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Motivational modulation of decision making processes

Piech, Richard M.

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By Richard M. Piech

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Summary

The experiments described in this thesis aim at investigating the influence of appetitive motivation on decision making. The single experiments address distinct components of decision making. All experiments include some form of manipulations of participants' desire to eat. We analyzed the effects of such manipulations on participants' behavioral responses and the responses of their neural systems.

Experiment 1 investigated the dependence of cognitive flexibility on motivational factors. It showed that cognitive flexibility was affected by either hunger or desire. The results demonstrate that changes in motivational state can produce altered cognitive flexibility levels and point to a psychological interface between motivation and cognition.

Experiment 2 targeted the neural basis of motivational modulations identified in experiment 1. It showed differences between the activations associated with the cognitive processes, depending on participants' hunger state. The results show that motivation can modulate prefrontal activity associated with cognitive processes.

Experiment 3 examined the influence of motivational state on the representation of incentive value. Activity in the amygdala was consistent with the representation of attractiveness, while the orbitofrontal cortex showed a response pattern indicating integration of incentive value with hunger state.

Experiment 4 targeted the selection of an option among others. Choice guided by affective processes activated the insula, anterior temporal cortex and the medial OFC, consistent with involvement of the insula in gustatory and interoceptive perception processes and of the anterior temporal cortex in affective and mnemonic processing. It also dissociated the role of medial and lateral orbitofrontal cortex in choice.

Thus, the results of the experiments show that the cognitive and motivational systems are dependent on each other. The understanding of the interactions of cognition and motivation will be crucial for the understanding of decision making.

Chapter 1: Introduction

This thesis discusses a series of experiments addressing processes which are ultimately prerequisites or components of decision making. Specifically, the experiments investigate the influence that appetitive motivation has on such processes. Motivational changes are induced through a manipulation of participants' desire to eat. Participants are tested in separate sessions, either sated or after a period of fasting. The experiments exploit the increased motivation to eat which follows fasting. In one of the experiments (1), desire to eat is also manipulated through exposure to food cues. Throughout the text, the conditions of satiety versus increased appetite in combination with food or non-food cue exposure are referred to as different motivational states. These manipulations are hypothesized to induce changes akin to those observed following shifts in emotional state. Indeed one aim of the work in this thesis is to consider similarities in the effect of motivational and emotional changes on cognitive and decision making processes.

The studies presented in this thesis focus on specific aspects of the decision making process, such as attentional focus of cognition, the valuation of predicted reward and the choice mechanisms for prospective action. Crucially, all of these are probed under different motivational states. Experiments 1 and 2 investigate an early aspect of the decision making process, the allocation of attention. They are aimed at determining how a change in the motivational state influences attentional focus of cognition. The particular question focused on is whether increased desire to eat has an effect on the tendency to make intradimensional or extradimensional shifts of attention. In experiment 1, the behavioral changes in shifting performance are documented, while appetite is increased through fasting or exposure to food cues. Experiment 2 utilizes fMRI and compares participants' performance while

sated or hungry. The aim of the study is to determine the pattern of brain activity during attentional shifts and how it varies with motivational state.

Making correct decisions depends crucially on the accurate valuation of the available options in the light of current need (Padoa-Schioppa & Assad, 2006). Experiment 3 is an fMRI study which focuses on the representation of anticipated value, and how the value representation changes depending on motivational state. Participants are asked to imagine being in a restaurant as they read food item descriptions taken from restaurant menus. The neural representation of highly valued and less highly valued items is then compared between one sated and one hungry experimental session.

Whereas experiment 3 targets the prerequisite of a decision - the representation of anticipated value, experiment 4 addresses the subsequent process: the choice between options with different properties. Participants choose between food items described in menus. The design allows the identification of brain activity related to choice guided by incentive value, compared with a control condition in which choice is guided by value-irrelevant properties. Choices are then compared in different motivational states.

The organization of the text of this thesis is as follows: Chapter 1 first offers definitions of crucial concepts and their interdependence in the context of the thesis. These concepts are decision making, emotion, motivation, and cognition. This is followed by an introduction of the current state of knowledge on selected themes in decision making research. The Chapter finishes with an outlook on the four experiments described in Chapters 2-5. Chapter 6 offers possible interpretations of the findings, and suggests avenues for future research.

Decision making

Decision making is a vast concept, not only in general but also within the context of neuroscience (Balleine, 2007). Decision making research in that context utilizes a number of approaches. The methods for data acquisition include traditional behavioral experiments across several species as well as lesion studies, brain imaging techniques and neurophysiological recordings. Investigations of decision making focus on various aspects of the phenomenon. They range from saccadic eye movement decisions to look at and perceive certain stimuli over others, representation of value and outcome prediction, cognitive strategies, to the investigation of the process of selection and the evaluation of decisions after their outcome (Daw, O'Doherty, Dayan, Seymour, & Dolan, 2006; Glimcher, 2003; Kringelbach, 2005). The experiments described here explore a small set of 'decisions', as well as their underlying components, using behavioral performance measures and functional magnetic resonance imaging (fMRI). Of particular interest is the affective-cognitive interaction, meaning the influence a changing affective state has on the (mainly cognitive) processes which lead to decision making. The opposite direction of influence, the impact of a cognitive manipulation on decision making, is also the subject of a study (experiment 4), in which choice between differently valued options is guided by value-irrelevant properties.

Decision making as studied in this thesis is the process by which animals choose between several options of behavior, which are usually competing, based on the anticipated value of the outcome of the choice (Bogacz, 2007; Dickinson & Balleine, 2002; Fellows, 2007; Hampton & O'Doherty, 2007; Tobler, O'Doherty, Dolan, & Schultz, 2007). A simplified exemplary sequence of processes contributing to decision making is the following: (1) identifying goals and calculating their expected value, (2)

identifying actions to achieve such goals and calculating their likelihood of success, (3) selecting and performing a chosen action sequence, and (4) assessing the consequences and feeding them back into subsequent value assessments.

The experiments described here address three of the listed processes: the focus of attention to include or exclude stimuli as meaningful units (experiments 1 and 2), assessing expected value based on mnemonics and subjective motivational state (experiment 3), and selecting among options with differing expected values (experiment 4). The dependence of these processes on the state of the organism and on executive strategies will be investigated and assessed with performance measures and the recordings of the accompanying brain activity.

Emotion

There are numerous approaches to defining emotion. Ekman (e.g. 1992) lists six basic emotions, such as fear and happiness. Both his categorization and inclusion criteria are based mainly on perception of universal facial expressions, i.e. expressions which are reliably identified as representing one emotion across a number of cultures. Others stress the role of emotions in interacting with reward contingencies of the environment (Rolls, 2005). A well established view links emotions closely with the physiological state of the body (Bechara, Damasio, & Damasio, 2000).

Although there used to be a great deal of debate and controversy over what emotions really are, e.g. the controversy between Zajonc and Lazarus (Lazarus, 1991; Zajonc, 1980), emotion research has made great progress without a perfect definition. This is not a satisfying state, and the effort to validly define emotions continues (Zinck & Newen, 2008). However, in the light

of the origin of emotions, they appear to be mechanisms and strategies which evolved to aid coping with recurrent problems organisms might encounter (Tooby & Cosmides, 2005). Faced with stimuli of varying degrees of complexity, from visual or auditory patterns to social constellations, emotions have the capacity to tag such stimuli with a reference to the goals of the organism as either good and aiding the goals, or as bad and hindering them. This reference then has the potential to guide behavior. On a basic level, the guidance is the decision between approaching in order to acquire resources, or withdrawing in order to avoid harm (Carver & White, 1994).

Emotions are often considered to have three response components, which tend to be studied separately: the subjective emotional experience (Barrett, Bliss-Moreau, Duncan, Rauch, & Wright, 2007), the physiological responses of the body (Cacioppo, 2004), and the creation of a behavioral tendency or motivation (Cardinal, Parkinson, Hall, & Everitt, 2002). The component mainly addressed in the described experiments is the last one, the motivational consequences of fasting and exposure to food cues, and their impact on decision making processes as indexed by behavioral responses.

Motivation

Motivation is the force that drives all of behavior. Assessing motivation directly is challenging, as it is primarily manifested in behaviors resulting from it. It is nevertheless a useful concept in the study of behavior because it allows the convergence of all approaches attempting to explain 'why' certain behaviors happen, i.e. what their sources are, on a level which reaches beyond small behavioral fragments. The sources of motivation are manifold, from needs of basic survival to social desires for respect or image. Of significance within the context of experiments described here is the motivation to eat. Among factors

which contribute to peoples' motivation to eat are: homeostatic nutrient need states (hunger), hedonic properties of food (because some dishes are really tasty), acquired feeding patterns (meal times), social expectations (dinner with friends), or the combination of any of the mentioned factors. The affective component referred to in the described experiments is the changing motivation to eat. It is manipulated in two ways. Firstly, the physiological motivation to eat is increased through a period of fasting before experimental sessions (experiments 1-4). In addition, experiment 1 modulates motivation to eat by exposing participants to food cues (pictures of attractive food dishes). To confirm the success of the manipulation, motivation to eat is assessed through participant self reports of hunger level. This self-report also provides a link between the overlapping concepts of emotion and motivation. People report affective arousal (craving) to food cues and hunger, in much the same way as showing affective responses to stimuli from more traditional domains such as fear, or happiness (Kapp, Whalen, Supple, & Pascoe, 1992; Volkow et al., 2002).

Previous work provides some evidence that motivational changes like the induction of hunger or appetite influence different stages of the DM process. Hunger biases attention to food-related stimuli (Mogg, Bradley, Hyare, & Lee, 1998), and increases the memory advantage for food items (Morris & Dolan, 2001). A common feature of the effects described in these studies is that hunger influences aspects of cognition directly relevant to the satiation of hunger. There is very little evidence of an impact of hunger on a higher level cognitive function that may be not directly relevant to food acquisition. An exception constitutes a study by Diano and colleagues (2006), who showed that the neuropeptide Ghrelin, which is produced by the stomach and contributes to the hunger signal, improves non-food related spatial learning and memory performance by acting on synapses in the hippocampus. The

limited amount of evidence for hunger effects on cognition leads Dye and Blundell (2002) to argue that a stable optimal level of cognitive functioning is so crucial for survival that it might be strongly protected against short-term dietary fluctuations. In experiment 1, we show one way in which the manipulation of desire to eat by either fasting or exposure to food cues affects attentional shifting when that is not directly related to the hunger state.

The Relationship of Emotion and Motivation

An issue which requires clarification for the discussion of the presented experiments is the relationship of emotion and motivation. The aim of the studies conducted was to shed light on emotion-cognition interactions in the human brain within the context of decision making. The manipulations we utilized are as described above as changes of motivational state, however. The link between the motivational manipulations used in our studies and the concept of emotion becomes clear by distinguishing the temporal components of motivation, in particular the difference between preparatory and consummatory components, as postulated by the incentive salience model (Berridge & Robinson, 1998). The model assumes that motivation to obtain reward has a preparatory component that is characterized by the anticipation of an event, and a consummatory component, when that event actually happens. The components are frequently referred to as 'wanting' and 'liking', with wanting representing the desire to achieve an event or state, and liking the actual consummation of a motivational goal, like eating or drinking. The two components have been shown to be distinguishable based on the neural systems they are supported by (Berridge, 2004). In the context of food and a restaurant visit, the actions that lead to entering a restaurant and choosing certain items from the menu are based on anticipation of motivationally

relevant events, i.e. prospective choice or decision making. The eating itself constitutes the 'consumption' of the event. The experiments described here deal only with anticipatory motivation. This is similar to many emotions, which constitute the anticipation of a relevant event, as fear or disgust – examples of 'basic' emotions (Ekman, 1992) - are anticipations of adverse events like pain or ingestion of harmful agents. In this sense, both fear and desire can be seen as the anticipation of an event with value qualities – one negative, one positive – which will influence decision making directly as a result of the expectation of the value.

Apart from the incentive salience model, the concepts of emotion and motivation overlap to the degree that it is difficult to distinguish between them. Emotions often have a motivational component, even if it is not always visible in the form of an action. Fear makes one hide or escape, disgust spit out, and sadness withdraw. Even emotions with less obvious associated motor functions, for example happiness, coincide with motivation to celebrate or in fact recreate whatever caused the emotion to begin with. On the other hand, motivation usually results from emotions. Although many of our actions seem to occur without a close link to an emotion (like work), most of them are performed in anticipation of some reward and are thus linked to emotions that occur as such reward is experienced. In this text, hunger manipulations will be treated as changes in motivational state, as hunger affects behavior by eliciting food seeking and contributes to the initiation of feeding (Erlanson-Albertsson, 2005). This can manifest itself in humans by searching for a restaurant, ordering food and eating it when hungry, even in the absence of additional motivating factors like time of day or company. It is worth noting, however, that there also is a subjective emotional quality to hunger, often expressed in food preferences. The mentioned restaurant search and the food order, i.e. a

person's food preferences will likely be affected by the feeling experienced when previously eating certain categories of food in certain places.

Cognition

The expression 'cognition' refers to a number of processes performed by the brain which are perceived as one category (Posner, 1973). The criteria for category inclusion are not always clear, but cognition is often associated with 'cold', logical, and rational information processing as opposed to 'hot', illogical and irrational affect (see below). In spite of the lacking clear inclusion criteria, there is an impressive agreement about what cognition is. The number of processes considered as cognitive is large (Cabeza & Nyberg, 2000), they include perception, attention, memory, reasoning, and planning. The function of some cognitive processes is associated with high-level, executive goals, implying deliberate control, as it may be required when the execution of a task conflicts with salient distractions. Attempts to define cognition by the neural structures cognitive processes engage will have to face circularity problems, in addition to the fact that an increasing amount of 'cognitive' structures in the brain are shown to also have non-cognitive properties. As such, it is of greater utility to focus on individual fractional processes in order to understand how the 'cognitive' system works.

The Relationship of Emotion and Cognition

The notion that cognition and emotion are separate domains, with similarly separate neural systems which house them, has been challenged and revised from many perspectives, but continues to invite criticism (Pessoa, 2008). The most influential line of argument came from findings of economists on decision

making. 'Classic' decision making models, as for example expected utility models (Schoemaker, 1982), saw decision making as a highly cognitive and rational process of choosing among alternatives with differing value. Tversky and Kahneman (1974) demonstrated that in some circumstances, as under conditions of uncertainty, subtle and apparently irrelevant factors influence choices decisively. Their work was not directly aimed at emotional influence on decisions, but it clearly showed the importance of non-rational, intuitive influences on decision making. Their findings were considered support for the notion that humans do not base their decisions on purely cognitive considerations but are susceptible to irrational (in so far as non-logical) influences. After that, work from the laboratory of Antonio Damasio and others attempted to shed light on just what those irrational influences were and how they influenced decisions (Damasio, 1994). With his colleagues Damasio provided evidence that decision making in humans depends on affective influences (e.g. Bechara et al., 2000) and that their physiological correlates might provide a mechanistic basis for that influence. According to their model – the somatic marker hypothesis (SMH) - the affective arousal experienced (consciously or not consciously) coupled with an emotionally significant event or stimulus is stored by the brain as an association between that event and a physiological state. That association constitutes a marker signal. At a later time point, this marker signal can be activated by precursors of such events. A choice between options is then based on the marker signal which labels each option (Bechara & Damasio, 2005; Damasio, 1996). Alternative concepts of the mechanisms exerting emotional influence on decision making suggest that SMH is an unnecessarily complicated account of the phenomenon and that central neural signals suffice for that purpose (Rolls, 1999, p. 73) (Braesicke et al., 2005), but support the importance of emotion in decision making.

Along with the philosophical divide between emotion and cognition, and the advancement of functional localization as an organizing principle of the nervous system, there has been a consistent effort of neuroscientists to define emotional and cognitive divisions of the brain. As a consequence, some neural structures and cortical areas are currently strongly associated with emotion, while others are ascribed to cognition. For example, no other structure of the brain is linked to emotion as closely as the amygdala. In fact, LeDoux' (1996) popular book termed 'The Emotional Brain' talks almost exclusively about the amygdala. It is worth pointing out that the amygdala is a complex of several nuclei which appear to have distinct functions (Swanson & Petrovich, 1998) and contribute in differing degrees to cognition. When visual stimuli are presented to participants in fMRI experiments, the ones which are emotionally significant often receive more attentional resources (Pessoa, Kastner, & Ungerleider, 2002). There is correlational support from fMRI studies (Vuilleumier, 2005) as well as causal evidence from lesion studies (Anderson & Phelps, 2001); (El-Amamy & Holland, 2007), that the amygdala underlies these effects. While the aspect of the stimulus it responds to in those experiments is affective, its response modulates perception through attentional mechanisms – a typical cognitive process.

On the other hand, one cortical area strongly linked with cognition in the human brain is the dorsolateral prefrontal cortex (DLPFC) (Miller & Cohen, 2001). It has been shown to be active in a variety of tasks, the essence of which seems to be their high cognitive demand (Duncan & Owen, 2000). But even the DLPFC has been shown to be sensitive to affective stimuli. When participants are instructed to maintain pictures in working memory – a cognitive process – the activity in their DLPFC was shown to depend on the emotional value of the current picture (Perlstein, Elbert, & Stenger, 2002), demonstrating sensitivity to affective content. Participants instructed to inhibit responses after

the presentation of words displayed a greater activation of the DLPFC when the word had a negative emotional connotation, than when it was neutral (Goldstein et al., 2007). In experiment 1, we will investigate how the cognitive process of attentional shifting is affected by motivational modulation. In experiment 2 we will test the susceptibility of DLPFC activation to affective manipulation.

Evidence linking the emotional and cognitive systems of the brain also comes from research in substance abuse and addiction. The initial appeal of substances of abuse results from their action on affective brain systems like the mesolimbic dopamine pathway, involving the midbrain ventral tegmental area and the nucleus accumbens, associated with reward processing (Koob & Le Moal, 2001; Volkow, Fowler, Wang, & Swanson, 2004). Repeated intake of the substance leads to transitions in the brain systems underlying consumption behavior (Everitt & Robbins, 2005; Robinson & Berridge, 1993, 2003), and crucially has a number of consequences on cognitive functioning, including attentional bias (Hester, Dixon, & Garavan, 2006), weakened control over (Baler & Volkow, 2006; Garavan, Hester, Murphy, Fassbender, & Kelly, 2006), and monitoring of behavior (Hester, Simões-Franklin, & Garavan, 2007). The changes in cognitive functioning seem to be of such character that they contribute to further consumption of the substance (Garavan & Hester, 2007).

A broad distinction between cognition and emotion (in particular but not exclusively its motivational component), is that cognition provides inherent tools to understand the world, whilst emotion provides the tools to react to and survive in it. In healthy functioning individuals' cognition and emotion interact to attain their goals and are integrated in a number of neural structures, including the amygdala, striatum, and ventral, medial and lateral sections of the PFC (Pessoa, 2008).

Prediction and Value

As noted above, the prediction of value associated with an option and the choice from several options are crucial components of decision making. Both functions seem to be represented within the prefrontal cortex (PFC), especially the orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC). The role of the PFC in decision making has been studied from a number of perspectives, including neuropsychology and neurophysiology (Koechlin & Hyafil, 2007). In the context of the experiments described here, I will focus on selected neuroimaging studies. The OFC shows selective responses to manipulations of value, particularly valence and quality, associated with rewarding stimuli (Anderson et al., 2003; Small et al., 2003). But the relationship between signal from the OFC and value seems to depend on more than just one factor. For example, it seems to represent value of food related stimuli depending on the hunger state of the participants (Hinton et al., 2004). This suggests that the OFC integrates the state of the organism with value properties of stimuli, to produce a value signal which is based on integrated information from several sources (Rolls, 2004). That value signal appears to then be used by the mOFC to evaluate the higher-level decision making strategy of the organism (Haddon & Killcross, 2005; Wallis, 2007). Subregions of the OFC seem to play distinct roles in that process, with a marked division between the medial and lateral areas contributing to approach and avoidance functions, respectively (Arana et al., 2003; Elliott, Dolan, & Frith, 2000).

In experiment 3, we investigate representation of value in the OFC based on mnemonic processes and as a function of current organism state. Experiment 4 sheds light on how executive functions can modulate PFC activity.

Corticostriatal Networks and Neurotransmitter Systems

The neurotransmitter that has classically been closely linked to decision making is dopamine (DA), due to its supposed connection to reward. In the human brain, DA originates in the midbrain, in particular in the ventral tegmental area (VTA) and substantia nigra pars compacta (SNpc). Dopaminergic connections from there target the basal ganglia, but also cortical areas, especially the PFC. After initial findings of DA responses to administration of palatable food in animals, DA was thought to signal reward (Wise & Rompre, 1989). Later it became clear that increased DA levels in the midbrain represent a positive reward prediction error (meaning that an event was more rewarding than expected), while decreases represented the opposite (Hollerman & Schultz, 1998). Partly because of symptom observations after disruptions of the DA system in disorders like Parkinson's Disease (PD), DA was assigned an increasing number of functions, related to reward, but also to some cognitive functions. Recently, clarification of the role of DA in some of those functions has been attempted, e.g. in the context of drug abuse (Di Chiara & Bassareo, 2007), but also including the assignment of DA to different, sometimes contradicting functions through separate time courses of DA action (Schultz, 2007). Below, I will address the significance of DA in the motivational system, especially in relation to hunger, and its impact on cognitive flexibility, as those are of importance in the presented experiments 1 and 2.

The mesolimbic dopaminergic pathway innervating the ventral striatum is a core component of the brain's motivational arousal system: food-associated stimuli produce increased DA in the ventral striatum of animals and humans, whilst damage to the ventral striatum, or disruption of its dopaminergic innervation, abolishes motivational arousal for food, sex and drugs (Everitt et al., 1999; Hall, Parkinson, Connor, Dickinson, & Everitt, 2001;

Parkinson et al., 2002; Volkow et al., 2002; Wyvell & Berridge, 2000). DA is also implicated in cognitive flexibility. For example, DA antagonists impair attentional set-shifting in humans and rats (Floresco, Magyar, Ghods-Sharifi, Vexelman, & Tse, 2005; Mehta, Manes, Magnolfi, Sahakian, & Robbins, 2004), DA medication recovers shifting deficits in Parkinson's patients (Cools, Barker, Sahakian, & Robbins, 2001) and specific deficits in cross-dimensional shifting of attention, including perseveration, are thought to be due to dysfunction in the dopaminergic innervation of PFC-caudate interactions (Chudasama & Robbins, 2006). Whilst the studies in this thesis were not designed to identify DA contributions to motivation and decision making, the target regions of DA activity were examined in the neuroimaging experiments.

Other neurotransmitter systems that have been suggested to play a role in decision making processes are the serotonin system (Tanaka et al., 2007), which seems to play a role in representing delayed rewards, and the opioid system (Redish & Johnson, 2007) possibly involved in evaluation of hedonic value. The exploration of these systems is a promising endeavor for future research.

Reward Representation in the Striatum

The striatum is the input structure of the basal ganglia, consisting of the putamen, nucleus accumbens (NAcc) and the caudate. As stated above, the striatum receives dopaminergic projections from the midbrain. Its anatomical connections allow it to influence both cognitive processing as well as motor output, which puts it in the position of integrating affective influences into cognition and behavior (Alexander & Crutcher, 1990; Flaherty & Graybiel, 1994). Event-related fMRI experiments probing the actor–critic model showed that the dorsal striatum displays activations consistent with maintaining

information about the outcome of actions (the 'actor'), whereas the ventral striatum is associated with predicting future reward (the 'critic'), (Barto, 1995; J. O'Doherty et al., 2004). The position of the dorsal striatum in the dopaminergic motivational system and responsiveness to food related stimuli (Volkow et al., 2002), as well as influence on cognitive processing, makes the striatum a possible site of affective influence on attentional focus that is the focus of experiment 1, and an area of interest for investigating action selection processes in experiment 4.

A mechanism which would allow motivation and cognition to interact could consist of cross-circuit dopaminergic interactions within corticostriatal circuitry, which consists of a number of loops connecting the striatum with the cortex, presumed to subserve differing functions (Haber, Fudge, & McFarland, 2000);(Parkinson, Cardinal, & Everitt, 2000). For the case of food-related manipulation as utilized in experiment 1, arousal induced by food cues presumably triggers DA release in the mesolimbic system, which in turn modulates the dopaminergic innervation of the nigrostriatal system resulting in a change in the balance of set-shifting behavior, indicating altered cognitive flexibility (Haber et al., 2000). Experiment 1 presents data on the relationship between food-related motivation induced through fasting or exposure to appetitive stimuli, whereas experiment 2 investigates the neural basis of attentional shifting under conditions of hunger or satiety.

Decision Making Aspects addressed in Experiments 1-4

The flexibility of attention allocation is an early step in the decision making process. Experiments 1 and 2 target affective influence on how flexibly attention can be allocated. Participants complete a task which incorporates voluntary switches of attention. The attentional task used allows distinguishing

between intradimensional and extradimensional switches, operationalized as shifting attention between different stimuli in the same category (intradimensional, or 'small', switch), and between different stimuli in two distinct categories (extradimensional, or 'big', switch). The tendency of participants to make 'big' or 'small' switches is then assessed, indicating the degree of their current cognitive flexibility. Motivational impact on flexibility is assessed by exposing participants to food or nonfood cues before the tasks, as well as by asking them to fast prior to one of the two experimental sessions. While experiment 1 explores the behavioral impact of the motivational flexibility, experiment 2 contrasts the brain activity recorded with fMRI during 'big' and 'small' attentional switches, both during a sated and a hungry session.

The accurate prediction of reward plays a crucial role in decision making. Experiment 3 is an fMRI study investigating the interaction between representation of anticipated reward and hunger level. It focuses on the dissociable roles of the OFC and the amygdala in incentive value representation. In the experiment, participants read food item descriptions similar to those on restaurant menus. They then indicate how much they like each item. The fMRI signal from low value items is compared with high value items. The affective system is manipulated by asking participants to fast prior to one of the two experimental sessions. The representation of value is then compared across the sessions.

Whereas experiment 3 investigates incentive value representation that is a prerequisite of decision making, experiment 4 targets the process following value representation, which is the choice between options with different values. Participants again read restaurant menu item descriptions while fMRI signal is being recorded. For this experiment, each trial presents them with three food options to choose from. To assess which neural sites are activated during choice guided by incentive value, this process is contrasted with choice based

on a value-irrelevant criterion, the ease of preparing a food item. The activation of the neural sites activated for affect-guided choice is compared between the sated and hungry states.

Chapter 2: Modulation of cognitive flexibility by hunger and desire

[Portions of this chapter are adapted from an article in press: Piech RM, Hampshire A, Owen AM, Parkinson JA. Modulation of cognitive flexibility by hunger and desire. *Cognition & Emotion*]

Introduction

The complex environment we live in requires the maintenance of a consistent response pattern to certain conditions but also the ability to adapt when conditions change. This demand for both consistency and adaptation is reflected by cognitive processing systems that monitor and finely tune behavior in order to achieve goals (Cools & Robbins, 2004). The prefrontal cortex (PFC), along with its associated striatal circuitry, is thought to play an important role in such monitoring, maintenance and flexibility (Miller & Cohen, 2001). Cognition and behavior should also be modulated by external and internal environmental variables, such as hunger and the availability of food. So, for example, an increase in hunger brought about by fasting should bias attention and behavior towards food-related stimuli and foraging, whereas foraging should be trumped, in attentional and behavioral terms, by imminent threat and predation. To date, little work has examined the interface between food-related motivational variables and cognitive flexibility (Morris & Dolan, 2001).

Cognitive flexibility can be captured by performance on tasks that contrast different kinds of attentional shifting such as the WCST and its analogues (Downes et al., 1989; Owen et al., 1992; A. C. Roberts, Robbins, Everitt, & Muir, 1992). A typical task consists of a solution search during which attention has to be transferred from one perceptual dimension to another, following a rule, in order to identify a target stimulus from one of the perceptual

dimensions (for example, houses versus faces). This task requires a combination of consistency, once a target has correctly been identified, and flexibility, in identifying a new target once the old one is no longer correct. Intradimensional shifts (IDs) are those where the participant continues to search for targets within the same dimension (continuing to pursue houses), whereas, if the participant chooses to change dimension (switching from houses to faces), then they make an extradimensional (ED) shift. These two types of shift are conceptually (and potentially neurobiologically) separable – foraging for food requires a complex balance between dimensional maintenance and shifting.

Hunger plays a central role in energy regulation and affects behavior by eliciting food seeking and contributing to the initiation of feeding. Since food acquisition success partly depends on elaborate strategic behaviors, one would expect adjustments of the cognitive system to hunger to be adaptive. Consistent with this, it has also been shown that individuals suffering from eating disorders, such as anorexia nervosa – an extreme state environment, show selective cognitive deficits relating to their ability to shift set: an apparently selective increase in perseverative errors (M. E. Roberts, Tchanturia, Stahl, Southgate, & Treasure, 2007; Steinglass, Walsh, & Stern, 2006). Further, set-shifting processes depend upon corticostriatal circuitry (Chudasama & Robbins, 2006; Rogers, Andrews, Grasby, Brooks, & Robbins, 2000), re-entrant loops between areas in the prefrontal cortex and the basal ganglia (Alexander, DeLong, & Strick, 1986), and dysfunction of this system has also been implicated in anorexia nervosa (Husain et al., 1992).

One might therefore hypothesize that state-dependent manipulations of hunger should produce a modulatory influence over cognitive processing, and in particular set-shifting, by reducing the tendency to make ED shifts. The mesolimbic dopamine (DA) system, providing a modulatory input to

corticostriatal circuitry, has been widely implicated in stimulus-induced motivational arousal and so a more specific hypothesis is that hunger, induced not by food deprivation, but by the presentation of food-associated appetitive stimuli should also modulate set-shifting behavior. Therefore, in the current study, healthy volunteers completed a set-shifting task (the set-shifting task itself did not involve food-associated stimuli; the visual category dimensions were pictures of faces or houses) whilst they were either hungry or sated (physiological manipulation) and after being exposed to either appetitive food cues, or control (flower) stimuli (desire manipulation). The specific task to assay cognitive flexibility was chosen for several reasons: critically, the task allows identification of the exact target that participants have chosen and this enables categorization of specific shifting behavior and error type (e.g. ED versus ID shifts); it uses non-novel dimensions and manipulations to reduce the impact of learned irrelevance; the use of partial feedback also equates experienced reward contingencies for both ID and ED shifts. Thus ID and ED shifting behavior is cleaner in terms of task processing and also for subsequent experimental analysis. It is also worth noting that this specific task has been shown to activate ventrolateral PFC and anterior cingulate in ED shifting, two areas that are also implicated in affective influences over cognition (Hampshire & Owen, 2006).

Method

Participants

Sixteen students (9 female, average age 20.3 years, SD = 2.8), participated in the experiment as part of their course credit. For the hungry condition, they were instructed to not eat for 5 hours prior to the experiment. The study was approved by Local Research Ethics Committee.

Design

The two participant-related within-subject factors were State (Physiological: hungry vs. sated) and Desire (Stimulus-induced: food vs. nonfood) and their effect was assessed on various measures of attentional set-shifting including the number of ID and ED shifts, as well as associated errors and reaction times. Measures of self-reported hunger were also recorded.

Procedure

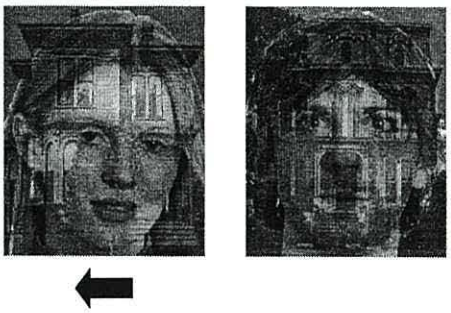
Set-shifting tasks are commonly derived from traditional rule-learning paradigms such as the Wisconsin card-sorting task; in essence, the participant's role was to identify a target stimulus from an array of four exemplars which themselves came from two categories (faces and buildings; (Hampshire & Owen, 2006), their Figure 1, page 1681, my Figure X-0.5). Each array of stimuli was presented as two superimposed pairs presented on either side of a computer screen. So, on each side of the screen were a building stimulus and a face stimulus (the transparency of the stimuli were set such that both stimuli were visible and identifiable. On each trial, the participants were required to indicate using the keyboard on which side of the screen they thought the target was located. Participants made a response to indicate which side of the screen they believed the correct stimulus to be. Following a response, the stimuli disappeared from the screen, prior to a new trial commencing. Feedback was provided on every second response ('correct' or

'incorrect' was presented on the screen for 0.6 s, indicating whether the two preceding stimuli they had chosen were both the target or not). Each trial consisted a different combination of the house and building stimuli (though always one house and one building per compound).

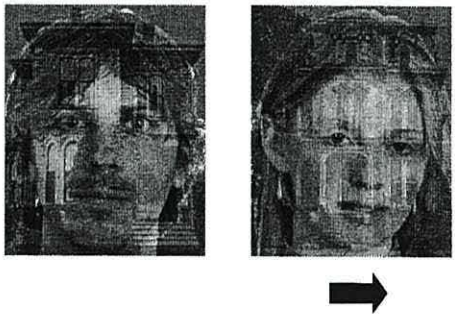
After 6 correct responses to the target (i.e., 3 positive feedback events), a change of target occurred. The change was either a new target of the same dimension (requiring an intradimensional shift) or a new target in the other dimension (requiring an extradimensional shift). The new target could also be in the form of a stimulus group change, in which new compound stimulus pairs were presented (i.e. a novel set of house and face stimuli were introduced), or simply in the form of a rule change, in which the group would stay the same and a previous nontarget would become the target (i.e. the existing house and face compounds were retained, but the specific target stimulus was changed). Participants were clearly instructed to keep responding to the correct target until informed that it was no longer the target and to respond 'as quickly and accurately as possible'. The task duration was 8 minutes. The crucial cognitive process we were interested in was the participants' shift of their responding to a different category (ED shift), or to a different item in the same category (ID shift). This design was adopted primarily to allow participants to dictate the pace of events and to determine for themselves the number of shifts to make during their time on task – an important consideration given our hypothesized effect of motivational manipulations on the tendency to initiate shifting behaviour. Secondarily, the design was based on previous work (Hampshire and Owen, 2006) in order to allow comparison of results and to prepare for future exploration of these manipulations within a neuroimaging context.

During task performance, the participant could shift their responding to a new target at any time (though this was most likely following feedback of an incorrect response). As the computer tracked the stimulus that the participant

had previously responded to, it was possible to determine how often they made an ID shift (changing targets within the same dimension e.g. one face to the other face) and how often they made an ED shift (e.g. changing from a face to a building). Thus it was possible to calculate differences in the tendency to make correct and incorrect ID and ED shifts across the task. For the analysis, as well as calculating the number of correct shifts that a participant made, we also counted the *number of errors* committed when the participant shifted their responding to a new target in either the same (ID) or the alternate dimension (ED): after each change, the number of responses before finding the correct target was counted. In some trials the participant first found and then lost the new target before reaching criterion (6 correct responses). The incorrect responses which followed loosing the target were counted as errors in completing the switch. Thus we could analyze the total number of errors made on the task, as well as the ratio of ED and ID errors. To achieve the latter, an index of cognitive inflexibility, we calculated the ratio of ED errors committed to total errors committed (the sum of ED and ID). This is referred to as the Inflexibility Ratio (IR); a higher number reflecting a greater proportion of responses taken to shift across categories (ED) than within (ID). Importantly, this reflects the ratio of errors made when an individual chose to make either an ED or ID shift, independently of whether the correct target actually changed.



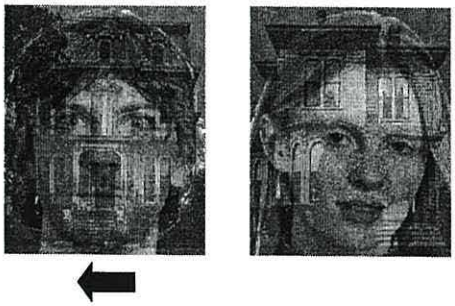
The participant sees four items, two faces and two buildings. He/she has to identify the target. On the first trial, that means just picking one. In this case the participant chooses the woman and presses the left key. (The black arrow only appears in this illustration, not in the experiment).



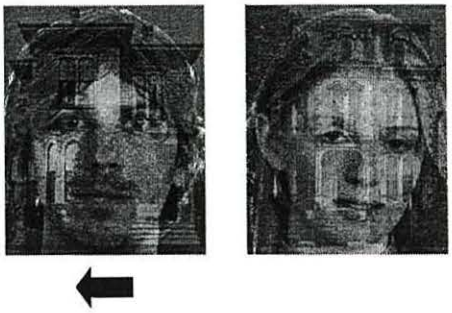
The same four stimuli, but rearranged, appear on the next screen. Participants are instructed to stick to the same target between feedbacks. Here, this means pressing right for the woman again.

INCORRECT

The next screen delivers feedback.



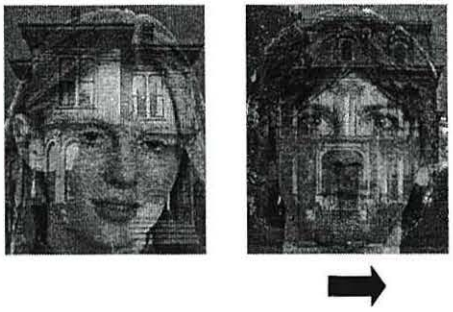
The next trial follows. The woman turned out to not be the target. The participant decides to find out if the man is the target and indicates left.



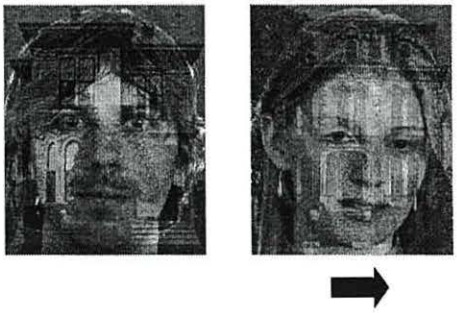
The man is on the left again.

INCORRECT

The man is not the target, either.



The next trial follows. The woman and the man both turned out to not be the target. The participant decides to find out if one of the houses is the target, and chooses the one with pillars.



The house with pillars is on the right again.

CORRECT

The feedback indicates that the current target is correct. Now that the participant found the target, he/she is supposed to keep indicating that target. A change of the target happens after six responses or three positive feedback events. Changes can be indicated by a new group of stimuli or the 'incorrect' feedback.

Figure X-0.5. Example trials for the beginning of the task as it would be seen on a computer screen. The first screen is in the top left column. Descriptions of actions of a hypothetical participant are below each screen.

Notably, the events crucial for the analysis happen during the solution search *after* a target change: the main comparison of interest is the number of errors committed before finding the target after a within-category (ID) switch versus a between-category switch (ED).

A second comparison of interest was between reversals and shifts. A *reversal* is a target change within *the same* set of stimuli. In such a case, the four items displayed remain the same, but the target is now a new one (note that reversals can be intradimensional switches or extradimensional switches). A shift is a target change elicited by the appearance of a set of four new stimuli. Again, such a shift can be intradimensional or extradimensional.

Participants came to the laboratory on two consecutive days, once for the hungry and once for the sated condition. The sessions were identical, with half the participants starting with the hungry one. During each session the participants completed two equivalent versions of the set-shifting task and watched a presentation (induction procedure) prior to each run of set-shifting. The desire-induction presentation consisted of 50 pictures of food (4s each, 1s interval) and participants were asked to imagine what the food would taste like when eaten. In the control condition, the pictures depicted flower arrangements (nonfood) and the participants were asked to imagine what it would be like to buy the flowers. The sequence of the presentations was counterbalanced. **Figure 1** shows the procedure.

After the first presentation, participants completed the attentional shifting task. Then the participants viewed the other set of pictures (food or nonfood), again followed by the task. At the beginning of each session and after each component of the experiment, the participants completed a short self-report questionnaire that included scales of happiness, arousal, hunger, and fullness.

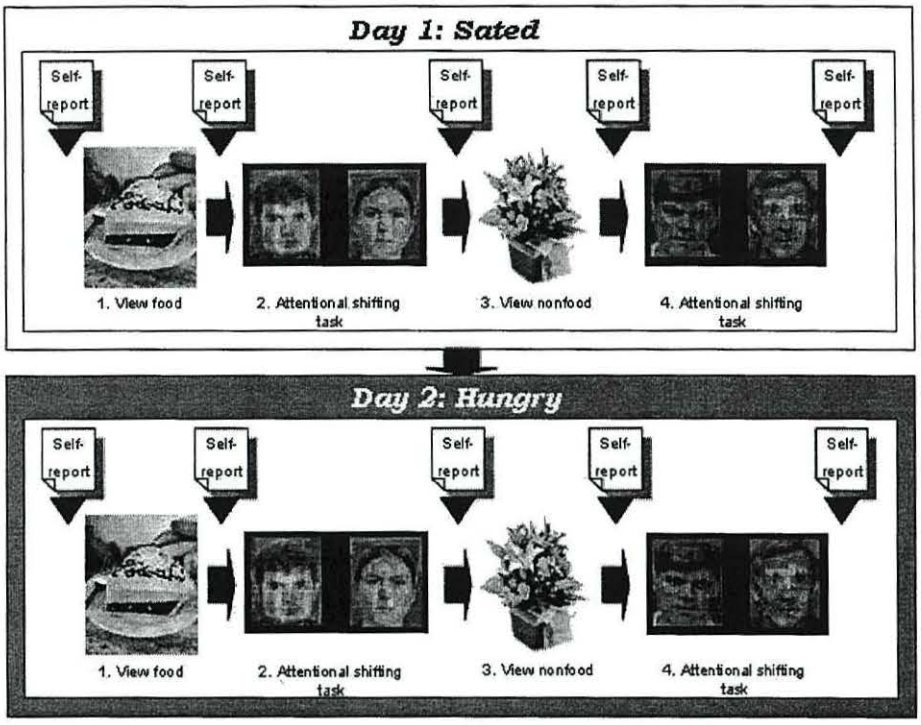


Figure 1. Experimental procedure. Note that sated and hungry sessions were balanced between day 1 and day 2. The time when food or nonfood was presented was also balanced.

Results

State Manipulation

The self-reported hunger scores from each condition (taken immediately after the induction procedure) are shown in **Figure 2.** A 2 x 2 repeated measures analysis of variance (ANOVA) with the factors State (Hungry, Sated), and Desire (Food, Nonfood: presentation of food items and flower arrangements, respectively) was carried out. The first factor represents physiological, deprivation-induced hunger for food, and the second stimulus-induced desire for it. We display the data clustered for 4 conditions: Sated-Nonfood, Sated-Food, Hungry-Nonfood and Hungry-Food. The ANOVA revealed two main effects but no interaction ($F(1,15) = 0.494$, $MSE = 36$), showing that participants indeed indicated themselves more hunger during the Hungry than during the Sated session ($F(1,15) = 22.77$, $MSE = 22{,}201$, $p < .0005$). They also indicated more hunger after exposure to Food stimuli than after exposure to Nonfood stimuli ($F(1,15) = 7.56$, $MSE = 1463$, $p = .02$).

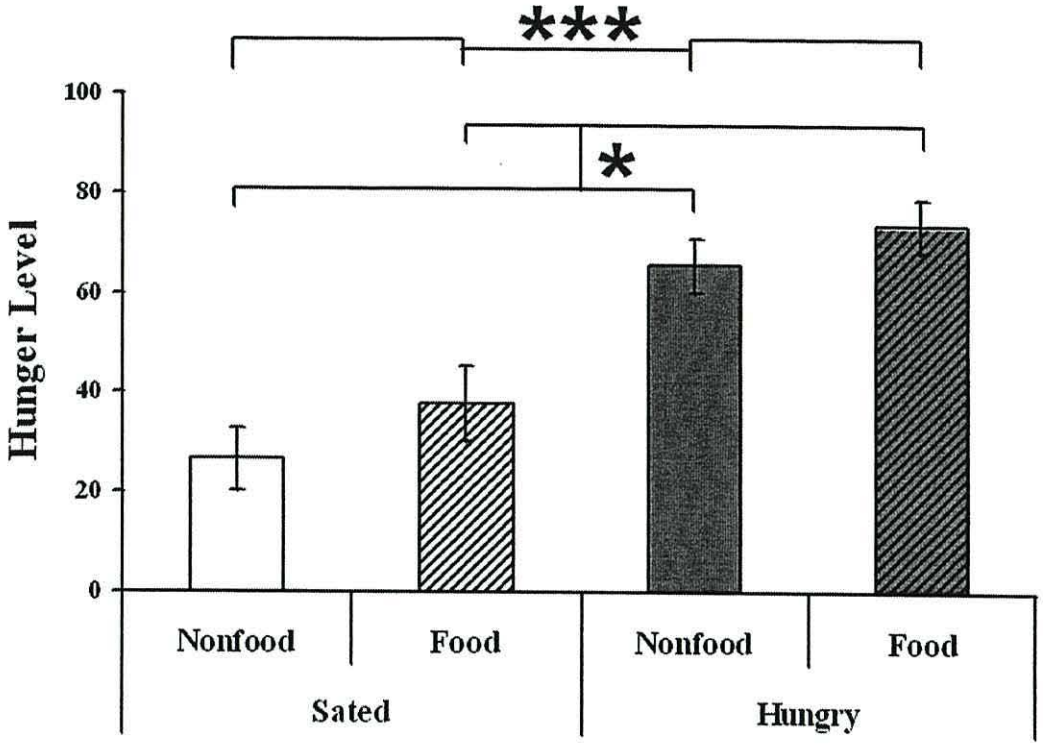


Figure 2. Mean hunger level for all conditions (0-100: extremely hungry). State: 'Sated' and 'Hungry'. Desire: 'Nonfood', viewing of nonfood pictures; 'Food', viewing of food pictures. Levels are higher for Hungry than Sated conditions, and higher for the 'Food' than 'Nonfood' conditions. Error bars indicate the standard error.

(*: $p < .05$; ***: $p < .001$)

To specifically evaluate the impact of the food pictures on stimulus-induced desire, we compared hunger scores before and after the induction procedures (prior to shifting task). **Figure 3** shows hunger rating increases from before to after the picture presentation. There was a large significant increase in hunger for the food presentation ($t(15) = 4.75$, $p < .0005$) whilst the change after the presentation of nonfood was not different from zero ($t(15) = 1.03$, $p = .32$).

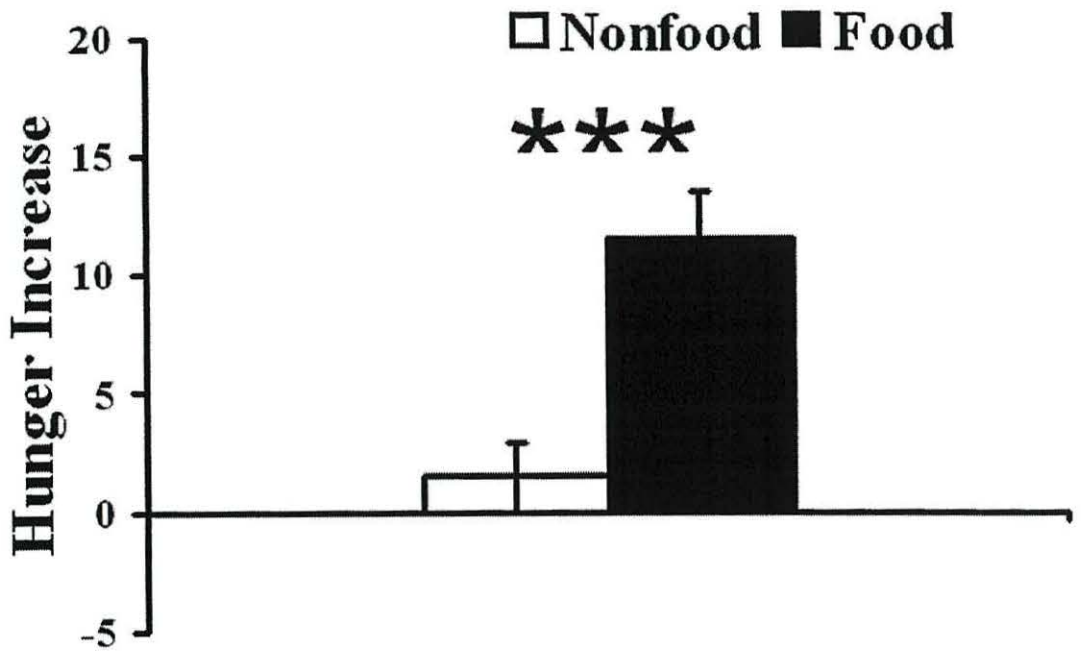


Figure 3. Mean hunger increase after viewing of nonfood and food. Increase is greater for food than for nonfood. Change after the presentation of nonfood is not different from zero. Error bars indicate the standard error.

(***: $p < .001$)

Set-Shifting Performance

In the attentional shifting task, the average number of targets identified by the participants was 67 (SD=14.1; range: 40-86). Since the task was time-limited, the total number of each type of event varied between individuals, the averages were 81 ED shifts and 57 ID shifts. The number and type of shifts did not differ across the conditions (*F*s < 2). (All analyses including gender and order as factors did not reveal any effects of interest.)

To further analyze the shifting data, we counted the *number of errors* each time the participant decided to shift their responding to a new target in either the same (ID) or the alternate dimension (ED): after each change, the number of responses before finding the correct target was counted. Thus we

could analyze the total number of errors made on the task, as well as the ratio of ED and ID errors. To achieve the latter, an index of cognitive inflexibility, we calculated the ratio of ED errors committed to total errors committed (the sum of ED and ID). This is referred to as the Inflexibility Ratio (IR); a higher number reflecting a greater proportion of responses taken to shift across categories (ED) than within (ID). Importantly, this reflects the ratio of errors made when an individual chose to make either an ED or ID shift, independently of whether the correct target actually changed. As can be seen in **Figures 4-6** the manipulations of State and Desire did influence the number of errors made when making ID and ED shifts, as well as the reaction times for participants making correct shifts. Broadly speaking those conditions which produced an increase in self-reported hunger appeared also to produce a greater number of errors, with ED shifts appearing more sensitive to errors than ID shifts. In contrast, reaction times appeared to increase with hunger, particularly following induction of desire by food-associated cues.

Initially, we conducted an analysis of the total number of errors committed using a 2 x 2 ANOVA with the factors State (Hungry/ Sated) and Desire (Food /Nonfood). The ANOVA indicated no difference between the Sated and Hungry State as such ($F(1,14) = 0.69$, $MSE = 30.10$), but a higher number of errors after viewing Food pictures i.e. a main effect of Desire ($F(1,15) = 5.72$, $MSE = 162.36$, $p = .03$), an effect that seems particularly pronounced in the Hungry-Food condition (**Figure 4**), although there was no significant interaction. In general, the aroused motivational state induced by the presentation of food cues impaired shifting behavior as measured by total errors during shifts.

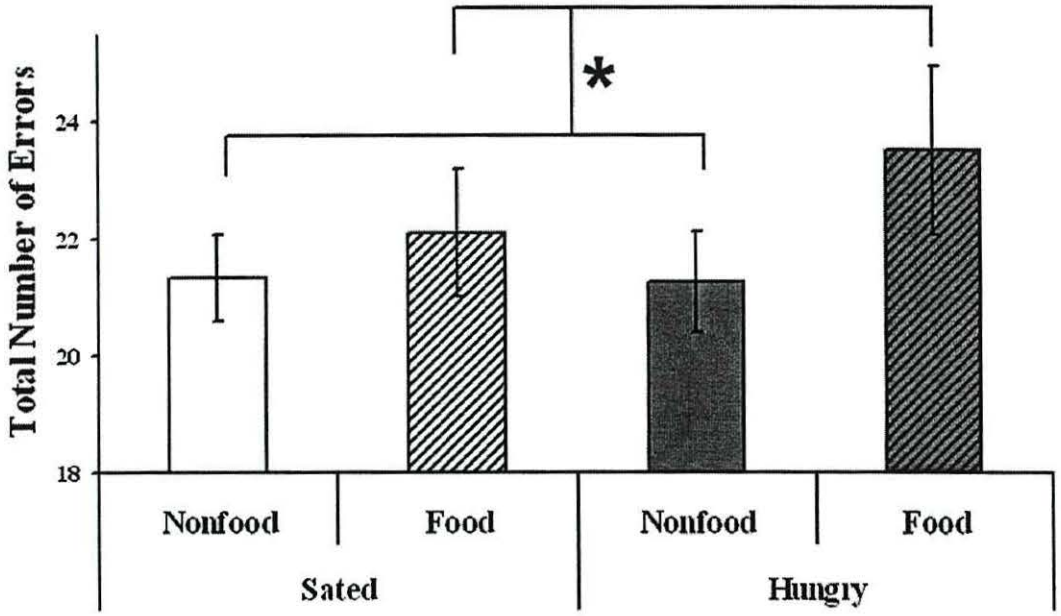


Figure 4. Mean total number of errors committed in all conditions. The presentation of food items increased the total number of errors, but fasting alone had no impact. Error bars indicate the standard error.

(*: $p < .05$)

To explore the types of error made, A 2 x 2 repeated measures ANOVA of the IR was performed with the factors State (Hungry/ Sated), and Desire (Food/ Nonfood). The ANOVA revealed a State by Desire interaction ($F(1,15) = 6.36$, $MSE = 0.01$, $p = .02$, **Figure 5a**) reflecting higher IR scores in conditions Sated-Food and Hungry-Nonfood than for Sated-Nonfood and Hungry-Food. This non-linear relationship between State and Desire suggests that a single 'hunger' manipulation (be it Hunger or Food) increases the ratio of ED to ID errors. Surprisingly, ratios were very similar after either Sated alone (without a presentation of food pictures) or with both Hunger and Food induction together. A plot of the total numbers of both ID and ED errors (**Figure 5b**) reveals that

the decreased IR in the Hungry-Food condition does not reflect a decrease of ED errors, but an increase in ID errors. This was confirmed by a 2 x 2 x 2 ANOVA with the factors State (Hungry/ Sated), Desire (Food/ Nonfood) and Shift (ID/ ED) revealing a three-way interaction ($F(1,15) = 6.45$, $MSE = 15.47$, $p = .023$) as well as two main effects: Induction ($F(1,15) = 5.23$, $MSE = 18.23$, $p = .04$) reflected as increased overall errors following Food presentations; and Shift ($F(1,15) = 7.22$, $MSE = 18.99$, $p = .017$) reflecting increased errors during ED shifts, relative to ID shifts.

The task is essentially based on guessing and the difficulty lies mostly in keeping attending to the target and then successfully shifting attention. There is no strategy which the participants could follow to achieve better results and they can't 'learn' to do the task better. However, it is still possible that they develop some strategies which they think are good. This would require a 'qualitative' analysis of single subject data, which may yield interesting results.

Whilst the factor of gender produced no significant effects or trends on task performance, the analysis of order produced a trend towards an order by Desire interaction ($F(1,14) = 3.96$, $MSE = 11.45$, $p = .07$). The presentation of food stimuli (Desire manipulation) prior to set-shifting induced a numerically greater number of errors irrespective of order (whether a participant saw food images or flower images first) though this was primarily driven in the food-first order. (All other analyses including gender and order as factors did not reveal any effects of interest, Fs < 2.)

The hunger level within-conditions is rather homogeneous, as shown by the error bars of Figure 2, so performance differences within that narrow band would be difficult to detect in a sample of this size. An interesting additional analysis would be to group participants not based on the condition they were in, but on hunger level. This could provide additional evidence for the

differences found being mostly due to the 'pure' hunger signal, or whether hunger and desire differed qualitatively.

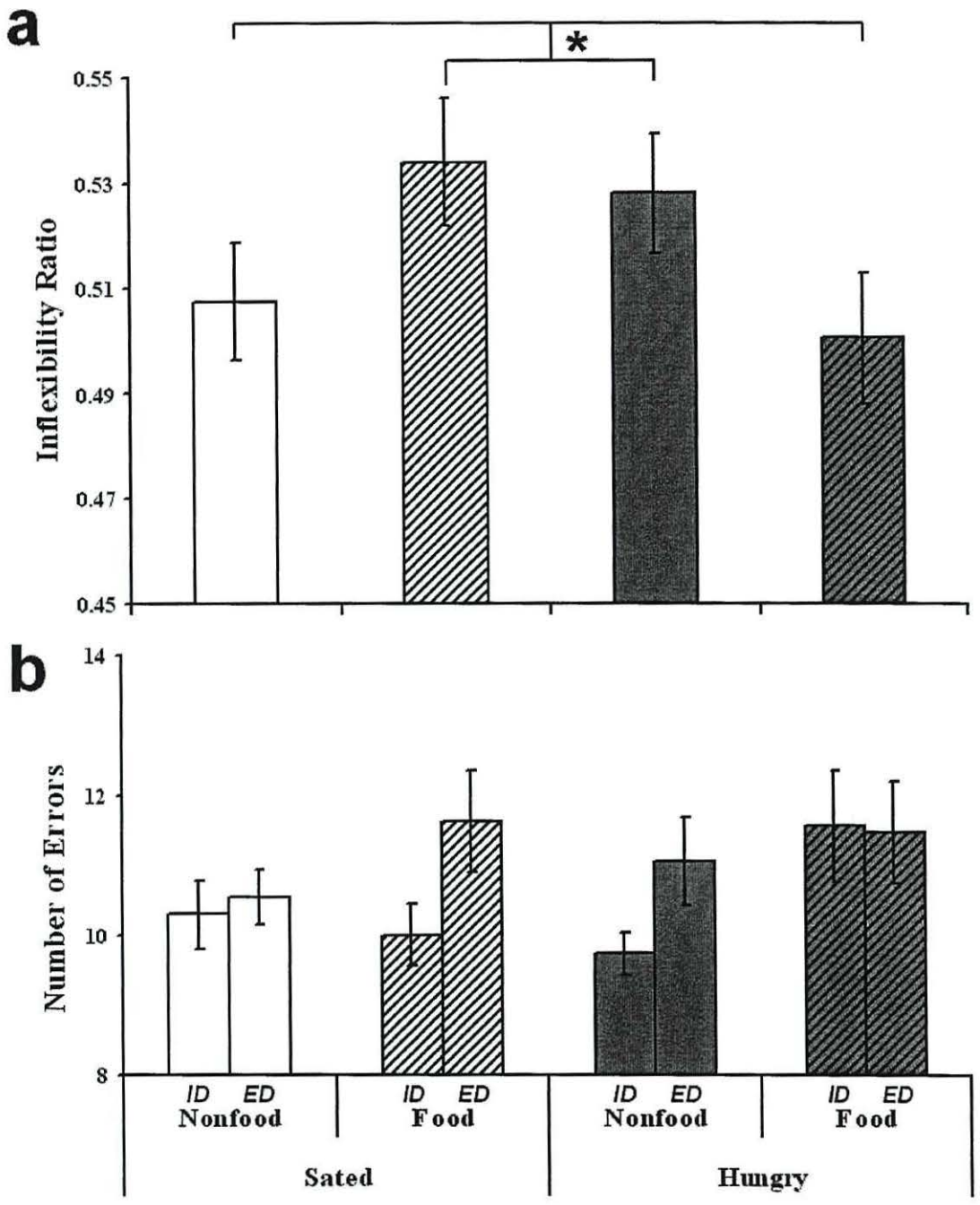


Figure 5. Errors committed in the shifting task. ***a)*** Mean inflexibility ratio (IR; calculated as ED errors / ED + ID errors) for all conditions. Inflexibility is higher for Sated-Food and Hungry-Nonfood than for Sated-Nonfood and Hungry-Food

conditions. ***b)*** Mean number of ID and ED errors committed in all conditions. Error bars indicate the standard error.

(*: $p < .05$)

Next, the analysis focused on response times during shifting. Each time when the participant shifted target to either the same (ID) or the opposite dimension (ED), the time between stimulus onset and the response via keyboard was measured. A 2 x 2 x 2 repeated measures ANOVA was performed with the factors State (Hungry/ Sated), Desire (Nonfood/ Food), and Shifts (ID/ ED). It revealed a State by Shifts interaction ($F(1,15) = 20.87$, $MSE = 676{,}430$, $p = .0004$, **Figure 6**; all other Fs < 2), suggesting that response time difference between ID and ED responses is not equal for the sated and hungry states. Exploration of simple-interaction effects using follow-up ANOVAs revealed that ED responses were slower than ID when participants are Sated ($F(1,15) = 17.87$, $MSE = 477{,}020$, $p = .0007$), but that there was no speed difference when participants were hungry ($F(1,15) = 0.48$, $MSE = 17{,}298$). This suggests that the State and Induction elicited changes in error rates is not a consequence of increased response speed and instead suggests that increased hunger appears to slow response times, perhaps towards a ceiling reflected in ED reaction times.

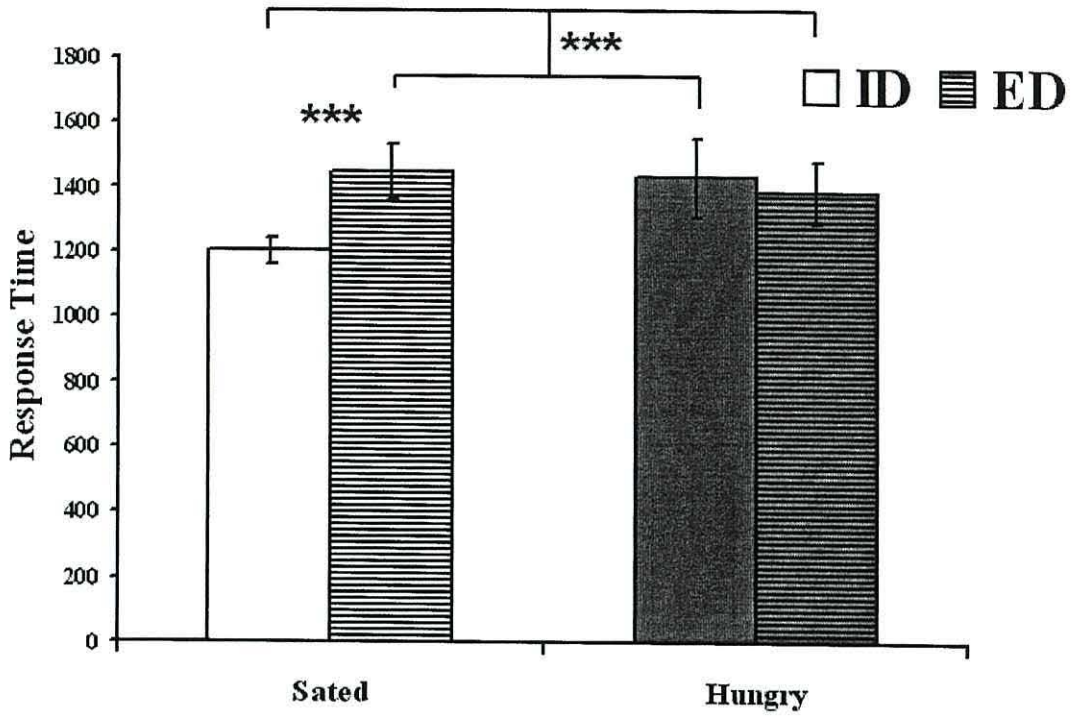


Figure 6. Mean response time for correct ID and ED shifts. The analysis revealed an interaction between the state and shifts. Therefore, the results are presented collapsed over the desire factor. ED shifts are slower than ID shifts in the sated state, but not in the hungry state. Error bars indicate the standard error.

(***: $p < .001$)

Discussion

This study shows that cognitive flexibility as assessed by set-shifting performance is susceptible to subtle changes in motivational state that can, and do, occur in our everyday lives. This is in contrast with cognitive effects induced by extreme states like hypo- and hyperglycemia (Strachan, 2005). Asking participants to fast for 5 hours prior to testing significantly increased self-reported hunger, as did presenting participants with a 4-minute slideshow of food-related cues and asking them to think about the stimuli presented. Such changes in perceived hunger state did not have the hypothesized impact on a participants' tendency to initiate shifting strategies, as measured by the overall number and type (ID versus ED) of shifts made by participants on the present task. However, state-changes did have an impact on the number of errors made by participants whilst shifting, and also on their reaction time to initiate shifts. Induction of desire, by stimulus presentation, but not by fasting, produced a significant increase in total errors on the task. Further, comparison of error data for ID and ED shifts, suggests that ED-shifting is initially more sensitive to disruption by motivational manipulations, howsoever induced, and that ID errors appear as hunger becomes more extreme. Finally, response time data suggest that impairments in shifting are not the result of a speed-accuracy trade-off and instead may reflect a gross increase in distractibility induced by hunger, or alternatively, a more subtle modulation of cognitive flexibility by state-induction.

Hunger and cognition

Only a few studies have explored the relationship between appetite and cognition. For example, fasting-induced hunger during learning has been demonstrated to improve long-term memory for food-related cues (Morris &

Dolan, 2001). It has also been shown that fasting produces attentional biases towards food cues, using variants of the Stroop task or with the dot-probe task, and that these biases appear to relate to participants' self-reported hunger levels (Green, Elliman, & Rogers, 1996; Mogg et al., 1998). It is worth emphasizing that in the present study the greatest effects on cognition were observed, not following fasting, but following the manipulation that we have described as stimulus-induced desire – there are clear implications for this finding to society with its ubiquitous prevalence and availability of food and food-stimuli.

The non-linear relationship between hunger and errors during set-shifting (**Figures 5a** and **b**) suggests that ED shifts, the ability to disengage current strategies and apply new ones, are more susceptible to state manipulations. One reason for this may be that when either of the hunger manipulations was employed alone it focused cognition on the current target dimension resulting in a greater number and proportion of ED shifting errors (and a slight tendency to reduced ID errors). When the motivational manipulations were combined the participants may have lost their top down structure in the solution search and began to have trouble with cognitive flexibility in general. Whilst these error data are broadly consistent with the hypothesis that motivation should impact upon cognition, the current results did not show a change in the tendency of participants to initiate ID or ED shifts following changes in hunger. However, the current cognitive task did not employ food-related dimensions or targets, and so it is possible that selective effects of hunger on shifting strategies may require food-stimuli to be present as targets (or distractors) of behaviour. Therefore, hunger-state may produce a gross impact upon cognitive performance in general, as evidenced by increased error rates during shifts in the current task, and may be hypothesized to have more selective effects on cognitive flexibility when task-

related parameters are motivationally salient; a domain for future exploration and an interesting neurobiological challenge for the brain in determining the motivational salience and congruence of environmental stimuli.

The neurobiology of motivation-cognition interactions

Patients suffering from Anorexia Nervosa (AN) show deficits in cognitive flexibility (reviewed by M. E. Roberts et al., 2007) which have been argued to be perseverative in nature and selective to extradimensional set-shifting (intact memory, verbal fluency, attention; (Steinglass et al., 2006)). It is likely that these deficits are mediated by structural abnormalities in corticostriatal circuitry including metabolic, receptor-based and structural differences observed in striatum between AN sufferers and controls (Delvenne, Goldman, De Maertelaer, & Lotstra, 1999; Frank et al., 2005; Husain et al., 1992). Previous fMRI analysis of the task used in the current study has demonstrated activity in ventrolateral prefrontal cortex and anterior cingulate cortex during ED shifting – both areas implicated in affective influences over cognition and also cortical afferents to striatal circuitry. Indeed, attentional set-shifting is believed to be dependent upon corticostriatal circuitry (Chudasama & Robbins, 2006; Crofts et al., 2001; Dias, Robbins, & Roberts, 1996; Hampshire & Owen, 2006; Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Rogers et al., 2000). It has been argued that the contribution of corticostriatal circuitry to AN may be in the form of a global distortion in cognitive flexibility, perhaps reflecting developmental traits of compulsivity, perfectionism or rigidity (Holliday, Tchanturia, Landau, Collier, & Treasure, 2005; Tchanturia et al., 2004). Alternatively, the extreme motivational state experienced by individuals with AN may also produce specific foraging-related influences on flexibility and switching i.e. an increased distractibility by food stimuli and an increased tendency to focus on food and food-related behavioral strategies.

Recent research has shown that the increases in shifting errors shown in AN sufferers do not relate to symptom severity and remain present in recovered patients (Tchanturia et al., 2004). Therefore shifting deficits in AN sufferers have been argued to represent trait markers, perhaps as a result of genetic loading, or developmental factors (Holliday et al., 2005; M. E. Roberts et al., 2007). However, this does not preclude state influences on set-shifting performance in either AN sufferers, or the population at large as demonstrated by the current study. Thus, developmental influences on corticostriatal circuitry may underlie trait-based cognitive inflexibility, whilst state-fluctuations, particularly anticipation-induced, may be reflected by labile fluctuations in neurotransmission in the system (Parkinson et al., 2000).

Dopamine (DA), and in particular the *mesolimbic* pathway innervating the ventral striatum, is a core component of the brain's motivational arousal system: food-associated stimuli produce increased DA in the ventral striatum of animals and humans, whilst damage to the ventral striatum, or disruption of its DA-ergic innervation abolishes motivational arousal for food, sex and drugs (Everitt, 1990; Everitt et al., 1999; Hall et al., 2001; Parkinson et al., 2002; Volkow et al., 2002; Wyvell & Berridge, 2000). DA is also implicated in cognitive flexibility; so for example, DA antagonists impair set-shifting in humans and rats (Floresco et al., 2005; Mehta et al., 2004), DA medication recovers shifting deficits in Parkinson's patients (Cools et al., 2001), and specific deficits in ED shifting, including perseveration, are thought to be due dysfunction in the DA-ergic innervation of PFC-caudate interactions (Chudasama & Robbins, 2006). Therefore, a mechanism by which motivation and cognition can interface is via DA *across* corticostriatal circuits (Haber et al., 2000; Parkinson et al., 2000). In this case, arousal and desire induced by food cues trigger DA release in the mesolimbic system, which would in turn modulate the DA-ergic innervation of the mesocortical and nigrostriatal system

resulting in a change in the balance of set-shifting behavior (Haber et al., 2000).

Conclusion

Cognitive flexibility has been shown to differ across individuals (Wager, Jonides, & Smith, 2006), is affected in neuropsychological disorders (Owen et al., 1993), and been shown to change as a result of exogenous manipulations of neurotransmitters such as dopamine and serotonin (Ornstein, 2000; Rogers et al., 1999; Rogers & Robbins, 2001). The current study adds to this data-set by demonstrating that changes in motivational state can also produce significant changes in set-shifting behavior.

There are several important implications of this study: firstly, it demonstrates a psychological interface between motivation and cognition; secondly it implicates corticostriatal circuitry, and in particular interactions between ventral striatal and caudate components, in this motivation-cognition interface; thirdly, it reinforces the contention that cognitive performance is sensitive to everyday fluctuations in motivational state; fourthly, it also implicates state-dependent influences in eating disorders including both AN and obesity; finally, it demonstrates that passive presentation of food-cues can produce a greater impact on cognition than fasting – as such, the ubiquitous nature of food-related stimuli in our society may indicate a significant contributory factor to current trends in overeating.

Chapter 3: Attentional set-shifting and state-dependant prefrontal activity

Introduction

Contemporary research into higher-cognitive or 'executive' function, is beginning to elucidate underlying psychological processes and their neural basis (Duncan & Owen, 2000; Miller & Cohen, 2001). For example, Hampshire and Owen recently identified several prefrontal cortical (PFC) regions underlying specific aspects of attentional control (Hampshire & Owen, 2006). Using a rule-based task, they showed that whilst the DLPFC was activated throughout solution-searching, reflecting a general monitoring role (Bor, Duncan, Wiseman, & Owen, 2003; Petrides, 1994), the ventrolateral PFC (VLPFC) showed selective activity only when an individual shifted attention from one domain to another (Hampshire & Owen, 2006; Nakahara, Hayashi, Konishi, & Miyashita, 2002). This suggests a specific role of VLPFC in implementing rule-based control over attention by identifying the appropriate domain in which to search for a target. Hampshire and Owen (2006) also observed orbitofrontal activity during positive and negative feedback. Indeed, there appears to be a growing consensus that the OFC is involved in guiding behavior based on reinforcement in the environment (O'Doherty, 2004; Rolls, 2000) with a possible role for the medial OFC (MOFC) in coding positive events and their meaning (Arana et al., 2003; Hampshire & Owen, 2006), whilst the LOFC may reflect processing of negative events, or alternatively, the required change in behavior as a result of negative expectations or events (Elliott et al., 2000).

Natural behavior is not carried out in the abstract and neutral context of a laboratory, but is instead directed by input from motivation systems that dictate the nature of possible goals and hence the type of stimuli in the

environment that will act as targets for attention. The PFC is likely to play a role in identifying such goal-relevant features and may direct cognitive systems and behavior based on incoming signals relating to state (both external and internal). The MOFC has been implicated in integrating state-related information with the expected value of goals (Hinton et al., 2004; O'Doherty, 2004; Rolls, 2000) and so may provide a dual role in cognitive tasks by processing task-relevant feedback as well as homeostatic information important for broader strategic goal-setting by the individual (Miller, 2000).

There is mounting evidence that affective information about environmental stimuli can influence early perceptual processes i.e. bias brain activity towards those stimuli (Morris, Ohman, & Dolan, 1998; Vuilleumier, 2005). However, only a few studies have explored the effect of shifts in motivational state on specific cognitive processes, other than in extreme aberrant states such as anorexia nervosa (M. E. Roberts et al., 2007). So, for example, by manipulating hunger in healthy controls, Morris and Dolan (2001) showed a state-dependent enhancement of memory for food pictures. In other words, hungry participants remembered food stimuli better than non-food stimuli, for which there was no state-dependent facilitation. These data are in many ways equivalent to a larger literature on emotion-enhanced memory – the phenomenon through which emotionally laden (visual) stimuli are remembered better than control stimuli – demonstrating parallel psychological processes to emotion-laden and motivation-laden stimuli. Likewise, it is accepted that affective stimuli can produce attentional biases (Matthews & MacLeod, 1994) and has also been shown that changes in hunger state can produce similar effects with food stimuli (Green, Rogers, & Elliman, 2000; Mogg et al., 1998). Consequently, there is evidence that changes in motivational state which shift the value of environmental stimuli (for example by

increasing a food item's value through increased hunger) set in motion equivalent processes that are known to sub-serve emotional stimuli.

The studies mentioned above refer to motivational influence on cognitive processes which target specifically directly relevant stimuli, such as food cues. In a recent study (Piech et al. *in press*, Chapter 2), we explored the behavioral effects of manipulating hunger state on attentional set-shifting in an attempt to explore the motivation-cognitive interface. In this case, the target stimuli (faces and buildings) were not specifically relevant to the motivational shift, and so the resulting effects were a reflection of the generic influence of motivation on cognition. At a psychological level, such effects are accounted for by theories such as Fredrickson's 'broaden and build' model of positive emotions, which suggests why increased cognitive flexibility may be adaptive in the absence of hunger (Fredrickson, 1998; Fredrickson & Branigan, 2001). The model states that positive affect, as opposed to negative affect such as hunger state, is associated with features like cognitive flexibility, which promote 'broadening', including exploration and thinking in new ways. Repeated periods of 'broadening' accumulate and lead to 'building' of new resources, knowledge, problem solving strategies, social bonds. These resources are adaptive in that they aid survival chances of an individual.

At a neurobiological level, several models have argued that a dopaminergic gating signal instructs the PFC whether to maintain a rule or change it (Stefani & Moghaddam, 2006). Indeed, dopamine is implicated not only in cognitive aspects of attentional control, but also in the anticipatory arousal induced by hunger and exposure to food-related cues (Berridge, 2004). In our behavioral study, we observed that increases in self-reported hunger were accompanied by an increase in ED errors, suggesting a general within-dimension focusing of attention induced by a simple manipulation of hunger (Chapter 2). The current study aimed at exploring the neural basis of this

hunger-induced attentional focus using the set-shifting paradigm designed by Hampshire and Owen (2006). Using a counterbalanced multiple-session within-subjects design, subjects were scanned whilst carrying out the attentional set-shifting task in both hungry and sated states. The task consisted of a solution search during which attention had to be transferred from one perceptual dimension to another, following a rule, in order to identify a target stimulus from one of the perceptual dimensions. This task required the ability to shift attention within and between dimensions. Neural activity for each shift type in the sated state could then be compared to previous work into the neural basis of attentional control, and could also be compared to activity in the hungry state to identify the influence of changes in state on higher-order processes. We anticipated modulation of activity by hunger to be reflected in the mesolimbic and mesocortical dopamine systems with a particular focus on areas of the PFC known to be involved in set-shifting.

Method

Design

Sixteen volunteers (8 female) with an average age of 28.4 (SD = 6.0), underwent fMRI recording during two one-hour sessions, one in the hungry, and one in the sated condition. The two recordings happened ca. one week apart, and the sequence of conditions was balanced for all participants. For the hungry condition, participants were instructed to not eat for 6 hours prior to the experiment. Before the experiment, participants completed a practice block of the task. Each session consisted of three 10 minutes blocks of the attentional shifting task described below. After the recording, participants reported their hunger level. They were debriefed after the second session. The study was approved by the University Research Ethics Committee.

Task

In the set-shifting task used (described in detail in Chapter 2), the participants had to determine which object was the target in a stimulus group consisting of two faces and two buildings. The stimulus group was presented as two compound stimulus pairs appearing on the left and right of the screen. Both compound stimulus pairs consisted of a face and a building superimposed on each other.

On each trial, the participants were required to indicate using a keypad on which side of the screen they thought the target was located. Every second response, feedback was presented on the screen for 0.6 s, indicating whether the two preceding stimuli they had chosen were both the target or not. After 6 correct responses to the target (i.e., 3 positive feedback events), a change of target occurred. The change was either a new target of the same dimension (requiring an intradimensional shift) or a new target in the other dimension

(requiring an extradimensional shift). The new target could also be in the form of a stimulus group change, in which new compound stimulus pairs were presented (requiring a 'shift'-switching process), or simply in the form of a rule change, in which the group would stay the same and a previous non-target would become the target (requiring a 'reversal'-switching process).

Participants were clearly instructed to keep responding to the correct target until informed that it was no longer the target and to respond 'as quickly and accurately as possible'. The crucial cognitive processes we were interested in were two-fold: firstly, the participants' shift of their responding to a different category (ED shift), as opposed to a shift to a different item in the same category (ID shift), and secondly the participants' shift of their responding following a stimulus group change (shift: SH), as opposed to following a rule change (reversal: RV). Trial duration was determined by participants' responses. The average number of targets identified by the participants per session was 50 (SD=15.6; range: 18-73). Since the task was time-limited, the total number of each type of event varied between individuals, the averages were 131 ED shifts, 64 ID shifts, 33 set changes and 25 reversals (all per session).

Those processes were modeled for the fMRI analysis in the following manner: Each event was defined by individual type of volunteer response. We modeled four types of events in which participants shifted their attention: ID shift, ED shift, set change shift, and rule change shift. During an ID shift, the participant's focus of attention switched between stimuli of the same category (e.g. from one building to another building). During an ED shift, the focus of attention switched between the categories (e.g. from a building to a face). In the fMRI analysis, subtracting ID shifts from ED shifts would yield activity related to the extradimensional component of attentional shifting, since the

change of attention to stimulus type was the only component of ED shifts absent in ID shifts.

The final general linear model used to analyze the fMRI data included 24 regressors. These include nine types of events and six motion regressors. The nine event-types are entered twice, for the sated and the hungry session. The events modelled were:

CFalse:	incorrect feedback before the reversal
CN:	Non shifts when the target is known
CTrue	correct feedback when the target is known
edWC	ED shifts during solution search
idWC	ID shifts during solution search
RV	Rule-change switch (reversal)
SH	Set-change switch (shift)
WFalse	incorrect feedback during solution search
WTrue	correct feedback during solution search

The motion predictors included transitions along the three axes and rotations around them.

Set change shifts and rule change shifts occurred after the participant correctly identified a previous target and a new item became the new target. A set change shift would become necessary if the previous group of four stimuli was replaced by a new one. A rule change shift would occur if the stimuli stayed the same but the target changed. In the fMRI analysis, subtracting set change shifts from rule change shifts would yield activity related to the reversal component of attentional shifting, since the reversal of attention to a previously

present non-target was the only component of rule change shifts absent in set change shifts.

FMRI data acquisition and analysis

A 1.5 T Philips MRI scanner was used to acquire 14 T2* weighted slices per volume (4mm slices with 1mm gap, resulting in 3.75mm x 3.75mm x 4mm voxel size), with a repetition time of 1.1 s. The slices were tilted by 30 degrees from the ACPC axial plane to reduce susceptibility artifacts. Thus the recorded volume included the entire prefrontal cortex, subcortical structures and excluded the parietal cortex and ventral parts of the cerebellum. The first five volumes of each scan were discarded to avoid differences in T1-saturation. Pre-processing and statistical analysis were performed using BrainVoyager QX (Brain Innovation, The Netherlands). The functional images were slice-time acquisition corrected, subject motion corrected, spatially normalized to Talairach space (Talairach & Tournoux, 1988), smoothed with an 8 mm full width at half maximum Gaussian kernel, and the events were modeled as described above, with the duration corresponding to the period from stimulus onset to response.

The fMRI data were analyzed in two stages, with the region-of-interest (ROI) approach and as an exploration of activity in the prefrontal cortex (PFC). In the first stage, regions of the lateral PFC shown previously to have a role in attentional shifting were examined. We used four ROIs in our analysis: the ventrolateral prefrontal cortex (VLPFC) and dorsolateral prefrontal cortex (DLPFC), each in both the right and left hemisphere. The VLPFC and DLPFC have been associated with a variety of attentional tasks, with their exact roles in attentional shifting explored by Hampshire and Owen (2006). The anatomical locations of the VLPFC and DLPFC were based on averaged coordinates taken from an analysis of varied tasks requiring attention (Duncan

& Owen, 2000). We created our ROIs by drawing cubes with 8 mm sides centered around those coordinates, which were for the VLPFC x = -39, y = 20, z = 2 and x = 39, y = 20, z = 2, and for the DLPFC: x = -38, y = 30, z = 22 and x = 38, y = 30, z = 22. Voxel time series were percent-normalized for each run and signal for the events of interest was extracted for the individual ROIs and subjected to statistical higher level group random-effects analyses. Following the ROI analysis, we explored the events corresponding to attentional switches using an unconstrained whole-brain random-effects analysis and focusing on activity in the PFC in order to confirm that our ROI analysis had indeed identified the main regions of significant activity for each contrast.

Results

Behavioral analysis

Hunger Manipulation

After each scan, participants reported how hungry they felt. The scores reflected higher hunger levels for the Hungry than the Sated session. On a scale from 1 to 7 (7 = extremely hungry), the average scores were 5.6 and 2.4, respectively ($t(15) = 6.60$, $p < .0001$, Fig. X1).

Set-Shifting Performance

In the attentional shifting task, the average number of targets identified by the participants per session was 50 (SD=15.6; range: 18-73). Since the task was time-limited, the total number of each type of event varied between individuals, the averages were 131 ED shifts, 64 ID shifts, 33 set changes and 25 reversals (all per session). The number and type of shifts did not differ between the Sated and Hungry sessions. (all Fs < 2.3).

To further analyze the shifting data, we counted the *number of errors* each time the participant decided to shift their responding to a new target in either the same (ID) or the alternate dimension (ED): after each change, the number of responses before finding the correct target was counted. We then conducted an analysis of the number of ID and ED errors committed using a 2 x 2 ANOVA with the factors State (Hungry/ Sated) and Shift (ID / ED). The ANOVA indicated an overall higher number of ED than ID errors, (main effect for Shift: $F(1,15) = 9.13$, $p = .009$; Fig. X2*A*), but crucially, there was no difference in the total number of errors between the Sated and Hungry sessions ($F(1,15) < 1$). The ratio between ID and ED errors did also not differ between the Sated and Hungry sessions ($F(1,15) < 1$).

We then analyzed the number of errors committed depending on whether the target changed with a contingency change (reversal: RV) or set change (shift: SH). A 2 x 2 ANOVA with the factors State (Hungry/ Sated) and Switch (RV / SH) indicated that there was no difference between the overall number of RV and SH errors and no difference in the total number of errors between the Sated and Hungry sessions (*Fs* < 2.2). The ratio between RV and SH errors did also not differ between the Sated and Hungry sessions (*F* < 1; Fig X2*B*).

Next, the analysis focused on response times during shifting. Each time when the participant shifted target to either the same (ID) or the opposite dimension (ED), the respective time was measured. A 2 x 2 repeated measures ANOVA was performed with the factors State (Hungry/ Sated), and Shifts (ID/ ED). It revealed a main effect for Shifts, with ED shifts being faster than ID shifts ($F(1,15) = 36.58$, $p < .0001$; Fig. X3). The equivalent analysis of reversal and shift switching events revealed a main effect for Switch, with RV switches being faster than SH switches ($F(1,15) = 51.20$, $p < .0001$). No other effects were observed in the response time analysis (Fs < 3.2). The results show that ED and RV switches were performed faster than their respective comparison switches, but that the difference was equivalent in the Sated and Hungry conditions.

In general, the motivational state induced in the Hungry condition did not produce overall performance differences, which would be a confounding factor in the interpretation of the imaging data.

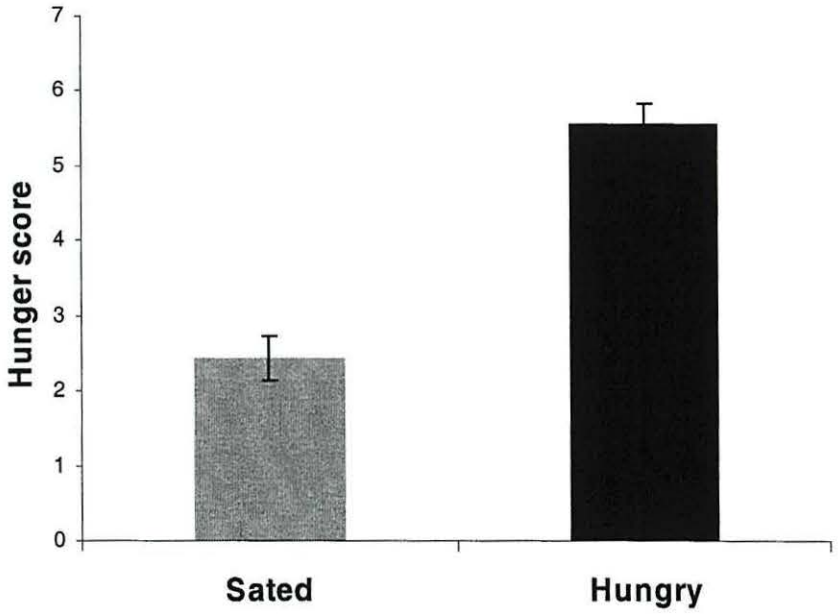


Fig X1. Mean hunger level for the Sated and Hungry sessions (1-7; 7: extremely hungry). The level is higher for the Hungry session ($t(15) = 6.60$, $p < .0001$). Error bars indicate the standard error.

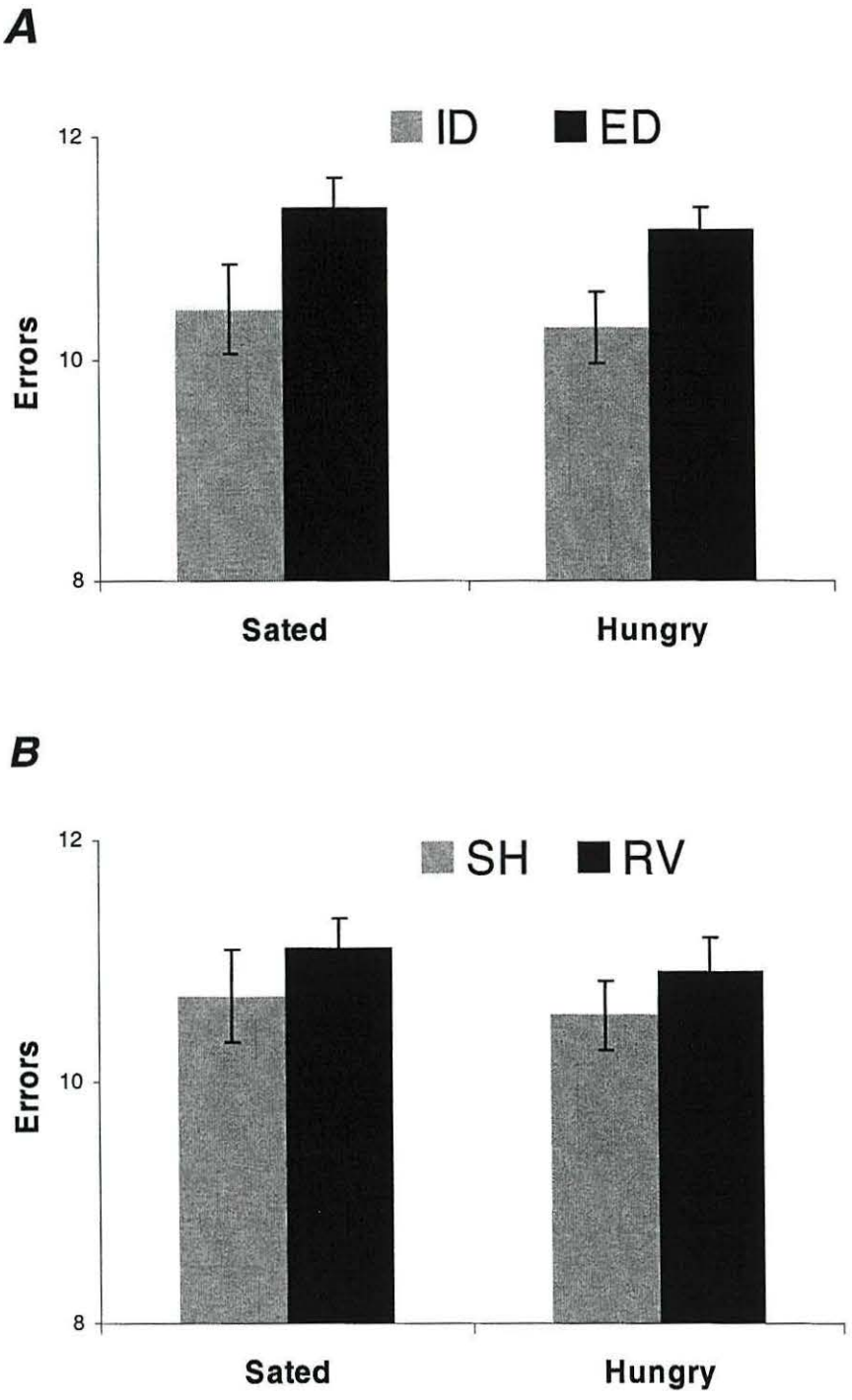


Fig X2. Errors committed in the shifting task. ***A)*** Mean number of Intradimensional (ID) and Extradimensional (ED) switch errors committed in the Sated and Hungry conditions. Overall, more ED than ID errors were committed, ($F(1,15) = 9.13$, $p = .009$), but there was no difference in the number of errors between the Sated and Hungry sessions ($F(1,15) < 1$). ***B)***

Mean number of Shift (SH) and Reversal (RV) errors committed in the Sated and Hungry conditions. There was no difference between the overall number of RV and SH errors and no difference in the total number of errors between the Sated and Hungry sessions (*Fs* < 2.2).

Error bars indicate the standard error.

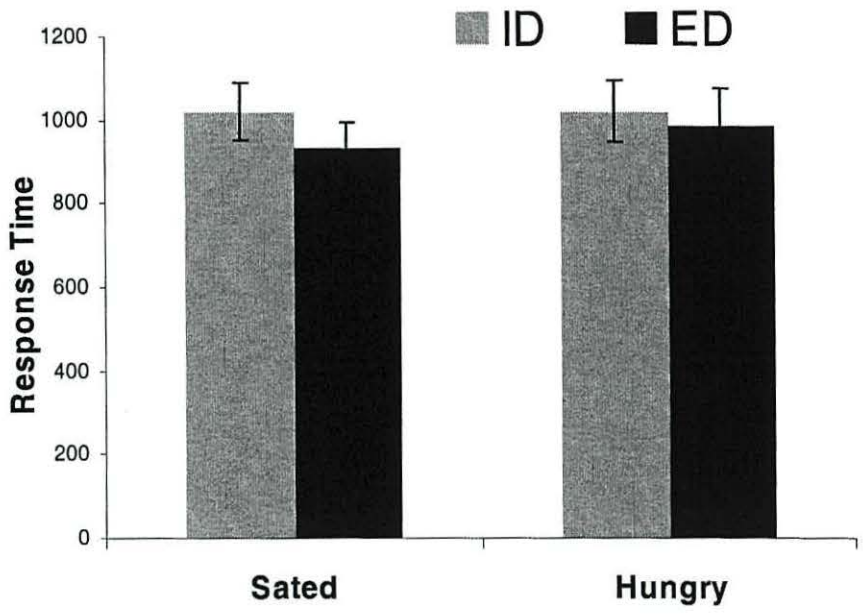


Fig X3. Mean response time for ID and ED shifts. The analysis revealed a main effect for Shifts, with ED shifts being faster than ID shifts ($F(1,15) = 36.58$, $p < .0001$). There was no main effect or interaction with the State factor (Fs < 2). Error bars indicate the standard error.

Event-related fMRI analysis

Sated session

Shifts in the focus of attention between stimulus types (extradimensional shifts) were compared with shifts within stimulus type (intradimensional shifts) in order to isolate the **extradimensional component** of attentional shifting. The VLPFC was significantly activated in the contrast ($t(15) = 3.69$, $p = .009$; all p-values corrected for multiple comparisons). The DLPFC was also activated ($t(15) = 4.11$, $p = .004$; Fig. 1). This contrast confirmed the role of VLPFC in ED shifting, but suggests an involvement of the other part of the lateral PFC, the DLPFC, to a similar degree.

To confirm the result of the ROI analysis, we conducted a whole brain analysis for the same contrast. The analysis produced an activation peak which was located at $x = 40$, $y = 27$, $z= 15$, which overlapped with our ROI (DLPFC). This peak could only be detected after substantially lowering the statistical threshold, however ($t(15) = 2.42$, $p = .029$; for the PFC exploration, we report whole-brain p-values that are not corrected). The contrast also revealed a peak at $x = 53$, $y = 29$, $z = 24$ (BA 46; $t(15) = 2.67$; $p = .017$; Fig. 2a). An exploration of the activity in the striatum revealed a peak in the left caudate ($x = -15$, $y = 16$, $z = 11$; $t(15) = 3.40$; $p = .004$).

Shifts in attentional focus due to reward contingency change (reversals) were then compared with shifts due to set change, in order to isolate the **reversal component** of attentional shifting. The activation pattern of the ROI for this contrast, the lateral OFC, could not be confirmed ($t(15) = -0.32$, $p = 1$). An exploration of the ROIs of the lateral PFC (VLPFC and DLPFC) did not hint towards their involvement in the reversal process. The whole brain analysis for this contrast in the sated condition yielded no activity peaks in the PFC at statistical thresholds as low as $p > .05$.

Hungry Session

In the Hungry condition, the contrast revealing activity related to the **extradimensional component** of attentional shifting did not show a significant activation of the lateral PFC, neither for the VLPFC, nor the DLPFC ($t(15) = -0.49$, $p = 1$, and $t(15) = -0.95$, $p = 1$, respectively, Fig. 1). This is in stark contrast to the Sated session and the assumed role of the VLPFC in extradimensional shifting.

Since the ROI analysis showed no increased activity related to extradimensional shifting in the lateral PFC ROIs, we investigated if ED shifting increased activation in a separate region of the PFC. We conducted a whole brain contrast separately for the hungry state. The analysis produced an activation peak which was located lateral to our ROI ($x = 52$, $y = 26$,$z = 17$, BA 44; $t(15) = 3.80$, $p=.002$; Fig. 2a).

The pattern of activity in the ROIs differed significantly between the Sated and Hungry conditions. While an overall difference between sessions might be expected, the differences here are more specific. In relation to the extradimensional shifting component, the lateral PFC seemed to be involved in the process when participants are Sated, but not when they are Hungry. This was confirmed with a 2 x 2 repeated measures ANOVA with the factors Site (VLPFC, DLPFC) and State (Sated, Hungry). This analysis revealed only a main effect of State ($F(1,15) = 12.86$, $p = .003$, other $Fs < 1$; Fig. 1) We emphasize that this is not a baseline difference. The calculations are based on difference values between shifting processes including differing sub-processes. While differences in magnitude could therefore be explained by baseline changes, the absence of a difference for the contrasted processes cannot. To confirm this finding we calculated the equivalent ANOVA for the same ROIs but a different contrast, the contrast revealing activity related to the reversal component of shifting. The 2 x 2 ANOVA (factors: Site [VLPFC, DLPFC] and

State [Sated, Hungry]) reveals a main effect for Site ($F(1,15) = 5.65$, $p = .031$), but crucially no main effect for State ($F(1,15) = .272$, $p = .610$). There is also no interaction ($F(1,15) < 1$). Thus, the pattern of higher activity in the lateral PFC in the Sated state seems to be specific to the extradimensional shifting process.

The contrast revealing activity related to the **reversal component** of attentional shifting did not show significant activation in the predicted ROI, the lateral OFC ($t(15) = -0.93$, $p = 1$) during the hungry session. Exploration of other ROIs did not point to increased activity related to the reversal component. Performing the whole-brain contrast in order to locate peaks near the ROI yielded an activity peak at the left pole of the PFC ($x = -32$, $y = 62$, $z = 12$; $t(15) = 6.01$, $p = .00002$; Fig 2b).

The ROI analyses were based on averaged signal from the left and right hemispheres, as an preliminary analysis revealed no main effects of laterality or interactions with other factors. That was the case for both the extradimensional shifting and reversal components (all $Fs < 2$).

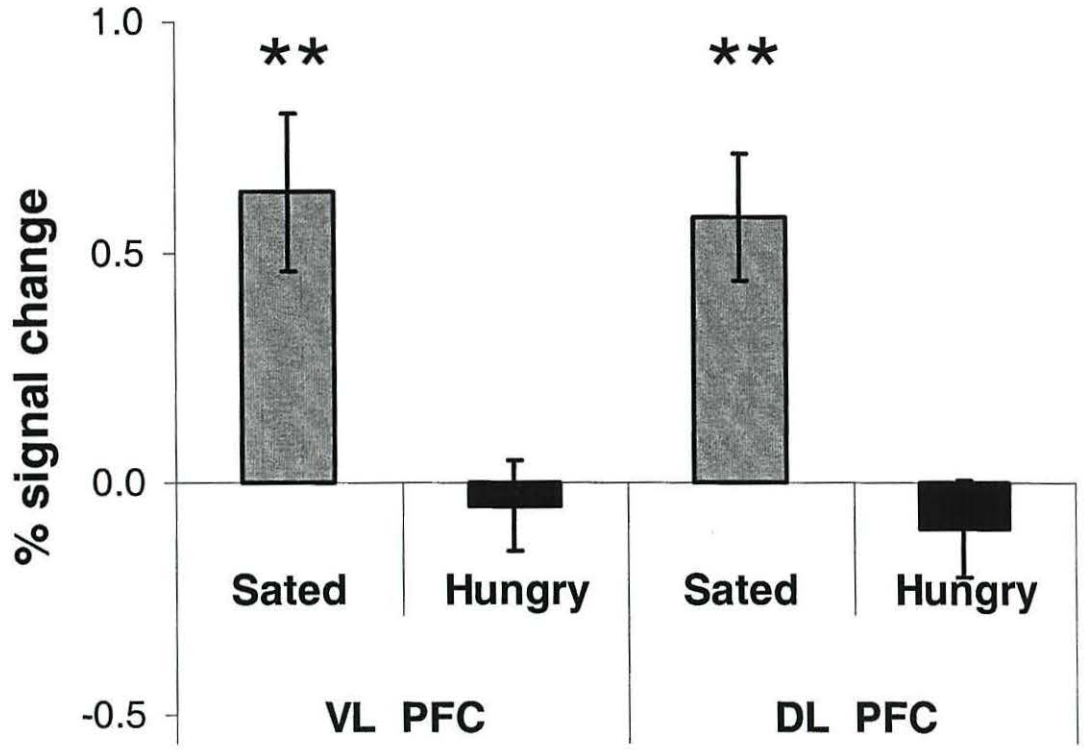


Figure 1: Percent signal change attributed to the extradimensional component (contrast: ED shifts - ID shifts), for two regions of interest: the ventrolateral prefrontal cortex (VL PFC) and dorsolateral prefrontal cortex (DL PFC). During the Sated session, the extradimensional component activates both the VL PFC and DL PFC. That is not the case during the Hungry session.

**: $p > .01$

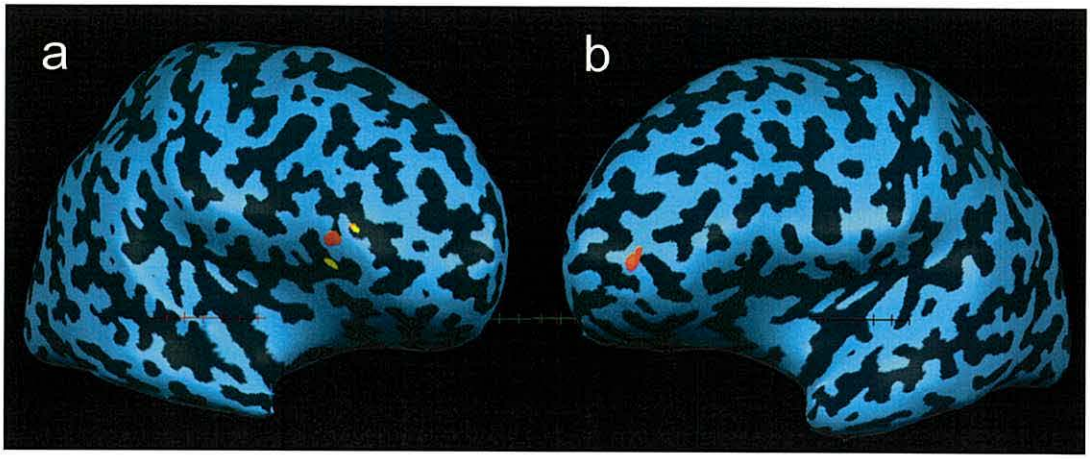


Figure 2. Activity peaks in the prefrontal cortex (PFC). a) Extradimensional component (contrast: ED shifts - ID shifts). In Yellow: activity during the Sated session. Peak locations: x = 53, y = 29, z = 24; t(15) = 2.67; p = .017, and x = 40, y = 27, z= 15, t(15) = 2.42, p = .029. The latter is the most ventral in the panel and overlaps with our a priori region of interest (ROI), the dorsolateral prefrontal cortex (DLPFC). Both are displayed at low statistical thresholds. In Orange: activity during the Hungry session. Peak location: x = 52, y = 26,z = 17, BA 44; t(15) = 3.80, p=.002. b) Reversal component (contrast: contingency reversal – contingency shift). In Orange: activity during the Hungry session. Peak location: x = -32, y = 62, z = 12; t(15) = 6.01, p = .00002.

Discussion

Our experiment set out to investigate the neural basis of attentional set-shifting under conditions of varying motivational levels. Previously, attentional set-shifting has been shown to be dependent upon corticostriatal circuitry (Chudasama & Robbins, 2006; Crofts et al., 2001);(Dias et al., 1996; Monchi et al., 2001; Rogers et al., 2000). Using fMRI in humans, Hampshire and Owen (2006) made a case for a crucial role of the lateral PFC in set-shifting. In a previous experiment, we showed that attentional set-shifting can be susceptible to motivational manipulations (Piech et al. *in press*, Chapter 2) and speculated that levels of dopamine may contribute to that effect. The current experiment confirmed the involvement of the ventrolateral PFC in extradimensional shifts of attention for the sated state. The dorsolateral PFC was similarly involved in that process. The pattern of activation during attentional shifts was different for the hungry state, however. Extradimensional shifting was reflected by activity which peaked dorsally to the activity in the sated state. Furthermore, the reversal of attention in the hungry state coincided with an activation peak in Brodmann area 10 in the frontal pole. This contrasts with previously reported activations in the lateral orbitofrontal cortex associated with this process in sated participants (Hampshire & Owen, 2006). One explanation for the current results is that coordinated activity in the PFC was shifted by hunger induction from one functional circuit to another. A plausible mechanism underlying such an effect would be offered by a consideration of the PFC and its subcortical targets as part of a larger cortico-striatal network, the function of which is modulated by monoamines such as dopamine (Alexander & Crutcher, 1990). Changes in motivational state might then shift the balance of PFC activity resulting in changes in cognitive performance.

The corticostriatal circuitry crucial to set-shifting is linked through its dopaminergic modulation to the brain's motivational arousal system, in particular the mesolimbic pathway innervating the ventral striatum. Dopamine's role in set-shifting is supported by observations that dopamine antagonists impair set-shifting in humans and rats (Floresco et al., 2005; Mehta et al., 2004), dopaminergic medication recovers shifting deficits in Parkinson's patients (Cools et al., 2001), and specific deficits in extradimensional shifting, including perseveration, are thought to be due to dysfunction in the dopaminergic innervation of PFC-caudate interactions (Chudasama & Robbins, 2006). Therefore, cross-circuit dopaminergic interactions within corticostriatal circuitry would present a plausible mechanism by which motivation and cognition can interact (Haber et al., 2000; Parkinson et al., 2000). The different pattern of activity we identified during set-shifting in the sated and hungry state may therefore reflect dopaminergic modulation of PFC activity evidenced by a shift in the emphasis of activity from one corticostriatal loop to another. Although we found no evidence of subcortical activity differences (e.g. such as in the striatum), which might be expected given that dopaminergic modulation of the PFC would originate in subcortical structures, this may be accounted for by the smaller volume of those structures, rendering them more difficult to detect at the signal resolution achieved in this study. A possible mechanism would originate in arousal induced by hunger, which then may trigger dopamine release in the mesolimbic system, that would in turn modulate the dopaminergic innervation of the nigro- and meso-striatal systems, resulting in a change in the activity in the PFC.

It should be noted that the expected behavioral effects of hunger were not observed on the set-shifting paradigm in this current study: hunger-induction did not increase ED errors as was predicted. This may account for the lack of significant changes in subcortical activity as the bias in activity

induced by hunger may have been too subtle to observe. However, changes in brain activity induced by experimental manipulation (e.g. hunger induction) need not always result in behavioral sequelae. And so the lack of observed behavioral effect of the motivational shift, does not detract from the significant shift in neural activity within the PFC across the two motivational states.

In order to obtain robust behavioral and corresponding neural effects, future work may focus on employing a more powerful motivational induction technique, such as a longer fasting phase. Morris and Dolan (2001) asked their participants to fast for 16 hours. We originally refrained from using such an extended period to make the manipulation more ecologically valid. Alternatively, a different induction technique could be used. Indeed, dopamine activation is often observed in animals following the presentation of food-related cues (Bassareo & Di Chiara, 1999; Phillips, Ahn, & Floresco, 2004) as opposed to fasting. In our behavioral study (Chapter 2), the induction of desire by cue presentation had actually more influence on the total number of shifting errors committed, pointing to the power of such an induction. A final avenue for future exploration would be to include food-related stimuli as targets for attentional control to assess the power that motivational state has on goal-relevant cognitive processing.

Cognitive flexibility indexed by set-shifting has been shown to be affected in neuropsychological disorders (Owen et al., 1993), and to change as a result of exogenous manipulations of neurotransmitters such as dopamine and serotonin (Ornstein, 2000; Rogers et al., 1999; Rogers & Robbins, 2001). The current study shows that the neural representations of processes associated with cognitive flexibility can be altered by different motivational state of the participants.

Chapter 4: Neural representation of incentive value change accompanying intrinsic motivational increase

Introduction

Human eating behavior is controlled by a number of factors, ranging from genetic to cultural ones (Barsh, Farooqi, & O'Rahilly, 2000; Clement et al., 1998; de Castro, Bellisle, Feunekes, Dalix, & De Graaf, 1997). For the current study, we selected two factors which have recently been the object of discussion in the context of eating motivation (Beaver et al., 2006; Hinton et al., 2004; Holsen et al., 2005; Smeets & Westerterp-Plantenga, 2006). The first motivating factor is a person's current level of food deprivation, or 'hunger'. Hunger within the context of the current study is a physiological need state, reflecting amongst others blood glucose levels and stomach volume expansion (Flint et al., 2006). Hunger in such sense motivates individuals to seek food and eat (Erlanson-Albertsson, 2005).

The second factor of interest are the properties of a food item or dish in question (we will use the word 'dish' in the text since that is what reflects our stimulus material). We term this factor 'attractiveness'. Attractiveness refers to how nice a person thinks a dish would be – if he/she ate it. It is not the hedonic experience of pleasure or aversion as a function of actual taste of the food, but the level of expected appreciation of a dish based on learning, in particular an individual's experience of eating such or similar dishes. Thus, it resembles an 'all time' ranking of dishes by one individual created by his/her 'long-term' dining history. The level of anticipated attractiveness can therefore be retrieved during via imagery, mere observation of a dish, or the reading of its description.

Previous studies investigating the neural substrates of food intake contributions focusing on hunger state and food properties include neurophysiology recordings from the rodent and non-human primate brain and

human neuroimaging studies. They consistently show a role of the orbitofrontal cortex (OFC) and the amygdala in those functions. Neurons in the primate caudolateral OFC (Rolls & Baylis, 1994), have been shown to respond to pleasant taste and odor stimuli (Rolls & Scott, 1995). Such responses can be reduced or abolished by linking a previously pleasant stimulus with an aversive event (Critchley & Rolls, 1996), or by extensive feeding of the animal with specifically that taste, or its components, creating sensory-specific satiety (Rolls & Treves, 1998; Schultz, Tremblay, & Hollerman, 1998). Such experimental designs allow the manipulation of stimulus value while keeping its physical properties constant, and thus provide a valuable tool for dissociating representations of taste from those of its value. Their results suggest the anterior OFC activity recorded during pleasant taste reception is not likely to represent taste identity (Yaxley, Rolls, & Sienkiewicz, 1988), but rather taste value (Rolls, 2005), which changes rapidly for a given stimulus depending on the hunger state of the animal (Schultz, Tremblay, & Hollerman, 2000).

The primate amygdala seems to subserve some similar functions as the OFC. Like the OFC, it responds to pleasant taste and odor stimuli (Rolls, 1992), and is able to adjust to value changes of the same stimulus. While the adjustment may not happen as rapidly as in the OFC in primates (Wilson & Rolls, 2005), it may be just as rapid or more so in rodents (Schoenbaum, Chiba, & Gallagher, 1999). Value representation in the amygdala seems to follow a very similar pattern to that of the OFC (Cardinal et al., 2002), but recent imaging work in humans has suggested some functional dissociations. Studies using affective stimuli which allow dissociating valence from intensity showed representations of intensity in the amygdala and of valence in the OFC. This holds true for both odors (Anderson et al., 2003) and tastes (Small et al., 2003).

The described studies suggest a crucial role of the OFC and the amygdala in the perception of taste and its value during and after ingestion. It is however essential for both humans and non-human animals to be able to evaluate potential foods before consumption. This is possible by creating associations between taste and other aspects of food, like smell or sight. Such associations then enable organisms to generate evaluation responses to those aspects (Rolls, 2000). Recent studies employing PET-imaging in humans showed that value representation in the OFC and in the amygdala accompanies even as abstract representations of food as the text of restaurant menu items displayed on a screen (Arana et al., 2003; Hinton et al., 2004). The current experiment seeks to elaborate on those studies with a refined design and the use of fMRI which offers advantages in spatial and temporal resolution over PET (Aine, 1995).

The aim of the current study was to investigate how hunger and attractiveness contribute to the 'incentive value' of a dish. Incentive value in this context expresses how desirable a dish is at a given moment, or how much one wants a dish, (Dickinson & Balleine, 2002). Our goal was to identify neural sites at which the factors hunger and attractiveness as well as their interactions are represented. Participants completed a version of the restaurant task (Arana et al., 2003), while undergoing an fMRI recording. They were asked to imagine being in a restaurant and were presented restaurant menu items. The task was to read each item description, to imagine it, and to rate how much they liked the dish. The rating served as an index of the current incentive value of the dish. To allow assessment of the role of the hunger factor, participants completed two otherwise identical experimental sessions, once while sated and once while hungry. This experimental design allowed us to address three questions. 1) Which brain structures respond to dish descriptions in a pattern consistent with the representation of attractiveness?

2) Which brain structures respond to dish descriptions in dependence on the hunger state, indicating the integration of attractiveness and hunger? 3) Which brain structures are activated by dishes that are particularly susceptible to incentive value changes due to hunger?

To answer the first question, we inspected the neural responses to different levels of attractiveness. These were operationalized by dish descriptions rated high or low by participants. A previous study using positron emission tomography (PET) with a similar task identified the amygdala and the orbitofrontal cortex (OFC) as regions representing the value of menu items (Arana et al., 2003). We used those results to form our hypotheses and neural regions of interest, but modified the design to allow clearer distinctions between conditions. Arana et al. (2003) presented groups of items in blocks consisting of previously determined high value or low value items. Using event-related fMRI, we were able to present single items rather than groups of three, precluding 'mixing' of different attractiveness levels. We were also able to ask participants to rate each item immediately after presentation. The assignment of items to the high attractiveness or low attractiveness group would then occur based on the instant rating, rather than a general previous preference. By the same token, the impact of the hunger factor on subjective incentive value could be assessed instantly. This allowed a tighter assessment of the neural correlate of immediate incentive value, and its dependence on the hunger level.

Our second question concerned the impact of the hunger factor on incentive value. Each participant completed two recordings, about one week apart, once while sated and once while hungry. This allowed us to compare the representations of attractiveness under different hunger states. Taking that approach in their PET study, Hinton et al. (2004) confirmed Arana and colleagues' finding of value representation in the amygdala and OFC. They

also found an area of the OFC which responded to value levels differently depending on the hunger level. Our study was designed to test the Hinton et al. (2004) findings with an event-related fMRI design and tighter control of conditions and, significantly, combine both attractiveness of single dish ratings and hunger manipulations in one experiment.

Our second question targeted the impact of hunger on attractiveness of dishes as an abstract dimension, i.e. it searched for a hunger driven change of the difference between the collection of attractive and the collection of not attractive dishes. In contrast to that, our final question addressed hunger driven change of attractiveness of single, concrete dishes. The aim of this search was to single out dishes whose attractiveness levels are susceptible to increased (or decreased) hunger, and identify the neural activation that distinguishes them from other dishes. Humans rate food stimuli differently depending on how hungry they are, a change that is reflected by the neural responses (Kringelbach, O'Doherty, Rolls, & Andrews, 2003). We wanted to explore the observation that some foods seem particularly attractive when one is hungry (Hill, Magson, & Blundell, 1984). For many of us - on the way home after a late night of work, 'starving' - a baby spinach salad with dried cranberries and low fat dressing will be no match to an order of French fries. Shortly after a satisfying meal, however, the competition is likely to be different: overall satiety may diminish the advantage the fries held as an calorifically much richer food (Warwick, Hall, Pappas, & Schiffman, 1993). More than that, sensory-specific satiety (Sørensen, Møller, Flint, Martens, & Raben, 2003) for the starchy and oily food might even reverse the relationship and allow the assignment of a higher value to the salad. (An additional factor might be the altered impact of cultural beliefs about what one 'should' eat, see discussion.) In the final analysis step, we identified dishes which displayed a value increase in the hungry experimental session, and compared neural activity they elicit to dishes

which do not follow that pattern. We discuss the results of that analysis in the 'Value change between sessions' section of our results.

Method

Design

Eight volunteers (3 female) with an average age of 27.9 (SD = 4.1), underwent fMRI recording during two one-hour sessions, one in the hungry, and one in the sated condition. The two recordings happened ca. one week apart, and the sequence of conditions was balanced for all participants. For the hungry condition, participants were instructed to not eat for 6 hours prior to the experiment. Before the experiment, participants completed an extended questionnaire indicating their food preferences. The information from it was then used to design individual menu item lists for the main experiment, which would include a variety of highly valued and less valued items, but no items evoking negative responses like disgust. Each session consisted of three blocks of approximately 10 minutes of the restaurant task described below. Immediately after the recording, participants reported their hunger level. They were debriefed after the second session. The study was approved by the University Research Ethics Committee.

Task

In the 'restaurant task' used, participants imagined they were going to a restaurant for an evening meal (Arana et al., 2003). In the scanner, they were presented food menu items on a screen (no actual food was presented). An example of a menu item typically rated as highly palatable is: "Aromatic Crispy Duck: Duck, marinated in oriental spices, deep fried until golden and crispy, served with a Hoi Sin sauce, Chinese pancakes, spring onions, and cucumber." An example of a menu item typically rated lower is: "Seared Spiced Plaice Steak: Plaice steak, lightly spiced, and served with a black bean salsa on top of wild rice with sautéed young spinach and sliced button mushrooms."

Participants' task was to read each menu item, to imagine what it would be like to be presented with it in a restaurant, and to indicate how much they would like an item in such a situation. Participants indicated their rating of each item on a scale from 1 to 4 (4: would like it very much) using a keypad. Each session consisted of 3 scans of 7.5 minutes, and 36 menu ratings per scan. Each menu item appeared on the screen for 9 seconds. The fixation interval between item presentations varied between 1 and 3 seconds. Only the duration between item onset and response (i.e. not the entire 9 seconds) was modeled for the fMRI analysis.

fMRI data acquisition and analysis

A 1.5 T Philips MRI scanner was used to acquire 22 T2* weighted slices per volume (5mm slices, resulting in 3.75mm x 3.75mm x 5mm voxel size), with a time repetition of 2.2 s. The slices were tilted by 30 degrees from the ACPC axial plane to reduce susceptibility artifacts. Thus the recorded volume included the entire brain volume excluding only ventral parts of the cerebellum. The first five volumes of each scan were discarded to avoid differences in T1-saturation. Preprocessing and statistical analysis were performed using BrainVoyager 2000 and BrainVoyager QX (Brain Innovation, The Netherlands). The functional images were slice-time acquisition corrected, subject motion corrected, spatially normalized to Talairach space (Talairach & Tournoux, 1988), and smoothed with an 4 mm full width at half maximum Gaussian kernel.

The events for the fMRI signal were modeled as follows. Duration always corresponded to the period from onset of the menu item to participants' rating. For the *attractiveness representation* analysis, items rated 4 and 3 were modeled together as high incentive events, items rated 1 and 2 as low incentive events. This allowed the data to be analyzed as two factors with two

conditions each: hunger state (hungry, sated) and attractiveness (high, low). For the attractiveness *change* analysis, food items were grouped depending on their rating across sessions. Items which received a higher rating during the hungry session were modeled as 'hunger foods', items with the opposite pattern as 'satiety foods' and items with no change in rating as 'neutral foods'. In order to more precisely characterize hunger foods and satiety foods, we asked a separate group of eight participants to rate each dish on two scales: sweetness and fatness. Each scale had three points, low, medium and high.

For the region of interest (ROI) analysis, peak coordinates were taken from previous research as indicated in the results section. For the orbitofrontal cortex ROIs, the z coordinate was increased by 10mm as the original sites were outside the brain for our participant sample. Around the peak voxels, small volumes were constructed as cubes with 7mm sides. Voxels which displayed missing signal in some conditions were excluded from analysis. Voxel time series were z-score-normalized for each run and signal for the events of interest was extracted for the individual ROIs and subjected to statistical higher level group random-effects analyses.

The general linear model used for the attractiveness representation analysis included 15 regressors. These were four rating events, six motion regressors, and one artefact regressor. The rating events were entered twice, for the sated and the hungry session. The motion predictors included transitions along the three axes and rotations around them. The artefact regressor was entered at points where gross head movement were detected.

The general linear model used for the attractiveness change analysis included 12 regressors. These two rating events for both hunger foods and satiety foods, one rating event for neutral foods, and the same motion and artefact regressors as above.

For the exploratory analyses, an unconstrained whole-brain random-effects analysis was conducted to identify activity peaks corresponding to the processes of interest. For that analysis, the p-values are reported not corrected for multiple tests.

Results

Behavioral analysis

Prior to the experiment, participants indicated the level of hunger they felt on an analog scale which was later converted into values from 0 (not hungry at all) to 100 (extremely hungry). Confirming the experimental manipulation, participants reported higher levels of hunger during the hungry session (Hungry: 81, SE = 3.1; Sated: 22, SE = 3.0; $t(5) = 9.63$, $p < .0005$).

Next, participants completed the restaurant task in the fMRI scanner, giving a rating to each displayed dish description. The list of dishes each participant received was individually created using the answers participants gave to a food preference questionnaire approximately one week prior to the first session. The participants' incentive value ratings are displayed in **Figure 1**. A repeated measures ANOVA with factors hunger state (sated, hungry) and rating (1 – 4(high)) revealed that overall, participants reported more high than low ratings (linear main effect for rating; $F(1,7) = 11.68$, $p = .011$). This result validates the lists of items used as adequate stimuli for activating the brain system underlying incentive evaluation processes. An interaction effect showed that more high ratings were reported in the hungry condition ($F(1,7) = 9.00$, $p = .020$).

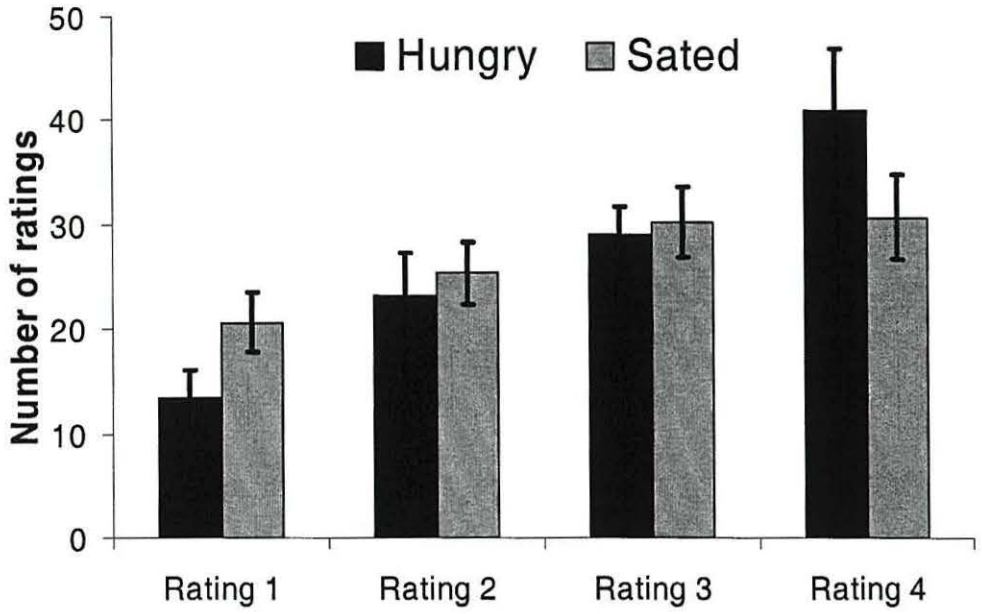


Figure 1. Frequency of ratings of menu items indicated by participants during the recording sessions. The rating scale ranges from 1 to 4, with 1 indicating low attractiveness and 4 high attractiveness. There is a linear main effect for rating ($F(1,7) = 11.68$, $p = .011$), indicating that participants reported more high than low ratings. There is also an interaction ($F(1,7) = 9.00$, $p = .020$) showing that more high ratings were reported in the hungry condition. For the analysis of fMRI data, ratings 1 and 2 were collapsed and considered as low, ratings 3 and 4 were considered as high. Error bars represent standard error of the mean.

Next, we aimed to establish if rating the attractiveness of dishes was more difficult in some conditions than in others. Based on the assumption that more difficult ratings require more time, we analyzed rating response times (time between stimulus onset and rating (**Fig. 2**). An ANOVA equivalent to the one reported above revealed no effect for state or an interaction with state ($Fs < 1$), indicating that rating difficulty did not differ between the sated and hungry sessions. There was a linear and a quadratic main effect for rating ($F(1,7) =$

6.32, p = .040, and F(1,7) = 18.00, p = .004, respectively). Follow-up tests showed that the 'extreme' ratings (1 and 4) were made faster than middle ratings (2 and 3; t(7) = 4.24, p = .016), and that ratings defined as 'high' for the imaging analysis (3 and 4) were slightly faster than 'low' ratings (1 and 2; t(7) = 3.43, p = .033).

Figure 2. Response time for ratings of menu items completed by participants during the recording sessions. There is a linear and a quadratic main effect for rating (F(1,7) = 6.32, p = .040, and F(1,7) = 18.00, p = .004, respectively). Follow-up tests indicated that the ratings 1 and 4 were made faster than ratings 2 and 3 (*t*(7) = 4.24, p = .016), and that ratings defined as 'high' for the imaging analysis (3 and 4) were slightly faster than 'low' ratings (1 and 2; t(7) = 3.43, p = .033).

Event related fMRI analysis

Attractiveness representation

Studies which utilized PET to study the representation of attractiveness in a similar task (Arana et al., 2003; Hinton et al., 2004) established the amygdala and medial OFC (mOFC) as structures which responded with increased activation to items indicated as highly valued by participants. In order to confirm and specify those findings in the context of fMRI, we compared differences between high and low attractiveness menu items (rated by the subjects as 4 or 3, and 1 or 2, respectively). The whole-brain analysis of this comparison revealed activity in the left amygdala ($x = -14$, $y = -7$, $z = -16$, $t(7) = 13.14$, $p < .000005$; **Fig. 3**), a region very close to the one reported by Arana et al. (2003). On the whole-brain analysis level, there was no activation peak in the mOFC for this contrast. When a volume in the mOFC equivalent to the one reported by Arana et al. (2003), (the coordinates used here: center at $x = -8$, $y = 44$, $z = -10$, volume is a cube with a wall of 7mm) was subjected to a region of interest (ROI) analysis, the extracted signal displayed an interaction pattern (**Fig. 4**). A repeated measures ANOVA with two factors, hunger state (sated, hungry) and attractiveness rating (low, high) showed no main effect for rating or hunger state (Fs < 2), but an interaction of the two factors ($F(1,7) = 8.80$, $p = .021$). Follow-up t-tests revealed the following response pattern: the region discriminated between high and low attractiveness items when participants were hungry, with a higher response to high attractiveness items during the hungry session ($t(7) = 3.36$, $p = .012$). In the sated session, the responses did not differ ($t < 1.5$). This somewhat contrasts Hinton et al. (2004), who only report a main effect for attractiveness for this region of the OFC. They also report an interaction, but for a more lateral volume of the OFC (however, the response pattern reported there differs, see discussion). The equivalent

analysis of that ROI based on our data (the coordinates used here: x = -26, y = 56, z = 0) confirmed the previous results also revealing an interaction ($F(1,7) = 10.76$, $p = .013$), in the absence of main effects (Fs < 2).

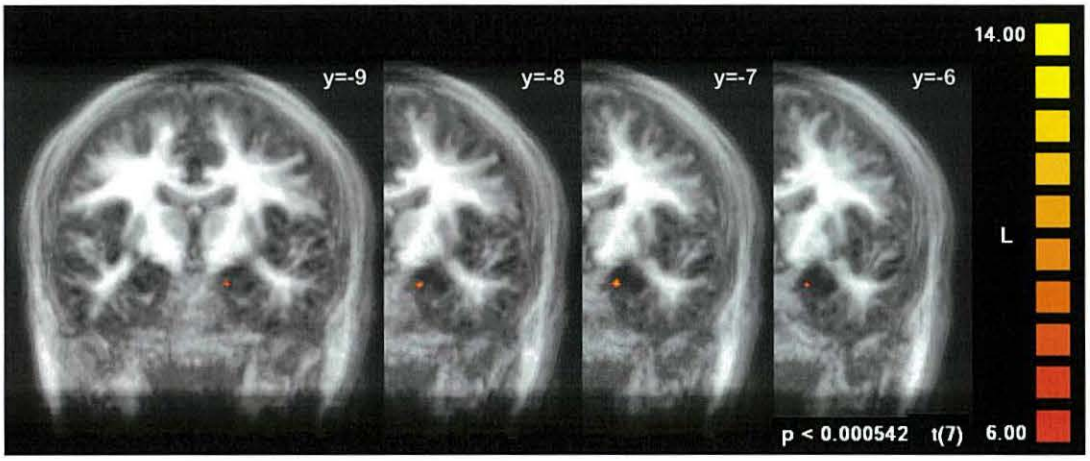


Figure 3. Significant BOLD changes in the main effect contrast of attractiveness, with low ratings subtracted from high ratings. Four coronal sections illustrating the left amygdala (maximum peak at x = -14, y = -7, z = -16, $t(7) = 13.14$, $p < .000005$). The map is displayed over the averaged anatomy of all participants, and at a more lenient statistical threshold for demonstrational purposes.

Figure 4. Estimate of activation in an region of interest located in the medial prefrontal cortex. (center peak at x = -8, y = 44, z = -10) for high and low attractiveness ratings in the hungry and sated conditions. The activation shows an interaction pattern of the two factors (hunger state and attractiveness rating, $F(1,7) = 8.80$, $p = .021$). The region responds more strongly to high than to low value items during the hungry session ($t(7) = 3.36$, $p = .012$). In the sated session, the responses do not differ ($t < 1.5$)

Attractiveness change between sessions

The analysis of food attractiveness ratings between the sessions revealed that some items were considered more desirable and rated higher when participants were hungry ('hunger foods'). The next step of the analysis was therefore the comparison of neural activity associated with these foods compared to ones which remained at the same rating level across the sated and hungry sessions ('neutral foods').

In order to explore all possible sites activated by hunger foods, we conducted an unrestricted whole brain analysis in which we subtracted activity

elicited by neutral foods from that elicited by hunger foods. Increased activity was found in the left thalamus (within the dorsomedial nucleus; x = -6, y = -13, z = 6, t(7) = 8.14, p < .0001; **Fig. 5a**), and at three sites in the right insular cortex. Those included one anterior (x = 38, y = 16, z = 12, t(7) = 5.32, p = .001), one mid-insular (x = 38, y = -7, z = 4, t(7) = 5.60, p < .001) and one posterior site x = 30, y = -16, z = 21, t(7) = 5.67, p < .001; **Fig. 5b**). Additional clusters of activity were found in the inferior parietal lobe, the occipital cortex and lateral prefrontal cortex (**Table 1**).

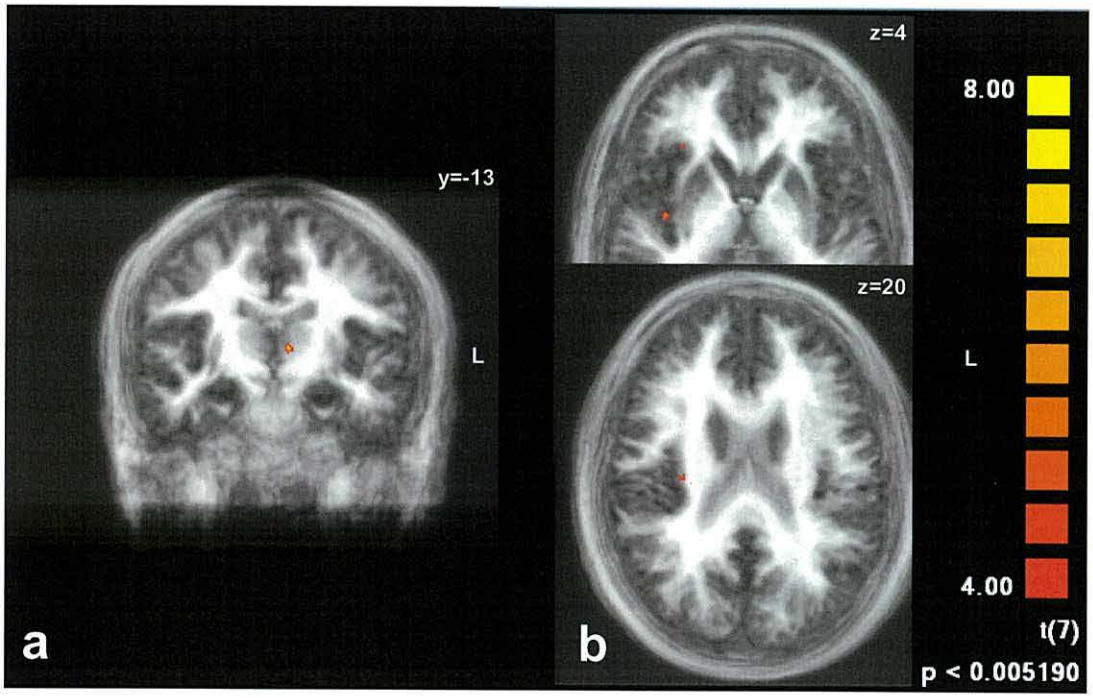


Figure 5. Significant BOLD changes in the contrast of foods which increase in rating value for the hungry session (hunger foods) minus foods which do not change their rating value between the sated and hungry session (neutral foods). Panel **a**: coronal slice of an area in the left Thalamus, likely in the dorsomedial nucleus: x = -6, y = -13, z = 6, t(7) = 8.14, p < .0001. Panel **b**: Three sites in the right insular cortex (axial slices). Anterior insular cortex (maximum peak at x = 38, y = 16, z = 12, t(7) = 5.32, p = .001), mid-insular

cortex (maximum peak at x = 38, y = -7, z = 4, t(7) = 5.60, p < .001), and posterior insular cortex (maximum peak at x = 30, y = -16, z = 21, t(7) = 5.67, p < .001). Additional clusters of activity for this contrast are listed in Table 1.

Regions	left / right	Coordinates x	y	z	t-value	p-value
Thalamus	L	-6	-13	6	8.14	.00008
Insula	R	38	16	12	5.32	.00110
	R	38	-7	4	5.60	.00082
	R	30	-16	21	5.67	.00076
Inferior parietal lobe	R	57	-25	28	6.92	.00023
Occipital cortex	R	19	-67	3	8.69	.00005
	R	8	-94	3	8.19	.00008
Lateral PFC	R	47	36	22	5.31	.00111

Table 1. Significant BOLD changes in the contrast of hunger foods minus neutral foods resulting from an unrestricted whole-brain analysis.

Within the analysis of changes in attractiveness ratings we also identified items which showed the opposite pattern from hunger foods. Such items were considered more desirable and rated higher when participants were sated ('satiety foods'). The whole brain contrast subtracting neutral foods from satiety foods identified increased activity in the anterior caudate nucleus (x = -13, y = 16, z = 13, t(7) = 6.92, p < .0005; **Fig. 6**) and the superior frontal gyrus (x = 13, y = 29, z = 52, t(7) = 5.17, p = .001).

We furthermore speculated that hunger and satiety foods may have different nutritional characteristics. The ratings of sweetness and fatness each dish received from a separate sample of eight participants did not distinguish between hunger and satiety foods (all *t*s < 1). We then modeled the fMRI data according to the sweetness and fatness ratings of the dishes. The signal

extracted from sited activated by hunger and satiety foods did not differentiate between items high and low in fat or sugar (all *t*s < 1).

Overall, our results show that participants' hunger influenced their food evaluation to give more items a higher incentive rating. Evaluating the descriptions of highly attractive food items strongly activated the left amygdala. The activation of areas in the medial OFC for high incentive items was dependent on the participants' hunger level.

When participants changed their incentive ratings of the same food item between the sated and hungry sessions, the direction of the change was reflected by activations in distinct areas of the brain. 'Hunger foods' activated the thalamus and the insula, while 'satiety foods' activated the caudate nucleus and the superior frontal gyrus. This might indicate that dissociable neural signatures of foods inform the valuation of food items which depends on the physiological need state.

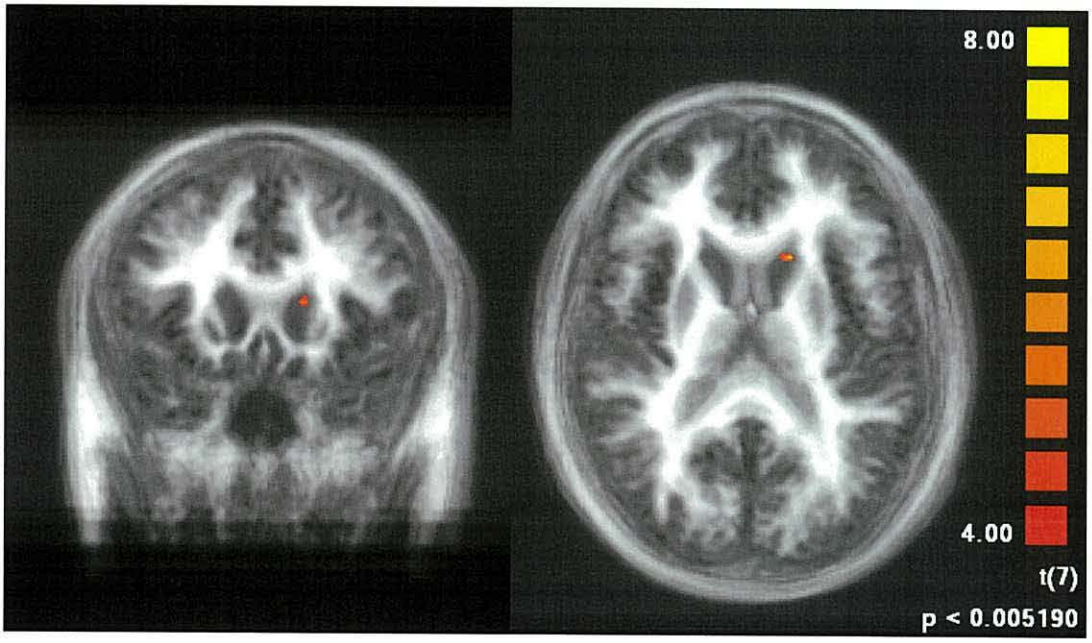


Figure 6. Significant BOLD changes in the contrast of foods which increase in rating value for the sated session (satiety foods) minus foods which do not

change their rating value between the sated and hungry session (neutral foods). Coronal slice and axial slices of an area in the anterior caudate nucleus ($x = -13$, $y = 16$, $z = 13$, $t(7) = 6.92$, $p < .0005$). An additional cluster of activation for this contrast was found in the superior frontal gyrus ($x = 13$, $y = 29$, $z = 52$, $t(7) = 5.17$, $p = .001$, not displayed).

Discussion

The aim of the current study was to investigate how hunger and attractiveness contribute to the incentive value of a dish, and at which neural sites these factors and their integration are represented. We also aimed to explore the neural activity elicited by dishes that are particularly susceptible to incentive value changes driven by hunger.

To probe the representation of attractiveness, we contrasted dishes rated high with ones rated low on that criterion. The contrast revealed a strong activation of the amygdala, adding evidence of its role in value representation. Animal research emphasizes the role of the amygdala in the process of associative learning, i.e. of creating representations of links between stimuli and their reward values (Cardinal et al., 2002). No explicit learning in the sense of creating new links took place in our experiment, but the ability to associate a value (and thus rate the attractiveness) of an originally neutral stimulus, like a text description of a dish, relies on such associations having occurred during past food consumption of the participants (Rolls, 2000). Rodent studies suggest that divisions of the amygdala store representations which allow access of conditioned stimuli (in our case represented by the menu items), to their current value for an organism (Cardinal et al., 2002). This is based on observations that rodents, but also monkeys with amygdala lesions show insensitivity to the devaluation of stimuli in satiation paradigms (Hatfield, Han, Conley, Gallagher, & Holland, 1996; Malkova, Gaffan, & Murray, 1997). Interestingly, one study conducted with rhesus monkeys shows that such insensitivity crucially depends on the communication of the amygdala with the OFC (Baxter, Parker, Lindner, Izquierdo, & Murray, 2000). This will be discussed below. The described features of amygdala function also offer an alternative for Damasio's somatic marker hypothesis (Damasio, 1994), in that

the conditioned stimulus has the potential to elicit a value tag and arousal. These properties are similar to the 'somatic marker', but offer a more parsimonious mechanism because they do not rely on peripheral physiological activation.

Human neuroimaging and lesion studies show that the amygdala plays a central role in the processing of affective stimuli (Zald, 2003). It has been shown to increase activation to appetitive stimuli such as sweet taste, pretty faces and pleasant pictures (Aharon et al., 2001; Garavan, Pendergrass, Ross, Stein, & Risinger, 2001; J. O'Doherty, Rolls, Francis, Bowtell, & McGlone, 2001). This has lead to the question what role the amygdala actually plays in the processing of those stimuli, i.e. which aspects it represents. Emotional responses and responses to affective stimuli in general can be viewed as having two dimensions, how pleasant or unpleasant they are (valence dimension) and how activating they are (intensity dimension, also linked to arousal, (Lang, Bradley, & Cuthbert, 1993)). Two influential studies attempted to dissociate these dimensions in the chemosensory domain and found evidence suggesting that the amygdala codes the intensity of stimuli, dissociating its function from that of the OFC (Anderson et al., 2003; Small et al., 2003). Using affective words - a set of stimuli more comparable to ours – Lewis and colleagues (Lewis, Critchley, Rothstein, & Dolan, 2007) confirmed a role of the amygdala in the representation of intensity, but found the dissociation from the OFC less clear (they also found value representations in the amygdala). Challenging results to the intensity hypothesis came form a study by Winston and colleagues (Winston, Gottfried, Kilner, & Dolan, 2005). They used neutral odors varying in intensity to show that the amygdala coded for intensity only in positive or negative stimuli. This was a crucial manipulation as it shows that activity in the amygdala represents the integrated valence and intensity of affective stimuli rather than just the intensity dimension. This is in

agreement with findings from animal studies suggesting that amygdala subserves the integration of value with sensory properties of stimuli (Cardinal et al., 2002).

Our result showing increased amygdala activity for high attractiveness dishes confirms its role in representing appetitive value. We did not attempt to systematically vary intensity, but it is likely that it covaried with value, in particular in light of the fact that we explicitly avoided dishes which participants might find aversive (and thus only included neutral to positive valence). Our results concur with previously documented ones in a similar experimental design by Arana et al. (2003) and Hinton et al. (2004). Both those studies found increased amygdala responses to dishes valued higher by participants. Compared to those, our activation was statistically more robust, likely due to closer control of conditions in our study, through the use of only one dish per trial and an immediate attractiveness rating after each trial. We found that amygdala activation reflected attractiveness, but did not interact with hunger level. This reflects the findings of Hinton et al. (2004), but is somewhat inconsistent with findings from animal literature, which suggest that value representation in the amygdala is sensitive to internal motivational state as for example hunger or satiety (Hatfield et al., 1996; Malkova et al., 1997; Rolls, 1992). There are at least three possible explanations for this discrepancy. The first and most trivial is that our experimental design coupled with fMRI as recording technique is not sensitive enough to detect an interaction of two factors in that area. That is in spite of the fact - as will be outlined below - that the current task in conjunction with fMRI seems to be more sensitive than the combination of longer menus and PET used by Hinton et al. (2004). This is supported by the fact that we found interaction patterns for both investigated sites in the OFC, for one of which Hinton et al. (2004) only detected a main effect. Alternatively, this aspect of amygdala function might actually differ

between humans and other animals. In primates, state dependent representation of value can be found in both the amygdala and the OFC (Wilson & Rolls, 2005), suggesting this function might be to some degree shared between those structures. This is supported by the finding that the connection of the amygdala and the OFC is necessary for state dependant representation of value in rhesus monkeys (Baxter et al., 2000). The equivalent of the OFC in rodents is however markedly less developed (Uylings & van Eden, 1990), and so the balance might be shifted more towards the amygdala. It in fact seems to adapt to changing values quicker than the OFC (Schoenbaum et al., 1999), in contrast to that of the primate (Rolls, 1992). A third explanation of the discrepancy follows form the limited spatial resolution of fMRI and PET. The amygdala is a complex structure comprised of a number of nuclei (Swanson & Petrovich, 1998; Zald, 2003). It is commonly subdivided into the basolateral amygdala (BLA) and the central nucleus of the amygdala (CnA) and research on rodents indeed identified a number of functional dissociations between BLA and CnA, including their role in state dependant representation of value (Cardinal et al., 2002). Our results may not reflect state dependant representation of value in the amygdala because it averages over structures with somewhat different functions and therefore different response properties. This issue should be addressed in the future by using high field fMRI to record signal from a restricted volume of the brain.

Arana et al. (2003) used a similar experimental design to ours and found a site in the OFC to code for the equivalent of our attractiveness factor. We used the coordinates of that site to define a region of interest (ROI; we had to increase the z coordinate by 10mm however, as for our sample the original volume corresponded to participants' eyes) and subjected the signal extracted from it to a statistical analysis including both factors, attractiveness and hunger. The analysis revealed an interaction pattern for the two factors.

Specifically, the site responded differently to high and low levels of attractiveness, but selectively so only during the experimental session when participants were hungry. It showed a stronger response to high than to low attractiveness items when participants were hungry, but not when they were sated (Fig. 4). This suggests that this OFC area represents subjective incentive value which depends not only on the properties of the stimulus, but also on the internal state of participants. It is likely that Arana et al. (2003) essentially obtained the same result in their study, but because they did not manipulate hunger, they interpreted the difference as a main effect, which truly was masking an interaction. This view is supported by a second analysis that Arana et al. (2003) conducted: when they compared the signal from the amygdala and OFC with individual participant ratings, they found a significant covariation for the amygdala, but not for the OFC.

A study which added a hunger manipulation to the design used by Arana et al. (2003) was conducted by Hinton et al. (2004). Their results confirm our speculations. Firstly, they do find a site in the OFC which shows a response pattern indicating an interaction of attractiveness and hunger. Our analysis of the signal from a small volume around the equivalent peak coordinates also revealed an interaction pattern for the factors attractiveness and hunger. Secondly, they too, found a main effect for attractiveness at the site reported by Arana et al. (2003). We suspect they failed to detect an interaction at that site due to design restrictions imposed by using PET and the grouping of stimuli. This is supported by the fact that the main effect is found using a whole brain analysis, not an ROI approach as in our case. Additionally, signal extraction from the site where they confirm an interaction (for both their (their Fig. 5b) and our data) reveals a telling pattern. The difference between high and low attractiveness dishes is actually reversed for the sated session, making it more detectable as an interaction than the pattern from the other site.

Our claim that our results are a closer assessment of the influences of hunger state on incentive value is also supported by the fact that we actually found a behavioral effect of the hunger manipulations. Our participants rated more items as highly attractive (rating 4) and fewer as not attractive (rating 1) when they were hungry, as opposed to when they were sated (Fig. 2). Participants in the Hinton et al. (2004) study reported equal attractiveness levels after the sated and hungry conditions.

To summarize, our results suggest a representation of attractiveness in the amygdala, which is in agreement with its role suggested by animal and human imaging studies. Our results also suggest the role of OFC in integrating attractiveness and motivational state of the individual, rather than in coding attractiveness independent of motivation. One site showing this integration pattern seems to discriminate between attractive and less attractive foods when it counts, i.e. when one is hungry, but is indifferent to them when the individual is sated.

In the final exploration of the results of our study we shifted the focus from abstract categories of highly attractive and less attractive foods to individual dishes and how their perceived value can be altered by increased motivation in the form of hunger. We first identified which items received a higher rating when participants where hungry ('hunger foods') and then contrasted the neural activity they elicited with that of items which showed no rating change between the sessions ('neutral foods'). The rationale for this exploration arises from the simple observation that hunger is adaptive. Our organisms evolved the capacity to detect fullness levels of energy storage systems and to create hunger and the motivation to seek food and eat, when they reach certain depletion levels (Schwartz, Woods, Porte Jr, Seeley, & Baskin, 2000). An interesting issue in this context is how selective such motivation can be. If the goal to be achieved by hunger motivation is the

restocking of energy levels, it would be adaptive to aim the motivation towards foods that are particularly dense in calories and assign them with high motivational values when an organism is very hungry and its energy reserves particularly depleted. This does indeed seem to be the case (Warwick et al., 1993). In the context of our study, we were interested in the neural signature of dishes that were rated as more attractive when participants were hungry than when they were sated. Such foods – if consumed – would be likely to activate representation of fat or dense carbohydrates in the brain. The question we asked was whether the mere descriptions would be powerful enough to produce such discriminative activations.

Depletion of energy is not the only physiological need state which can be amended through selective motivation to eat. Organisms need to take in a variety of nutrients and other chemicals and keep them within a certain bandwidth of levels in order to survive. Examples are the need for vitamins, certain amino acids, trace elements. Is it possible that our motivation to eat is selective at picking the correct foods to provide us with these substances? There is strong evidence that organisms can develop a specific thirst for salty water and assign it with great motivational value when sodium levels are depleted (Rolls, 2000). In the context of our study, we were interested to see if foods which seem more desirable when one is not hungry, and restoring energy levels is not the priority, are characterized by a neural imprint which reflects their potential value to the organism.

The biological mechanisms to obtain certain nutrients might be complemented by cultural ones, such as beliefs about what one should eat. In today's western culture those appear to include foods believed to be healthy, such as vegetables and fruit. Motivation to eat elicited by such cognitive concepts is likely to arise from top-down controlled processes (Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002). As these are frequently

accompanied by activations in the lateral PFC and the anterior cingulate cortex, activations in those areas may be expected for 'satiety foods'. (The power of the influence of top-down processes may also be dependent on hunger state, i.e. it might be more pronounced when basic energy needs are satisfied. This would be an interesting question to test with an suited experimental design.)

To address the question of specific food motivation, we first contrasted hunger foods with neutral foods. This contrast was conducted collapsed for both the sated and hungry session of each participant. The resulting activation map corresponds to the activation by dishes that are particularly susceptible to value increase which goes along with greater hunger. This analysis revealed activations in several regions: peaks in the thalamus, the insula, lateral prefrontal cortex, parietal cortex and occipital cortex were identified (see Table 1). Interpretation of these findings is somewhat speculative, as we only had cautious hypotheses regarding that contrast. It also has some additional limitations linked to individual participant responding. The numbers of items in the conditions differed: the comparison condition with neutral foods had about twice as many events as the hunger foods condition, resulting in different error margins. The overall attractiveness level of the dish groups compared was not controlled for, and could have been higher for one of the groups. Since the number of hunger foods was low, we had to collapse the data from the sated and hungry sessions to increase power. Keeping these issues in mind, the pattern of activity elicited by the hunger foods is nevertheless interesting and provides a starting point for further research with improved experimental designs. Above all, it appears that hunger foods are not just the 'good' foods, since the activation pattern for hunger foods differed from that for high incentive foods. Neither the amygdala nor the OFC were significantly activated by hunger foods. Thus, the property which empowers them to be more

desirable during the hungry state seems to be distinguishable from overall high incentive value. We speculated that it might be certain nutritional attributes which characterize a 'hunger food'. To investigate this speculation, we asked participants (separate from the participants in the original study) to rate all the displayed food items on two scales: sweetness and fatness. Hunger foods did not show a sweetness or fatness difference from neutral foods (or satiety foods). We then modeled the fMRI data according to their sweetness and fatness ratings, and did not find differences in the regions included in the hunger foods' imprint. Putting these observations together, it seems that neither palatability nor perceived fat or sugar content determine the incentive increase which accompanies increased hunger in some foods. Nevertheless, some of the structures activated by hunger foods seem to be in an exceptionally good position to determine suitability of certain foods for certain states. Both the thalamus and the insular cortex have previously been shown to encode hunger signals (Tataranni et al., 1999). The dorsomedial nucleus of the thalamus is closely connected to the prefrontal cortex, which allows it to coordinate hunger state and executive decision making. Activity in the insula can be found as a response to sensory properties of actual foods, particularly fat content (de Araujo & Rolls, 2004), and general interoception (Craig, 2002). These response properties would enable this section of the cortex to contribute to decisions combining information about specifics of food and the physiological state of the body. The activity in the parietal, occipital, and prefrontal cortices are more likely to be connected to physical differences in the appearance of the food descriptions, and different working memory loads. Whether the activity we found in the thalamus and insula indeed represents the processes we speculate on, deserves separate investigation.

The activity peaks we found for 'satiety foods' stem from an analysis which was based on very few items (only few items were rated higher by the

participants when they were sated rather than hungry) and is thus difficult to interpret. Potentially, rating a food as highly desirable when sated involves highly conscious, cognitive processes based on declarative knowledge about issues like health. The activity in the prefrontal cortex and in the rostral caudate nucleus might support such cognitive processes (Bunge et al., 2002).

Overall, the results of our study show that the amygdala represents incentive value in written descriptions of affectively relevant stimuli. We demonstrate that areas of the orbitofrontal cortex integrate overall attractiveness of dishes with motivational state. We also suggest the thalamus and insula as structures that potentially help to choose the right food items at the right time.

Chapter 5: Neural correlates of affective influence on choice

Introduction

Our everyday lives consist of a stream of choices. By the time we arrive at work in the morning, we have already selected a shirt, a route, and coffee with or without cream. Many choices are made with some degree of automaticity, as conscious processing of all of them would quickly saturate our cognitive capacity and preclude a fluent pursuit of our goals (Marois & Ivanoff, 2005). Others, however, are preformed in a consciously controlled manner, as they require a flexible adaptation to the current task. The current study was designed to investigate such choices. Making correct choice decisions depends crucially on the accurate valuation of the available options in the light of attaining the current goals of an individual. The current goals can be manifold: they can consist of achieving physiological homeostasis like relieving hunger feelings, or of more abstract goals like beating a friend at chess. Notably, the valuation of – sometimes identical - choice options depends on the currently active goal (Ferguson & Bargh, 2004). Preparing a quick meal might be evaluated as a good choice if satiation of hunger is the goal, but it is a poor choice if the goal is to complete a chess victory. The critical concept in this scenario is that of the current value of each option.

The representation of value in the human brain has been studied utilizing brain imaging recordings of responses to affective, in most cases positive stimuli. Those included primary reinforcers like food, smell and flavor (Anderson et al., 2003; Small & Prescott, 2005; Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001), but also pleasant pictures (Garavan et al., 2001), and abstract stimuli associated with reward, like descriptions of food (Arana et al., 2003). These and other studies suggest a network of structures, including the

amygdala, the OFC, the insula and the anterior cingulate to represent aspects of value representation.

In the context of decision making research, an important question is how different aspects of value representation guide choice processes, and which neural structures are involved in their computation. A few previous studies have addressed that issue. Arana et al. (2003) found increased activation in the medial OFC and the medial striatum in a condition which required choosing, in addition to evaluating food options. Winston and colleagues (Winston, Strange, O'Doherty, & Dolan, 2002) showed enhanced activity in the ventromedial PFC and the somatosensory cortex when emotional information processing was the participants' goal rather than when it happened incidentally. Paulus and Frank (2003) showed that a beverage preference judgment engaged the ventromedial PFC, the anterior insula and sections of the parietal and cingulate cortices more strongly than a visual discrimination task. These studies suggest a network of structures, most notably the ventral and medial PFC, as the anatomical sites underlying evaluation and choice processes. They do not, however, identify the specific structures involved in guiding choice with different aspects of the options to be selected. The current study was intended to address this issue.

The choices humans make are influenced by a number of factors (Sugrue, Corrado, & Newsome, 2005). Classic decision making models, for example expected utility models (Schoemaker, 1982), considered choice behavior as a highly rational cognitive process. The rationality of choice was challenged by Simon (1972), as well as by the work of Tversky and Kahneman (1974), who demonstrated that under some circumstances choices can deviate from the rationally optimal. Their findings initiated the idea that humans do not always base their decisions on purely cognitive considerations but are also susceptible to irrational influences. Later work from the laboratory of Antonio

Damasio and others attempted to shed light on those irrational influences and their impact on decisions (Damasio, 1994). With his colleagues Damasio provided evidence that decision making in humans depends on affective influences (Bechara et al., 2000) and that their physiological correlates might provide a mechanistic basis for that influence.

The aim of the present study was to identify the neural structures involved in guiding choice with different aspects of the options to be selected. In particular, we set out to identify neural sites active during choice behavior that is guided by an affective process – the assignment of an incentive value to a stimulus, and during choice guided by a cognitive process – the assignment of a procedure to a stimulus. To do that we chose to explicitly control the basis of choice by instructing participants to use a specific criterion – affective or non-affective - to guide their choice while selecting from restaurant dish options. Participants in the study completed the following task while undergoing an fMRI recording. They were asked to imagine being in a restaurant and studying the menu to make a selection. During each experimental trial, they were presented three menu items. Their task was to read each item description, to imagine it, and to choose one of them. The critical manipulation was implemented through an instruction prior to each trial: in half the cases, participants were asked to choose which item they would like to *order and eat* if they were actually in a restaurant ('eat' condition). In the other half of the trials, participants were instructed to choose which item they consider the *easiest to cook* ('cook' condition). Thus, both conditions required a consideration of the properties of the dishes and a selection process. In the first condition, however, choices were guided by affective properties, in the second by cognitive-procedural properties of the stimuli.

Following a similar goal as our study, Goel and Dolan (2003) reported an association of ventral PFC regions with 'hot', emotional selection, and of

lateral PFC regions with 'cold', cognitive selection processes. The crucial development in our study is that while Goel and Dolan (2003) used stimuli with different levels of emotional content in their conditions, we kept the stimuli in both conditions identical, only varying the participants' task.

The 'eat' condition in our study represents processes of affect-guided choice. The investigation of affective influences on choice, especially in the context of food selection, needs to consider the relationship between value and motivation. In particular, the affective value of an option may be susceptible to changes driven by an altered motivational state. Several studies have shown that altering the motivational state of participants by changing their hunger level has an impact on decision making and neural responses associated with relevant stimuli (Hinton et al., 2004; Kringelbach et al., 2003; Small et al., 2001). Our goal was to investigate whether neural activity during choice guided by affective information was susceptible to manipulation of motivation. Therefore, we conducted the experiment in two otherwise identical sessions, one during which participants were sated, and one in which they were hungry. We hypothesized that the increased motivation to eat would have an impact on the processes involved in choosing food based on its expected reward properties, but not based on the procedural properties of its preparation.

In summary, participants in the current study made selections from restaurant menu items presented on a screen, once while they were hungry and once while sated. They were instructed to make their selection based on either the desirability of the dishes or the complexity of their preparation. Thus, the conditions discriminated choices guided by affective information from choices guided by cognitive information, in sessions when the motivation to eat was high or low, with a task that is frequently encountered in everyday life.

Method

Design

Eight volunteers (3 female) with an average age of 27.9 (SD = 4.1), underwent fMRI recording during two one-hour sessions, one in the hungry, and one in the sated condition. The two recordings happened ca. one week apart, and the sequence of conditions was balanced for all participants (The recordings were made in conjunction with those for another study, 'Neural representation of incentive value change accompanying intrinsic motivational increase', with the same participants). For the hungry condition, participants were instructed to not eat for 6 hours prior to the experiment. Before the experiment, participants completed an extended questionnaire indicating their food preferences. The information from it was then used to design individual menu choice options for the main experiment, which would include a variety of items, with explicitly no items evoking negative responses like disgust. Each session consisted of three blocks of approximately 12 minutes length. Immediately after the recording, participants reported their hunger level. They were debriefed after the second session. The study was approved by the University Research Ethics Committee.

Task

Participants were asked to imagine being in a restaurant for an evening meal. While in the scanner, they were presented with three dish descriptions from restaurant menus in each trial, with all three presented on one screen (on top, middle, and bottom of screen; no actual food was presented). They were instructed to study the menu items to make a selection. Their task depended on an instruction which appeared on the screen prior to each trial. For the 'eat' condition, participants' task was to read each item description, and to choose

the one they would select in a restaurant. For the 'cook' condition, the selection was to be based on the complexity of preparation, i.e. participants were asked to choose the one which they thought would be the easiest to cook. The order of trials was semi-randomized. Participants indicated their choice by pressing the top, middle or bottom key on a keypad.

An example of three choice options would be: (1) "Tender roast lamb served with roast potatoes, cabbage, sweetcorn, and mint sauce." (2) "Succulent chunks of lamb in a thick creamy gravy with chestnut mushrooms, onions and leeks oven baked to perfection." (3) "Bite size chicken pieces marinated in sherry garlic, soy sauce and lemon juice. Served with assorted vegetables and rice." Each session consisted of 3 scans of 11 minutes, and 24 menu ratings per scan. Each menu selection appeared on the screen for 22 seconds after a trial instruction ('eat' or 'cook') of 1 to 2 seconds. The fixation interval between presentations varied between 1 and 3 seconds. Only the duration between item onset and response (i.e. not the entire 22 seconds) was modeled for the fMRI analysis.

fMRI data acquisition and analysis

A 1.5 T Philips MRI scanner was used to acquire 22 T2* weighted slices per volume (5mm slices, resulting in 3.75mm x 3.75mm x 5mm voxel size), with a time repetition of 2.2 s. The slices were tilted by 30 degrees from the ACPC axial plane to reduce susceptibility artifacts. Thus the recorded volume included the entire brain volume excluding only ventral parts of the cerebellum. The first five volumes of each scan were discarded to avoid differences in T1-saturation. Preprocessing and statistical analysis were performed using BrainVoyager 2000 and BrainVoyager QX (Brain Innovation, The Netherlands). The functional images were slice-time acquisition corrected, subject motion

corrected, spatially normalized to Talairach space (Talairach & Tournoux, 1988), and smoothed with a 4 mm full width at half maximum Gaussian kernel.

The events for the fMRI signal were modeled as follows. Duration always corresponded to the period from onset of the menu item to participants' choice response (about 12 seconds). For the event-related fMRI analysis, eat and cook trials were modeled as separate events for both the sated and hungry sessions. This allowed the data to be analyzed as two factors with two conditions each: hunger state (hungry, sated) and task (eat, cook).

For the region of interest (ROI) analysis, peak coordinates were taken from previous research as indicated in the results section. Around the peak voxels, small volumes were constructed as cubes with 7mm sides. Voxel time series were z-score-normalized for each run and signal for the events of interest was extracted for the individual ROIs and subjected to statistical higher level group random-effects analyses.

The general linear model used for the fMRI data analysis included 11 regressors. These were two trial types (eat and cook), six motion regressors, and one artefact regressor. The eat and cook trials were entered twice, for the sated and the hungry session. The motion predictors included transitions along the three axes and rotations around them. The artefact regressor was entered at points where gross head movement were detected.

For the exploratory analyses, an unconstrained whole-brain random-effects analysis was conducted to identify activity peaks corresponding to the processes of interest. To identify clusters of activity, a display with a p-value of .001 was used. For the exploratory analysis, the p-values are reported not corrected for multiple comparisons.

Results

Behavioral analysis

Immediately after the experiment, participants indicated the level of hunger they felt. Confirming the experimental manipulation, participants reported higher levels of hunger during the hungry session ($t(5) = 9.63$, $p < .0005$).

The first step of the analysis aimed to establish if choices in the 'eat' and 'cook' conditions during the sated and hungry sessions differed in difficulty. Based on the assumption that more difficult choices require more time, we analyzed the time taken to make a selection (time between stimulus onset and the selection (**Fig. 1**)). The average response times were 12.7s, 12.4s, 12.1s, and 12.0 s for the 'hungry & eat', 'hungry & cook', 'sated & eat', and 'sated & cook' conditions, respectively. A repeated measures ANOVA with factors task (eat, cook) and session (sated, hungry) revealed that there was no difference between the conditions, with the *F*-values for the main effects and interaction below 1.5. We therefore concluded that the response time as an indicator of task difficulty suggested that it did not differ between the conditions.

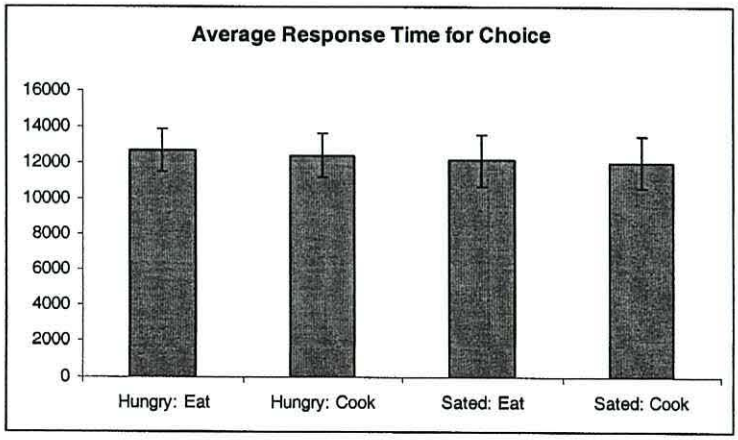


Figure 1. Response time for choices completed by participants for the 'eat' and 'cook' conditions during both recordings, i.e. during the hungry and sated

sessions. There was no significant difference between the conditions (Fs < 1.5). The y-scale indicates time in milliseconds, the error bars one standard error of the mean.

Event related fMRI analysis

Affect-guided and cognition-guided choice behavior

The difference between the two experimental conditions of interest to us, related to the processes required to inform the choice decision of participants. In both the 'eat' and 'cook' conditions, the choice required using memory and imagination to make the response. However, in the 'eat' condition, the choice was based on the projected rewarding quality of the menu item incentive value, whereas in the 'cook' condition, the choice had to be based on cognitive knowledge of procedures required for the preparation of a menu item. We therefore expected that subtracting the cook-related from the eat-related activity would emphasize the impact of appetitive anticipatory processes on decision making, while the opposite subtraction would emphasize utilization of cognitive information for decision making.

To analyze the fMRI data, we conducted a whole brain contrast of activity during affect-guided choice minus activity during cognition-guided choice. Employing a statistical threshold of .001, increased activity was found in the central part of the left insula ($x = -31$, $y = 7$, $z = 6$, $t(7) = 5.82$, $p < .001$), in the left medial temporal gyrus ($x = -60$, $y = 4$, $z = -17$, $t(7) = 8.42$, $p < .0001$) and in the caudal OFC (left caudal straight gyrus: $x = -1$, $y = 8$, $z = -17$, $t(7) = 6.75$, $p < .0005$; see **Fig. 2**).

The reverse subtraction, revealing activity related to cognition-guided choice, showed peaks in the medial PFC ($x = -14$, $y = 40$, $z = 1$, $t(7) = 7.00$, $p < .0005$), in the anterior cingulate gyrus ($x = 0$, $y = 26$, $z = 6$, $t(7) = 7.18$, $p <$

.0005), and in the lateral OFC (inferior frontal gyrus, x = -40, y = 32, z = -8, t(7) = 7.09, p < .0005; see **Fig. 3**).

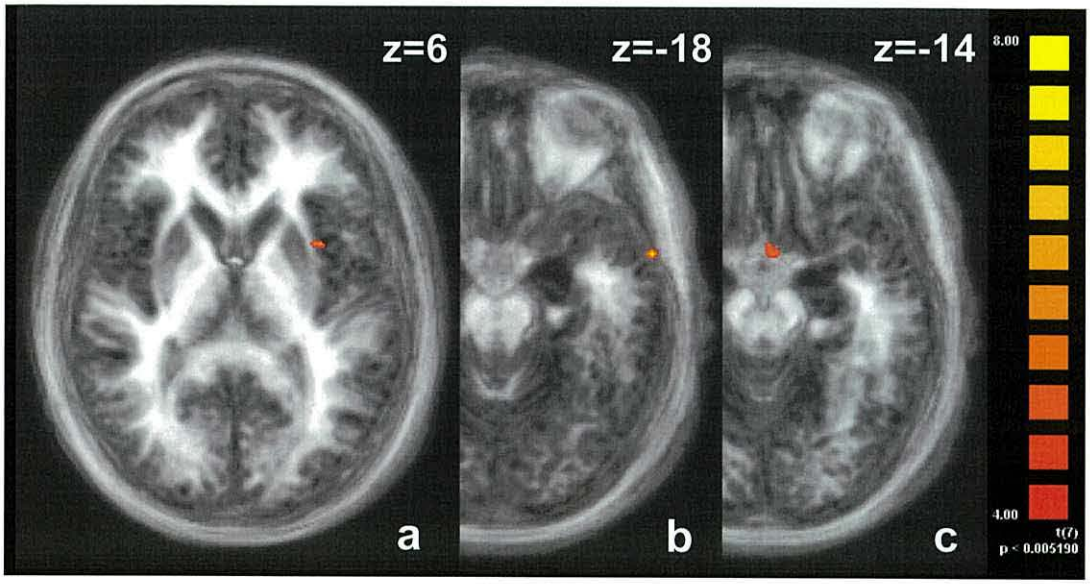


Figure 2

Caption Figure 2.

Significant BOLD changes in the contrast revealing activity for affect-guided choice (subtracting the cook condition from the eat condition). Three axial sections illustrating **a)** the central part of the left insula: x = -31, y = 7, z = 6, t(7) = 5.82, p < .001), **b)** the left medial temporal gyrus (x = -60, y = 4, z = -17, t(7) = 8.42, p < .0001), and **c)** the left caudal straight gyrus (x = -1, y = 8, z = -17, t(7) = 6.75, p < .0005). The map is displayed at a statistical threshold of .005 for demonstrational purposes.

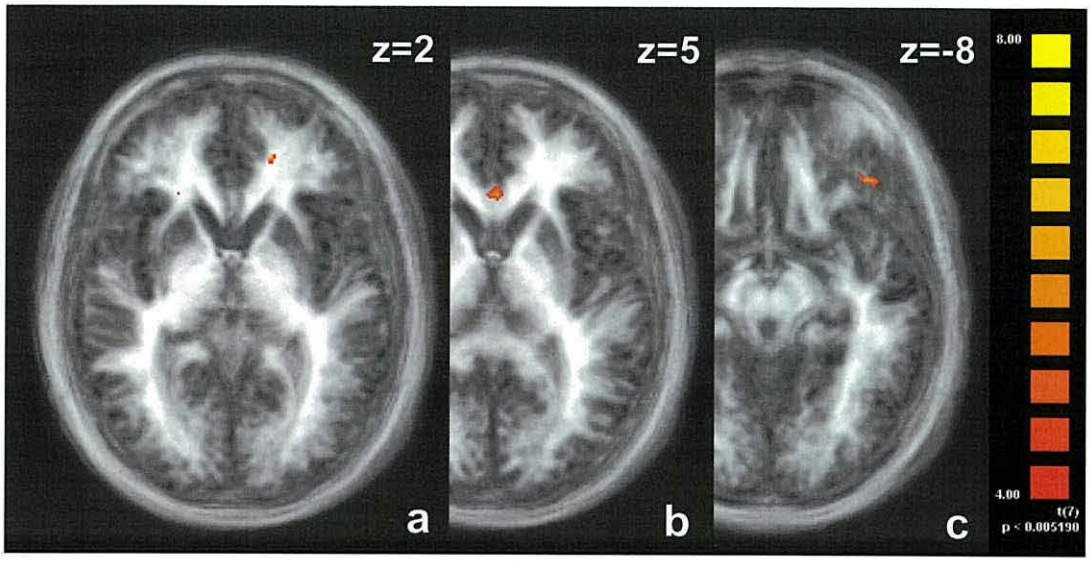


Figure 3. Significant BOLD changes in the contrast revealing activity for cognition-guided choice (subtracting the eat condition from the cook condition). Three axial sections illustrating **a)** the medial PFC (x = -14, y = 40, z = 1, t(7) = 7.00, p < .0005), **b)** the anterior cingulate gyrus (x = 0, y = 26, z = 6, t(7) = 7.18, p < .0005), and **c)** the left lateral OFC (inferior frontal gyrus, x = -40, y = 32, z = -8, t(7) = 7.09, p < .0005).

To investigate the impact of motivational state on task related activity, we conducted an interaction analysis, with a contrast that would reveal areas activated more strongly for the eat condition, but only in the hungry state. A whole brain analysis followed by inspection of the activation patterns of potentially involved areas showed that no such area could be identified.

Overall, we found that affect-guided choice behavior activates a different set of areas compared to equivalent choice behavior when it is solely based on procedural information which is not related to reward. Within this study, we could not locate areas which would respond in a pattern consistent with an interaction between the task and the motivational state in the predicted fashion. This stands in contrast to experiment 3, which did show interactions of

similar kind. Possible explanations for this discrepancy will be offered in the discussion section of this chapter.

Discussion

We found that our affective choice condition activated the insula, the anterior temporal lobe and medial orbitofrontal cortex, while the cognitive choice condition activated the lateral orbitofrontal cortex and the anterior cingulate.

The insular cortex subserves a variety of functions related to interoception (Craig, 2002; Critchley, Wiens, Rotshtein, Oehman, & Dolan, 2004) and the perception of taste and its reward qualities (de Araujo & Rolls, 2004). Most notably, it has been shown to represent interactions of reward value with motivational states (Hinton et al., 2004; Small et al., 2001). The activation of the insula found during affect guided choice in our study is likely to represent expected gustatory qualities of the presented items, upon which the decision regarding which item would be most preferred to eat must be based.

The anterior temporal lobe (ATL) including the rostral superior and medial temporal cortices remains one of the least explored areas of the cortex. There is some evidence that it plays an important role in emotional, visual and memory processing, in particular linking emotional value with subjective experience (Karnath, 2001; Mesulam, 1985). Pessoa's (2008) review of emotional and cognitive brain systems considers the ATL as an extended emotional region. The activation of the anterior medial temporal gyrus we identified during the affective choice condition supports a role of that area in emotional function. A crucial aspect of this result might be the ATL's involvement in both emotional processing and in memory, because the affective choice task performance depends on retrieving the reward value of dishes as they are imagined, based most likely on a person's memories of eating such or similar foods. The activation we observed in the ATL also emphasizes the value of the current paradigm for future investigations of this little studied area of the cortex.

The orbitofrontal cortex (OFC) is widely thought to represent reward value (Rolls, 2000), as it has been shown to respond to a number of positive stimuli, among them tastes and odors. Besides that, the OFC has also been shown to represent negative stimuli, and reward value change (Kringelbach et al., 2003; Small et al., 2001). This combination of observations has led to claims that the OFC represents both primary reinforcer value and processes associated with the learning of value change and in the control and correction of behavior driven by reward (Rolls, 2000).

We found that the OFC showed a different pattern of activation for affect guided choice processing and cognition guided processing. During affect guided choices, an area of the medial OFC was activated, whereas during cognition guided choices, an activity peak was found in a lateral area of the OFC. This maps well onto previous findings regarding the dissociation of function for medial and lateral OFC. Small et al. (2001) observed in their study that as the value of a food (chocolate) decreased with consumption, activity in the medial OFC decreased as well, whereas activity in the lateral OFC increased, suggesting that the first represented rewarding, the latter aversive value. O'Doherty and colleagues (J. O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001) came to a similar conclusion, as their value reversal learning task produced medial OFC responses to rewarding, and lateral OFC responses to punishing stimuli. Elliott et al. (2000) reviewed work on OFC function, which they conducted in their own laboratory and concluded that the results are consistent with the representation and monitoring of current value in the medial OFC, and the suppression of a previously rewarded response in the lateral OFC. In the current study, medial OFC activation occurred during affectively guided choice, when representation of the anticipated reward value is necessary to make the correct decision. Lateral OFC was activated during cognitively guided choice, when it is appropriate to ignore or suppress the

reward value of the food items and the choice decision needs to be based on a different criterion. It is therefore possible that a process similar to suppression as suggested by Elliott et al. (2000) takes place during our task.

The anterior cingulate cortex (ACC) has been implicated in an array of functions, including processing of sensory, motor, emotional and cognitive information. This multitude makes it, along the ATL and the prefrontal pole, one of the more enigmatic areas of the cortex. A common denominator in ACC function appears to be the monitoring of conflict (Botvinick, Cohen, & Carter, 2004). In an attempt to specify the function of the ACC and its subdivisions, Bush and colleagues (Bush, Luu, & Posner, 2000) reviewed findings from neuroimaging, lesion and physiological studies. They suggested a separation of the ACC in dorsal and ventral areas, corresponding to Brodmann areas 24 and 32, with the dorsal division frequently active in cognitive tasks, and the (rostral-) ventral areas involved in affective tasks. The activation peak we identified in the ACC for cognition guided choice falls into the rostral-ventral division of BA 32. In agreement with the cited work, it might represent an affective conflict monitoring process. This is a plausible explanation if one assumes that the affective representation of the choice options potentially occurs automatically, and that it is a process which during the cognitively guided choice might create a conflict needed to be monitored. This interpretation of the ACC activity would converge with the activation in the lateral OFC found in the same condition.

We designed our experiment to be conducted in two sessions, while the participants were either sated or hungry. The goal of this manipulation was to allow us to identify regions that show an interaction response pattern. Specifically, we expected a site which represents taste would be involved in the affective choice more strongly when participants are hungry. We did not find an area which would show a significant activation with this pattern. This is

somewhat surprising, as the study reported in the previous chapter did show interactions of similar kind, i.e. between hunger manipulation and food value ratings. A likely explanation emerges if one separates the 'eat' task in a hypothetical 'value representation' process, and a 'selection based on value' process, informed by the first. Contrasting the eat and cook tasks then reveals differences in the selection process involved in the tasks. This selection process may be the same when participants are sated as when they are hungry. The other process, that of value representation, would however be expected to be altered for the hungry condition. Considering that some degree of value representation happens incidentally, even if it is not required by the task (Winston et al., 2002), it would follow that value representation changes occurred in both the eat *and* cook tasks, precluding the detection of an interaction. This pattern may be exacerbated by the fact that not all food items are likely to have increased in value as a consequence of hunger. Although we did not record value ratings in this study, the study in which we did shows that some items are actually rated lower when participants are hungry (see Chapter 4). Such a result might have further diluted the effect of value increase, since the current study compared affect guided and cognition guided choice for all the food items presented.

It is also possible that we limited the possibility of discovering an interaction with another aspect of the experimental design. By using the contrast 'eat' minus 'cook' to uncover affectively guided choice processes, and the opposite for cognitively guided choice, we excluded areas active in both tasks. This possibility could in future research be increased by including an otherwise equivalent baseline condition with no choice processes. The contrast of choice versus no choice would then reveal a larger network of areas involved in choosing. Those could then be inspected as regions of interest for activity consistent with our predicted interaction pattern.

In the current study we instructed participants to choose food menu items based on their anticipated taste or ease of preparation, aiming to elicit affect guided and cognition guided choice. During affective choice, structures representing primarily taste, value, and memory (the insula, medial orbitofrontal cortex, anterior temporal lobe) were active. During cognitive choice, the structures used involved ones implicated in suppression and conflict monitoring. These results show that using affective or cognitive criteria for choice is associated with the use of distinct neural structures.

Chapter 6: Discussion

The experiments described in this thesis were aimed at investigating the influence of appetitive motivation on decision making. The single experiments addressed distinct components of decision making: the guidance of attention in experiments 1 and 2, value assignment in experiment 3 and choice processes in experiment 4. All experiments included manipulations of participants' desire to eat. The effects of such manipulations on participants' behavioral responses and the responses of their neural systems were then analyzed. This final chapter of the thesis includes a short recapitulation of the results, general limitations of the described studies, a consideration of the results within the wider context of the literature, and an outlook on future research in the area of affect and decision making.

Experiment 1

In experiments 1 and 2, my focus was the flexibility of attention allocation in the decision making process. Experiment 1 investigated the tendency of participants to make extradimensional rather than intradimansional shifts of attention depending on two motivational factors: hunger level and food 'desire' level. Hunger level in participants was manipulated by fasting, the desire level through exposure to appetitive pictures of food. The tendency of participants to make successful extradimensional shifts indicated the level of their cognitive flexibility. The experiment showed that induction of desire, but not fasting, produced an overall impaired shifting performance. Cognitive flexibility was affected by either of the factors, hunger or desire, if induced separately, in that it impaired performance specifically on extradimensional attentional shifts. The combination of hunger and desire produced a deficit in performance on both extradimensional and intradimensional attentional shifts. The results of this

study demonstrate that changes in motivational state induced through both fasting and cueing with visual stimuli can produce significant changes in set-shifting behavior. The study demonstrates a psychological interface between motivation and cognition, and crucially it reinforces the contention that cognitive performance is sensitive to everyday fluctuations in motivational state.

Experiment 2

To investigate the neural basis of the effects of motivational state on attentional shifting found in experiment 1, we conducted a follow-up study using fMRI with focus on PFC function. To simplify the design and optimize power, we only manipulated the hunger factor between the two recording sessions. The task used remained mostly unchanged. We found considerable differences between the activations associated with the cognitive processes, depending on whether participants were sated or hungry. Basing our analyses on previous investigations of the neural bases of attentional shifting, we confirmed the involvement of the ventrolateral PFC in extradimensional shifts for the sated session. In contrast to previous studies, we found that the dorsolateral PFC also contributed to the process of extradimensional shifting. Under the hunger condition, the activation pattern was different, with extradimensional shifts eliciting activity in a PFC region dorsal to the one identified for the sated session. The reversal of attention, previously (in sated participants) found to activate the orbitofrontal cortex, was accompanied during the hungry session by activation in the frontal pole. These results lead us to the conclusion that motivational state can modulate prefrontal activity associated with cognitive processes, even if there is no direct link between the motivation (here in the

form of hunger level) and the cognitive process in question (here the shifting of attention).

Experiment 3

In the previous experiments, I showed that changes in motivational state can influence cognition in general. In the next two experiments I examined the influence of motivational state on food-related cognition. Specifically, in experiment 3, we investigated the influence of motivation on the representation of incentive value. We found that activity in the amygdala was consistent with the representation of attractiveness across the two levels of motivation. Two volumes in the anterior OFC, which we subjected to ROI analyses, showed a response pattern indicating the role of the OFC in integrating attractiveness with hunger state. This is consistent with theoretical accounts of OFC function (Rolls, 2000), and may be a more precise account on OFC function than previous studies using a similar experimental design to investigate the role of the OFC in incentive value representation (Arana et al., 2003).

In an exploratory analysis of this dataset, we singled out a category of stimuli based on the attractiveness ratings of participants in the study. We isolated dishes whose ratings showed an interaction with the motivational state, i.e. which received a higher incentive value when participants were hungry. We termed them 'hunger foods'. To obtain information about the processing of these items, we compared activity elicited by them with items which didn't show a rating value change. The result was an activation pattern which showed increased activity in several structures, particularly in the thalamus and the insular cortex. It is notable that while the structures activated are reportedly involved in the processing of motivational stimuli like food and its properties (de Araujo & Rolls, 2004; Glimcher & Lau, 2005), they are not

identical with structures activated by attractiveness of dishes. This observation invites the interpretation that the quality which makes the value of these items susceptible to hunger increase is not simply their overall palatability. It does not support the view that attractive foods simply seem even more attractive when a person is hungry. It appears that there is some other quality, or combination of qualities, which contributes to that motivational susceptibility. We speculated that it might be certain nutritional attributes which characterize a 'hunger food'. To investigate this speculation, we asked participants (not the ones who participated in the original study) to rate all the displayed food items on two scales: sweetness and fatness. Hunger foods did not show a sweetness or fatness difference from neutral foods (or satiety foods). We then modeled the fMRI data according to their sweetness and fatness ratings, and did not find differences in the regions included in the hunger foods' imprint. Putting these observations together, it seems that neither palatability nor perceived fat or sugar content determine the incentive increase which accompanies increased hunger in some foods. Finding this driving component remains a future challenge. This interpretation needs to be treated with caution for a number of reasons, some of them mentioned in the discussion of the experiment in Chapter 4. The analysis was exploratory, and many crucial factors were not controlled for. The fMRI signal and the property ratings came from different subjects in different contexts. Perhaps most crucially, the absence of evidence is not evidence of absence, and so we may find evidence to support some of our hypotheses with more powerful experimental designs. Thus, the present findings have the potential to stimulate research on properties that drive value increase with changing motivation.

Experiment 4

During the making of decisions, choice between options follows the assessment of anticipated value of these options. While experiment 3 investigated the representation of incentive value, experiment 4 targeted the selection of an option among others. We compared choice behavior guided by affective processes with that guided by cognitive processes and found that the affective condition activated the insula, anterior temporal cortex and the medial OFC. These activations are consistent with involvement of the insula in gustatory and interoceptive perception processes and of the anterior temporal cortex in affective and mnemonic processing. The activation of medial OFC is likely to represent the appetitive value of the stimuli, which the decision to select one of the dishes is based upon. During the cognitively guided choice condition, when value representation is not useful and might on the contrary be distracting from the task, there was no significant activation in the medial OFC, but in a lateral OFC area, consistent with its contribution to inhibitory mechanisms (Elliott et al., 2000). In the cognitive choice condition, the anterior cingulate cortex was also activated, possibly reflecting monitoring of conflict between the affective processing of the stimuli and the cognition-guided choice to be made (Botvinick et al., 2004). In the context of affect-cognition interaction, the activity found in the cognitive choice condition reflects successful cognitive influence on affective processes.

Limitations of the Studies

A common problem in brain imaging research (fMRI as well as PET) is the fact that it uses multiple dependent variables, which require multiple statistical tests. In fact, every recorded voxel in the brain volume has its own time course

and is a single variable. The brain volume and voxel size which we used in the experiments described in this thesis is typical and results in tens of thousands of voxels and the equivalent number of tests. Conducting such a high number of statistical tests requires a correction of the significance values. It is possible to correct for family wise errors as common in behavioral experiments, but the number of comparisons necessary makes the correction exceptionally (and unjustifiably) conservative (Bandettini, Jesmanowicz, Wong, & Hyde, 1993). In fact, such a correction would render all of the reported activations not significant, including the overwhelmingly robust activation of the amygdala in experiment 3 (the t-value for that comparison was equal to 13, a family wise error correction would lead to a p-value of .13). There is a number of approaches to deal with this issue, all of them being unsatisfactory is some respect (Friston et al., 1995). The mentioned family wise error correction (FWE, almost identical to the 'Bonferroni' method) is too conservative, producing a large type II error. The common 'false discovery rate' (FDR, Benjamini & Hochberg, 1995) correction is thought to work well when targeting activation 'peaks', but ignores the width of activation patches (and thus the fact that the time courses of adjacent voxels are not independent), rendering it also too conservative, in some circumstances as much so as FWE correction. Another approach is the reporting of uncorrected values at an arbitrarily (but based on a large body of research) defined threshold. This approach usually decreases the chance of type II error, offers more transparency, and is frequently used (Huettel, Song, & McCarthy, 2004, p. 343ff). We report activations which reach an uncorrected p value of .001 in all whole brain contrasts. The possibly best solution to the multiple comparisons issue are so called Monte Carlo methods, which use the acquired data in randomizations to calculate the true probability of obtaining each activation cluster (Forman et al., 1995). This option is computationally very intensive, and was used only on

selected whole brain contrasts in additional analyses of the reported experiments.

Another valid approach for dealing with the multiple tests problem of imaging data is not correcting for, but avoiding a large number of tests. This can be achieved by inspecting previously defined anatomical structures or regions of interest (ROIs). We applied the approach in all our fMRI studies. This method is however limited to areas about which specific predictions can be made, and thus needs to be supplemented by whole brain analyses.

All the contrasts discussed in our fMRI experiments are based on the assumption of additivity of processing in the brain. The logic of it is that if a brain area is at 'idle' during one task and active during another, the subtraction of activity during the first task from the second results in activity related to the processes involved in the second task. It also means that if an area has the property of being activated by several processes, the employment of e.g. two of them during a task will result in more activity than the employment of just one (Ramnani & Owen, 2004). While these assumptions hold true for many circumstances, there are also some limitations, which concern the results of our studies. In experiments 1 and 2, the issue at stake is the additivity of several cognitive processes. The shifting of attention, no matter whether within a category or between categories, involves a number of subcomponents, like disengaging attention from the previous target, inhibiting it from moving to irrelevant stimuli, moving attention (the actual 'shift'), holding it on the new target. For the contrast of intradimensional (ID) and extradimensional (ED) shifts, we assume that the only additional process during EDs is the extradimensional component. While IDs might require processes A, B, and C, EDs call for A, B, C, *and* D, and the difference therefore reflects D, which itself is localized by activity found for that contrast. Conceptually, this is correct, but it assumes that processes A, B, and C stay the same across conditions. While

we intuitively don't have a reason to question that, it goes against the observation that some areas are more active (at levels of significance equivalent to the ones reported for the opposite contrast) for the ABC, than for the ABCD condition (see also Hampshire & Owen, 2006). This issue will be difficult to ultimately resolve, but it suggests that the additivity of processing cannot always be granted in our design. Future designs should therefore attempt to further disentangle the processes involved and create contrasts with fewer components involved, as well as other methods of analyzing the fMRI signal, e.g. with model based predictions.

The next issue arises from a problem most psychological experiments share, which is that the difficulty to know whether participants are actually performing the processes an experimental task requires them to. The sources of error here are numerous, and I will only point out one, that of timing. The action of selecting from three options, which is the object of our study in experiment 4, is a complicated one in that it requires a number of processes which take a considerable amount of time. It involves reading, activating memories, identifying values or procedural concepts, comparing them, and picking one. The time it takes is rather long – participants in our experiment needed as long as 20 seconds for one trial. While it is reasonable and necessary to assume that for the comparison conditions all the processes are the same except for the difference due to different experimental instruction, the large number of components and lengthy time of each trial induces a considerable source of error. This is usually the case with designs targeting 'high-level' functions (e.g. social affiliation as opposed to angle perception), but design improvements as well as cross validation of the results with other methods have the potential to substantially improve the reliability of the conclusions drawn from this kind of experiments.

One final point is related to the interpretation of activation peaks found in our experiments. In what is considered a well designed fMRI study, one would target a process well known to engage a brain region, employ a task which induces two or more different variants of the mentioned process, and compare the activity level in the region of interest to detect differences between the variants. The differences can then be interpreted to be reflecting the experimental manipulation of the process in question. This is a very convincing approach, but one restricted to brain regions well known to engage certain processes and to processes which can be manipulated to produce a number of equivalent variants. These restrictions make it clear why I chose not to use examples in the description of this hypothetical design – it is an ideal scenario rarely realizable. Many fMRI experiments utilize processes less well defined. Frequently, a task of interest is chosen, and hypotheses are made about its computational properties and components. Processes thought to actually happen are then inferred from the detected activity in brain regions believed to be involved in certain functions. The drawing of conclusions based on data acquired with this approach, as used for a subset of analyses in experiments 2, 3, and 4, is referred to as 'reverse inference'. It assumes that the presence of brain activity can indicate the employment of a particular function. Such reasoning can be flawed to the degree to which brain structures are not specialized for a single domain of functions, i.e. when the domain selectivity of a region is low (Poldrack, 2006). This is a crucial perspective in the interpretation of imaging data, and needs to be considered when drawing conclusions from the described experiments. However, other perspectives need to also be considered. Reverse inference can be crucially improved by including not only domain, but also complexity information and other task characteristics (Christoff & Owen, 2006). The fully valid 'forward' inference, i.e. 'if task A is executed, area X is activated', is useful to some degree, but carries

the danger of piling up an intransparent list if trivial task-activity connections. The good, tightly designed research programs require prior knowledge about brain areas and cognitive processed that can only be obtained through initial exploratory studies which often use reverse inference. Lastly, neuroimaging research follows a gradient of process complexity, with some of them earlier in the chain (checkerboard perception) than others (attributing intentions based on social stereotype). Some of the more complex processes, in the opinion of the author the ones more interesting and more relevant to the problems our society faces, are very resistant to disentangling into single components. Only such parsing however would allow the study of those processes with better, in the sense of tighter, experimental designs. The study of complex behavior with neuroimaging should not be abandoned because it cannot be reduced to components of the same level as that of object perception.

Additional limitations

The conceptualization of ID and ED shifts originally stated that EDs would be the 'bigger' shifts. This has now been corrected. It is also not necessarily the case that ED shifts are more difficult than ID shifts. While the analysis of response times in the literature (e. g. Hampshire et al., 2006) and in the sated condition of my experiment 1 suggests that ED shifts are slower, the reverse is the case in experiment 2. The reason why performing better at ED shifts is considered as an indicator of cognitive flexibility is that ED shifts require an additional rule change for determination of the target. The identity of the target changes in both ID and ED shifts, thus this is equivalent in both conditions, but for ED shifts, the category a person must attend to also changes, requiring more tolerance to change, or additional tolerance to change on a different level, which I understand as more flexibility.

Many fMRI experiments published today have a sample size of about 16. Based on analyses of power, samples as large as 27, or individually defined samples based on BOLD signal variation in the areas of interest have been suggested. While the sample in experiments 3 and 4 is rather small, it allowed me to confirm hypotheses about the amygdala and OFC, involving a main effect and two factor interaction. However, a substantially larger sample would have allowed informative additional analyses of the data, as described in the following paragraph.

Some previous studies investigating the effects of fasting recorded more objective measures of hunger state through analyses of among others blood levels of sugar and insulin. We refrained from such measurements, although they would have made our results and arguments stronger. Aside from that, there is not a single physiological measure that translates into the feeling of hunger, and whether the physiology of energy regulation or the subjective experience of hunger is a more interesting factor in experimental psychology, remains debatable.

Possible additional analyses

Chapter 3

Even thought the task I used in the experiment is relatively easy to do, it requires a number of different cognitive processes, each of which may be interesting to study. The GLM model used in my analysis contains 9 different events, and is not exhaustive. The analysis as it was implemented focuses on ID and ED shifts, as the hypotheses which led to the study concerned those. Nevertheless, singling out other events and studying their neural correlated could produce very interesting results. The same applies to further fractionating of events like ID and ED shifts. I shall be more specific in the next paragraph.

In my analysis, I used averages of all ID shifts and all ED shifts. Not all of those event are identical, however. Each ID shift can follow either a rule-change, i.e. be combined with a reversal, or follow a set-change and be combined with a shift. They are different in that the information of a target change is provided earlier for the set-change – in the form of four new stimuli – and in that a reversal requires the ignoring of the previous target. For a set-change, the previous target is not present on the screen any more.

Furthermore, by contrasting all events during which the target was known with all events during which that wasn't the case, a network related to something like 'solution search' could be identified. Using the nodes of that network as ROIs, differences between ID and ED shifts for the sated and hungry conditions could be investigated. This would be a more sensitive approach to finding interactions between attentional shifting processes and motivation.

The assumption for some of the main reported analyses is that the sole difference between ID and ED shifting processes is the additional extradimensional component in the latter. This assumption can be challenged. In such a case, ID shifting would not provide an appropriate control condition for ED shifts. An alternative approach to investigating ID and ED shifts would be to provide each with its own baseline process. An adequate baseline may be comprised of *late* events during a successful trial, when the participant attends to the current target (just like in the first shift-event), but doesn't have to shift from a different one on the previous screen (unlike in the first shift-event).

It has been proposed that the response to the second screen of a trial could provide a baseline to the response to the first screen. Since negative or positive feedback follows immediately after the second screen, such a baseline would be confounded by processing the different types of feedback.

In the analysis of the behavioral data, the number of responses needed to find and consistently keep responding to the target is considered as the number of errors. The single errors which amount to the total number may however be of different nature. Some may be due to perseveration – keeping responding to a previous, but no longer valid target – others may be due to 'flexibility' which is out of control, i.e. when the participant chooses a different target every time. It is also possible that a participant shifts successfully from a previous target but is unlucky and commits several non-perseverative errors. Analysing different kinds of errors separately may yield additional information about why they are committed, and if they differ between the sated and hungry states.

Chapter 4

For the attractiveness change analysis, the baseline I used for contrasting activity related to both hunger and satiety foods was the activity elicited by neutral foods, i.e. by dishes which received the same rating during the sated and hungry session. This comparison seemed suited, as neutral foods did not show an attractiveness change in either direction as a result of the hunger manipulation. Such neutral foods however included dishes that varied significantly as to their attractiveness level. Dishes which were rated both times as 1 as well as those rated both times as 4 were included. This fact could have diluted some of the effects of interest. Foods rated as a 4 in the sated condition could have reached a ceiling, although they might have been even more attractive during the hungry condition. Thus, it is likely that some true 'hunger foods' were actually in the baseline condition for hunger foods. The reverse might have happened for satiety foods. An informative additional analysis would take this into account and separate neutral foods in subcategories. The

thus obtained activity sites could then be used in a new approach to the fat and sugar content questions described in the Appendix (p. 151 ff).

Chapter 5

As noted above, subtracting the eat and cook conditions from above eliminated areas which might have been significantly involved in both processes. This could be amended in future designs by including an additional condition which would provide a more appropriate baseline. In such a condition participants would be instructed to always select the bottom item among the options. Compared with the other two tasks, the 'choice making' component would be eliminated. A contrast would then reveal areas activated by choice as such, and could be inspected for differential activation for the eat and cook conditions and interactions with the hunger level. I found such a choice versus no-choice comparison in the literature (Arana et al. 2003). I used the coordinates extracted for a region in the caudate nucleus as an ROI on my data, but did not find differences between conditions. Using such a condition within my experiment would have provided a better baseline, as the results would make a more accurate statement about common and distinct activations related to cognition and affect guided choice.

Implications of the current work and future directions

The complexity of the environment humans live in requires the maintenance of a consistent response pattern under certain conditions but also the ability to adapt when conditions change. Cognition and behavior could therefore be modulated by external and internal environmental conditions, such as hunger and the availability of food. Since food acquisition success partly depends on elaborate strategic behaviors, one would expect adjustments of the cognitive

system to hunger to be adaptive. The results of experiment 1 do indeed show that cognitive flexibility is affected by hunger. A single hunger increase (through desire manipulation or fasting) impairs extradimensional shifting of attention, while a double increase (through desire manipulation and fasting) impairs any kind of attentional shifting. This pattern could be interpreted as increasingly rigid focusing of attention with increasing hunger. One possible explanation is that in the context of foraging, it may be adaptive to keep focused on just one task (presumably food acquisition) and to avoid any distractions when hungry. Support for this idea would come from experiments demonstrating that attentional shifts towards food items are enhanced in the hungry state. That is because rigidly focusing on one task would not be adaptive if the current focus was something else than food. One would also expect that foraging should be trumped, in attentional and behavioral terms, by imminent threat and predation.

Showing decreased cognitive flexibility, or being 'focused', seems a good cognitive state to be in at any time, not only when looking for food. There is however a case for being more flexible and less focused when the need to restore energy is absent. That case was made by Fredrickson in the broaden-and-build theory of positive emotions (Fredrickson, 2004). I extend the reach of the theory to motivational states. The central point of the theory is that in contrast to negative emotions which are restrictive in that they prepare an individual for either one specific or a rather small number of actions, positive emotions allow quite the opposite. In the short term, they are thought to *broaden* an individual's repertoire of thoughts and actions, which allows exploration, taking interest in novel items and concepts, and thinking in new ways. Over time, periods of 'broadening' accumulate and lead to *building* of new resources, knowledge, problem solving strategies, social bonds. These resources are adaptive in that they aid survival chances of an individual.

Support for this view has mostly been provided by cognitive and behavioral studies related to flexible thinking and creativity (Fredrickson, 1998; Isen, 1987), but there is also some evidence based on physiological data. Fredrickson and Levenson (1998) suggest that the often observed lack of a physiological response pattern in positive emotions might be due to a missing close link between emotion and action as it is present in negative emotions. An earlier account of the differences between positive and negative states (Nesse, 1990) points in a similar direction, stating that the function of positive emotions is 'coping' with opportunities. In the context of set-shifting experiments, it would be telling to observe if a motivational state can be created which enhances cognitive flexibility beyond its level in the mere absence of desire to eat.

One aim of experiments 3 and 4 was to examine the role of the amygdala in the processing of appetitive stimuli. Animal research shows that the amygdala is crucial for the process of creating representations of links between stimuli and their reward values. Divisions of the amygdala store representations which allow access of conditioned stimuli to their current value for an organism (Cardinal et al., 2002). This is based on observations that rodents and monkeys with amygdala lesions show insensitivity to the devaluation of stimuli in satiation paradigms (Hatfield et al., 1996; Malkova et al., 1997).

Experiments conducted on humans also show that the amygdala plays a central role in the processing of affective stimuli (Zald, 2003). Studies dissociating the valence and intensity dimensions of emotional responses first suggested that the amygdala codes the intensity of stimuli (Anderson et al., 2003; Small et al., 2003). A subsequent study showed that the amygdala coded for intensity but that this signal was also bound with the quality, or valence, of the stimulus (Winston et al., 2005). Thus its function was specified to represent the integrated valence and intensity of affective stimuli rather than

just the intensity dimension. This is in agreement with findings from animal studies suggesting that amygdala subserves the integration of value with sensory properties of stimuli (Cardinal et al., 2002).

One of the results of experiment 3 shows increased amygdala activity for high attractiveness dishes, confirming its role in representing appetitive value. This supports the results from previous studies using a similar experimental design (Arana et al., 2003; Hinton et al., 2004) and strengthens their significance by demonstrating a more robust activation of the amygdala by appetitive value. The analysis of experiment 3 data showed that amygdala activation reflected attractiveness, but that it did not depend on hunger level. A similar finding emerged from the study by Hinton and colleagues (2004), but it is somewhat inconsistent with findings from animal literature. Those suggest that value representation in the amygdala is sensitive to internal motivational state, as for example to hunger or satiety (Hatfield et al., 1996; Malkova et al., 1997; Rolls, 1992). This discrepancy can be explained through a lack of experimental power to detect an interaction of two factors in that area, through limited spatial resolution of the method used in the reported experiments, or through differences in human and non-human amygdala function. I will shortly address the three possibilities.

Hinton and colleagues (2004) found one main effect and one interaction for two investigated OFC sites and a main effect for the amygdala. Experiment 3 identified patterns consistent with an interaction for both OFC sites. This is likely due to increased power over the previous study. Taking a hypothetical next step, further increasing the power of the experimental design may reveal an interaction for the amygdala as well.

The spatial resolution of fMRI and PET is important because the amygdala is a complex structure comprised of a number of nuclei (Swanson & Petrovich, 1998; Zald, 2003). Its subdivisions, for example the basolateral

amygdala (BLA) and the central nucleus of the amygdala (CnA) appear to have distinct functions related to value processing, including their role in state dependant representation of value (Cardinal et al., 2002). The results of experiment 3 may overlook state dependence of value representation in a subdivision of the amygdala because they are obtained by averaging over structures with different functions. Conducting future studies at high field may help resolving this issue.

Alternatively, the discussed aspect of amygdala function might actually differ between humans and other animals. In primates, state dependent representation of value can be found in both the amygdala and the OFC (Wilson & Rolls, 2005), suggesting this function might be to some degree shared between those structures. In fact, the connection of the amygdala and the OFC was actually shown to be necessary for state dependant representation of value in rhesus monkeys (Baxter et al., 2000). But the equivalent of the OFC in rodents is markedly less developed (Uylings & van Eden, 1990), and so the balance in those animals might be shifted more towards the amygdala being responsible for state dependant representation of value. The rodent amygdala adapts quicker to changing values than the OFC (Schoenbaum et al., 1999), in contrast to that of the primate (Rolls, 1992). It is possible that in humans as in other primates, the function of state dependant representation of value relies more heavily on the OFC and less so on the amygdala, which would be consistent with the result of experiment 3.

While there is ample evidence for a role of the amygdala in emotional processing, some have pointed out that it responds not only to emotional information, but to all biologically relevant stimuli (Whalen, 1998). Our results support this view, as we show amygdala activations related to descriptions of food items, which are not necessarily emotional, but clearly biologically relevant. More recent evidence suggests that even the biologically relevant

category isn't sufficiently inclusive in this context. In particular, amygdala responses in mice and humans have been showed to non-biological stimuli (tones) which code uncertainty (Herry et al., 2007).

As discussed above, a number of studies provide evidence of value representation in both the amygdala (Zald, 2003) and in the OFC (Rolls, 2000). An aim of the experiments described in this thesis was to investigate and possibly dissociate the particular roles of those structures in the representation of value. In experiment 3, I used an ROI in the OFC from a previous study, which found increased activity in the area corresponding to high incentive value (Arana et al., 2003). Subjecting the signal from that ROI to an analysis with both factors included in experiment 3, attractiveness and hunger, revealed an interaction pattern. Specifically, the site responded differently to high and low levels of attractiveness, but selectively so only when participants were hungry. This suggests that this OFC area represents subjective incentive value which depends not only on the properties of the stimulus, but also on the internal state of participants (and see Schoenbaum et al., 1999). Hinton and colleagues (2004) also added a hunger manipulation to the design used by Arana and colleagues. Their results are confirmed and extended by those of experiment 3. While Hinton and colleagues localize two OFC sites, one of which displays a main effect and one an interaction, experiment 3 indicates interaction patterns for both sites of the OFC, possibly because it is more sensitive than the PET design in combination with using groups of stimuli.

While experiment 3 established that the OFC integrates stimulus properties with the motivational state to create a value representation, experiment 4 investigated the role of the OFC in guiding choice processes. It showed that the OFC displayed a different pattern of activation for affect guided choice processing and cognition guided processing. During affect guided choices, an area of the medial OFC was activated, whereas during

cognition guided choices, an activity peak was found in a lateral area of the OFC. Previous studies which dissociated the function of the medial from that of the lateral OFC found that the former is associated with reward value monitoring, and the latter with aversive value, punishment or inhibitory processes (Elliott et al., 2000; J. O'Doherty, Kringelbach et al., 2001; Small et al., 2001). In experiment 4, medial OFC activation accompanied affectively guided choice, suggesting that representation of the anticipated reward value was necessary to make the correct choice. Lateral OFC was activated during cognitively guided choice, when it was useful to ignore or suppress the reward value of the food items.

Human decision making depends to a significant degree on evaluating options in the light of environmental and intrinsic contexts (Doya, 2008). The context of interest for the studies conducted for this thesis were the different levels of food-related motivation. Experiment 1 demonstrates a motivational modulation of attention allocation, which may be accounted for by advantages such an effect produces for foraging and its reversal in exploration and creativity. Experiments 2-4 suggest which neural structures may contribute to contextual modulations of decisions. Experiment 2 shows a shift of switch-related activity in the lateral PFC in hungry participants. In experiment 3, the amygdala is activated by high value abstract stimuli, independent of motivational state. Amygdala's close anatomical link to the PFC (Zald, 2003) make it plausible that its signal is fed to the OFC where it is integrated with information about the current hunger level of the individual. The patterns of interaction between attractiveness and hunger in the OFC, found in experiment 3, support this view. The hunger signal used by the OFC is likely to come from midbrain nuclei which detect blood energy levels and connect to the hypothalamus, although the experiments reported here did not address this issue. The OFC may be in the position to integrate hunger level not only with

information about attractiveness derived from the amygdala, but also from other structures coding stimulus features, such as the insular cortex. This area of the cortex is located adjacent to the OFC and it includes the primary taste cortex (de Araujo & Rolls, 2004). Several insular sites were activated by 'hunger foods' in experiment 3, suggesting that the activation of the insular cortex may help to assay the specific sensory and nutritive qualities of prospective meals and determine which dishes are particularly desirable when an individual is hungry. The functions of the OFC shown in the reported experiments include not only sensitivity to motivational state, but also to goal demands. In experiment 4, different sections of the OFC were activated depending on whether representation of value was useful or had to be inhibited. The results of the reported experiments emphasize the potential of the OFC to integrate learned associations, stimulus properties and context information from different sources, which makes it a crucial structure in decision making.

The research described in this thesis attempted to investigate affective influences on components of the decision making process. It should be continued in several directions. Beginning with the attentional component of decision making, research on cognitive flexibility should be enriched by operationalizations of the concept other than the difference between intra- and extradimensional shifts we used. This line of research may be linked to the concepts of the exploit – explore dilemma (Daw et al., 2006), curiosity, and creativity. The exploit – explore dilemma is a choice we are faced with on a daily basis, most of the time probably without awareness of it. The dilemma is essentially the choice between old, tried and true options, and new ones. It arises when we have to choose between obtaining a goal through behavior with a known relationship between investment and reward, or alternatively trying a novel behavior – with unknown contingencies. The latter has then

potential to be more rewarding, but also carries the risk of being less so. Constant exploiting would mean always sticking to the first available option, which might be suboptimal for the acquisition of reward. Constant exploring, however, means frequent heavy losses, so a balance between the two must be found that is ideal for fitness. This balance addresses a surprising multitude of situations, and offers access to fascinating fields like the study of curiosity and creativity. While the investigation of the focus of attention in experiments 1 and 2 may make a contribution to the field, other paradigms are needed (Daw et al., 2006).

The affective manipulation used in our experiments included fasting and exposure to appetitive food cues. Exploration of the identified effects should include other motivational domains. The relationship of the motivational and cognitive domain should be focused on, For example, in experiment 1, the motivational modulation of hunger and desire levels had no direct link to the cognitive process of attentional shifting. In experiment 3, on the other hand, the increased level of hunger was directly related to the value rating of an food menu item. Finding affect-cognition interactions in the same domain might help us to create models of the interactions, which we then may be able to apply to less obvious connections.

The advancements in fMRI methodology could be used to take the investigation of the impact of affect on decisions in a new direction. On the one hand, model based fMRI (J. P. O'Doherty, Hampton, & Kim, 2007) could be used as a powerful tool to measure the affective impact on decision making. On the other hand, great progress has been made with the effort to predict behavior (or cognitive representations) based on brain activation (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Haynes & Rees, 2007). In a scenario where the decision is between two options and the parametric affective influence favors one of them, a model could be derived

which calculates what level of affective influence would tip the choice from one option to the other. By correlating the model with BOLD signal derived from the brain, areas involved in such a calculation could be identified. Further analyses might allow a prediction of the impact of affect on choice derived from the recorded fMRI signal.

The described experiments target the influence of affect on decision making processes through modulation of attentional focus or value assessments. The opposite scenario, the influence of cognitive or executive processes on affect has been somewhat neglected. While there exists a considerable literature on the executive influence on emotion (Ochsner & Gross, 2005), the topic has not been addressed in the same breadth within the frame of decision making. This might be due to the perception that purely executive decision making has been exactly what research on affective influences has been challenging. That, however, is a separate issue from the investigation of executive modulation, possibly in the form of overriding of affective tendencies, in decision making. We tried to shed some light on that relationship in experiment 4, showing that an instruction to use non-affective properties to guide choice lead to an activity pattern pointing to conflict monitoring and inhibitory processes.

Our results confirm the growing line of research which shows that the cognitive and affective systems are dependent on each other and can only in exceptional cases be viewed as truly separate. The understanding of the interactions of cognition and affect will be crucial to finding the neural basis for complex behaviors like the arriving at decisions. True progress will however require a more adequate replacement for the cognitive and affective categories. So far, they often continue being used for the purpose of disclosing their flaws. A deeper level of understanding how affect shapes decisions is

likely to go beyond identifying where cognition and affect interact, and to explain how the brain integrates both to shape thought and behavior.

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Appendix

Chapter 3

In order to validate the choice of the size and location of ROIs in Chapter 3, I searched the data for peaks near the ROIs, which might have been missed. I used lenient statistical thresholds and the whole-brain signal. Restricting the signal to anatomical subparts of the brain (like the OFC) would yield potential benefits for subsequent statistical tests, but activity peaks should be principally observable already on the whole-brain level. The figures displayed in this section (Figures Apx 1-4) show these 'nearest peaks'. The ROI analysis included a total of seven locations: medial OFC, lateral OFC (right and left), ventrolateral PFC (right and left) and dorsolateral PFC (right and left).

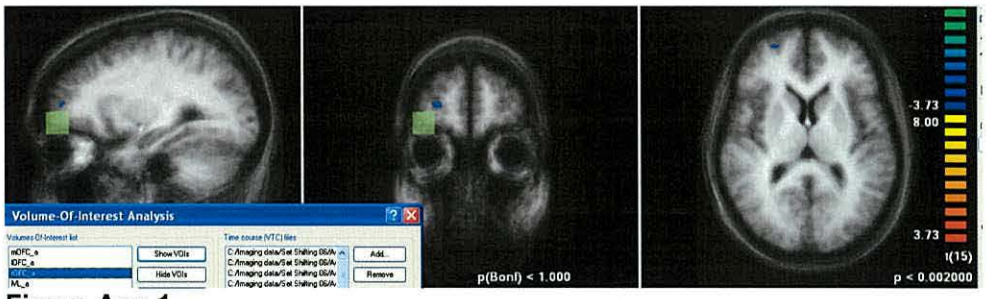

Figure Apx 1

Activity related to the extradimensional component during the sated session in relation to the lateral OFC region of interest.

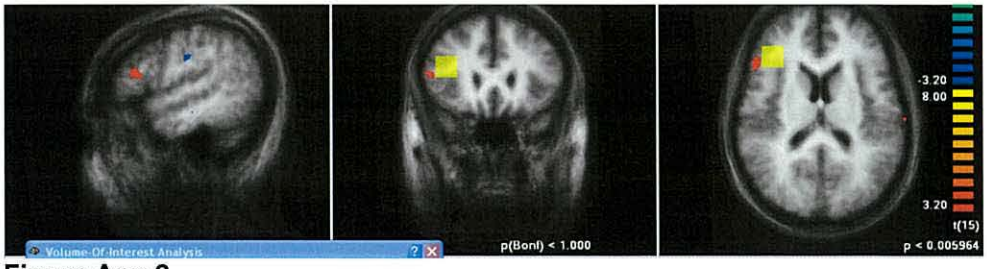

Figure Apx 2

Activity related to the extradimensional component during the hungry session in relation to the dorsolateral PFC region of interest.

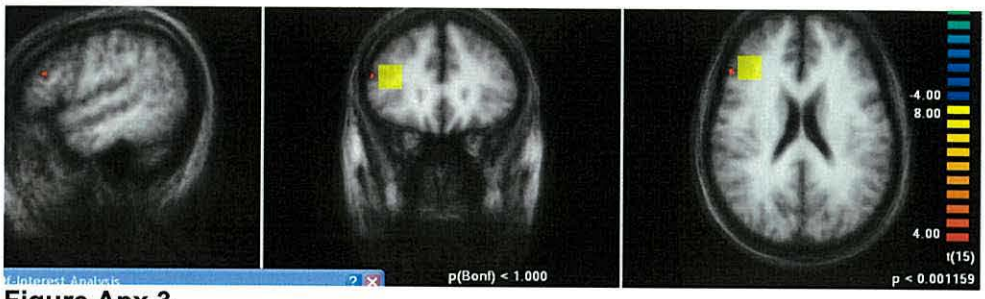

Figure Apx 3

Activity related to the extradimensional component during the both sessions in relation to the dorsolateral PFC region of interest.

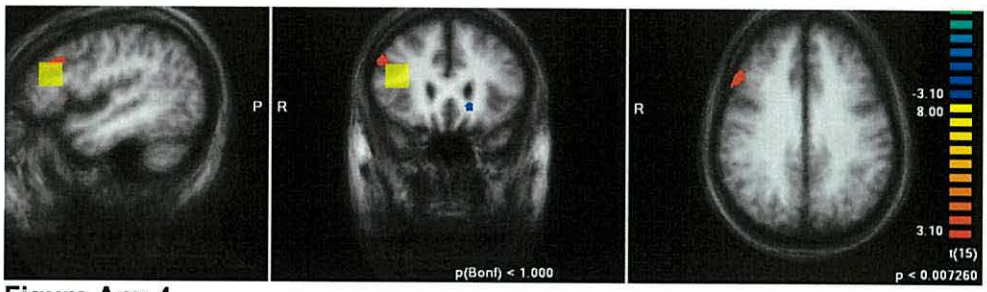

Figure Apx 4

Activity related to the reversal component during the sated session in relation to the dorsolateral PFC region of interest.

One of the main goals of the experiment was to locate brain structures which display an interaction pattern for the process of attentional shifting with the motivational state of hunger. I identified three regions which would be well situated for such a function: the amygdala, the hypothalamic region and the ventral striatum / nucleus accumbens. Performing an interaction contrast on the whole-brain data did not produce activity elevations in the specified areas. This was again done with an advancing lenient statistical threshold, to a point at which extracted signal parameters from a peak (any peak, even outside the

anatomical ROIs), would fail to show a significant effect if subjected to an ANOVA.

Figures Apx 5-7 show the resulting contrast images for the ID versus ED interaction with hunger state. I also performed this procedure with SH versus RV and positive events versus negative events, with no affirmative results.

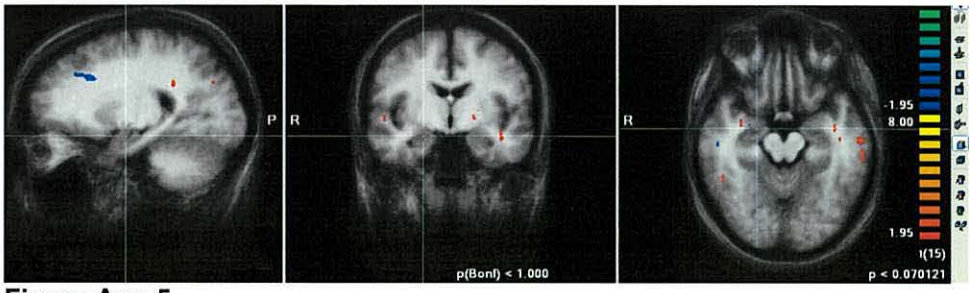

Figure Apx 5

Activations with a response pattern consistent with an interaction of the extradimensional component with the hunger state. The crosshairs point to the amygdala. The significance level is .07 uncorrected.

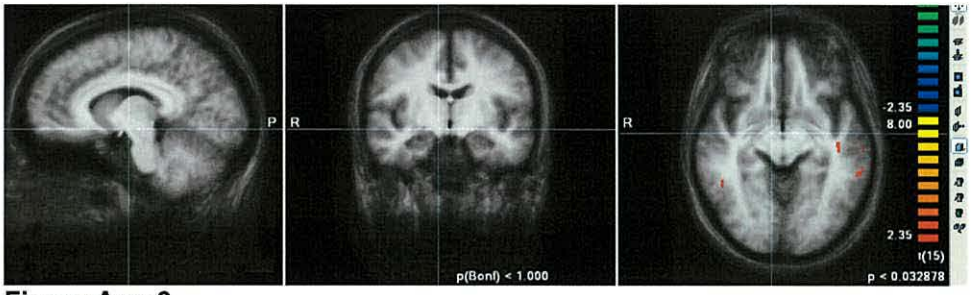

Figure Apx 6

Activations with a response pattern consistent with an interaction of the extradimensional component with the hunger state. The crosshairs point to the hypothalamic region. The significance level is .03 uncorrected.

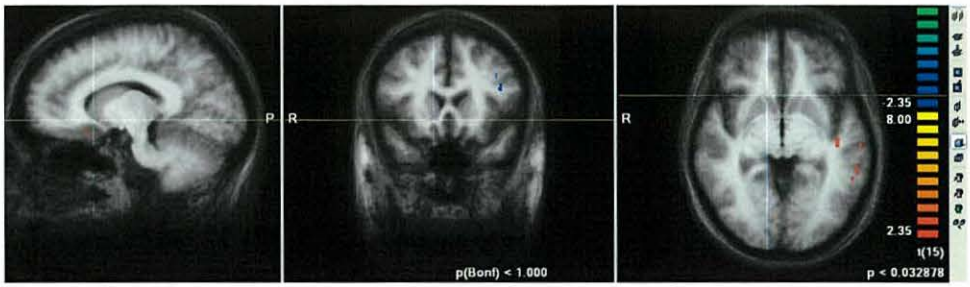

Figure Apx 7

Activations with a response pattern consistent with an interaction of the extradimensional component with the hunger state. The crosshairs point to the ventral striatum / nucleus accumbens. The significance level is .03 uncorrected.

Chapter 4

Varying hunger levels is a very useful form of motivational modulation, as it can be reliably induced by fasting. In addition, it can be parametrically varied, in order to obtain different levels of hunger. Thus, one could ask which levels of hunger have what impact on valuation of dishes. Results obtained from such analyses would add strength to conclusions from correlational relationships, such as in the current fMRI design. This experiment was not designed with a parametrical question in mind, but the data may be analyzed by further differentiating the hungry group into high and low levels of hunger. While the narrow distribution of hunger level within the sessions does not spark much optimism (Figure Apx 8), one cannot rule out that some effects may be found. Should that be the case, additional experiments with a modified design could be developed.

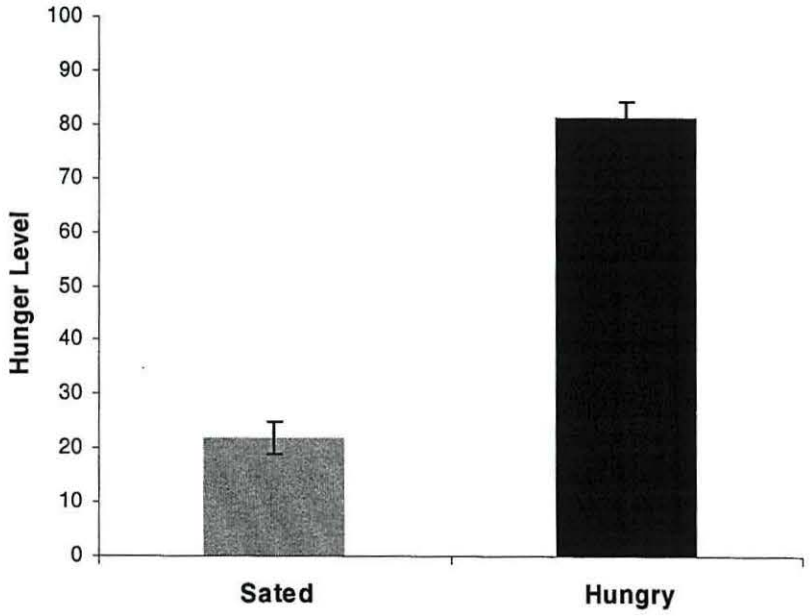

Figure Apx 8

Hunger level reported by participants in Experiments 3 and 4.

One of my hypotheses for the classification of hunger and satiety foods was that fat and sugar content might be a crucial factor. I therefore used the activations found for hunger and satiety foods in the 'incentive change' analysis as ROIs in a separate analysis of the fMRI data based on ratings of fattiness and sweetness of each dish. The logic was that certain areas respond strongly to say hunger foods, they may do that because that dish is fatty, sweet, or a combination of both. A different pattern may emerge for satiety foods. More specifically, I modeled the fMRI data according to how fatty and sweet each dish was. I then extracted estimates of activity related to fattiness and sweetness from sites which were activated by hunger or satiety foods. Figures Apx 9-12 show the results. In summary, activity in the explored ROIs did not reflect fattiness or sweetness ratings of the dishes.

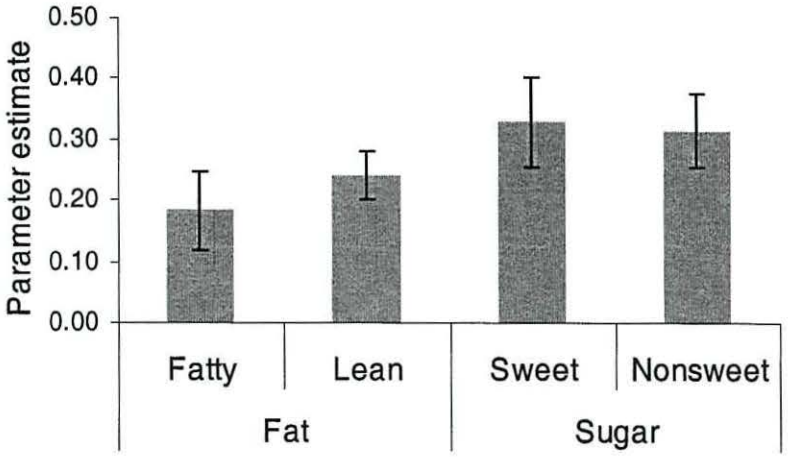

Figure Apx 9

Parameter estimate (beta-values) of activity related to dish ratings in the thalamic region. The differences are statistically not significant.

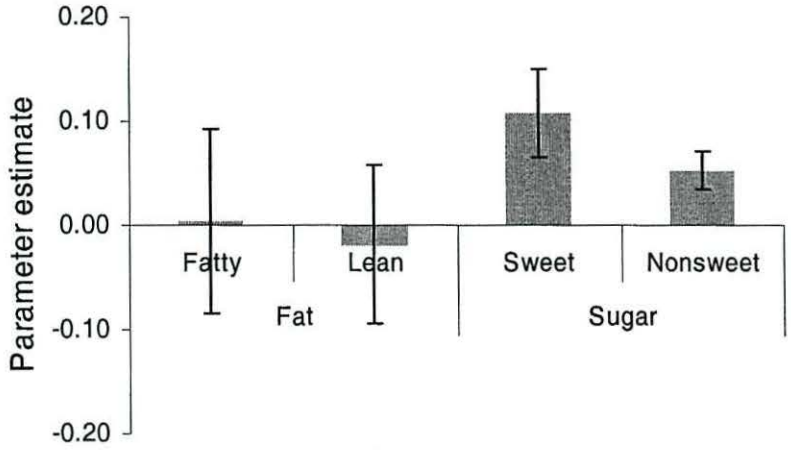

Figure Apx 10

Parameter estimate (beta-values) of activity related to dish ratings in the insula. (This is the anterior of the two identified sites, the pattern is similar for the other site). The differences are statistically not significant.

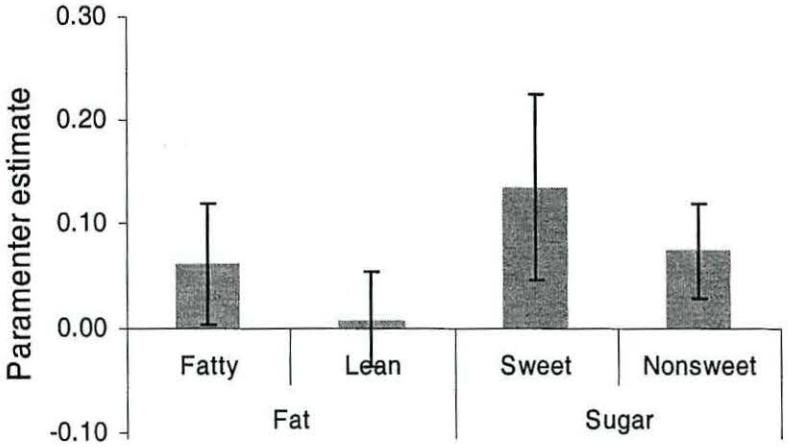

Figure Apx 11

Parameter estimate (beta-values) of activity related to dish ratings in the caudate. The differences are statistically not significant.

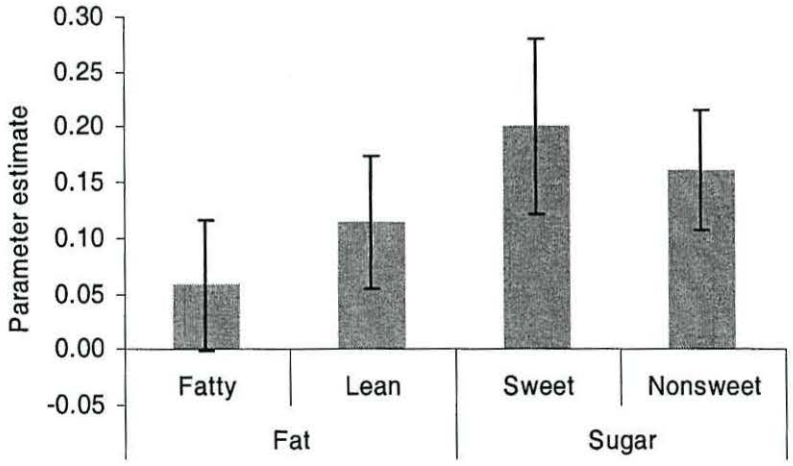

Figure Apx 12

Parameter estimate (beta-values) of activity related to dish ratings in the frontal gyrus. The differences are statistically not significant.

Chapter 5

As argued in the Appendix section for Chapter 4 (p. 151), the narrow distribution of hunger level within the sessions limits the prospect of finding informative results by further dividing the sample along the hunger dimension

(into groups of hungry and very-hungry, for example). Considering that no effects of hunger were found in this experiment, inspecting the response patterns of extreme participants may provide hints for the choice of fasting length in future experiments.