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NEURAL MECHANISMS OF EMOTIONAL REGULATION AND DECISION MAKING

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Till min pappa

ABSTRACT

Emotions influence our perception and decision making. It is of great importance to understand the neurophysiology behind these processes as they influence human core functions. Moreover, knowledge within this field is required in order to develop new medical therapies for pathological conditions that involve dysregulation of emotions.

In this thesis the neural mechanisms of emotional regulation and decision making were investigated using different pharmacological manipulations and brain imaging. In Study I, we examined whether a CCK_b-receptor and a mu-opioid receptor agonist could modulate emotional perception of visual stimuli in opposite directions. In Study II and III, we examined if amygdala, a subcortical structure involved in emotional coding, was involved in social punishment and neural processing of unfairness. The participants played an economic game that examined their proneness to hand out social punishment and their processing of unfairness. Prior to the game, participants had been treated with either an active drug (oxazepam or madopark) or placebo. With this intervention we could manipulate the participants' behavior and brain activity. Lastly, in Study IV we investigated neural mechanisms of hypothetical bias; that is, the difference between a real decision versus a hypothetical decision.

In summary we found, in Study I, that the CCK-opioid system can modulate emotional visual perception in opposite directions. In Study II we demonstrate that amygdala is involved in social punishment and neural processing of unfairness. The degree to which participants gave out social punishment was suppressed with oxazepam without affecting the participants' perception of unfairness. In Study III we noted that madopark increased amygdala activity in response to unfairness without detectable changes in behavior. In Study IV, we showed that real decisions, in comparison to hypothetical decisions, involve amygdala processing and amygdala activity co-varies positively with the real cost for the participants.

In conclusion, this thesis demonstrates that specific neuromodulatory systems participate in emotional regulation and decision making. Our findings also prompt an ethical discussion as we show that a commonly used drug influences core functions in the human brain that underlie individual autonomy and decision making.

SAMMANFATTNING PÅ SVENSKA

Känslor påverkar vår upplevelse av världen och vår förmåga att fatta beslut. Det är därför viktigt att förstå de underliggande hjärnprocesser för dessa fenomen eftersom de påverkar på grundläggande mänskliga beteenden. Kunskap inom området krävs för att kunna utveckla nya medicinska behandlingar för sjukdomstillstånd där bristande känslomässig reglering är ett problem.

I denna avhandling utredde vi vilka delar av hjärnan som reglera våra känslor och beslutsfattning samt vilka ämnen i hjärnan som styr dessa processer. Vi studerade detta genom att påverka försöksdeltagarnas beteende med läkemedel samtidigt som vi undersökte deras hjärnaktivitet. I Studie I utredde vi huruvida två läkemedel (pentagastrin och remifentanil) kunde påverka upplevelsen av känslomässiga bilder i motsatta riktningar. I Studie II och III undersökte vi om amygdala, en "primitiv" hjärnstruktur som bearbetar känslor, var inblandad i social bestraffning och bearbetning av orättvisa. Deltagarna spelade ett ekonomiskt spel, som undersökte deras benägenhet att utdela social bestraffning och bearbetning av orättvisa, samtidigt som de mottagit antigen *en* aktiv läkemedelsbehandling oxazepam (lugnande läkemedel) eller madopark (stimulerande läkemedel), eller ett sockerpiller. Således, kunde vi påverka deras beteende och hjärnaktivitet. I Studie IV undersökte vi vilka delar av hjärnan som ligger bakom "hypotetisk påverkan", det vill säga, skillnaden mellan att fatta ett riktigt beslut jämfört med att ta ett hypotetiskt beslut.

I korthet rapporterar vi, i Studie I, att pentagastrin och remifentanil kan påverka känslomässiga synintryck i motsatta riktningar. I Studie II visar vi att amygdala deltar i social bestraffning och bearbetning av rättvisa. Graden av att utdela social bestraffning minskade med oxazepam utan att påverka deltagarnas upplevelse av orättvisa. I Studie III demonstrerar vi att madopark ökade amygdala aktivitet som svar på orättvisa utan att märkbart påverka beteende. I Studie IV visar vi att riktiga beslut i jämförelse med hypotetiska beslut involverar amygdala.

Sammanfattningsvis, visar denna avhandling att specifika hjärnområden respektive vissa ämnen i hjärnan deltar i regleringen av känslor och beslutsfattning. Våra fynd uppmanar även till en etisk debatt då vi visat att vanligt förekommande läkemedel kan påverka beslutsfattning utan att påverka ens förnimmelse av situationen.

LIST OF PUBLICATIONS

I.   **Gospic K.**, Gunnarsson T., Fransson P., Ingvar M., Lindefors N., Petrovic P. (2008) Emotional Perception Modulated by an Opioid and a Cholecystokinin Agonist. Psychopharmacology 197(2):295-307. Reproduced with kind permission from Springer Science and Business Media.

II. **Gospic K.**, Mohlin E., Fransson P., Petrovic P., Johannesson M, Ingvar M. (2011) Limbic Justice - Amygdala Involvement in Immediate Rejection in the Ultimatum Game. PLoS Biology 9(5):e1001054.

III. **Gospic K.**, Mohlin E., Fransson P., Petrovic P., Johannesson M, Ingvar M. (2011) Limbic Justice Revisited – Dopamine Fuels Social Punishment. Submitted.

IV. **Gospic K.**, Sundberg M., Mader J., Fransson P., Petrovic P., Isacsson G., Karlström A., Ingvar M. (2011) Altruism Costs - the Cheap Signal from Amygdala. Submitted.

ADDITIONAL PUBLICATION

I.   Olofsson JK., **Gospic K.**, Petrovic P., Ingvar M., Wiens S. (2011) Effects of Oxazepam on Affective Perception, Recognition, and Event-Related Potentials. Psychopharmacology 215(2):301-309.

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LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
AI	Anterior insula
BNST	Bed nucleus of stria terminalis
BOLD	Blood onset level dependent
CCK	Cholecystokinin
dACC	Dorsal anterior cingulate cortex
DG	Dictator game
dlPFC	Dorsolateral prefrontal cortex
fMRI	Functional magnetic resonance imaging
FWE	Family wise error
GLM	General linear model
MEG	Magnetoencephalography
mPFC	Medial prefrontal cortex
OFC	Orbitofrontal cortex
PAG	Periaqueductal grey
PPI	Psychophysiological interaction
rACC	Rostral anterior cingulate cortex
SN	Substansia nigra
SPM	Statistical parametric mapping
STAI	State trait anxiety index
TMS	Transcranial magnetic stimulation
UG	Ultimatum game
VAS	Visual analogue scale
vmPFC	Ventromedial prefrontal cortex
VTA	Ventral tegmental area

1 PROLOGUE

The main theme for this thesis is Neuroeconomics, a multidisciplinary field that integrates methods from economics, psychology, and neuroscience to study human decision making (Clithero et al., 2008). By combining behavioral economic paradigms with mathematical models, pharmacological manipulations and neurophysiological methods, the field has been fruitful and gained new insights about choice behavior. This multidisciplinary approach has also yielded challenges in terms of validity of suggested theoretical models and interpretation of biological data. One important difference in traditions between economics and neuroscience (and a source of misinterpretation) is that the former does not necessarily need to fit theoretical models with behavioral data as long as the mathematical proofs are correct (Camerer, 2003). Thus, mathematical models that are anatomy free and presented without experimental anchoring (Rangel et al., 2008) easily create interdisciplinary conflicts when these models are used as the only approach. In contrast, neuroscientific and psychological models usually rest on behavioral observations of human behavior i.e. empirical data.

In order to bridge these various differences, it is of importance that different views are merged. In the three latter studies, in this thesis, we try to apply an integrative approach aiming to make the economic, the mathematic and the neuroscientific sciences come closer together.

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2 INTRODUCTION

2.1 EMOTIONS

2.1.1 Definition and function

An emotion is defined as a collection of responses that are triggered from the brain to the body and from parts of the brain to other parts of the brain (Damasio, 2001). These communications are of both neural and humoral nature and the result of this communication is an emotional state (Damasio, 2001). The main function with emotions is to adapt us to various situations. Therefore, emotions evaluate situations in terms of goals i.e. if we should approach or avoid the situation. They also prepare us to act, by giving priority to specific actions that are urgent (Adolphs, 2010).

An important distinction to make is the one between emotion and feeling; an emotion is the physiological response associated to an emotional event. For example, when we encounter a snake during a forest hike we will react with increased heart rate and sweating before becoming aware of the snake (Gazzaniga et al., 2002; LeDoux, 1999). These physiological adjustments are our emotional response to the snake and are triggered foremost by the subcortical structure amygdala (Davis, 1997).

A feeling is defined as a complex mental state resulting from an emotional state and involves bodily and cognitive changes (Damasio, 2001). Another term for feeling is feeling state (Craig, 2009). The concept of feeling states is based on the notion that a cortical structure called insula provides a neural correlate for all subjective feelings from the body. Interestingly, it seems that our experience of an emotion is our perception of the bodily state that is associated with the physiological changes induced by the emotional response (Craig, 2009).

2.1.2 Classification of emotions

There are various systems and scales to classify emotions. The most known and used ones are: the Ekman classification and the Lang arousal/valance classification. In the early 70's Paul Ekman conducted facial expression studies all over the world. The discovery from his journeys was that some facial expressions could be observed across the globe, independently of culture and geographical location. Based on observed facial

expressions Ekman suggested that there are six basic emotions i.e. anger, fear, happiness, sadness, disgust and surprise (Gazzaniga et al., 2002).

Peter Lang proposed another type of emotional categorization based on the level of arousal and valance (Bradley and Lang, 1994; Lang et al., 2001). Arousal reflects our level of excitement in relation to the stimulus whereas valance is linked to whether we consider a stimulus to be good or bad. Lang's model quantifies emotional intensity with the help of a 2-dimensional coordinate system where valance is measured on the x-axis, arousal is measured on the y-axis and origo corresponds to a neutral stimulus. The more positive a stimulus is, the higher the value on the x-axis; the more exciting a stimulus is, the higher the value on the y-axis.

2.1.3 Emotional regulation

Emotional regulation refers to the heterogeneous set of processes by which the brain influences which emotions we have, when we have them, and how we experience and express these emotions (Gross, 2002). The ability to regulate emotions is important for adaption and helps us to act functionally. Thanks to the evolved human frontal lobes, our ability to regulate emotions is superior to other animals.

Emotional regulation can be divided into attentional control and cognitive control (Ochsner and Gross, 2005). Both these aspects of emotional regulation involve *cortical* control which may also be referred to as top-down control (see also section 2.1.4). Different types of emotional regulation engage different neural networks. Attentional control can be divided in to selective attention and attentional distraction. In selective attention, imaging studies have demonstrated that lateral prefrontal cortex is involved in evaluating whether stimuli are good or bad whereas prefrontal cortex (PFC) and parietal cortex participate in attentional distraction (McRae et al., 2010; Ochsner and Gross, 2005). Cognitive change has many facets and can be divided into: anticipation, extinction, placebo, and reappraisal (Ochsner and Gross, 2005). In addition, meditation could be seen as a particular form of emotional regulation. Different kinds of networks are involved depending on the meditation technique. A concise presentation about different strategies for emotional regulation will be presented below.

2.1.4 Top-down control

Top-down control reflects cortical regulation and is the highest level of control that the brain can exert of any physiological process (Roepstorff and Frith, 2004). As a result, top-down control is an important part of the emotional regulation system (Mobbs et al., 2006; Petrovic et al., 2005). All types of top-down control do not solely involve emotional regulation but also other regulatory processes e.g. pain regulation (Colloca and Benedetti, 2005; Petrovic, 2002).

The neural mechanisms involved in top-down control can be context dependent and hence vary with the specific situation. Extinction, placebo, and reappraisal are all examples of top-down control and may be present in either an emotional or pain context or a combination of both. The following sections will briefly present the neural mechanisms of different contexts where top-down control is present.

2.1.4.1 Extinction

Emotional regulation has been widely studied in the context of fear and extinction. Fear extinction is the process where a conditioned fear stimulus is relearned and stripped of its emotional content so it will not be fearful anymore. Importantly, old fear memories are not removed by extinction (Myers and Davis, 2006) instead, a new memory is created in which the amygdala output is inhibited. There is solid evidence that amygdala is involved in fear expression (Davis, 1997) and ventromedial PFC (vmPFC) is important for the fear extinction process (Bishop, 2007). vmPFC participates in extinction by stimulating GABAergic neurons in amygdala which in turn inhibits amygdala output (fear expression) via GABAergic neurons (Bishop, 2007).

2.1.4.2 Placebo, expectation and anticipation

The placebo effect is a psychobiological phenomenon that leads to a clinical improvement (Colloca and Benedetti, 2005). The effect is not due to one single mechanism, but many. For example, positive expectation of improvement and Pavlovian conditioning are important components. Interestingly, it has been shown that administration of an exogenous opioid (remifentanil) and placebo induced expectation of pain relief, activates the same brain regions i.e., rostral anterior cingulate cortex (rACC), orbitofrontal cortex (OFC) and anterior insula (AI) (Petrovic, 2002). In the same study, it was also demonstrated that there was a co-variation between rACC,

pons, medulla and periacqueductal grey (PAG) (Petrovic, 2002). These results suggest that the opioid system is part of a descending modulating circuit that regulates placebo analgesia (Colloca and Benedetti, 2005; Hoffman et al., 2005; Levine et al., 1978). In contrast to the opioid system, the cholecystokinin (CCK) system participates in nocebo. Benedetti et al. demonstrated that the CCK antagonist proglumide could enhance pain relief if a placebo response was induced i.e. expectation of pain relief. When proglumide was given as a hidden injection it did not induce any pain reduction. This indicates that the CCK system can modulate expectation pathways in an opposite direction, compared to opioids (Colloca and Benedetti, 2005).

Anticipation is closely related to expectation and placebo and cannot be clearly segregated from them. Anticipation involves the act of predicting and its function is to make accurate predictions of events that lead to improved time and accuracy of behavioral responses (Posner and Petersen, 1990). Brain areas (i.e. dorsolateral PFC (dlPFC), medial PFC (mPFC) and OFC) that participates in anticipation of pain relief are closely related to areas involved in placebo (Carlsson et al., 2000; Colloca and Benedetti, 2005).

Importantly, placebo responses can be induced for other modalities than just pain relief. For example, expectation of immune-suppression leads to decreased levels of cytokines (Colloca and Benedetti, 2005). In a similar manner, Parkinson patients can induce expectation effects for motor improvement when given placebo treatment; this expectation leads to dopamine release in striatum (Colloca and Benedetti, 2005). In conclusion, the above studies show that the brain uses specific networks and neuromodulatory systems to regulate placebo responses.

2.1.4.3 Reappraisal

Reappraisal is a voluntary and cognitive process in which we can change the way an emotion is interpreted (Kalisch, 2009; Lazarus, 1991). This process can both up- and down-regulate an emotional response. For example, if a subject views an unpleasant picture of a person dying, the subject can up-regulate this emotion by thinking that the person in the picture is suffering or down-regulate the emotion by thinking that the scene is taken from a movie and is therefore not real. Reappraisal that reduces negative

emotions activate frontal regions like dlPFC, mPFC and dorsal ACC (dACC) while reducing activity in amygdala (Phillips et al., 2008).

2.1.4.4   Meditation

Meditation is a family of mental training practice which evokes a physiological state that induces physical and mental relaxation (Brefczynski-Lewis et al., 2007; Rubia, 2009). Meditation has been shown to have a positive effect on depression and anxiety related symptoms (Rubia, 2009). Experienced meditators react less to stressful stimuli in terms of reduced psychological and physiological reactivity to emotional stimuli (Rubia, 2009). In clinical practice, meditation based methods, like acceptance commitment therapy, have become a target of interest to treat emotional disorders as it seems to regulate emotional processing (Pull, 2009).

In general, different meditation strategies give rise to a variety of neural responses (Rubia, 2009). Meditation techniques using concentration on an object elicit neural activation in the fronto-parietal network (Brefczynski-Lewis et al., 2007) whereas techniques that focus on mindful breathing activate insula, mPFC and ACC (Farb et al., 2007; Hölzel et al., 2007). Hence, it seems that meditation can engage neural networks involved in attentional and emotional processing.

2.1.5   The anatomy of the emotional brain

Specific anatomical regions in the brain work partly alone and in networks to mediate emotional responses, feeling states, and emotional regulation (Craig, 2009; Davis, 1997; Mesulam, 1998; Ochsner and Gross, 2005). A particular region may be very important for a specific state, but not always necessary; this implies that brain regions are dependent on each other. Brain imaging techniques, psychophysiological methods and lesion studies have taught us which brain regions are specifically important for emotions. The following sections will briefly go through the brain structures involved in emotional processes.

2.1.5.1   Periaqueductal grey

PAG is a columnar organized region localized in the midbrain surrounding the aqueduct. PAG can be divided into three main sections, the ventrolateral, the lateral and the dorsolateral part. Quite simply, the ventrolateral PAG is involved in passive

responses whereas the lateral/dorsolateral parts are involved in active responses. More specifically, the ventrolateral PAG is involved in freezing responses whereas the rostral part of both the lateral PAG and the dorsolateral PAG mediate fight behavior, in contrast to the caudal part of both lateral PAG and the dorsolateral PAG that mediate flight behavior (Bandler et al., 2000; Bandler and Shipley, 1994).

2.1.5.2 Amygdala

Amygdala is an evolutionary ancient subcortical structure whose role has been emphasized within emotional research. Anatomically, amygdala can be divided into a number of regions; the basolateral nucleus, the central nucleus and the bed nucleus of the stria terminalis (BNST) have been of particular interest to emotional research (LeDoux, 1999). The first two structures are part of amygdala and entail amygdala's input level respectively output level. In contrast, the BNST is not actually amygdala, but part of the "extended amygdala" (Walker et al., 2003).

Amygdala function has been related to fear processing while BNST has been shown to be more related to anxiety processing (Walker et al., 2003). More specifically, the amygdala is involved in an extensive amount of emotional processes e.g. fear recognition, fear learning, fear processing, aggression, and trustworthiness (Ferris et al., 2008; Phelps and LeDoux, 2005). Lesions in amygdala lead to impaired fear recognition, fear conditioning and social judgment (Adolphs et al., 2005; Adolphs et al., 1998; Bechara et al., 1995).

The amygdala plays various but important roles in decision making, but the causality of amygdala involvement in these processes has not been shown. Previous imaging studies have found that amygdala responds to: value encoding at the time of the decision, self-blamed regret, breaking a promise, ambiguity, and the framing effect (Baumgartner et al., 2009; Brand et al., 2007; De Martino et al., 2006; Hsu et al., 2005; Jenison et al., 2011; Nicollea et al., 2011). Although these various functions have been suggested for amygdala, the common denominator for all these functions is value coding; that is, are incoming stimuli worth paying attention to and remembering?

An important aspect to add is whether amygdala codes for valance or arousal. Some studies controlling for arousal suggest that amygdala is more involved in arousal

processing than value per se (Haber and Knutson, 2009). This interpretation is in line with studies that show rapid amygdala habituation to emotional stimuli (Haber and Knutson, 2009). The observation that amygdala activity in response to reward stimuli decreases with time while striatal activity (nucleus accumbens) increases over time (Gottfried et al., 2003) has generated the hypothesis that the striatum is more directly involved in reward processing than amygdala. However, it has been shown that amygdala activity is reduced with devaluation (Gottfried et al., 2003) and there is an extensive literature on amygdala's importance in recognizing emotions (Adolphs, 2002; O'Doherty, 2004). Thus, it may be more plausible that value is an interaction between intensity (arousal) and valance rather than valance alone (O'Doherty, 2004).

2.1.5.3   Orbitofrontal cortex

OFC is a cortical region located in the frontal lobes that is important for reward processing. In particular, OFC provides a representation of each specific reward or affective value in a common currency and is very plastic to changes as it updates reward values continuously (Rolls and Grabenhorst, 2008). For example, OFC represents the affective value of food only when it is rewarding. In real life, this phenomenon can be represented by people craving dessert even though they are no longer hungry. The neural mechanism behind this fact is that the main course is no longer rewarding as we are fed to satiety with it. Yet introduction of a dessert would be coded as rewarding as it represents something affectively valuable and novel.

Importantly, OFC only signals reward value and not intensity or identity, it is also central for representing motivational value for primary and secondary reinforces as well as reward expectation of pain relief in placebo (Petrovic et al., 2010).

In decision making paradigms OFC signals expected value (see section 2.2.3) and reward on a continuous scale (Rolls and Grabenhorst, 2008). OFC has also been shown to be involved in regret as it codes for the outcome of the non-chosen alternative where a greater reward could have been obtained compared to the chosen alternative (Coricelli et al., 2007).

It has been suggested that OFC may be functionally divided into a medial part and a lateral part, respectively, an anterior-posterior dimension (Kringelbach, 2005). The

medial part has been paired with monitoring learning and memory of reward value while the lateral part has been linked to evaluation of punishment that can change behavior. The anterior-posterior feature to this division entails that more abstract representations are made more anteriorly (e.g. monetary gain and loss) whereas more simple representations are made more posteriorly (e.g. taste).

2.1.5.4 Insula

Insula is a limbic structure that is involved in interoceptive representation (Craig, 2009). Previous brain imaging studies have shown that insula participates in pain perception, heartbeat awareness, neural processing of unfairness, self-recognition, time perception and empathy (Craig, 2003; Craig, 2009; Sanfey et al., 2003; Singer et al., 2006). The common nominator for these different functions is that insula processes interoception i.e. provides a representation of the current homeostasis of the body.

From a functional anatomical view, insula can be divided into a posterior part and an anterior part. Interestingly, it seems that the posterior part represents the "true" sensory state (interoception) of the body's homeostasis whereas the anterior part maps "as if body loops" (Bechara and Damasio, 2005); that is, it simulates how we would feel if we were to be happy, sad, or in pain. Accordingly, the more abstract representation of a (feeling) state the more anterior parts of the insula participate in the neural processing of that stimulus (Craig, 2009). As a result of insula's role in representing the body's homeostasis these functions are also important for the representation of feeling states (Craig, 2003; Craig, 2009).

Anterior insula (AI) is important for decision making; in a very influential study on the Ultimatum Game (UG) (see section 2.4.3.2), Sanfey et al. found that insula was involved in neural processing of unfairness and correlated with rejection rate of unfair monetary proposals (Sanfey et al., 2003). Insula is part of the empathy network and is sensitive to social interactions (Singer et al., 2004; Singer et al., 2006). In an imaging study, Singer et al. showed that empathy for pain (i.e. watching someone else suffer from pain) activated affective parts of the pain matrix (including AI) but not sensory components of the pain matrix (Ingvar, 1999; Singer et al., 2004). It has been suggested that when we watch someone else suffer from a pain stimulus, AI maps how we would feel if that particular event would have happened to ourselves. As a result, our ability to

relate to someone else's suffering seems to be an important component in neural processing of empathy.

In a follow up study, Singer et al. examined how interactions in the UG modulated participants' emphatic responses when they watched proposers receiving pain stimuli (Singer et al., 2006). Interestingly, it was showed that AI activity went down in male participants when they watched other participants (proposers), who had previously treated them unfairly, receiving pain stimuli. In contrast, insula activity increased when they watched fellow participants (proposers), who had previously treated them fairly, receiving pain stimuli (Singer et al., 2006). These results suggest that insula is sensitive to social interactions in choice situations and participates in empathic processes.

2.1.5.5 *Dorsolateral prefrontal cortex*

Dorsolateral prefrontal cortex (dlPFC) is a cortical area important for working memory, upholding rules, cognitive control, and emotional regulation (Fuster, 1999; Levy and Goldman-Rakic, 2000; Miller and Cohen, 2001; Ochsner and Gross, 2005). Notably, the last statement concerning emotional regulation might not be true as recent studies have shown that when controlling for emotional bias, dlPFC is still active (Golkar et al.). This suggests that the actual role for dlPFC is to uphold rules and information.

Experimental conditions that activate dlPFC are those where participants are asked to hold a task in memory over delay, follow instructions, and maintain and manipulate information (Baker et al., 1996; Barch et al., 1997). MacDonald et al. showed that dlPFC was specifically involved during task preparation which implies that dlPFC is involved in control implementation by representing and actively maintaining the attentional demands of the task (MacDonald et al., 2000).

In decision making, dlPFC has been suggested to override selfish impulses (Knoch et al., 2006) and uphold goal values (Camus et al., 2009). Disruption of dlPFC activity has shown to increase selfish behavior (Knoch et al., 2006) and decrease values ascribed to a choice (Camus et al., 2009). These studies on decision making imply that dlPFC is involved in inhibition and value computation at the time of the choice.

2.1.5.6 Anterior cingulate cortex

ACC is a cortical structure located in the frontal lobe. ACC is involved in conflict monitoring and conflict resolution. Depending on which kind of conflict the participant is faced with (i.e. cognitive or affective) different regions of the ACC will be involved in the conflict monitoring and resolution.

The Color Stroop task is the classical test to detect conflict in the dACC (Bush et al., 2000). In the Color Stroop task, participants are asked to name the color in which a word is written. The word can either be congruent or incongruent with the color. For example, a congruent task with low conflict would be the word RED as the word fits with the color. An incongruent task with high conflict would be GREEN where the word green is incongruent with the color blue. Comparing incongruent tasks to congruent tasks yields activation in dACC. This suggests that dACC is involved in neural processing of *cognitive* conflicts.

Variations of the Stroop task have been used to investigate emotional conflict and conflict resolution. In the "Emotional Word Counting Stroop" participants are asked to state the number of times by which non-emotional or emotional words (e.g. "lamp" or "murderer") appears on a screen (Bush et al., 2000). In comparison to non-emotional words the emotional word counting task activates rostral ACC (rACC). Other versions of emotional Stroop tasks have shown similar results (Etkin et al., 2006). Interestingly, Etkin et al. demonstrated that a congruent task followed by a second incongruent task increased the participants' performance on the second task in terms of reaction time and correct answer. This improvement followed the rACC activity; accordingly, it has been suggested that rACC also resolves *emotional* conflicts in addition to monitoring them (Etkin et al., 2006). These results support the suggestion that the rACC does indeed participate in top-down regulation of emotions.

2.1.6 The neural network constituting the emotional brain

As presented above, there are a number of brain structures that are important in emotional processing and regulation. Individual regions are important per se but it is their role in the emotional neural networks that makes up the whole. The brain works in reciprocal communicating networks to handle information processing (Mesulam, 1998) and the following section is a brief summary of how different emotional structures are connected to each other.
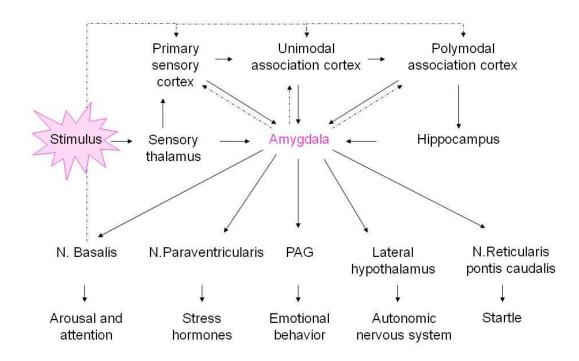
PAG receives input from various regions e.g. the spinal cord, the central nucleus of amygdala, nucleus tractus solitarius, PFC, insula, and ACC (Bandler and Shipley, 1994). PAG outputs brain stem and spinal cord which enables PAG to modulate autonomic responses and pain processing (Bandler and Shipley, 1994).

Amygdala can be viewed as the node in emotional processing as it has extensive mutual connections to structures like striatum, OFC, insula, and ACC. Amygdala evaluates reward value of a stimulus at an early stage (Baxter and Murray, 2002; O'Doherty, 2004) and the connection between amygdala and OFC is important for valuation of a stimulus. In addition, the amygdala input to OFC contributes to reward value representation in OFC (Schoenbaum et al., 2003). Amygdala and OFC are also connected to striatum, a nucleus that is also important for reward processing. In concert, these three structures are coding for predicted future reward (O'Doherty, 2004). This representation of predicted future reward is implicated in guiding action selection (O'Doherty, 2004).

The amygdala does not only signal reward, it can also signal aversion. For example, exposure to an unpleasant odorant increases both activity in amygdala and OFC whereas less aversive odorants decrease amygdala processing alone, without affecting OFC activity (Zald and Pardo, 1997). Amygdala activity has also been observed in other aversive contexts e.g. monetary loss aversion and uncertainty (De Martino et al., 2010; Hsu et al., 2005; Tom et al., 2007).

Amygdala also outputs to brain nuclei like PAG, nucleus paraventricularis, nucleus basalis, and the lateral hypothalamus. Together, these structures give rise to physiological responses that characterize emotional expressions and feeling states (Figure 1). For example, in the case of fear, we get increased heart rate and sweating as well as elevated concentrations of stress hormones. All these bodily changes contribute to a feeling state of fear.

OFC is a node for multisensory integration and receives input from all modalities. OFC is connected to other structures important for emotional processing i.e. amygdala, striatum, insula, ACC, and mPFC (Rolls and Grabenhorst, 2008). As mentioned earlier OFC is important for evaluating and learning whether a stimulus is of value or not.

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Figure 1. From stimulus to behavior. Amygdala holds a key position in mediating emotional behavior. There is a "low road" via sensory thalamus directly to amygdala which enables fast emotional responses whereas the "high road" via cortical structures constitutes a slower affective neural processing. Amygdala communicates with different nuclei to mediate emotional behavior and physiological changes associated to the specific emotional state. The figure is based on information found in texts by Davis, Le Doux and Pessoa (Davis, 1997; LeDoux, 1999; Pessoa, 2011).

Lesions in OFC lead to inappropriate responses, e.g. responding to a non-rewarding stimulus (Rolls and Grabenhorst, 2008).

Insula is closely connected bi-directionally to amygdala, OFC, nucleus accumbens, ACC, dlPFC, and prefrontal areas. Thus, insula, a structure that is mainly involved in interoceptive representation, receives and conveys input to limbic structures that are especially important for reward value assessment (Singer et al., 2009). The insula and ACC connection seem to be of particular importance in emotional regulation. It has been suggested that these areas act as limbic sensory and limbic motor cortices respectively, constituting the feeling and the motivation that comprise an emotion (Craig, 2009). Additionally, signals from insula and ventral striatum represent important input to the mPFC when calculating costs versus gains (Haber and Knutson, 2009).

dlPFC receives input from sensory cortices and has extensive output connections with the motor system e.g. pre-motor areas, rostral cingulate cortex, superior colliculus, cerebellum, and the basal ganglia (Miller and Cohen, 2001). It is believed that dlPFC can exert control (inhibition) over behavior through these structures. dlPFC also have mutual connections with vmPFC (Miller and Cohen, 2001); consequently, information from wide-ranging brain systems can be integrated on a fairly local circuitry in the PFC.

ACC is closely connected to amygdala (Etkin et al., 2011; Walton et al., 2007) and receives emotional information from this structure. ACC is important for regulating amygdala input (Bishop, 2007; Etkin et al., 2006) and the importance of ACC regulation of amygdala input is reflected in patients who suffer from anxiety disorders. These patients usually have a hyperactive amygdala function (Stein et al., 2007) and a deficit in cortical regulation (of amygdala) which results in anxiety associated symptoms (Bishop, 2007; Etkin and Wager, 2007).

2.1.7 From stimulus to behavior

There are two major paths by which emotional information can reach the brain. The first and most direct one is the "low road" which goes via thalamus to the amygdala and then results in a behavioral response (LeDoux, 1999; Öhman, 2005) (Figure 1). The second path, the "high road," goes first via cortex before it reaches the amygdala and thereafter gives rise to a behavioral response (Gazzaniga et al., 2002; LeDoux, 1999) (Figure 1). In the mirror of the Cannon-Bard versus James Lang theories, it seems that the above processes run in parallel and we experience feeling states (Craig, 2009) both as a consequence of bodily reactions (James Lang) and vice versa i.e. the experience of a feeling state can also alter bodily processes (Cannon-Bard) (Gazzaniga et al., 2002). This means that some processes are automatized; a classical example is the one where a hiker discovers a snake in the forest. Before he knows it his heart is pounding and his blood pressure has increased (Gazzaniga et al., 2002). By using the low road we are able to adjust rapidly to situations that are crucial. If these processes were to take longer i.e. if we were to use cognitive computational skills instead, the snake would already have attacked. Hence, rapid automatic responses have evolved as they promote survival.

2.1.8 Emotional perception

Perception includes the physiological systems that are active in interpreting sensory stimuli. As we have different modalities of sensory stimuli, both separate and overlapping systems are involved in the neural process of perception (Gazzaniga et al., 2002). Emotional perception can also vary in modality, for example, a picture of a loved one is a visual emotional stimulus while a punch in the face is an emotional sensory stimulus. Common for the different modalities is that they have primary cortices (e.g. primary visual cortex and primary sensory cortex) in which the signal is interpreted and conveyed to more multi-sensory areas (e.g. OFC) in order to create a more complex and complete experience (Rolls, 2004). These multi-sensory areas are in turn connected to other structures involved in emotional processing (e.g. amygdala and insula) (Rolls, 2004).

2.1.9 Evolutionary perspective

Evolution has helped organisms to evolve and adapt in the most efficient way (Hau and Wikelsk, 2001). Emotions and human facial expressions represent biologically developed adaptations (Öhman, 2009). Fear, for example, is a signal reflecting potential threat and risk of being harmed. As a result, emotions help us value and remember things that are considered to be important and we remember emotional events better than neutral ones as they carry salient information (Gospic et al., 2008).

With evolution, some neural processes have become automatic in order to save computational power and to be able to execute actions as rapidly as possible when needed. For example, it is very convenient to have jumped over a snake before even noticing it on a more conscious level (Gazzaniga et al., 2002). These automatic instant processes are located in the most evolutionary old parts of the neural system like the spinal cord, brain stem and the amygdala (Jarvis et al., 2005; Kolb and Whishaw, 2003; LeDoux, 1999).

With time, the human brain has evolved cortical structures that are able to compute future representations as well as upholding concepts of strategical thinking and planning (Fuster, 2008). These structures are mainly located in the frontal part of the brain and the more anterior/lateral the part is, the more evolutionary young it is (LeDoux, 1999). Even though humans carry a heritage of neural wiring similar to

reptiles, we have evolved complex cortical structures that enable us to inhibit and regulate these "primitive" impulses in order to quickly adjust to new environments.

2.1.10 Pharmacological manipulation of feeling states and perception

From clinical practice we have learned that it is possible to manipulate feeling states and perception. For example, anxiolytic drugs can reduce anxiety in patients suffering from anxiety disorders (Basile et al., 2004). Some drugs may induce unwanted changes of feeling states e.g. pentagastrin (cholecystokinin (CCK)) can induce panic attacks (Bradwejn, 1992) while L-DOPA (precursor to dopamine) can increase aggressiveness and impulsiveness (Cools and Robbins, 2004; Nelson and Trainor, 2007). Conventional pain-killers like anti-inflammatory substances can decrease pain perception by reducing noxious input to the brain (Rang et al., 2003) while opioids can modulate perception by changing both the noxious input to the brain and the perception of how a painful stimulus is experienced (Fields, 1999; Vogt, 1993).

In conclusion, these findings show that both feeling states and perception can be pharmacologically manipulated. The following sections describe the effects of the four drugs, used in this thesis, on behaviors related to emotional perception and decision making.

2.1.10.1 Cholecystokinin

CCK is an excitatory, gut-brain peptide that acts on g-protein coupled CCK receptors. CCK acts on CCK_a and CCK_b receptors. Both receptor types are found in the gut and the brain, but the CCK_a receptor is the predominant receptor in the gut while the CCK_b receptor is the predominant receptor in the brain. The expression of the CCK_b receptor is particularly high in the amygdala, hippocampus, and PFC (Radu, 2005).

Peripherally, CCK induces the release of bile and in the brain CCK participates in the regulation of satiety, pain, and anxiety (Radu, 2005). The functions of the CCK system have been mostly studied in pain. For example, animal studies have demonstrated that CCK concentration increases in ACC after axotomy (model for phantom pain) which has been suggested to contribute to the subjective experience of pain (Gustafsson et al., 2000). In humans, the CCK system has been shown to be involved in nocebo and it acts in an opposite direction, compared to the opioid system (Colloca and Benedetti, 2005).

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CCK can also, in higher doses, induce anxiety as well as panic attacks (Bradwejn, 1992; deMontigny, 1989), and on a functional anatomical level, these states seems to co-vary with amygdala and insula activity (Eser et al., 2009; Javanmard et al., 1999). Together, these findings make the CCK system an interesting target for studying emotion related processes. In Study I (Gospic et al., 2008), we investigated if the CCK system may modulate emotional perception in a similar way as it modulates pain.

2.1.10.2 Opioids

The opioid system is commonly known to induce pain relief and induce pleasantness (Berridge, 2003; Fields, 1999; Koob et al., 1989). Opioids may target one or many of the different kinds of opioid receptors and each of the receptor types has endogenous peptides that target them specifically. For example, beta-endorphin targets the mu-receptor, enkephaline targets the delta, and the mu-receptor and dynorphine targets the kappa-receptor. Opioid receptors are found both peripherally and centrally. In the brain, high opioid receptor concentrations are found in amygdala, insula, and ACC (Vogt, 1993; Zubieta and Koeppe, 2001).

Previous studies on pain have shown that the opioid system participates in the placebo response (Colloca and Benedetti, 2005; Levine et al., 1978). For example, Petrovic et al. demonstrated that similar brain regions (including ACC) are activated when an external opioid is administered and when a placebo response is induced. In Study I, we investigated if the opioid system could modulate emotional perception in a similar manner as it regulates pain.

2.1.10.3 Benzodiazepines

Benzodiazepines are pharmacological substances that target neural inhibitory GABA receptors. GABA receptors are abundant in the amygdala (Braestrup et al., 1977) and benzodiazepines can potentiate GABA activity (Rang et al., 2003), reduce behavioral signs of aggression (Nelson and Trainor, 2007), and decrease amygdala activity in emotional tasks (Arce et al., 2006; Paulus et al., 2005). Clinically, benzodiazepines are used to reduce anxiety (Basile et al., 2004).

Studies on decision making and the GABA system have shown that alcohol (GABA receptor stimulator) and diazepam increase risk taking behavior (Deakin et al., 2004;

Lane et al., 2004). In Study II, we investigated the behavioral and neural effects of the benzodiazepine oxazepam on decision making in the UG.

2.1.10.4 Dopamine

In the brain, dopamine producing neurons are found in the substansia nigra (SN) and ventral tegmental area (VTA) (Vallone et al., 2000). SN and VTA project, via the nigrostriatal pathway, the mesolimbic pathway, and the mesocortical pathway to striatum, amygdala, insula, and ACC. These regions have a high density of dopamine receptors and are important for emotional motivation and cognitive processing (Alcaro et al., 2007; Hurd et al., 2001).

Dopamine is best known for its role in the reward system (see section 2.2). Nevertheless, dopamine is not only part of the reward system it also plays an important role in mediating aggression (Kennealy, 2008; Nelson and Trainor, 2007). Enhanced dopamine activity increases impulsivity and aggression in subjects with normally functioning dopamine systems (Arce and Santisteban, 2006; Giammanco et al., 2005) and dopamine antagonists can be used clinically to treat aggression (Nelson and Trainor, 2007). Experimentally, it has been demonstrated that cocaine administration (increases dopamine levels) to healthy subjects increased aggression (Licata et al., 1993). Licata et al. found that participants who had been treated with cocaine and lost a time reaction task, handed out greater electrical shocks (social punishment) to fellow competitors than placebo treated participants (Licata et al., 1993). The above findings suggest that there is a *link* between the dopamine system, aggression, and social punishment.

Interestingly, reward circuitries are anatomically interconnected with emotional structures that mediate aggressive reactive responses (Iversen and Iversen, 2007) and this has been demonstrated on an experimental level. de Quervain et al. showed that the most punish-prone subjects in a social game setting had the highest brain activity in reward related circuits (de Quervain et al., 2004; Singer et al., 2006). Remarkably, social punishment of norm violators can be satisfying.

In Study III, we investigated how dopamine administration affected social punishment in a socially interactive economic game (UG) (see section 2.4.3.2). In the UG there are

two strong conflicting options presented to the responder; i.e. either to maximize his/her own monetary reward or enforce fairness by punishing the other player, at a personal cost, for treating him/her unfairly.

2.2 REWARD

Reward is fundamental for decision making and goal directed behaviors as it entails which outcome is associated with the greatest benefit. The reward system can be looked at from different perspectives; importantly the various views are not mutually exclusive but can co-exist. Common for all models is that they involve dopamine signaling.

2.2.1 Liking and wanting

Reward can be divided into two parts "liking" and "wanting." Liking reflects the hedonic aspect of a stimulus and wanting accounts for the incentive salience that promotes approach and utilization of reward. Both liking and wanting are part of a reward system and during recent years research has shown that distinct neuroanatomical and neurochemical substrates separate them (Berridge et al., 2009). While liking has been associated with the opioid system, wanting has been linked to the dopamine system. The anatomical network for liking and wanting seems to be partly overlapping and partly separated (Berridge et al., 2009). The common denominator for both liking and wanting is that they involve the nucleus accumbens and the ventral pallidum; however, very specific parts of these structures respond to either liking or wanting (Berridge et al., 2009).

Behavioral studies in humans seem to be in line with Berridge's theoretical framework e.g. it has been shown that healthy subjects who were given dopamine treatment preferred smaller but instant rewards to larger delayed rewards (Pine et al., 2010). This result can be interpreted as dopamine increases wanting. In addition, it has been suggested that dopamine can be viewed as a general reinforcer of motivational salience (Matsumoto and Hikosaka, 2009). Hence, elevated levels of dopamine could therefore increase subjects wanting to act and not only increase the wanting of having something (e.g. food). Indeed, Berridge has suggested that an urge to act (action salience) can be equivalent to wanting an external stimulus (Berridge et al., 2009).

2.2.2 Reward prediction error signal

Apart, from the dopamine system being involved in wanting, another line of work has proposed that dopamine participates in mediating the "reward prediction error signal" in reward learning (Schultz, 2000; Schultz, 2007). Dopamine has also been proposed to signal predictions of future rewards by evaluating the difference between expected rewards and the reward prediction signal (O'Doherty, 2004).

2.2.3 Expected value

Computational frame works have presented the importance of dopamine signaling in expected value computations (Fox and Poldrack, 2009).

Expected value = probability of something to happen x value

Expected value and reward prediction error signals are jointly important for how people perceive profits and losses. In one study, subjects played a 50-50 gamble where they in one version could win either $8 or $32 and in a second version, lose either $8 or $32. Subjects could not influence the game as it was a pure 50-50 gamble and their task was to report how they felt about the outcomes. Participants reported that they felt slightly happy when they lost $8 as they had avoided a loss of $32; in contrast, they felt rather unhappy when winning $8 as they had not won $32 (Peterson, 2007). Hence, the subjects' assessment of the true outcome versus the expected value guided how they felt about the end result.

2.2.4 Reward circuitry

There are a number of anatomical structures that participate in the neural processing of reward. As mentioned in earlier sections structures like amygdala, OFC, and ventral striatum (nucleus accumbens) are the most important areas as they integrate and process reward related information (O'Doherty, 2004; Schoenbaum et al., 2003). Common for all structures is that they receive dopaminergic input from VTA and SN which is important for conveying reward prediction error signals (Vallone et al., 2000).

An excessive access to dopamine has shown to increase the temporal discounting rate and impulsive behavior (Pine et al., 2010; Voon et al., 2010a; Voon et al., 2010b). Stress seems to have similar effects as dopamine on impulsivity (Diller et al., 2011; van

den Bos et al., 2009; Voon et al., 2010a) and it is believed that this effect is due to glucocorticoid-induced stimulation of dopaminergic transmission (Piazza and Le Moal, 1997). Over all, an imbalanced dopamine system results in impaired decision making.

Pathological gamblers have an imbalance in their dopamine system (Reuter et al., 2005; Voon et al., 2007). In particular, they are more insensitive to rewards than healthy controls (van Holst et al., 2010). On a functional anatomical level, this insensitivity corresponds to a decreased neural response, compared to controls, in the ventral striatum and the vmPFC when receiving monetary gains (Reuter et al., 2005). Gamblers who have the most severe problems are also the ones showing the greatest decrease in ventral striatal activity (Reuter et al., 2005). Similarly, drug addicts also have a problem with impulsiveness and it has been shown that they have a steeper delayed discounting curve than healthy controls (Monterosso et al., 2007; Peters and Büchel, 2011). That is, they prefer short term rewards to long term rewards, in a much greater extent than healthy controls.

2.3 DECISION MAKING

2.3.1 Definition and function of decision making

Decision making is defined as the cognitive process of selecting an outcome out of many alternatives (Coricelli et al., 2007). Every decision that we make results in a choice that either has a mental representation or is an actual action. The function of decision making is to help us adjust rapidly to new environments as we are constantly exposed to external information (Gospic et al., 2011).

2.3.2 The link between decision making and emotions

Emotions have shown to have a great impact on decision making and do indeed make us "irrational" according to economic theory. Early on, Tversky and Kahneman demonstrated that contextual framing (emotions) affects decisions e.g. if one is to choose between a certain reward outcome and a risky reward outcome (i.e. a suggestion presented with a certain probability) the majority will go for the certain alternative even though the risky choice has the same expected outcome. In contrast, when we are to choose between a certain loss and a risky loss we go for the risky loss (Tversky and Kahneman, 1981). Thus, depending on if we are facing rewards or losses we behave differently as we let ourselves be guided by our emotions.

In the 90's Antonio Damasio presented his "somatic marker hypothesis" on how emotional processes affect decision making (Damasio, 1994). The theory emerged from observations of patients suffering from brain lesions; it was noted that patients suffering from frontal brain lesions made decisions against their best interests (Bechara and Damasio, 2005). To investigate this phenomenon further, Damasio et al. studied these patients during a card game (Iowa gambling task). Damasio el al. demonstrated that those patients with lesions in amygdala and vmPFC made more risky choices and their overall monetary gain was less compared to controls. When skin conductance response (SCR) was measured, it was shown that control subjects elevated their SCR prior to choosing a risky card deck whereas this response was abolished in amygdala and vmPFC lesioned patients. From these results it was concluded that these patients were not guided by any emotional signals. Hence, Damasio demonstrated that an emotional process guides decision making and contributes to advantageous choice behavior (Bechara and Damasio, 2005).

There are various studies showing how emotions affect choice behavior. Depending on how we evaluate/reappraise a situation we can affect loss aversion. For example, if a potentially risky choice is considered as one choice out of many we tend to be less risk aversive. On the contrary, if we consider an individual choice as the only choice, people tend to be more loss aversive (Curley et al., 2007). Our feeling states also modulate our selling behavior. Lerner et al. showed that participants who were sad tended to sell their goods for a lower price and buy goods at a higher price (reduced endowment effect) than they would if they had a neutral mood (Lerner et al., 2004). On a related note, angry subjects in comparison to fearful subjects were more prone to make risk-seeking choices (Lerner and Keltner, 2001).

2.3.3 Neural mechanisms of decision making

All decisions are associated with an uncertainty, an expected value, and short versus long term rewards (Rushworth and Behrens, 2008; Tobler et al., 2009). The neural mechanisms of uncertainty, expected value and reward, involve emotional processing. Hsu et al showed that the level of ambiguity correlated positively with amygdala and OFC activity, and negatively with the striatum (Hsu et al., 2005). Moreover, expected value was guided by the striatum to ensure maximal gain (Hsu et al., 2005).

Several animal species favor short term rewards as they lack the ability to plan for the future (Stuphorn, 2005). The ambiguity of not knowing when to access food e.g. makes them act instantly. A similar behavior can be observed in children but as the frontal lobes evolve with age, individuals are able to consider long term rewards and future aspects (Fuster, 2008). Still, people struggle between the conflict of short and long term reward (Gilbert and Wilson, 2007; McClure et al., 2004). For example, subjects prefer $10 immediately to $11 tomorrow; in contrast, if subjects are offered $10 in a year or $11 in one year and one day, subjects do not mind waiting an extra day for the extra dollar (McClure et al., 2004). Conclusively, the time factor (temporal discounting) influences how much we are willing to post pone reward.

Many studies have shown the importance of emotional processes in decision making. Damasio et al. demonstrated that amygdala, OFC and vmPFC are important for accurate risk behavior as patients with lesions in these structures had increased risk seeking behavior (Bechara et al., 2003). De Martino et al. demonstrated that amygdala participates in the framing effect, previously described by Tversky et al. (De Martino et al., 2010; De Martino et al., 2006; Tversky and Kahneman, 1981). Interestingly, DeMartino et al. also demonstrated that patients with amygdala lesions are not affected by the framing effect as amygdala damage eliminates monetary loss aversion (De Martino et al., 2010).

Neural reward circuits are also important for decision making as we prefer the choices that maximize our gain (reward). For example, observing products that we like activates subcortical brain regions like nucleus accumbens (Knutson et al., 2008) and cortical regions such as vmPFC cortex (Paulus and Frank, 2003), both related to emotional reward processing in terms of wanting and liking (Berridge and Kringelbach, 2008; Kringelbach and Berridge, 2009) (see section 2.2.1). Activity in these regions, together with insula, are also predictive of purchase (Knutson et al., 2007).

2.3.4 A model for decision making

There is an abundant amount of theoretical models by which attempts have been made to explain human decision making. In the present thesis we have adopted the two-level model presented by Gläscher et al. (Gläscher et al., 2010). Therefore, only the two-level model will be presented below.

2.3.4.1   Two-level model

The model by Gläscher et al. entails that there is model-free reinforcement learning (RL) and model-based RL. The model-free RL system denotes that action values are learned directly by trial and error without creating any model of the surrounding environment. In contrast, model-based RL refers to a system that learns action values by building and using a cognitive map/model of the environment. Additionally, prediction errors are important for both approaches but in different manners (Gläscher et al., 2010).

By combining computational learning models with functional imaging data Gläscher et al. found that model-free RL was associated with subcortical processing and model-based RL was linked to cortical processing. Gläscher et al. suggests that decision making involves at least two neural networks that seem to have distinct neural correlates. As a result, both sub-cortical and cortical levels may influence the decision making and the major difference is that the cortical level has a richer representation of future outcomes of a decision (Fuster, 2008; Gläscher et al., 2010; Pezzulo and Rigoli, 2011). These two functional anatomical entities are also linked to an evolutionary hierarchy where instant automatic processes are driven by phylogenetically older structures (subcortical) whereas contemplated actions are processed by phylogenetically younger structures (cortex) (Fuster, 2008; Kolb and Whishaw, 2003; LeDoux, 1999).

In Study II and III, we suggest that instant social punishment (rejection) is amygdala driven whereas a slower and more contemplated rejection decision is more cortically driven (Sanfey et al., 2003). In Study IV, we generalize this idea and suggest that instant real decisions are subcortically driven while contemplated hypothetical decisions are more cortically driven. An alternative view on our implemented two-level model would be to introduce an intermediate level represented by insula and OFC. The hierarchy would then be: subcortical, intermediate and cortical. We call this the modified two-level model (see section 6.8). This idea would be in agreement with both the evolution and the development of the brain (Singer, 2006). The purpose of adding a third level would be to stratify instant reactive processes from fast salient emotional processes. Both are rapid responses but instant reactive responses can trigger an

immediate behavior whereas fast salient responses are on the border of not being fully automatic and not being fully contemplated.

Other important aspects in our model have been to emphasize the importance of time and positive and negative consequences associated with a single choice (Gospic et al., 2011). Every decision entails a short and a long term aspect and each aspect has pros and cons. This means that even though a person faces a choice that requires a simple "yes" or "no" answer (like in the UG), a particular choice needs to be considered in these dimensions. Animals that are mostly subcortically driven and lack the ability of projecting themselves in the future make decisions on a subcortical level (Stuphorn, 2005); nonetheless, these decisions may still account for some future consequences linked to the choice even though the animal does not perceive these per se at the time of the decision.

In previous standard economic models, one has only considered the aspects of hyper-rationality and pay-off maximization which has entailed that some money (reward) is more than no money (no reward) (Güth et al., 1982); however, these models have not considered other aspects that may influence choice behavior e.g. the importance of implementing fairness or maintaining a good reputation (Camerer, 2003). Hence, our anatomy-informed model adds new information to a previous economic model that has not fully considered how anatomical hierarchies, time, and different kinds of consequences affect human choice behavior (see also section 6.8 and Table 1).

2.3.5 Rationality

The definitions of rationality are many and the discussion around the concept of rationality has been topical since Aristotle (Hutchinson, 1986). One way of summarizing rationality is: "rationality involves thinking and behaving reasonably or logically. Rational beliefs are those that are internally consistent, and rational arguments are those that obey the rules of logic" (Colman, 2003).

The economic science defines rational behavior as: "the recommendation always to behave so as to maximize the expected time utility per time unit" (Good, 1952). Economic rationality of utility, as derived from classical game theory, predicts that the participants, in experimental economic games, should always maximize their payoff

(Von Neumann et al., 1953). In real life, this prediction is only true for autistic persons (Sally and Hill, 2006) and brain lesioned patients (Shiv et al., 2005). Behavioral studies, in healthy control subjects, have shown that the economic rationality of utility prediction is experimentally invalid. In fact, decision making processes in healthy control subjects are influenced by a number of factors e.g. emotions (Bechara et al., 2003; De Martino et al., 2006; Tversky and Kahneman, 1981).

In recent years, neural correlates of economic "irrationality" have been studied with the framing effect paradigm. In this paradigm participants are presented risky monetary gains, risky monetary losses, safe monetary gains and safe monetary losses (De Martino et al., 2006). Overall, participants prefer safe gains to risky gains even though they have the same expected value. In contrast, when participants are presented to alternatives that involve losses, they are more prone to be risky even though the alternatives have the same expected value (Tversky and Kahneman, 1981). These behaviors are, according to economic theory, irrational as two equal outcomes that have the same probability to occur should not be treated differently (Tversky and Kahneman, 1981).

In a study by De Martino et al. they investigated neural correlates of the framing effect (De Martino et al., 2006; Tversky and Kahneman, 1981). Interestingly, they found that neural correlates of rationality, in contrast to emotional processes, were cortically located. They showed that people who were the least affected by the framing effect had enhanced activity in orbital and medial PFC and vmPFC (De Martino et al., 2006). In contrast, activity related to "irrationality" and the actual framing effect was associated with amygdala activity. Two studies have investigated the effect of amygdala lesion on the framing effect; one study showed that amygdala lesions abolished the framing effect (De Martino et al., 2010) whereas the other study did not (Talmi et al., 2009). The reason for the latter result may be that the amygdala lesioned model they used (Urbach-Wiethe disease) was not a pure model of amygdala lesion or amygdala does not play a causal role in the framing effect (Talmi et al., 2009).

The emotional network seems to be important for "irrational" behavior. Greene et al. showed that participants who were are asked to judge the appropriateness of two similar alternatives in a moral dilemma with identical outcomes, activated emotional

networks when the action was personal compared to impersonal (Frith and Singer, 2008; Greene et al., 2001). In contrast, cortical structures appear to be important for "rational" behavior. A couple of studies have shown that patients with lesions in the vmPFC behave more irrationally in economic games than control subjects (Bechara et al., 1998; Koenigs and Tranel, 2007; Moretti et al., 2009).

In conclusion, the above mentioned studies make it evident that emotional processing affects decision making and contributes to "economic irrationality." On the other hand, as "irrationality" has survived evolutionary selection, it is valid to question what rationality really is. One distinction to make is that one could classify rationality according to economic rationality versus biological rationality. The biological rationality would then entail the choice(s) that is/are most likely to increase the survival of the organism which may be a decision that is emotionally biased. Previous definitions have omitted the time aspect that is associated with all choices. For example, one decision may be very rational from a short term perspective but may not be as rational from a long term perspective. A way to exemplify this is with economic games, where rational behavior is considered to be the choices that maximize one's monetary pay-off. Notably, this view does not consider aspects important for future interactions e.g. the importance of implementing social rules and reputation building (Camerer, 2003).

2.3.6 Other factors biasing decision making

There are a vast number of factors that may affect decision making (Anderson and Dickinson, 2010; Güroglu et al., 2010; Heine et al., 2008; Henrich et al., 2005; Symmonds et al., 2010). The section above presented the most important factor of them all i.e. emotional bias. In the following paragraphs a few additional concepts will be presented to give a broader perspective on how easily affected our decisions are, from instant changes in bodily homeostasis to more permanent variations in our genetic code (Roiser et al., 2009; Symmonds et al., 2010).

Body homeostasis, like sleep status and metabolic state, influence choice behavior. For example, subjects who have been sleep-deprived are more likely to reject unequal splits in the UG compared to subjects who have slept. Sleep deprived subjects do also trust others less in a trust game compared to subjects who have slept (Anderson and

Dickinson, 2010). Symmonds et al. demonstrated that a person's metabolic state can alter economic decision making under risk. Interestingly, participants who had just eaten made more risky choices compared to before the meal (Symmonds et al., 2010).

The concept of time is an influential factor on decision making (Gilbert and Wilson, 2007; McClure et al., 2004; Smith and Silberberg, 2010). Our own mental representation of an event in relation to the time when it will occur influences decisions in the sense that the further away in time the event is the more positive we are. This is due to that when we imagine an event e.g. attending a lecture distant in time, we usually consider the positive parts like the lecture itself. However, as the lecture approaches we start considering how to get there etc. which might make us less enthusiastic to attend (Gilbert and Wilson, 2007).

Smith et al. demonstrated that participants playing the UG (see section 2.4.3.2) made different decisions depending on if they waited 1 minute or 5 minutes before they made their choice (Smith and Silberberg, 2010). After 1 minute of waiting, participants favored rejection over pay-off maximization but when participants had waited 5 minutes before they replied they favored to maximize their monetary profit. Importantly, the pay-off maximization behavior observed in autistic people, brain lesioned patients, and Chimpanzees (Jensen et al., 2007; Sally and Hill, 2006; Shiv et al., 2005) can be reproduced in healthy controls, provided that the temporal domain is manipulated accordingly (Smith and Silberberg, 2010).

Other people's intentions affect decision making (Güroglu et al., 2010); subjects who played the UG rejected unfair offers more frequently when the proposer had a fair alternative to offer. In line with this concept a number of studies have shown that playing the UG with a computer decreases the rejection rate of unfair proposals (Sanfey et al., 2003) while a similar interaction in the prisoner's dilemma game (see section 2.4.3.4) results in decreased cooperation (Rilling et al., 2004).

The representation that we picture others to have of us can change choice behavior. Heine et al. 2008 studied the way westerners (Americans) compared to South-East Asian (Japanese) subjects evaluated themselves. Subjects performed a self-evaluation task in front of a mirror and in a room with no mirror (without knowing that the mirror

played a part in the experiment). Results showed that the self-evaluation performed in front of the mirror was much harsher compared to the self-evaluation made in a room without a mirror (Heine et al., 2008). The authors suggested that this change in choice behavior was due to perspective taking i.e. how you see yourself compared to how others see you. Interestingly, this effect was only present in Americans and not in Japanese subjects indicating that cultural norms play a role in perspective taking and decision making.

In recent years, there have been several studies that have shown that genetic variations influence decision making (Cesarini et al., 2008; Dreber et al., 2009; Knafo et al., 2008; Krugel et al., 2009; Reuter et al., 2010; Roiser et al., 2009; Zhong et al., 2010). For example, it has been shown that homozygote carriers of the short allele of the serotonin transporter gene (5-HTTLPR)(more serotonin in the synaptic cleft) are more prone to choose safe options than risky options, compared to homozygote long allele carriers (less serotonin in the synaptic cleft) (Roiser et al., 2009). Moreover, the long allele carriers had an increased coupling between amygdala and ACC when they made risky options compared to short allele carries. Thus, variations in functional anatomical coupling may be one of the underlying mechanisms that explain how genetic variations may influence choice behavior.

2.3.7 Risk, ambiguity, loss aversion and trust

Risk and ambiguity are two factors that impact decision making (Singer et al., 2009). Risk means that the participant is aware of the risk his/her choice has e.g. when drawing a card from a deck with a known composition. Ambiguity means that a subject is unaware of the card deck composition, meaning that if s/he draws a card from that deck the chance of getting a specific card is unknown.

Hsu et al. showed that different neural mechanisms are involved in ambiguity versus risk (Hsu et al., 2005). Increased amygdala activity and OFC activity was seen during ambiguous choices versus risky choices while increased striatal activity was observed during risky choices compared to ambiguous choices (Hsu et al., 2005). Interestingly, it was also demonstrated that patients with lesions in the OFC were indifferent to risk and ambiguity. In a similar manner, amygdala lesioned patients are also known to be risk and ambiguity neutral (Brand et al., 2007; De Martino et al., 2010). AI has also been

suggested to be involved in risk and ambiguity processing (Singer et al., 2009) and insula lesioned patients show impaired decision making (Weller et al., 2009). Yet the results from Weller et al. are more complex and may be due to inconsistencies in the location of lesion, lesion size and comorbid effects. Importantly, these results suggest that human decision making depends on an intact insula (Singer et al., 2009; Weller et al., 2009).

Loss aversion is closely related to risk as a risky choice may involve a potential loss. In general, people tend to be more sensitive to losses than gains. Subjects reject gamble proposals that state a 50/50 chance of gaining or losing money, unless the gain is twice the amount of loss (Tversky and Kahneman, 1992). Recently, this behavioral phenomenon was linked to functional neuroanatomical correlates. Indeed, it was demonstrated that the response curve in striatum was steeper and negative for losses compared to gains where the response was more blunt and positive (Tom et al., 2007).

Trust is constituted by a certain expectation of someone and is closely related to risk as increased trust in someone is associated to a lower risk. Brain imaging studies have demonstrated that the perception of trust is closely related to amygdala (Winston et al., 2002). Kosfeld et al. demonstrated that trustworthiness could be manipulated by the neuropeptide oxytocin (Kosfeld et al., 2005). Subjects who received oxytocin tended to trust and be more willing to take risk arising from social interactions. This phenomenon is probably due to the fact that oxytocin decreases amygdala activity/output (Debiec, 2005; Huber et al., 2005; Petrovic et al., 2008). In support, a lesion study showed that amygdala damage led to increased trust (Adolphs et al., 1998).

2.4 COOPERATION AND PUNISHMENT

2.4.1 Cooperation

Cooperation is found at different levels in nature and is a prerequisite for evolution to create new civilizations (Nowak and Sigmund, 2005). Humans have an exceptional ability to cooperate and this behavior can be observed both in modern societies as well as within groups of hunters/gathers (Fehr and Fischbacher, 2003). A unique feature of human cooperation is that we collaborate with others that we are not genetically related to (Fehr and Fischbacher, 2004; Henrich, 2003). This behavior to cooperate with genetically different individuals is only found in humans, bees and ants (Fehr and

Fischbacher, 2003). The evolution of collaborative skills and the ability to sustain cooperation rely on several functions unique to humans e.g. patience, precise numerical discrimination, working memory capacity, and inhibitory control (Fehr and Fischbacher, 2004). The incentives for cooperation are many, but reputation building and reciprocal gains may be considered to be two of the most important. Reputation building is part of an indirect reciprocity model where third parties reward other group members with a good status, provided that they can get a good reputation themselves by doing so (Fehr and Fischbacher, 2003). Reciprocal gains are based on reciprocal altruism where reward and punishment are executed if there is a long term interest for doing so (Fehr and Fischbacher, 2004). Both these factors can be observed in games where players have repeated interactions.

2.4.2 Punishment

Punishment and the threat of punishment is an influential tool to maintain social cooperation (Jensen, 2010) and discourage norm violators (Fehr and Fischbacher, 2004). A common repertoire of human behavior is to punish other individuals who break social norms set by the group. The act of punishment serves to protect both personal and group interests (Seymour et al., 2007). It is also a crucial part of sustained cooperation (Binmore, 2008).

A number of social interactive paradigms can be used to study cooperation and punishment. The following sections will describe the rules and experimental findings of the four most commonly used games i.e. the public goods game, the dictator game (DG), the UG, and the prisoner's dilemma. In Study II and III, we used the UG to study neural mechanisms of fairness and social punishment.

2.4.3 Paradigms to study cooperation and punishment

2.4.3.1 Public goods game

The public goods game is a classical game to study social cooperation and punishment. In this game, every player is provided with a sum of money; every player has the choice to either contribute to a public fund or keep their money. If a player chooses to invest the money in the public fund this money will be multiplied by a predetermined factor and then distributed to all the players participating in the game. The greatest group benefit is that every individual invests money in the public fund. Nonetheless,

the biggest benefit for the individual is to defect (free-ride) because then the individual will both keep his/her own money and receive money from the public fund in which other players invested in. When players are allowed to punish the free-riders, the norm violators quickly adapt to the rules of the group and start investing in the public fund. With punishment the free-rider problem can be avoided and a new game equilibrium is reached (Seymour et al., 2007).

2.4.3.2 Ultimatum Game

The UG is a simple illustration of altruistic punishment and studies the participants' proneness to punish (Güth et al., 1982). In the UG a proposer suggests how to split a sum of money between him/herself and a subject (responder). The offers can be either fair or unfair and the responder can choose either to accept or reject the monetary split. If the responder accepts the offer the suggested split will be realized in terms of real money. In contrast, if the responder rejects the offer neither of the two receives any money. Interestingly, responders tend to reject unfair 20/80 offers (20 % to the responder and 80% to the proposer) approximately 50% of the time, even at a personal cost (Camerer, 2003; Gospic et al., 2011; Sanfey et al., 2003).

The UG can be played either repeatedly or with single interactions. In the former situation proposers adjust their behavior towards more fairness if they are punished by the responder and it is beneficial for the responder him/herself to punish the proposer as this will yield a fairer split in the coming interactions (Fehr and Fischbacher, 2003). The responder will have incentives to build his/her reputation in the eyes of the proposer and the social group (Camerer, 2003). Similar behavior is seen in single shot games when the proposer knows that his/her previous behavior will *not* be reported to the upcoming responder (Gospic et al., 2011). According to economic theories there is no reason for the proposer to play fair in single shot interactions as the players will never meet again. Nonetheless, an abundant number of studies (Gospic et al., 2011; Sanfey et al., 2003), have observed that proposers still cooperate in single shot interactions and concluded that humans are strong reciprocals meaning that they reward others for cooperating (altruistic reward) and punish norm violators (altruistic punishment) (Fehr and Fischbacher, 2003; Fehr and Fischbacher, 2004). This behavior creates incentive to cooperate even during single interaction or when reputation gains are absent.

An important aspect to consider when playing the UG is which incentives participants have to play the game. Smith demonstrated in the early 60's that behavior differed between participants who were rewarded with points and participants who were rewarded with real money (Camerer, 2003). Subjects who were rewarded with fictional points tended to behave unpredictably as they got bored by the experiment. In contrast, participants who receive real money tended to behave more consistently and did not get bored as easily as participants receiving fictional points. Consequently, paying participants became a norm within experimental economics.

2.4.3.3 Dictator Game

The DG has been used to investigate if humans still maintain a high level of cooperation in the UG when the responder is not allowed to punish the proposer. The DG is similar to the UG with one exception; the recipients are not allowed to respond to the offers i.e. the recipients are basically given an amount of money by the proposers (Sanfey and Dorris, 2009). According to economic theory the proposers should maximize their own monetary pay-off i.e. giving no money to the recipients, but experiments have shown that the proposers still share some money (pure altruism) with the recipients. The offers made by the proposers to the recipients in the DG are 40% smaller compared to the offers made in the UG (Camerer, 2003). This indicates that punishment is a prerequisite to sustain high level cooperation. The fact that the proposers still offer the recipients an amount of money suggests that part of the motive when making fair proposals in the UG is altruistic and not purely strategical (Camerer, 2003).

2.4.3.4 Prisoner's dilemma

Previous brain imaging studies have used the "prisoners' dilemma" to study human cooperation (Rilling et al., 2002). In the prisoners' dilemma two participants independently from each other choose whether to cooperate or not. There are 4 possible outcomes: player A and player B can both choose to cooperate, defect, or one of them may choose to cooperate while the other one may defect. If both players choose to cooperate they will both be rewarded. If player A chooses to defect while player B chooses to cooperate player A will be rewarded and vice versa. If both players choose to defect they will be harshly punished. Hence, depending on player B's decision the individual (player A) will either be rewarded or not.

2.4.4 Neural correlates of cooperation

In a study by Rilling et al. it was demonstrated that mutual cooperation between two human partners in the prisoner's dilemma activated rACC, OFC, and anteroventral striatum (Rilling et al., 2002). From these results, the authors interpreted that social cooperation is rewarding and cortical control is used to inhibit selfish inputs.

2.4.5 Neural correlates of punishment

Social punishment is a must to maintain social cooperation and interestingly, the act of punishment has been shown to be satisfying. de Querivan et al. found that the most punish-prone subjects in a social trust game setting had the highest brain activity in reward related circuits (de Quervain et al., 2004; Singer et al., 2006). In particular, striatal activity correlated positively with the act of punishment. The authors concluded that the reward system participates in altruistic punishment and caudate activation especially, may reflect the anticipated satisfaction from punishing defectors. This result gives an indication of why people may be prone to punish social norm violators.

Amygdala is crucial for both the mediation of aggressive responses (Bosch and Neumann, 2010; Ferris et al., 2008; Hermans et al., 2008; Mehta and Beer, 2010) and of biasing decision making (Adolphs et al., 1998; Bechara et al., 2003; De Martino et al., 2006). Reactive aggressive actions are automatic and present when we react to challenging situations like localizing danger, competing for resources and establishing social dominance (Archer, 2009; Giammanco et al., 2005). The UG is an economic game reflecting these aspects, i.e. two individuals competing for the same resource and trying to establish a good reputation. Interestingly, it has been showed that anger is a better predictor of rejection behavior than fairness in the UG (Pillutla and Murnighan, 1996). Moreover, amygdala involvement has been observed in third party punishment. Buckholtz et al. showed that subjects who were to decide upon appropriate punishments for crimes (third party punishment) activated areas involved in emotional processing i.e. amygdala, mPFC, and posterior cingulate. In Study II and III, we hypothesized that amygdala would be involved in social punishment in the UG.

2.5 FAIRNESS AND UNFAIRNESS

Fairness and unfairness are two words that stand in close relation as they are each other's counterparts. Fairness can be defined as: reasonableness, equitableness,

impartiality and unfairness may be defined as unreasonableness, inequitableness and bias (Longman, 1993). Even though the definitions of fairness and unfairness are rather clear, their neural underpinnings are less understood. Nevertheless, an amount of studies have examined these concepts in different cultures, patient cohorts, species (e.g. Capuchin monkey), and age groups (Almås et al., 2010; Brosnan and de Waal, 2003; Fehr et al., 2008; Henrich et al., 2005; Koenigs and Tranel, 2007).

2.5.1 Neural correlates of fairness and unfairness

Neural correlates of fairness and unfairness have mainly been studied with the UG and brain imaging. In the UG, perception of fairness, compared to unfairness, has been associated with neural activity in ventral striatum, amygdala, and OFC (Tabibnia et al., 2008). The opposite contrast, i.e. unfairness versus fairness, has been shown to activate amygdala, bilateral insula, dlPFC, and ACC (Gospic et al., 2011; Sanfey et al., 2003).

Recently there has been a discussion whether concepts of fairness/unfairness necessarily need to have a cortical representation as extensive literature on decision making related to inequality has shown that actions to implement justice (rejecting unfair proposals in the UG) can be cortically independent. For example, behavioral studies in children, with a less developed prefrontal cortex, have shown that inequity aversion is present in the absence of "theory of mind" (Takagishi et al., 2010). Similarly, Capuchin monkeys (Brosnan and de Waal, 2003), and patients with prefrontal lesions (Koenigs and Tranel, 2007) also show an intact rejection response to unfair offers. In Study II and III, we presented a model where we reconcile the views of cortical and subcortical functions related to fairness and social punishment. Concomitantly, we also investigated subcortical substrates of fairness and social punishment.

Perception of fairness has also been studied with an inequity paradigm; in a study by Tricomi et al. subjects were divided in to two groups, one of the groups received $50 while the other group received $20. Subjects were then asked to transfer money between each other/groups. Interestingly, the low paid group showed increased reward related activity (i.e. in striatum and vmPFC) when the money was transferred to them while the high paid group showed the same kind of neural activity when money was transferred to a subject in the low paid group. This indicates that there are neural

correlates for advantageous and disadvantageous inequality (Tricomi et al., 2010) and the neural activity in striatum seems to reflect different things in each group. Izuma et al. has shown that both social rewards and monetary rewards share neural correlates (Izuma et al., 2008). Therefore, the striatal activity in the low paid group might have reflected a pure monetary gain while the corresponding activity in the high paid group may have mirrored a social reward.

2.5.2 Factors affecting concepts of fairness and unfairness

A great number of factors can affect fairness and social punishment. People from different cultures can act very differently in the UG. Populations in Peru have been shown to give very unfair proposals and accepting unfair proposals to a greater extent than people in western cultures. Interestingly, these populations are some of the few that in fact act as game theory predicts! In contrast, groups in Papua New Guinea give hyperfair proposals and show a greater rejection rate to unfair proposals (Henrich, Boyd et al. 2005). People in western cultures tend to give and accept proposals close to 50-50. Personality traits do also affect behavior in the UG and the DG. For example, schizotype personalities, compared to healthy controls, offer more money in the UG and DG and accept more unfair offers (van 't Wout and Sanfey 2011).

2.5.3 Development of fairness and unfairness

Behavioral studies made in children have offered the opportunity to study the development of fairness. In an influential study by Fehr et al., they let children share pieces of candy with other children in three different contexts (Fehr et al., 2008). First, in the "prosocial context" the child could choose one candy for him/herself and one candy for the partner (1,1) or one candy for him/herself and no candy for the partner (1,0). Second, in the "envy context" the child could choose one candy for him/herself and one candy for the partner (1,1) or one candy for him/herself and two candies for the partner (1,2) .Third, in the "sharing context" the child could choose one candy for him/herself and one candy for the partner (1,1) or two candies for him/herself and zero candy for the partner (2,0). Interestingly, they demonstrated that children at the age of 3-4 behaved selfishly, children at the age of 5-6 were intermediate and children at the age of 7-8 had a strong sense of fairness as they choose the "1,1" conditions most often. Children without siblings were more likely to share than children with siblings and the youngest child of a family was less likely to share than children with younger siblings.

Almås et al. demonstrated that elderly children (11-19 years old) playing the DG did not show any differences in mean share (Almås et al., 2010). The degree of selfishness was also similar over all age groups. However, with age they noted that the acceptance for inequalities in performance increased whereas the youngest participants were strict egalitarians i.e. considering all inequalities to be unfair. These results indicate that cognitive maturation and social experience can bias the concept of fairness preferences.

2.6   ALTRUISM

Altruism can be defined as selfless care for others or a behavior that is costly to the actor and beneficial to the recipient (www.dictionary.com). Hence, altruism deviates from economic beliefs of profit maximization. From a biological aspect, altruism means that the actor increases the chance of someone else to reproduce while lowering its own chances (Glimcher, 2008). There are different motives that might explain this kind of behavior e.g. warm-glow and signaling of wealth and prestige (Glimcher, 2008; Harbaugh et al., 2007).

Within the animal kingdom altruism is usually exerted towards relatives, this has been considered as beneficial as the actor and the recipient share ancestry. Nevertheless, humans seem to be one of few species that exerts altruistic behavior to non-genetically related individuals (Henrich, 2003) and the question why we display this kind of behavior is still not clear. Brain imaging studies have shown that donating money to charity activates structures involved in reward processing i.e. ventral striatum (Harbaugh et al., 2007; Hare et al., 2010; Izuma et al., 2010) and emotional regulation i.e. ACC (Moll et al., 2006). These studies indicate that altruism is rewarding.

2.7   HYPOTHETICAL BIAS

When people state their willingness to pay for something, the amount differs from the behavior when faced with a real purchase (Johannesson et al., 1998). The difference, between a hypothetical reply and the real act is called hypothetical bias (Johansson-Stenman and Svedsäter, 2007; Kang et al., 2011). The underlying reasons to this fact are multifaceted. For example, real choices have a cost for the decision maker. Thus, when we make a real choice we have to deal with the direct comparison between a loss (e.g. money or time) and the gain (e.g. goods or favors). In contrast, hypothetical

choices do not cost anything in real terms and we do not have to face any particular consequences (Kang et al., 2011).

2.7.1 Neural correlates of hypothetical bias

There has only been one previous study, to our knowledge, that has studied the neural correlates of hypothetical bias. In the study by Kang et al. they demonstrate that the same neural network (i.e. mOFC, ventral striatum and ACC) was involved in both real and hypothetical decisions but the activity in this neural network was more expressed for real decisions compared to hypothetical decisions. In Study IV, we continued to investigate underlying mechanisms of hypothetical bias. In contrast to the study by Kang et al., our study design was considerably sharper as it had a precision timing for the actual decision, involved public goods, and had a between group design.

2.7.2 Factors that affect hypothetical bias

A number of factors can affect the degree of hypothetical bias. From a methodological point of view it is important to know that hypothetical bias tends to be greater in between subjects comparisons compared to within subject comparisons (Johansson-Stenman and Svedsäter, 2008). Participants also value products differently depending on if they have a known market price (i.e. private goods) or not (i.e. public goods). For example, it is easy to know that a pair of brand sneakers is a bargain if they are sold for $10 while it is harder to know the value of three square meters of a national park. Therefore, hypothetical bias is usually higher for public goods, than for private goods, as they lack value anchors (Murphy et al., 2005).

Certainty ratings of how sure participants are of their hypothetical choices tend to abolish hypothetical bias (Blumenschein et al., 2008) and hypothetical bias seems to increase with the degree of uncertainty (Ladenburg and Olsen Boye, 2010). Hypothetical bias can also vary with culture, in both directions. That is, in some cultures (e.g. western cultures) people tend to exaggerate their hypothetical choices compared to their real choices whereas in some African cultures the situation is reversed; that is, the hypothetical choices are understated in comparison to the real choices (Ehmke et al., 2008).

2.7.3 Donation paradigms

A variety of experimental set-ups can be used to study hypothetical bias. A commonly used paradigm is a donation task. In this task, participants are either allocated to a "real" group or a "hypothetical" group, in a between group design. As a show-up fee, all participants are given an amount of money. Participants are then presented to a number of proposals e.g. "You donate $10, we donate $5." The proposals contain a co-donation by the lab (we) as it is an incentive for the participant to donate money inside the experiment and not after the experiment.

In the real group, participants make decisions that can have a cost for them. That is, if they choose to accept a donation proposal, the stated amount will be paid by both the participant and the lab (provided that the particular proposal is randomly selected to be realized). On the other hand, if they choose to decline a proposal no money will be paid. In the hypothetical group, the participants make similar decisions but with the exception that no costs will be associated with their decisions as they are only hypothetical. In Study IV, we adapted a version of this donation task to study neural mechanisms underlying hypothetical bias.

2.7.3.1 Factors affecting donation

There are a great number of factors that influence donation behavior. Field experiments have shown that revealing the name of the donor makes people donate more money and previous donors are more likely to give and contribute more than first time donors (Landry et al., 2008). The physical attractiveness of a fundraiser also affects the raised amounts and this variable is at least as important as any economic incentives offered (Landry et al., 2006).

A recent imaging study on the topic revealed that participants donated more money to charities when they were observed; concomitantly, these donations yielded a higher neural activity in the striatum (Izuma et al., 2010). Personal monetary gain without a social cost (i.e. not being observed) also yielded increased striatal activation. These findings indicate that social rewards may be as rewarding as pure monetary rewards. It also implies that the brain uses a common currency to evaluate these two different modalities.

Recently, studies have indicated that genetic polymorphisms may affect donation behavior (Knafo et al., 2008; Reuter et al., 2010). Reuter et al. investigated the influence of the COMT Val158 polymorphism, (an enzyme metabolizing dopamine) on donation behavior (Reuter et al., 2010). They demonstrated that subjects carrying at least one copy of the Val allele (i.e. having an increased enzyme activity and less available dopamine in the synaptic cleft) donated almost twice as much money as carriers of Met/Met (Reuter et al., 2010). This indicates that genetic variability affecting the brain's neurochemical balance can influence donation behavior.

2.8 SEX DIFFERENCES

A number of studies have noted sex differences between males and females in brain anatomy and function (Hines, 2010). However, there is a great inconsistency in the literature concerning sex differences, especially in the economic literature (Eckel and Grossman, 2008). Observed sex differences may be due to both nature and nurture (i.e. culture) as game behavior and risk taking belong very much to the cultural domain (Henrich et al., 2005). From an experimental point of view, the main reason for inconsistent results is that various methodological approaches are used.

First, different types of games are studied e.g. the public goods game, the UG, and the DG. Second, some games are performed as single shots while others are repeated. Third, some studies give the participants information about the other players while others keep the anonymity of the players. Fourth, the risk for the participants may vary, depending on if the strategy or the game method is applied. In the strategy method the respondent makes the decision at the same time as the proposer while the game method lets the responder make his/her decision after the proposer. Consequently, in the game approach the responder knows the outcome once his/her decision has been made (Eckel and Grossman, 2008). Fifth, some studies let the participants interact before the actual game. Sixth, studies may apply different reimbursement methods.

A UG study by Solnick et al, which had a similar experimental design to Study II and III (single-shot but strategy method), showed no sex differences in rejection rate (Solnick, 2001). In contrast, Eckel et al. observed sex differences in a punishment game where the participants could choose either to split a larger amount of money with a previously unfair player or a smaller amount of money with a previously fair player

(Eckel and Grossman, 1996). Females were more prone, than males, to split money with the fair player when the cost was low. Nevertheless, this propensity for females was abolished when the cost to implement fairness was higher. Interestingly, male choices to split money with the fair player did not vary with the cost; they behaved the same in both conditions (Eckel and Grossman, 1996). Andreoni et al showed that males and females differ in donation behavior in the DG (Andreoni and Vesterlund, 2001). The differences went in the opposite direction depending on the price for donation. Females donated more money, compared to males, when the price for donation was high. In contrast, males donated more money, compared to females, when the price for donation was low (Andreoni and Vesterlund, 2001). Lastly, in a study by Brown-Kruse, it was demonstrated that males donated more money at higher rates, than females, in a public goods game (Brown-Kruse and Hummels, 1993). Taken together, the literature on sex differences on economic decisions is inconsistent.

As for sex differences in the UG and other related games, sex differences in hypothetical bias paradigms are ambiguous. Again, these differences may depend on methodological inconsistencies. In a choice experiment where participants were asked to express their willingness to pay to protect the forest, Ladenburg et al. found that females were more susceptible to starting point bias (reference prices) and hypothetical bias than men who expressed more stable preferences (Ladenburg and Olsen Boye, 2010). The authors suggest that this difference is partly due to that females are more uncertain of their choices than men.

3 METHODS

3.1 ETHICAL APPROVAL AND INFORMED CONSENT

All studies included in this thesis were approved by the governmental regional ethical review board in Stockholm, Sweden. Every single subject in this thesis gave their informed consent (in writing) to participate.

3.2 SUBJECTS

Common to all four studies were that subjects were recruited by advertisement and were healthy with no past or present history of psychiatric or neurological illness. They were right handed, non-smokers, and fluent in Swedish. All female participants negated that they were pregnant. Over all, participants took no medications but females were allowed to take contraceptives. Subjects who took mild allergic medications (e.g. beta agonist inhalation) were accepted as long as it had not been taken prior to the experiment. (Please see the original research articles for more specific details.) All subjects were asked to fill out a medical screening questionnaire prior to the experiment; this procedure enabled us to exclude subjects that were unhealthy or fulfilled a contraindication for magnetic imaging examination.

3.3 SUBJECTIVE RATINGS AND QUESTIONERS

Visual analogue scales (VAS) (Wewers and Lowe, 1990) were used in Study I to assess subjective experience of pleasantness, unpleasantness, drowsiness and the ability to focus. In Study II and III VAS were used to assess the likeability of the proposers. State trait anxiety index (STAI) was used in Study I and II to measure both state and trait anxiety (Spielberger, 1970).

3.4 PICTURE STIMULI

In Study I, we used standardized picture material from the international affective picture system (IAPS) (Lang et al., 1999). The IAPS material contains neutral, pleasant and unpleasant pictures that are classified according to their arousal, valance and dominance. These pictures have been rated by males, females, and children according to a scale that ranges from one to nine. A higher figure corresponds to a higher intensity of arousal or positive valance. Neutral pictures are considered to have an arousal and valance around five. In Study I, the picture material was balanced for facial content.

In Study IV, only a few pictures were depicted from the IAPS material. The majority of pictures were found on the internet and the reason for this was that not enough pictures in the IAPS material represented our donation categories. The pictures found on the internet were rated, by three experimenters, for valance and arousal according to the IAPS convention. In addition, the pictures were also balanced for complexity and facial content.

3.5 FUNCTIONAL MAGNETIC IMAGING

Functional magnetic imaging (fMRI) measures changes in blood oxygenation in the brain by detecting the blood onset level dependent (BOLD) signal. The BOLD signal reflects the ratio between deoxygenated blood which is paramagnetic (gives strong signal) and oxygenated blood (gives weak signal) that is diamagnetic. When blood flow to a neural area increases the deoxygenated blood is washed out and a signal drop is detected. In recent years, studies have shown that the BOLD signal corresponds to changes in local field potentials which mirror post synaptic activity i.e. input to a neural population (Arthurs and Boniface, 2002; Lauritzen, 2005).

3.5.1 Statistical parametric mapping

Statistical parametric mapping (SPM) is a method that is used to analyze fMRI data (http://www.fil.ion.ucl.ac.uk/spm/) and make inference about effects of interest (Friston, 2007). The initial steps in the analysis include the following preprocessing operations: realignment, slice timing correction, co-registration/estimation, segmentation, normalization, and smoothing.

During the scanning process subjects are asked to lie very still. Nevertheless, it is impossible to lie totally still during a whole experiment. Therefore, motion correction (realignment) is a necessary step in data preprocessing. Realignment is the process that corrects data for movements in six dimensions. This correction places all the pictures taken from one subject in the same space and assures a homogenous anatomical reference (Friston, 2007). It is considered that an acceptable level of movement is maximum 3 mm and subjects who move more than 3 mm should be excluded. Importantly, none of our participants were excluded due to too much motion; in fact, a majority of our subjects, in all three fMRI studies, moved less than 2 mm.

In fMRI, all slices making up a volume are acquired at different time points. During this time, the BOLD signal changes. In order to compensate for the time it takes to collect a volume and the BOLD signal changes during this time a normalization procedure is made. This normalization technique is called slice timing correction (Ashburner et al., 2005).

As all brains are anatomically unique there is a need to normalize subjects' brains to a template brain. This process is called normalization and enables inter-individual comparisons (Ashburner et al., 2005). The anatomical template used in this thesis was taken from the Montreal Neurological Institute (MNI).

The last preprocessing step is called smoothing and is necessary to reduce anatomical variability between subjects and to increase the signal to noise ratio (SNR). In the smoothing processes a Gaussian kernel is used to convolve the data i.e. each voxel is replaced by an average voxel calculated from the surrounding voxels (Ashburner et al., 2005).

After preprocessing single-subject analyses and multi-subject analyses were performed. To find more details about the particular models used in this thesis please see the original research articles.

3.5.2 General linear model

To make statistical inferences about fMRI data it is common to use the general linear model (GLM). The method breaks down raw data into effects and errors by using the following equation (Friston and Stephan, 2007):

$$y(t) = X\beta + \varepsilon$$

The y equals the measured BOLD signal i.e. the observed response variable. This variable is also the dependent variable and is a function of time (t). X corresponds to the model's design matrix and includes the explanatory variables; these variables are the independent variables. The beta quantifies how much each predictor (independent variable) independently influences the dependent variable (y). The ε represents the error term and reflects variance in the data (y) which is not explained by the linear

combination of predictors (x). Moreover, the GLM assumes Gaussian spherical errors which mean that the errors are independent and identically distributed.

3.5.3 Hypothesis testing

In science the common scenario is that one wants to disprove the null hypothesis i.e. that there is no effect. To do this there are different methods. One frequent method that has been used throughout this thesis is the T-test statistics.

3.5.4 T-statistics

The T-statistics gathers evidence about the null hypothesis. When the T-statistic value is high the null hypothesis is usually false and when the value is low the null hypothesis is commonly true. In SPM we get the T-statistics by dividing the "contrast of estimated parameters" with the square root of the "variance estimate." By using this approach we can separate whether there is a difference between an active experimental state and a control condition.

3.5.5 Multiple comparisons

In fMRI, several brain volumes are collected during an experiment. Each of the brain volumes consist of more than 100 000 voxels and all these voxels are analyzed by the SPM program. When statistical calculations are made and a p-value of 0.05 is used more than 5000 voxels will be significant by chance. Therefore, it is of importance to adjust for multiple comparisons. Unless otherwise stated the imaging data in this thesis have been family wise error (FWE) corrected to minimize this problem.

3.5.6 Psychophysiological interaction

Psychophysiological interactions (PPI) measures whether there is an interaction between the psychological state and the functional coupling between two brain areas (Friston et al., 1997). The aim with PPI analysis is to look for areas which have a higher correlation with the time-course in the seed region in one psychological context compared to another. To perform this analysis an interaction variable between the time course of the experiment and the seed region is created. Thereafter, the analysis investigates if the interaction variable correlates with any other brain regions. To avoid problems with correlations which are e.g. driven by a shared task input, the

psychological and physiological time-courses from which the interaction term in the GLM was derived from, were included as covariates of no interest (Friston et al., 1997).

3.5.7 Methodological considerations

3.5.7.1 Baseline

Which baseline that has been used, is an important aspect to reflect upon when critically scrutinizing brain imaging studies. fMRI is a methodology based on contrasts, where one condition is compared to another. Importantly, there is no zero or tonic level of brain activity and hence, an implicit baseline is always used. Stark et al. demonstrated that depending on which "baseline" they used in a cognitive memory paradigm, they could either reduce, eliminate, or reverse a neural activity of interest during a cognitive task (Stark and Squire, 2001). Thus, the use of baseline is crucial to what results one receives. In Study II, III, and IV, we mentioned that we have compared different conditions to "baseline." In these studies we don't refer to any active baseline; instead, we have zeroed out all variables in the GLM model, with the exception of the variable of interest that has been set to one.

3.5.7.2 Reverse inference

Reverse inference refers to the procedure by which the engagement of a particular cognitive process is inferred from the activation of a particular brain region. However, such interpretation is not valid (Poldrack, 2006) and such information alone does not provide convincing evidence that an anatomical region in the brain can be tied to a specific cognitive function.

Importantly, there are a couple of factors that can enhance the evidence for reverse inference (Poldrack, 2006). First, the higher *selectivity* of the response of a particular brain region to a certain task, the higher the probability that the reverse inference provides useful information. That is, if a particular region is only activated by a very particular task. Second, if the proposed region of interest gets enhanced activity by other regions that are known to be connected to the specific region, this adds value to the interpretation. Third, the smaller the brain region, the more confident one can be as smaller regions seem to have more distinct functions. Fourth, converging behavioral evidence, that is, the degree of a behavioral outcome that co-varies with neural activity also strengthens the evidence of reverse inference.

In the three imaging studies presented in this thesis, the selectivity was quite good and our main region of interest was fairly small. We could also provide converging behavioral evidence, so the results obtained in the presented studies are of good methodological practice. Nevertheless, our results need to be replicated and studied from additional angles in order to provide even stronger evidence.

3.5.7.3 *Voxel-level, cluster-level and set-level corrected results*

The functional brain imaging studies in this thesis report results that are either voxel-level, cluster-level, or set-level corrected. This following section will briefly explain the differences between the three levels and the inference that can be made from these corrections (for more detailed information please see Friston et al. (Friston et al., 1996)).

First, voxel-level correction means that a specific voxel in the search (brain) volume is unlikely to have occurred by chance. If the voxel is just a single voxel in a larger volume, the result is more likely to have occurred by chance (type 1 error). In contrast, if the significant voxel is part of a cluster i.e. it is surrounded by a group of voxels, the probability that the voxel has been activated by chance is rather low. Such a result also gives a strong indication of localization.

Second, cluster-level correction indicates that a group of adjacent localized voxels contributes to a significant activation even though the individual voxels themselves are not significant. It is not possible to localize more specifically where in the cluster the "significant" activity is.

Third, set-level correction refers to a number of clusters composing an activation that is unlikely to have taken place by chance. Although we cannot assign any regionally defined effects of set-level corrected results we can state that somewhere in one or more of these clusters there is brain activity going on that is not a result of chance. In Study III, we used a bilateral amygdala mask and reported set-level significant results. Importantly, these results are statistically *valid,* this means that they can be inferred as there is a significant activity going on in amygdala. However, we cannot state where in amygdala the activity is localized.

In conclusion, the three levels of significance answer three different questions i.e. 1) Is this specific voxel significantly active? 2) Is there any significant activity in this cluster? and 3) Is there any significant activity in this network (set)?

3.6 BEHAVIORAL ANALYSES

3.6.1 Study I

The statistical analysis of the VAS ratings and the score in the recognition test was carried out using non-parametric tests. Friedman's test was used to calculate the main effect of picture content and drug effect, while the Wilcoxon signed rank test evaluated the specific contrasts. The correlation analysis examining the relationship between the STAI and the VAS ratings was carried out using the non-parametric test Spearman's rho. A parametric two-way repeated measurement analysis of variance analyzed the main effects of drug treatment and picture content on heart rate and reaction time. Specific contrasts were then evaluated with the Student's t test. A value of $p < 0.05$ was considered as significant. All the results from the specific contrasts (both parametric and non-parametric) were corrected for multiple comparisons using the Bonferroni correction.

3.6.2 Study II and III

The effect of the treatment on rejection rate for unfair proposals was first analyzed with a Mann-Whitney U test (one-tailed in Study II and two-tailed in Study III), since we could not assume normally distributed data. To control for stake size, sex, and ordering of decisions we analyzed the individual choices with probit regressions, since each individual decision was binary in nature (i.e. "yes" or "no"). Standard errors were clustered on subjects to account for repeated measures. Since no fair offers were rejected we restricted our attention to the unfair responses. Differences in ratings of fairness and likeability were analyzed with the Mann-Whitney U test. We used two-tailed tests as we had no prior assumption about the direction of a potential treatment effect.

3.6.3 Study IV

In order to establish the existence of a hypothetical bias in our experimental setting we investigated, with a mixed panel logit regression, if there were any discrepancies between real and hypothetical decisions. The mixed logit model describes behavior in

terms of probabilities that an individual will, or will not, donate money. Furthermore, the probabilities were dependent on: stake level, donation, gender, hypothetical, or real treatment, donation target (Swedish Childhood Cancer Foundation, Stockholm City Mission, Doctors Without Borders, Water Aid Sweden, Urskog 2000, Vi-Skogen, Save the Seals in the Baltic and Save the Tigers (WWF)) and some interactions between these variables. The marginal willingness' to pay for these four categories was given by the quota between the marginal utility of donations ("total donation" parameter) and the marginal utility of spending money ("you pay" parameter).

4 AIMS

The general aim of this thesis was to investigate neural mechanisms of emotional regulation and decision making using different pharmacological manipulations and brain imaging techniques.

• In Study I, we aimed to investigate if CCK and remifentanil could modulate visual emotional perception in opposite directions.

• In Study II, we aimed to examine if amygdala was involved in social punishment and if oxazepam could reduce emotional processing in the UG and decrease rejection rate of unfair proposals concomitantly with decreasing amygdala activity.

• In Study III, we aimed to replicate Study II and examine if L-DOPA could potentiate emotional processing in the UG and increase rejection rate of unfair proposals concomitantly with increasing amygdala activity.

• In Study IV, we investigated neural mechanisms of hypothetical bias.

5 RESULTS AND BRIEF DISCUSSION

5.1 STUDY I

The CCK and opioid neuromodulatory systems work in opposite directions and can modulate emotional states and noxious input in opposite directions. In Study I we generalized this idea and investigated if the CCK and opioid neuromodulatory systems worked in opposite directions to modulate emotional perception. Subjects were presented neutral and unpleasant pictures while one of three treatments was randomly administered: the CCK_b receptor agonist pentagastrin (0.1 μg/kg), the mu-opioid receptor agonist remifentanil (0.0625 μg/kg), or saline. Self-ratings of the emotional experience of pictures and drugs were sampled together with psychological tests and recording of heart rate. We showed that pentagastrin (CCK) treatment increased the rating of unpleasantness for both neutral and unpleasant pictures, while it decreased the rating of pleasantness for the neutral pictures. These effects did not correlate with the degree of general unpleasantness induced by the drug. Remifentanil treatment increased the pleasantness for the neutral pictures. While pentagastrin treatment induced a heart rate increase, unpleasant pictures induced a heart rate decrease, and the magnitude of change in heart rate correlated positively for these conditions. Thus, we propose that the CCK and the opioid system are involved in regulating emotional perception. The effects of remifentanil were more complex than our hypothesis. This suggests that different opioids may play various roles in modulation of emotional perception.

5.2 STUDY II

A previous influential study (Sanfey et al., 2003) on the UG has suggested that a cortical structure (i.e. insula) has a pivotal role for rejection in the UG. This view is not in line with other studies on decision making that have shown that amygdala is important for decision making. In Study II, we examined if amygdala, a subcortical structure important for decision making, was involved in neural processing of unfairness and rejection behavior in the UG. We also proposed an anatomy-informed model that aimed to reconcile these views. Furthermore, we introduced a design that detects the functional anatomical response of a reactive aggressive reaction in response to unfair UG proposals. We used an fMRI compatible UG paradigm to study the early components of decision making and challenged our paradigm with the introduction of an anxiolytic drug (oxazepam 20 mg), as to perturb the elicited behavioral and neural

response. Oxazepam treatment, compared to placebo, decreased the rejection rate (from 37.6 % to 19.0 %) concomitantly with a diminished amygdala response to unfair proposals. This effect was observed in spite of an unchanged feeling of unfairness and likeability of the proposers. In the control group, rejection was directly linked to increased amygdala activity. These results allow a functional anatomical detection of the early neural components of rejection associated with the initial reactive emotional response. Hence, the act of immediate rejection seems to be mediated by the limbic system and is not solely driven by cortical processes as previously suggested. Our results also prompt an ethical discussion as we demonstrated that a commonly used drug influences core functions in the human brain that underlies individual autonomy and economic decision making.

5.3   STUDY III

The dopamine system is known to enhance reactive aggressive responses and impulsivity. In contrast to Study II, we were interested to investigate if dopamine treatment (100 mg madopark) could increase rejection of unfair proposals in the (UG) concomitantly with increasing amygdala response. The same experimental procedure, as presented in Study II, was performed in Study III with the exception of pharmacological treatment. Dopamine treatment, compared to placebo, *tended* to drive behavior towards an increased rejection rate (from 20.1 % to 26.7 %, n.s.) concomitantly with increasing amygdala activity in response to unfair proposals without affecting perception of fairness or likeability of the individual proposers. This result is in agreement with our previous study where we demonstrated the opposite effect with an anxiolytic drug intervention. Our results indicate that amygdala participates in rejection behavior and neural processing of unfairness. As dopamine treatment increased activation in nucleus caudatus in all proposal conditions our study suggests that dopamine affects reward circuitries in both unfair and fair situations. Ergo, the neural mechanisms by which dopamine affects behavioral and neural responses in the UG may be more complex than just increasing aggression.

5.4   STUDY IV

People tend to exaggerate hypothetical decisions compared to real decisions. The discrepancy between a hypothetical choice versus a real choice is called hypothetical bias. In Study IV, we investigated neural mechanisms of hypothetical bias with a

donation paradigm using fMRI. Subjects were divided into two different groups, one hypothetical and one real. Subjects in the real group made choices that could cost (i.e. if they choose to accept a donation proposal and if that proposal was randomly selected to be realized) while subjects in the hypothetical group made hypothetical choices that did not cost. Previous fMRI studies have demonstrated that amygdala is involved in instant aversive decision making and costly calculations whereas cortical structures have been shown to participate in contemplated decisions. We hypothesized that amygdala would be involved in real decisions while cortical structures would be associated with hypothetical decisions. We demonstrated that there was a functional limbic involvement in hypothetical bias behavior. Real donations (choices) activated the amygdala more than hypothetical donations. Donations were more common at low stake levels, compared to high stake levels, and at the low levels there was more expressed amygdala activation. The act of donation was linked with both amygdala activation and an increased activity in the caudate nucleus and ACC. Interestingly, insular activity in response to the presentation of a charitable organization predicted upcoming donation behavior, i.e. the more activation that was observed in the insula the greater was the likelihood of donation. In conclusion, we have segregated the neural mechanisms involved in hypothetical bias. Our findings imply that the emotional system has an important role in real decision making as it signals what kind of cost and reward an outcome is associated with.

6 GENERAL DISCUSSION

The general aim of this thesis was to investigate neural mechanisms of emotional regulation and economic decision making using pharmacological interventions and fMRI. Overall, we demonstrated that neuromodulatory systems are involved in the regulation of emotional perception and economic decision making.

6.1 THE OPIOID SYSTEM BEYOND THE HYPOTHESIS

In Study I, we show that the CCK and opioid system are involved in regulating emotional perception in a similar manner as they modulate pain processing. In line with our hypothesis, we found that both neutral and unpleasant pictures were experienced as more unpleasant after pentagastrin treatment. The results for remifentanil treatment were more complex. There was a trend that the unpleasant pictures were experienced as more pleasant after remifentanil treatment, but remifentanil did not decrease unpleasantness for aversive pictures as hypothesized. This may be explained by the mu-opioid system as not being involved in suppressing emotional aversive processing, as it suppresses nociceptive processing. This would be in line with animal studies which have shown that the delta, but not the mu-opioid, system is involved in the modulation of aversive non-noxious processing. These findings indicate that a mu-opioid agonist may be more effective in augmenting a pleasant response than suppressing an unpleasant process to external input, which is in line with the idea that we perceive emotions in a multidimensional space and not via a mutually exclusive one-dimensional scale (Larsen et al., 2001; Rolls, 1995; Schimmack, 2001).

In Study I, we did not detect any interactions between any factors e.g. picture content and drug treatment. As a consequence, we can only say that the CCK-opioid system had a general effect on emotional processing, but we cannot distinguish more specific roles than that. This was the main reason we did not continue to investigate these systems further.

6.2 PRECISE TIMING

The fMRI studies presented in this thesis are unique, in comparison to previous studies on the same topics (Kang et al., 2011; Sanfey et al., 2003), in that they have a very precise timing for when the decisions were actually made. Prior studies have only used

imprecise onset times for when the decisions of the participants were made. For example, in Sanfey et al. they defined the time of the decision to four seconds after the actual monetary proposal had first been presented (Sanfey et al., 2003). This method only allowed for detection of slower neural processes. As our onset time design was very accurate, it enabled us to detect rapid and transient processes in subcortical structures like the amygdala. By using this approach we could contribute with the novel findings that the amygdala is involved in social punishment and hypothetical bias, something that had not been shown before.

6.3 COMPARING OUR RESULTS WITH PREVIOUS STUDIES

Three previous imaging papers, besides Study III, have been published on the UG (Rilling et al., 2004; Sanfey et al., 2003; Tabibnia et al., 2008). The paper by Sanfey et al. has been the most influential and the study closest to ours.

The study by Rilling et al. primarily investigated questions related to theory of mind and playing the UG against a computer versus a human being. Therefore, this study is not very compatible to ours. The last study by Tabibnia et al. studies fairness and not unfairness (rejection rate). Their study design also has a major shortcoming as their paradigm is non-jittered. Hence, there is a time-lock between face presentations and the proposal as well as the next event. Thus, their effects that relate to the fairness presentation cannot be separated from the face presentation (it is known that face presentation triggers an amygdala response (Vuilleumier and Pourtois, 2007)). In our judgment, the most valid study to compare our results with is Sanfey et al. (Sanfey et al., 2003).

In Study II and III, parts of our main effects of unfair proposals are, at first glance, in variance with the results presented by Sanfey et al. (Sanfey et al., 2003). The reason for that is that we implemented a more conservative statistical correction procedure than Sanfey et al. (Gospic et al., 2011). Importantly, post hoc analyses in Study II and III revealed that our data gave rise to Z-scores in the same range as the values presented for insula activation in Sanfey et al. (Gospic et al., 2011; Sanfey et al., 2003).

Other factors that may have contributed to different results are number of trials and stake levels. The participants in Sanfey et al. only watched 10 trials with human

partners (out of 30) whereas our participants were presented with 45 trials (all by human partners); consequently our studies had more power to detect smaller differences. Lastly, participants in Sanfey et al. played about stake levels reaching from $1 to $5 whereas our participants played about stakes reaching from $3 to $38. This could have affected the "realness" of the study which we know from Study IV activates amygdala as well as how emotionally involved participants became in the task as more money was at stake in our studies. All in all, the apparent differences in neural activity between our UG studies and Sanfey et al. can be accounted for methodologically.

6.4 THE REALNESS OF THE PROPOSER

In Study III, we noted that the overall rejection rate was low compared to Study II and other UG studies (Crockett et al., 2010; Sanfey et al., 2003). At first glance this may seem as the responders in Study III were more selfish. In the post hoc interviews some subjects stated that even though an offer seemed unfair they did not want to reject it because then the responder would not receive any money. Some participants stated that the proposers were probably "poor students" and it would be better that an unfair split was realized than neither of them getting any money. This kind of reasoning indicates that participants were involved in complex reasoning and expressed a great deal of empathy. Our results imply that the more "real" the proposer is to the participant the less rejection rate. This result is in contrast to other studies that demonstrated that human offers compared to computerized offers were more often rejected (Rilling et al., 2004; Sanfey et al., 2003). In addition, Sanfey et al. only presented pictures of their proposers while we showed movie clips; this may account for some of the differences. These differences could also be explained by cultural differences or type of student cohort. Nevertheless, these are just speculations and these findings need to be more thoroughly investigated.

6.5 THE REALNESS OF THE PROPOSAL

The "realness" of the proposal seems also to be an important factor affecting rejection rate. In our UG studies, 3 out of 45 proposals were realized whereas the studies made by Crocket et al. (Crockett et al., 2010; Crockett et al., 2008) only realized one or two proposals, out of 96 proposals. This may have induced a hypothetical bias; i.e. our studies might have been more real than previous studies which could have caused a lower rejection rate. The realness in our studies can also have contributed to our

detection of amygdala activity, as we show in Study IV that real decisions involve more limbic processing than hypothetical decisions. Unfortunately, there are no behavioral studies which have investigated the effect of the amount of realized proposals to hypothetical decisions in the UG. Importantly, these are key aspects for future research to clarify.

Similar to the UG studies, one can also question the realness of the real group in Study IV, as only one proposal was realized. Nevertheless, we were still able to demonstrate a difference between the groups which indicates that the real proposals were at least more real than the hypothetical proposals. It is likely that the results could have been even stronger if more offers had been realized. Due to economic costs not all of the proposals could be realized.

6.6 INSULA ACTIVITY - A REFLECTION OF FEELING STATE

In Study IV, we demonstrated that increased insula activity during the presentation of the donation target predicted acceptance behavior. This result may be interpreted as the more the subjects got emotionally involved in a donation target (picture) the more empathic they became and the more proposals they accepted. It is plausible that the insula activity reflects the subjects' ability to emotionally simulate themselves in the context presented to them. One may speculate that this could either have contributed to a feeling state of pity or warm-glow. In the context of the UG (Study II and III), insula activity may represent something similar i.e. we get more emotionally engaged when someone treats us unfairly. All these findings fit well into the frame work of feeling states, empathic processes, and neural predictors of purchase (Craig, 2009; Knutson et al., 2007; Singer et al., 2006). Thus, insula participates in processes that involve interoception and emotions.

6.7 ONE BLOB - DIFFERENT PROCESSES

In Study IV, we showed that there was a functional limbic involvement in hypothetical bias behavior. In concordance with Study II and III, where real instant decisions were made, we showed in Study IV that amygdala was more involved in real decisions than hypothetical decisions. Moreover, amygdala activity followed the actual cost for the participant than stake level per se as low stake proposals were more frequently accepted.

In Study IV, we could not separate which effects that were related to the "real factor" versus donation behavior, especially, as the latter variable differed between males and females. Nonetheless, we can most likely state that the amygdala signal reflects some sort of real signal because if the amygdala signal was only dependent on donation behavior one could speculate that opposite donation behaviors would cancel each other. Alternatively, different donation behaviors could have given rise to the "same" amygdala activity but mirror different processes.

In the interaction contrast (real group versus hypothetical group) where we compared low stakes versus high stakes across the whole sample, we detected an increase in amygdala activity in the real group. Even though the overall donation behavior differed between males and females both groups still donated more money for low stakes which indicates that amygdala signals the real cost of donation.

One can question how amygdala could signal for two different states, the real factor and the actual cost. A plausible explanation would be that there is a time domain effect that is not caught with fMRI i.e. the real factor may be the initial response to a donation proposal whereas the actual cost may be a secondary feed-back response that is signaled later in time. This discussion is also valid for Study II and III where we could not completely differentiate rejection behavior from the neural processing of unfairness. Again, it is plausible that these processes give rise to similar signals, but are separated in time. Conclusively, as the time resolution in fMRI is not optimal to detect adjacent voxels, these phenomena are something that need further investigation (see section 8).

6.8   EVIDENCE FOR A MODIFIED TWO-LEVEL MODEL

In all three imaging studies we demonstrate that amygdala, a subcortical structure, is involved in immediate rejection of unfair proposals in the UG and hypothetical bias. Thus, opposed to previous studies on the same matter (Kang et al., 2011; Sanfey et al., 2003) we showed that it is not only cortical structures that are involved in rejection

Anatomy	Time domain	Representation	Valuation	Action Selection	Outcome evaluation	References
Frontal Cortex	Extended future	Rich explicit model	Comparing models	Considered and complex	Model comparison	Fuster 1999/2008
Insula/OFC	State holding	Feelings	Implicit composite	By influence up or down	Changed state	Craig 2009 Rolls 2008
Amygdala	Immediate reaction	Sparse	Simple +/-	Immediate and schematic	Removal of motivation	Vuilleumier 2001/2005 Le Doux 1999

Table 1. Schematic overview of the modified two-level model for decision making. This model suggests that there are three anatomical levels that accounts for five domains i.e. information about time, stimuli representation, reward, action selection and outcome evaluation. This table is based on information from a number of studies (Craig, 2009; Fuster, 1999; Fuster, 2008; LeDoux, 1999; Rolls and Grabenhorst, 2008; Vuilleumier, 2005; Vuilleumier et al., 2001).

behavior, neural processing of unfairness and hypothetical bias, but subcortical structures like the amygdala play an important role as well.

In Gospic et al. we reconciled how cortical and subcortical mechanisms contribute to choice behavior by applying a two level model for decision making (Gläscher et al., 2010; Gospic et al., 2011)(section 2.3.4.1). In this thesis we present a *modified* model where we introduce an intermediate level and five domains (see below) that account for each of these levels (Table 1).

More specifically, our model proposes that there are two major anatomical levels (the cortical and subcortical level) and one intermediate anatomical level that influence decision making. Common to all three levels is that they contain information about the time domain, stimuli representation, reward, action selection, and outcome evaluation. In our model we suggest that the cortical level (frontal cortex) upholds a rich informed choice model where future considerations can be processed and different outcomes can be compared (Fuster, 1999). We also suggest that there is an intermediate level represented by the insula and OFC that represents the individuals' current state and feelings and can influence both cortical and subcortical structures as well as adjusting homeostasis to current contextual changes (Craig, 2009).

Lastly, we suggest that there is a subcortical level represented by the amygdala that is responsible for immediate emotional reactions evaluated in simple positive or negative matters and that affects motivation status. Results from Study II, III, IV and Sanfey et

al. fit well into this framework and as our imaging studies show activations in areas belonging to all these levels it indicates that all these systems work in parallel even though one/some level/s can be more pronounced in one context and less active in another context (Gospic et al., 2011; Sanfey et al., 2003). Importantly, we have access to all these different levels to enable the best possible adaption to the current context.

6.9   THE QUESTION OF CAUSALITY

The development of fMRI has led to more advanced techniques to investigate causality of neuroanatomical structures in human behavior. From a simplified view, there are three generations of fMRI studies.

The first generation investigated which areas were activated in response to a certain stimulus. Making reverse inference from these kinds of findings does not reveal much about causality (see section 3.5.7.2). The second generation of fMRI studies investigated neuropsychological phenomena in a similar manner as the first generation, with one exception, they had a hypothesis as to which regions would be involved. The third generation studies evoke activation according to the second generation approach, with the addition that these activations are challenged with e.g. pharmacological interventions or transcranial magnetic stimulation (TMS). The third generation studies are the ones that come closest to investigating whether a structure plays a causal role in behavior. Still, these interventions cannot fully verify causality as they are not 100 % specific. For example, we do not know exactly where the receptors that we affect with pharmacological interventions are located. We just assume that we affect the regions with the highest density of the receptor type that is of interest to us. In addition, we do not know if the drug we are using affects any other neurochemical system that may actually cause the effect we observe. TMS is not a perfect method either, as stimulation of one area also affects activity in remote interconnected regions (Driver et al., 2009). Therefore, one cannot exclude that more distant areas may cause the observed affect even though the target area of stimulation may be rather specific. Furthermore, TMS is unfortunately a difficult method to use in paradigms like UG and the donation task as one of the regions of interest (amygdala) is located deep in the brain and hard to reach.

In this thesis, we introduced two studies, Study II and III, which belong to the third generation of fMRI studies. In Study II and III, we show that an anxiolytic drug could

reduce amygdala activity concomitantly with decreasing social punishment whereas a stimulating drug could increase amygdala activity and drive behavior towards an increased rejection rate. Accordingly, we were able to induce a behavior, social punishment, and then manipulate it in two opposite directions in parallel with decreasing or increasing the neural activity in a specific and well-defined neuro-anatomical structure. This method enabled us to approach the question whether amygdala is causally involved in social punishment or not. Based on the results from Study II and III it is possible to assume that amygdala is causal for social punishment (rejection) in the UG; however, a more definite step to clarify this would be to use a lesion technique; this method will be further discussed in section 8.

6.10 MANIPULATING HUMAN AUTONOMY PROMPTS AN ETHICAL DISCUSSION

In Study II and Study III we showed that rejection behavior could be pharmacologically manipulated without changing either perception of unfairness or likeability of the proposers. As decision making is a core function of human behavior and constitutes a corner stone of autonomy, the finding that pharmacological manipulations can affect choice behavior without being recognized by the individual prompts an ethical discussion. In Sweden the use of anxiolytic drugs (oxazepam) is high, especially in the elderly population (Hoffmann et al., 2006), and L-DOPA is a common treatment for Parkinson's disease (Katzenschlager and Lees, 2002). Hence, it seems ethical to inform patients and their families about potential effects of these substances on their behavior and weigh these potential effects to the benefits of the medical treatment.

Moreover, these facts raise a question - how are our societies affected when a large part of the population is under such treatment? One can speculate that this may have a particular impact when people in power are under pharmacological influence. For example, what would happen if prime ministers, stock brokers and CEOs constantly kept prioritizing pay off maximization over implementation of justice based on drug use? Could that possibly lead to war, financial bubbles, and humanitarian catastrophes *or* bring peace, financial stability, and equality? Nothing is certain, but it is worth contemplating about and something to investigate further.

7 CONCLUSIONS

This thesis demonstrates that neuromodulatory systems like the CCK-opioid system, the GABA system and the dopamine system are important for modulating emotional perception and economic decision making. We also showed that amygdala is important for instant rejection behavior and neural processing of unfairness as well as for real choice behavior. Seemingly, the common denominator for amygdala activity in the three brain imaging studies may be that it is involved in instant valuation processing of incoming stimuli. Lastly, we demonstrate that economic decision making can be pharmacologically manipulated without changing the perception of unfairness.

8 FUTURE PERSPECTIVES

By identifying neural mechanisms of emotional regulation and decision making we can understand underlying physiological processes of human behavior. This kind of knowledge can lead to better predictions of human behavior which is beneficial for both individuals as well as for societies. In particular, this knowledge can be used to build better societies and develop treatment for patients who suffer from emotion related pathologies and/or impaired decision making.

In Study I, it was not clear what kind of role the opioid system played in emotional regulation. Ergo, it would be of importance to identify more specific roles for different opioid peptides on emotional regulation. One would also require stronger behavioral results i.e. detection of interactions before proceeding to fMRI. This would probably mean that other types of paradigms should be used to detect such potential effects. In future fMRI studies it would be interesting to investigate where CCK-opioid system exerts its effect.

We noted, in Study II and III, that amygdala was involved in both neural processing of unfair proposals and rejection behavior. It is of great importance to separate these two processes, for example by using magnetoencephalography (MEG). Since the fMRI technique is limited in the temporal domain (seconds), it is not possible to detect *very* fast transient processes (milliseconds). It is for future research to rule out the time aspects of the instant aggressive response and perception of unfairness and how these phenomena can be regulated by cortical structures. In Study III, there were two contrasting hypotheses of how dopamine would affect rejection behavior. We noted that dopamine administration drove behavior towards an increased rejection rate; the underlying reason this was observed is still speculation. Hence, it is of value to thoroughly investigate how the amygdala interacts with other neural structures. The causal role of amygdala involvement in the above stated processes could be investigated in detail by recruiting amygdala lesioned patients to play the UG.

In Study IV, we observed amygdala involvement in real decisions versus hypothetical decisions and the amygdala signal co-varied with the cost that the participants faced. Some very obvious continuation studies would be to investigate whether hypothetical

bias could be pharmacologically manipulated in a similar manner to Study II and III and examine if hypothetical bias is present in amygdala lesioned patients. It would also be of great interest to see if experienced meditators would behave differently in a hypothetical bias context compared to controls as meditators possess a unique ability to regulate emotions (Rubia, 2009) and behave more rationally in economic games (Kirk et al., 2011).

As in the previous fMRI studies, we could not distinguish the temporal resolution of amygdala activity in Study IV. Hence, it would be meaningful to separate amygdala responses related to the instant reactive response from feed-back signals with MEG. Similarly, it would also be of interest to segregate signals related to the "real factor" versus donation behavior. The donation behavior itself could also be more thoroughly studied by understanding if amygdala activity that has been generated by two different behaviors reflects the same kind of processing.

We observed a variety of unexpected gender differences in Study II, III, and IV. These observations highlight the importance of studying both genders in economic paradigms. As seen in the introduction, there have been economic studies performed on the topic before, but they have varied to a great extent in methodological approach; thus, none of the studies have been replicated nor enabled comparisons with previous studies. It would be of great value and importance to systematically investigate behavioral and neural gender differences in economic experimental paradigms.

Conclusively, in order to get a greater picture of what mechanisms are involved in emotional regulation and decision making the phenomena needs to be studied from multiple angles using different kinds of brain imaging techniques, pharmacological manipulations, genetics, and subject cohorts. Physiological and behavioral data also need to be more integrated with other sciences to give as complete picture as possible. For example, an interesting fusion according to my own opinion would be between neuroscience and physics.

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