The Impact of Emotions on Attention and Decision Making

Benedetto De Martino

2008

A thesis submitted to University College London
For the degree of Doctor of Philosophy

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Acknowledgements

I wish to thank a number of people for providing a great deal of help with the work presented in this thesis. First and foremost I thank Raymond Dolan (my primary supervisor) for support and advice throughout my PhD, and also Geraint Rees (secondary supervisor). I also thank the many colleagues at the Wellcome Trust Centre for Neuroimaging, UCL, for many fruitful discussions (in particular Dharshan, Hugo and Demis); the supporting staff who have provided invaluable help throughout the period (including Peter, Eric, Amanda, Jan, David, Michelle and Chris); and Karl Friston for his invaluable comments and suggestions. I wish to thank the organizers of the Wellcome PhD programme in Neuroscience (in particular David Attwell), and my fellow "Wellcomes" (Velia, Roby, Alex and Izumi). The most important thanks go to my family Bruno and Alida and Ambra and to my future wife Jessica that have always helped and supported me throughout my PhD.

Abstract

Emotional information is widely acknowledged to play a role in shaping human behavior. In particular, emotions, by modulating attentional capacity, provide an evolutionary advantage by facilitating quick responses to potential threat. By contrast, the impact of emotions on the decision-making processes is often seen as engendering suboptimal or even so-called "irrational" decisions

In this thesis, I combine innovative experimental paradigms with functional magnetic resonance imaging (fMRI) and behavioral pharmacological manipulations to explore how at neurobiological level these processes share similar mechanisms. In doing so, I aim to attempt a reconciliation of the aforementioned contrasting views on emotion.

I examined four key aspects of interaction between emotion and both attention and decision-making: firstly, I investigated how the human brain is able to process emotional stimuli in conditions of limited attentional resources whilst subjects were engaged in an attentional blink paradigm. Secondly, using a similar paradigm and three different drug manipulations I examined the role of noradrenaline in modulating this process. Thirdly, I have studied how the human brain processes contextual emotional information when choice options are presented. Finally I extend my research to study how during economics transactions (in which the contextual emotional information is rooted in the subjects own role as either seller or buyer) an item's value representation in the brain affects the decision process.

I conclude that my results provide neurobiological support for theoretical accounts on how emotions plays a critical role in modulating complex cognitive capacity, such as attention and decision-making. Specifically, the findings suggest that the increased detection of emotional stimuli under attentional load is mediated by a frontal top-down control mechanism. The findings also show how phasic release of noradrenaline plays a crucial role in mediating this ability. My studies also provide empirical evidence that an amygdala-based emotional system is responsible for a bias in decision-making showing that the integration of emotional and analytic information is expressed in orbital and medial frontal cortex enabling the subjects to resist the bias. Finally, I show that a discrepancy in item evaluation during economic transaction is encoded in the ventral striatum.

My overall findings enable a specification of the biological mechanisms by which emotions modulate and shape human attention and decision-making and point, under certain experimental situations, to shared mechanisms.

Table of Contents

Index of Figures

Chapter 1

Introduction

1.1 Outline of thesis

In this chapter (***Chapter 1)*** I will review literature in the fields of psychology, neuroscience and economics, which addresses the subject of emotional processing and its modulation of cognitive activities such as attention and decision-making. This review contextualises the experimental studies on attention and decision-making that are presented in the body of this thesis.

In ***Chapter 2*** I explain the methods used in the experiments described in this thesis. I describe the physics of magnetic resonance and the neurophysiology underlying the blood oxygen level-dependent (BOLD) signal, which is my prime measure of neuronal activity. Spatial preprocessing of fMRI images is described as well as the statistical models employed in making inferences about task-related regional brain activations.

In ***Chapter 3*** I present an fMRI experiment designed to investigate how the human brain is able to process emotional stimuli in conditions of limited attentional resources whilst subjects are engaged in an attentional blink paradigm. I provide neurobiological evidence that the increased detection of emotional stimuli under attentional load is mediated by a frontal top-down control.

In ***Chapter 4*** I present results of three experiments designed to examine how nordrenaline (NA) regulates an enhancement in attention for the emotional stimuli. These experiments use a modification of the attentional blink paradigm; using three different

drug manipulations I will show how noradrenalinen contributes to this process. These results will be interpreted in the context of an established theoretical account of the noradrenergic function.

In ***Chapter 5*** I present the findings of an fMRI experiment that explores how the human brain processes contextual emotional information when choice options are presented ("framing effect"). I provide empirical evidence that an amygdala-based emotional system is responsible for the framing bias in decision-making. In addition, I demonstrate how the integration of emotional and analytic information expressed in the orbital and medial frontal cortex enables subjects to resist this bias.

In ***Chapter 6*** I describe the results of a behavioural experiment that investigated how contextual emotional information affects the decision making of people affected by autism spectrum disorder (ASD), employing the framing paradigm used in the fMRI study presented in the chapter 5. These data show that ASD subjects are less susceptible the framing bias. These findings are discussed in the context of the current dominant theory on autism, as well as in relation to decision-making theories.

In ***Chapter 7*** I present the findings of an fMRI experiment which aims to investigate how the brain represents values during economics transactions (in which the contextual emotional information is rooted in the subjects own role as either seller or buyer). I

provide experimental evidence that during an economic transaction the ventral striatum encodes values on a relative rather than on absolute metric.

In ***Chapter 8*** I integrate the results presented in the previous chapters with current theoretical accounts developed in psychology, neuroscience, and economics, of how emotions modulate complex cognitive capacity such as attention and decision-making.

1.2 Historical perspectives on the study of emotional processing

The word emotion is a composite word formed from the two Latin words: **ex** (out, outward) and **motio** (movement, action, gesture). Already the etymology of the word emotion embodies the motivational aspect of emotions in directing animal and human behaviour. Emotions embody both psychological and physiological states, which inform an organism about the value of action and events, which in turn exert an influence on behaviour.

1.2.1 The James-Lange theory and Cannon's critique

In the 1872, Charles Darwin acknowledged that the two most crucial features of emotional processing are its physical expression and its motivational impact. In his book "*The expression of the emotions in man and animals*" he proposed that the expressions of emotions in humans (for example the shedding of tears when upset, or the baring of teeth when angry) are vestigial patterns of actions, that were adaptive in our environment of

evolutionary adaptiveness (Darwin, 1859). A decade later, the American psychologist William James proposed that emotions reflect the experience of sets of bodily changes that occur in response to distinct emotive stimuli (James, 1884); the Danish physician Carl Lange independently developed an analogous hypothesis (Lange, 1885). The James–Lange theory was challenged in the 1920s by Walter Cannon, on the following grounds: (1) the total surgical separation of the viscera from the brain in animals does not impair emotional behaviour; (2) bodily or autonomic activity cannot differentiate separate emotional states; (3) bodily changes are typically too slow to generate emotions; (4) artificial hormonal activation of bodily activity is insufficient to generate emotion. Cannon's criticism of the James–Lange theory arose from his investigations with Bard into the effects of brain lesions on the emotional behaviour of cats. Decorticated cats were liable to make sudden, inappropriate and ill-directed anger attacks (Bard and Rioch, 1937). On this basis Cannon and Bard argued that if emotions were the perception of bodily change, then they should be entirely dependent on having intact sensory and motor cortices (Bard, 1928; Cannon, 1927; Cannon, 1931). They argued that since the removal of the cortex did not eliminate emotions, James and Lange must be wrong. However, recent research has cast doubt on Cannon's claims, showing that emotions are less intense when the brain is disconnected from the viscera as in Cannon's studies, and that some artificial manipulations of organ activity can induce emotions (Harro and Vasar, 1991). Indeed implicit in their critique is a conflation of emotional experience (feeling states) and emotional expression (overt bodily manifestation of emotion). Nevertheless, on the

basis of their experimental observations, Cannon and Bard proposed the first substantive theory of the brain mechanisms of emotion. They argued that the hypothalamus is the brain region most involved in an emotional response to stimuli and that such responses are inhibited by evolutionarily more recently evolved neocortical regions (Bard, 1928). Removal of the cortex frees the hypothalamic circuit from top–down control, allowing uncontrolled emotions.

1.2.2 The limbic system: Papez's circuit and "triune architecture" of the brain proposed by McLane

In 1937, James Papez proposed a central neural circuitry of emotion, known as the 'Papez circuit' (Papez, 1995). Papez proposed that sensory input into the thalamus diverged into upstream and downstream components, providing the separate streams of 'thought' and 'feeling'. The thought stream was transmitted from the thalamus to the sensory cortices, especially the cingulate region. Through this route, sensations were turned into perceptions, thoughts and memories. Papez proposed that this stream then continued beyond the cingulate cortex, through the cingulum pathway, to the hippocampus and, through the fornix, to the mammillary bodies and thence back to the anterior thalamus via the mammillo-thalamic tract. The feeling stream, on the other hand, was transmitted from the thalamus directly to the mammillary bodies, allowing the generation of emotions (with downward projections to the bodily systems).

Paul MacLean in 1949 proposed an anatomical hierarchical model of the emotional brain inspired to its evolutionary development. MacLean proposed that our skull holds not one brain, but three, each representing a distinct evolutionary stratum formed upon an older layer, akin to geological stratification (MacLean, 1949). He called this organization the "triune brain architecture ."

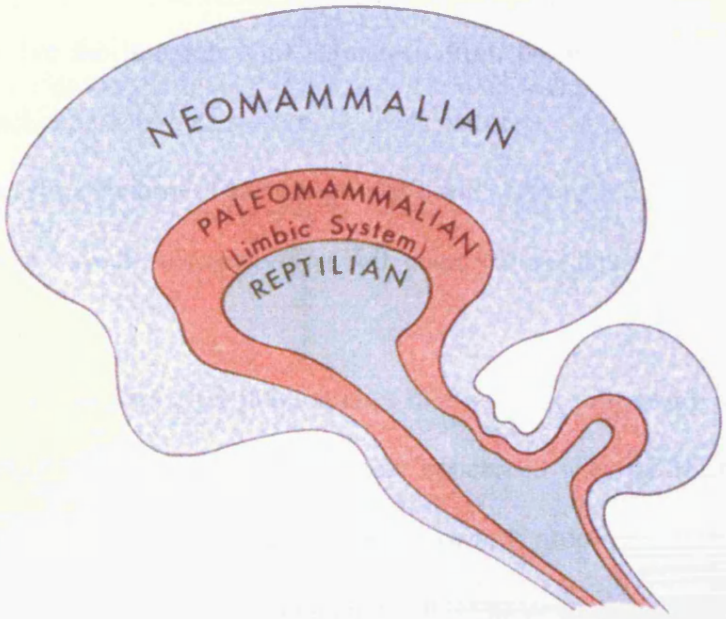

Figure I.I Original drawing of the triune architecture of the human brain proposed by MacLeane

The first part is the evolutionarily ancient 'reptilian' brain (the striatal complex and basal ganglia) he propopsed as the seat of primitive emotions such as fear and aggression. The second is the 'paleomammalian' brain (which he originally called the 'visceral brain'), which augments primitive reptilian emotional responses such as fear and also elaborates

the social emotions. This brain system includes many of the components of the Papez circuit — the thalamus, hypothalamus, hippocampus and cingulate cortex — along with important additional structures, in particular the amygdala and the PFC. Finally, the 'neomammalian' brain consists mostly of the neocortex, which interfaces emotion with cognition and exerts top–down control over the emotional responses that are driven by lower systems (Figure I.I). MacLean's essential idea was that emotional experiences involve the integration of sensations from the world with information from the body. MacLean's limbic system concept survives to the current day as the dominant conceptualization of the 'emotional brain', although concepts at the core of the original theory have been criticized on both empirical and theoretical grounds.

Several decades after these studies in emotional processing, the emergence of cognitive science shifted the interest of those concerned with the relation between psychological functions and neural mechanisms toward processes (for instance, perception and memory) that are readily thought of in terms of computer-like operations. From the start, cognitive scientists claimed that their field was not about emotion (Neisser, 1967). The cognitive approach came to be the dominant approach in psychology and brain science, and research on emotions was neglected.

1.2.3 A renewed interest in affective neuroscience: Damasio's somatic markers hypothesis and LeDoux's emotional brain

The work of Antonio Damasio and his colleagues has sparked a renewed interest in emotional processing and its interactions with cognitive processes. Their somatic marker hypothesis builds on the earlier ideas of James and Lange, promoting the role of bodily feedback in emotion (Damasio et al., 1994). Somatic markers are physiological reactions (such as shifts in autonomic nervous system activity) that mark previous emotionally significant events. Somatic markers therefore provide a signal delineating those current events that have had emotion-related consequences in the past. These signals allow individuals to track situations of uncertainty where decisions need to be made on the basis of the emotional properties of the present stimulus. In particular, somatic markers allow decisions to be made in situations where a logical analysis of the available choices proves insufficient. Damasio's group has used human lesion studies to support these arguments, arguing that these somatic codes are processed in the ventromedial PFC (Damasio et al., 1990).

Meanwhile, LeDoux and colleagues have revitalized another area of research on emotional processing: that which began with the seminal work of Pavlov in 1927 on conditioning (Pavlov, 1927). LeDoux and colleagues used fear-conditioning paradigms to study how emotional information is processed and prioritized (LeDoux, 1996). In fear conditioning, arbitrary stimuli come to acquire fear-inducing properties when they occur

in conjunction with a naturally threatening event such as an electric shock. For example, if a rat hears a tone followed by a shock then after repeated such pairings it will respond fearfully to the tone when presented alone, showing alterations in autonomic (heart rate and blood pressure), endocrine and motor (for example, freezing) behaviour, along with analgesia and somatic reflexes such as a potentiated startle response (figure I.II). This body of research has highlighted the roles of two afferent routes involving the amygdala that mediate such conditioning (LeDoux, 2000). The first is a direct thalamo–amygdala route, that processes crude sensory aspects of incoming stimuli and relays this information directly to the amygdala, allowing for an early conditioned fear response to any of these crude sensory elements which are signals of threat. The second route is a thalamo–cortico–amygdala pathway that allows a more complex analysis of the incoming stimulus and delivers a slower, conditioned emotional response (figure I.II).

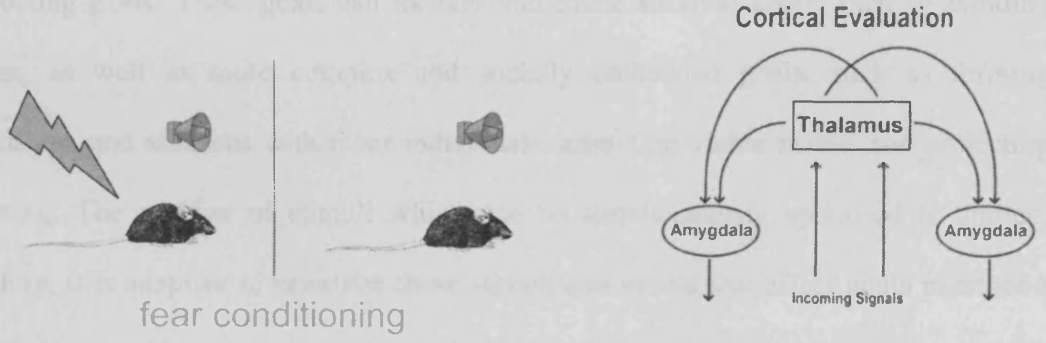

Figure I.II Fear conditioning

On the left a schematic representation of the fear conditions in rats: an acoustic tone (conditioned stimulus) is paired with an electric shock (conditioned stimulus). The rat after the conditioning will show a fear response to the acoustic stimulus. On the right a

diagram of the two neural pathways that mediate the fear conditioning: the amygdala-thalamus pathway and the thalamus-cortex-amygdala pathway.

1.3 Emotional modulation of Attention

"Everyone knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration, of consciousness are of its essence"

William James "The Principles of Psychology" 1980

Attention directs cognitive resources toward those aspects of the world that are more important than others. Emotional significance is a prime marker of importance to the organism. Indeed, as shown in the previous paragraph, many definitions of emotion are inherently tied to the concept of motivation or goal-relevance. A stimulus or event is appraised as emotional when it has potential consequences for either furthering or obstructing goals. These goals can include immediate survival goals, such as avoiding danger, as well as more complex and socially embedded goals, such as forming friendships and alliances with other individuals, attracting viable mates, and protecting offspring. The number of stimuli which can be simultaneously appraised is limited: therefore, it is adaptive to prioritize those stimuli and events that affect goals in either a positive or negative way. Because evaluating emotional significance is a means of tagging stimuli or events according to their importance, it stands to reason that emotional significance should be an important factor guiding attentional selection.

In this section I will review the scientific literature on how selective attention can be influenced by emotional meaning, considering the behavioral evidence and the potential neuropsychological mechanisms. The discussion of whether the emotional meaning of a stimulus can be encoded "automatically," or preattentively it is beyond the interest of this chapter: for extensive reviews of this topic see (Dolan, 2002; Pourtois et al., 2006; Vuilleumier and Pourtois, 2007).

1.3.1 Emotional control on selective attention: psychological evidences

Several researchers e.g., (Ohman et al., 2001; Robbinson, 1998) have proposed that the emotional significance of stimuli is first evaluated pre-attentively; then, subsequently, stimuli that have been tagged with emotional significance are prioritized for access to selective attention mechanisms that operate within a limited-capacity system. As explained in the first section of this chapter, early studies in cognitive science which aimed to formulate an information-processing model of the mind underplayed the role of the emotions: however, the idea that the emotional meaning of a stimulus can influence selective attention is not new. For example, research in the 1950s described the phenomenon in which a person's own name can capture attention, even when embedded in a stream of information that is otherwise effectively ignored (Moray, 1959). Since this early demonstration, a wealth of studies using a variety of paradigms has confirmed that emotionally relevant stimuli are likely to capture attention. A recent study by Anderson & Phelps, 2001(Anderson and Phelps, 2001) demonstrated the influence of emotion on

attention using an "attentional blink" paradigm (Raymond et al., 1992). A similar experimental paradigm was used in the experiments described in chapters three and chapter four of this thesis. The attentional blink paradigm involves a rapid serial presentation of visual stimuli in which subjects are required to identify two targets (T1 and T2) embedded in a stream of stimuli. A common finding has been that it is difficult to detect a second target in the series if that second target closely follows the first target (Raymond et al., 1992). Anderson and Phelps (2001) demonstrated that participants were more likely to detect the second target (T2) if it was emotional, and that the effect was strongest with shorter lags between the first and second target, when the second target was usually the most difficult to detect. Interestingly, patients with amygdala damage did not exhibit this effect, providing evidence for the amygdala's role in detecting emotional significance (Anderson and Phelps, 2001).

Evidence from clinical neuropsychology also supports the idea that emotionally significant information is especially likely to capture attention. Several relevant studies have focused on patients with unilateral neglect, who typically have right-hemisphere damage and who fail to attend to stimuli in the left half of space (Vuilleumier and Schwartz, 2001a; Vuilleumier and Schwartz, 2001c). The term extinction refers to the phenomenon in which a neglect patient is unable to attend to left-side stimuli when right-side stimuli are also present, presumably because these stimuli compete for access to attention and the stronger right-side stimuli "extinguish" the weaker, contralesional left-

side stimuli. An intriguing aspect of this syndrome is that extinction of a left-side stimulus is less likely when that stimulus is emotionally salient (Vuilleumier and Schwartz, 2001a; Vuilleumier and Schwartz, 2001c). This finding implies that emotional salience adds a "boost," helping a stimulus that would otherwise be extinguished to gain access to conscious attentional processes.

The study of attentional biases toward emotional information has consistently emphasized the role of individual differences. A large body of research has indicated, for example, that very anxious individuals are more likely to display attentional biases toward threatening information than less anxious ones (Bishop et al., 2004b). Individual differences in personality structure have also been linked to differences in attentional bias: for example, more anxious individuals are more likely than controls to display attentional biases toward threatening stimuli (Bishop et al., 2004b).

1.3.2 Emotional control on selective attention: neural mechanisms

The neurophysiological literature suggests that there are two primary neural mechanisms by which emotional significance can influence selective attention. Firstly, sensory processing of a stimulus can be enhanced in a *bottom-up* fashion by amplification of neural activity in the regions encoding that stimulus; such bottom-up influence is likely to involve input from the amygdala to sensory cortical areas. The second mechanism of emotional influence on attention involves executive attention, which imposes processing priorities in a *top-down* manner and primarily involves frontal lobe regions.

1.3.1.1 Bottom-up control

One neural mechanism of selective attention is the enhancement of processing in neural areas that represent a selected stimulus (Corbetta and Shulman, 2002; Desimone and Duncan, 1995; Driver and Frith, 2000). For example, attentional selection of a specific visual object is postulated to involve amplification of activity in that portion of extrastriate cortex that represents the object, thus biasing competition in favor of the selected stimulus (Desimone, 1998). Attentional modulations have also been identified for feature-selective responses in visual areas (e.g. when attending to colour versus motion, (Corbetta et al., 1990)) and for particular directions of motion (Saenz et al., 2002); together with differential responses to particular stimulus categories, such as visual words versus objects (Rees et al., 1999) or faces versus houses in the FFA and parahippocampal place area (PPA). Studies in monkeys have also demonstrated that single-cell firing rates within the extrastriate visual cortex are influenced by selective attention (Moran and Desimone, 1985). Moreover, during rapid perceptual learning, increased activity in inferior temporal regions is associated with correct recognitions of the object or face (Dolan et al., 1997).

Attentional factors related to task-relevance are not the sole modulatory influences upon visual processing. The emotional value of a stimulus may also produce analogous effects typified by relatively enhanced and/or sustained neural responses for emotional relative to neutral stimuli (Vuilleumier and Driver, 2007).

Indeed, numerous studies have found increased activity in cortical visual processing areas when participants view emotionally provocative images, compared to when they view neutral images (Lane et al., 1997a; Lang et al., 1998; Paradiso et al., 1999; Vuilleumier and Driver, 2007). In particular, fMRI studies of face processing have repeatedly shown that emotional facial expressions can produce significant increases in activation of the amygdala, and also for face-responsive regions within the visual cortex (e.g. FFA in lateral fusiform gyrus) (Vuilleumier and Pourtois, 2007). Such increases are typically greater for negative facial expressions associated with a possible threat, such as fear (Pourtois et al., 2006; Surguladze et al., 2003; Vuilleumier, 2005; Vuilleumier et al., 2001)

Other studies have found increased fusiform activity in response to fearful faces (Armony and Dolan, 2002; Morris et al., 2001). Interestingly, one study (Lane et al., 1999) reported that activity in a common area of visual cortex was modulated both by an emotional salience manipulation and by an attentional load manipulation, providing evidence that emotional salience and attention have similar locus of effect on visual cortex.

Together, these results support the idea that emotional significance leads to amplified neural representations at the cortical level, a primary mechanism thought to implement selective attention. Yet questions remain. How, for instance, is the amplification process initiated? What mechanisms cause the visual cortical areas to become more active when they are representing emotionally salient stimuli? Converging evidence from both animal

and human research suggests that the emotion-related modulation of visual processing involves the amygdala, which is known to be implicated in fear processing and fear-related learning (LeDoux, 2000; Phelps and LeDoux, 2005) as described in the paragraph 1.1.3 of this chapter. One possibility is that projections from the amygdala to the sensory cortex may contribute to the amplification of cortical representations (Lang et al., 1998; Morris et al., 1998; Vuilleumier et al., 2001; Vuilleumier and Driver, 2007). The amygdala is an important structure in the initial encoding of emotional significance and it is known to have reciprocal connections with early cortical sensory areas (Amaral, 1982). Furthermore, Morris, Friston, and colleagues (Morris et al., 1998) reported evidence for functional connectivity between the amygdala and extrastriate cortex while participants viewed emotional faces; specifically, the correlation between amygdala activity and extrastriate activity was influenced by the emotionality of the face. Moreover, a combined fMRI-lesion study (Vuilleumier et al., 2004) demonstrated that amygdala lesions can abolish the enhanced visual activation for fearful faces relative to neutral faces, even if the visual areas remain structurally and functionally intact. These authors also found a significant inverse correlation between the severity of structural amygdala damage and the enhancement of fusiform activity by fearful faces, observed selectively within each hemisphere. These data (Vuilleumier et al., 2004) provide direct evidence that the amygdala influences processing in remote visual cortical areas, normally boosting the representation of fear-related faces in fusiform cortex, in a way that is disrupted after amygdala damage.

Therefore, a likely bottom-up mechanism for attentional amplification of emotional stimuli suggests amygdala detects an emotionally significant stimulus and sends a boosting or modulating signal to the cortical areas responsible for building a detailed representation of that stimulus (figure I.III).

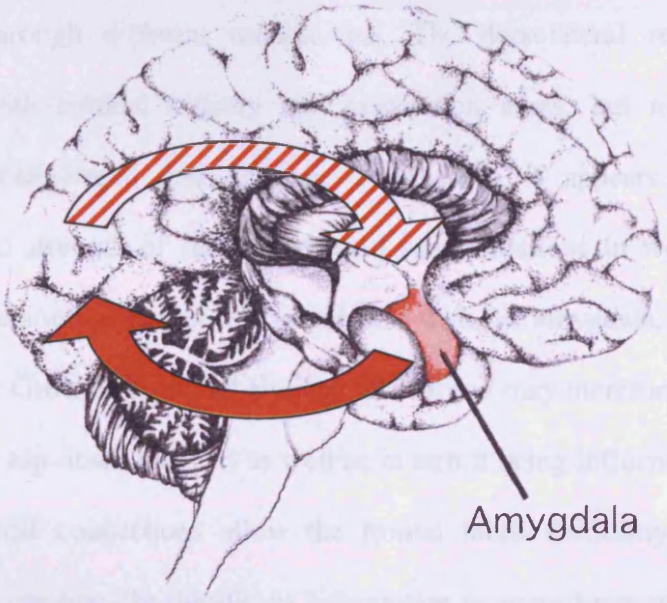

Figure I.III Diagram of the amygdala bottom-up control on visual cortical areas

The amygdala nucleus is represented in red. The hatched arrow represents the feed-forward input from the sensory (visual areas) cortex to the amygdala. The solid red arrow represents the feedback input from the amygdala to the sensory cortex.

1.3.1.2 Top-down control

Whereas the amygdala can send bottom-up influences that amplify emotionally significant cortical representations, other processes may act in a top-down fashion to modulate the selection of emotional information. Such top-down processes are likely to involve both the main subdivisions of the prefrontal cortex, the dorsolateral and ventromedial regions. Anatomical evidence suggests that these two sub-regions, which are reciprocally interconnected, may influence selective attention to emotional information through different mechanisms. The dorsolateral region has reciprocal connections with cortical sensory and association areas, but not directly with the amygdala (Groenewegen and Uylings, 2000), and it appears to be involved in maintaining the strength of selected cortical representations in working memory. The ventromedial region has reciprocal connections with the amygdala, among other regions (Amaral, 1982; Groenewegen and Uylings, 2000), and may therefore modulate amygdala processing in a top-down manner, as well as in turn it being influenced by the amygdala. These anatomical connections allow the frontal lobes flexibility in the selection or suppression of emotionally significant information in accordance with current goals and task demands. Although many different interpretations of dorsolateral function have been proposed (see (D'Esposito, 2007; Kimberg et al., 2000), for a review), one idea gaining currency is that the dorsolateral region is involved in selecting and maintaining task-relevant attributes represented by other areas of the brain (Miller and Cohen, 2001). Single-cell recordings in monkeys have demonstrated that some dorsolateral region

(DLPFC) cells maintain their firing rate during the delay period between a cue and the relevant response, thus indicating that these cells may be involved in working memory (Romanski, 2004). Recent animal research has shown that activity in the extrastriate visual cortex is influenced by top-down signals from the frontal lobes (Tomita et al., 1999). These findings are consistent with other neuroimaging evidence that the frontal cortex is involved in imposing top-down control that selects and maintains task-relevant representations (Hopfinger et al., 2000; MacDonald et al., 2000; Weissman et al., 2002). A recent study has confirmed that this top-down modulation require a synchronization between frontal and paretial cortex (Buschman and Miller, 2007)

Recent studies have shown that one area within the frontal lobes that seems to respond in the evaluation of emotional stimuli valence is dorsolateral prefrontal cortex (DLPFC) (Dolcos et al., 2007; Grimm et al., 2006). The DLPFC could therefore impose an attentional set that selects for information according to its emotional significance, or relevance to personal goals, by maintaining activation in posterior regions that represent an emotionally significant object or event. Although DLPFC seems a good candidate cortical area in modulating attention for emotional stimuli further empirical investigation are required to support this hypothesis.

More experimental evidence has been produced in support of a key role for orbitomedial prefrontal cortex (OMPFC) in the top-down modulation of attentional enhancement of emotional stimuli. OMPFC, including the ventromedial prefrontal cortex, the orbital

cortex and the cingulate cortex, is closely connected with subcortical limbic regions such as the amygdala (Barbas, 2000; Groenewegen and Uylings, 2000). Evidence from single-cell recording in an epileptic patient indicates that the ventromedial region of OMPFC detects emotional significance rapidly (Kawasaki et al., 2001), while studies on nonhuman primates have demonstrated that the orbital region of the OMPFC codes for stimulus-reward associations (Kringelbach, 2005). Furthermore, damage to the human OMPFC is known to produce socioemotional and motivational deficits (Bechara et al., 2005). Although the cingulate cortex has long been recognized to play a role in emotional responsivity (Papez, 1995), recent evidence indicates that the most ventral portions of the cingulate cortex are especially involved in tasks designed to tap emotional functions (Bush et al., 2000; Whalen et al., 1998), whereas the dorsal portions are more closely involved in conflict monitoring and response preparation (Braver et al., 2001; Rushworth et al., 2005).

Few studies to date have investigated the potential role of the OMPFC in attention to emotional information. Armony and Dolan (Armony and Dolan, 2002) found that focusing attention on the spatial location of an emotionally relevant stimulus was associated with increased activity in bilateral OMPFC as well as bilateral frontal eye fields and parietal cortex, regions known to be associated with spatial shifts of attention. One interpretation of these findings is that the OMPFC is associated with directing attention toward emotionally significant targets. Supporting this interpretation, several

other studies have also found increased activity in the anterior cingulate cortex during selective attention to emotional information (Elliott et al., 2000; Lane et al., 1997a). In addition, Whalen, Bush, and collegues (Whalen et al., 1998) found that the ventral anterior cingulate was more active when participants had to ignore emotional information, compared to when they had to ignore neutral information. Together, these results indicate that the orbito-medial prefrontal cortex (OMPFC), and the anterior cingulate in particular, may be involved when participants select between competing representations that differ in their emotional salience (Elliott and Dolan, 1998).

In addition to a role for prefrontal regions in enhancing attentional processing of emotionally relevant information, this region may also be involved in selecting against, or suppressing, emotionally relevant information. Indeed, several studies have indicated that amygdala activity can be modulated by emotion regulation strategies, a modulation that appears to be under frontal lobe control. One study (Schaefer et al., 2002) found that amygdala activity was influenced by task instructions either to passively view aversive pictures or to maintain an emotional response to the pictures, indicating top-down influences on subcortical emotional processing. These authors did not, however, investigate the source of the top-down signals. Other evidence has supported an hypothesis that the top-down influence comes from the frontal lobes. For example, patients with orbitofrontal damage fail to habituate to repeated aversive stimuli (Rule et al., 2002), implying that this region is normally involved in inhibiting emotional responses. Ochsner and collegues (Ochsner et al., 2002) reported that instructing

participants to reappraise aversive stimuli in unemotional terms decreased activity in the amygdala and increased activity in frontal regions. Taken together, these studies indicate that the regulation of emotional responses is likely to involve top-down control from the frontal lobe that modulates amygdala responsivity (figure I.IV). This top-down modulation may be elicited either by explicit task instructions or by endogenous personal goals and strategies of emotional regulation.

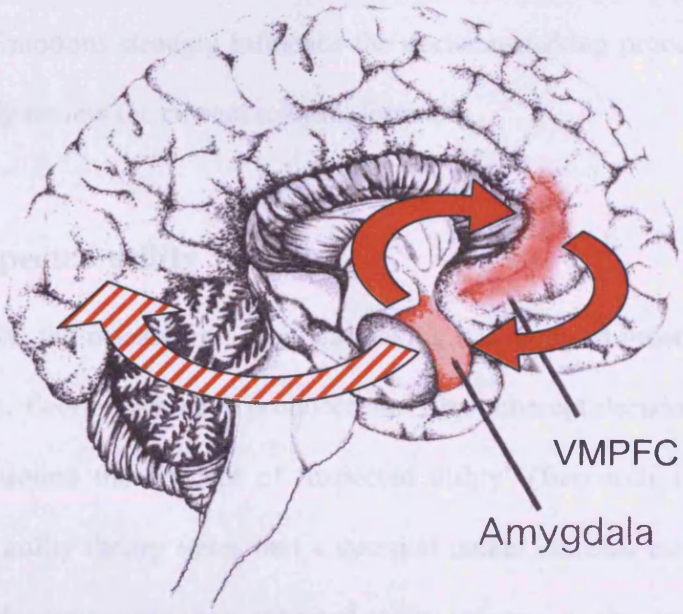

Figure I.IV Diagram of the ventral part of orbito-medial prefrontal cortex (VMPFC) top-down control on amygdala and visual cortical areas

The amygdala nucleus and the VMPFC are represented in red. The hatched arrow represents the input from the sensory (visual areas) cortex to the amygdala. The solid red arrows represent both the feedback and feed-forward input from the amygdala to the VMPFC.

1.4 Emotional modulation of Decision-Making

In the previous section I briefly reviewed the scientific literature on how emotional information modulates attention, enhancing the neural processing for stimuli tagged with emotional valence. This capacity clearly constitutes a strong evolutionary adaptation, since it efficiently allocates limited computational resources to stimuli that are relevant for the individual's fitness (e.g. predators, food, mate partners). Once this information is processed the individual will often take an action that it is the result of a decision-making process. Emotions strongly influence the decision-making process, and in this section I will briefly review the current relevant literature.

1.4.1 Expected utility Theory

Historically, the research on decision-making has received most attention in the field of economics. Economists have produced the first coherent decision making theory, which revolves around the concept of 'expected utility' (Bernoulli 1738) (Bernoulli, 1954). Expected utility theory states that a decision maker chooses between risky or uncertain prospects by comparing their expected utility values, i.e., the weighted sums obtained by adding the utility values of outcomes multiplied by their respective probabilities as described by the equation $EU=\sum_{1:i} p_i(u)_i$. However, this formulation of utility neglect the role of emotions in the decision making process. Jeremy Bentham (1789) independently from Bernoulli proposed another variant of utility in which emotions figure prominently (Bentham, 1789). Because Bentham viewed utility as the net sum of positive over negative emotions, he devoted a substantial part of his treatise on utility to a discussion of

the determinants and nature of emotions. Neoclassical economists later constructed their new approach to economics on the theoretical foundation of utility (von Neumann and Morgestern, 1944; P.Samuelson 1947). However, they rapidly became disillusioned with utility's psychological underpinnings and sought to expunge emotion from the utility construct. This process culminated in the development of "ordinal utility" and the "theory of revealed preference" which state that while the utility of a particular good cannot be measured using an objective scale, all the information about the consumer's real utility a are expressed by the subject's ranking of the different alternatives. This theory construed utility as an index of preference rather than of happiness. In von Neuman and Morgestern,'s (von Neumann and Morgestern, 1944) axiomatic version of utility theory the concept of ordinal utility and revealed preferences eliminated the alleged superfluous intermediate step of feelings and emotions that had proved difficult to quantify. Revealed preference theory simply equates unobserved preferences with observed choice. According to this view, decision-makers act "as if" they were fully rational, unemotional creatures, following a few simple rules ("axioms"). These axioms are the core of utility theory (von Neumann and Morgestern, 1944).

From the very beginning, rational utility theory was challenged by empirical evidence. In 1953 Maurice Allais described in his seminal paper (Allais, 1953) a striking violation (the "Allais paradox") of the "independence axiom" of utility theory. The Allais paradox shows that a significant majority of real decision makers order uncertain prospects in a

way that is inconsistent with the notion that choices are independent of irrelevant alternatives. The Allais paradox by showing the inadequacy of the independence axiom (a core axiom in EU theory) cast serious doubts on the validity of the classical utility theory (von Neumann and Morgestern, 1944). Simon (1956) was an early proponent of a different approach from utility theory based upon bounded rationality and concepts such as satisficing (as opposed to maximizing). The theory of bounded rationality relaxed several assumptions of the standard utility theory taking account of cognitive limitations to mental knowledge and capacity (Simon, 1982).

1.4.2 Prospect Theory

From the early 1970s, the psychologists Amos Tversky and Daniel Kahneman began to use economic models as a benchmark against which to contrast their psychological models. They argued that heuristic short-cuts created probability judgments which deviated from statistical principles (Tversky and Kahneman, 1974). In their 1979 paper "Prospect theory: decision making under risk", they documented violations of expected utility and proposed an axiomatic theory, grounded in psychophysical principles, to explain these violations (Kahneman and Tversky, 1979). One crucial innovation of prospect theory was the introduction of a new value function (figure I.V) that was able to explain several empirical anomalies (e.g. loss aversion, framing effect) that the were not captured by canonical utility function at the core of the expected utility theory proposed by Bernoulli (1738) (Bernoulli, 1954) and formalized by von Neumann and Morgenstern (von Neumann and Morgestern, 1944) (figure I.V).

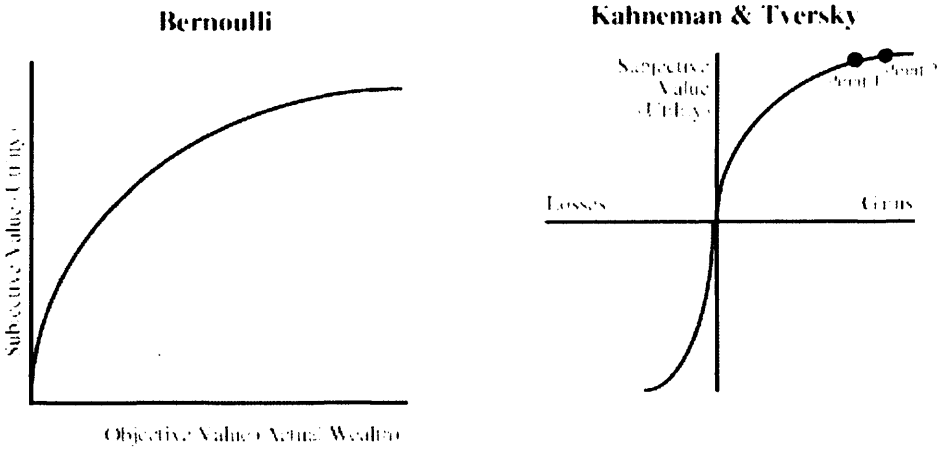

Figure I.V Canonical utility function and Prospect Theory utility function

The first diagram represents the utility function proposed by Bernoulli that it is at the core of the classical utility theory. On the y-axis is represented the subjective value (utility); on the x-axis is represented the actual objective value (expected value). In graphical terms, subjective value or utility is a concave function of money — i.e., the millionth dollar a person acquires has less utility than the first dollar he or she acquires. The second diagram represents the utility function proposed by Kahneman and Tversky that it is at the core of prospect theory. In graphical terms, subjective value or utility is actually an asymmetrical function of the absolute size of a subject's gains or losses. More details about the characteristics of these curves are given in the main text.

Three features characterize this value function: (1) it is concave in the domain of gains, (manifested in risk averse behaviour); (2) it is convex in the domain of losses (manifested in risk seeking behaviour); and (3) the function is sharply kinked at the reference point, producing a curve which is steeper for losses than for gains (Kahneman and Tversky, 2000). Prospect theory introduced two innovative concepts: "loss aversion" and the "reference point". These two concepts are able to account for several anomalies in the original expected utility theory. The observation that losses loom larger than gains is readily explained if these choice prospects are evaluated on different limbs of the value

function described above. Another consequence of the prospect theory is that the perception of reference point is strongly influenced by contextual information, in particular information of an emotional type. This effect was described for the first time by Kahneman and Tversky (Tversky and Kahneman, 1974) as the "framing effect". In their original formulation they presented a group of subjects with a hypothetical scenario called the "Asian disease problem":

Imagine that the U.S. is preparing for the outbreak of an unusual Asian disease, which is expected to kill 600 people. Two alternative programs to combat the disease have been proposed. Assume that the exact scientific estimates of the consequences are as follows:

At this point the group was split in two subgroups, which were presented with the following options:

(1) For the first group:

*If **Programme A** is adopted, 200 people will be saved.*

*If **Programme B** is adopted, there is 1/3 probability that 600 people will be saved and 2/3 probability that no people will be saved.*

(2) For the second group:

*If **Programme C** is adopted 400 people will die.*

*If **Programme D** is adopted, there is 1/3 probability that nobody will die and 2/3 probability that 600 people will die.*

The majority of subject in the first group chose Programme A (72%) over Programme B (28%) but in the second group the majority of subjects chose Programme D (78%) over

Programme C (22%). The only difference between program A and C and between program B and D it is in the way the options are presented or framed (death rate or survival rate). Thus, this pattern of choice represents a violation of the independence axiom of rational choice theory. On the contrary, prospect theory successfully explains this anomaly as a change in the perception of the reference point. The first group appraises the outcomes of the decision as a gain and show a risk adverse behaviour (preferring 'sure' choice A over 'risky' choice B) in accordance with the concave shape of the value function (figure I.V). Conversely the second group appraises the outcomes of the decision as a loss, and shows a risk-seeking behaviour (preferring 'risky' choice D over 'sure' choice C) in accordance with the convex curve in the loss domain (figure I.V).

These core ideas of prospect theory—that the value function is kinked at the reference point and that decision-makers are loss averse—became useful to economics when Thaler (1980) used prospect theory to explain riskless choices. For Thaler, loss aversion explained a violation of consumer theory that had identified and labelled as the "endowment effect" (Thaler, 1980). According to this effect, the selling price for consumption goods exceeds the buying price, often by a factor of 2 or more. The value of a commodity to an individual appears to be higher when that commodity is viewed as something that could potentially be forsaken, and lower when the same good is evaluated as a potential gain (Kahneman et al., 1990; Kahneman et al., 1991).

1.4.3 Research in Psychology and Economics on emotions and decision-making

Several investigators have elaborated the cognitive strategies underlying judgment and choice through models of constructed preferences (Gilovich et al., 2002; Payne et al., 1992; Slovic et al., 2002; Slovic et al., 2007; Slovic et al., 1977). Despite an initial emphasis on the cognitive mechanisms involved in decision making, recent researchers have acknowledged the role played by emotions in this process. One early proponent of the emotional modulation of decision making was Zajonc (1984), who argued that emotional reactions to stimuli occur automatically, guiding information processing and judgment (Zajonc, 1984). According to Zajonc, all perceptions contain some emotion. "We do not just see *a house*: we see a handsome house, an ugly house, or a pretentious house." In the last twenty years, Slovic, Fischhoff, and Lichtenstein have carried out extensive investigations into the role of emotional information on risk perception (Fischhoff et al., 1993; Loewenstein et al., 2001; Slovic et al., 2002; Slovic et al., 2007; Slovic et al., 1980; Slovic et al., 1981). They propose an 'affect heuristic' that highlights the importance of affect for risk perception and risk-related behaviour. They have reported that people's perception of the risks of hazardous technologies or activities are influenced by risk dimensions that have little to do with consequentialist aspects (i.e., possible outcomes and their probabilities). Instead risk perception is dominated by emotional aspects.

An extensive analysis on emotional states and their relevance for economics has been carried out by George Loewestein (Loewenstein and Lerner, 2003). He proposed that although immediate decisions are strongly influenced by emotional, "visceral" states (e.g. hunger, sexual desires, pains), individuals are generally incapable of anticipating the magnitude of these influences when they occur in the future. This creates a significant problem for decision-makers who would like to maximize their utility. Nevertheless emotions can have a contrasting effect on subsequent decisions. For example, positive emotional states have been shown to improve future decision-making (Estrada et al., 1994; Isen et al., 1988; Isen and Patrick, 1983), while on the contrary, negative emotions produce a narrowing of attention and a failure to search for new alternatives (Fiedler 1988). Isen and colleagues also proposed that the anticipated pain for a loss is greater for people in a positive mood that for those in a negative mood; this leads to a greater risk aversion among those in a good mood as they strive for "mood maintenance" (Arkes et al., 1988; Isen et al., 1988; Isen and Patrick, 1983; Kahn and Isen, 1993). These effects have been shown to have a substantial impact on real financial decision-making (Moore and Chater, 2003). Hsee and Rottenstreich (Hsee and Rottenstreich, 2004) have recently shown that when people rely on emotions in the decision making process, their evaluation is more strongly influenced by the nature of the stimulus than by the scope of their decisions. This evidence posits two differentiated value-systems: "valuation by feelings" and "valuation by calculation".

1.4.4 Research in Neuroscience on emotions and decision-making

The research in neuroscience on emotion and decision-making has been strongly influenced by the pioneering studies conducted by Pavlov in the late 1920s on learning and motivation. In his most famous experiment Pavlov showed that a conditioned stimulus (e.g. the ringing of a bell) produces behavioural change in an animal once it is paired with a conditional rewarding stimulus (e.g. food) or punishment (e.g. pain) (Pavlov, 1927). Based on the results of his research Pavlov defined reward as an object able to produce changes in behaviour. This definition of reward stimuli largely overlaps with one of the descriptions of emotional stimuli given at the beginning of this chapter. The concept of Pavlovian conditioning was extended by Skinner in the 1940s to include instrumental conditioning in which the conditional stimulus is substituted by a conditional action that the animal needs to perform in order to receive the reward (Skinner, 1938). Three factors govern conditioning: contiguity, contingency, and prediction. Contiguity requires that reward follows the conditioned stimulus/action by an optimal interval of a few seconds. The contingency requirement postulates that a reward needs to occur more frequently in the presence of a stimulus compared with its absence. The stimulus becomes a reward predictor only if the occurrence of the conditioned stimulus predicts a reward with a higher incidence than when no stimulus is present. Finally, the importance of the notion of prediction error is derived from Kamin's blocking experiment (Kamin, 1969), which postulates that if a reward is fully predictable it does not contribute to learning, even when it occurs in a contiguous and contingent manner. This idea was fully conceptualized in associative learning rules (Rescorla and

Wagner, 1972), according to which learning advances only to the extent to which a reinforcer is unpredicted and slows progressively as the reinforcer becomes more predictable. Formally prediction error denotes the discrepancy between a received reward and its prediction. All three aspects can be summarized by the Rescorla-Wagner equation: $\Delta V=\alpha(\beta)(\lambda-V)$ in which the changes in associative value of the conditioned stimulus and the reward in a trial are proportional to the saliency of the stimulus (α), the contingency of the stimulus to the reward (β) and prediction error (λ–V) term which asymptotically approaches zero after several learning trials (figure I.VI).

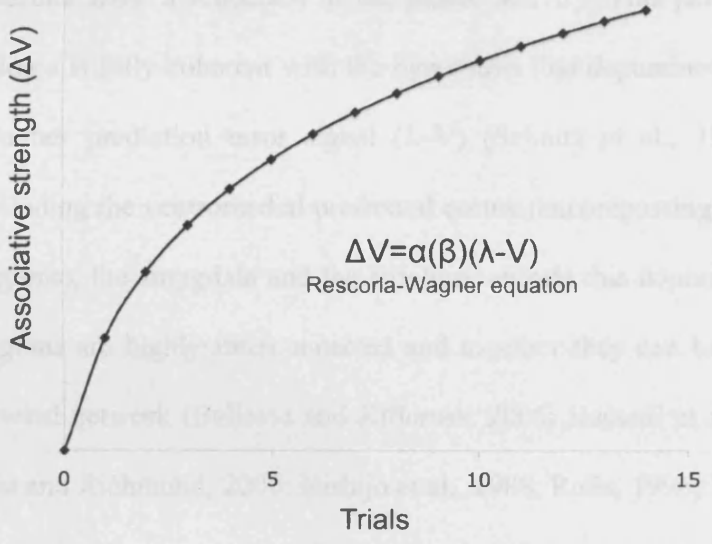

Figure I.VI Rescorla-Wagner learning equation
This graph represents the learning curve during conditioning (generated from the Rescorla-Wagner learning equation). On the x-axis is represented the increase (change in ΔV) in associative value between conditioned stimulus and the reward as function of the numbers of trials (y-axis).

In a landmark paper, Schultz and colleagues demonstrated that midbrain dopamnergic neurons activity code a prediction error signal according to the Rescorla-Wagner learning equation (Schultz et al., 1997). The dopaminergic neurons, before a Pavlovian conditioning procedure, are activated by the delivery of a primary reward (e.g. food). After the conditioning (according to the Rescorla-Wagner learning rule) the dopaminergic signal is shifted from the time when the primary reward is delivered, to the time when the unconditioned stimulus (e.g. bell's ring predicting a future reward) is presented. Most interestingly, once the animal is fully conditioned, if the experimenter does not deliver the reward at the time that the animal is expecting it, the dopaminergic neurons show a reduction in the phasic activity. This pattern of activity of dopamine release is fully coherent with the hypothesis that dopaminergic neurons emit a Rescorla-Wagner prediction error signal (λ–V) (Schultz et al., 1997). Several brain regions, including the ventromedial prefrontal cortex (encompassing orbital and medial prefrontal regions), the amygdala and the striatum, encode this dopaminergic reward signal. These regions are highly interconnected and together they can be considered as an integrated reward network (Balleine and Killcross, 2006; Hassani et al., 2001; Kringelbach, 2005; Liu and Richmond, 2000; Nishijo et al., 1988; Rolls, 1996; Tremblay and Schultz, 1999). In particular, the vental striatum is one of the core regions involved in representing the associative value between a stimulus/action and a reward. Electrophysiological studies in monkeys show that the striatum computes the value of a stimulus/action (Samejima et al., 2005). The human ventral striatum has also been shown to have a critical role in the representation of an option value encoding a prediction error signal (Knutson et al., 2001;

Knutson et al., 2005; O'Doherty, 2004; O'Doherty et al., 2002). Another recent study confirmed that the striatal representation of value in humans is causally dependent on the dopaminergic modulation (Pessiglione et al., 2006). In particular, the human striatum responds to the magnitude of a predicted reward (expected value) (Knutson et al., 2005; Tobler et al., 2007; Yacubian et al., 2006).

Another key region in reward processing is the amygdala. Anatomically, this area is connected with all the main structures I have previously defined as the reward network (the medial and orbital parts of prefrontal cortex, ACC and ventral striatum). This region has been proposed to encode the emotional and motivational aspects of value. Although research on the amygdala has often emphasized its role in the process of negative emotion like fear (LeDoux, 1996), research has shown that the amygdala also plays a key role in linking stimulus/action with the current values for both negative (aversive) and positive (appetitive) outcomes (Baxter and Murray, 2002; LeDoux, 1996). For example, monkeys with lesions in the amygdala are insensitive to changes in the value of a (Malkova et al., 1997). Moreover, neurons in the monkey amygdala have been shown to be susceptible to the affective aspect of a reinforcer. For example, neurons in the amygdala fire strongly in response to the sight of watermelon and, but their firing is sharply reduced after a piece of salted watermelon is presented (Nishijo et al., 1988; Nishijo et al., 1998). Notably, the activity of these neurons is consistent with a role for

this region in mediating reinforcer-devaluation effects. These results have been also confirmed in humans (Gottfried et al., 2003).

What I have broadly defined as the reward network also includes a large part of prefrontal cortex namely the orbital and medial prefrontal cortex (OMPFC). One of the first associations between OMPFC and reward processing comes from a study on stimulus-reward reversal (Mishkin, 1964). A monkey learns that choosing one of two objects will lead to a reward. When the contingencies reverse the monkey must learn that to get a reward he now has to choose the previously unrewarded object. Monkeys with lesions of OFC are impaired at the task (Mishkin, 1964). Following the reversal, they were unable to inhibit responding to the previously rewarded object, a behavior called perseveration. This impairment strongly resembles the impoverishment in decision-making shown by subjects with damage to OMPFC when tested on the Iowa gambling task (Bechara et al., 1997; Bechara et al., 2005; Bechara et al., 2000; Bechara and Van Der Linden, 2005).

In the Iowa gambling task subjects are asked to extract one card at time from one of four decks of cards: two of the four decks produce large gains but also large losses (high risk decks), while the other two decks lead smaller gains but also smaller losses (low risk decks). After a certain number of trials, healthy volunteers will start to prefer the low risk decks, realising that the high risk decks leads to higher losses in the long run. Patients with OMPFC lesion persevere in preferring the high risk decks (Bechara et al., 1997; Bechara et al., 2005). Interestingly, when healthy subjects choose the high risk decks,

they show an increase in autonomic emotional response, revealed by the increase in the skin conductance response (SCR). This SCR response is totally abolished in OMPFC patients. Damasio and colleagues explain this and other experimental evidence with the so-called somatic-marker hypothesis (Bechara et al., 2005) (briefly presented in the paragraph 1.1.3 of this chapter). But the somatic marker hypothesis is not the only explanation of these results. A recent study challenged this interpretation, proposing that the deficits on the gambling task might have arisen from the problems that OFC patients have in reversing stimulus-reward association (Fellows and Farah, 2005).

Experimental evidence shows that OMPFC is crucially involved in reward processing (Dolan, 2002; Kringelbach, 2005; O'Doherty, 2004; Rolls, 1996); however, it is still debated which aspect of reward is encoded by OMPFC. There are at least two aspects of reward: the incentive aspect (wanting) and the hedonic aspect (liking) (Robinson and Berridge, 1993). It has been proposed that where the dopaminegic striatal signals have a role in motivational aspects of reward, that OMPFC has a more flexible role in linking the reward to the hedonic experience (Kringelbach, 2005). For example, simple action-reward association does not seems to require OMPFC; animals with bilateral OFC removal can still be motivated to work for a reward (Izquierdo et al., 2004; Pears et al., 2003), and can make Pavlovian associations (Pickens et al., 2003). However, in more complex decisions is necessary to compare different aspects of a decision by integrating different sensory dimensions of a reward in order to determine the option value.

Anatomically, the OMPFC is ideal for the multimodal integration of the parameters necessary to evaluate an outcome, since it receives inputs from all sensory (Kringelbach, 2005). Indeed, patients with OFC damage have difficulty integrating multiple attributes pertaining to a decision (Fellows and Farah, 2005). More generally, the fact that the OMPFC uses different sources of information seems to play a critical role in computing a common value currency (Padoa-Schioppa and Assad, 2006; Tremblay and Schultz, 1999).

Chapter 2

Methodology

This chapter reviews the methodologies used in the experiments described in the experimental sections.

2.1 Functional Magnetic Resonance Imaging (fMRI) – Part I: Physics principles

Functional magnetic resonance imaging (fMRI) measures an haemodynamic response to index neural activity in the brain. fMRI is based on the principle that more active neurons increase the consumption of oxygen carried by haemoglobin in red blood cells from local capillaries. The local response to this oxygen utilisation is an increase in blood flow to regions of increased neural activity leading to local changes in the relative concentration of oxyhemoglobin and deoxyhemoglobin. The magnetic resonance (MR) signal of blood changes as a function of the level of oxygenation is the basis blood-oxygen-level dependent (BOLD) contrast (for a full review see (Logothetis, 2002)).

2.1.1 Magnetic resonance imaging (MRI): basic principles

2.1.1.1 Spin and radiofrequency pulse

Nuclei with an odd total number of protons and neutrons, such as the hydrogen (^{1}H) nuclei in the water, posses a magnetic property called spin, which refers to the rotation of the nucleus along its axes. In the MRI the subject's brain is immersed in a strong static magnetic field (B_0) that induce the ^{1}H nuclei in the brain tissue to align to the direction of the magnetic field. Such alignment is however not perfect, and the axis of spin will precess around the direction of the magnetic field at a frequency, called *Lamor frequency*,

determined by the strength of the static magnetic field and the type of nucleus in question.

Quantum mechanics states that a spin can have different energies depending on the orientation of its magnetic moment with respect to the applied magnetic field: when the magnetic moment is aligned with the field, its energy will be lower than when it opposes the field. For the simple spin system of ^{1}H, the magnetic moment can have two orientations with respect the magnetic field, either against it (high energy state) or with it (low, ground energy state). The amount of energy required to flip orientations is so small that the normal thermal energy available at room temperature is enough to flip spins. Spins can be excited from the ground to the high energy state by applying an oscillating radiofrequency electromagnetic field (B_1) perpendicular to the main magnetic field (B_0, applied in the *z* plane). To achieve the most efficient transfer of energy, the oscillation frequency of the B_1 field should be the same as the spin resonance (Larmor) frequency (e.g. 63.9 MHz for a proton in a 1.5 Tesla field). When a radiofrequency (RF) pulse matches wit the Lamor frequency applied to the nuclei, the axis of spin of the nuclei deviates from the static position. The degree to which the axis of spin deviates is also called the *flip angle*, which can be controlled by varying the strength, and duration, of the RF pulse. Thus, when the flip angle is set at 90 degrees, as in all fMRI experiments described in this thesis, the RF pulses causes the axis of the spinning nuclei to change from the direction of the magnetic field to a perpendicular direction (90 degree rotation).

It is this transverse component that gives rise to a detectable NMR signal. Following the above example, when the B_1 field is turned off after this 90° pulse (produced by the RF pulse), the magnetisation vector will rotate about B_0 in the *xy* plane with the spin resonance frequency.

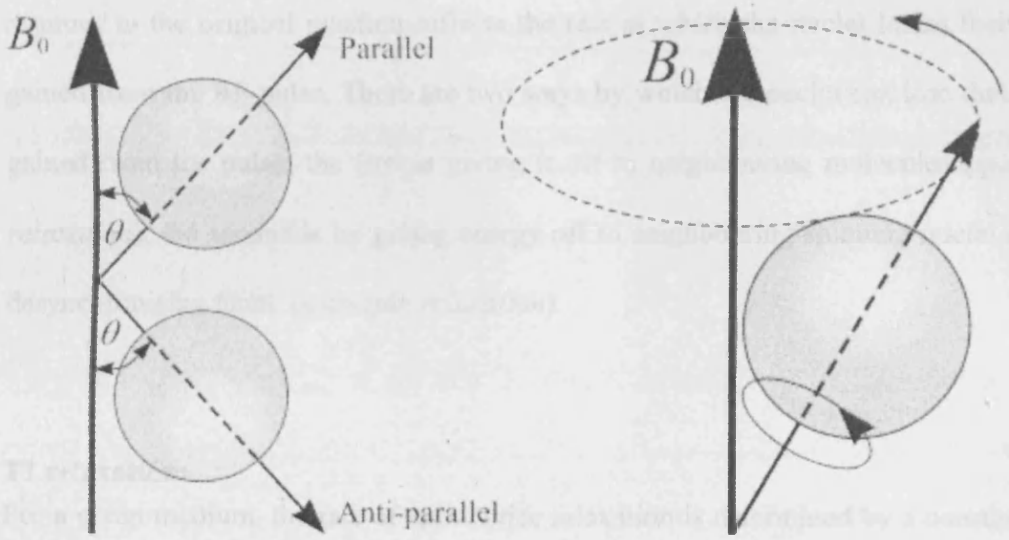

Figure II.I Magnetic Spin
The first diagram represents the two possible states of a proton (H) immersed in a magnetic field; respectively either parallel (spin ½) or anti-parallel (spin -½). The second diagram represents how a spinning nucleus (H) becomes perpendicular to the direction of the magnetic field (90 degree rotation) as a result of the RF pulse.

This is observable because the oscillating magnetic field induces a voltage in a coil positioned in the *xy* plane (Faraday's Law). MRI systems are designed to measure the transverse magnetisation, so the receiver coils, which may be the same as those used to apply the RF pulses, are sensitive only to the transverse component. The initial amplitude of the detected RF signal is proportional to the number of protons in the sample (the

proton density). The greater the proton density, the greater the magnetisation hence the greater the signal detected by the RF coils.

2.1.1.2 Relaxation

Since the RF pulse is only transient, the orientation of the axis of spin will eventually resume to the direction of the static magnetic field. The rate at which the axis of spin resumes to the original position reflects the rate at which the nuclei losses their energy gained from the RF pulse. There are two ways by which the nuclei can lose their energy gained from the pulse: the first is giving it off to neighbouring molecules (*spin-lattice relaxation*); the second is by giving energy off to neighbouring spinning nuclei and thus desynchronising them (*spin-spin relaxation*).

T1 relaxation:

For a given medium, the rate of spin-lattice relaxation is determined by a constant called T1. Protons that have been excited to the higher energy state dissipate this energy to molecules of the surrounding structure ('lattice') as heat. T1 differs for different materials, because different molecules have different mobilities and thus different rates of taking away energy from the exited spinning nuclei. For example, the protons in water have a longer T1 than those in fat because the carbon bonds in fat resonate near the Larmor frequency, which facilitates the transfer of energy to the lattice. In the human brain, the different water content of grey and white matter (71% and 84%, respectively)

means that T1 contrast can be used to provide contrast between these two tissues. This is indeed the basis for structural MRI imaging.

T2 relaxation:
In a perfectly uniform magnetic field the T2 relaxation or spin-spin relaxation describes the disappearance of coherence of the magnetic moment in the *xy* plane. The term spin-spin refers to the fact that interactions between protons determine the rate of T2 relaxation. No energy is actually lost; rather, energy is exchanged between protons, and there is a loss of "order" or increase of entropy. As neighbouring spins pass energy from one to another, their rotations become desynchronised.

Although, a perfectly uniform magnetic field cannot be produced, T2 dephasing will still occur. The inhomogeneity of the magnetic fields affects the T2 relaxation. The combined effect of true T2 and the magnetic field inhomogeneity is called 'apparent' T2 relaxation or shortly T2*. Since the BOLD signal measured in fMRI depends on T2* constant in a certain medium, which in turns depend on the homogeneity of the local magnetic field, an increase in the ratio of oxyhaemoglobin to deoxyhaemoglobin, following change in neural activity, is reflected by an increase in the BOLD signal.

2.1.1.3 Frequency and phase encoding

Placing a sample within a homogenous B_0 field will not produce tomographic MR images for the simple reason that all protons will experience (roughly) the same magnetic field and, hence, the frequencies of their emitted signal will all be identical. In MRI, a second

magnetic field (called a gradient field) is applied so that protons within the sample will emit different frequency signals that are dependent on their spatial position. In other words, as the magnetic field varies across the object, the resonance frequencies of spins (their Larmor frequencies) also vary. The spins' resonance frequencies are, therefore, determined by their location along the gradient axis. The number of spins resonating at a particular frequency determines the amplitude of that frequency in the spectrum of observable resonance frequencies. For each frequency component of the measured signal, the known value of the applied gradient strength and direction can be used to calculate the position from which the signal came.

Combining a frequency gradient with a pulse of the appropriate frequency and bandwidth can excite a small slice of the sample, allowing a slice by slice investigation of the sample. If the signal is acquired immediately after slice selection, its spectrum would be a one-dimensional projection of spin density for the spins in the selected slice. To produce a two-dimensional image of spin densities in the sample, encoding along a second axis is required. Thus, along the first axis locations are encoded by frequencies while locations along the second axis are encoded by phase. Location-dependent phase is achieved by temporarily switching on a linear gradient along the second axis. During gradient application, local magnetisation vectors will rotate with different frequencies depending on their positions within the gradient. These spins will possess different histories, reflected in phase differences among their magnetisation vectors dependent on their

positions along this second axis. The duration of the applied phase encoding gradient dictates the degree to which local transverse magnetisations are dephased. A series of increasing gradient pulse lengths will enable a reconstruction of the frequencies giving rise to the dephasing of transverse magnetisation. Hence, despite the fact that phase is being manipulated in the second axis, the amplitudes of spin frequencies are again determined and expressed as a spin density projection along the phase encoding axis.

2.1.1.4 Voxels

Step-wise increases in both gradients divide the sample into small cubes, or voxels (volume-elements). Spins in one voxel experience the same frequency and phase encoding. The signal of a given voxel is the sum of all spin contributions. Hence spins within a voxel cannot be distinguished from each other. The resolution of the image depends on the size of the voxels, which is determined by the step size of the gradients. Increasing the size of the voxel increases its signal and therefore its signal to noise. However, larger voxels are more likely to encompass groups of spins with very different behaviour, which could evoke a misleading signal (referred to as the partial volume effect). The fMRI experiments described in this thesis have resolution of 3x3x3 voxels/mm

2.1.1.5 Image contrast

Image contrast is based on the difference in signal intensity between areas of different structure or composition in an image. The MR signal intensity from a given voxel arises from a complex interaction of many different factors including T1 and T2 relaxation times, proton density, RF pulse characteristics and magnetic susceptibility (magnetic susceptibility refers to the fact that the net field experienced by a given nucleus depends on other magnetic spins or electron clouds in their environments). The relative contribution of some of these factors to the transverse magnetisation may be manipulated by controlling the timing of the RF pulses (known as pulse sequence parameters). The timing parameters are the repetition time (TR; the time required to acquire each image volume, i.e. the time between two consecutive 90° RF pulses) and echo time (the time between the initial 90° RF pulse and 180° pulse along an axis in the *xy* plane). A short TR and TE will emphasise the T1 characteristics of the tissue and produce a "T1 weighted" image. A long TR and TE produce a "T2 weighted image". Since the data sampling rates depends on the TR, it is desirable to have a short TR rather than a long one. However, because the TR depends upon the strength of the scanner and from other basic imaging parameters of a chosen sequence, the only way to reduce the TR is to reduce the number of slices acquired in a single EPI image. For a more extensive review see Liang and Lauterbur (2000).

2.1.2 functional Magnetic Resonance Imaging (fMRI): basic principles

2.1.2.1 BOLD contrast in fMRI

The BOLD (**B**lood **O**xygenation **L**evel **D**ependent) effect was observed initially in animal based experiments (Ogawa et al., 1990a; Ogawa et al., 1990b). As described it is based of the bloods magnetic properties varying as a function of its oxygenation level. In fact the cellular component of blood contains red blood cells (erythrocytes), which contain haemoglobin, the protein responsible for oxygen transport. Oxygen binds to iron, a constituent of the haem component of haemoglobin. When haemoglobin has no oxygen bound, each haem group has a net magnetic moment because of iron's 4 unpaired electrons (Pauling and Coryell, 1936). As soon as oxygen is bound, this net moment disappears due to a redistribution of the available electrons between iron and oxygen. The magnetic state of blood therefore reflects its level of oxygenation.

The T2* of water protons is influenced by interactions between the protons themselves and also by local B_0 inhomogeneities caused by different magnetic properties of various molecules. Paramagnetic molecules, such as deoxyhaemoglobin, have a local magnetic field gradient. This local gradient will contribute to the decay of transverse magnetisation and consequently shorten the T2* decay time. Hence, changes in the level of deoxyhaemoglobin (more precisely, changes in the ratio of deoxyhaemoglobin to oxyhaemoglobin) should result in changes in T2*.

2.1.2.2 Neurophysiology of the BOLD signal

It has been known for over 100 years (Roy and Sherrington, 1890) that changes in blood flow and blood oxygenation in the brain (collectively known as hemodynamics) are closely linked to neural activity. However, the precise relationship between neural signals and BOLD is still incompletely understood and remains under active research. It has been suggested that the intensity of the BOLD signal in human MT\V5, a visual area sensitive to motion, correlates linearly with the firing rates of neurons in the monkey's homologue of the same area (Rees et al. 2000). By conducting simultaneous recording in the same monkey area in the MR scanner, Logothesis and colleagues (2001) demonstrated that the intensity of the BOLD signal correlates with both local field potential and the associated firing rates. However, it seems to be the case that the BOLD signal correlates better with the intensity of local field potential (LFP's) than neuronal firing rates (Logothetis et al., 2001). Although an exact and straightforward physiological interpretation of the BOLD signal is not possible, it is still possible to compare the BOLD signals associated with different experimental conditions. Given that the BOLD signal is likely to have a positive relationship with both synaptic activity, and action potentials, we can still interpreter the BOLD signal as increased *activation* in that area for that specific experimental condition. It is however important to be cautious due to the fact that that such a concept of *activation* does not distinguish between whether synaptic activity is inhibitory or excitatory.

The time course of the BOLD signal following transient neural activity in a local area

has important implications for the interpretation and design of experiments. After transiently evoked neural activity, the BOLD signal typically takes 1-2 seconds to start deviating significantly from baseline, reaches a peak at 5-6 seconds, and returns back to baseline by 12-15 seconds with a small undershoot before returning to the initial state (Malonek and Grinvald, 1996) and figures. This entire temporal profile is called the *haemodynamic response.*

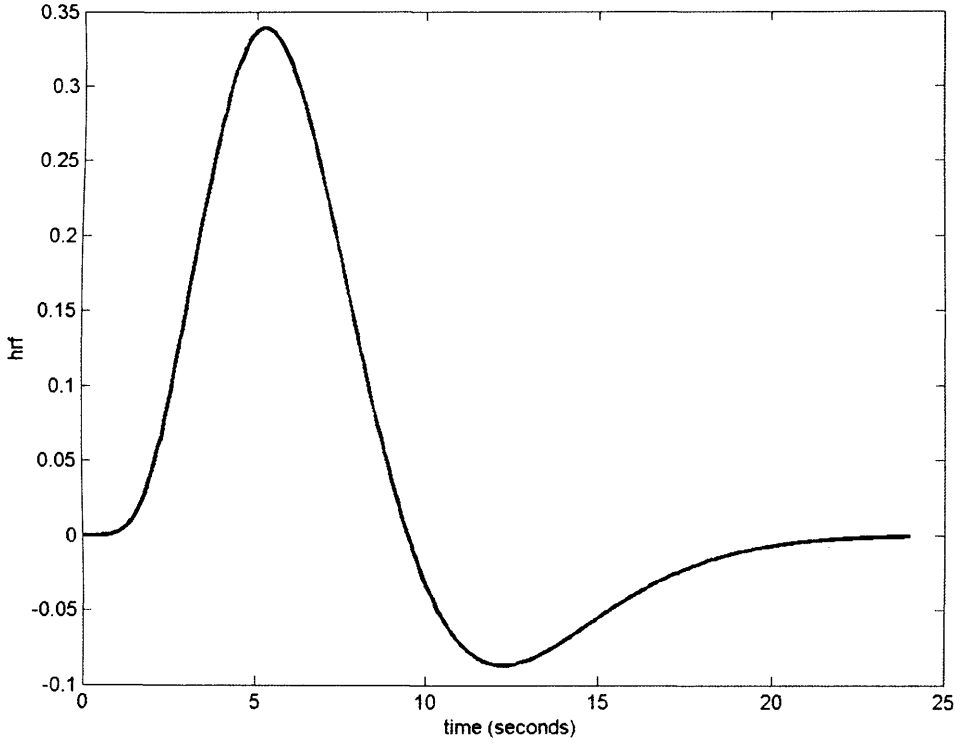

Figure II.II Haemodynamic function
This graph represents the temporal evolution of the blood release at capillary level that follows the neural action potential (the basis of the BOLD signal). On the y axis is plotted the haemodynamic response function (hrf) and on the x axis is plotted the time in seconds. As evident from this graph the haemodynamic change (hrf) is not instantaneous but peaks several seconds after the time of the neural action potential.

There is evidence that the profile of the haemodynamic response shows some variability between subjects (Aguirre et al., 1998) and between different areas. These variabilities pose important limitation in making temporal comparisons between activation in different brain areas (Moonen and Bandettini, 1999). Also, when two transient neural activations are too close in time, the intensity of haemodynamic responses may not add up linearly (Glover, 1999), making the interpretation of the BOLD activity difficult. Therefore, the trials in all fMRI experiments described in this thesis are placed at least 4 sec apart. The length of each trial in seconds is also always different from the TR and from any multiple of the TR in order in order to avoid a poor sampling of the haemodynamic response (Frackowiak, 2004).

Although the temporal resolution (seconds) of the BOLD signal in fMRI is somehow limited compared with other imaging techniques like EEG or MEG (milliseconds), it has reasonably good spatial resolution. The images acquired in the experiments described in this thesis have a spatial resolution in voxel (i.e, the smallest unit in a 3D image space) of 3 x 3 cubic mm. However, the spatial resolution of fMRI cannot be so easily quantified because there are a number of factors limiting the spatial resolution, rendering the actual resolution substantially lower than the voxel size. First, because the BOLD signal is only an indirect measure of local neural activity, is difficult to determine how close the change in oxyhaemoglobin/deoxyhaemoglobin ratio happens with respect to where neural activity occur (Matthews et al., 1999). Second, in a group analysis one also has to

consider variability in individual anatomy. Third, the functional images acquired are usually deliberately smoothed (as explained in the next session), thus reducing the spatial specificity. Finally, there may also be artefactual spatial distortions to the images acquired, the correction of which is not always straightforward (as explained in the next session). However despite these considerations, it has been shown that fMRI can yield results that are clearly suitable for analysis of a systems level neuroanatomy. For example it has been shown that BOLD signal can be used to reveal information as spatially fine-grained as retinotopic organization in the visual cortex (Engel et al., 1997).Also in terms its spatial specificity, fMRI is the best method for whole brain imaging, as compared with other neuroimaging techniques (e.g. EEG, MEG or PET) and it is therefore the method of choice for neuroanatomy studies.

2.2 Functional Magnetic Resonance Imaging (fMRI) – Part II: Statistical analysis

Functional neuroimaging techniques provide a means for making inferences about differences in regional brain activity between different conditions or states. To localise a function to a specific anatomical region it is critical that the experimental design allow one to unambiguously consider only the effect of the appropriate cognitive manipulation. In the fMRI studies presented in this thesis the identification of functionally specialised brain was achieved using statistical parametric mapping (SPM) (Frackowiak, 2004). Statistical parametric mapping is a voxel-based approach, employing classical inference,

to make some comment about regionally specific responses to experimental factors. In order to assign an observed response to a particular brain structure, or cortical area, the data must conform to a known anatomical space. Before considering statistical modeling, this chapter will briefly describe how a time-series of images are realigned and mapped into a standard anatomical space (e.g. a stereotactic space). The general ideas behind statistical parametric mapping are then described and illustrated with attention to the sorts of inferences that can be made with different experimental designs.

2.2.1 Pre-processing

The imaging time series is first realigned to a common reference frame to correct for subject movement during scanning. After realignment the data are transformed using linear and nonlinear mappings into a standard anatomical space (Friston *et al.*, 1995a). This normalisation procedure allows averaging data across subjects and permits data reporting within a standardised reference co-ordinate system.

2.2.1.1 Spatial and temporal realignment

Head motion during fMRI can give rise to artefactual change in signal intensity. Despite subjects being firmly immobilised with soft head pads, even the best subjects show movement up to a millimetre or so. Realignment removes variance from a time series which would otherwise be attributable to error (hence decreased sensitivity) or to evoked effects i.e. if movement is correlated with the cognitive task. In order to realign for all the images there is an estimation of 6 parameters of the affine 'rigid body' transformation

that minimises the [sum of squared] differences between each successive scan and the first. In three dimensions, a rigid body transformation can be defined by 6 parameters, typically three translations and three rotations about orthogonal axes. Using the first volume in an in an EPI series as a reference image all other images are spatially moved and/or rotated (adjusting the 6 parameters) until the difference is minimised.

In addition, it is necessary to perform a temporal realignment because multi-slice acquisitions, different slices will be acquired at slightly different times (Henson et al. 1999). In fMRI analysis, stimulus onset times are specified in scans, hence posing the problem for event-related fMRI studies (see later) that certain slices will be more sensitive to a particular model of haemodynamic responses. Temporal realignment ensures that the data from all slices within a given volume correspond to the same time point.

2.2.1.2 Spatial normalization

Spatial normalization is needed because the group analysis of brain imaging data typically takes a voxel-based approach as in the analysis of the data of individual subjects. For this reason it is necessary to ensure that the same coordinate is referring to the same brain area in different subjects. This is normally achieved by geometrically distorting the brains' images of individual subjects into a standard shape, and this procedure is known as spatial normalization (Friston et al., 1995). Early normalization

methods applied linear spatial transformation, which means for a given geometric plane, the subject's brain image is only starched evenly to mach the standard shape. However, nonlinear spatial transformation can be applied in addition to linear transformation in order to improve the normalization procedure (Ashburner and Friston, 1999), and it is applied to the pre-processing of all data described in this thesis. In this procedure the structural standard brain structure produced by Montreal Neurological Institute (MNI) is used as *template*. This template conforms to the geometric space and coordinate system of Talariach and Tournoux (1998) (Nowinski and Belov, 2003), such that x refers to the laterality of the location (positive is right), y refers to the anterior-posterior dimension (positive is anterior), and z refers to the dorsal-ventral dimension (positive is dorsal) and the origin (i.e. coordinate [0, 0, 0]) refers to the anterior commissure (AC), using millimetre (mm) as unit. Using a Bayesian framework is possible to estimate the parameters where one wants to find the deformation that is most likely given the data. The deformation is updated iteratively to minimise the sum of squared differences between the template and the deformed image and reflects the probability of actually getting that image if the transformation was correct. Prior information about the likelihood of a given transformation is incorporated by weighting the least squares (Ashburner et al., 1997).

2.2.1.3 Spatial smoothing

After normalisation, the fMRI data are smoothed by applying a Gaussian kernel (point spread function), of known width, to each voxel. The motivations for smoothing are:

1. Smoothing the data render them more parametric in their distribution and ensures the validity of parametric statistical tests.
2. Smooth data is one of the assumptions of Gaussian Field Theory (see later).
3. In order to average across subjects it is necessary to smooth so that regional effects are expressed at a spatial scale where homologies in functional anatomy exist over subjects.
4. The matched filter theorem states that the optimum smoothing kernel corresponds to the size of the effect anticipated.

All experiments described in this thesis are smoothed with a kernel of 8 mm.

2.2.2 General linear model (GLM)

The statistical tools used in brain imaging data analysis primarily apply the general linear model (GLM), which is the standard model for multiple regression. The statistical analysis of evoked haemodynamc responses tests for experimentally-induced effects at each intracerebral voxel individually and simultaneously. The time series data for each voxel is treated as independent, and the same regression model is applied to each voxel.

This approach is called a mass-univariate approach. The regression model is often called the design matrix a two dimensional array of numbers based on the experimental design.

2.2.1.3 Parameters estimation using the GLM

The regression process is also called parameter estimation. Commonly used parametric models, such as linear regression, t-tests and analysis of variance (ANOVA) are special cases of the general linear model. This model explains variation in the data, Y, in terms of a linear combination of the explanatory variables (x), plus an error term:

$$Y_j = x_{j1}\beta_1 + \ldots + x_{jl}\beta_l + \ldots + xj_L\beta_L + \varepsilon_j.$$

The β_l are unknown parameters, corresponding to each of the L explanatory variables for the *j*th observation of Y. The errors ε are assumed to be identically and normally distributed.

For *J* observations of Y, the general linear model can be expressed in matrix formulation:

$$\mathbf{Y} = \mathbf{X\beta} + \boldsymbol{\varepsilon}$$

for the column vector of observations **Y**, the column vector of error terms **ε** and the column vector of parameters **β**; $\boldsymbol{\beta} = [\beta_1 \ldots \beta_j \ldots \beta_J]^T$. Matrix **X**, of size *J* x *L*, is the

design matrix. This matrix has one row per observation and one column per model parameter. The number of parameters L is (usually) less than the number of observations J hence the simultaneous equations implied by the general linear model (obtained by expanding the matrix formulation with $\boldsymbol{\varepsilon}=\mathbf{0}$) cannot be solved (it is overdetermined). Therefore, some method is required for estimating parameters that "best fit" the data. The common method adopted is that of least squares.

Each column in the design matrix ($\mathbf{X}$) corresponds to some effect that one has built into the experiment, such as the alternating 'boxcar' function modelling alternating activation and control epochs in the experiment presented in chapter 3, or effects that may confound the results. The latter include a series of terms that are designed to remove, or model, low-frequency variations in signal due to artifacts such as aliased biorhythms or scanner drift. The relative contribution of each of these columns to the experimental variance (i.e. the parameter estimate for each column) is assessed using generalised least squares estimators.

Inferences about the parameter estimates are made using their estimated variances. This allows for two types of statistical test. One can test the null hypothesis that all the estimates are zero using the F statistic to give a SPM [F] or, alternatively, that some particular linear combination or "contrast" (e.g. a subtraction) of the estimates is zero using a SPM [T]. The T statistic is calculated by dividing the contrast (specified by contrast weights) of parameter estimates by the standard error of that contrast. This error

term is estimated using the variance of the residuals about the least squares fit. An example of contrast weights could be [1 –1 0 0 ...] to compare the differential responses evoked by two conditions that have been modelled by the first two condition-specific regressors (columns) in the design matrix.

As stated above, an important assumption in the analysis of time-series is that the residuals are identically and normally distributed. However, the haemodynamic response is of longer duration than the typical scan acquisition time, which leads to serial correlations among the error terms. The general linear model accounts for these autocorrelations by imposing a known temporal smoothing function on the time-series and adjusting the estimators and degrees of freedom accordingly (Worsley and Friston, 1995).

2.2.1.4 Choice of haemodynamic response function (HRF)

To take account of the latency of the hemodynamic response in the statistical analysis the regressors are *convolved* with a certain mathematical function to create the desired predicted temporal profile of the induced heamodynamic response. That mathematical function is called haemodynamic response function (HRF). The most commonly used HRF is a *canonical HRF* (Friston et al., 1998), which mathematically is a linear combination of two gamma functions. This function captures our current knowledge of

what the real HFR in the brain looks like, which has a bump-like shape that peaks at about 5-6 seconds after onset. When the vector containing the information about the temporal profile of the presentation of trials of a certain task condition is convolved with HRF function, graphically the bump-like shape are being inserted at the points where a trial is presented. (Figure I.II)

The canonical HRF it is used because it is assumed that our knowledge of the actual HRF is reasonably precise. In order to accommodate slight violations of the assumption that the actual HRF takes exactly the same form of the canonical HRF, non-linear derivatives of the canonical HRF can be included in the regression model. The two commonly used additional HRFs are the *temporal derivatives* and the *dispersion derivatives* of the canonical HRF (Friston et al., 1998). A further more flexible approach to model the actual HRF is to employ Fourier sets (Henson et al., 2002; Henson et al., 2001). A Fourier set is a collection of harmonic functions (i.e. sines and cosines). Given sufficient order (or size of the set), it can model any continuous curve. The advantage of the Fourier set is that does not make any strong assumption about the shape of the actual HRF. However, the disadvantages of the use the Fourier set is that there is no single regressor that stands out as the representative vector for a certain task condition. As explained in the follow sections, this complicates the statistical analysis at the group level. All the experiments described in this thesis use the canonical HRF to convolve the statistical regressors.

2.2.1.5 Event related design

Event-related fMRI can be defined as the use of fMRI to detect transient haemodynamic responses to brief stimuli or tasks (Friston et al., 1998). Event-related, or trial-based measurement is already standard in electrophysiology, namely stimulus-locked event-related potentials (ERP's). Previous functional imaging methods, such as PET, have limited temporal resolution necessitating measurement of prolonged states of brain activity. Such state-based designs were initially adopted in fMRI and referred to as epoch-related designs, the first experiment presented in this thesis being an example. Improvements in sensitivity and temporal resolution of fMRI have allowed an event-related approach. The event-related approach offers several advantages (Josephs, 1999).

1. The order of trials can be randomised hence the response to a trial is neither confounded by a subject's cognitive set nor systematically influenced by previous trials (Josephs, 1999).
2. Individual trials can be categorised or parameterised post-hoc according to a subject's performance.
3. Some experiments involve events that cannot be blocked, such as 'oddball' paradigms where the event of interest is a stimulus that violates the prevailing context.

4. Some events can occur unpredictably and can only be indicated by the subject (such as the spontaneous perceptual transitions measured by Portas and collegues (Portas, 2000).
5. Event-related fMRI allows more direct comparison with other techniques such as ERP or psychophysics.
6. Extensions to epoch-related designs. A state can be modelled, to first order, as a continuous train of events, each representing one trial within an epoch. This method also enables stimulus or response parameters to be modelled within an epoch. For example, the experiment presented in the chapter seven of this thesis was epoch-based, but analysed in an event-related manner to enable selling and buying trials to be modelled separately, and trial-by-trial within-epoch performance to be modelled parametrically.

In analysing event-related data, the explanatory variables are created by convolving a set of delta functions, indicating the onset times of a particular event, with a small set of basis functions that model the haemodynamic responses to those events (Josephs, 1999). All fMRI studies presented in this thesis are based on an event related design.

2.2.1.6 Inferences about subjects and populations: Random vs. Fixed effects analyses

The statistical inference drawn from fMRI time series may be of two types. Firstly, the results may be specific to the particular subject at the time of scanning. This fixed effects

inference is drawn from the effect size relative to the within subject variability. Highly significant results typically obtain from a fixed effects analysis because the degrees of freedom are high as they pertain to the number of scans across all subjects. The effect size is averaged across subjects hence six subjects are normally included in these analyses to provide a representative mean across subjects. However, the limitation of this type of analysis is that an effect size may be primarily driven by a few subjects. To overcome this one could perform a conjunction analysis across the six subjects which tests for regions commonly activated by a particular condition in all subjects. In essence, the fixed effects analysis is an extension of a case report, commonly used in clinical studies and animal lesion experiments, where an effect is observed in a particular subject and then this effect is replicated in further subjects.

Random effects analyses allow inferences to be made about the population from which the sample of subjects was drawn. One observation per subject per condition is entered into a random effects analysis (usually a contrast of parameter estimates from a 1^{st} level analysis). Hence the effect size is compared against the between subject variability in these contrasts. This type of analysis is, therefore, protected against the risk of being biased by strong effects in a subset of subjects. It follows that more subjects are required to achieve a significant result with random effects analyses, as the degrees of freedom depend on the number of subjects scanned, a suitable minimum number of subjects being 12. A random effects analysis was the default analysis for data presented in this thesis.

Random effects analyses are typically a one-sample t-test testing whether the estimated effect size (i.e. contrast) is significantly greater than zero across all subjects. In an fMRI experiment it is, however, unlikely that there is only one effect of interest. Take for example a 2x2 factorial design. Using one-sample t-tests to draw second level inferences would mean running separate analyses for each main effect and the interaction. An alternative is to conduct a repeated measures ANOVA, entering one observation for each of the four cells of the 2x2 design for each subject. It should, however, be noted that if more than one condition is entered into the second level analysis, an assumption of sphericity (e.g. homogeneity of co-variance) must be made. This assumes that the between subject, within-condition, variability is at the same level for each contrast observation (e.g. cell in the 2x2 factorial design).

2.2.1.6 Problem of multiple comparisons

The problem of multiple comparisons arises when we try to reject the null hypothesis by making more than one statistical test. In the mass-univariate approach implemented in SPM (described previously in this thesis) we test the significance of each voxel as if independent. If we threshold each individual voxel at an alpha value of 0.005 (i.e. we accept a voxel as significantly if the p-value of that voxel is smaller than 0.005) there is a greater than 0.005 chance that we would produce a false positive by mistakenly accepting that some voxel(s) in the brain are activated. The chance of false positive increase the more voxels we test, since in a brain imaging experiments we typical tests tens or

hundreds of thousands of voxels in each comparison. Hence, correcting for false positives is critical. To make sure that we have a reasonably family-wise alpha level, it is necessary to have a much more conservative voxel-level alpha value.

One formal and classical approach to the problem of multiple comparison is to apply Bonferroni correction (Dunn, 1961), which is a way of formally determining the voxel-level alpha value based on a desired family-wise alpha value. However, this approach can be too conservative unless one has an extremely good statistical power. An alternative approach is based on Gaussian random field theory (Worsley et al., 1996). Since brain images are typically spatially smoothed by the time they are entered into statistical analysis, it is possible to conceptualize the objects of statistical testes as smoothed clusters of voxels (called *resells*) instead of individual voxels. Since the problem of multiple comparisons is only severe when there are many statistical tests performed, by adopting this conceptualisation we lower the severity of the problem as there are always less resells than voxels in any smoothed image. Therefore, a correction based on the Gaussian random field theory typically gives a higher voxel-wise alpha value compared with the Bonferroni correction, depending on the smoothness of the images.

Although less conservative than the Bonferroni correction using the Gaussian random field theory, it is very likely to produce false negative and does not take in account any *a priori* anatomical and functional hypothesis on the a specific brain area. Another way of

dealing with the multiple comparison problem that take in account *a priori* information is called small volume correction (SVC). The role of family-wise correction is to ensure there is a reasonably small chance of mistakenly rejecting the null hypothesis that no voxel/resel in the whole brain is activated in a certain comparison. This null hypothesis, however, is rarely of interest to the researcher, unless the analysis performed is exploratory. Instead, in most comparisons performed in the experiments described in this thesis, there is a clear anatomical *a priori* hypothesis to test. Focusing on a few key regions of the brain dramatically reduces the problem of multiple comparisons. The requirement is that is necessary to define the region before the comparison is tested. This requirement is addressed by using results based on previous studies or from independent (i.e. orthogonal) statistical contrasst in the same experiment. SVC is normally based on Gaussian random field theory.

2.2 Drug experiments

2.2.1 Double blind design

Double-blind designs provides an especially stringent way of conducting an experiment, usually on human subjects, in an attempt to eliminate subjective bias on the part of both experimental subjects and experimenters. In most cases, double-blind experiments are held to achieve a higher standard of scientific rigour. In a double-blind experiment, neither the individuals nor the researchers know who belongs to the control and the experimental group. Only after all the data are recorded (and in some cases, analyzed) do the researchers learn which individuals are which. Performing an experiment in double-

blind fashion is a way to lessen the influence of the prejudices and unintentional physical cues on the results (the placebo effect, observer bias, and experimenter's bias). Random assignment of the subject to the experimental or control group is a critical part of double-blind research design. The key that identifies the subjects and which group they belonged to is kept by a third party and not given to the researchers until the study is over. Double-blind methods can be applied to any experimental situation where there is the possibility that the results will be affected by conscious or unconscious bias on the part of the experimenter. Double blinding is relatively easy to achieve in drug studies, by formulating the investigational drug and the control (either a placebo or an established drug) to have identical appearance (colour, taste, etc.). Patients are randomly assigned to the control or experimental group and given random numbers by a study coordinator, who also encodes the drugs with matching random numbers. Neither the patients nor the researchers monitoring the outcome know which patient is receiving which treatment, until the study is over and the random code is broken. Effective blinding can be difficult to achieve where the treatment is notably effective (indeed, studies have been suspended in cases where the tested drug combinations were so effective that it was deemed unethical to continue withholding the findings from the control group, and the general population), or where the treatment is very distinctive in taste or has unusual side-effects that allow the researcher and/or the subject to guess which group they were assigned to (Hoffer, 1967).None of these situations applies to the drug experiments described in this chapter four of this thesis.

Chapter 3

Enhanced processing of emotional information under limited attentional resources

The experiment described in this chapter employs fMRI and a modified version of an attentional blink paradigm to investigate neural mechanisms involved in the increased processing of emotional information (i.e. threatening targets) under conditions of limited attentional resources.

3.1 Introduction

Humans share with other animals a striking ability to detect a threatening stimulus. This capacity confers adaptive advantages, allowing organisms to commit attentional resources to goal-directed behaviour, whilst retaining an ability to respond quickly to potential harm. Several researchers have proposed that the emotional significance of stimuli are evaluated pre-attentively (Dolan, 2002; Palermo and Rhodes, 2007; Vuilleumier, 2005; Vuilleumier and Pourtois, 2007). Stimuli tagged with emotional significance are then prioritized for access to selective attentional mechanisms that operate within a limited-capacity system. Presumably, the brain has been designed by evolution to direct more cognitive processing toward those aspects of the world that are have survival importance. But what defines or determines "importance"? Emotional significance is a prime marker of importance to the organism.

Although cognitive neuoroscience has often been criticized for ignoring emotional relevance while pursuing an information-processing model of the mind, the notion that the emotional meaning of a stimulus can influence selective attention is not new. For example, research in the 1950s first described the phenomenon in which a person's own name can capture attention, even when embedded in a stream of information that is otherwise effectively ignored (Moray, 1959). Although mainly known for its contribution to the debate about early- versus late-selection theories of attention, the own name effect could be considered as early evidence for the role of personal meaning, and indeed

emotion, in guiding attention. Although less dramatic than the sound of a scream or the sight of a bloody murder, the sound of one's own name is emotionally meaningful because it is almost always self-relevant. Since this early demonstration, subsequent studies using a variety of paradigms have confirmed that emotionally relevant stimuli are likely to capture attention.

A recent behavioural study (Anderson and Phelps, 2001) demonstrated an emotional modulation of attention using an attentional blink paradigm, which involves rapid serial presentation of visual stimuli (RVSP). A common finding in this paradigm is difficulty detecting a second target if it follows too closely a first target (Raymond et al., 1992). This study showed that normal subjects were more likely to detect the second target if it was emotional whereas patients with amygdala lesions do not show this effect (Anderson and Phelps, 2001). Clinical neuropsychological studies on patients with unilateral neglect, who typically have right-hemispheric damage, and who fail to attend to stimuli in the left half of space, show a drastic reduction in their behavioural deficit when the left side is emotionally salient (Vuilleumier et al., 2001; Vuilleumier and Schwartz, 2001c). Finally, anxious individuals are more likely than controls to display attentional biases toward threatening stimuli (Bishop et al., 2004a; Bishop et al., 2004b).

The emotional significance of a stimulus can influence attentional process through two distinct mechanisms. A bottom-up boosting of activity in cortical regions coding for sensory attributes and top-down control from frontal areas that imposes priorities on

selective processing. In support of a bottom-up mechanism, numerous studies have found increased activity in cortical visual processing areas when participants view emotionally provocative images, compared to when they view neutral images (Lane et al., 1997c; Lang et al., 1998; Paradiso et al., 1999; Vuilleumier et al., 2001; Vuilleumier and Schwartz, 2001a). Likewise, activity in the fusiform face area increase when participants view emotionally expressive compared to neutral faces (Breiter et al., 1996; Vuilleumier et al., 2001). Other studies have found increased fusiform activity in response to fear-conditioned faces (Armony and Dolan, 2002; Morris et al., 2001).

Emotional information processing may benefit from top-down mechanisms of selective attention. In the case of emotional processing such top-down influences are likely to involve the prefrontal cortex, in particular the ventromedial regions and rostral cingulate cortex. These areas show close reciprocal connections with subcortical limbic regions such as the amygdala and ventral striatum (Groenewegen and Uylings, 2000; Wise, 2004) involved in early stages of processing emotional material. For example, focusing attention on the spatial location of an emotionally relevant stimulus is associated with increased activity in bilateral VMPFC (Armony and Dolan, 2002). One interpretation of these findings is that the VMPFC is associated with directing the spatial attention toward emotionally significant targets. Several other studies have also found increased activity in the anterior cingulate cortex (rACC) during selective attention to emotional information (Elliott et al., 2000; Lane et al., 1997c). In addition, rACC activity increase when

participants have to ignore emotional information, compared to when they have to ignore neutral information (Whalen et al., 1998). In this study, I employed fMRI and in the context of an attentional blink paradigm, to investigate how these two distinct mechanisms control an increased detection of threatening targets under conditions of limited attentional resources.

3.2 Materials and methods

3.2.1 Subjects

Fifteen healthy, right-handed subjects [8 males (mean age 23.4= years ± 1.9) 7 females (mean age 21.7 years ± 2.1)] were studied. All subjects had a university degree, or were in the process of obtaining one. The study was conducted with the approval of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee.

3.2.2 Experimental paradigm

In an attentional blink (AB) task subjects searched for two targets among an RSVP of 15 distrators items at fixation for 70ms each with no interstimulus interval. The first stimulus (T1) was a scene (either indoor or outdoor) and the second target (T2) was a face (either neutral or fearful (Marois et al., 2004). The distractors were scrambled images of the scene and face together, with each greyscale stimulus subtending 8.5° x 8.5°. All face stimuli were selected from the KDEF database (D. Lundqvist and J.-E. Litton, personal

communication; photographic face set available from the Department of Neurosciences, Karolinska Hospital, Stockholm, Sweden). The scrambled images originated from a pool of scene and face images (mixed in 50% proportion) and were created by dividing each quadrant of images into 25 squares randomly scrambling their position. Thin black grids were drawn over the scrambled and intact images to occlude the boundaries of blocks. A trial began with presentation of a fixation cross for a variable time between (2000-4000ms) before the onset of the RSVP, which consisted of 15 images each displayed on a screen for 70ms. All images were scrambled picture of scenes and faces (distractors) but two of the distractors were replaced by two intact target images (Marois et al., 2004).

At the end of RVSP subject reported the identity of both targets using a keypress in two response period of 4000ms each. During the T1 response period a display was shown with three options: NoScene, Indoor or Outdoor. Subjects indicated by a keypress whether no scene, an outdoor scene or an indoor scene was presented. For T2 response subjects were shown the face that had been presented during the current trial together with two other faces of the same gender (male or female) and expression (neutral or fearful) and were asked to indicate using a keypress the face shown at T2. A scene target (T1) and face target (T2) was presented every trial. T1 was presented randomly between the 2nd to 7th position during the RVSP, where T2 was always presented after 5 distractors (350ms) from T1. A total of 144 trials were presented in 3 sessions of 48 trials each.

The participants task was to identify both targets identity at the end of each trial. The first target (T1) was always a scene (either indoor or outdoor) followed, after 5 intervening distractors (350ms lag), by another target (T2) which was always a face (either neutral or fearful) Figure III.I. This experimental design allowed me to identify the neurobiological underpinnings supporting an increased capacity to process emotional stimuli, under conditions of high attentional load.

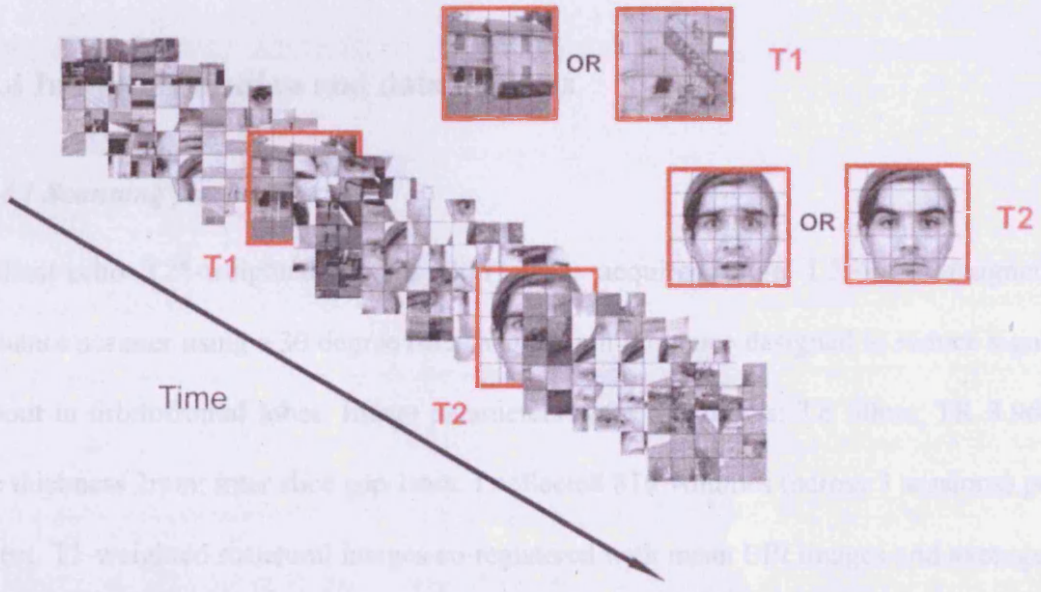

Figure III.I The emotional attentional blink task

Subjects were asked to search for two targets (T1 and T2) embedded in between 13 distrators items at fixation for 70ms each with no interstimulus interval. The first stimulus (T1) was a scene (either indoor or outdoor) and the second target (T2) was a face (either neutral or fearful). The distractors were scrambled images of the scene and face together. The two targets were always separated by 5 distractors (350ms). At the end of the rapid

visual stimuli presentation (RVSP) subjects were asked to report by a keypress whether no scene, an outdoor scene or an indoor scene was presented (T1 response 4 sec). Subsequently they were asked to identify the identity of the face T2 by keypress in a forced choice between 3 faces one of them was the one presented in the trial (T2 response 4 sec). Note that the red frame is showed here only for display purpose and was not part of the original stimuli.

3.2.4 Image acquisition and data analysis

3.2.4.1 Scanning parameters

Gradient-echo T2*-weighted images (EPI) were acquired on a 1.5 Tesla magnetic resonance scanner using a 30 degree titled acquisition sequence designed to reduce signal dropout in orbitofrontal lobes. Image parameters were as follows: TE 50ms; TR 3.96s; slice thickness 2mm; inter slice gap 1mm. I collected 810 volumes (across 3 sessions) per subject. T1-weighted structural images co-registered with mean EPI images and averaged across subjects to allow group level anatomical localization. Images were analyzed using the statistical parametric software SMP2 (Wellcome Department of Imaging Neuroscience London http://www.fil.ion.ucl.ac.uk/spm). Preprocessing consisted of spatial realignment and normalization to a standard EPI template, and spatial smoothing (8mm kernel).

3.2.4.2 Voxel-based analysis

The fMRI data were analyzed in an event-related manner using the general linear model (GLM), using SPM2. After discarding the first six image volumes from each run to allow for T1 equilibration effects, image volumes were realigned and co-registered to each subject's structural scan. Subject-specific regressors of interest were assembled by convolving δ functions (corresponding to the time of onset of the beginning of the RVSP) with a canonical hemodynamic response function (HRF). I removed low frequency fluctuations by a high-pass filter with a cut-off at 128 s. A correction for temporal autocorrelation in the data (AR 1 + white noise) was applied. Four regressors of interest were built according to the trial type and the subjects' responses and were include in the GLM. The onset was locked to the beginning of the RVSP. Two nuisance regressors (T1 incorrect trials and T2 response period) were included in the GLM. Parameter estimates were used to calculate the appropriate linear contrast. These contrast images were then entered into a one-sample t test across all subjects (random effects analysis). The resulting Z statistic images were thresholded at $Z > 3.1$ corresponding to $P < 0.001$ uncorrected. I report results in a priori regions of interest (FFA, amygdala, striatum, ACC) previously identified in neuroimaging studies on emotional regulation of attention [6, 7, 10, 16, 22] at $P < 0.001$ uncorrected for multiple comparisons. I also performed a small volume correction (SVC) using a sphere of 10mm radius centered on coordinates of a priori regions of interest (rACC: [x= -38, y=-50, z=-22] (Bush et al., 2000); ventral striatum: [x= ±22 y=10, z=-10] (Seymour et al., 2005)). The SVC procedure, as implemented in SPM2 using the family-wise error (FWE) correction ($p < 0.05$), allows

results to be corrected for multiple non-independent comparisons with a defined region of interest. Activations in other regions are reported if they survive whole-brain correction for multiple comparisons at $P < 0.05$ (FWE).

3.2.4.3 ROI-based analysis

I performed a region-of-interest (ROI) analysis in the bilateral FFA with the MarsBaR SPM toolbox: (http://marsbar.sourceforge.net/). The ROI's for the FFA were defined by the SPM cluster ($P<0.05$ whole-brain corrected for multiple comparisons) contrasting the activity during the entire task against baseline. Thus, the ROI is orthogonal and unbiased with respect to all the contrasts of interests. Using the MarsBaR SPM toolbox, I obtained parameter estimates for all voxels within this region, for the group as a whole. These parameter estimates were averaged across the ROI, and specific effects tested by one-sample t tests.

3.3 Results

3.3.1 Behavioural results

This experimental paradigm elicited in the subjects a robust attentional blink effect. For the entire scanning period participants were able to detect the T1 scene 91.7% of the trials. After correct T1 detection subjects could correctly report the T2 face stimuli significantly more often when the face was fearful (Fearful-T2) versus when it was

neutral (Neutral-T2) 58.8% vs. 46.8% ($t_{(14)}$=5.2 $p<0.001$ two tailed paired t-test) (Figure III.IIa).

The 2x2 fully factorial design employed in the experiment allowed me to study how the emotional valence of the T2 face, that was either fearful or neutral (Fearful-T2 vs. Neutral-T2), affects correct or incorrect T2 face detection (Correct-T2 vs. Incorrect-T2). Reaction times (RTs) for T2 targets were analyzed by repeated measures ANOVA. It was possible to detect a shortening in reaction times (RT's) for correct T2 detection (mean value 2.76 ±0.20 sec) relative to incorrect T2 detection (mean value 2.95 ±0.28 sec), a reduction that was statistically significant ($F_{(1,14)}$=22.6 $p<0.001$) (Figure III.IIb). By contrast the emotional valence of the T2 face stimulus (fearful vs. neutral) did not produce significant changes in reaction time ($F_{(1,14)}$=2.8 $p=0.11$). Note that RTs were used in the fMRI analysis as measure of confidence for the T2 correct identification (see methods session in this chapter).

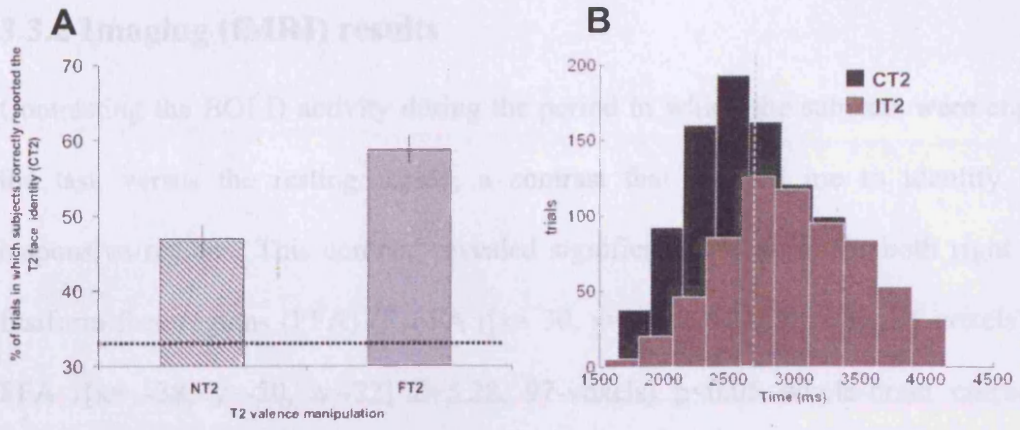

Figure III.II Behavioural results

(A) *The graph shows the x percentage (%) increase of trials in which the subject correctly reported the T2 face identity (CT2) for a T2 fearful face condition (FT2 58.8% ; S.E. 1.85) with respect to a T2 neutral face condition (NT2 46.8% ; S.E. 1.95) FT2 vs. NT2 ($t(14)=5.2$ $p<0.001$ two tailed paired t-test). In both the T2 detection was significantly above chance level of 33% (forced choice between tree faces) represented in the graph with a dashed line (NT2: $t(14)=7.05$ $p<0.001$, FT2: $t(14)=13.9$ $p<0.001$ two tailed one-sample t-test).* ***(B)*** *The histograms represent the reaction time (RT) distributions for number of trials. In black is shown the condition in which the T2 face was correctly reported (CT2) and in brown the condition in which the T2 face was incorrectly reported (IT2). The two distributions partially overlap with the RT mean value significantly shorter in the CT2 versus the IT2 ($F(1,14)=22.6$ $p<0.001$). The dashed line represent the median split for the CT2 condition (see material and methods chapter).*

3.3.2 Imaging (fMRI) results

Contrasting the BOLD activity during the period in which the subjects were engaged in the task versus the resting period, a contrast that enabled me to identify stimulus responsive regions. This contrast revealed significant activation for both right and left fusiform face regions (FFA) (R-FFA ([x= 30, y=-48, z=-24] Z=5.88, 25-voxels) and L-FFA ([x= -38, y=-50, z=-22] Z=5.28, 97-voxels) $p<0.05$ whole-brain corrected for multiple comparisons (FWE)). The location of these two clusters of activity is consistent with FFA activity previously reported (Kanwisher et al., 1999) (Figure III.IIIa). These clusters were then used to define regions of interest (ROIs) in which I performed a statistical analysis between the different conditions during the AB task.

Activity in both FFA's significantly predicted subjects' ability to report correctly face identity in the response period (R-FFA Z=3.27 $p<0.05$, L-FFA Z=5.32 $p<0.05$) (Figure III.IIIb). Neither the left or right FFA showed increased activity for fearful face T2 compared to neutral (Fearful-T2 vs. Neutral-T2), although I observed trend level effect in the L-FFA (Z=2.01 p=0.11). Nevertheless in the trials in which the T2 were incorrectly reported L-FFA I showed a significant increase in activity (Z=2.56 $p<0.05$) for fearful T2, targets versus neutral T2 (Fearful-T2_Incorrect-T2 vs. Neutral-T2_Incorrect-T2). No significant interaction between valence of the target T2 (Fearful-T2 vs. Neutral-T2) and increased performance in T2 detection was observed suggesting that the FFA activity cannot fully account for the behavioural increase in T2 fearful face detection.

A **B**

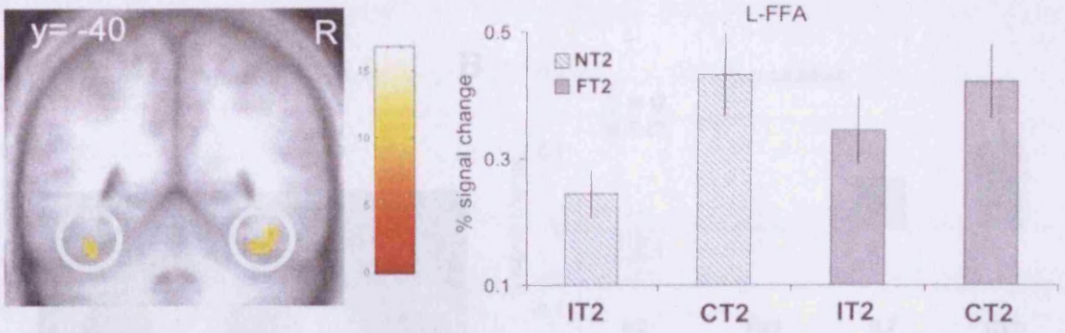

Figure III.III Fusiform face area (FFA)

(A) *Coronal section of SPMs showing both fusiform face areas (FFA) contrasting activity during the entire task against the baseline (R-FFA ([x= 30, y=-48, z=-24] Z=5.88, 25-voxels L-FFA ([x= -38, y=-50, z=-22] Z=5.28, 97-voxels p<0.05 whole-brain corrected for multiple comparison FWE). Both clusters were used to identify respective regions of interests used in a ROI's analysis that revealed a significant increased activation in the CT2 versus IT2 (R-FFA Z=3.27 p<0.05, L-FFA Z=5.32 p<0.05). L-FFA showed a non-significant trend for FT2 versus NT2 (Z=2.01 p=0.11) with a significant simple effect in the IT2 condition FT2_IT2 versus NT2_IT2 (Z=2.56 p<0.05)* ***(B)*** *Plot of signal percentage changes for the L-FFA cluster.* SVC).

Using a voxel based analysis I then identified regions showing an increase in activity for fearful T2 faces versus neutral T2 faces (Fearful-T2 vs. Neutral-T2). Bilateral ventral striatum showed a significant increase in BOLD activity: R-striatum ([x= 20, y=16, z=0] Z=4.08, 68-voxels, p<0.001 uncorrected and p<0.05 SVC), L-striatum ([x= -26, y=14, z=-4) Z=3.63, 8-voxels, p<0.001 uncorrected and p<0.05 SVC). Figure III.I

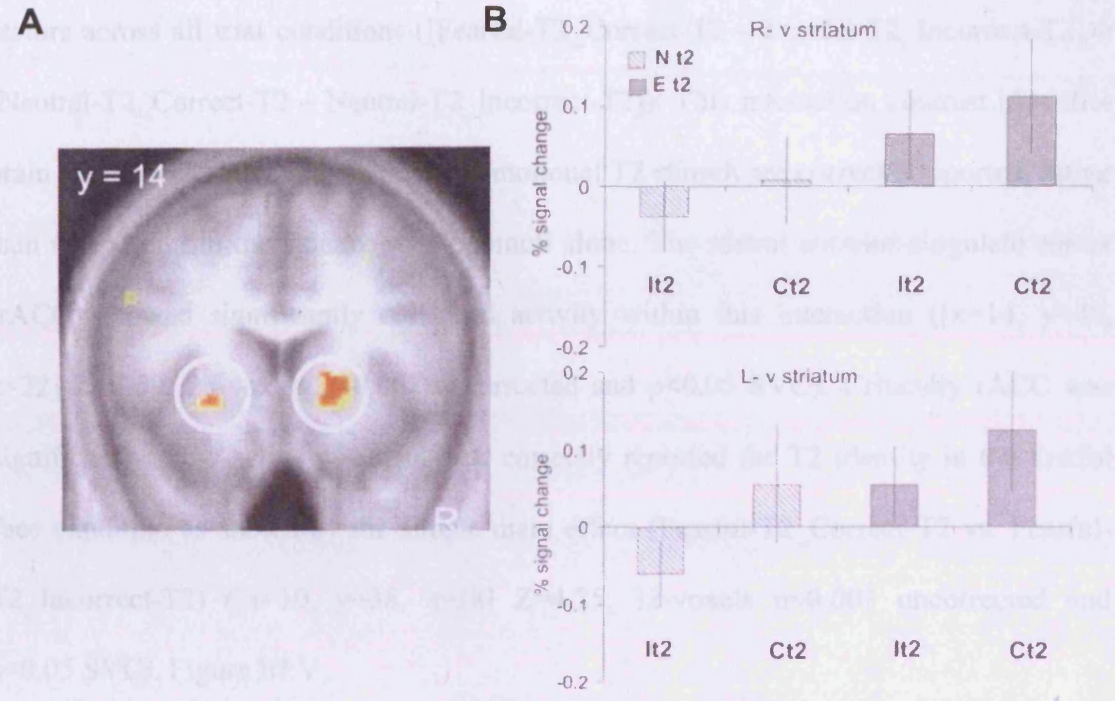

Figure III.IV: Ventral striatum

(A) SPM showing response in both ventral striatum nuclei for the FT2 versus NT2 statistical contrast R-striatum ([x= 20, y=16, z=0] Z=4.08, 68-voxels, p<0.001 uncorrected), L-striatum ([x= -26, y=14, z=-4) Z=3.63, 8-voxels, p<0.001 uncorrected and p<0.05 SVC). ***(B)*** *Plot of signal percentage changes for the both ventral striatum nucleai clusters.*

The fully factorial design of the fMRI experiment described in this chapter allowed me to examine how emotional valence of T2 (Fearful-T2 vs. Neutral-T2) modulated accuracy in T2 detection (Correct-T2 vs. Incorrect-T2), the principal aim of the study. The most direct way to determine at neural level an effect of T2 valence on the T2 response

accuracy is to identify brain areas showing a significant interaction between the two factors across all trial conditions ([Fearful-T2_Correct-T2 – Fearful-T2_Incorrect-T2] > [Neutral-T2_Correct-T2 – Neutral-T2_Incorrect-T2]). This interaction contrast identifies brain areas specifically activated when emotional T2 stimuli are correctly reported, rather than responding to the valence of T2 stimuli alone. The rostral anterior cingulate cortex (rACC) showed significantly enhanced activity within this interaction ([x=14, y=40, z=22] Z=3.59, 25-voxels $p<0.001$ uncorrected and $p<0.05$ SVC). Critically rACC was significantly more active when subjects correctly reported the T2 identity in the fearful face condition as shown by the simple main effect (Fearful-T2_Correct-T2 vs. Fearful-T2_Incorrect-T2) ([x=10, y=38, z=18] Z=4.25, 32-voxels $p<0.001$ uncorrected and $p<0.05$ SVC). Figure III.V

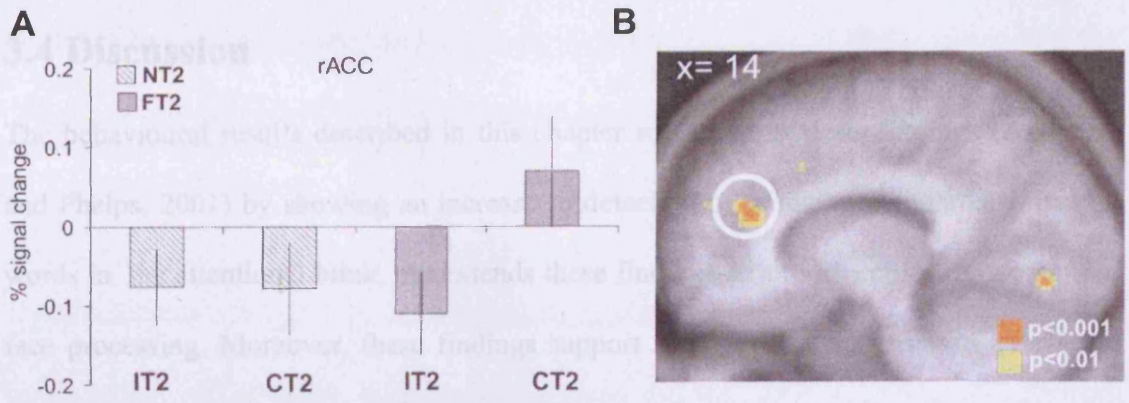

Figure III.V: Rostral anterior cingulated cortex (rACC)

(A) Plot of signal percentage changes for the rACC cluster. ***(B)*** *Sagittal SPM image during the interaction contrast ([FT2_CT2 – FT2_IT2] > [NT2_CT2 – NT2_IT2]) showing the activity of the rACC ([x=14, y=40, z=22] Z=3.59, 25-voxels p<0.001 uncorrected and p<0.05 SVC) is modulated by the T2 identification (CT2 vs. IT2) selectively in the when the T2 stimulus was a fearful face (FT2). rACC is significantly more active simple effect (FT2_CT2 vs. FT2_IT2) ([x=10, y=38, z=18] Z=4.25, 32-voxels p<0.001 uncorrected and p<0.05 SVC) .*

3.4 Discussion

The behavioural results described in this chapter replicate previous findings (Anderson and Phelps, 2001) by showing an increase in detection of arousing compared to neutral words in the attentional blink, but extends these findings to a more ecological context of face processing. Moreover, these findings support a model that suggests an overlap in face identity and face expression recognition processes in contrast with a view that proposes two distinct parallel mechanisms (Calder and Young, 2005). Reaction time for the correctly reported target was significant shorter supporting a more complete and accurate processing of these targets.

While previous fMRI studies have examined the neurobiology of this attentional blink effect using neutral stimuli (Marois et al., 2000; Marois et al., 2004) the present study is the first to investigate the associated mechanisms underlying a reduced blink effect for emotional T2 items. The fMRI data show a significant increase in FFA activity for faces that subsequently would have been correctly reported. These results support claims data that (Kanwisher et al., 1997; Kanwisher et al., 1999), detection and identification of faces, critically depends on FFA activity (Grill-Spector et al., 2004). Moreover in trials where a fearful face was incorrectly reported L-FFA showed increased activity for fearful faces compared to the neutral ones. This finding is in keeping with previous findings that reported an increase in FFA activity for fearful unattended faces versus neutral unattended faces (Vuilleumier, 2005; Vuilleumier et al., 2001; Vuilleumier and Schwartz,

2001a) in a spatial divided attention task. These results extend these research to the domain of non-spatial attention, and supports a model that proposes enhanced processing of emotional stimuli even under conditions where they do not reach full awareness (Vuilleumier and Driver, 2007). These data show that FFA activity is critically associated with the correct face identification and is to some degree modulated by face emotionality. Nevertheless, because FFA activity did not show an interaction between valence of the target T2 and increased performance in T2 detection these observations cannot fully explain the behavioural increase in T2 fearful face detection.

Comparing brain activity in trials where the T2 target was a fearful face with trials where T2 was a neutral face as associated with activity increase in bilateral ventral striatum. These areas are implicated in anticipation of reward stimuli (O'Doherty, 2004; Schultz, 2006), anticipation of aversive stimuli as well as anticipation or experience of painful stimulation (Jensen et al., 2003; Salamone, 1994; Seymour et al., 2007; Seymour et al., 2005). Previous neuroimaging studies also show that ventral striatum is more active when subjects are exposed to unpleasant visual stimuli (Paradiso et al., 1999). It has also been suggested that striatum is implicated in responding to arousing stimuli (Horvitz, 2002). Furthermore, evidence from animals and humans literature, show that ventral striatum plays a key role in instrumental learning and goal-directed behaviour (Hollerman et al., 2000). These data are in keeping with this of role of the striatum in motivation and adaptation of behavior related to affective (Everitt et al., 1999; Robbins and Everitt, 1996; Schultz, 2006).

The rostral anterior cingulate cortex (rACC) showed an increase in activity for the critical interaction contrast that delineated brain areas underpinning an increase in detection for fearful T2 targets seen in the behavioural findings. The rACC (Brodman areas 24 a-c and 32) is considered to have distinct anatomical and functional characteristics compared with the more caudal part of the anterior cingulate cortex (cACC) (Bush et al., 2000). At neuroanatomical level this area shares reciprocal connections with amygdala, nucleus accumbens, anterior insula, and orbitofrontal cortex. At functional level convergent evidence shows that rACC has a primary role in processing emotional information and regulating emotional responses (Bush et al., 2000). In particular rACC activity is implicated in awareness for emotional material (Carretie et al., 2001; Lane et al., 1997a; Lane et al., 1998; Simpson et al., 2001), attention to emotional stimuli (Fichtenholtz et al., 2004; Vuilleumier and Schwartz, 2001a) and rating of affect intensity (Taylor et al., 2003). During anxiety, altered response of rACC has been associated with impaired processing of treat-related attentional competitors (Bishop et al., 2004a; Bishop et al., 2004b) and appraisal of emotional material (Kalisch et al., 2006). More generally rACC activity has been shown as crucial for selective attention to emotional information (Elliott and Dolan, 1998; Elliott et al., 2000; Lane et al., 1997a). The behavioural manipulation in this study allowed me to show that rACC plays a key role in early stages of the emotional processing (Kalisch et al., 2006). These results extend the functional role of rACC to include mediating selective enhancement in detecting potential threat under conditions of limited attentional capacity, as elicited by the attentional blink paradigm.

A previous study (Anderson and Phelps, 2001) using a word RVSP, with either a neutral or an arousing T2, demonstrated that patients with left amygdala damage have a significant behavioural disadvantage in emotional T2 detection. Indeed, theoretical models of emotional modulation of AB predicts that amygdala plays a key role in mediating this effect (Fragopanagos et al., 2005; Palermo and Rhodes, 2007). In this study I did not find a statistically significant amygdala activation in the critical interaction ([Fearful-T2_Correct-T2 – Fearful-T2_Incorrect-T2] > [Neutral-T2_Correct-T2 – Neutral-T2_Incorrect-T2]) or in the main effect of fearful versus neutral T2 even at more liberal threshold of $P<0.05$ uncorrected. This finding does not exclude a possible involvement of amygdala in this task. In fact the statistical power of the analysis was limited by the number of events and brief presentation of the target. This may have made it more difficult to detect rapid changes in amygdala, particular when considering the low signal to noise ratio in this subcortical area (LaBar et al., 2001). Additionally, all faces, even neutral ones especially when presented briefly may have potential emotional significance and can activate amygdala (Wright and Liu, 2006).

Finally, these data suggests a model in which early top-down control exerted by rACC is required for enhanced processing of threat targets. In fact the stimulus driven bottom-up activity in visual areas, although necessary for the correct T2 process, does not appear sufficient to explain enhanced behavioural processing of the fearful T2 targets. One possibility is that enhanced activity in rACC, triggered by subcortical areas (e.g. striatum)

sensitive to stimulus valence, mediates correct target identification by gating the access of the potentially threatening stimulus to full awareness.

In conclusion, using a modification of an attentional blink task in which I manipulated the emotional valence of a face T2 target, I observed a significant increase in correct detection of fearful compared to neutral targets. These data replicate previous findings using words as arousing stimuli (Anderson and Phelps, 2001). These behavioural results demonstrate that even when humans are unable to detect non-threatening stimuli due to attentional overload, they retain the ability to detect emotional items. The imaging data indicates that although bottom-up activity in visual areas like FFA is necessary for the correct stimulus detection is not accountable for the increased detection of threatening targets. Instead frontal rACC activity mediates a top-down control on attention and awareness for emotional items even in conditions in which normal attentional capacity is limited.

3.4 Appendix (SPM significant activation tables)

Abbreviations:
FT2: Fearful face target T2
NT2: Neutral face target T2
CT2: Correctly identified face target T2
IT2: Incorrectly identified face target T2

Table 1. Brain areas significantly more active during interaction contrast ([FT2_CT2 – FT2_IT2] > [NT2_CT2 – NT2_IT2])

All values $p<0.001$ uncorrected with all clusters exciding an extent threshold of 5 voxels
*statistically significant activation (see Methods)

Region	Laterality	x	y	z	z-score
rACC *	R	14	40	22	3.59
Cerebellum	L	32	-76	-30	4.04
Inferior postcentral sulcus	R	56	-10	26	3.89
Lingual gyrus	R	14	-78	-8	3.69

Table 2. Brain areas significantly more active during interaction contrast (FT2 > NT2)
All values $p<0.001$ uncorrected with all clusters exciding an extent threshold of 5 voxels
*statistically significant activation (see Methods)

Region	Laterality	x	y	z	z-score
Ventral striatum *	R	20	16	0	4.08
	L	-28	14	-4	3.63
Lingual gyrus	R	8	-78	4	3.59

Table 3. Brain areas significantly more active during interaction contrast (CT2 > IT2)All values p<0.001 uncorrected with all clusters exciding an extent threshold of 5 voxels *statistically significant activation (see Methods)

Region	Laterality	x	y	z	z-score
Posterior insula	L	-42	-8	16	4.64
	L	-32	-2	2	4.05
Inferior frontal sulcus	R	30	54	10	4.98
	R	44	48	2	3.91
Superior frontal sulcus	L	-26	46	38	4.14
Orbitofrontal cortex	R	32	42	-16	3.51
	L	-34	22	-20	4.21
ACC	R	2	32	28	3.67
Pre-SMA	L	-4	10	46	3.67
Cerebellum	L	-36	-68	-46	3.50
Inferior parietal gyrus	R	66	-42	22	4.98

Chapter 4

Noradrenergic neuromodulation of human attention for emotional and neutral stimuli

In this chapter I describe three experiments involving a pharmacological manipulation of an emotional attentional blink paradigm: the aim of these experiments is to define the role of noradrenaline in modulating attention to neutral and emotional information.

4.1 Introduction

Norepinephrine (NE) is a monoaminergic neurotransmitter released by ascending projections from the locus coeruleus (LC). The LC is located within the dorsal wall of the rostral pons, in the lateral floor of the fourth ventricle. Norepinephrine neurones project bilaterally (i.e. they send signals to both sides of the brain) from the locus coeruleus along distinct pathways to multiple cortical and subcortical areas in the central nervous system (Figure IV.I).

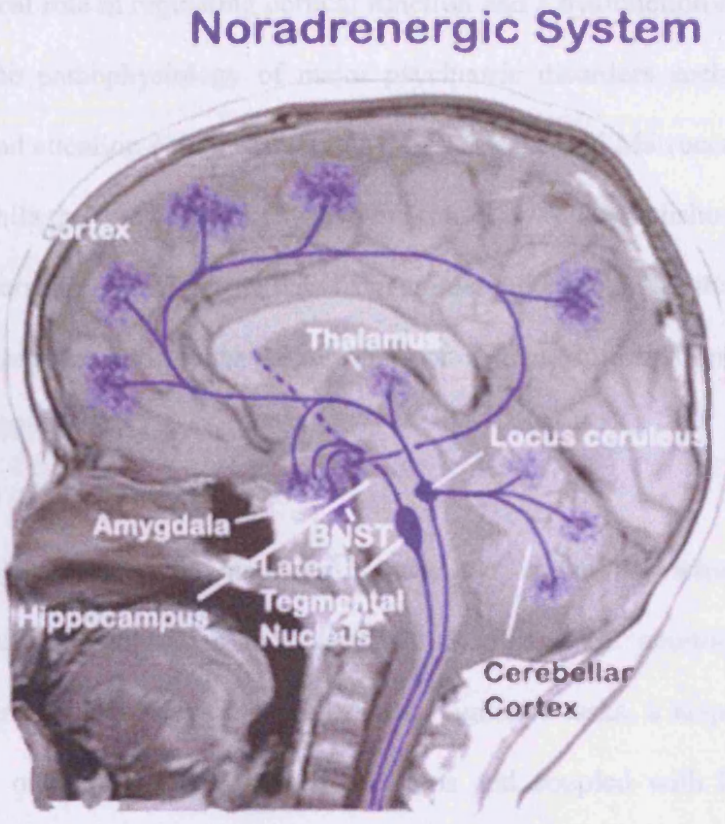

Figure IV.I Projections of the NE system in the CNS

The figure shows cortical and subcortical targets of the NE neurons ascending from the two sites of origin of noradrenergic neurons in the mid-brain respectively (the locus coeruleus and lateral tegmental nucleus).

NE mediates its physiological effect by activating a class of G protein-coupled-receptors, called adrenergic receptors, that are primarily divided in the two groups α and β. Within this broad class are subgroups α_1 and α_2 and β_1, β_2, and β_3. The α_2 receptors are often located at pre-synaptic level and have an inhibitory effect on the NE release.

NE plays a critical role in regulating cortical function and a dysfunction of this system is implicated in the pathophysiology of major psychiatric disorders such as depression, schizophrenia and attention deficit disorder (ADHD) (Beane and Marrocco, 2004; Pliszka et al., 1996). While the role of the NE system in arousal is well established (Jouvet, 1969; Robinson and Berridge, 1993), recent data from animal models suggest that it also plays a role in facilitating the processing of relevant, or salient, information (Berridge and Waterhouse, 2003; Yu and Dayan, 2005).

Electrophysiological studies in monkeys indicate two modes by which LC activity modulates attention (Aston-Jones and Cohen, 2005). Phasic LC neuronal activation is evoked by salient or goal-relevant stimuli during vigilance tasks, a response positively associated with outcomes in task-related decisions and coupled with highly accurate responses (Aston-Jones et al., 1994). Phasic responses are evoked against the background of (and are in turn modulated by) tonic LC activity which correlates with general arousal levels (Aston-Jones et al., 1991; Aston-Jones et al., 1994).

Recently it has been shown (Strange and Dolan, 2007) that the cortical circuitry activated by salient stimuli is inhibited by the pharmacological blockade of the noradrenergic system. In this chapter I demonstrate a role for ß-adrenergic receptors in this process. This differs from previous psychopharmacological experiments addressing NE modulation of attention, which have typically examined the effects of α2-adrenergic

receptor agonists such as clonidine (Coull et al., 2001). Subjects receiving clonidine (as opposed to a placebo) are impaired in the task of target discrimination (Clark et al., 1986), and additionally report withdrawal and difficulties with concentration. Clonidine acts on presynaptic α2-adrenergic auto-receptors to inhibit NE release: thus clonidine-induced impaired attention may reflect decreased arousal, or the decreased stimulation of predominantly postsynaptic α_1- or ß-adrenergic receptors due to a presynaptic inhibition of NE release. Given that the $ß_1ß_2$-adrenergic antagonist propranolol is non-sedating (Harmer et al., 2001), its administration enables the investigation of the adrenergic role in attention without sedation, as well as localising particular attentional effects to a particular receptor subtype.

To investigate noradrenergic modulation of human attention I implemented a modification of the RSVP attentional-blink (AB) paradigm, in which subjects view a rapid sequence of visual stimuli (RSVP) (Raymond et al., 1992) with a requirement to identify embedded targets under different pharmacological manipulations. A classic finding in the AB task is that the identification of a target stimulus (T1) causes transient impairment in detecting a subsequently presented second target (T2), an effect reduced with the increasing temporal lag between the two targets.

Of particular interest to the present study is a finding that the AB can be modulated by the emotional significance of stimuli. Thus, an arousing T2 stimulus is detected more often

than a neutral T2 (Anderson and Phelps, 2001), although this effect is not present in patients with amygdala damage (Anderson and Phelps, 2001). This is equivalent to the studies of episodic memory which show that memory is normally enhanced in the recording of emotional events, except in patients with amygdala lesions (Cahill et al., 1994; Strange et al., 2003). Enhanced emotional memory is abolished by propranolol (Cahill et al., 1994; Strange et al., 2003), which leads to an hypothesis that the emotional modulation of the AB might also be abolished by ß-adrenergic blockade. However, in light of recent finding (Strange and Dolan, 2007) that propranolol modulates the cortical circuitry involved in salience detection, the effects of propranolol on the AB may be more complex, i.e. there may be a generic effect of ß-adrenergic blockade on T2 detection.

Prior to the first experiment, subjects received either propranolol or placebo in a double-blind fashion (Exp.1). In Exp. 2, subjects performed a more difficult version of the task, to address possible ceiling effects in Exp. 1. As an additional manipulation, subjects were randomised to receive either placebo, propranolol or the selective norepinephrine reuptake inhibitor (SNRI) reboxetine. Thus, this experimental design enabled me to investigate the effects of adrenergic modulation, inhibitory and facilitatory, on an attention paradigm in which both the salience and valence of the T2 target could be manipulated. In a third experiment, I tested for the contribution of peripheral ß-blockade to the attentional effects observed with propranolol by administering nadolol, a ß-blocker that does not cross the blood-brain barrier (BBB). Exp. 3 also included a group which

received a lower dose of propranolol to determine whether modulatory effects observed in Exps. 1 and 2 were dose dependent.

4.2 Materials and methods

Ninety-six healthy right-handed native English-speaking subjects took part in the three separate studies. All volunteers gave informed consent, were free of neurological, psychiatric and physical illness and had not been on medication for $\geq$ 3 months. The study was approved by the National Hospital for Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee.

Within the critical experiments described in this chapter, each trial consisted of 15 words, 2 targets (bright green) and 13 distractors (black), presented either for 130ms or 110ms each and immediately followed by a subsequent T2 stimulus (Figure IV.II). In half the trials the T2 stimuli consisted of arousing words (e.g. rape, incest) and in the other half neutral words. Difficulty was manipulated by introducing different temporal lags. Prior to the first experiment, subjects received either propranolol or placebo in a double-blind fashion (Exp.1). In Exp. 2, subjects performed a more difficult version of the task (i.e. 110 ms stimulus presentation) and were randomised to receive placebo, propranol 40mg or the selective Norepinephrine reuptake inhibitor (SNRI) reboxetine. In Exp. 3, subjects performed the same version of the task used in the exp.2 and were randomised to receive placebo, propranol 20mg or the nadolol a beta-blocker that unlike propranolol act only at peripheral level because does not pass the BBB. Thus, this experimental design enabled us to investigate the effects of adrenergic modulation, inhibitory and facilitatory,

on an attention paradigm in which both the salience and valence of the T2 target could be manipulated.

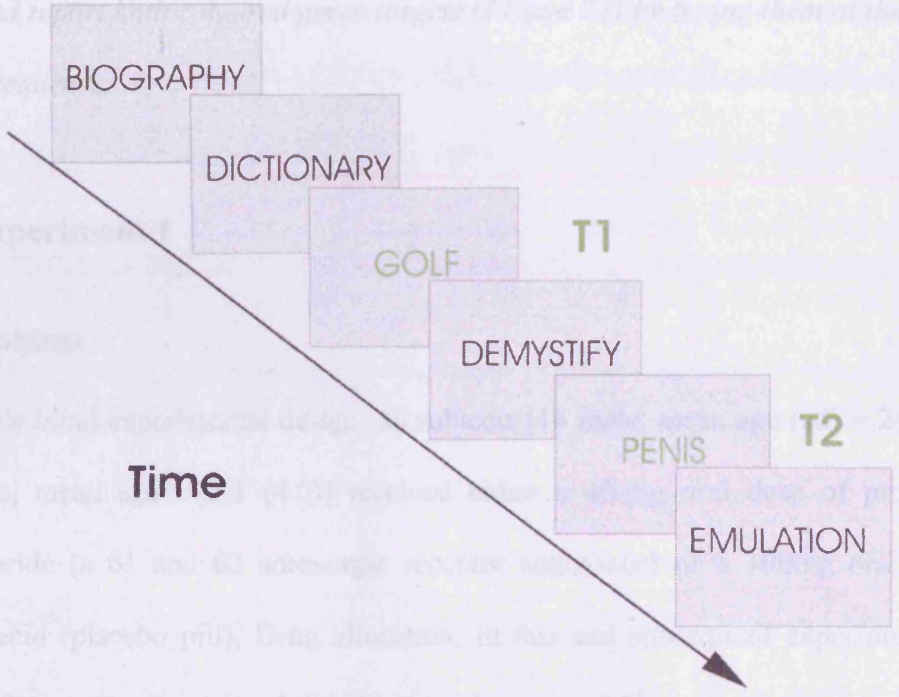

Figure IV.II Schematic diagram of the AB task

Each trial consisted of 15 words [2 targets (bright green) and 13 distractors (black)] each presented for 130ms (Exp. 1) or 110ms (Exp. 2) and immediately followed by the subsequent stimulus. In half the trials the T2 stimuli consisted of an arousing word (e.g. rape, incest) and in the other half T2 were neutral words (eg. pepper, omit). The neutral and emotional stimuli were matched for average word length, word frequency and interletter frequency. Order or presentation of emotional and neutral trials was random.

The temporal lag between the first target (T1) and the second target (T2) was variable. At early lag (<500 ms SOA) the detection of target T2 is more susceptible to the attentional blink compared with late lag (>500 SOA). The subjects' task was to monitor the RSVP stream and report both coloured green targets (T1 and T2) by typing them at the end of a stimulus sequence

4.2.1 Experiment 1

4.2.1.1 Subjects

In a double blind experimental design, 36 subjects [18 male, mean age (sd) = 24.2 (3.9); 18 female, mean age= 23.1 (4.0)] received either a 40-mg oral dose of propranolol hydrochloride (a ß1 and ß2 adrenergic receptor antagonist) or a 100mg oral dose of ascorbic acid (placebo pill). Drug allocation, in this and subsequent experiments, was balanced for gender. In view of the kinetics of propranolol's peak plasma concentration (1-2h), the attentional-blink task commenced 90 minutes following drug administration. Blood pressure was measured immediately before drug administration (time 0 min) and the attention task (time +90min).

4.2.1.1 Stimuli

I used a modification of the RSVP paradigm (Anderson and Phelps, 2001; Raymond et al., 1992) where each trial consisted of 15 words [2 targets (bright green) and 13 distractors (black)] each presented for 130ms and immediately followed by the

subsequent stimulus (Figure IV.II). Six trial lags were introduced from lag 2 [1 distractor presented between the two targets (T1-T2) SOA=260ms] to lag 7 [6 distractors presented between the two targets (T1-T2) SOA=910ms]. In half the trials the T2 stimuli consisted of an arousing word (e.g. rape, incest) and in the other half T2 were neutral words (eg. pepper, omit). The neutral and emotional stimuli were matched for average word length, word frequency and interletter frequency. Presentation order of emotional and neutral trials was random. The subjects' task was to monitor the RSVP stream and report both coloured green targets (T1 and T2) by typing them at the end of a stimulus sequence (trials in which a T1 target was not reported correctly were discarded from the analysis of T2 effects).

4.2.1.1 Statistical data analysis

Following the analysis of Anderson and Phelps (Anderson and Phelps, 2001), data were segregated into early (lags 2-3, 260-390ms) and late lag phases (lags 6-7, 780-910ms). I performed a 2x2x2 drug (propranolol 40 mg, placebo) x valence of T2 stimulus (emotional, neutral) x lag (early vs late) analysis of variance (ANOVA). I also performed a post-hoc two sample unequal variance single-tailed t-test to analyze all simple effects using the statistical software SPSS (http://www.spss.com).

4.2.2 Experiment 2

4.2.2.1 Subjects

In a double blind experimental design 30 subjects [15 male, mean age (sd) = 24.7 (2.8); 15 female, mean age = 23.3 (3.1)] were allocated to one of three equal sized groups and received either a 40-mg oral dose of propranolol, a 4mg oral dose of reboxetine methansulphonate (a selective norepinephrine reuptake inhibitor) or a 100mg oral dose of ascorbic acid (placebo pill). In view of the kinetics of propranolol and reboxetine's peak plasma concentration (1-2h and 1.5h respectively), the attentional-blink task commenced 120 minutes following drug administration. One subject in the propanolol group was excluded from further analysis because performance was more than two standard deviations below the group average.

4.2.2.2 Stimuli

The task used was identical to Exp.1 except for two critical modification; time of stimulus presentation was decreased from 130 ms in Exp.1 to 110ms; targets were separated by six different time lags ranging from 1 to 9 distractors presented between the two targets (lags 2-3-4-7-8-9) [e.g. lag 2 (T1-T2) SOA=220ms; lag 9 (T1-T2) SOA=990ms].

4.2.2.3 Statistical data analysis

Data were collapsed into early (lags 2-3-4, 220-440ms) and late lags (lags 7-8-9, 770-990ms) and a drug (propranolol 40 mg, reboxetine, placebo) x T2 valence (emotional, neutral) x lag (early, late) 3x2x2 ANOVA performed. For each drug group I also performed a 2x2 drug (drug, placebo) x T2 valence (emotional, neutral) ANOVA I also

performed a post-hoc two sample unequal variance single-tailed t-test to analyze all simple effects.

4.2.3 Experiment 3

4.2.3.1 Subjects

In a double blind experimental design 30 subjects [15 male, mean age (sd) = 25.2 (3.7); 15 female, mean age = 25.5 (3.9)] were allocated to one of three equal size groups and received either a 20mg oral dose of propranolol, a 40mg oral dose of nadolol (a ß1 and ß2 adrenergic receptor antagonist that does not cross the BBB) or a 100mg oral dose of ascorbic acid (placebo pill). In view of the kinetics of propranolol and nadolol peak plasma concentration (1-2h), the attentional-blink task commenced 120 minutes following drug administration. One subject in the propanolol group was excluded from further analysis because his performance was more than two standard deviations below the group average (task outlier). Three subjects in the placebo group were excluded (two because task outliers and one because was not native English speaker).

4.2.3.2 Stimuli

The task used was identical to Exp.2 using the same equipment.

4.2.3.3 Statistical data analysis

After exclusion criteria, the size of the placebo group was reduced (7 subjects). Thus, to retain sufficient statistical power I collapsed data from the current placebo group with the placebo group from Exp. 2. Data were collapsed into early (lags 2-3-4, 220-440ms) and late lags (lags 7-8-9, 770-990ms) and separate analyses performed for each drug group (propanolol 20mg, nadolol 40 mg) versus placebo i.e. separate group (drug x placebo) x T2 valence (emotional, neutral) x lag (early, late) 2x2x2 ANOVAs.

4.3 Results

4.3.1 Experiment 1

Experiment 1: This psychopharmacological experiment demonstrated that ß-adrenergic blockade by propranolol significantly impaired detection of T2 targets independent of their emotional valence (i.e. emotional and neutral) (Figure IV.III). In both placebo and drug groups, I observed enhanced reporting of emotional, relative to neutral, T2 stimuli as well as a proportional increase in detecting both types of T2 stimuli with increasing T1-T2 lag, in agreement with previous observations (Anderson and Phelps, 2001). In the placebo group at early lag the percentage of T2 correctly reported for neutral T2 (NT2) was 86.99% ± 2.42 and for emotional T2 (ET2) was 93.93 % ± 1.43, at late lag these value increased to NT2 =92.62 %± 1.28 and to ET2 =95.8 %± 1.13. Conversely in the 40 mg propranolol group at early lag was NT2 =80.69 %± 1.90 and ET2 =91.26 %± 1.93, at late lag NT2 =88.18 %± 1.90 and ET2 =93.84 %± 1.47 respectively (see table 1 for a summary).

A drug (propranolol, placebo) x T2 valence (neutral, emotional) x lag (early, late) 2x2x2 ANOVA yielded significant main effects of treatment ($F_{(1,34)}$=4.98, $p<0.05$), T2-valence ($F_{(1,34)}$=51.31, $p<0.0001$) and lag ($F_{(1,34)}$=26.33, $p<0.0001$). In line with the observation of Anderson and Phelps that affective modulation of the attentional blink is most pronounced at early lags, I found a lag x T2-valence interaction significant at trend level ($F_{(1,34)}$=3.72 P=0.062). Critically, there was no significant interaction between T2-valence and drug manipulation ($F_{(1,34)}$=2.65, p=0.29) indicating that propranolol impaired detection of the T2 target independently of valence (i.e. emotional or neutral T2 stimuli) (Figure IV.III). The simple effects for T2 correctly reported between the two groups (placebo, propranolol) was significant for the neutral T2 $p<0.05$ $t_{(1,19)}$=2.04 but not significant for the emotional T2 p=0.13 $t_{(1,19)}$=1.13. Furthermore, no significant interaction was found between lags (early, late) and drug manipulation (propranolol, placebo) ($F_{(1,34)}$=0.51 P=0.476) showing that the effect of propranolol is present across all lags. Figure IV.IIIc shows the percentage (% ± S.E) of correctly reported emotional (E) and neutral (N) T2 for early (260-390 ms - SOA) and late lags (780-910 ms - SOA). Importantly, performance on T1 target detection was not statistically different between placebo (96.27%) and propranolol (96.18%) groups ($t_{(1,19)}$=0.17 P>0.05 one-tailed independent-samples t-test).

As seen in Figure IV.III, performance in both placebo and drug groups at late lags approached ceiling levels, which may have obscured differential effects at these later lags. Thus, in Exp. 2 I reduced the interstimulus interval, making T2 detection more

difficult. Removing this ceiling effect enabled us to test the further hypothesis that increasing NE levels, with the SNRI reboxetine, would enhance T2 detection.

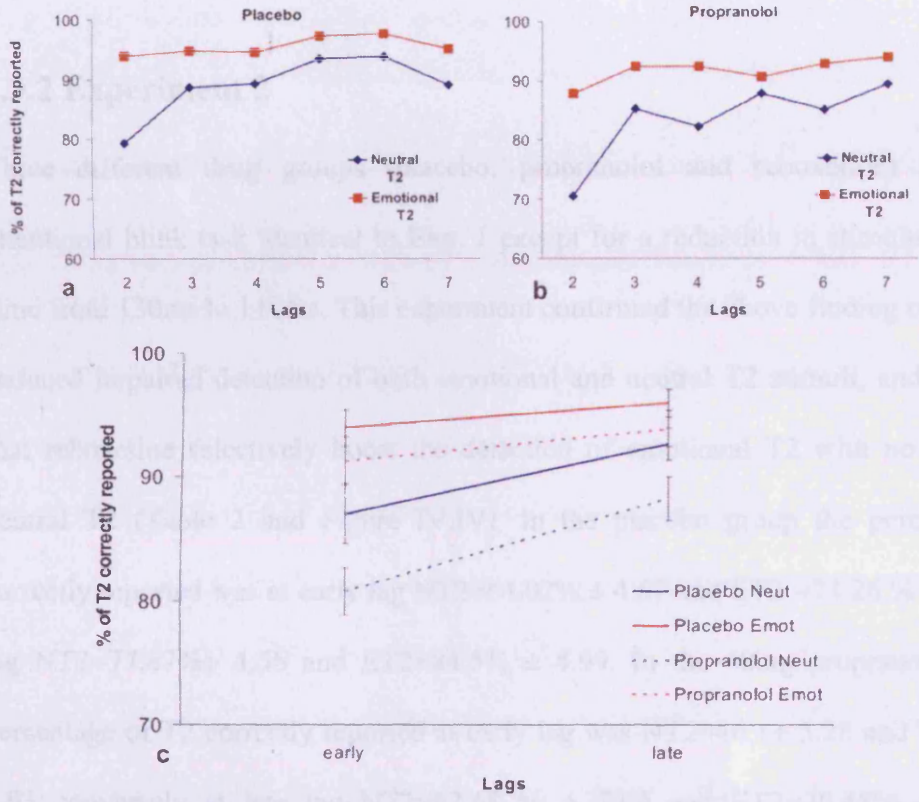

Figure IV.III Behavioural results of Experiment1

The panels (a-b) show the percentage (%) of T2 stimuli correctly reported for each T1-T2 temporal lag for (a) placebo and (b) propranolol (40 mg) groups. In both groups T2 detection improves with increasing temporal lags, and is significantly higher for emotional T2 (red squares) compared with neutral T2 (blue diamonds). The administration of propranolol significantly impairs T2 detection independently of valence. (c) Impaired emotional (red lines) and neutral (blue lines) T2 detection

produced by propranolol (dashed lines) relative to placebo (solid lines) is more marked at early lags (260-390 ms - SOA), when attentional demand is higher, compared with late lags (780-910 ms - SOA).

4.3.2 Experiment 2

Three different drug groups (placebo, propranolol and reboxetine) performed an attentional blink task identical to Exp. 1 except for a reduction in stimulus presentation time from 130ms to 110ms. This experiment confirmed the above finding of propranolol-induced impaired detection of both emotional and neutral T2 stimuli, and demonstrates that reboxetine selectively boost the detection of emotional T2 with no effect on the neutral T2 (Table 2 and Figure IV.IV). In the placebo group the percentage of T2 correctly reported was at early lag NT2=64.02% ± 4.67 and ET2 =74.26 % ± 5.65, at late lag NT2=77.87%± 4.56 and ET2=84.5% ± 4.99. In the 40mg propranolol group the percentage of T2 correctly reported at early lag was NT2=46.1± 5.28 and ET2=61.6 %± 5.93 conversely at late lag NT2=62.68 % ± 7.69 and ET2=70.48% ±7.62. In the reboxetine group at early lag the percentage of T2 correctly reported was NT2=62.8 %± 3.65 and ET2=82.64 %± 4.18 at late lag NT2=80.95 % ± 2.05 and ET2=90.23 % ± 1.92. (see table 2 for a summary)

Figure IV.IVc shows the percentage (% ± S.E) of correctly reported emotional (E) and neutral (N) T2 for early (220-440 ms - SOA) and late lags (770-990 ms - SOA). A drug

(placebo, propranolol, reboxetine) x T2 valence (neutral, emotional) x lag (early, late) 3x2x2 ANOVA yielded a significant main effect of drug ($F_{(1,27)}$=5.44, p<0.01), T2-valence ($F_{(1,27)}$=73.8, p<0.0001) and lag ($F_{(1,27)}$=93.54, p<0.0001). The 3-way interaction drug x T2-valence x lag was also significant ($F_{(2,27)}$=3.46, p<0.05).

In order to investigate the effects of drug relative to placebo, I performed two further 2x2x2 ANOVAs. The effect of propranolol in a drug (placebo, propranolol) x T2-valence (neutral, emotional) x lag (early, late) 2x2x2 ANOVA yielded a significant main effect of drug manipulation ($F_{(1,18)}$=4.58, p<0.05), T2-valence ($F_{(1,18)}$=24.87, p<0.0001) and lag ($F_{(1,18)}$=86.51, p<0.0001). The interaction between T2-valence and drug manipulation was not significant ($F_{(1,18)}$=0.62, p=0.44). The simple effects for T2 correctly reported between the two groups (placebo, propranolol) was significant for the neutral T2 p<0.01 $t_{(1,19)}$=2.53 and at trend level for the emotional T2 p=0.07 $t_{(1,19)}$=1.53. These data replicate the results of Exp. 1, confirming that propranolol impairs T2 detection independently of T2 emotional valence. As in Exp. 1, the degree of affective modulation was most pronounced at early lags, evident in a significant interaction of lag x T2-valence ($F_{(1,18)}$=6.59 P<0.05). Again, no significant interaction was found between lags (early, late) and drug manipulation (propranolol, placebo) ($F_{(1,18)}$=0.05 P=0.862). Finally, in this more difficult version of AB task T1 detection is impaired in the propranolol group relative to placebo (82.13% vs. 89.28% correct, respectively; $t_{(1,19)}$=1.84 P<0.05 one-tailed independent-samples t-test).

By contrast, reboxetine evoked a selective enhancement in emotional T2 detection. A drug (placebo, reboxetine) x T2 valence (neutral, emotional) x lag (early, late) 2x2x2 ANOVA yielded a significant main effect of T2 valence ($F_{(1,18)}$=107.89, p<0.0001) and lag ($F_{(1,18)}$=54.39, p<0.0001), but the main effect of reboxetine relative to placebo was not significant ($F_{(1,18)}$=0.57, p=0.46). However, the interaction between T2-valence and drug manipulation was significant ($F_{(1,18)}$=10.61, p<0.005). The simple effects for T2 correctly reported between the two groups (placebo, reboxetine) was not significant for the neutral T2 p=0.66 $t_{(1,19)}$=0.44 and at trend level for the emotional T2 p=0.07 $t_{(1,19)}$=1.54. These data demonstrate that enhanced NE levels selectively improve detection of an emotional T2 stimulus with no effect on a neutral T2. Again, detection of emotional relative to neutral T2 stimuli was greatest at early lags for both groups indexed by a significant interaction of lag x T2-valence ($F_{(1,18)}$=22.8 P<0.001). By contrast, a lag (early, late) x drug manipulation (reboxetine, placebo) interaction was not significant ($F_{(1,18)}$=0.036 P=0.852), indicating that the behavioural effect of reboxetine is present across all lags.

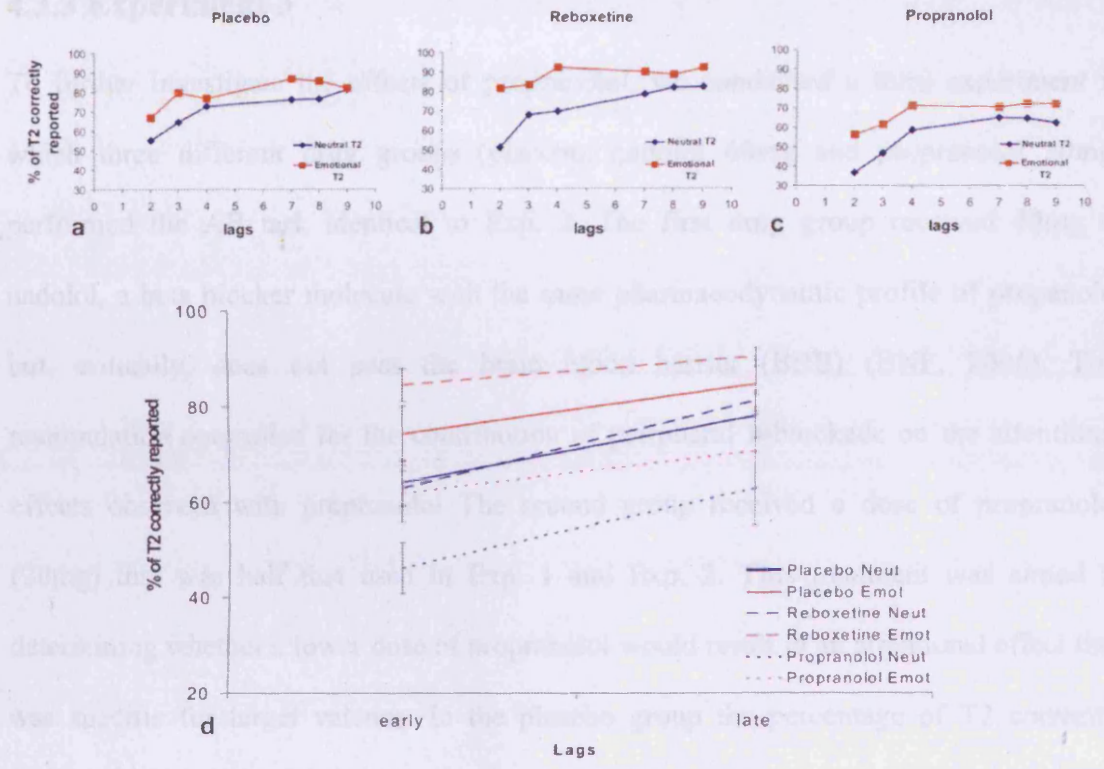

Figure IV.IV Behavioural results of Experiment 2

The panels (a-b-c) show the percentage of T2 stimuli that are correctly reported for each T1-T2 temporal lag respectively in the placebo, reboxetine and propranolol groups. In all groups T2 detection improved with increasing temporal lags and is significantly enhanced for emotional (red squares) relative to neutral (blue diamonds) T2 detection. (b) As in Exp. 1, propranolol significantly impairs T2 detection independently of valence. (c) Conversely reboxetine significantly enhances detection of emotional T2 with no effect on neutral T2. (d) T2 target detection in placebo (solid lines), propranolol (small dashed lines) and reboxetine (large dashed lines) groups on early lag (220-440 ms - SOA), when the attentional demand is higher, compared with late lags (770-990 ms - SOA) for emotional (red lines) and neutral (blue lines) T2 stimuli.

4.3.3 Experiment 3

To further investigate the effects of propranolol, we conducted a third experiment in which three different drug groups (placebo, nadolol 40mg and propranolol 20mg) performed the AB task identical to Exp. 2. The first drug group received 40mg of nadolol, a beta blocker molecule with the same pharmacodynamic profile of propanolol but, critically, does not pass the brain blood barrier (BBB) (BNF, 2006). This manipulation controlled for the contribution of peripheral ß-blockade on the attentional effects observed with propranolol The second group received a dose of propranolol (20mg) that was half that used in Exp. 1 and Exp. 2. This treatment was aimed at determining whether a lower dose of propranolol would result in an attentional effect that was specific for target valence. In the placebo group the percentage of T2 correctly reported was at early lag NT2=59.19% ± 3.44 and ET2 =75.32 % ± 3.58, at late lag NT2=76.45 % ± 3.13 and ET2=86.68 % ± 3.21. In the 20mg propranolol group the percentage of T2 correctly reported at early lag was NT2=65.40 %± 6.40 and ET2=78.20 %± 6.31 conversely at late lag NT2=80.43 % ± 5.02 and ET2=87.62 % ± 4.27. In the 40mg nadolol group at early lag the percentage of T2 correctly reported was NT2=62.24 %± 4.76 and ET2=76.82 %± 5.57 at late lag NT2=76.59 % ± 4.08 and ET2=88.07 % ± 3.69 (see table 3 for a summary).

T2 target detection did not differ between nadolol and placebo groups (Figure IV.V). The drug (placebo, nadolol) x T2 valence (neutral, emotional) x lag (early, late) 2x2x2 ANOVA yielded a significant main effect of T2 valence ($F_{(1,25)}=89.16$, $p<0.0001$) and lag

($F_{(1,25)}$=12.45, p<0.005), but no significant main effect of drug relative to placebo ($F_{(1,25)}$=0.06, p=0.80) or drug x T2-valence interaction ($F_{(1,25)}$=1.48, p=0.23) (Table 3 and Figure IV.V). These results confirm that the modulatory effects of propranolol observed in Exp. 1 and Exp. 2 are due to central activity.

Performance in the low dose propanolol group (20mg) was equivalent to that of the placebo group. The drug (placebo, propanolol low dose 20 mg) x T2 valence (neutral, emotional) x lag (early, late) 2x2x2 ANOVA yielded a significant main effect of T2 valence ($F_{(1,24)}$=49.33, p<0.0001) and lag ($F_{(1,24)}$=68.99, p<0.0001), but no main effect of drug relative to placebo ($F_{(1,24)}$=0.42, p=0.52). Critically, there was no significant interaction between drug and T2-valence ($F_{(1,24)}$=1.08, p=0.31) (Table 2 and Figure IV.V). Thus, only the higher propranolol dose (40mg) impairs target detection, an effect that is independent of target valence. A lower propranolol dose does not impair detection of neutral or emotional T2 detection.

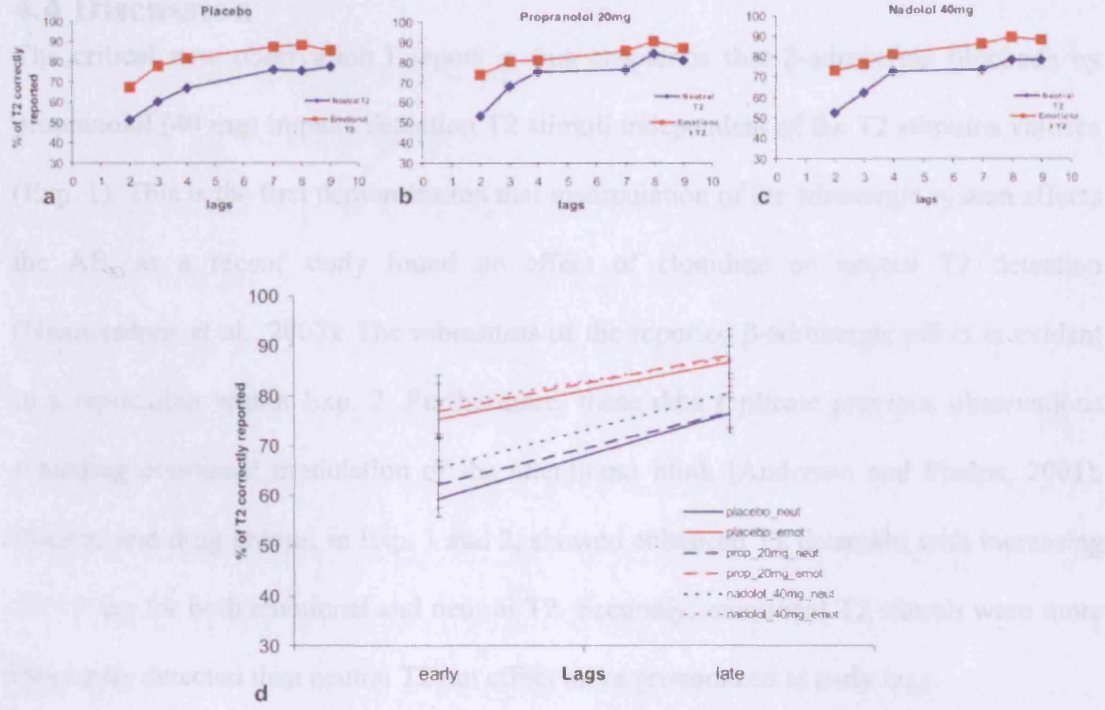

Figure IV.V Behavioural results of Experiment 3

The panels (a-b-c) show the percentage of T2 stimuli that are correctly reported for each T1-T2 temporal lag respectively in the placebo, nadolol and propranolol low dose (20 mg) groups. In all groups T2 detection improved with increasing temporal lags and is significantly enhanced for emotional (red squares) relative to neutral (blue diamonds) T2 detection. Both propanolol 20 mg (b) and nadolol 40 mg (c) do not show significant differences from the placebo group. (d) T2 target detection in placebo (solid lines), nadolol 40 mg (small dashed lines) and propanolol 20 mg (large dashed lines) groups on early lag (220-440 ms - SOA), when the attentional demand is higher, compared with late lags (770-990 ms - SOA) for emotional (red lines) and neutral (blue lines) T2 stimuli.

4.4 Discussion

The critical new observation I report in this chapter is that β-adrenergic blockade by propranolol (40 mg) impairs detection T2 stimuli independent of the T2 stimulus valence (Exp. 1). This is the first demonstration that manipulation of the adrenergic system affects the AB, as a recent study found no effect of clonidine on neutral T2 detection (Nieuwenhuis et al., 2007). The robustness of the reported β-adrenergic effect is evident in a replication within Exp. 2. Furthermore, these data replicate previous observations regarding emotional modulation of the attentional blink (Anderson and Phelps, 2001). Placebo and drug groups, in Exp. 1 and 2, showed enhanced T2 detection with increasing T1-T2 lag for both emotional and neutral T2. Secondly, emotional T2 stimuli were more frequently detected than neutral T2, an effect more pronounced at early lags.

A recent, comprehensive account of the role of NE in attention is derived from monkey electrophysiological experiments, which indicate two modes of LC activity(Aston-Jones and Cohen, 2005). Phasic LC neuronal activation is evoked by salient or goal-relevant stimuli during vigilance tasks (Aston-Jones et al., 1994). Phasic responses are evoked on the background of, and in turn modulated by, tonic LC activity which correlates with general arousal levels (Aston-Jones et al., 1991; Aston-Jones et al., 1994). Whereas the LC phasic response itself is relatively brief in duration (typically of 50–100 ms), the ensuing neuromodulatory effects of NE on target cortical areas are known to be sustained relative to the LC phasic response.

One hypothesis on the neurobiological underpinnings of the attentional blink suggests that it is a product of the temporal dynamics of the LC–NE system (Nieuwenhuis et al., 2005c). Although NE may potentiate processing in cortical areas, local NE release within LC is thought to be auto-inhibitory, due to effects of NE at presynaptic and dendritic α_2 autoreceptors (Egan et al., 1983; Washburn and Moises, 1989; Williams et al., 1985). This auto-inhibition results in a refractory-like period after a LC phasic response, during which a subsequent LC phasic discharge is rarely observed (Aston-Jones et al., 1994; Usher et al., 1999). This refractoriness peaks approximately 50–100 ms following the LC phasic response, typically 200–250 ms after the eliciting stimulus, and usually lasts 200 ms or until about 400–450 ms post-stimulus. The length of the refractory period coincides with the T1 and T2 temporal lag in which the blink for the second stimulus T2 is most marked (Nieuwenhuis et al., 2005a). Thus, this theory predicts an effect of NE modulation on both emotional and neutral T2 detection.

The behavioural effects described in this chapter can therefore be explained via an extension of this AB-NE model (Nieuwenhuis et al., 2005a) in which I also model the salience level of the T2 target (arousing or neutral). Previous studies demonstrate that arousing stimuli presented in different modalities induce a robust phasic discharge of NE neurons in LC (Aston-Jones and Bloom, 1981; Foote and Morrison, 1987). Therefore, the enhanced detection of emotional relative to neutral T2 stimuli, demonstrated by Anderson

and Phelps (Anderson and Phelps, 2001), and replicated in Exp. 1 and 2, can be attributable to an increase in NE release elicited by emotional, relative to neutral, stimuli.

Propranolol has been demonstrated to reduce the phasic response elicited by novel stimuli in rats (Kitchigina et al., 1997). The observed effects that I report following propranolol administration can thus be explained in terms of a reduced impact of LC phasic response to targets. A critical observation in these data is that propranolol treated subjects show impaired T2 detection, relative to placebo, for both neutral and emotional T2. Importantly, emotional T2 items, eliciting an increase in NE release, are still detected more frequently than neutral T2 even in the presence of propranolol. According to the model I propose, the behavioral effect in target detection is relative to the magnitude of NE release, assumed to be larger for an arousing T2. Note that the task I used required subjects to report both T1 and T2 stimuli correctly. The NE-AB hypothesis (Nieuwenhuis et al., 2005b) states that initial T1 detection is mediated by phasic LC activity, with the subsequent LC refractory period leading to impaired T2 detection. If propranolol inhibits phasic LC activity, it follows that T1 detection should also be impaired by beta-blockade. In Exp. 2, in which an increase in task difficulty prevented T1 detection ceiling effects, I showed a significant impairment for T1 detection in propranolol compared with the placebo group.

One of the aims of Exp. 3 was to determine whether a lower dose (20 mg) of propranolol would yield valence-specific effects on T2 detection. In other words, I tested whether less

β-adrenergic blockade could be sufficient to abolish enhanced detection of emotional T2 targets, without affecting neutral T2 detection. I did not, however, observe any difference in T2 detection for either neutral or emotional targets between the propranolol 20 mg group and placebo. Exp. 3 also served to demonstrate that administration of nadolol, a peripherally acting β-adrenergic antagonist, has no effect on T2 detection, thus indicating that the attentional effects of propanolol are centrally mediated.

In addition to demonstrating attentional impairment evoked by blocking the β-adrenergic system, administration of a selective NE reuptake inhibitor (SNRI) in Exp. 2 also enabled examination of the attentional effects of increased NE concentration at the synaptic level. Here I provide evidence for reboxetine-evoked enhanced attention, which, in contradistinction to the impairment observed with propranolol, is an effect dependent on the emotional salience of the target. That reboxetine failed to improve neutral T2 detection accords with previous data showing no effect of reboxetine on a neutral continuous performance attention task (Plewnia et al., 2006).

Reboxetine-induced enhanced emotional T2 detection can potentially be explained in terms of the NE-AB hypothesis (Nieuwenhuis et al., 2005b). Previous studies demonstrate increased concentration of cortical NE, particularly in frontal cortex, following acute reboxetine administration (Sacchetti et al., 1999). By contrast, in the locus coeruleus, NE reuptake inhibitors attenuate the firing activity of LC-NE neurons via

α_2-adrenergic autoreceptor over-activation (Beique et al., 2000; Kasamo et al., 1996; Lacroix et al., 1991)Thus, SNRIs mediate two opposite effects: at a cortical level they potentiate attentional gain but also, at the level of LC, SNRIs increase the refractory period via presynaptic α_2 receptors. These two NE influences may produce opponent effects on T2 detection involving facilitation and impairment in the AB task. In Exp. 2 I found that reboxetine selectively boosted detection of arousing T2 stimuli with no effect on neutral T2. These findings can be reconciled with the proposed model if, for neutral T2 detection, the facilitatory and impairing effects of reboxetine are in relative equilibrium, resulting in no net effect on neutral target detection. Conversely the boost in NE elicited by the arousing T2 positively interacts with this state of equilibrium thereby significantly improving target detection for emotional items.

The results described in this chapter show a dissociation in the effects of propranolol on attention from effects previously reported on episodic memory (Strange et al., 2003)=. Whereas the effect of propranolol is selective for the emotional modulation of memory, I demonstrate for the first time in humans (Exp. 1 and 2) that engagement of ß-adrenergic receptors in the central nervous system is essential for optimal target detection independent of stimulus valence. Moreover I demonstrate that the increase in NE levels (Exp. 2) selectively improves detection of arousing stimuli. These attentional effects of pharmacological manipulation of the NE system in human subjects support and extend current theoretical models of the role of NE in attention.

4.5 Appendix (tables of the behavioural scores)

Table 1* (experiment 1)

Early Lag	Late Lag
Placebo	*Placebo*
N =86.99% ± 2.42	N =92.62 %± 1.28
E =93.93 % ± 1.43	E =95.8 %± 1.13
Propranolol 40mg	*Propranolol 40mg*
N =80.69 %± 1.90	N =88.18 %± 1.90
E =91.26 %± 1.93	E =93.84 %± 1.47

**N=percentage of neutral T2 correctly reported*
E=percentage of emotional T2 correctly reported

Table 2* (experiment 2)

Early Lag	Late Lag
Placebo	*Placebo*
N =64.02% ± 4.67	N =77.87 % ± 4.56
E =74.26 % ± 5.65	E =84.5 % ± 4.99
Propranolol 40mg	*Propranolol 40mg*
N =46.1 %± 5.28	N =62.68 % ± 7.69
E =61.6 %± 5.93	E =70.48 % ± 7.62
Reboxetine 4mg	*Reboxetine 4mg*
N =62.8 %± 3.65	N =80.95 % ± 2.05
E =82.64 %± 4.18	E =90.23 % ± 1.92

**N=percentage of neutral T2 correctly reported*
E=percentage of emotional T2 correctly reported

Table 3* (experiment 3)

Early Lag	**Late Lag**
Placebo	*Placebo*
N =59.19% ± 3.44	N =76.45 % ± 3.13
E =75.32 % ± 3.58	E =86.68 % ± 3.21
Nadolol 40mg	*Nadolol 40mg*
N =62.24 %± 4.76	N =76.59 % ± 4.08
E =76.82 %± 5.57	E =88.07 % ± 3.69
Propranolol 20mg	*Propranolol 20mg*
N =65.40 %± 6.40	N =80.43 % ± 5.02
E =78.20 %± 6.31	E =87.62 % ± 4.27

**N=percentage of neutral T2 correctly reported*
E=percentage of emotional T2 correctly reported

Chapter 5

Contextual information and decision-making: "the framing effect"

The experiment described in this chapter shows how the human brain process contextual emotional information when the choice options are presented and how this information biases the decision process.

5.1 Introduction

A central tenet of rational decision-making is logical consistency across decisions, regardless of the manner in which available choices are presented. The assumption that preferences are not affected by inconsequential variations in the description of outcomes has been called extensionality (Arrow, 1982) and invariance (Tversky and Kahneman, 1986), and is considered an essential aspect of rationality.

Invariance is violated by framing effects, where extensionally equivalent descriptions lead to different choices by altering the relative salience of different components of the problem. Kahneman and Tversky originally described this deviation from rational decision-making, which they termed the 'framing effect' as a key aspect of Prospect Theory (see introduction section 1.3.2) (Kahneman and Tversky, 1979). From the time of this pioneering work the proposition that human decisions are 'description-invariant' is challenged by a wealth of further empirical data in both laboratory and field research (Kahneman and Tversky, 2000; McNeil et al., 1982).

The framing effect exerts a very systematic and widespread decision bias that may have critical consequences for human social organization. For example in a particular type of framing effect, where a choice between two options A and B is affected by designating either A or B as a default option; it is known that the option designated as the default has a large advantage in such choices. This effect can have a dramatic impact on the welfare of a society as demonstrated by a recent report (Johnson and Goldstein, 2003). These

authors compared the proportions of the population enrolled in organ donation programs in seven European countries in which enrolment was the default and four in which non-enrolment was the default. Averaging over countries, enrolment in donor programs was 97.4 percent when this was the default option, 18 percent otherwise (Johnson and Goldstein, 2003).

The failure to address invariance raises significant doubts about the descriptive realism of rational-choice models (Tversky and Kahneman, 1986), the overwhelmingly dominant view in economics theory. Indeed this model assumes that people are rational-agents and that their choices reflect a comprehensive algorithmic calculation of all the relevant details of the decision that excludes the irrelevant ones (i.e. the frame). In particular, this view of decision-making have tended to emphasize the operation of analytic processes in guiding choice behavior.

Psychology has long accepted that intuitive or emotional responses play a key role in human decision-making. An early proponent of the importance of affect in decision-making was Zajonc (1980) (Zajonc, 1984), who argued that affective reactions to stimuli are often the very first reactions, occurring automatically and subsequently guiding information processing and judgment. One of the most comprehensive and dramatic theoretical accounts of the role of emotion in decision making was proposed by the neurologist, Antonio Damasio (Damasio et al., 1994). Damasio observed that patients

with damage to the ventromedial frontal cortices of the brain who retain their basic intelligence, memory, and capacity for logical thought intact are impaired in their ability to "feel" (i.e. associate affective feelings and emotions with the anticipated consequences of their actions). Close observation of these patients led Damasio to argue that this type of brain damage induces a form of acquired sociopathy (Damasio et al., 1990) that destroys the individual's ability to make rational decisions; that is, decisions that are in his or her best interests. Persons suffering this damage became socially dysfunctional even though they remain intellectually capable of analytical reasoning.

Thus, when taking decisions under conditions when available information is incomplete or overly complex, as in social interactions, subjects rely on a number of simplifying heuristics, or efficient rules of thumb, rather than extensive algorithmic processing (Gilovich et al., 2002). One suggestion is that the framing effect results from systematic biases in choice behaviour arising from an affect heuristic underwritten by an emotional system (Gabaix and Laibson, 2003; Slovic et al., 2002). However, despite the substantial role of the framing effect in influencing human decision-making, the underlying neurobiological basis is not understood. In this chapter, I have investigated the neurobiological basis of the framing effect by means of functional magnetic resonance imaging (fMRI) and a novel financial decision-making task.

5.2 Materials and methods

5.2.1 Subjects

Twenty healthy, right-handed subjects [11 males (mean age 22.3 years ± 2.1) 9 females (mean age 22.7 years ± 2.5)] were studied. All subjects had a university degree, or were in the process of obtaining one. The study was conducted with the approval of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee.

5.2.2 Experimental paradigm

The experiment was divided into three parts: an instruction phase, a scanning phase during which subjects performed the task, and the post-scan debriefing session. In the instruction phase, the subjects were familiarized with the decision-making task, and given a number of practice trials. They were also told that during the task they would not receive feedback concerning the outcomes of their decisions, but instead receive a sum proportional to their total winnings at the end of the experiment (between £10-£50).

The scanning phase of the experiment was divided into three sessions of 17 minutes each. Each session was composed by 96 trials (32 Loss frame, 32 Gain frame and 32 catch trials), ordered pseudorandomly. At the beginning of each trial participants were shown a message indicating the starting amount of money that they would receive (e.g. 'You

receive £50') (2 sec). Four different starting amounts were used in the experiment (£25-£50-£75-£100). Subjects were instructed that they would not be able to retain the whole of this initial amount, but would next have to choose between a sure or a gamble option (4 sec). The sure option was presented in the Gain frame trials as an amount of money retained from the starting amount (e.g. keep £20 of a total of £50) and in the Loss frame trials as the total amount of money lost from the starting amount (e.g. lose £30 of a total of £50. The gamble option was identical for both frames and represented by a pie-chart depicting the probability of winning or losing.

Four different probabilities were used in the study, such that the probability of winning (or losing) in a given trial was either 20%, 40%, 60%, or 80%. All experimental variables (total starting amount, percentage of the money offered, number of trials per session) were fully balanced between the frame conditions. The expected outcomes of sure and gamble options were always equivalent in each trial (with the exception of the catch trials, see below), and also mathematically equivalent between frames.

Subject were given 4 seconds in which to respond, using an MRI-compatible keypad, operated with their right hand. Given the equivalence of the choices in terms of expected outcomes, "catch" trials (32 trials each session) were included to ensure that subjects remained actively engaged in the decision-making task throughout the course of the experiment. In these catch trials, for both frames, expected outcomes for the sure and gamble option were markedly unbalanced: in half of the trials ("gamble weighted") the

gamble option was highly preferable (e.g. 95% probability of winning by taking the gamble option versus a sure choice of 50% percent of the initial amount) and for the other half of trials ("sure weighted") the sure option was preferable (e.g. 5% probability of winning by taking the gamble option versus a sure choice of 50% percent of the initial amount). As in the main experimental trials, the catch trials were also presented in either a Gain or a Loss frame.

5.2.3 Behavioural data analysis

The behavioural data were analyzed using the statistical software SPSS (http://www.spss.com). The main effect of the frame was calculated from the percentage of trials in which subjects chose the "gamble" option within each frame, using a double-tailed paired t-test. Risk-seeking and risk-averse behavior was defined with respect to risk-neutral behavior (i.e. gambling in 50% of trials), tested with a single tail one-sample t-test. The different percentages of the amount offered (20%, 40%, 60%, 80%) together with the behavioural results for both frame conditions were included as factors in a 4X2 analysis of variance (ANOVA). A similar ANOVA was performed for the initial amounts presented (£25, £50, £75, £100).

A single paired double-tailed t-test was calculated for the reaction time (RT) (risk decision, no-risk decision) for both frame conditions. A rationality index (level of

sensitivity to the frame effect) was calculated for each subject from the difference between the proportion of trials in which a given subject chose the gamble option in the Loss frame, as compared to the Gain frame. This value was then linearly transformed into a rationality index, ranging from 0 (least rational) to 1 (most rational).

5.2.4 Image acquisition and data analysis

Gradient-echo T2*-weighted images (EPI) were acquired on a 1.5 tesla magnetic resonance scanner using a 30 degree titled acquisition sequence designed to reduce signal dropout in orbitofrontal lobes. Image parameters were as follows: TE 50ms; TR 3.96s; slice thickness 2mm; inter slices gap 1mm. I collected 810 volumes (across 3 sessions) per subject. T1-weighted structural images co-registered with mean EPI images and averaged across subjects to allow group level anatomical localization. Images were analyzed using the statistical parametric software SMP2 (Wellcome Department of Imaging Neuroscience London www.fil.ion.ucl.ac.uk/spm). Preprocessing consisted of spatial realignment and normalization to a standard EPI template, and spatial smoothing (8mm kernel). The fMRI data were analyzed in an event-related manner using the general linear model, using the SPM2 statistical analysis software. After discarding the first six image volumes from each run to allow for T1 equilibration effects, image volumes were realigned and co-registered to each subject's structural scan. Subject-specific regressors of interest were assembled by convolving δ functions (corresponding to the time of onset of the choice pair, for each condition) with a canonical hemodynamic response function

(HRF). I removed low frequency fluctuations by a high-pass filter with a cut-off at 128 s. A correction for temporal autocorrelation in the data (AR 1 + white noise) was applied. Parameter estimates were used to calculate the appropriate linear contrast. These contrast images were then entered into a one-sample t test across all subjects (random effects analysis).

The experiment constituted a 2x2 factorial design with the first factor representing the task condition (Gain frame, Loss frame) and the second representing the behavioural decision of each subject on a trial by trial basis, during the gambling task in the scanner (gamble option, sure option). The primary aim of our neuroimaging analysis was to determine which brain regions mediate the frame effect, that is subjects' behavioral tendency to be risk-averse in the Gain frame (i.e. prefer the sure option), and risk-seeking in the Loss frame (i.e. prefer the gamble option). The interaction contrast speaks directly to this question and identifies brain areas more active when subjects chose in accordance with the frame effect (i.e. G_sure + L_gamble), as opposed to when their decisions ran counter to their general behavioral tendency (G_gamble + L_sure). Crucially, this interaction contrast, as opposed to simple effects contrasts (e.g. G_sure – G_gamble), is balanced with respect to both decision type (sure or gamble) and valence of the frame (Gain or Loss). Hence, brain activations identified in this interaction contrast, therefore, are uncontaminated by effects attributable to either decision type or valence of the frame alone.

A simple correlation analysis was performed to identify voxels in which activity in the frame effect contrast [(G_sure + L_gamble) - (G_gamble + L_sure)] for a given subject directly correlated with their rationality index. The resulting Z statistic images were thresholded at $Z > 3.1$ corresponding to $P < 0.001$ uncorrected. We report results in a priori regions of interest (insula, amygdala, striatum, DLPFC, OMPFC, ACC) previously identified in neuroimaging studies on emotional regulation or decision-making (Adolphs, 2002; Bush et al., 2000; Knutson et al., 2005; Montague et al., 2006a; O'Doherty et al., 2002; Phelps et al., 2004) at $P< 0.001$ uncorrected for multiple comparisons. Activations in other regions are reported if they survive whole-brain correction for multiple comparisons at $P < 0.05$. For display purposes in this chapter, statistic images are shown with $Z>2.6$ corresponding to $P<0.005$.

5.3 Results

Participants (20 university students or graduates) performed the behavioral task (figure V.I) inside an fMRI scanner, allowing us to obtain continuous measures of regional brain activity.

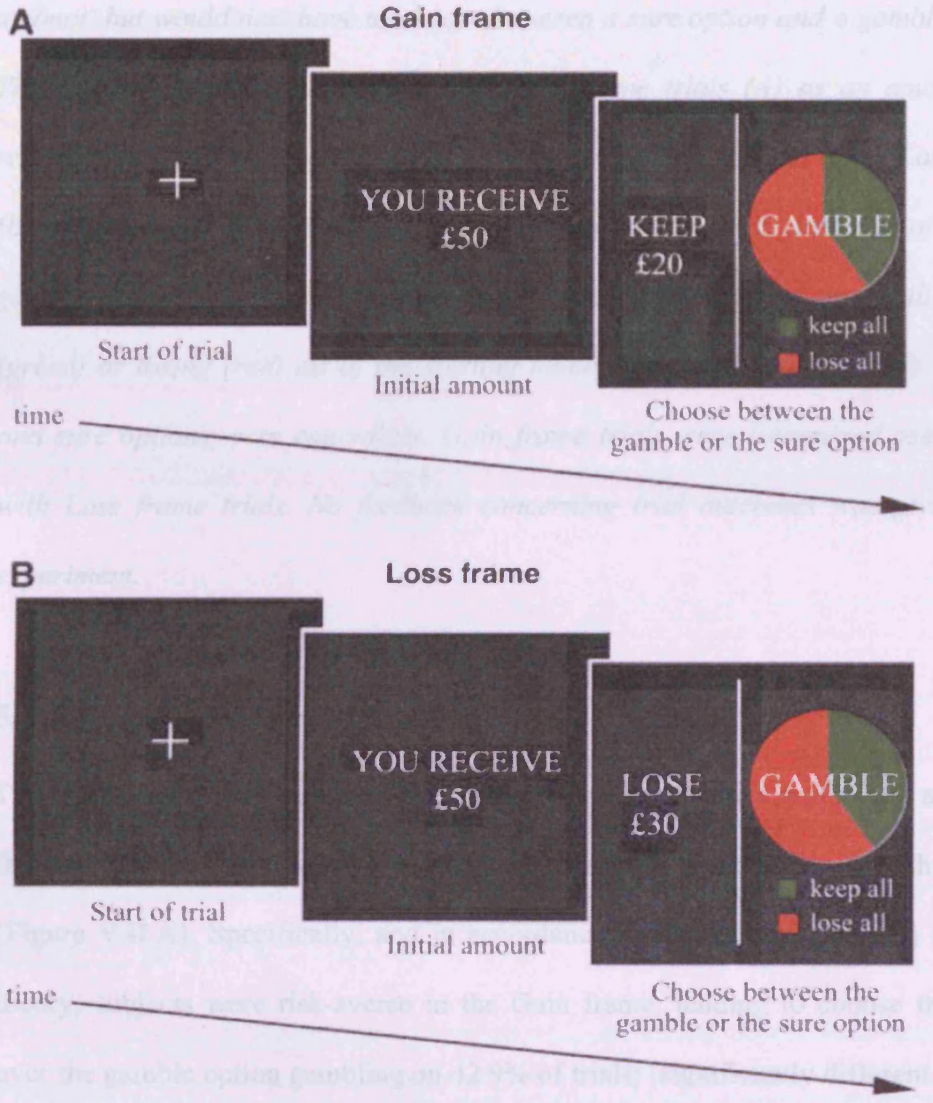

Figure V.I. The financial decision-making task.

At the beginning of each trial, participants were shown a message indicating the starting amount of money that they would receive (e.g., ''You receive £50'') (duration 2 s). Subjects were instructed that they would not be able to retain the whole of this initial

amount, but would next have to choose between a sure option and a gamble option (4 s). The sure option was presented in the Gain frame trials (A) as an amount of money retained from the starting amount (e.g., keep £20 of the £50) and in the Loss frame trials (B) as an amount of money lost from the starting amount (e.g., lose £30 of the £50). The gamble option was represented as a pie chart depicting the probability of winning (green) or losing (red) all of the starting money. The expected outcomes of the gamble and sure options were equivalent. Gain frame trials were intermixed pseudo-randomly with Loss frame trials. No feedback concerning trial outcomes was given during the experiment.

5.3.1 Behavioural results

The behavioral results indicated that subjects decisions were significantly affected by the framing manipulation, with a marked difference in choices between the two frames (Figure V.II.A). Specifically, and in accordance with predictions arising from prospect theory, subjects were risk-averse in the Gain frame, tending to choose the sure option over the gamble option gambling on 42.9% of trials; [significantly different from 50% ($P < 0.05$, $t_{19} = 1.96$)], and were risk-seeking in the Loss frame, preferring the gamble option gambling on 61.6% of trials; [significantly different from 50% ($P < 0.005$, $t_{19} = 3.31$)]. At the end of the scanning session the subjects were debriefed and asked about their strategies when performing the task, and about their awareness of the frame manipulation. Despite the marked though variable impact of the frame on subjects' choice behavior (Fig. V.II. B), the majority (16/20) of subjects were unaware of any

biasing effect when specifically questioned in a debriefing session that followed the experiment.

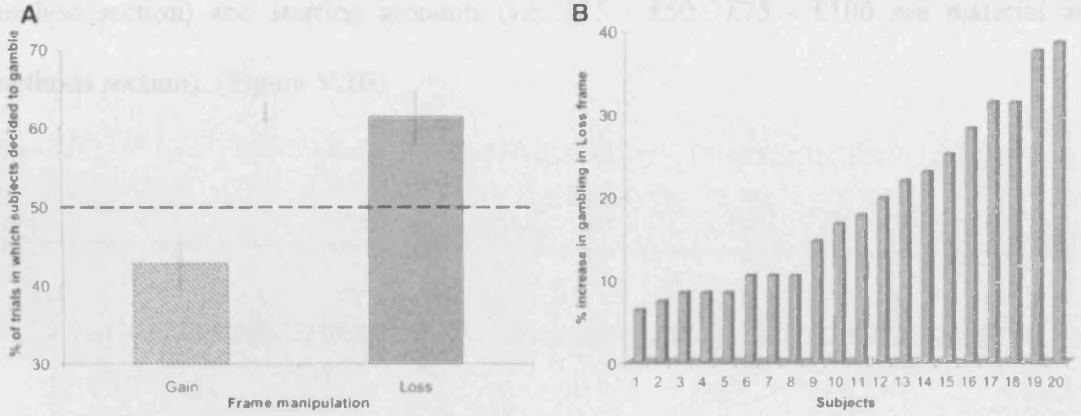

Figure V.II. Behavioral results.

(A) Percentages of trials in which subjects chose the gamble option in the Gain frame and the Loss frame. Subjects showed a significant increase in the percentage of trials in which the gamble option was chosen in the Loss frame with respect to the Gain frame [61.6% vs 42.9% (P <0.001, t_{19} = 8.06)]. The dashed line represents risk neutral behavior (choosing the gamble option in 50% of trials). Error bars denote SEM. (B) Each bar represents, for each individual subject, the percentage difference between how often subjects chose the gamble option in the Loss frame as compared to the Gain frame. A hypothetical value of zero represents a complete indifference to the framing manipulation (i.e., fully ''rational'' behavior). All participants, to varying degrees, showed an effect of the framing manipulation.

The behavioural effect of the framing manipulation framing effect was consistently expressed across different probabilities (i.e. 20% - 40% - 60% - 80% see material and method section) and starting amounts (i.e. £25 - £50 £75 - £100 see material and methods section). (Figure V.III)

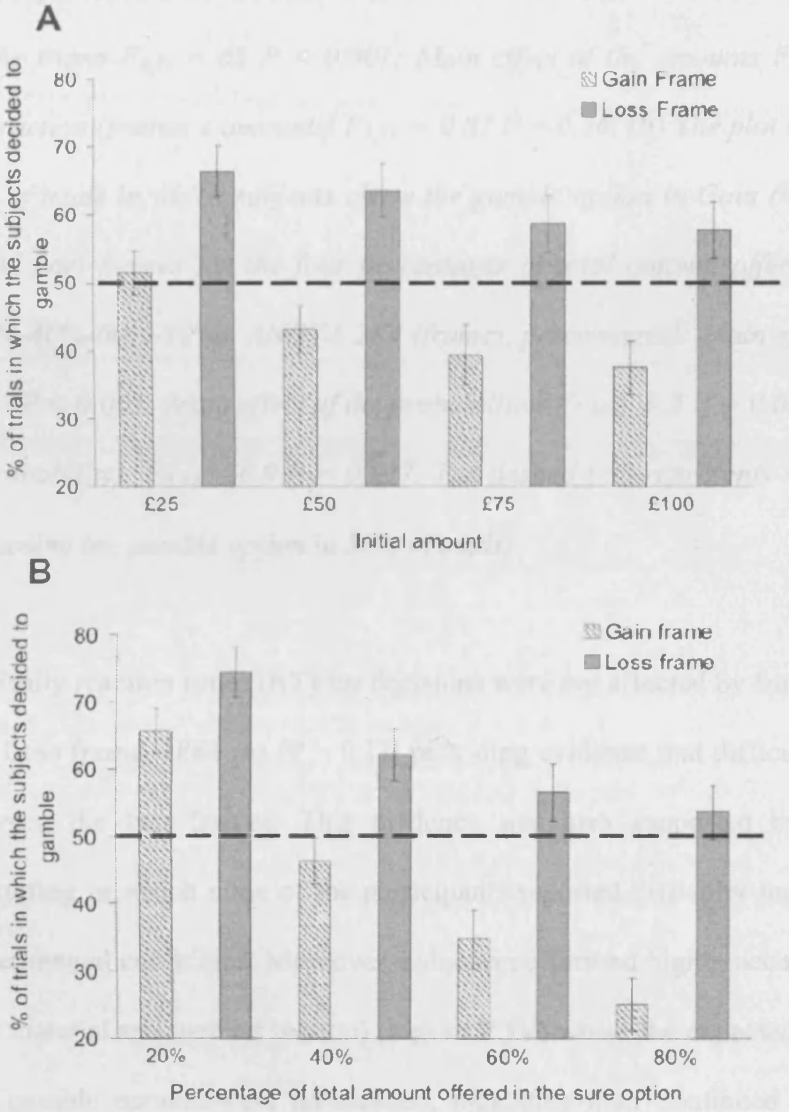

Figure V.III Behavioural results: decisions across varying amount and probabilities.

(A) The plot shows the percentages (%) of trials in which subjects chose the gamble option in the Gain (hatched bar) and Loss (solid bar) frames, for the four different

starting amounts (£25-£50-£75-£100). ANOVA 2X4 (frames, initial amounts): Main effect of the frame $F_{1,19} = 65$ $P < 0.001$; *Main effect of the amounts* $F_{1,19} = 14$ $P < 0.001$; *Interaction (frames x amounts)* $F_{1,19} = 0.87$ $P = 0.36$. *(B) The plot shows the percentages (%) of trials in which subjects chose the gamble option in Gain (hatched bar) and Loss (solid bar) frames for the four percentages of total amount offered in the sure option (20%-40%-60%-80%). ANOVA 2X4 (frames, percentages): Main effect of the frame* $F_{1,19} = 65$ $P < 0.001$; *Main effect of the probabilities* $F_{1,19} = 9.2$ $P = 0.007$; *Interaction (frame x probability)* $F_{1,19} = 6.9$ $P = 0.017$. *The dashed line represents risk-neutral behaviour (choosing the gamble option in 50% of trials)*

Critically reaction times (RT) for decisions were not affected by frame [Gain frame, 1895 ms; Loss frame, 1884 ms ($P > 0.1$)] providing evidence that difficulty was well matched between the two frames. This evidence was also supported by subjects' post-scan debriefing in which none of the participants reported difficulty increased for any of the experimental conditions. Moreover, subjects performed highly accurately on catch [trials (see material and method session) (Figure V.IV) where the expected outcomes of the sure and gamble options were unbalanced, indicating their continued engagement with the task throughout the experiment.

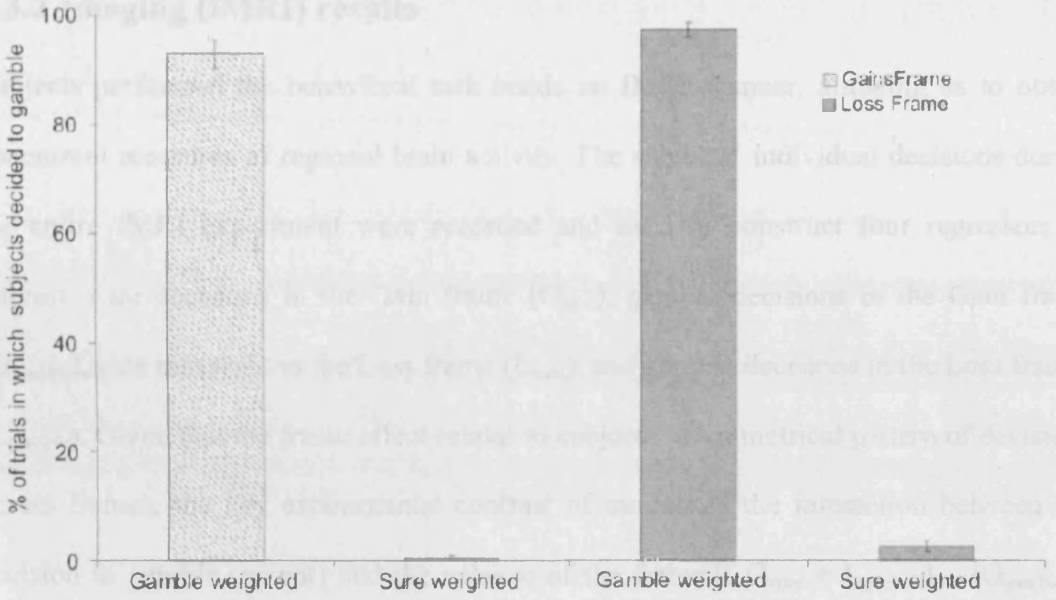

Figure V.IV Behavioural results for catch trials.

In this type of trial (33% of the all trials) the expected outcomes of the sure and gamble option were markedly unbalanced. Two type of catch trials were used for each: gamble weighted - where the sure option was 50% of the starting amount and the gamble option was a 95% probability of winning the starting amount; and sure weighted - where the sure option was 50% of the starting amount and the gamble option was a 5% probability of winning the starting amount. The plot shows the percentages (%) of trials in which subjects chose the gamble option in the Gain (hatched bar) and Loss frames (solid bar), for the gamble weighted and sure weighted conditions. The subjects were highly accurate in making optimal choices in these catch trials, providing evidence of continued engagement with the task throughout the experiment.

5.3.2 Imaging (fMRI) results

Subjects performed the behavioral task inside an fMRI scanner, allowing us to obtain concurrent measures of regional brain activity. The subjects' individual decisions during the entire fMRI experiment were recorded and used to construct four regressors of interest: sure decisions in the Gain frame (G_{surc}), gamble decisions in the Gain frame (G_{gamblc}), sure decisions in the Loss frame (L_{surc}), and gamble decisions in the Loss frame (L_{gamblc}). Given that the frame effect relates to subjects' asymmetrical pattern of decisions across frames, the key experimental contrast of interest is the interaction between the decision to gamble (or not) and the valence of the frame:[(G_{surc} + L_{gamblc}) – (G_{gamblc} + L_{surc})]. It is noteworthy that this interaction contrast is balanced with respect to both decision type and frame valence. Consequently, it was possible to identify brain areas that were more active when subjects chose in accordance with the frame effect (i.e., G_{surc} + L_{gamblc}), as opposed to when their decisions ran counter to their general behavioral tendency (G_{gamblc} + L_{surc}). This contrast revealed significant activation in the bilateral amygdala (Fig. V.V, A and B). To ensure that this activation in the amygdala was not being driven by a significant effect in one frame alone (e.g., Loss frame), I conducted an independent analysis for each frame. This confirmed that robust activation in the amygdala was equally observed for simple effects of decision type (sure or gamble) in each frame separately. Thus, amygdala activation was significantly greater when subjects decided to choose the sure option in the Gain frame [G_{surc} - G_{gamblc}] [Montreal Neurological Institute (MNI) space coordinates (x, y, z) 18, –4, –24; Z score = 4.0], and the gamble option in the Loss frame [L_{gamblc} - L_{surc}] [MNI space coordinates –16, 0, –26;

Z score = 3.80; 12, 2, –22; Z score 0 4.67], in keeping with a central role in mediating the frame effect.

A different pattern of brain activation was identified when subjects made decisions that ran counter to their general behavioral tendency. In this reverse interaction contrast :[(G_{gamble} + L_{sure}) – (G_{sure} + L_{gamble})], it was observed enhanced activity in the anterior cingulate cortex (ACC) (Figure V.V, C and D) (and to a lesser extent in the bilateral dorsolateral prefrontal cortex at an uncorrected threshold of P <0.005; Figure V.V, E) when subjects chose the gamble option in the Gain frame and the sure option in the Loss frame.

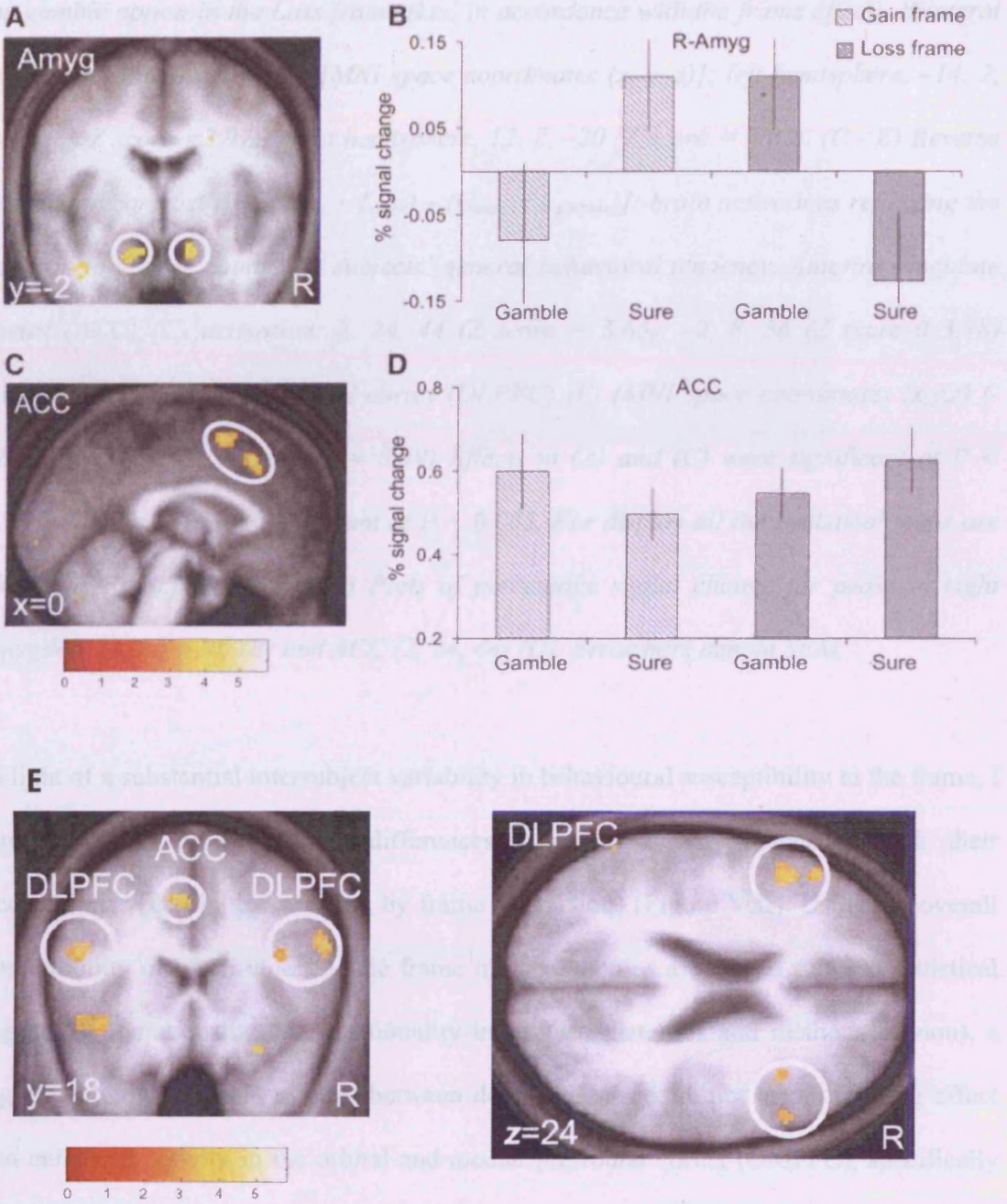

Figure V.V fMRI whiten subjects results .

(A) Interaction contrast :[(G_{sure} + L_{gamble}) – (G_{gamble} + L_{sure})]: brain activations reflecting subjects' behavioural tendency to choose the sure option in the Gain frame and

the gamble option in the Loss frame (i.e., in accordance with the frame effect). Bilateral amygdala (Amyg) activation [MNI space coordinates (x, y, z)]: left hemisphere, –14, 2, 24 (peak Z score =3.97); right hemisphere, 12, 2, –20 (Z score = 3.82). (C - E) Reverse interaction contrast :[(G_{gamble} + L_{sure}) – (G_{sure} + L_{gamble})]: brain activations reflecting the decision to choose counter to subjects' general behavioral tendency. Anterior cingulate cortex (ACC) (C) activation: 2, 24, 44 (Z score = 3.65); –2, 8, 56 (Z score 0 3.78) Bilateral dorsolateral prefrontal cortex (DLPFC) (E) (MNI space coordinates (x,y,z) (-48,18,24 z = 3.61; 56,18,28 z = 3.49) Effects in (A) and (C) were significant at P < 0.001; and in (E) were significant at P < 0.005. For display all the statistical maps are shown at P< 0.005. (B and D) Plots of percentage signal change for peaks in right amygdala (12, 2, –20) (B) and ACC (2, 24, 44) (D). Error bars denote SEM.

In light of a substantial intersubject variability in behavioural susceptibility to the frame, I next identified subject-specific differences in neural activity associated with their decision bias (that is, the decision by frame interaction) (Figure V.II). Using the overall susceptibility of each subject to the frame manipulation as a between subjects statistical regressor, operationalized as a rationality index (see materials and methods session), a significant correlation as evident between decreased susceptibility to the framing effect and enhanced activity in the orbital and medial prefrontal cortex (OMPFC), specifically in the right orbitofrontal cortex (R-OFC; r = 0.8, P < 0.001) and the ventromedial prefrontal cortex (VMPFC; r = 0.75, P < 0.001) (Figure V.VI). In simple terms, those

subjects who acted more rationally exhibited greater activation in OMPFC associated with the frame effect.

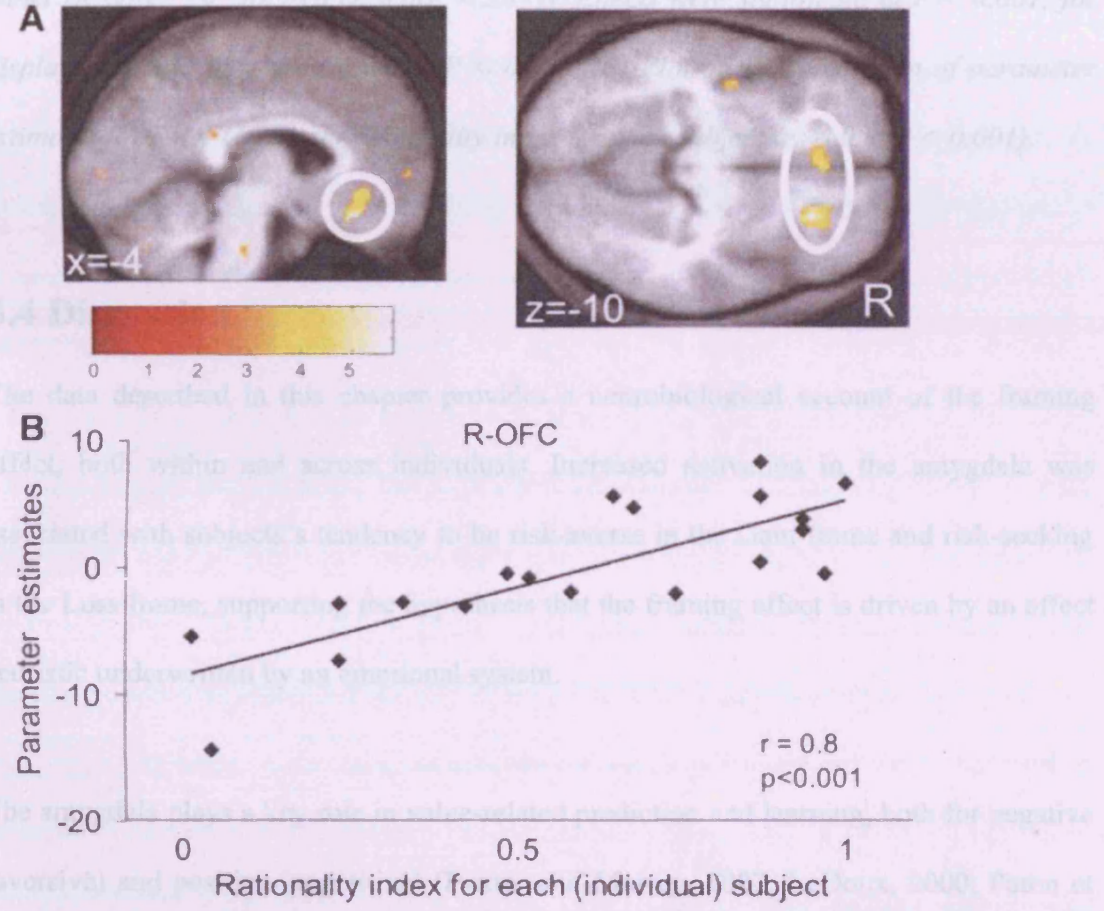

Figure V.VI Between subjects fMRI results.

Rationality across subjects: fMRI correlational analysis. Regions showing a significant correlation between rationality index [between-subjects measure of susceptibility to the framing manipulation; see materials and methods session] and the interaction contrast image:[(G_{sure} + L_{gamble}) – (G_{gamble} + L_{sure})] are highlighted.

(A) Orbital and medial prefrontal cortex (OMPFC) [MNI space coordinates (x, y, z)]: VMPFC (left panel), –4, 34, –8 (Z score = 4.56); OMPFC and R-OFC circled in right panel [R-OFC: 24, 30, –10 (Z score = 5.77)]. Effects were significant at P < 0.001; for display purposes they are shown at P < 0.005. (B) Plot of the correlation of parameter estimates for R-OFC with the rationality index for each subject (r = 0.8, P < 0.001).

5.4 Discussion

The data described in this chapter provides a neurobiological account of the framing effect, both within and across individuals. Increased activation in the amygdala was associated with subjects's tendency to be risk-averse in the Gain frame and risk-seeking in the Loss frame, supporting the hypothesis that the framing effect is driven by an affect heuristic underwritten by an emotional system.

The amygdala plays a key role in value-related prediction and learning, both for negative (aversive) and positive (appetitive) (Baxter and Murray, 2002; LeDoux, 2000; Paton et al., 2006). Furthermore, in simple instrumental decision-making tasks in animals, the amygdala appears to mediate decision biases that derive from value related predictions (Corbit and Balleine, 2005). In humans, the amygdala is also implicated in the detection of emotionally relevant information present in contextual and social emotional cues (Adolphs, 2006). It was previously shown that activation in the amygdala during the passive viewing of surprised faces is significantly modulated by the valence of preceding

verbal contextual information (Kim et al., 2004). The data in the current study extend the role of the amygdala to include processing positive or negative emotional information communicated by the frame in the context of a decision-making task. In our study, activation of the amygdala was driven by the combination of a subject's decision and the frame in which it took place, rather than by the valence of the frame per se. Consequently, these findings indicate that frame-related valence information is incorporated into the relative assessment of options to exert control over the apparent risk sensitivity of individual decisions.

The observation that the frame has such a pervasive impact on complex decision-making supports an emerging role for the amygdala in decision-making (Balleine and Killcross, 2006; Hsu et al., 2005). When subjects' choices ran counter to their general behavioral tendency, there was enhanced activity in the ACC. This suggests an opponency between two neural systems, with ACC activation consistent with the detection of conflict between predominantly "analytic" response tendencies and a more "emotional" amygdala-based system (Botvinick et al., 2001; Miller and Cohen, 2001). The experimental design described in this chapter allowed me to distinguish the anatomical bases of the frame effect, both within and between subjects.

Interestingly, amygdala activity did not predict the substantial intersubject difference in terms of susceptibility to the frame effect. Instead, subjects' susceptibility to the frame showed a robust correlation with neural activity in the OMPFC. It is noteworthy that

there exists strong reciprocal connections between the amygdala and the OMPFC (Amaral, 1982), although each may contribute distinct functional roles in decision-making (Winstanley et al., 2004). Lesions of the OMPFC cause impairments in decision-making often characterized as an inability to adapt behavioural strategies according to the consequences of decisions, leading to impulsivity (Bechara et al., 1994; Rolls et al., 1994). It is thought that the OMPFC, incorporating inputs from the amygdala, represents the motivational value of stimuli (or choices), which enables it to integrate and evaluate the incentive value of predicted outcomes in order to guide future behavior (Schoenbaum et al., 2006; Schoenbaum et al., 2003). These data raise an intriguing possibility that more "rational" individuals have a better and more refined representation of their own emotional biases that enables them to modify their behavior in appropriate circumstances, as, for example, when such biases might lead to suboptimal decisions. As such, our findings support a model in which the OMPFC evaluates and integrates emotional and cognitive information, thus underpinning more "rational" (i.e., description-invariant) behaviour.

The findings described in this chapter suggest a model in which the framing bias reflects an affect heuristic by which individuals incorporate a potentially broad range of additional emotional information into the decision process. In evolutionary terms, this mechanism may confer a strong advantage, because such contextual cues may carry useful, if not critical, information. Neglecting such information may ignore the subtle

social cues that communicate elements of (possibly unconscious) knowledge that allow optimal decisions to be made in a variety of environments. However, in modern society, which contains many symbolic artifacts and where optimal decision-making often requires skills of abstraction and decontextualization, such mechanisms may render human choices irrational (Stanovich and West, 2002).

5.4 Appendix (SPM significant activation tables)

Table 1. Brain areas significantly more active during interaction contrast [(G_sure + L_gamble) - (G_gamble + L_sure)]

All values $p<0.001$ uncorrected.
*statistically significant activation (see Material and methods session)

Region	Laterality	x	y	z	z-score
Amygdala *	L	-14	2	-24	3.97
	R	12	2	-20	3.82
Inferior temporal gyrus	L	-42	-4	-32	4.83
Middle temporal gyrus	L	-66	-28	2	4.43

Table 2. Brain areas significantly more active during interaction contrast [(G_gamble + L_sure) - (G_sure + L_gamble)]

All values p<0.001 uncorrected.
*statistically significant activation (see Material and methods session)

Region	Laterality	x	y	z	z-score
Anterior cingulate cortex*	R	-2	8	56	3.78
	L	2	24	44	3.65
Cerebellum	L	-34	-56	-44	5.56
Superior frontal sulcus	R	10	-6	72	4.62

Table 3. Brain areas significant correlation between rationality index (between-subjects measure of susceptibility to the framing manipulation, see Methods) and the interaction contrast image [(G_sure + L_gamble) - (G_gamble + L_sure)].

All values p<0.001 uncorrected.
*statistically significant activation (see Material and methods session)

Region	Laterality	x	y	z	z-score
Orbitofrontal cortex (OFC) *	R	24	30	-10	5.77
Ventromedial prefrontal cortex (VMPFC)*		-4	34	-8	4.56

Chapter 6

Contextual information and decision-making in Autism

The experiment described in this chapter shows how subjects affected by autism spectrum disorder (ASD) are less influenced by contextual emotional information when choice options are presented, and consequently show a reduced framing bias.

6.1 Introduction

First described by Kanner (Kanner, 1943) and Asperger (Asperger, 1944), autism is a neuro-developmental disorder characterised by severe deficits in social interaction, qualitative impairments in communication and repetitive and stereotyped patterns of behaviour, interests and activities. The last twenty years have seen the acceptance of the concept that autism is a spectrum of disorders rather than a single syndrome. Autism Spectrum Disorders (ASD), also known as Pervasive Developmental Disorders (PDD), is thus an "umbrella category" which includes several autism-related disorders.

Several cognitive theories have been proposed in the attempt to explain the peculiar pattern of behaviour associated with ASD (for an extensive review see (Baron-Cohen and Belmonte, 2005)).

In an early study conducted by Bartlett (Bartlett, 1932), participants were asked to recall a story they had been told previously. Surprisingly, while most people would recall the general plot rather than precise details, people who would now be diagnosed autistic were able to recall exact words of the story but not the plot. Starting from this evidence Frith and Happe proposed what is called the weak central coherence theory in autism (Frith and Happé, 1994). According to this theory people with autism have a strong tendency to focus on the specific details rather than the global aspect of an object of interest, and are unable to integrate several pieces of information into a meaningful whole.

This theory may explain the uneven profile of abilities and deficiencies in autistic individuals. For instance, they show a clear superiority on the Embedded Figures Task where patients are asked to locate a small part within a global picture (Shah and Frith, 1993) but perform poorly in an homographs task where they must integrate the context of the sentence in order to understand the meaning of the word (Happe, 1997) or in a task where they have to arrange sentences to form a coherent context (Jolliffe and Baron-Cohen, 2000).

Another defining aspect of autistic behaviour is reflected in an inability to attribute mental states to others, known as *mentalizing*. This is an automatic ability necessary for effective social communication. A lack of intuitive mentalizing, and a consequential inability to experience appropriate emotional reactions to another person's mental state (i.e. empathy), results in autistic individuals having severe social impairments.

The first experimental evidence for a mentalizing failure in children with autism was demonstrated using what has been called the "Sally and Ann task" (Baron-Cohen et al., 1985). In this pictorial task (see cartoon on the side from (Baron-Cohen et al., 1985)), a first doll, Sally, puts a ball in her basket; while Sally is away, Ann takes Sally's ball and places it in her own box; then, Sally comes back and children are asked "where will Sally look for her ball?". Strikingly, 80% of children with autism will answer "in the box": they cannot understand that *Sally does not know that her ball has been moved.* By contrast, the majority of children with the same mental age, even those with lower general intellectual ability, such as children with Downs syndrome, answer correctly (Baron-Cohen et al., 1985).

Recently it has been proposed that several critical aspects of the autistic behaviour may be explained by an imbalance in empathizing and systemizing behaviours (E-S theory) (Baron-Cohen et al., 2000). According to this view autistic individuals show increased analytical coupled with impaired empathic ability. The enhancement in systemizing is associated with some areas of cognitive strength and can explain the autistic person's increased attention to details rather than context, described by the Weak Coherence

theory (Frith and Happé, 1994). By contrast the inability to empathize can account for the social and emotional deficits as well as a lack of mentalizing ability.

6.2 Materials and methods

6.2.1 Subjects

Thirty-two subjects participated in the study. Of these 32, three subjects were excluded: one subject 2 was found to be on antipsychotic drug treatment (Olanzapine), one subject had learning difficulties and a third was excluded because he was statistical outlier (his score on the framing effect was more than twice the standard deviation above the mean of their group). Two subjects who were taking an SSRI (selective serotonin reuptake inhibitors) antidepressant medication were not excluded, since we had no reason to suspect these drugs would interfere with the cognitive abilities involved in the task. Therefore, after exclusion of these four subjects, 14 subjects remained in in the ASD group and 15 subjects in the control group.

In the ASD group, there were 10 males and 4 females, the mean age was 34.8 years (standard error mean: ±2.1) and the mean full-scale IQ score was 112.1 ± 3.6 (mean verbal IQ score: 112.6 ± 3.1 and mean performance IQ score 109.0 ± 4.3). All ASD subjects had received a clinical diagnosis of autism or autism spectrum disorder by a specialized clinician prior to inclusion. In addition, all subjects had an independent Autism Diagnostic Observation Schedule (ADOS) assessment to quantify the degree of impairment across different domains (Lord et al., 2000). The ADOS is a research standardized test which provides an index of autistic symptoms observed on a particular

occasion. All subjects took module 4 (designed to assess adults), and received two scores: a communication score (labelled "ADOS score 1" in Appendix 1) on which the ASD cut-off is 2 and the autism cut-off is 4; and a reciprocal interaction (or "social") score (labelled "ADOS score 2") on which the ASD cut-off is 4 and the autism cut-off is 7. Overall, the total ADOS score cut-off for ASD is 7 and the cut-off for autism is 12. We note, however, that the ADOS classification is not a clinical diagnosis (i.e.: based on standardised DSM-IV/ICD-10 criteria, see Table 1) and, whilst it may contribute to diagnosis cannot replace full systematic assessment by a specialized clinician. For this reason, two ASD subjects (subject 24 and subject 33) had clinical diagnoses of autism although scoring below the ADOS cut-off for autism.

In the Control group there were 11 males and 4 females, the mean decimal age was 32.2 ± 2.2 and the mean full-scale IQ score was 116.5 ± 2.0 (mean verbal IQ score: 114.8 ± 2.2 and mean performance IQ score: 115.6 ± 2.2). There were no significant differences between the two groups in age (P=0.41, 2-tailed independent t-test), full-scale IQ score (P=0.29, 2-tailed independent t-test), verbal IQ score (P=0.56, 2-tailed independent t-test) or performance IQ score (P=0.17, 2-tailed independent t-test).

The study was conducted with the approval of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee.

6.2.2 Experimental paradigm

The experiment was divided into three parts: an instruction phase, a task phase during which subjects performed the task (during this phase the skin conductance response (SCR) was recorded), and a questionnaire session. In the instruction phase, subjects were familiarized with the decision-making task, and given a number of practice trials before starting the main behavioural task. The behavioural task they were asked to perform was identical to the one used in the fMRI experiment described in chapter 5.2.2.

6.2.2 Skin conductance response (SCR)

The basic measure here is an elevation of the electrical conductance of the skin, known as the Skin Conductance Response (SCR), when an external stimulus is presented. The physiological mechanism underlying the SCR has been the subject of much debate. It is now agreed that the presentation of the external stimulus gives rise to emotion-evoked sweating generated by the eccrine sweat glands. When sweat fills the glands, the overall resistance of the "circuit" that they constitute decreases and thus the skin conductance (which is simply the inverse of resistance) is increased.

As sweat glands are under exclusive sympathetic cholinergic sudomotor fibre control, there is a high correlation between the SCR and peripheral sympathetic activity. Central influences on the control of the SCR is more complex and still not completely understood as excitatory and inhibitory control of the sympathetic nervous system is distributed

among several brain regions and structures. Three main structures thought to play a role in the generation of SCR: ipsilateral regions of the limbic system, such as the cingulate gyrus, the amygdala, and hypothalamus have excitatory influences on electrodermal activity; contralateral premotor cortex and basal ganglia involve both inhibitory and excitatory control; lastly, the reticular formation of the brainstem is also associated with skin conductance responses (Dawson et al., 2000).

6.2.3 Questionnaires

Once the task was completed, the subject was left alone in a separate room and asked to fill in two questionnaires (see Appendix 2): the short form of the Need for Cognition (which was labelled as "Part 1") and the Cognitive Reflexion Test (labelled "Part 2").The Need for Cognition questionnaire, first introduced by Cacioppo and Petty as a 34 item test (Cacioppo and Petty, 1982), was designed to assess "the tendency for an individual to engage in and enjoy thinking". A shorter form of the scale, consisting 18 items, (Cacioppo et al., 1984) was used here. : for each of the 18 statements, the subject had to say whether he considered that it was "extremely uncharacteristic" (score=1), "somewhat uncharacteristic" (score=2), "uncertain" (score=3), somewhat characteristic (score=4) or extremely characteristic (score=5) of himself. Half of the statements (items 3, 4, 5, 7, 8, 9, 12, 16, 17) were reverse scored, for example a "4" was considered as a "2", and a "1" as a "5". The global Need for Cognition score for each subject was obtained by summing the score of each item and was therefore over a total of 90 points.

The second questionnaire was the Cognitive Reflection Test (Frederick, 2005). The Cognitive Reflection Test (CRT) comprises three items (see Appendix 1). Each item consists in a short puzzle such as the following: "A bat and a ball cost $1.10 in total. The bat costs $1.00 more than the ball. How much does the ball cost?" In this problem, as in the two others of the CRT, an intuitive answer immediately springs to mind (which would be here: "10 cents"). However, on considering the problem more carefully it becomes clear that the correct answer is "5 cents" and not "10 cents" (the correct answer for item (2) being: "5 minutes", and that of item (3): "47 days"). For each participant, the CRT score indicates the number of items that were correctly answered: that is, 0, 1, 2 or 3. All three problems of the CRT are not difficult in the sense that anyone can easily understand the solution when explained. However, getting the right solution requires voluntary suppression of the intuitive response. It can be conjectured that the CRT provides a measure of impulsivity, or "cognitive reflection", rather than a measure of the intellectual ability.

6.2.4 Behavioural data analysis

The behavioural data were analyzed using the statistic software SPSS. The main effect of the frame was calculated in each group (i.e. ASD and Control) from the percentage of trials in which subjects chose the "gamble" option within each frame, using a double-tailed paired t-test. A single paired double-tailed t-test was calculated for the reaction time (RT) (risk decision, no-risk decision) for both frame conditions. The level of sensitivity to the frame effect was calculated for each subject from the difference between

the proportion of trials in which a given subject chose the gamble option in the Loss frame, as compared to the gamble in the Gain frame. The main effect and interactions within and across group were analyzed by a 2x2x2 ANOVA with two within subjects factors namely frame (gains and losses frame) and choice (risky and sure choice) and group (ASD and Control) as a between subjects factor.

6.2.4 SCR data analysis

In our experiment, two Ag/AgCl electrodes (skin conductance recorder: AT-64, Autogenic Sytems Laboratory®) were attached using surgical tape to the palmar surface of subjects distal phalanges of the second and fourth fingers of the left hand. Conductive gel was applied between the skin and the electrodes. SCR signal and event markers were sent to an analogue-to-digital amplifier (CED-Power1401®) then acquired on two different channels using the software Spike2 (v5, Cambridge Electronic Design).

Skin conductance responses and event markers were recorded at 100 Hz. The window of interest was defined as the 5 seconds following the subject's decision. Baseline skin conductance was calculated by averaging the skin conductance level during the 0.5s prior to the presentation of the frames. Amplitude of the SCR was defined as the difference between the time-window peak value and the baseline. Only amplitudes greater than 0.01 micro siemens (μS) were included to ensure only trials resulting in a skin conductance response were captured. In order to eliminate non-physiological SCR response (less than

10% of the entire data set) were removed from the data analysis SCRs by visual inspections. For every subject, we determined the amplitude for each trial and then calculated the mean amplitude for each separate condition. Due to a technical failure, skin conductance for one subject (ASD) could not be analyzed. In order to get SCR amplitudes in standard deviations, four more subjects (2 in each group) were removed from the analysis due to a poor quality of their SCR data. Finally, we performed a Z-transformation of SCR amplitudes in order to normalize the SCR data (Yaremko, 1986).

SCR results were analyzed using a 2x2x2 ANOVA: The within subjects factors were Frame (Losses_Frame; Gains_Frame), Choice (Risky_choice; Sure_choice) with Group (ASD; Control) as a between subject factor. In order to get SCR amplitudes in standard deviations we performed a Z-transformation of SCR amplitudes.

6.3 Results

6.3.1 Behavioural results

In the ASD group, the mean proportion of trials in which the subjects decided to gamble in the gain frame was 34.52% (standard error mean: ± 4.99) and 42.19% (± 13.34) in the loss frame. Therefore, the mean framing effect (calculated as the % increase gamble in the loss frame compared with the gain frame) in this group was +7.66% (± 1.95). In the control group, the subjects gambled in 43.75% (± 4.72) of the trials in the gain frame and 57.99% of the trials in the loss frame (± 4.70), giving a mean framing effect of +14.24%

(± 1.68) showing a susceptibility to the frame that was twice that seen in the ASD group (see Figure VI.I).

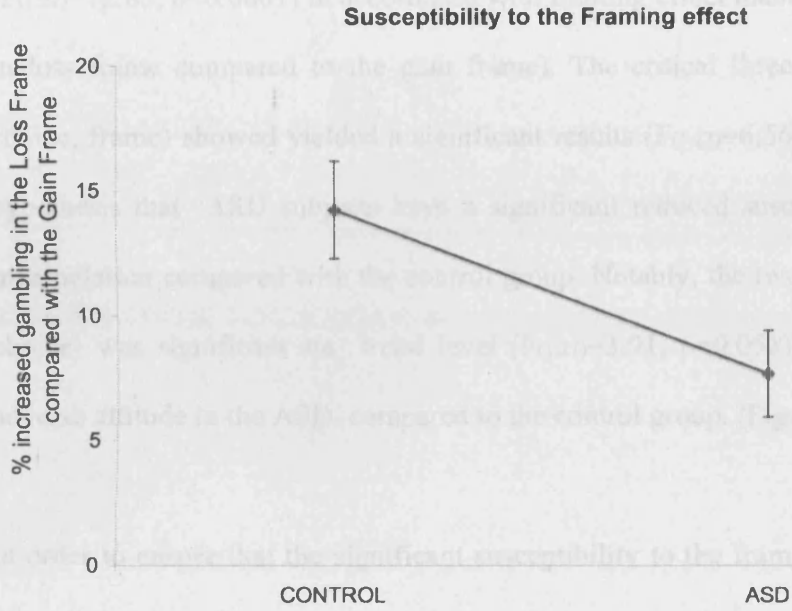

Figure VI.I Susceptibility to the framing manipulation.

The graph represents the susceptibility to the framing manipulation defined as percentage (%) increased gambling in the Loss Frame compared with the Gain Frame (y axis) in both groups, Control +14.24% (± 1.68) *and ASD* +7.66% (± 1.95) *(x axis).*

The effect in the control replicated the findings of the fMRI experiment reported in chapter 5. Notably, both the ASD group and the Control group showed a significant framing effect (i.e. gambling more in the loss frame than in the gain frame) (ASD Group: $P<0.005$, $t_{(13)}= 3.92$ and Control Group $P<0.0001$, $t_{(13)}= 8.48$ double-tailed test paired t-

test Figure VI.II). A group (ASD, Control) X frame (Gain, Loss) x choice (Risky, Sure) 2x2x2 ANOVA yielded a highly significant interaction between choice and frame ($F_{(1,27)}=72.83$, $p<0.0001$) in accordance with framing effect manipulation (increase in risk in loss frame compared to the gain frame). The critical three-way interaction (group, choice, frame) showed yielded a significant results ($F_{(1,27)}=6.56$, $p<0.02$) supporting our hypothesis that ASD subjects have a significant reduced susceptibility to the framing manipulation compared with the control group. Notably, the two-way interaction (group, choice) was significant ata trend level ($F_{(1,27)}=3.91$, $p=0.058$), indicating a mild risk-adverse attitude in the ASD compared to the control group. (Figure VI.II)

In order to ensure that the significant susceptibility to the frame in the ASD group was unrelated with an increased risk-aversion in this group, the 2x2x2 ANOVA analysis was repeated covarying out from the frame manipulation individual subject risk tendency calculated as percentage of risky. This analysis corroborated the results from the previous analysis and again yielded a highly significant three-way interaction (group, choice, frame) ($F_{(1,27)}=10.03$, $p<0.005$).

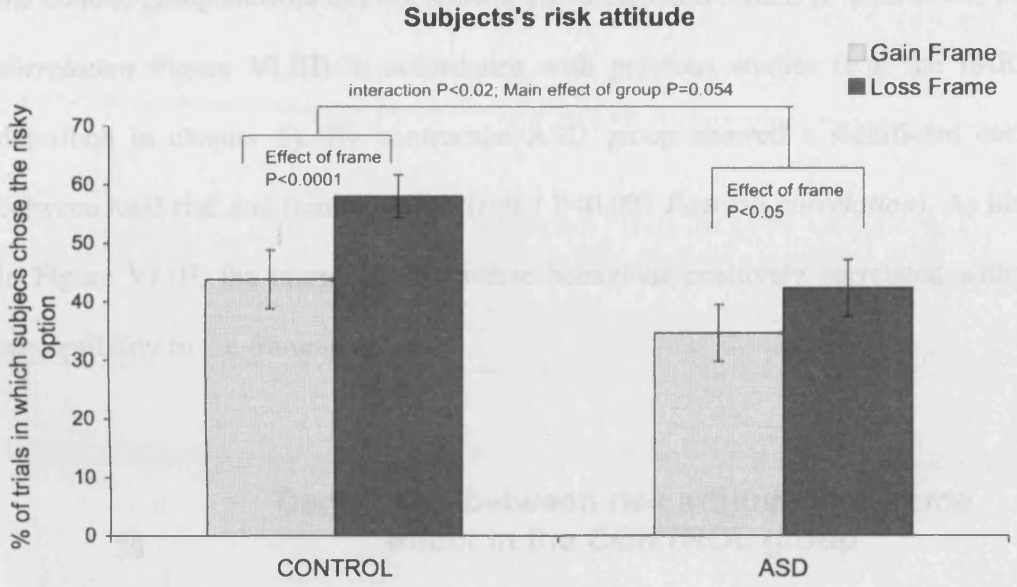

Figure VI.II Subjects' risk attitude

The graph represents the subjects' risk attitude defined as percentage (%) of trials in which subjects chose the risky option rather than the sure option for both frames manipulations: loss frame (black) and gain frame (grey) in both groups (x axis).

In order to further explore the relationship between general risk-attitude and susceptibility to the framing effect I performed a simple correlation between frame effect (i.e. % increased gambling in the loss frame with respect to the gain frame) and total risk (i.e. % of the gambling choices independent from the framing manipulation). The correlation between these two variables yielded no significant results across the two groups (r=0.1 P=0.5 *Pearson-correlation*). However, when the two groups were considered separately

the control group showed did not show a significant correlation (r=0.02 P>0.5 *Pearson-correlation* Figure VI.III) in accordance with previous studies (e.g. the fMRI study described in chapter 5). By contrastthe ASD group showed a significant correlation between total-risk and framing effect (r=0.7 P<0.005 *Pearson-correlation*). As illustrated in Figure VI.III, the increased risk-averse behaviour positively correlated with greater susceptibility to the framing effect.

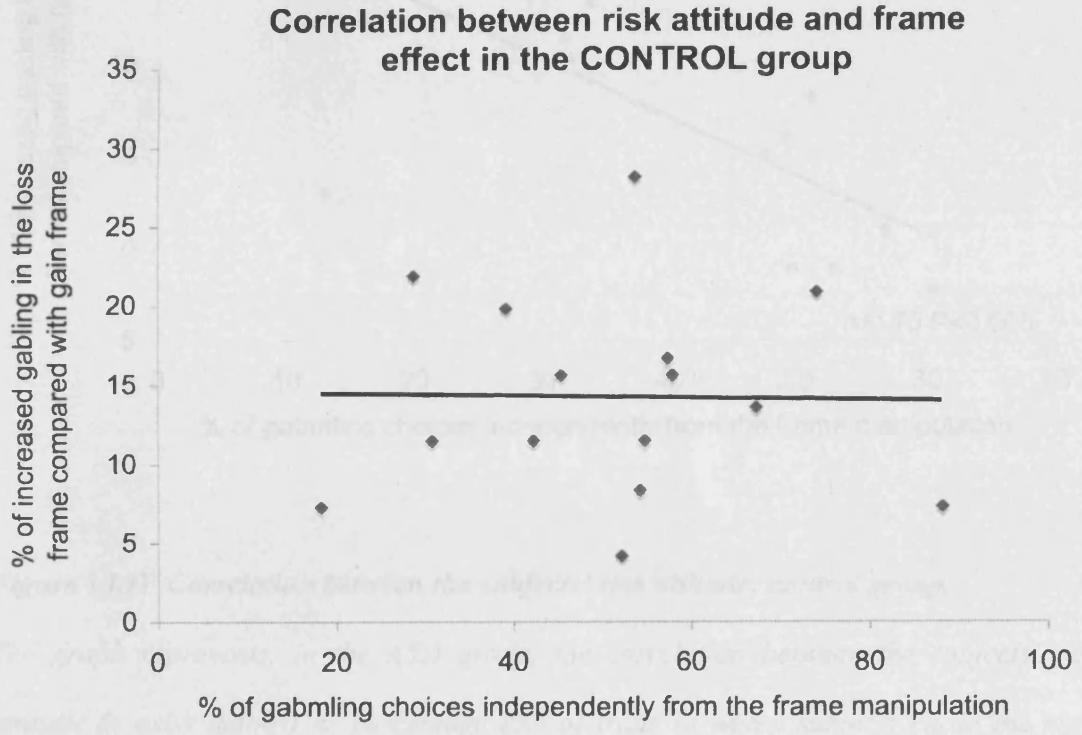

Figure VI.III Correlation between the subjects' risk attitude: control group.

The graph represents, in the control group, the correlation between the subjects' risk attitude (x axis) defined as percentage (%) of trials in which subjects chose the risky option rather than the sure option for both frames manipulations and the susceptibility to

the frame manipulation (y axis) defined as percentage (%) increase of gambling choice in the loss frame compared with the gain frame.

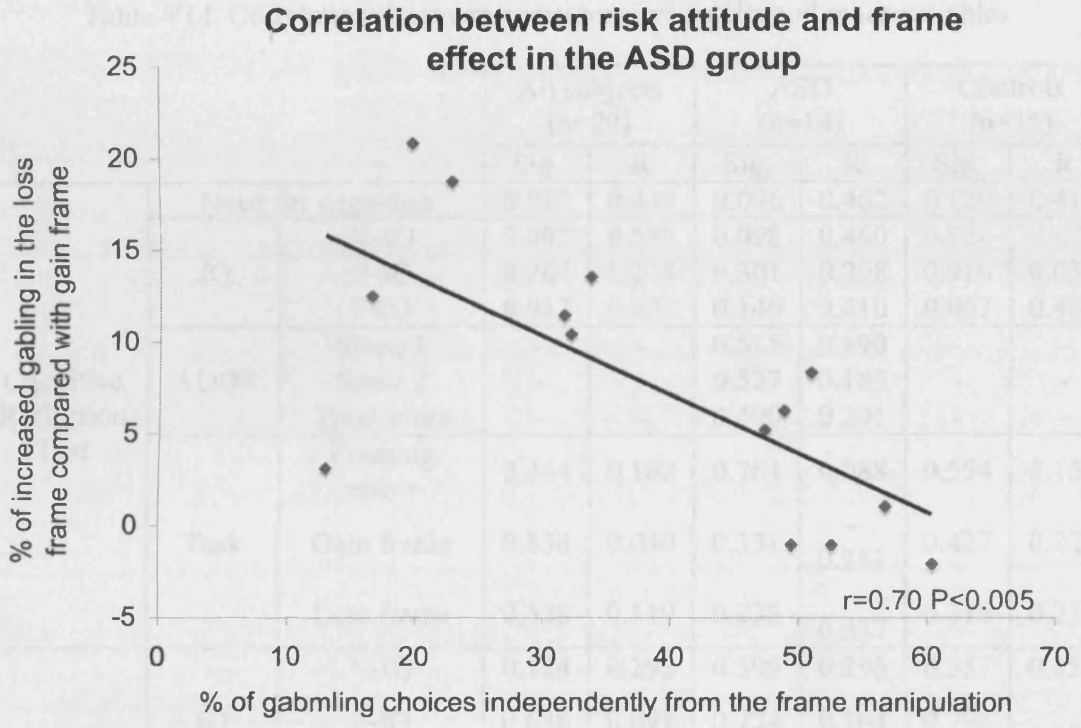

Figure VI.IV Correlation between the subjects' risk attitude: control group.

The graph represents, in the ASD group, the correlation between the subjects' risk attitude (x axis) defined as percentage (%) of trials in which subjects chose the risky option rather than the sure option for both frames manipulations and the susceptibility to the frame manipulation (y axis) defined as percentage (%) increase of gambling choice in the loss frame compared with the gain frame.

6.3.2 Questionnaire correlations

The results for the Cognitive Reflection Test (CRT) and Need for Cognition (NC) questionnaire are summarized in table VI.I.

Table VI.I. Correlations between questionnaires results and other variables

			All subjects (n=29)		ASD (n=14)		Controls (n=15)	
			Sig.	R	Sig.	R	Sig.	R
Cognitive Reflection Test	Need for cognition		**0.017**	**0.440**	0.096	0.462	0.120	0.419
	IQ	V-IQ	**0.002**	**0.559**	0.098	0.460	**0.006**	**0.676**
		P-IQ	0.264	0.214	0.301	0.298	0.910	0.032
		F-IQ	**0.017**	**0.439**	0.146	0.410	0.067	0.485
	ADOS	Score 1	-	-	0.515	0.190	-	-
		Score 2	-	-	0.527	0.185	-	-
		Total score	-	-	0.490	0.201	-	-
	Task	Framing effect	0.344	0.182	0.764	0.088	0.594	0.150
		Gain frame	0.838	0.040	0.331	-0.281	0.427	0.222
		Loss frame	0.538	0.119	0.238	-0.337	0.318	0.277
Need for cognition	IQ	V-IQ	0.124	0.292	0.309	0.293	0.357	0.256
		P-IQ	0.638	0.091	0.724	0.104	0.793	-0.074
		F-IQ	0.266	0.214	0.456	0.217	0.660	0.124
	ADOS	Score 1	-	-	0.364	-0.263	-	-
		Score 2	-	-	0.054	-0.525	-	-
		Total score	-	-	0.078	-0.486	-	-
	Task	Framing effect	0.894	0.026	0.938	-0.023	0.766	-0.084
		Gain frame	0.991	0.002	0.712	-0.109	0.818	0.065
		Loss frame	0.945	0.013	0.582	-0.161	0.900	0.036

Across all subjects, the mean CRT score was 1.28 (SEM: ± 0.22) and the mean NC score was 63.76 (± 2.30). In the ASD group, the mean CRT score was 1.07 (± 0.29) and the mean NC score was 61.86 (± 3.99). In the control group, the mean CRT score was 1.47 (± 0.32) and the mean NC score was 65.53 (±: 2.52). There was no significant difference in the mean scores of both questionnaires between the two groups (see table VI.I.). On an independent samples double-tailed t-test, the P-value for difference of means between the ASD and the control group was not significant either for the CRT scores (P=0.369, $t_{(27)}$=-0.193) or the NC score (P=0.436, $t_{(27)}$=-0.791). On bivariate correlation tests, both the CRT and NC scores failed to correlate significantly with most variables (see table VI.I.). Among all the possible correlations, the only variables to correlate significantly with the CRT were IQ score, particularly verbal IQ (V-IQ; P=0.002, R=0.559 on all subjects; P=0.006, R=0.676 in controls and P=0.098, R=0.460 in the ASD group). The framing effect did not correlate with either test in either group with no significant difference in the framing effect evident across the two groups for subjects who scored high on the CRT (score ≥ 2, P=0.141) or on the NC (score > 60, P=0.347).

6.3.2 SCR results

The mean SCR amplitude in the Control group was 0.51μS (S.E. 0.02 μS) for the sure choices in the gain frame and 0.50μS (S.E. 0.02 μS) for the risky choices in the gain frame. By contrast SCR mean values were 0.57μS (S.E. 0.03 μS) for sure choices in the loss frame and 0.59μS (S.E. 0.03 μS) for risky choices. In the ASD group the SCR mean

amplitude value were 0.72 μS (S.E. 0.02 μS) for the sure choices and 0.75μS (S.E. 0.02 μS) for the risky choices in the gain frame. By contrast the SCR mean values were 0.70μS (S.E. 0.03 μS) for sure choices in the loss frame and 0.71μS (S.E. 0.02 μS) for risky choices. Figure VI.V

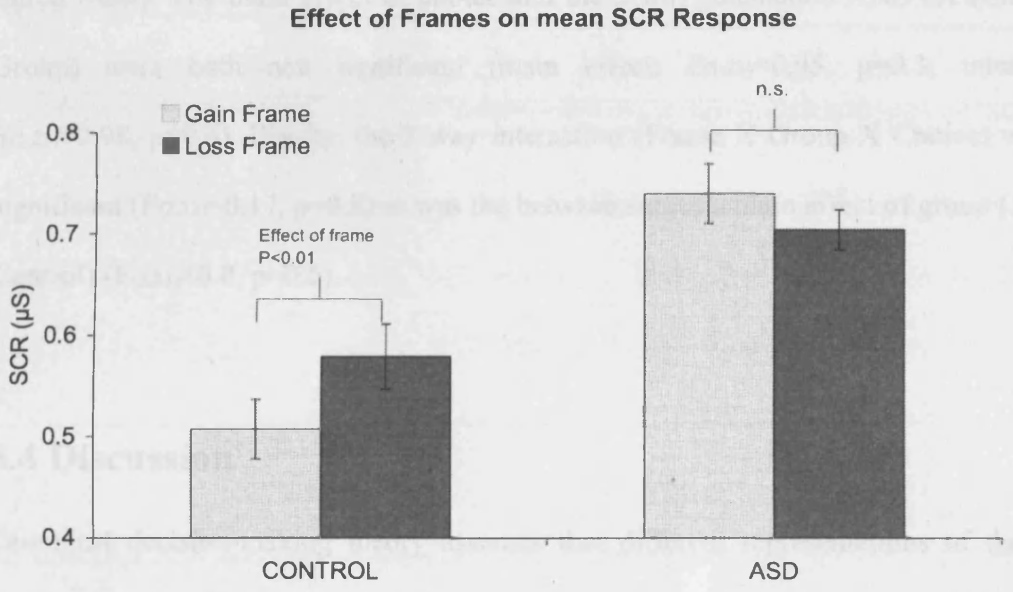

Figure VI.V Effect of frames on SCR response

The graph represents the subjects mean skin conductance response (SCR) amplitude in micro-simens (μS) for both frames manipulations: loss frame (black) and gain frame (grey) in both groups (x axis)

2x2x2 ANOVA (Frame X Choice X Group) on SCR results revealed a significant main effect of frame ($F_{(1,23)}$=4.84, $p<0.05$) and a significant 2 way interaction (Frame X Group) ($F_{(2,23)}$=4.86, $p<0.02$) indicating that within the the control group the loss frame caused an increase in SCR response compared with the gain frame ($t_{(14)}$=3.19, $p<0.01$, double-tailed paired t-test) a response not seenin the ASD group ($t_{(11)}$=0.95, p=0.3 double-tailed paired t-test). The main effect of choice and the 2 way interaction ANOVA (Choice X Group) were both non significant (main effect: $F_{(1,23)}$=0.95, p=0.3; interaction: $F_{(2,23)}$=0.98, p=0.4). Finally, the 3 way interaction (Frame X Group X Choice) was not significant ($F_{(2,23)}$=0.17, p=0.8) as was the between subjects main effect of group (ASD X Control) ($F_{(2,23)}$=0.8, p=0.5).

6.4 Discussion

Canonical decision-making theory assumes that different representations of the same choice problem should yield the same preference (invariance axiom) (Arrow, 1982; Luce, 1957; von Neumann and Morgestern, 1944). Nevertheless, countless empirical data have demonstrated that people are remarkably susceptible to the way in which options are presented in striking conflict with the economic accounts of rationality (Kahneman and Tversky, 1984). Prospect theory described for the first time this systematic violation of the standard model as "framing effect" (Kahneman and Tversky, 1979; Tversky and Kahneman, 1981) (see chapter five).

In this chapter I provide empirical evidence that individuals affected by autism spectrum disorder (ASD) are less susceptible to the framing effect and consequently show a more "rational" choice pattern, in accord with dominant models in economics. Although individuals affected by ASD were susceptible to the framing manipulation (i.e. risk seeking in the loss frame and risk averse in the gain domain) they nevertheless showed a reduced susceptibility compared with a matched control group. Moreover, in the control group, the autonomic response (SCR) for the negative frame (loss frame) was significantly higher than the SCR elicited by the positive frame (gain frame), supporting previous evidence (chapter 5) on the key role of the emotions in the framing bias (De Martino et al., 2006; Kahneman and Frederick, 2007). By contrast, the ASD group displayed no differential change in SCR between the two frames manipulation suggesting a lack of normal processing of emotional information carried by the frames.

Recent theoretical accounts of decision-making have proposed a "two-systems" model in human judgment (Evans, 2003). This view proposes that human decision-making arises from a combination of intuitive thinking and analytic processing. The intuitive type of reasoning is rapid and capable to process a large amount of information in parallel but prone to mistakes and strongly influenced by contextual emotional information (Kahneman, 2003). On the contrary, an analytical type of reasoning is more accurate but slow and computationally demanding. According to this view, the framing bias reflects an affect heuristic by which normal individuals incorporate a potentially broad range of additional emotional information into the decision process. In evolutionary terms, this

mechanism may confer a strong advantage, because such contextual cues may carry useful, even critical, information. This ability is particularly crucial in a social context in which subtle contextual cues communicate knowledge elements (possibly unconscious) that allow optimal decisions to be made in uncertain environments (Stanovich and West, 2002).

People affected by ASD show a reduced procession of emotional contextual information present in the framing manipulation with a consequently increased resistance to the framing bias. In fact, the contextual information in the framing task does not carry any supplemental. At the same time, the ability to process and integrate contextual emotional cues has great advantages in social environments where a large part of the information exchanged between individual is implicit. Individual affected by ASD often show strong impairment in social context may be due to their inability to process these emotional cues.

In the context of the "two-systems" model of decision-making described above, these results suggest that ASD individuals have an increased tendency toward the analytic type of decision-making, due to an impairment within their intuitive reasoning mechanisms. This interpretation is also in keeping with the empathizing-systemizing (E-S) theory of autism, described in the introduction to this chapter (Baron-Cohen and Belmonte, 2005). The E-S theory proposes that the imbalance between analytic and empathic behaviour is

responsible for the ASD social impairments and at the same time for their enhanced analytical skills. During the framing task, ASD subjects were better able to ignore the contextual information and isolate the critical information about the expected value of the sure and risky options. This result is consistent with other experimental findings that form the basis of the weak coherence theory in autism (Frith and Happé, 1994) described at the beginning of this chapter.

Moreover, at the neurophysiological level, the findings presented in the previous chapter (De Martino et al., 2006; Kahneman and Frederick, 2007) showed engagement of an amygdala-based emotional as a function of the framing effect. These results, combined with the SCR data, support an hypothesis that a lesser susceptibility to the framing manipulation in ASD may be due to an impaired processing of the emotional cues due to an amygdala deficit. A wealth of empirical data supports this hypothesis. Firstly, histopathological abnormalities of the amygdala such as an increased cell density and a reduced dendritic arborisation have been described in autism (Bauman and Kemper, 1994). Moreover, Howard and colleagues (Howard et al., 2000) suggested that people with high-functioning autism showed a similar neuropsychological profile to that seen in patients with amygdala lesions, particularly a selective impairment in the recognition of facial expressions of fear. Lastly, several imaging studies demonstrate blunted activation of the amygdala in ASD during tasks which involved processing of facial expressions (Baron-Cohen et al., 2000; Critchley et al., 2000).

In conclusion, our results extend our understanding of cognitive impairments in ASD to the domain of decision-making, an under-explored aspect of autistic behaviour. At the same time, the data provide support for a "two-systems" model of decision-making, and challenge the economic rational model that, paradoxically, seems better suited to predict the choices of ASD as opposed to healthy individuals. The study I describe in this chapter suggests that normative economic rationality as expresses in hyper-analytic reasoning may not always be advantageous given that ASD subjects have such profound deficits in social contexts.

6.5 Appendix (questionnaire)

Short form of the Need for Cognition Scale

Instructions:

For each of the statement below, please indicate to what extent the statement is characteristic of you. If the statement is extremely uncharacteristic of you (not at all like you), please write a "1" to the left of the question; if the statement is extremely characteristic of you (very much like you) please write a "5" next to the question. Of course, a statement may be neither extremely uncharacteristic nor extremely characteristic of you; if so, please use the number in the middle of the scale that describes the best fit. Please keep the following scale in mind as you rate each of the statement below:

1 = extremely; 2 = somewhat; 3 = uncertain; 4 = somewhat; 5 = extremely uncharacteristic uncharacteristic characteristic characteristic

Item Number	Item Wording	Rating (1-5)
1.	I would prefer complex to simple problems.	
2.	I like to have the responsibility of handling a situation that requires a lot of thinking.	
***3.**	Thinking is not my idea of fun.	
***4.**	I would rather do something that requires little thought than something that is sure to challenge my thinking abilities.	
***5.**	I try to anticipate and avoid situations where there is a likely chance I will have to think in depth about something.	
6.	I find satisfaction in deliberating hard and for long hours.	
***7.**	I only think as hard as I have to.	
***8.**	I prefer to think about small daily project than long-term ones.	
***9.**	I like tasks that require little thought once I've learned them.	
10.	The idea of relying on thought to make my way to the top appeals to me.	
11.	I really enjoy a task that involves coming up with new solutions to problems.	
***12.**	Learning new ways to think doesn't excite me very much.	
13.	I prefer my life to be filled with puzzles that I must solve.	
14.	The notion of thinking abstractly is appealing to me.	
15.	I prefer a task that is intellectual, difficult and important to one that is somewhat important but does not require much thought.	
***16.**	I feel relief rather than satisfaction after completing a task that required a lot of mental effort.	
***17.**	It's enough for me that something gets the job done; I don't care how or why it works.	
18.	I usually end up deliberating about issues even when they do not affect me personally.	

* Item reverse-scored

The Cognitive Reflection Test

(1) A bat and a ball cost $1.10 in total. The bat costs $1.00 more than the ball. How much does the ball cost? _____ cents

(2) If it takes 5 machines 5 minutes to make 5 widgets, how long would it take 100 machines to make 100 widgets? _____ minutes

(3) In a lake, there is a patch of lily pads. Every day, the patch doubles in size. If it takes 48 days for the patch to cover the entire lake, how long would it take for the patch to cover half of the lake? _____ days

Chapter 7

Contextual information and the neural representation of value: "the endowment effect"

The experiment described in this chapter shows how the contextual information rooted in the subjects' position as either a seller or as buyer, during economic transactions, change the price and the neural representation of an item's value.

7.1 Introduction

People accord a higher value to objects they own relative to ones they do not own. This "endowment effect" (Thaler, 1980) violates classical economic theory, which asserts that a person's willingness to pay (WTP) for a good should equal their willingness to accept (WTA) compensation for its loss (Willig, 1976). The endowment effect has significant implications for macroeconomics and law including the efficient allocation of property rights (Coase, 1960).

The attribute of value is highly contextual. This is well illustrated by the endowment effect where subjects value a good they own substantially more than an identical good available for purchase. In a seminal experiment, subjects designated as sellers accepted a minimum of $7.00 (WTA) to part with a mug they had been given, whilst those designated as buyers were only willing to pay a maximum of $2.00 (WTP) (Kahneman et al., 1990). This WTA-WTP discrepancy is not explicable by classical economic theory which asserts that preferences are independent of entitlements (Willig, 1976). Prospect theory embraces such findings by proposing that the value of a good (or an option) depends critically on a reference point (Kahneman et al., 1991), such that buyers evaluate the object as a potential gain whereas sellers view the transaction as a potential loss, demanding a higher price due to loss aversion (Kahneman et al., 1991; Kahneman and Tversky, 1979). Although the endowment effect is a robust empirical observation (Kahneman et al., 1990; Knetsch and Sinden, 1984; Thaler, 1980) with profound

macroeconomic implications (Coase, 1960; Kahneman et al., 1990), its neurobiological underpinnings are unknown. Here, using fMRI during an economic exchange paradigm, I demonstrate the neurobiological mechanisms underlying this effect.

7.2 Materials and methods

7.2.1 Subjects

Twenty-five subjects participated in the study. All subjects had a university degree, or were in the process of obtaining one. A highly significant behavioural endowment effect (i.e. WTP>WTA) ($P<0.0001$ $t_{17}=5.02$ double-tailed paired t-test) was observed across the entire group (n=25) who participated in the scanning phase of the experiment, confirming the robustness of this experimental protocol in eliciting a reliable endowment effect. A group of eighteen subjects [10 males (mean age 22.2 years ± 3.1) 8 females (mean age 24.6 years ± 3.5)] were included in the final imaging analysis which was designed specifically to reveal brain regions mediating the endowment effect. One subjects was excluded due to excessive head movement in the scanner. Six subjects, who pursued a deviant strategy with no theoretical basis in the literature (WTP>WTA: significant reverse endowment effect $p<0.01$), were excluded after two sessions. Evidence obtained from debriefing these individuals indicated that their pattern of behavior resulted from a misconstrual of the experimental goals as maximisation of the number of successful market transactions effected by the BDM mechanism, rather than pursuing an overall financial gain. The study was conducted with the approval of the National Hospital for

Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee.

7.2.2 Experimental paradigm

The subjects were instructed carefully on all aspects of the experiment to ensure that they clearly understood the nature of the task. To enhance clarity, subjects were trained using a detailed computer tutorial. Finally, subjects were required to correctly complete a questionnaire prior to proceeding to the scanning phase to ensure that instructions were completely understood by the subject. The paradigm was divided in three phases: endowment, scanning and transaction phases respectively.

7.2.2.1 Endowment phase

Prior to scanning, each subject was asked to choose either of two distinct decks (red or green) each containing 18 lottery tickets. Subjects were endowed (i.e. given) with the deck they selected (e.g. red), and instructed that they would have the opportunity during scanning to buy tickets belonging to the other deck. Subjects were also endowed with an amount of cash (£36) with which to buy tickets.

Each deck was composed of 18 tickets, each having a different value on the front ranging between £2 and £36, in increments of £2. On the back of each ticket was written, hidden by a black scratchable covering, the amount that the ticket was actually worth (in pence and pounds). Subjects were told that this amount was determined randomly by a

computer program, and therefore equally likely to be any figure between £0 and the amount written on the front of the ticket. As such, the expected value of the ticket was one half of the amount written on the front of the ticket.

7.2.2.2 Scanning Phase

The scanning phase was divided in four sessions of 12 minutes each.

During each trial, a screen displayed one of three tickets: 1) a ticket from the deck subjects had selected (e.g. red ticket: selling transaction) 2) a ticket from deck they did not select (e.g. green ticket: buying transaction) 3) a ticket from a third deck (yellow: evaluate condition).

Five different experimental conditions were employed, and presented in pseudorandom order:

1. *Subject's selling transaction (You_SELL)* : The screen displayed one of the subject's own tickets (i.e. taken from the deck they had selected prior to scanning). By moving a cursor on a bar subjects were asked to state the *minimum selling price (WTA)* that they would be happy to accept during the transaction phase, prices ranging between zero and the value indicated on the front of the ticket.

2. *Subject's buying transaction*: The screen displayed a ticket from the deck that the subject did not select prior to scanning (e.g. green). By moving a cursor on a bar

subjects were required to state the *maximum buying price (WTP)* that they would accept to pay during the transaction phase. Possible prices ranged between zero and the value indicated on the front of the ticket.

3. *Subject's evaluate condition*: The screen displayed a ticket from a third deck (i.e. yellow). By moving a cursor on a bar subjects were asked to state the amount they felt the ticket was worth (i.e. evaluation price). The yellow deck was not used in the transaction phase. Possible prices ranged between zero and the value indicated on the front of the ticket.

4. *Computer's selling transaction*: The screen displayed one of the subject's own tickets (i.e. taken from the deck they had selected prior to scanning). The computer produced a *minimum selling price* for that ticket by showing a box on the price bar. The price was randomly generated such that it was greater than 0.5xEV and less than 1.5 x EV (EV=expected value of the ticket). and represented by a box positioned on the price bar . The subject was required to accept this price and was required to move the cursor in the box with the computer price.

5. *Computer's buying transaction*: The screen displayed a ticket from the deck that the subject did not select prior to scanning (e.g. green). The computer produced a *maximum buying price* for that ticket by showing a box on the price bar. The subject was required to move the cursor to within the position of the box. The price selected by the computer was determined as described above. The subject was required to accept this price and was required to move the cursor in the box with the computer price.

7.2.2.3 Transaction Phase

At the end of the scanning phase one of the four sessions was randomly assigned and one ticket for selling, and one for buying, was extracted from this session. These two tickets were used to perform a real money transaction using the Becker-DeGroot-Marschak (BDM) mechanism (Becker et al., 1964). The BDM mechanism is widely used in experimental economics as an incentive-compatible procedure for eliciting non-strategic reservation prices.

Selling transaction: One of the selling tickets was randomly extracted for the transaction (e.g. the ticket with £20 written on the front). A single ball was extracted from a bingo cage which contained a quantity of balls numbered from 1 to n (in increments of 1; where n=value written on the ticket) . The value on the ball extracted from the cage yielded the BDM buying price in pounds (e.g. £12). The amount in pence was determined by a roll of dice (e.g. £12.30). If the subject's (or the computer's) *minimum selling price* (WTA: e.g. £8 for that ticket was lower than the BDM price (e.g. £ 12.30) the subject received

the *BDM buying price* (e.g. £12.30) and sold the ticket. Alternatively, if the subject's price (e.g. £14.60) was higher than the BDM price the transaction did not go through and the subject kept his/her ticket. In this case she/he was allowed to scratch the back of her/his ticket and receive in cash the amount written on the back of the ticket.

Buying ticket transaction: One of the buying tickets was randomly extracted for the transaction (e.g. the ticket with £8 written on the front). A ball was extracted from a bingo cage which contained a quantity of balls numbered from 1 to n (in increments of 1; where n=value written on the ticket). The value on the ball extracted from the cage yielded the BDM buying price in pounds (e.g. £5). The amount in pence was determined by a roll of dice (e.g. £5.40). If the subject's (or the computer's) *maximum buying price* (WTP: e.g. £3) for that ticket was lower than the *BDM selling price* (e.g. £5.40) the transaction did not go through and the subject kept his/her money without receiving the ticket. Otherwise if the subject's price (£6) was higher than the BDM price (e.g. £5.40) she/he received the ticket paying the BDM price (e.g. £5.40) with the subject's amount cash received at beginning. In this second case, the subject was allowed to scratch the back of her/his ticket receiving in cash the winning amount of that ticket.

Subjects were given their total winnings at the end of the experiment. This was derived from 1) Cash remaining from the initial endowment they received at the start of the experiment (£36) 2) Cash gained from a selling transaction going through (at a price

determined by the BDM) 3) Cash gained from receiving the amount written on the back of a ticket (that they had either acquired through a buying transaction, or not sold).

7.2.3 Behavioural data analysis

Behavioral data were analyzed using the statistic software SPSS. I calculated, for each subject, the WTA (selling price) and WTP (buying price) for each individual ticket averaging the subject's prices across the 4 scanning sessions. These results were collapsed across all subjects for a group level analysis. The behavioural endowment effect (WTA-WTP prices discrepancies) was calculated using a double-tailed paired t-test. The evaluate condition (e.g. ticket that were not traded) was used to estimate the subjective EV (sub-EV) for each ticket and each subject. Again the difference between WTA /sub-EV and WTP/sub-EV was calculated, either at subject level and at group level, using a double-tailed paired t-test.

7.2.4 Image acquisition and data analysis

Gradient-echo T2*-weighted images (EPI) were acquired on a 1.5 tesla magnetic resonance scanner using a 30 degree titled acquisition sequence designed to reduce signal dropout in orbitofrontal lobes. Image parameters were as follows: TE 50ms; TR 3.96s; slice thickness 2mm; inter slices gap 1mm. I collected 648 volumes (across 4 sessions) per subject. T1-weighted structural images co-registered with mean EPI images and averaged across subjects to allow group level anatomical localization. Images were analyzed using the statistical parametric software SMP2 (Wellcome Department of

Imaging Neuroscience London www.fil.ion.ucl.ac.uk/spm). Preprocessing consisted of spatial realignment and normalization to a standard EPI template, and spatial smoothing (8mm kernel). The fMRI data were analyzed in an event-related manner using the general linear model, using the SPM2 statistical analysis software. After discarding the first six image volumes from each run to allow for T1 equilibration effects, image volumes were realigned and co-registered to each subject's structural scan. Subject-specific regressors of interest were assembled by convolving δ functions (corresponding to the time of onset of the choice pair, for each condition) with a canonical hemodynamic response function (HRF). I removed low frequency fluctuations by a high-pass filter with a cut-off at 128 s. A correction for temporal autocorrelation in the data (AR 1 + white noise) was applied. Parameter estimates were used to calculate the appropriate linear contrast. These contrast images were then entered into a one-sample *t* test across all subjects (random effects analysis). The primary aim of this neuroimaging analysis was to identify brain regions mediating the endowment effect. To highlights brain areas where activity correlated with the magnitude of the price discrepancy in the buy and sell domains it was constructed a General Linear Model (GLM) with 4 regressors coding each condition separately (You_Buy; You_Sell; Computer_Buys; Computer_Sells). The onset of these regressors was time locked when the initial message appeared on the screen. Conditions were modelled with a boxcar function of 8.5 seconds (the entire time in which the condition was on the screen and the subjects were stating their prices). Two other trial-by-trial parametric regressors where included for each condition: one regressor encoded the sub-

EV and the other encoded the percentage deviation in price from the sub-EV. The first parametric regressor (sub-EV) was calculated using the prices that subjects stated in the You_Evaluate condition (averaged across the 4 sessions). The second parametric regressor encoded the percentage change in subject's prices (or the computer's price) from the sub-EV for each specific ticket, in both the buying and selling domain. As an example: if a ticket had a maximum payoff of £20 and the sub-EV was £10 and subject WTA = £12; then the percentage price deviation was coded as +20%. By contrast if the subject price = £8 the percentage price deviation was coded as -20%. The two parametric regressors (sub-EV and % price deviation from sub-EV) were fully orthogonal.

Since the endowment effect reflects a disparity between the WTA and WTP prices, this neuroimaging analysis which was optimized to highlights activity correlated with the magnitude of the price discrepancy in the buy and sell domains. As such, a brain region that plays a central role in mediating the endowment effect (i.e. the WTA-WTP disparity) should exhibit greater activity on a given trial when a subject assigns a higher price in the sell domain, or a lower price in the buy domain. Hence I tested for an interaction across the parametric regressors encoding trial-by-trial percentage price deviation from the sub-EV [(You_Sell – You_Buy) – (Computer_Sells – Computer_Buys)], for each individual subject. This contrast isolates brain regions specifically associated with the endowment effect and subtracts out regions whose activity also correlate with increasing selling and decreasing buying prices in the computer condition. This interaction contrast was

subsequently taken to the random effects level to perform a group analysis in line with established procedures, by means of a one-sample t-test (Friston, 1995).

Furthermore it was also performed a between subjects analysis as follows: for each subject the size of the behavioural WTA-WTP disparity was calculated by subtracting the mean selling prices from the mean buying prices for all the tickets traded during the experiment. A simple correlation analysis was performed to identify voxels in which activity in the endowment statistical contrast [(You_Sell – You_Buy) – (Computer_Sells – Computer_Buys)] for a given subject directly correlated with the size of WTA-WTP disparity across the entire experiment.

I report results in a priori regions of interest (striatum. insula, OMPFC) motivated by the fact that these are regions typically identified in neuroimaging studies financial gain evaluation (Knutson et al., 2007; Knutson et al., 2005; Nieuwenhuis et al., 2005c; O'Doherty, 2004; Seymour et al., 2007; Tom et al., 2007) at $P < 0.001$ uncorrected for multiple comparisons ($Z<3.1$) (unless otherwise stated) and/or at $P < 0.05$ small volume correction for multiple comparison (SVC) using a 8mm sphere centred on the peak activity for the a priori regions of interest as reported by previous studies. Activations in other regions are reported if they survive whole-brain correction for multiple comparisons at $P < 0.05$. For display purposes in this paper, statistic images are shown with $Z>2.6$ corresponding to $P<0.005$.

7.3 Results

Prior to fMRI scanning participants received a deck of lottery tickets whose maximum payoff ranged from £2 to £36, as well as a cash sum (£36). The fMRI experiment consisted of four pseudorandomly presented conditions. "You_Sell" required subjects to assign a minimum selling price (WTA) for their own lottery tickets. "You_Buy" required subjects to assign a maximum buying price (WTP) for another deck of lottery tickets. "Computer_Sell" and "Computer_Buy" conditions involved a computer randomly selecting a maximum selling or buying price which subjects were passively required to accept. Additionally, a fifth condition "You_Evaluate" required subjects to assign a value to a given ticket without an ensuing transaction. This last condition provided a means to estimate, for each participant, the subjective expected value (sub-EV) of a given ticket independent of a subjects' position in a transaction. Finally, at the end of scanning, one sell and one buy trial (either "You" or "Computer") were randomly selected and used to perform an actual economic transactions using the Becker–DeGroot–Marschak (BDM) incentive compatible scheme (Becker et al., 1964) (see session 7.2.2.3). At the end of the entire experiment, subjects received a real cash payment proportional to their total winnings calculated by adding together the amount of cash remaining from the initial endowment, cash earned through the sale of a ticket, and the amount concealed on the back of tickets remained in their possession.

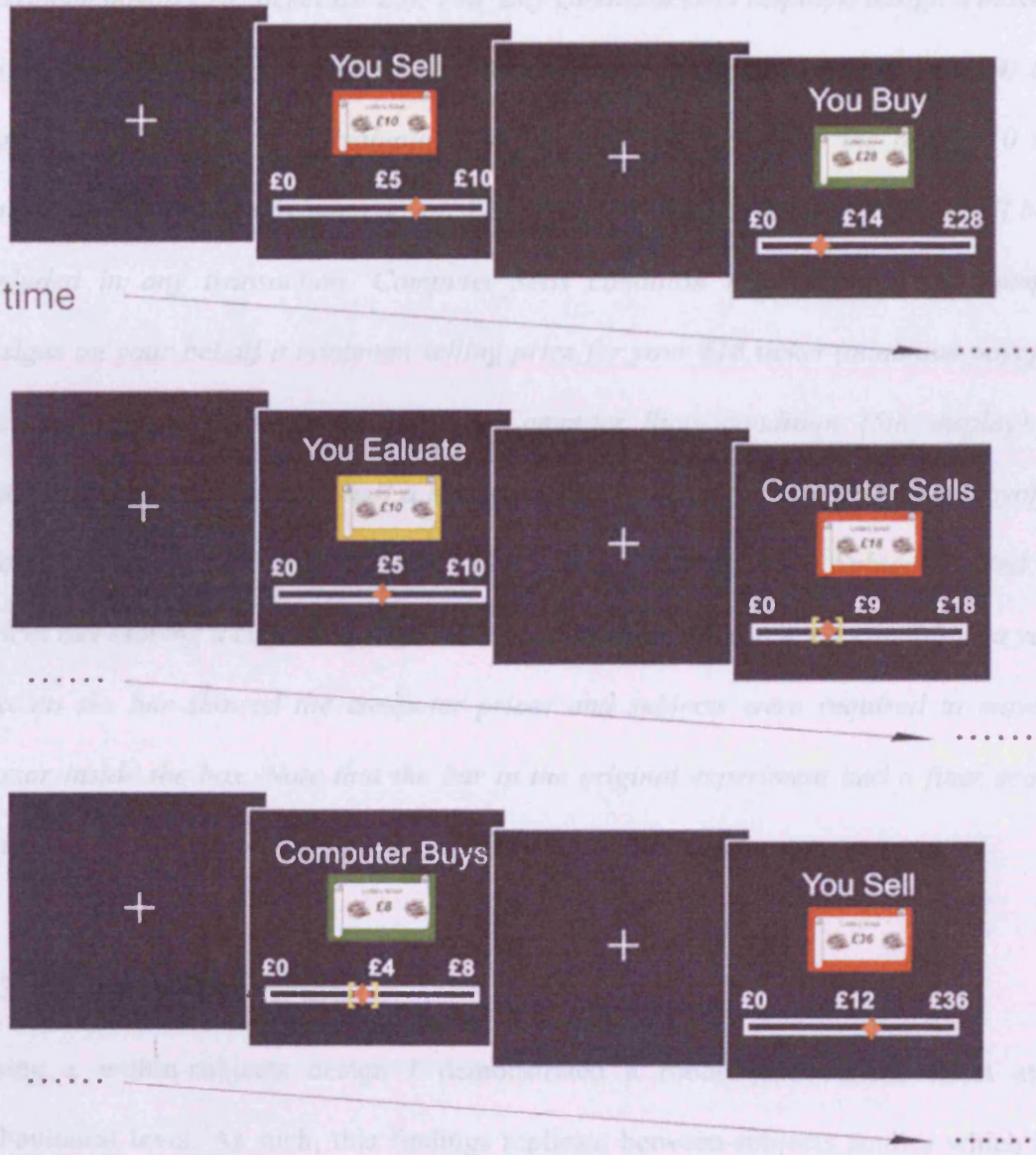

Figure VII.I. The endowment effect task.

The diagram represents schematically all the different conditions used in the scanning phase. Note that all the conditions were pseudorandomly intermixed. You_Sell condition (1st display): assign a minimum selling price for your £10 ticket (minimum payoff £0/

maximum payoff £10; ticket EV £5). You_Buy condition (2nd display): assign a maximum buying price for £28 (minimum payoff £0/ maximum payoff £28; ticket EV £14) ticket from the other deck. You_Evaluate condition (3rd display): state the price £10 ticket (minimum payoff £0/ maximum payoff £10; ticket EV £5) worth to, this ticket will be not included in any transaction. Computer_Sells condition (4th display): the computer assigns on your behalf a minimum selling price for your £18 ticket (minimum payoff £0/ maximum payoff £18; ticket EV £9). Computer_Buys condition (5th display): the computer assigns on your behalf a maximum buying price for £28 (minimum payoff £0/ maximum payoff £28; ticket EV £14) ticket from the other deck. Subjects stated their prices buy moving a cursor on a bar below the ticket. In the computer conditions a yellow box on the bar showed the computer prices and subjects were required to move the cursor inside the box. Note that the bar in the original experiment had a finer scale (5 ticks).

7.3.1 Behavioural results

Using a within-subjects design I demonstrated a robust endowment effect at the behavioural level. As such, this findings replicate between-subjects studies which have shown that there is a systematic increase in the minimum selling price (WTA) (Figure VII.II: red line), as compared to the maximum buying price (WTP) (Figure VII.II : green line) for a ticket (or object) with the same expected payoff ($P<0.0001$ $t_{17}=7.47$ double-tailed paired t-test). Importantly, in the evaluate condition, which did not involve any transactions, subjects assigned ticket prices (Figure VII.II: yellow line) that fell between

the overall average selling and buying prices, a price that was significantly different from both (buy-evaluate: $P<0.0001$ $t_{17}=9.57$; sell-evaluate: $P<0.0001$ $t_{17}=5.61$; double-tailed paired t-test).

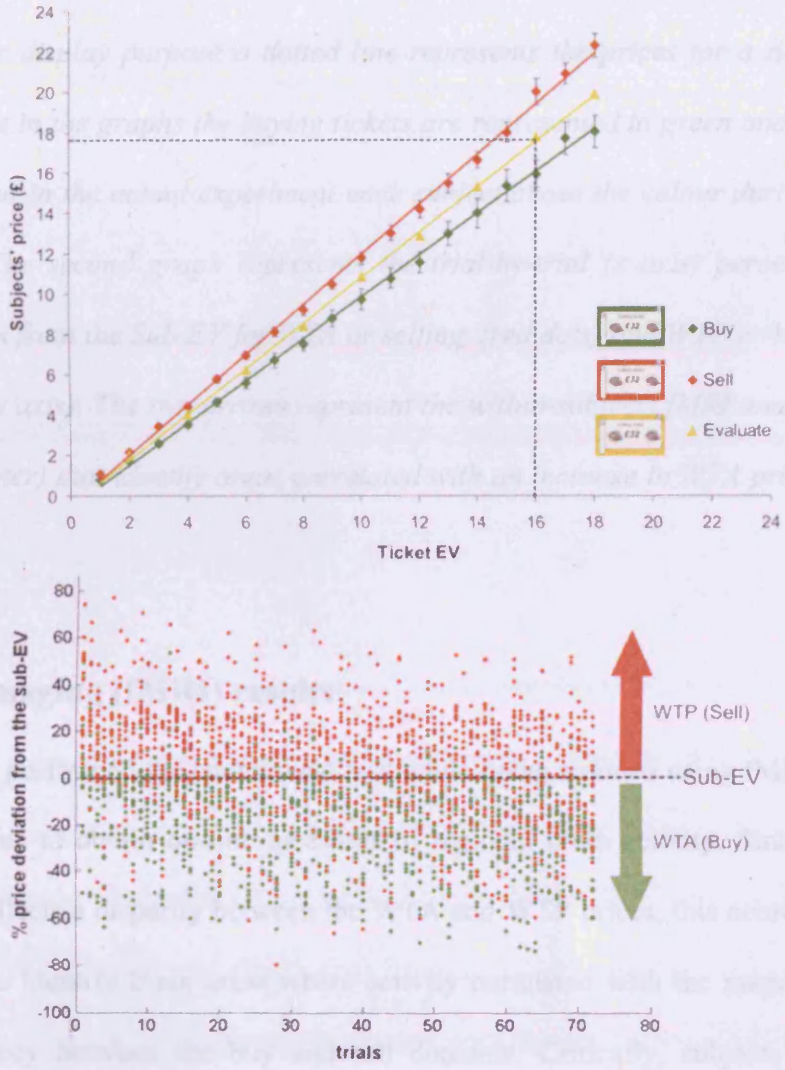

Figure VII.II. Behavioral results.

The first graph shows the prices that the all group of subjects (n.18) assigned to each ticket during the scanning phase. The ticket expected value (EV) it is represented on the x axis and the subjects' prices are on the y axis. The minimum buying prices (WTP – green line) are significantly lower than the maximum selling price (WTP – red line). The yellow

represent the evaluation prices that it is used to calculate the subjective ticket EV (Sub-EV). For display purpose a dotted line represents the prices for a ticket with £16 EV. Note that in the graphs the buying tickets are represented in green and the selling tickets in red but in the actual experiment each subject chose the colour during the endowment phase. The second graph represents the trial-by-trial (x axis) percentage (%) prices' deviation from the Sub-EV for WTA or selling (red dots) and WTP or buying (green dots) tickets (y axis). The two arrows represent the within-subjects fMRI analysis (see below in the chapter) that identify areas correlated with an increase in WTA price and a decrease in WTP.

7.3.1 Imaging (fMRI) results

Subjects performed the endowment task while being scanned using fMRI, a situation that enabled us to obtain on-line measures of regional brain activity. Since the endowment effect reflects a disparity between the WTA and WTP prices, this neuroimaging analyses sought to identify brain areas where activity correlated with the magnitude of the price discrepancy between the buy and sell domains. Critically, subjects exhibited a high degree of variability in the prices assigned to each ticket such that the magnitude of the percentage deviation of the WTA or WTP from the sub-EV (see methods) showed trial-to-trial variability. I therefore used individual subjects' prices, in both the sell and buy conditions (for both You and Computer), to construct four regressors coding for trial-by-trial percentage price deviations from the respective sub-EV (calculated on the basis of

the evaluation tickets). An additional regressor coding for the sub-EV of each individual ticket (calculated from the evaluate trials) was also included in the analysis. Of note, although the real expected ticket value (ticket-EV) was usually close to sub-EV I used the latter to calculate the percentage deviation in selling or buying prices. Indeed, using the sub-EV rather then ticket-EV is advantageous since it controls for a well-described distortion of outcome probability and general risk attitude (Kahneman and Tversky, 1979). These regressors were convolved with the haemodynamic response function (HRF) and used to construct a general linear model (GLM) for the statistical data analysis (Friston, 1995).

We reasoned that a brain region that plays a central role in mediating the endowment effect (i.e. the WTA-WTP disparity) should exhibit greater activity on a given trial when a subject assigns a higher price in the sell domain, or a lower price in the buy domain. Hence, these critical contrasts sought to identify brain areas where activity followed this prescribed pattern in our trial-by-trial parametric analysis (Figure VII.II b). In order to isolate brain regions specifically associated with the endowment effect, I also subtracted out non-specific activity correlated with increasing selling and decreasing buying prices in the computer condition.

Bilateral ventral striatum showed a pattern of activity consistent with the behavioural endowment effect (i.e. WTA>WTP), positively correlating with an increase in selling prices and a reduction in buying prices, an effect expressed solely when subjects

themselves were agents in the evaluation process from the act (i.e. subtracted out activity correlated with the computer conditions). I confirmed that this ventral striatal activity was not driven selectively by either the buy or sell condition, but by both conditions by examining correlations in the buy and sell domains separately (activity peaks: [x=26,y=14,z=0 $Z_{(score)}$ =3.56 62 voxels] P<0.001 uncorrected and P<0.05 SVC [x=-28,y=-6,z=-4 $Z_{(score)}$ =2.94 35 voxels]; [x=-16,y=6,z=8 $Z_{(score)}$ =2.86 14 voxels] P<0.005 uncorrected and P<0.05 SVC) (Figure VII.III). Thus, this region correlated significantly with increasing prices in the You_Sell condition (activity peak: [x=26,y=14,z=0 $Z_{(score)}$ =3.57 26 voxels] P<0.001 uncorrected and P<0.05 SVC), and decreasing prices in the You_Buy condition (activity peak: [x=24,y=20,z=-6 $Z_{(score)}$ =3.36 15 voxels] P<0.001 uncorrected and P<0.05 SVC), considered separately. Importantly, activity in the striatum did not correlate, even at a liberal threshold of p<0.01 uncorrected, either with sub-EV nor with the ticket-EV. I also identified increased bilateral anterior insula activity in the key interaction contrast (Figure VII.III and session 7.5). In contrast to the pattern of activation observed in the ventral striatum, insula activity correlated with decreasing prices in the You_Buy condition and not with increasing prices in the You_Sell condition.

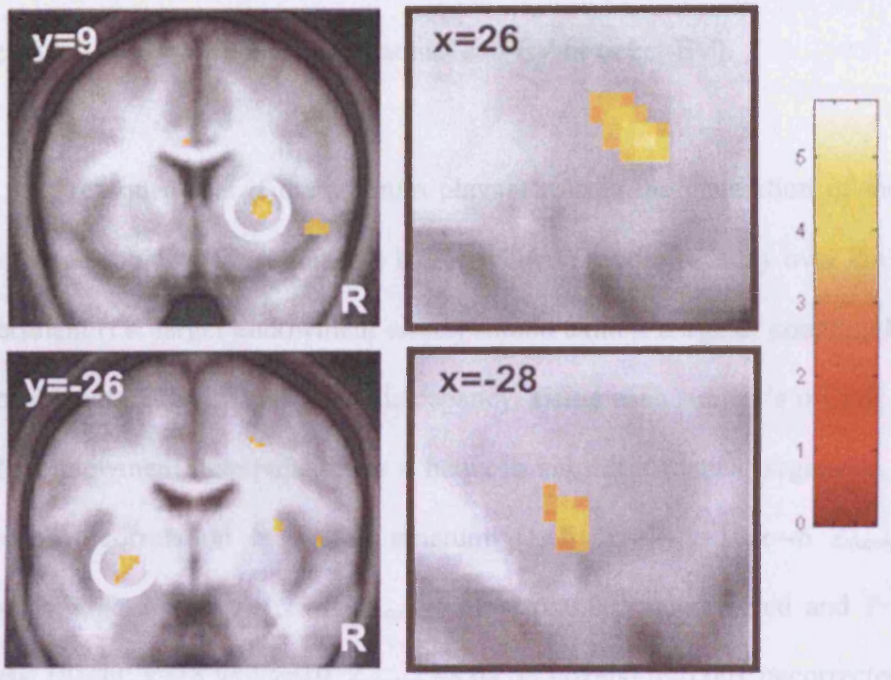

Figure VII.III. Within subjects fMRI results.

Striatal activations correlated with an increase in subjects' selling prices (WTA) price and a decrease in subjects' buying prices (WTP) subtracted from the increase in computers' selling prices (WTA) price and the decrease in computers' buying prices (WTP). The first panel shows the BOLD activation in anterior right striatum [x=26, y=14,z=0] in a coronal and sagittal plane, the second panel shows the activity of posterior left striatum [x=-28,y=-6,z=-4] in a coronal and saggital plane

These results demonstrate that ventral striatal activity tracks, on a trial-by-trial basis, in both buy and sell domains, a discrepancy between the price that subjects assign to a given ticket and their sub-EV. This pattern indicates that striatal activity reflects a computation of value scaled relative to a reference point (namely the deviation from the sub-EV) and

contingent upon a subject's position in the economic transaction, rather than computation based upon absolute value (i.e. the actual sub-EV or ticket-EV).

We next reasoned that if the striatum plays a role in the generation of the endowment effect, then subjects who showed a larger WTA-WTP discrepancy over the course of the experiment (i.e. larger endowment effect) should exhibit a tighter coupling between trial-by-trial striatal activity and price discrepancy. Using each subject's overall susceptibility to the endowment manipulation as a between subject statistical regressor, I observed a significant correlation in ventral striatum: [Left: x=-14,y=10,z=-6 $Z_{(score)}$ =3.88 116 voxels] [Right: x=18,y=4,z=-6 $Z_{(score)}$ =2.94] $p<0.005$ uncorrected and $P<0.05$ SVC 5 voxels; [Right: x=18,y=4,z=10 $Z_{(score)}$ =3.04 55 voxels] $p<0.001$ uncorrected and $P<0.05$ SVC). Thus, activity in ventral striatum not only tracked a price discrepancy on a trial-by-trial basis but also predicted individual subjects' susceptibility to the endowment effect manipulation.

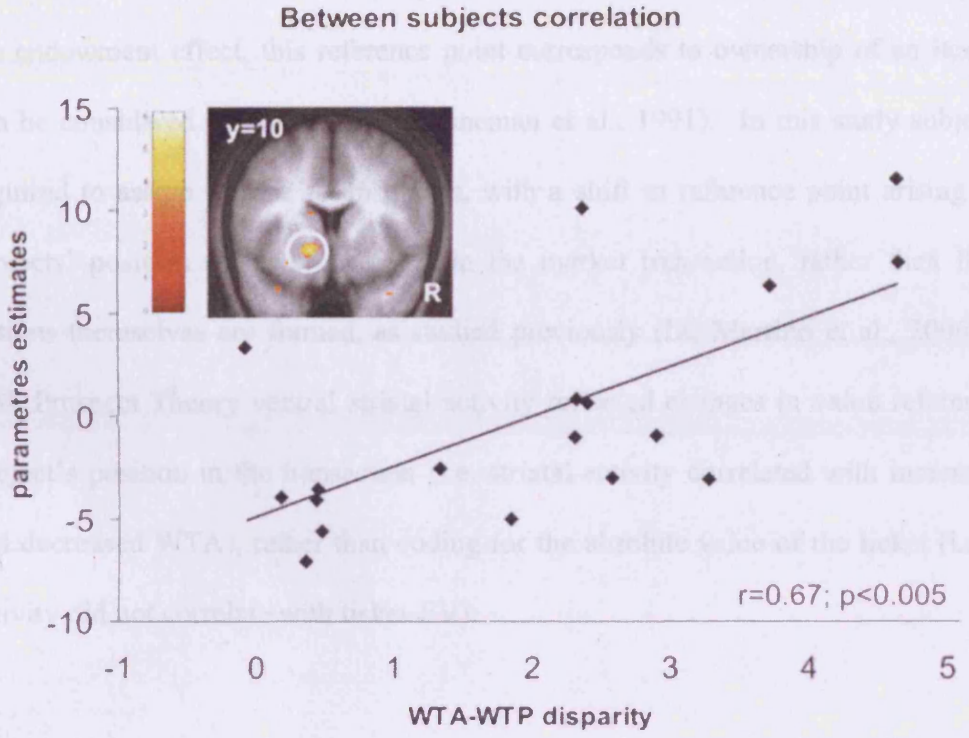

Figure VII.IV. Within subjects fMRIresults

This graphs represent the between subjects the significant (r=0.67; p<0.005) correlation between the BOLD activity (x axis) in the ventral striatum (SPM figure) and the size of WTA-WTP disparity (y axis) for each individual subject (black diamonds dots)

7.4 Discussion

Classical economic theory implies that the price assigned to an object during a costless market transaction (in which income effects are small) should reflect its absolute value (Willig, 1976), and is independent of a subject's role (i.e. as buyer or seller) in the transaction. By contrast, prospect theory proposes that the value of an item is not

appraised as an absolute quantity, but is calculated with respect to a reference point. In the endowment effect, this reference point corresponds to ownership of an item, which can be considered the *status quo* (Kahneman et al., 1991). In this study subjects were required to assign a price to an option, with a shift in reference point arising out of a subjects' position as buyer or seller in the market transaction, rather than from how options themselves are framed, as studied previously (De Martino et al., 2006). In line with Prospect Theory ventral striatal activity reflected changes in value referenced to a subject's position in the transaction (i.e. striatal activity correlated with increased WTP and decreased WTA), rather than coding for the absolute value of the ticket (i.e. striatal activity did not correlate with ticket-EV).

A considerable body of evidence implicates the striatum in encoding the motivational value of a stimulus, via a dopaminergic prediction error signal that registers the difference between an expected and obtained reward (Montague et al., 2006b; O'Doherty, 2004; Schultz, 2002; Schultz, 2006; Schultz et al., 1997). Several recent neuroimaging studies employing financial decision making tasks provide evidence that the human striatum computes several microeconomics parameters of anticipated gains (e.g. expected value, magnitude and probability of a gamble) (Knutson et al., 2005; Tobler et al., 2007; Yacubian et al., 2006) as well as predicting the likelihood of purchasing an item (Knutson et al., 2007). However, despite a wealth of behavioural evidence suggesting that in some situations humans encode value relative to a reference point, rather than in an absolute

fashion, previous studies have not investigated the neural basis of such computations. Here, we show that striatal representations index reference-level dependent value during market transactions, a situation when neural computations of value must incorporate the trade-off between the cost of the item and its expected value, rather than simply the magnitude of an expected gain (e.g. see (Knutson et al., 2005)).

The pattern of ventral striatal activity I describe dovetails with recent data which suggests ventral striatal responses to financial outcomes reflect a prediction-error type signal, (Nieuwenhuis et al., 2005c; Yacubian et al., 2006). The efficient estimation of value requires that the computation of reward magnitude is scaled on a predicted magnitude (Tobler et al., 2005) or that the value of a current event is computed in relation to an event that has not happened yet (Montague and Berns, 2002). These findings indicate that during market exchanges this value computation is dynamically referenced with respect to a subjects' role as a buyer or seller as predicted by prospect theory (Kahneman and Tversky, 1979). Further, these results offer new insights into how encoding within ventral striatum may underlie loss aversion (also see (Seymour et al., 2007; Tom et al., 2007)), a psychological phenomenon proposed to play a key role in the generation of the endowment effect.

How value is encoded in the brain remains a key question in neuroscience (Dayan and Abbott, 2001; Montague et al., 2006b), microeconomics (Camerer et al., 2005; Glimcher and Rustichini, 2004), reinforcement learning (Barto and Sutton, 1998) and animal

behaviour (Dickinson and Balleine, 1994; Schultz, 2004). The present study points to a neural basis for a core concept in behavioural economics, namely the computation of reference-dependent value, and localises this function to the ventral striatum. The wider implication of these findings is that, during economics transactions, human brains may represent value from a relative rather than absolute metric.

7.5 Appendix (SPM significant activation tables)

Table 1. Brain areas significantly more active during an increase in selling prices and a reduction in buying prices subtracted out non-specific activity correlated with increasing selling and decreasing buying prices in the computer condition [(You_Sell – You_Buy) – (Computer_Sells – Computer_Buys)]

All values $p<0.001$ uncorrected unless otherwise stated.
*statistically significant activation (see Methods)

Region	Laterality	x	y	z	z-score
Striatum *	R	26	14	0	3.56
	L	12	2	-20	2.86 ($p<0.005$)
Anterior Insula *	L	-48	22	4	3.69
	R	46	4	-8	3.62 ($p<0.005$)
Fusiform Gyrus	R	26	-42	-20	3.96
Occipital cortex	R	12	-84	22	3.76
		30	-86	22	3.92

Table 2. Brain areas significant correlation between each subject's overall susceptibility to the endowment manipulation and the interaction [(You_Sell – You_Buy) – (Computer_Sells – Computer_Buys)]

All values $p<0.001$ uncorrected unless otherwise stated.
*statistically significant activation (see Methods)

Region	Laterality	x	y	z	z-score
Striatum *	L	-14	10	-6	3.88
	L	-28	-12	10	3.56
	R	18	4	10	3.04
	R	18	4	-6	2.94 ($p<0.005$)
Anterior Insula *	L	-44	24	2	3.80
Posterior Insula	R	42	-22	2	4.24
Ventromedial prefrontal cortex (VMPFC)		-4	38	-20	3.50
Superior temporal gyrus	L	56	-8	-14	4.32
	R	58	-4	-18	3.85
Occipital cortex	L	-6	-76	4	4.24
	R	8	-76	22	3.31

Chapter 8

General discussion and conclusions

In this chapter I consider the experiments described in the previous chapters in a broader context, and offer general conclusions to this thesis.

8.1 Overview

Emotional information is widely acknowledged to play a key role in shaping human behaviour. The aim of this thesis has been to advance our understanding of the neurobiological mechanisms of how emotional information modulates the high cognitive abilities at both input and output level.

Emotions are useful markers in guiding an organism through life. Humans, like other animals, have limited computational abilities that must be allocated in an efficient way to guarantee their survival. Emotions function to prioritize the accessing of information at input level by modulating attentional capacities. The modulation of attention by emotion provides a clear evolutionary advantage in facilitating quick responses to potential threat. Emotions also modulate the decision-making processes that influence behavioural outputs. In contrast to the emotional modulation of attention, the impact of emotional information on the decision-making process is often seen, erroneously in most instances, as engendering suboptimal or even so-called "irrational" behaviour. For this reason a large majority of economic accounts of decision-making has neglected the role of emotions in shaping human choices.

The empirical work presented in the previous chapters is centred on two central issues 1) How the neural processing of stimuli is affected by their emotional content, and 2) How this emotional content influences decision-making processes and shapes the computation of value. In this discussion I attempt a reconciliation of the aforementioned contrasting views on emotion, and I aim to show how these process have a high level of concordance at a theoretical and neurobiological level.

8.2 Mechanisms by which emotional stimuli enhance attentional processing

In chapter three and chapter four of this thesis I addressed the problem of how emotional stimuli enhance attentional processing by using a modification of an attentional blink paradigm (AB) in the contexts of an fMRI experiment (chapter three) and a drug study (chapter four). This paradigm allowed me to investigate how the emotional stimuli modulate the allocation of limited attentional resources in time. A common finding of the attentional blink task is the difficulty of detecting a second target if it follows too closely in time a first target (Raymond et al., 1992). The interesting aspect of this paradigm is that AB is strongly susceptible to the emotional nature of the target.

Emotional targets are detected and processed in conditions in which similar neutral targets are extinguished from awareness (Anderson and Phelps, 2001). Unlike the previous studies, which I reviewed in section 1.2 of the introductory chapter, this approach allowed me to investigate how emotional information recruits supplementary resources in conditions of attentional overload. Another advantage of this experimental approach is the possibility of getting a quantitative behavioural measure (i.e. correct target detection) of the attentional processing of emotional compared with neutral stimuli. Moreover, while previous research (Vuilleumier and Schwartz, 2001b; Vuilleumier and Schwartz, 2001c) has focused on how emotional information engages spatial attentional resources, the attentional blink paradigm allows us to investigate how attention is

engaged in time. Two different versions of this paradigm were implemented in the experiments described in chapter three and chapter four.

Two concurrent biological models have been proposed about the emotional control of attention, a *bottom-up* and a *top-down* mechanism respectively. The *bottom-up* model predicts that the emotional valence of a target enhances the detection of the targets themselves, by triggering activity in cortices normally involved in processing that type of stimuli (i.e. visual cortex, auditory cortex). This model assumes that the amygdala is involved in tagging the stimuli as emotional and in boosting cortical processing. The *bottom-up* model is supported by a wealth of empirical data that shows how fearful stimuli produce increased activity in the sensory cortical areas (Lane et al., 1997b; Lang et al., 1998; Paradiso et al., 1999; Simpson et al., 2000; Wik et al., 1993). *Bottom-up* control seems to be an essential aspect of the processing of emotional targets. Indeed, it has been shown that there is also an increase in cortical processing when emotional stimuli are unattended, and consequently do not reach the subjects' awareness (Dolan, 2002; Pourtois et al., 2006; Vuilleumier et al., 2001).

However, it remains unclear whether *bottom-up* control alone can account for the increased awareness of or attention to emotional stimuli. A *top-down* model predicts an involvement of frontal areas (in particular OMPFC and rACC) in modulating the attention capacity for emotional targets. This model is supported by several investigations that found an increase in activity in these frontal cortical areas when subjects were

engaged in an attention task for emotional targets (Elliott and Dolan, 1998; Elliott et al., 2000; Lane et al., 1997a). Nevertheless, it is unclear whether this *top-down* control contributes to a behavioural enhancement in detection of emotional stimuli in situations of attentional overload.

The fMRI study presented in chapter three was designed to investigate the aforementioned questions. In particular, this study employed a version of the attentional blink paradigm in which the first targets were constituted by images representing "places" and the second targets by images representing "faces" (either neutral or fearful). This modified paradigm allowed us to distinguish activity elicited by the face target T2 (uncontaminated by the activity due to place target T1) in the fusiform face area (FFA) (Kanwisher et al., 1997). Using this experimental setup I was able to address the contribution of both mechanisms (i.e. *top-down* and *bottom-up*) in mediating the enhanced detection of the emotional targets. My findings showed that although activity in the FFA increased for emotional stimuli as predicted by the *bottom-up* model, this activity did not predict the increased behavioural detection of emotional targets. On the contrary, activity in the frontal regions, namely rostral anterior cingulate cortex (rACC), predicted an enhanced detection of emotional targets evident at a behavioural level. These results support the hypothesis that a *top-down* frontal control plays a crucial role in directing human attention towards emotional targets in conditions of limited resources.

Although this experiment demonstrated that the enhanced detection of emotional stimuli requires a *top-down* control elicited by the frontal cortex, it is still unclear how this frontal control is influenced by neuromodulators. The three experiments described in chapter four were designed to answer this question. These experiments implemented a modification of the AB paradigm (used in the fMRI experiment discussed above) together with a pharmacological manipulation of the adrenergic system. The choice to focus the investigation on the adrenergic system was guided by previous research that has indicated the key role played by noradrenaline in the control of attention and arousal (Aston-Jones and Cohen, 2005; Jouvet, 1969; Robinson and Berridge, 1993).

In the first experiment, described in chapter four, I showed that the administration of the beta-blocker propanolol produced a reduction in the detection of the second target T2 independently of its emotional valence. In the second experiment I replicated the results of the first experiment (i.e. impairment of target detection by propanolol), showing in addition that the administration of reboxetine (an inhibitor of NE reuptake) produces a selective boost in the detection of emotional targets, without affecting the detection of neutral ones. Finally, in the third experiment I confirmed that the effect of propanolol is centrally mediated and dose-dependent.

These results support the adaptive gain model proposed by Aston-Jones and Cohen (Aston-Jones and Cohen, 2005). This model is the most comprehensive theoretical account to date of the noradrenergic (NE) function in modulating attentional capacity.

The gain adaptive model is mainly based on experimental evidence that the phasic release of NE is associated with an increased target detection. On the contrary, an increase in tonic baseline level of NE boosts the distractibility of an animal, impairing the target identification (Aston-Jones et al., 1991; Aston-Jones et al., 1994). Thus, the adaptive gain model proposes that phasic release of NE is responsible for orienting attention towards motivationally relevant stimuli. It has recently been proposed at a theoretical level that the phasic release of NE can predict the dynamics of the AB (Nieuwenhuis et al., 2005b) (i.e. AB-NE model). Note that the original AB-NE model does not account for the emotional modulation of the AB paradigm. In order to explain the data presented in chapter four I formulated an extended version of this model able to account for the enacted detection of emotional targets (for a full description of this model see chapter four session 4.4). The original AB-NE model proposes that the detection of targets is a consequence of increased phasic discharge of the NE neurons in the locus coeruleus. Based on evidence from an animal literature that phasic release of NE is also elicited by the presentation of emotional stimuli, I proposed that the enhanced detection of emotional stimuli is due to the increased release of NE triggered by the emotional valence of the stimuli. A prediction of this hypothesis is that the block of the post-synaptic beta-receptors with propanolol should impair the detection of both emotional and neutral targets. This prediction is confirmed by the experiments 1 and 2 described in chapter four. On the contrary, the increase in the concentration of NE in the synaptic cleft caused by reboxetine produces two opposite effects: firstly, it inhibits the release of NE at the

level of the locus coeruleus by the alpha-2 pre-synaptic receptors; secondly, it boosts the NE signal from the beta and alpha-1 post-synaptic receptors, in particular within the frontal cortex where these receptors are most abundant (Sacchetti et al., 1999).

One intriguing possibility is that an increase in NE activity at the frontal level produced by reboxetine interacts synergistically with an increase in NE concentration produced by emotional targets. This functional interaction in `frontal cortex would explain why reboxetine selectively boosts the identification of the emotional stimuli without affecting the identification of neutral stimuli. This hypothesis is supported by the fMRI experiment described in chapter three, where I demonstrated that the increased detection of emotional targets is associated with a *top-down* frontal control as shown by the enhanced activity in rACC.

In conclusion, the experiments presented in chapters three and four show that emotional information modulates attention capacity by a *top-down* control from rACC and that this control is likely to be mediated by an increase in NE phasic release triggered by the emotional valence of targets.

8.2 Mechanisms by which emotional information is integrated in the decision process changing the brain value computation

In chapters five, six and seven I investigated how emotional information shapes decision-making and affects the neural computation of value. These issues were approached by looking at psychological phenomena not predicted by current rational modesl of choice developed in economics (Arrow, 1982; Luce, 1957; von Neumann and Morgestern, 1944). Using economic models as a benchmark against which to contrast psychological and neurobiological hypotheses is a very fruitful approach top decision making. In fact, economics has produced robust theoretical tools to investigate preference construction. Utility, risk, revealed preferences, efficiency and optimality are all useful conceptual tools for the investigation of how decisions and values are computed by the human brain. Nevertheless, as mentioned in section 1.3.1 of the introductory chapter, economic theories often fail to capture the real complexity of human choice behaviour. One of the major weaknesses in the economics neo-classical account of decision making is that the role of the emotions in shaping human choice has not been acknowledged. As discussed previously, emotions critically modulate every aspect of cognition. Here, I discuss how emotional information affects human behaviour at the output level, where preferences are revealed and actions performed.

My initial investigation focused on the contextual emotional information embedded in the presentation of choices. In chapter five I approached this problem by exploring the

neurobiological underpinnings of the "framing effect", a key element of prospect theory (Kahneman and Tversky, 1979; Kahneman and Tversky, 2000). The framing effect is a paradigmatic violation of an axiom at the core of the rational choice theory, namely the invariance axiom (von Neumann and Morgestern, 1944). This axiom prescribes that a variation of irrelevant features in the presentation of options, or outcomes, should not affect choice. Nevertheless, countless examples show that humans are indeed strongly and systematically affected by the way in which options are presented or "framed" (Kahneman and Tversky, 2000).

It has been proposed that the framing effect arises from an affective heuristic, underwritten by an emotional system, which is susceptible to contextual emotional information (Slovic et al., 2002). The experiment presented in chapter five was designed to test the neurobiological validity of this hypothesis. At the behavioural level, subjects showed risk-averse behaviour when options were cast as gain and risk-seeking behaviour when options were cast as loss as predicted by prospect theory (Kahneman and Tversky, 1979). The imaging results showed that amygdala activity was underpinning this pattern of choice. In contrast, ACC activity was consistent with a pattern of behaviour incongruent to the one elicited by the framing manipulation. These findings suggest that an initial emotional response was responsible for the change in risk attitude, and that the suppression of this response induced conflict. This interpretation of the results is compatible with the theoretical account of risk behaviour that proposes that humans perceive and process risk 'as' feeling (Loewenstein et al., 2001). Furthermore, many

theoretical accounts of decision-making have proposed a "two-system" model of judgment arising from the interaction between analytic and heuristic systems (Evans, 2003; Kahneman, 2003). According to this interpretive framework emotional cues present in the verbal labelling of options are processed by this heuristic system, and this system in turn affects the pattern of choices.

The study presented in chapter five supports the latter view and shows that amygdala activity plays a critical role in evaluations dominated by an heuristic decision system (Kahneman and Frederick, 2007). Finally, I showed that activity in the orbito and medial prefrontal cortex (OMPFC) predicts individual difference in susceptibility to the framing manipulation. More precisely, an increase in activity in this frontal area was associated with a diminished susceptibility to the framing effect and consequently with a more ratiional pattern of behaviour. It is noteworthy that there are strong reciprocal connections between the amygdala and the OMPFC (Amaral, 1982; Wallis, 2007). These anatomical interactions may have important functional roles in both decision-making and attention, as discussed previously.

One broader interpretation of the framing results is that frontal activity inhibits the initial emotional response elicited by amygdala activity by *top-down* control. This interpretation is supported by the empirical evidence from Damasio and colleagues (see session 1.1.3 of the introductory chapter) (Damasio et al., 1994). These authors demonstrated that patients

with lesions in OFC show impulsive behaviour, which may reflect the fact that they are unable to overwrite their initial emotional response (Bechara et al., 1994). In terms of the two-system theoretical account, my results suggest that the OMPFC is likely to impact on the construction of preferences by integrating the emotional and analytic information, thus underpinning more "rational" (i.e. description-invariant) behaviour.

My overall conclusion from the findings described in chapter five is that it suggests a model in which the framing bias reflects an affect heuristic by which individuals incorporate a potentially broad range of additional emotional information into the decision process. A puzzling aspect of these results is that although an affective heuristic often leads subjects toward irrational or suboptimal decisions, it was clearly favoured by evolution. An interesting possibility is that, in evolutionary terms, this mechanism may confer a strong advantage, because such contextual cues may carry useful, if not critical, information. This is particularly true for social animals like humans that are required to interpret the subtle social cues that communicate elements of (possibly unconscious) knowledge.

The experiment described in chapter six sheds light on the above hypothesis. This study investigated the effect of a framing manipulation on individuals affected by autism spectrum disorder (ASD) compared with matched control subjects. ASD is a developmental disorder characterized by widespread abnormalities of social interactions and communication, as well as severely restricted interests and highly repetitive

behaviour (Baron-Cohen and Belmonte, 2005; Frith and Happé, 2005). The results of this experiment show that ASD subjects are less susceptible to the framing manipulation in comparison with the control group.

In this study we also measured the skin conductance response (SCR) while the subjects were performing the task. The SCR is a well-established marker of an autonomic emotional reaction (Venables, 1991). The analysis of these data showed that while in the control subjects a SCR response was associated with the negative frame presentation, in the ASD group this response was totally abolished. Although the decision-making in ASD subjects have not been fully investigated, these results support the prediction from the current theoretical models on autism. In particular, the "empathizing-systemizing" theory in autism proposes that ASD is characterized by both an impoverished emotional response in social contexts and remarkable analytic strength (Baron-Cohen and Belmonte, 2005). The increased systemizing ability in ASD individuals is associated with an enhanced attention to details at the expense of a more global processing. This aspect of ASD has been replicated by several experiments using different paradigms (Baron-Cohen and Belmonte, 2005; Jolliffe and Baron-Cohen, 2000; O'Riordan et al., 2001; Plaisted et al., 1998; Shah and Frith, 1993) and it is the core of the "weak coherence hypothesis" of autism (Frith and Happé, 1994).

The inability to integrate contextual emotional information and the enhanced ability to perform analytic processing may be the basis for a reduced susceptibility of ASD individuals to the framing manipulation. This interpretation is supported by lack of SCR autonomic emotional responses to the negative frame presentation. In the fMRI study presented in chapter five I showed that activity in the amygdala underpins the framing bias. An intriguing possibility is that the lack of SCR in subjects affected by ASD may reflect a reduced amygdala response to the emotional contextual information embedded in the option presentation. This hypothesis is supported by convergent evidence for an amygdala deficit in autism (Baron-Cohen et al., 2000). Further experiments are required to test this hypothesis.

Interpreting these results in the framework of the "two-system" decisions model I suggest that ASD subjects may suffer from an impairment of the affective heuristic decision-system compensated by an enhancement of analytic capacities. This interpretation is also in keeping with the empathizing-systemizing theory presented above (Baron-Cohen and Belmonte, 2005). As mentioned earlier in this section, a heuristic decision-system is highly susceptible to the emotional information carried by verbal labelling of the options. Conversely, an analytic decision-system is by definition not influenced by contextual information irrelevant to the choice outcomes. Human life is characterized by many situations in which an ability to interpret subtle contextual emotional cues is advantageous. Social interactions are paradigmatic examples of such situations where the information is either excessive or overly complex to be efficiently processed by a full

analytic system. In these situations, the use of a quick intuitive heuristic can be extremely helpful. An affective heuristic processing complementing an analytic one may had been significantly advantageous in human evolution. Nevertheless, in modern society, where individuals are required to deal with symbolic and abstract artefacts, this affective heuristic may render human choices inconsistent.

In section 1.1 of the introductory chapter of this thesis, I defined emotions as complex psychological and physiological states that inform an organism about the value of an action or events, which in turn influences global aspects of behaviour. In chapters five and six I investigated the neural mechanisms by which this contextual emotional information impacts on choice behaviour. The experiment described in chapter six instead explored how value computation is informed and shaped by contextual emotional information. This study was inspired by a wealth of evidence showing that the attribution of value to an object is highly context-dependent. People value a good they own substantially more than an identical good available for purchase, even when the transaction costs are null. Prospect theory embraces such findings by proposing that the value of a good (or an option) depends critically on a reference point, such that buyers evaluate the object as a potential gain whereas sellers view the transaction as a potential loss, demanding a higher price due to loss aversion (see session 1.3.2 chapter one). This effect, described initially by Thaler (Thaler, 1980), the "endowment effect", shares some features with the framing effect described in chapters five and six. In the framing effect

the contextual information is explicitly given by the labelling of options, in the endowment effect the context is implicitly set by the subjects' relation (as buyer or seller) to an item.

Investigating the neurobiology that underpins the endowment effect, allowed me to dissect how the human brain performs a subjective value computation, and how this computation is shaped by context. The experiment showed that when people appraise the value of an object or an option this value is computed as a change from a "status quo" that in the endowment effect is represented by the ownership of the item (Kahneman et al., 1991). These findings contrast with the predictions of classical utility theory, which assumes that people compute value in an absolute fashion. At the neurobiological level, I showed that a reference-dependent value computation is localized to ventral striatum. Striatal activity in this study accounted for both the trial-by-trial price discrepancies and the susceptibility to the endowment effect across subjects. While the study described in chapter five showed how contextual emotional information changes the output of choice behaviour, this study showed how this information is already incorporated at the level of preference construction and value encoding.

8.3 Final conclusions

In this PhD thesis I combined different experimental approaches to investigate the neurobiological mechanisms by which emotional information modulates attention and decision-making. These two processes control the way in which organisms interact with

the external environment at both the input and the output level. Individuals have to deal with a large amount of information to ensure survival in a highly changeable environment. Human brains have developed efficient strategies to solve such uncertainty. One of these is by 'tagging' as emotional information that might be relevant for an individual's survival. Attention prioritizes the processing of this type of information, which in turn exerts an influence on behaviour by modulating a decision process. In this thesis I show that even in conditions of limited attentional resources individuals can still fprocess emotional information. The human brain achieves this through a *top-down* mechanism that it is likely to involve a phasic release of noradrenaline elicited by the emotional stimuli. This capacity has a clear evolutionary advantage in that it liberates individuals to engage in demanding tasks, whilst retaining an ability to respond to potential treat. In the second part of this thesis I dissected the neurobiological mechanisms by which this emotional information, embedded in the context in which options are presented, affects the decision-making process. I showed how an affective heuristic based on processing in the amygdala controls this process, and how the striatum incorporates this information at the level of value computations. I also showed that, similarly to attention, a frontal *top-down* mechanism modulates decision-making by integrating this emotional information with other type of information. Nevertheless, in the examples that I have used to investigate these mechanisms (i.e. framing effect and endowment effect), this contextual emotional information does not carry any supplemental information for the decision outcomes. As such, the change in behaviour

produced has been often defined as "irrational" by the canonical decision-making model developed in economics (Arrow, 1982; von Neumann and Morgestern, 1944). I argue, on the contrary, that the incorporation of emotional information into the decision process may be advantageous in other kinds of context, for instance in social interactions as suggested by the experiment on autistic spectrum disorder (ASD). Although this hypothesis requires further investigation, it may reconcile the contrasting views on the role of the emotion in decision-making.

In conclusion, the work presented in this PhD thesis shows how the combination of experimental (i.e. fMRI experiment, pharmacological studies and patient study) and theoretical approaches (i.e. psychology, economics and neuroscience) can illuminate the mechanisms through which emotion influences human behaviour from perception to action.

References

Adolphs, R. (2002). Neural systems for recognizing emotion. Curr Opin Neurobiol *12*, 169-177.

Adolphs, R. (2006). How do we know the minds of others? Domain-specificity, simulation, and enactive social cognition. Brain Res.

Aguirre, G. K., Zarahn, E., and D'Esposito, M. (1998). The variability of human, BOLD hemodynamic responses. NeuroImage *8*, 360–369.

Allais, M. (1953). La psychologie de l'home rationnel devant le risque: critique des postulats et axiomes de l'école Américaine. Econometrica *21*, 503-546.

Amaral, P., Pitkanen and Carmichael (1982) 'The Amygdala: Neurobiological aspects of emotion, memory and mental dysfunction.

Anderson, A. K., and Phelps, E. A. (2001). Lesions of the human amygdala impair enhanced perception of emotionally salient events. Nature *411*, 305-309.

Arkes, H. R., Faust, D., Guilmette, T. J., and Hart, K. (1988). Eliminating the hindsight bias. Journal of Applied Psychology *73*, 305-307.

Armony, J. L., and Dolan, R. J. (2002). Modulation of spatial attention by fear-conditioned stimuli: an event-related fMRI study. Neuropsychologia *40*, 817-826.

Arrow, K. J. (1982). Risk perception in psychology and economics. Economic Inquiry *20*, 1-9.

Ashburner, J., and Friston, K. J. (1999). Nonlinear spatial normalization using basis functions. Human Brain Mapping *7*, 254-266.

Ashburner, J., Neelin, P., Collins, D. L., Evans, A., and Friston, K. J. (1997). Incorporating prior knowledge into image registration. Neuroimage *6*, 344-352.

Asperger, H. (1944). Die „Autistischen Psychopathen" im Kindesalter. European Archives of Psychiatry and Clinical Neuroscience *117*, 76-136.

Aston-Jones, G., and Bloom, F. E. (1981). Nonrepinephrine-containing locus coeruleus neurons in behaving rats exhibit pronounced responses to non-noxious environmental stimuli. J Neurosci *1*, 887-900.

Aston-Jones, G., Chiang, C., and Alexinsky, T. (1991). Discharge of noradrenergic locus coeruleus neurons in behaving rats and monkeys suggests a role in vigilance. Prog Brain Res *88*, 501-520.

Aston-Jones, G., and Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci *28*, 403-450.

Aston-Jones, G., Rajkowski, J., Kubiak, P., and Alexinsky, T. (1994). Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. J Neurosci *14*, 4467-4480.

Balleine, B. W., and Killcross, S. (2006). Parallel incentive processing: an integrated view of amygdala function. Trends Neurosci.

Barbas, H. (2000). Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. Brain Res Bull *52*, 319-330.

Bard, P. A. (1928). A diencephalic mechanism for the expression of rage with special reference to the central nervous system. Am J Psysiol *84*, 490-513.

Bard, P. A., and Rioch, D. M. (1937). A study of four cats deprived of neocortex and additional portions of forebrain. John Hopkins Med J *60*, 73-153.

Baron-Cohen, S., and Belmonte, M. K. (2005). Autism: a window onto the development of the social and the analytic brain. Annu Rev Neurosci *28*, 109–126.

Baron-Cohen, S., Leslie, A. M., and Frith, U. (1985). Does the autistic child have a "theoryof mind"? Cognition *21*, 37-46.

Baron-Cohen, S., Ring, H. A., Bullmore, E. T., Wheelwright, S., Ashwin, C., and Williams, S. C. R. (2000). The amygdala theory of autism. Neuroscience and Biobehavioral Reviews *24*, 355-364.

Bartlett, F. C. (1932). Remembering: A study in experimental and social psychology: Cambridge (England: Cambridge University Press).

Barto, A. G., and Sutton, R. S. (1998). Reinforcment Learning: An Introduction, The MIT press).

Bauman, M. L., and Kemper, T. L. (1994). Neuroanatomic observations of the brain in autism. The neurobiology of autism, 119–145.

Baxter, M. G., and Murray, E. A. (2002). The amygdala and reward. Nat Rev Neurosci *3*, 563-573.

Beane, M., and Marrocco, R. T. (2004). Norepinephrine and acetylcholine mediation of the components of reflexive attention: implications for attention deficit disorders. Prog Neurobiol *74*, 167-181.

Bechara, A., Damasio, A. R., Damasio, H., and Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. Cognition *50*, 7-15.

Bechara, A., Damasio, H., Tranel, D., and Damasio, A. R. (1997). Deciding advantageously before knowing the advantageous strategy. Science *275*, 1293-1295.

Bechara, A., Damasio, H., Tranel, D., and Damasio, A. R. (2005). The Iowa Gambling Task and the somatic marker hypothesis: some questions and answers. Trends Cogn Sci *9*, 159-162; discussion 162-154.

Bechara, A., Tranel, D., and Damasio, H. (2000). Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. Brain *123 (Pt 11)*, 2189-2202.

Bechara, A., and Van Der Linden, M. (2005). Decision-making and impulse control after frontal lobe injuries. Curr Opin Neurol *18*, 734-739.

Becker, G. M., Degroot, M. H., and Marschak, J. (1964). Measuring Utility by a Single-Response Sequential Method. Behavioral Science *9*, 226-232.

Beique, J., de Montigny, C., Blier, P., and Debonnel, G. (2000). Effects of sustained administration of the serotonin and norepinephrine reuptake inhibitor venlafaxine: II. In vitro studies in the rat. Neuropharmacology *39*, 1813-1822.

Bentham, J. (1789). The Principles of Moral and Legislation, London).

Bernoulli, D. (1954). "Exposition of New Theory on the Measurement of Risk (1738)". Econometrica *22*, 22-36.

Berridge, C. W., and Waterhouse, B. D. (2003). The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res Brain Res Rev *42*, 33-84.

Bishop, S., Duncan, J., Brett, M., and Lawrence, A. D. (2004a). Prefrontal cortical function and anxiety: controlling attention to threat-related stimuli. Nat Neurosci *7*, 184-188.

Bishop, S. J., Duncan, J., and Lawrence, A. D. (2004b). State anxiety modulation of the amygdala response to unattended threat-related stimuli. J Neurosci *24*, 10364-10368.

BNF, ed. (2006). British National Formulary v.52 (London: British Medical Association and Royal Pharmaceutical Society of Great Britain).

Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., and Cohen, J. D. (2001). Conflict monitoring and cognitive control. Psychol Rev *108*, 624-652.

Braver, T. S., Barch, D. M., Gray, J. R., Molfese, D. L., and Snyder, A. (2001). Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors. Cereb Cortex *11*, 825-836.

Breiter, H. C., Etcoff, N. L., Whalen, P. J., Kennedy, W. A., Rauch, S. L., Buckner, R. L., Strauss, M. M., Hyman, S. E., and Rosen, B. R. (1996). Response and habituation of the human amygdala during visual processing of facial expression. Neuron *17*, 875-887.

Buschman, T. J., and Miller, E. K. (2007). Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. Science *315*, 1860-1862.

Bush, G., Luu, P., and Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci *4*, 215-222.

Cacioppo, J. T., and Petty, R. E. (1982). The need for cognition. Journal of Personality and Social Psychology *42*, 116-131.

Cacioppo, J. T., Petty, R. E., and Kao, C. F. (1984). The efficient assessment of need for cognition. Journal of Personality Assessment *48*, 306-307.

Cahill, L., Prins, B., Weber, M., and McGaugh, J. L. (1994). Beta-adrenergic activation and memory for emotional events. Nature *371*, 702-704.

Calder, A. J., and Young, A. W. (2005). Understanding the recognition of facial identity and facial expression. Nat Rev Neurosci *6*, 641-651.

Camerer, C. F., Loewenstein, G., and Prelec, D. (2005). Neuroeconomics:Why economics needs brains. Journal of Economic Literature *XLIII*, 9-64.

Cannon, W. B. (1927). The James-Lange theory of emotions: a critical examination and an alternative theory. Am J Psychol *39*, 106-127.

Cannon, W. B. (1931). Against James-Lange theory thalamic theories of emotions. Psychol Rev *38*, 281-295.

Carretie, L., Martin-Loeches, M., Hinojosa, J. A., and Mercado, F. (2001). Emotion and attention interaction studied through event-related potentials. J Cogn Neurosci *13*, 1109-1128.

Clark, C. R., Geffen, G. M., and Geffen, L. B. (1986). Role of monoamine pathways in attention and effort: effects of clonidine and methylphenidate in normal adult humans. Psychopharmacology (Berl) *90*, 35-39.

Coase, R. H. (1960). The Problem of Social Cost. The Journal of Law & Economics *3*, 1-44.

Corbetta, M., Miezin, F. M., Dobmeyer, S., Shulman, G. L., and Petersen, S. E. (1990). Attentional modulation of neural processing of shape, color, and velocity in humans. Science *248*, 1556-1559.

Corbetta, M., and Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci *3*, 201-215.

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 Neurosci *25*, 962-970.

Coull, J. T., Nobre, A. C., and Frith, C. D. (2001). The noradrenergic alpha2 agonist clonidine modulates behavioural and neuroanatomical correlates of human attentional orienting and alerting. Cereb Cortex *11*, 73-84.

Critchley, H. D., Daly, E. M., Bullmore, E. T., Williams, S. C. R., Van Amelsvoort, T., Robertson, D. M., Rowe, A., Phillips, M., McAlonan, G., and Howlin, P. (2000). The functional neuroanatomy of social behaviour. Brain *123*, 2203-2212.

D'Esposito, M. (2007). From cognitive to neural models of working memory. Philos Trans R Soc Lond B Biol Sci *362*, 761-772.

Damasio, A. R., Tranel, D., and Damasio, H. (1990). Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. Behav Brain Res *41*, 81-94.

Damasio, H., Grabowski, T., Frank, R., Galaburda, A. M., and Damasio, A. R. (1994). The return of Phineas Gage: clues about the brain from the skull of a famous patient. Science *264*, 1102-1105.

Darwin, C. (1859). On the Origin of Species by Means of Natural Selection, Murray, London).

Dawson, M. E., Schell, A. M., and Filion, D. L. (2000). The electrodermal system. Handbook of psychophysiology *2*, 200-223.

Dayan, P., and Abbott, L. F. (2001) Theoretical Neuroscience (MIT press).

De Martino, B., Kumaran, D., Seymour, B., and Dolan, R. J. (2006). Frames, biases, and rational decision-making in the human brain. Science *313*, 684-687.

Desimone, R. (1998). Visual attention mediated by biased competition in extrastriate visual cortex. Philos Trans R Soc Lond B Biol Sci *353*, 1245-1255.

Desimone, R., and Duncan, J. (1995). Neural mechanisms of selective visual attention. Annu Rev Neurosci *18*, 193-222.

Dickinson, A., and Balleine, B. (1994). Motivational control of a goal-directed action. Anim Learn Behav *22*, 1-18.

Dolan, R. J. (2002). Emotion, cognition, and behavior. Science *298*, 1191-1194.

Dolan, R. J., Fink, G. R., Rolls, E., Booth, M., Holmes, A., Frackowiak, R. S., and Friston, K. J. (1997). How the brain learns to see objects and faces in an impoverished context. Nature *389*, 596-599.

Dolcos, F., Diaz-Granados, P., Wang, L., and McCarthy, G. (2007). Opposing influences of emotional and non-emotional distracters upon sustained prefrontal cortex activity during a delayed-response working memory task. Neuropsychologia.

Driver, J., and Frith, C. (2000). Shifting baselines in attention research. Nat Rev Neurosci *1*, 147-148.

Dunn, O. J. (1961). Multiple Comparisons Among Means. Journal of the American Statistical Association *56*, 52-64.

Egan, T. M., Henderson, G., North, R. A., and Williams, J. T. (1983). Noradrenaline-mediated synaptic inhibition in rat locus coeruleus neurones. J Physiol *345*, 477-488.

Elliott, R., and Dolan, R. J. (1998). Activation of different anterior cingulate foci in association with hypothesis testing and response selection. Neuroimage *8*, 17-29.

Elliott, R., Rubinsztein, J. S., Sahakian, B. J., and Dolan, R. J. (2000). Selective attention to emotional stimuli in a verbal go/no-go task: an fMRI study. Neuroreport *11*, 1739-1744.

Engel, S. A., Glover, G. H., and Wandell, B. A. (1997). Retinotopic organization in human visual cortex and the spatial precision of functional MRI. Cerebral Cortex *7*, 181-192.

Estrada, C. A., Isen, A. M., and Young, M. J. (1994). Positive affect improves creative problem solving and influences reported source of practice satisfaction in physician. Motivation and emotion *18*, 285-299.

Evans, J. (2003). In two minds: dual-process accounts of reasoning. Trends in Cognitive Sciences *7*, 454–459.

Everitt, B. J., Parkinson, J. A., Olmstead, M. C., Arroyo, M., Robledo, P., and Robbins, T. W. (1999). Associative processes in addiction and reward. The role of amygdala-ventral striatal subsystems. Ann N Y Acad Sci *877*, 412-438.

Fellows, L. K., and Farah, M. J. (2005). Different Underlying Impairments in Decision-making Following Ventromedial and Dorsolateral Frontal Lobe Damage in Humans. Cerebral Cortex *15*, 58.

Fichtenholtz, H. M., Dean, H. L., Dillon, D. G., Yamasaki, H., McCarthy, G., and LaBar, K. S. (2004). Emotion-attention network interactions during a visual oddball task. Brain Res Cogn Brain Res *20*, 67-80.

Fischhoff, B., Bostrom, A., and Quadrel, M. J. (1993). Risk Perception and Communication. Annual Review of Public Health *14*, 183-203.

Foote, S. L., and Morrison, J. H. (1987). Development of the noradrenergic, serotonergic, and dopaminergic innervation of neocortex. Curr Top Dev Biol *21*, 391-423.

Frackowiak, R. S. J. (2004). Human Brain Function, Academic Pr).

Fragopanagos, N., Kockelkoren, S., and Taylor, J. G. (2005). A neurodynamic model of the attentional blink. Brain Res Cogn Brain Res *24*, 568-586.

Frederick, S. (2005). On the ball: Cognitive reflection and decision-making. Journal of Economic Perspectives.

Friston, K. (1995). Statistical Parametric Maps in Functional Imaging: A General Linear Approach. Hum Brain Mapp *2*, 189-210.

Friston, K. J., Ashburner, J., Frith, C. D., Poline, J. B., Heather, J. D., and Frackowiak, R. S. J. (1995). Spatial registration and normalization of images. Human Brain Mapping *2*, 1-25.

Friston, K. J., Fletcher, P., Josephs, O., Holmes, A., Rugg, M. D., and Turner, R. (1998). Event-related fMRI: characterizing differential responses. Neuroimage *7*, 30-40.

Frith, U., and Happé, F. (1994). Autism: Beyond "theory of mind." Cognition *50*, 115-132.

Frith, U., and Happé, F. (2005). Autism spectrum disorder. Current Biology *15*, 786-790.

Gabaix, X., and Laibson, D. (2003). A New Challenge for Economics: " The Frame Problem". Collected Essays in Psycohology and Economics, Oxford University Press.

Gilovich, T., Griffin, D., and Kahneman, D. (2002). Heuristics and Biases: the psychology of intuitive judgment, Cambridge University Press).

Glimcher, P. W., and Rustichini, A. (2004). Neuroeconomics: the consilience of brain and decision. Science *306*, 447-452.

Glover, G. H. (1999). Deconvolution of impulse response in event-related BOLD fMRI. NeuroImage *9*, 416-429.

Gottfried, J. A., O'Doherty, J., and Dolan, R. J. (2003). Encoding predictive reward value in human amygdala and orbitofrontal cortex. Science *301*, 1104-1107.

Grill-Spector, K., Knouf, N., and Kanwisher, N. (2004). The fusiform face area subserves face perception, not generic within-category identification. Nat Neurosci *7*, 555-562.

Grimm, S., Schmidt, C. F., Bermpohl, F., Heinzel, A., Dahlem, Y., Wyss, M., Hell, D., Boesiger, P., Boeker, H., and Northoff, G. (2006). Segregated neural representation of distinct emotion dimensions in the prefrontal cortex-an fMRI study. Neuroimage *30*, 325-340.

Groenewegen, H. J., and Uylings, H. B. (2000). The prefrontal cortex and the integration of sensory, limbic and autonomic information. Prog Brain Res *126*, 3-28.

Happe, F. G. E. (1997). Central coherence and theory of mind in autism: Reading homographs in context. British journal of developmental psychology *15*, 1-12.

Harmer, C. J., Perrett, D. I., Cowen, P. J., and Goodwin, G. M. (2001). Administration of the beta-adrenoceptor blocker propranolol impairs the processing of facial expressions of sadness. Psychopharmacology (Berl) *154*, 383-389.

Harro, J., and Vasar, E. (1991). Cholecystokinin-induced anxiety: how is it reflected in studies on exploratory behaviour? Neurosci Biobehav Rev *15*, 473-477.

Hassani, O. K., Cromwell, H. C., and Schultz, W. (2001). Influence of Expectation of Different Rewards on Behavior-Related Neuronal Activity in the Striatum. Journal of Neurophysiology *85*, 2477-2489.

Henson, R. N., Price, C. J., Rugg, M. D., Turner, R., and Friston, K. J. (2002). Detecting latency differences in event-related BOLD responses: application to words versus nonwords and initial versus repeated face presentations. Neuroimage *15*, 83-97.

Henson, R. N. A., Rugg, M. D., and Friston, K. J. (2001). The choice of basis functions in event-related fMRI. NeuroImage *13*, 127.

Hoffer, A. (1967). A theoretical examination of double-blind design. Can Med Assoc J *97*, 123-127.

Hollerman, J. R., Tremblay, L., and Schultz, W. (2000). Involvement of basal ganglia and orbitofrontal cortex in goal-directed behavior. Prog Brain Res *126*, 193-215.

Hopfinger, J. B., Buonocore, M. H., and Mangun, G. R. (2000). The neural mechanisms of top-down attentional control. Nat Neurosci *3*, 284-291.

Horvitz, J. C. (2002). Dopamine gating of glutamatergic sensorimotor and incentive motivational input signals to the striatum. Behav Brain Res *137*, 65-74.

Howard, M. A., Cowell, P. E., Boucher, J., Broks, P., Mayes, A., Farrant, A., and Roberts, N. (2000). Convergent neuroanatomical and behavioural evidence of an amygdala hypothesis of autism. Neuroreport *11*, 2931-2935.

Hsee, C. K., and Rottenstreich, Y. (2004). Music, pandas, and muggers: On the affective psychology of value. Journal of Experimental Psychology: General *133*, 23-30.

Hsu, M., Bhatt, M., Adolphs, R., Tranel, D., and Camerer, C. F. (2005). Neural systems responding to degrees of uncertainty in human decision-making. Science *310*, 1680-1683.

Isen, A. M., Nygren, T. E., and Ashby, F. G. (1988). Influence of positive affect on the subjective utility of gains and losses: It is just not worth the risk. Journal of Personality and Social Psychology *55*, 710–717.

Isen, A. M., and Patrick, R. (1983). The effect of positive feelings on risk taking: When the chips are down. Organizational Behavior and Human Performance *31*, 194-202.

Izquierdo, A., Suda, R. K., and Murray, E. A. (2004). Bilateral Orbital Prefrontal Cortex Lesions in Rhesus Monkeys Disrupt Choices Guided by Both Reward Value and Reward Contingency. Journal of Neuroscience *24*, 7540-7548.

James, W. (1884). What is an emotion? Mind *9*, 188-205.

Jensen, J., McIntosh, A. R., Crawley, A. P., Mikulis, D. J., Remington, G., and Kapur, S. (2003). Direct activation of the ventral striatum in anticipation of aversive stimuli. Neuron *40*, 1251-1257.

Johnson, E. J., and Goldstein, D. (2003). Medicine. Do defaults save lives? Science *302*, 1338-1339.

Jolliffe, T., and Baron-Cohen, S. (2000). Linguistic processing in high-functioning adults with autism or Asperger's syndrome. Is global coherence impaired? Psychological Medicine *30*, 1169-1187.

Josephs, O. (1999). Event-related functional magnetic resonance imaging: modelling, inference and optimization. Philosophical Transactions: Biological Sciences *354*, 1215-1228.

Jouvet, M. (1969). Biogenic amines and the states of sleep. Science *163*, 32-41.

Kahn, B. E., and Isen, A. M. (1993). The Influence of Positive Affect on Variety Seeking Among Safe, Enjoyable Products. The Journal of Consumer Research *20*, 257-270.

Kahneman, D. (2003). Maps of Bounded Rationality: Psychology for Behavioral Economics. The American Economic Review *93*, 1449-1475.

Kahneman, D., and Frederick, S. (2007). Frames and brains: elicitation and control of response tendencies. Trends in Cognitive Sciences *11*, 45-46.

Kahneman, D., Knetsch, J. L., and Thaler, R. H. (1990). Experimental Tests of the Endowment Effect and the Coase Theorem. Journal of Political Economy *98*, 1325-1348.

Kahneman, D., Knetsch, J. L., and Thaler, R. H. (1991). Anomalies - the Endowment Effect, Loss Aversion, and Status-Quo Bias. Journal of Economic Perspectives *5*, 193-206.

Kahneman, D., and Tversky, A. (1979). Prospect Theory: An Analysis of Decision Under Risk. Econometrica *47*, 263-292.

Kahneman, D., and Tversky, a. (1984). Choices, Values, and Frames. American Psychologist *39*, 341-350.

Kahneman, D., and Tversky, A. (2000). Choices, Values, and Frames, Cambridge University Press).

Kalisch, R., Wiech, K., Critchley, H. D., and Dolan, R. J. (2006). Levels of appraisal: a medial prefrontal role in high-level appraisal of emotional material. Neuroimage *30*, 1458-1466.

Kamin, L. J. (1969). Predictability, surprise, attention, and conditioning. Punishment and aversive behavior, 279-296.

Kanner, L. (1943). Autistic Disturbances of Affective Contact.

Kanwisher, N., McDermott, J., and Chun, M. M. (1997). The fusiform face area: a module in human extrastriate cortex specialized for face perception. J Neurosci *17*, 4302-4311.

Kanwisher, N., Stanley, D., and Harris, A. (1999). The fusiform face area is selective for faces not animals. Neuroreport *10*, 183-187.

Kasamo, K., Blier, P., and De Montigny, C. (1996). Blockade of the serotonin and norepinephrine uptake processes by duloxetine: in vitro and in vivo studies in the rat brain. J Pharmacol Exp Ther *277*, 278-286.

Kawasaki, H., Kaufman, O., Damasio, H., Damasio, A. R., Granner, M., Bakken, H., Hori, T., Howard, M. A., 3rd, and Adolphs, R. (2001). Single-neuron responses to emotional visual stimuli recorded in human ventral prefrontal cortex. Nat Neurosci *4*, 15-16.

Kim, H., Somerville, L. H., Johnstone, T., Polis, S., Alexander, A. L., Shin, L. M., and Whalen, P. J. (2004). Contextual modulation of amygdala responsivity to surprised faces. J Cogn Neurosci *16*, 1730-1745.

Kimberg, D. Y., Aguirre, G. K., and D'Esposito, M. (2000). Modulation of task-related neural activity in task-switching: an fMRI study. Brain Res Cogn Brain Res *10*, 189-196.

Kitchigina, V., Vankov, A., Harley, C., and Sara, S. J. (1997). Novelty-elicited, noradrenaline-dependent enhancement of excitability in the dentate gyrus. Eur J Neurosci *9*, 41-47.

Knetsch, J. L., and Sinden, J. a. (1984). Willingness to Pay and Compensation Demanded - Experimental-Evidence of an Unexpected Disparity in Measures of Value. Quarterly Journal of Economics *99*, 507-521.

Knutson, B., Fong, G. W., Adams, C. M., Varner, J. L., and Hommer, D. (2001). Dissociation of reward anticipation and outcome with event-related fMRI. Neuroreport *12*, 3683–3687.

Knutson, B., Rick, S., Wirnmer, G. E., Prelec, D., and Loewenstein, G. (2007). Neural predictors of purchases. Neuron *53*, 147-156.

Knutson, B., Taylor, J., Kaufman, M., Peterson, R., and Glover, G. (2005). Distributed neural representation of expected value. J Neurosci *25*, 4806-4812.

Kringelbach, M. L. (2005). The human orbitofrontal cortex: linking reward to hedonic experience. Nat Rev Neurosci *6*, 691-702.

LaBar, K. S., Gitelman, D. R., Mesulam, M. M., and Parrish, T. B. (2001). Impact of signal-to-noise on functional MRI of the human amygdala. Neuroreport *12*, 3461-3464.

Lacroix, D., Blier, P., Curet, O., and de Montigny, C. (1991). Effects of long-term desipramine administration on noradrenergic neurotransmission: electrophysiological studies in the rat brain. J Pharmacol Exp Ther *257*, 1081-1090.

Lane, R. D., Chua, P. M., and Dolan, R. J. (1999). Common effects of emotional valence, arousal and attention on neural activation during visual processing of pictures. Neuropsychologia *37*, 989-997.

Lane, R. D., Fink, G. R., Chau, P. M., and Dolan, R. J. (1997a). Neural activation during selective attention to subjective emotional responses. Neuroreport *8*, 3969-3972.

Lane, R. D., Reiman, E. M., Ahern, G. L., Schwartz, G. E., and Davidson, R. J. (1997b). Neuroanatomical correlates of happiness, sadness, and disgust. Am J Psychiatry *154*, 926-933.

Lane, R. D., Reiman, E. M., Axelrod, B., Yun, L. S., Holmes, A., and Schwartz, G. E. (1998). Neural correlates of levels of emotional awareness. Evidence of an interaction between emotion and attention in the anterior cingulate cortex. J Cogn Neurosci *10*, 525-535.

Lane, R. D., Reiman, E. M., Bradley, M. M., Lang, P. J., Ahern, G. L., Davidson, R. J., and Schwartz, G. E. (1997c). Neuroanatomical correlates of pleasant and unpleasant emotion. Neuropsychologia *35*, 1437-1444.

Lang, P. J., Bradley, M. M., Fitzsimmons, J. R., Cuthbert, B. N., Scott, J. D., Moulder, B., and Nangia, V. (1998). Emotional arousal and activation of the visual cortex: an fMRI analysis. Psychophysiology *35*, 199-210.

Lange, C. (1885). The Emotions (Dunlap, Edition).

LeDoux, J. E. (1996). The Emotional Brain, (Simon&Schuster, Edition).

LeDoux, J. E. (2000). Emotion circuits in the brain. Annu Rev Neurosci *23*, 155-184.

Liang, Z. P., and Lauterbur, P. C. (2000). Principles of Magnetic Resonance Imaging: A Signal Processing Perspective, (IEEE Press).

Liu, Z., and Richmond, B. J. (2000). Response Differences in Monkey TE and Perirhinal Cortex: Stimulus Association Related to Reward Schedules. Journal of Neurophysiology *83*, 1677-1692.

Loewenstein, G., and Lerner, J. S. (2003). The role of affect in decision making. Handbook of affective science, 619-642.

Loewenstein, G. F., Weber, E. U., Hsee, C. K., and Welch, N. (2001). Risk as feelings. Psychol Bull *127*, 267-286.

Logothetis, N. K. (2002). The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. Philosophical Transactions of the Royal Society B: Biological Sciences *357*, 1003-1037.

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., and Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. Nature *412*, 150-157.

Lord, C., Risi, S., Lambrecht, L., Cook, E. H., Leventhal, B. L., DiLavore, P. C., Pickles, A., and Rutter, M. (2000). The Autism Diagnostic Observation Schedule—Generic: A Standard Measure of Social and Communication Deficits Associated with the Spectrum of Autism. Journal of Autism and Developmental Disorders *30*, 205-223.

Luce, R. D. a. R., H. (1957). Games and Decisions, (John Wiley and Sons, edition).

MacDonald, A. W., 3rd, Cohen, J. D., Stenger, V. A., and Carter, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science *288*, 1835-1838.

MacLean, P. D. (1949). Psychosomatic disease and 'visceral brain': recent developments bearingon the Papez theory of emotions. Psychom Med *11*, 338-335.

Malkova, L., Gaffan, D., and Murray, E. A. (1997). Excitotoxic Lesions of the Amygdala Fail to Produce Impairment in Visual Learning for Auditory Secondary Reinforcement But Interfere with Reinforcer Devaluation Effects in Rhesus Monkeys. Journal of Neuroscience *17*, 6011-6020.

Malonek, D., and Grinvald, A. (1996). Interactions between electrical activity and cortical microcirculation revealed by imaging spectroscopy: implications for functional brain mapping. Science *272*, 551-554.

Marois, R., Chun, M. M., and Gore, J. C. (2000). Neural correlates of the attentional blink. Neuron *28*, 299-308.

Marois, R., Yi, D. J., and Chun, M. M. (2004). The neural fate of consciously perceived and missed events in the attentional blink. Neuron *41*, 465-472.

Matthews, P. M., Clare, S., and Adcock, J. (1999). Functional magnetic resonance imaging: Clinical applications and potential. Journal of Inherited Metabolic Disease *22*, 337-352.

McNeil, B. J., Pauker, S. G., Sox, H. C., Jr., and Tversky, A. (1982). On the elicitation of preferences for alternative therapies. N Engl J Med *306*, 1259-1262.

Miller, E. K., and Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. Annu Rev Neurosci *24*, 167-202.

Mishkin, M. (1964). Perseveration of central sets after frontal lesions in monkeys. The frontal granular cortex and behavior, 219–241.

Montague, P. R., and Berns, G. S. (2002). Neural economics and the biological substrates of valuation. Neuron *36*, 265-284.

Montague, P. R., King-Casas, B., and Cohen, J. D. (2006a). Imaging Valuation Models in Human Choice. Annu Rev Neurosci.

Montague, P. R., King-Casas, B., and Cohen, J. D. (2006b). Imaging valuation models in human choice. Annu Rev Neurosci *29*, 417-448.

Moonen, C. T. W., and Bandettini, P. A. (1999). Functional MRI, Springer).

Moore, S. C., and Chater, N. (2003) The Influence of Affect on Risky Behavior: From the Lab to Real World Financial Behavior. Proceedings of the 23rd Annual Conference of the Cognitive Science Society, Alterman,R., Kirsh,D. (ed.) , 1-6.

Moran, J., and Desimone, R. (1985). Selective attention gates visual processing in the extrastriate cortex. Science *229*, 782-784.

Moray, N. (1959). Attention in dichotic listening: Affective cues and the influence of instructions. Q J Exp Psychol *11*, 56-60.

Morris, J. S., Buchel, C., and Dolan, R. J. (2001). Parallel neural responses in amygdala subregions and sensory cortex during implicit fear conditioning. Neuroimage *13*, 1044-1052.

Morris, J. S., Friston, K. J., Buchel, C., Frith, C. D., Young, A. W., Calder, A. J., and Dolan, R. J. (1998). A neuromodulatory role for the human amygdala in processing emotional facial expressions. Brain *121 (Pt 1)*, 47-57.

Neisser, U. (1967). Cognitive psycology, Englewood Cliffs).

Nieuwenhuis, S., Aston-Jones, G., and Cohen, J. D. (2005a). Decision making, the P3, and the locus coeruleus-norepinephrine system. Psychol Bull *131*, 510-532.

Nieuwenhuis, S., Gilzenrat, M. S., Holmes, B. D., and Cohen, J. D. (2005b). The role of the locus coeruleus in mediating the attentional blink: a neurocomputational theory. J Exp Psychol Gen *134*, 291-307.

Nieuwenhuis, S., Heslenfeld, D. J., von Geusau, N. J. A., Mars, R. B., Holroyd, C. B., and Yeung, N. (2005c). Activity in human reward-sensitive brain areas is strongly context dependent. Neuroimage *25*, 1302-1309.

Nieuwenhuis, S., van Nieuwpoort, I. C., Veltman, D. J., and Drent, M. L. (2007). Effects of the noradrenergic agonist clonidine on temporal and spatial attention. Psychopharmacology (Berl).

Nishijo, H., Ono, T., and Nishino, H. (1988). Single neuron responses in amygdala of alert monkey during complex sensory stimulation with affective significance. Journal of Neuroscience *8*, 3570-3583.

Nishijo, H., Uwano, T., Tamura, R., and Ono, T. (1998). Gustatory and Multimodal Neuronal Responses in the Amygdala During Licking and Discrimination of Sensory Stimuli in Awake Rats. Journal of Neurophysiology *79*, 21-36.

Nowinski, W. L., and Belov, D. (2003). The Cerefy Neuroradiology Atlas: a Talairach-Tournoux atlas-based tool for analysis of neuroimages available over the Internet. Neuroimage *20*, 50-57.

O'Doherty, J. P. (2004). Reward representations and reward-related learning in the human brain: insights from neuroimaging. Curr Opin Neurobiol *14*, 769-776.

O'Doherty, J. P., Deichmann, R., Critchley, H. D., and Dolan, R. J. (2002). Neural Responses during Anticipation of a Primary Taste Reward. Neuron *33*, 815-826.

O'Riordan, M. A., Plaisted, K. C., Driver, J., and Baron-Cohen, S. (2001). Superior visual search in autism. J Exp Psychol Hum Percept Perform *27*, 719-730.

Ochsner, K. N., Bunge, S. A., Gross, J. J., and Gabrieli, J. D. (2002). Rethinking feelings: an FMRI study of the cognitive regulation of emotion. J Cogn Neurosci *14*, 1215-1229.

Ogawa, S., Lee, T. M., Kay, A. R., and Tank, D. W. (1990a). Brain Magnetic Resonance Imaging with Contrast Dependent on Blood Oxygenation. Proceedings of the National Academy of Sciences *87*, 9868-9872.

Ogawa, S., Lee, T. M., Nayak, A. S., and Glynn, P. (1990b). Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. Magn Reson Med *14*, 68-78.

Ohman, A., Flykt, A., and Esteves, F. (2001). Emotion drives attention: detecting the snake in the grass. J Exp Psychol Gen *130*, 466-478.

Padoa-Schioppa, C., and Assad, J. A. (2006). Neurons in the orbitofrontal cortex encode economic value. Nature *441*, 223-226.

Palermo, R., and Rhodes, G. (2007). Are you always on my mind? A review of how face perception and attention interact. Neuropsychologia *45*, 75-92.

Papez, J. W. (1995). A proposed mechanism of emotion. 1937. J Neuropsychiatry Clin Neurosci *7*, 103-112.

Paradiso, S., Johnson, D. L., Andreasen, N. C., O'Leary, D. S., Watkins, G. L., Ponto, L. L., and Hichwa, R. D. (1999). Cerebral blood flow changes associated with attribution of emotional valence to pleasant, unpleasant, and neutral visual stimuli in a PET study of normal subjects. Am J Psychiatry *156*, 1618-1629.

Paton, J. J., Belova, M. A., Morrison, S. E., and Salzman, C. D. (2006). The primate amygdala represents the positive and negative value of visual stimuli during learning. Nature *439*, 865-870.

Pauling, L., and Coryell, C. D. (1936). The Magnetic Properties and Structure of Hemoglobin, Oxyhemoglobin and Carbonmonoxyhemoglobin. Proceedings of the National Academy of Sciences *22*, 210-216.

Pavlov, I. P. (1927). Conditioned Reflexes: An Investigation of the Physiological Activity of Cerebral Cortex, London: Oxford University Press).

Payne, J. W., Bettman, J. R., and Johnson, E. J. (1992). Behavioral Decision Research: A Constructive Processing Perspective. Annual Review of Psychology *43*, 87-131.

Pears, A., Parkinson, J. A., Hopewell, L., Everitt, B. J., and Roberts, A. C. (2003). Lesions of the Orbitofrontal but not Medial Prefrontal Cortex Disrupt Conditioned Reinforcement in Primates. Journal of Neuroscience *23*, 11189.

Pessiglione, M., Seymour, B., Flandin, G., Dolan, R. J., and Frith, C. D. (2006). Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature *442*, 1042-1045.

Phelps, E. A., Delgado, M. R., Nearing, K. I., and LeDoux, J. E. (2004). Extinction learning in humans: role of the amygdala and vmPFC. Neuron *43*, 897-905.

Phelps, E. A., and LeDoux, J. E. (2005). Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron *48*, 175-187.

Pickens, C. L., Saddoris, M. P., Setlow, B., Gallagher, M., Holland, P. C., and Schoenbaum, G. (2003). Different Roles for Orbitofrontal Cortex and Basolateral Amygdala in a Reinforcer Devaluation Task. Journal of Neuroscience *23*, 11078.

Plaisted, K., O'Riordan, M., and Baron-Cohen, S. (1998). Enhanced Discrimination of Novel, Highly Similar Stimuli by Adults with Autism During a Perceptual Learning Task. The Journal of Child Psychology and Psychiatry and Allied Disciplines *39*, 765-775.

Plewnia, C., Hoppe, J., and Gerloff, C. (2006). No effects of enhanced central norepinephrine on finger-sequence learning and attention. Psychopharmacology (Berl) *187*, 260-265.

Pliszka, S. R., McCracken, J. T., and Maas, J. W. (1996). Catecholamines in attention-deficit hyperactivity disorder: current perspectives. J Am Acad Child Adolesc Psychiatry *35*, 264-272.

Portas, C. M. (2000). How does the brain sustain a visual percept? Proceedings: Biological Sciences *267*, 845-850.

Pourtois, G., Schwartz, S., Seghier, M. L., Lazeyras, F., and Vuilleumier, P. (2006). Neural systems for orienting attention to the location of threat signals: an event-related fMRI study. Neuroimage *31*, 920-933.

Raymond, J. E., Shapiro, K. L., and Arnell, K. M. (1992). Temporary suppression of visual processing in an RSVP task: an attentional blink? J Exp Psychol Hum Percept Perform *18*, 849-860.

Rees, G., Russell, C., Frith, C. D., and Driver, J. (1999). Inattentional blindness versus inattentional amnesia for fixated but ignored words. Science *286*, 2504-2507.

Rescorla, R. A., and Wagner, A. R. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. Classical conditioning II: Current research and theory, 64–99.

Robbins, T. W., and Everitt, B. J. (1996). Neurobehavioural mechanisms of reward and motivation. Curr Opin Neurobiol *6*, 228-236.

Robbinson, MD (1998). Running from William James' bear: A review of preattentive mechanisms and their contributions to emotional experience.
Cognition and Emotion *12*, 667-696.

Robinson, T. E., and Berridge, K. C. (1993). The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev *18*, 247-291.

Rolls, E. T. (1996). The orbitofrontal cortex. Philos Trans R Soc Lond B Biol Sci *351*, 1433-1443; discussion 1443-1434.

Rolls, E. T., Hornak, J., Wade, D., and McGrath, J. (1994). Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. J Neurol Neurosurg Psychiatry *57*, 1518-1524.

Romanski, L. M. (2004). Domain specificity in the primate prefrontal cortex. Cogn Affect Behav Neurosci *4*, 421-429.

Roy, C. S., and Sherrington, C. S. (1890). On the regulation of the blood supply of the brain. J Physiol *11*, 108.

Rule, R. R., Shimamura, A. P., and Knight, R. T. (2002). Orbitofrontal cortex and dynamic filtering of emotional stimuli. Cogn Affect Behav Neurosci *2*, 264-270.

Rushworth, M. F., Kennerley, S. W., and Walton, M. E. (2005). Cognitive neuroscience: resolving conflict in and over the medial frontal cortex. Curr Biol *15*, R54-56.

Sacchetti, G., Bernini, M., Bianchetti, A., Parini, S., Invernizzi, R. W., and Samanin, R. (1999). Studies on the acute and chronic effects of reboxetine on extracellular noradrenaline and other monoamines in the rat brain. Br J Pharmacol *128*, 1332-1338.

Saenz, M., Buracas, G. T., and Boynton, G. M. (2002). Global effects of feature-based attention in human visual cortex. Nat Neurosci *5*, 631-632.

Salamone, J. D. (1994). The involvement of nucleus accumbens dopamine in appetitive and aversive motivation. Behav Brain Res *61*, 117-133.

Samuelson, P. (1947). Foundations of Economics Analysis, (Enlarged ed., 1983).

Samejima, K., Ueda, Y., Doya, K., and Kimura, M. (2005). Representation of Action-Specific Reward Values in the Striatum. In Science (American Association for the Advancement of Science), pp. 1337-1340.

Schaefer, S. M., Jackson, D. C., Davidson, R. J., Aguirre, G. K., Kimberg, D. Y., and Thompson-Schill, S. L. (2002). Modulation of amygdalar activity by the conscious regulation of negative emotion. J Cogn Neurosci *14*, 913-921.

Schoenbaum, G., Roesch, M. R., and Stalnaker, T. A. (2006). Orbitofrontal cortex, decision-making and drug addiction. Trends Neurosci *29*, 116-124.

Schoenbaum, G., Setlow, B., Saddoris, M. P., and Gallagher, M. (2003). Encoding predicted outcome and acquired value in orbitofrontal cortex during cue sampling depends upon input from basolateral amygdala. Neuron *39*, 855-867.

Schultz, W. (2002). Getting formal with dopamine and reward. Neuron *36*, 241-263.

Schultz, W. (2004). Neural coding of basic reward terms of animal learning theory, game theory, microeconomics and behavioural ecology. Curr Opin Neurobiol *14*, 139-147.

Schultz, W. (2006). Behavioral theories and the neurophysiology of reward. Annu Rev Psychol *57*, 87-115.

Schultz, W., Dayan, P., and Montague, P. R. (1997). A neural substrate of prediction and reward. Science *275*, 1593-1599.

Seymour, B., Daw, N., Dayan, P., Singer, T., and Dolan, R. (2007). Differential encoding of losses and gains in the human striatum. J Neurosci *27*, 4826-4831.

Seymour, B., O'Doherty, J. P., Koltzenburg, M., Wiech, K., Frackowiak, R., Friston, K., and Dolan, R. (2005). Opponent appetitive-aversive neural processes underlie predictive learning of pain relief. Nat Neurosci *8*, 1234-1240.

Shah, A., and Frith, U. (1993). Why do autistic individuals show superior performance on the block design task. Journal of Child Psychology and Psychiatry *34*, 1351-1364.

Simon, H. (1982). Models of Bounded Rationality, Vol 1-2, MIT press).

Simpson, J. R., Jr., Drevets, W. C., Snyder, A. Z., Gusnard, D. A., and Raichle, M. E. (2001). Emotion-induced changes in human medial prefrontal cortex: II. During anticipatory anxiety. Proc Natl Acad Sci U S A *98*, 688-693.

Simpson, J. R., Ongur, D., Akbudak, E., Conturo, T. E., Ollinger, J. M., Snyder, A. Z., Gusnard, D. A., and Raichle, M. E. (2000). The Emotional Modulation of Cognitive Processing: An fMRI Study. Journal of Cognitive Neuroscience *12*, 157-170.

Skinner, B. F. (1938). The Behavior of Organisms: An Experimental Analysis, Appleton-Century-Crofts New York).

Slovic, P., Finucane, M., Perers, E., and MacGregor, D. (2002). The Affect Heuristic. Heuristic and Biases, Cambridge University Press, 397-420.

Slovic, P., Finucane, M. L., Peters, E., and MacGregor, D. G. (2007). The affect heuristic star, open. European Journal of Operational Research *177*, 1333-1352.

Slovic, P., Fischhoff, B., and Lichtenstein, S. (1977). Behavioral Decision Theory. Annual Review of Psychology *28*, 1-39.

Slovic, P., Fischhoff, B., and Lichtenstein, S. (1980). Facts and fears: Understanding perceived risk. Societal Risk Assessment: How Safe is Safe Enough, 181-214.

Slovic, P., Fischhoff, B., and Lichtenstein, S. (1981). Perceived Risk: Psychological Factors and Social Implications. Proceedings of the Royal Society of London Series A, Mathematical and Physical Sciences *376*, 17-34.

Stanovich, K., and West, F. (2002). Individual Differences in Reasoning. Heuristic and Biases, Cambridge University Press, 421-440.

Strange, B. A., and Dolan, R. J. (2007). Beta-adrenergic modulation of oddball responses in humans. Behav Brain Funct *3*, 29.

Strange, B. A., Hurlemann, R., and Dolan, R. J. (2003). An emotion-induced retrograde amnesia in humans is amygdala- and beta-adrenergic-dependent. Proc Natl Acad Sci U S A *100*, 13626-13631.

Surguladze, S. A., Brammer, M. J., Young, A. W., Andrew, C., Travis, M. J., Williams, S. C., and Phillips, M. L. (2003). A preferential increase in the extrastriate response to signals of danger. Neuroimage *19*, 1317-1328.

Taylor, S. F., Phan, K. L., Decker, L. R., and Liberzon, I. (2003). Subjective rating of emotionally salient stimuli modulates neural activity. Neuroimage *18*, 650-659.

Thaler, R. (1980). Toward a Positive Theory of Consumer Choice. Journal of Economic Behavior & Organization *1*, 39-60.

Tobler, P. N., Fiorillo, C. D., and Schultz, W. (2005). Adaptive coding of reward value by dopamine neurons. Science *307*, 1642-1645.

Tobler, P. N., Fletcher, P. C., Bullmore, E. T., and Schultz, W. (2007). Learning-related human brain activations reflecting individual finances. Neuron *54*, 167-175.

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*, 515-518.

Tomita, H., Ohbayashi, M., Nakahara, K., Hasegawa, I., and Miyashita, Y. (1999). Top-down signal from prefrontal cortex in executive control of memory retrieval. Nature *401*, 699-703.

Tremblay, L., and Schultz, W. (1999). Relative reward preference in primate orbitofrontal cortex. Nature *398*, 661-663.

Tversky, A., and Kahneman, D. (1974). Judgment under Uncertainty: Heuristics and Biases. Science *185*, 1124-1131.

Tversky, A., and Kahneman, D. (1981). The framing of decisions and the psychology of choice. Science *211*, 453-458.

Tversky, A., and Kahneman, D. (1986). Rational choice and the framing of decisions. Journal of Business *59*, S251–S278.

Usher, M., Cohen, J. D., Servan-Schreiber, D., Rajkowski, J., and Aston-Jones, G. (1999). The role of locus coeruleus in the regulation of cognitive performance. Science *283*, 549-554.

Venables, P. H. (1991). Autonomic activity. Annals of the New York Academy of Sciences *620*, 191-207.

von Neumann, J., and Morgestern, O. (1944). Theory of Games and Economic Behaviour, Princeton University Press).

Vuilleumier, P. (2005). How brains beware: neural mechanisms of emotional attention. Trends Cogn Sci *9*, 585-594.

Vuilleumier, P., Armony, J. L., Driver, J., and Dolan, R. J. (2001). Effects of attention and emotion on face processing in the human brain: an event-related fMRI study. Neuron *30*, 829-841.

Vuilleumier, P., and Driver, J. (2007). Modulation of visual processing by attention and emotion: windows on causal interactions between human brain regions. Philos Trans R Soc Lond B Biol Sci *362*, 837-855.

Vuilleumier, P., and Pourtois, G. (2007). Distributed and interactive brain mechanisms during emotion face perception: evidence from functional neuroimaging. Neuropsychologia *45*, 174-194.

Vuilleumier, P., Richardson, M. P., Armony, J. L., Driver, J., and Dolan, R. J. (2004). Distant influences of amygdala lesion on visual cortical activation during emotional face processing. Nat Neurosci *7*, 1271-1278.

Vuilleumier, P., and Schwartz, S. (2001a). Beware and be aware: capture of spatial attention by fear-related stimuli in neglect. Neuroreport *12*, 1119-1122.

Vuilleumier, P., and Schwartz, S. (2001b). Beware and be aware: Capture of spatial attention by fear-related stimuli in neglect. Neuroreport *12*, 1119–1122.

Vuilleumier, P., and Schwartz, S. (2001c). Emotional facial expressions capture attention. Neurology *56*, 153-158.

Wallis, J. D. (2007). Orbitofrontal Cortex and Its Contribution to Decision-Making. Annu Rev Neurosci.

Washburn, M., and Moises, H. C. (1989). Electrophysiological correlates of presynaptic alpha 2-receptor-mediated inhibition of norepinephrine release at locus coeruleus synapses in dentate gyrus. J Neurosci *9*, 2131-2140.

Weissman, D. H., Woldorff, M. G., Hazlett, C. J., and Mangun, G. R. (2002). Effects of practice on executive control investigated with fMRI. Brain Res Cogn Brain Res *15*, 47-60.

Whalen, P. J., Bush, G., McNally, R. J., Wilhelm, S., McInerney, S. C., Jenike, M. A., and Rauch, S. L. (1998). The emotional counting Stroop paradigm: a functional magnetic

resonance imaging probe of the anterior cingulate affective division. Biol Psychiatry *44*, 1219-1228.

Wik, G., Fredrikson, M., Ericson, K., Eriksson, L., Stone-Elander, S., and Greitz, T. (1993). A functional cerebral response to frightening visual stimulation. Psychiatry Res *50*, 15-24.

Williams, J. T., Henderson, G., and North, R. A. (1985). Characterization of alpha 2-adrenoceptors which increase potassium conductance in rat locus coeruleus neurones. Neuroscience *14*, 95-101.

Willig, R. D. (1976). Consumers Surplus without Apology. American Economic Review *66*, 589-597.

Winstanley, C. A., Theobald, D. E., Cardinal, R. N., and Robbins, T. W. (2004). Contrasting roles of basolateral amygdala and orbitofrontal cortex in impulsive choice. J Neurosci *24*, 4718-4722.

Wise, R. A. (2004). Dopamine, learning and motivation. Nat Rev Neurosci *5*, 483-494.

Worsley, K. J., Marrett, S., Neelin, P., Vandal, A. C., Friston, K. J., and Evans, A. C. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. Human Brain Mapping *4*, 58-73.

Wright, P., and Liu, Y. (2006). Neutral faces activate the amygdala during identity matching. Neuroimage *29*, 628-636.

Yacubian, J., Glascher, J., Schroeder, K., Sommer, T., Braus, D. F., and Buchel, C. (2006). Dissociable systems for gain- and loss-related value predictions and errors of prediction in the human brain (vol 26, pg 9530, 2006). Journal of Neuroscience *26*, -.

Yaremko, R. M. (1986). Handbook of Research and Quantitative Methods in Psychology, Lawrence Erlbaum Associates).

Yu, A. J., and Dayan, P. (2005). Uncertainty, neuromodulation, and attention. Neuron *46*, 681-692.

Zajonc, R. B. (1984). On the primacy of affect. American Psychologist *39*, 117-123.