DOHERTY, J.P., 2007. Determining the neural substrates of goal-directed learning in the human brain. *J Neuroscience*, **27**(15), pp. 4019-4026.
- VALENTIN, V.V. and O'DOHERTY, J.P., 2009. *Overlapping prediction errors in dorsal striatum during instrumental learning with juice and money reward in the human brain*. *J Neurophysiol*, **102**(6), pp. 3384-3391.
- VON NEUMANN, J. and MORGENSTER, O., 1944. Princeton: The Theory of Games and Economic Behaviour. Princeton University Press.
- VOORN, P. and OTHERS, 2004. Putting a spin on the dorsal-ventral divide of the striatum. *Trends Neuroscience*, **27**(8), pp. 468-474.
- WALLIS, J.D., 2011. Cross-species studies of orbitofrontal cortex and value-based decision-making. *Nat Neuroscience*, **15**(1), pp. 13-19.
- WALLIS, J.D., ANDERSON, K.C. and MILLER, E.K., 2001. Single neurons in prefrontal cortex encode abstract rules. *Nature*, **411**(6840), pp. 953-956.
- WESSEL, J.R., 2012. Error awareness and the error-related negativity: evaluating the first decade of evidence. *Front Hum Neurosci*, **6**, pp. 88.
- WEXLER, B. and LEVENSON, L., WARRENBURG, S., PRICE, L.H., 1994. Decreased perceptual sensitivity to emotion-evoking stimuli in depression. *Psychiatry Res*, **51**(2), pp. 127-138.
- WICKER, B., KEYSERS, C., PLAILLY, J., ROYET, J.P., GALLESE, V. and RIZZOLATTI, G., 2003. Both of us disgusted in my insula: the common neural basis of seeing and feeling disgust. *Neuron*, **40**(3), pp. 655-64.
- WILSON, F.A. and ROLLS, E.T., 2005. *The primate amygdala and reinforcement: a dissociation between rule-based and associatively-mediated memory revealed in neuronal activity*. *Neuroscience*, **133**(4), pp. 1061-72.
- WISE, R.A., 2008. Dopamine and reward: the anhedonia hypothesis 30 years on. *Neurotx Res*, **14**(2-3), pp. 169-83.
- WISE, R.A., 2004. Dopamine, learning and motivation. *Nat Rev Neuroscience*, **5**(6), pp. 483-494.

WISE, R.A., 2002. Brain reward circuitry: insights from unsensed incentives. *Neuron*, **36**(2), pp. 229-240.

WORSLEY, K.A.O., 2002. *A general statistical analysis for fMRI data*. *NeuroImage*, **15**(1), pp. 1-15.

WORSLEY, K., 2003. Detecting activation in fMRI data. *Stat Methods Med Res*, **12**(5), pp. 401-418.

ZEKI, S. and ROMAYA, J.P., 2008. Neural correlates of hate. *PLoS One*, **3**(10), pp. e3556.

ZIGMOND A. and SNAITH, R., 1983. The hospital anxiety and depression scale. *Acta Psychiatr Scand*, **67**, pp. 361-370.

ZINK, C.F., TONG, Y., CHEN, Q., BASSETT, D.S., STEIN, J.L. and MEYER-LINDENBERG, A., 2008. Know your place: Neural processing of social hierarchy in humans. *Neuron*, **58**(2), pp. 273-283.

ZONTA, M., ANGULO, M.C., GOBBO, S., ROSENGARTEN, B., HOSSMANN, K.A., POZZAN, T. and CARMIGNOTO, G., 2003. Neuron-to-astrocyte signalling is central to the dynamic control of brain microcirculation. *Nat Neuroscience* **6**(1), pp. 43-50.

#### Web references

<http://www.fil.ion.ucl.ac.uk/spm> (accessed May 18, 2016).

<http://aston.sona-systems.com> (accessed May 18, 2016).