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Zusammenfassung

Vasopressin (AVP) ist ein Peptidhormon, welches eine zentrale Rolle für die Regulation des Sozialverhaltens des Menschen und weiterer Säugetierarten spielt. Während in Studien mit Tiermodellen (z.B. Wühlmäuse und Goldhamster) ein Einfluss von AVP auf verschiedene Aspekte des Sozialverhaltens gezeigt wurde, ist das Wissen über die Wirkung von AVP auf das Sozialverhalten beim Menschen und dessen neuronale Grundlagen bisher begrenzt. In der vorliegenden Dissertation wird der Einfluss von AVP auf das Verhalten und die korrespondierenden neuronalen Prozesse in drei verschiedenen sozialen Interaktionssituationen mittels der funktionellen Magnetresonanztomographie (fMRT) und intranasaler Applikation von AVP untersucht.

Die erste Studie untersucht, wie intranasal appliziertes AVP die neuronalen Korrelate von automatisch induzierter emotionaler Empathie, sowie automatisch induzierten Mentalisierungsprozessen moduliert. Basierend auf der Annahme, dass alleine das Beobachten eines emotionalen Zustandes einer anderen Person dieselben Repräsentationen in der beobachteten Person aktiviert, wurde für diese Studie ein Paradigma gewählt, bei dem Probanden Bilder präsentiert wurden, die verschiedene soziale Situationen beinhalteten, sowie Situationen, in der nur eine einzelne Person abgebildet war. Des Weiteren waren die dargebotenen Bilder von negativer oder von neutraler Valenz. Die Variation von emotionalem und sozialem Inhalt der Bilder diente dabei der differenzierten Untersuchung des Einflusses von AVP auf die neuronalen Korrelate von automatisch induzierter emotionaler Empathie, als auch automatisch induzierten Mentalisierungsprozessen. In diesem Experiment zeigte sich eine vasopressininduziert erhöhte Aktivität der rechten Amygdala während der Betrachtung von negativen Bildern, auf denen eine gefährliche, soziale Interaktion präsentiert wurde. Zusätzlich konnte eine erhöhte funktionelle Konnektivität zwischen der rechten Amygdala und dem medialen präfrontalen Kortex während der Betrachtung dieser Bilder beobachtet werden. Die Arbeiten von Zink et al. (2010) berücksichtigend, führt dies zu der Annahme, dass inhibitorische Einflüsse des medialen präfrontalen Kortex auf die Amygdala durch intranasales AVP gehemmt werden, was zu einer erhöhten neuronalen Aktivität in der Amygdala führt. Aus evolutionärer Sichtweise könnte diese vasopressininduzierte Erhöhung der Amygdalaaktivität einen Überlebensvorteil darstellen, da wir auf für uns gefährliche Stimuli schneller reagieren können.

In einem zweiten fMRT-Experiment wurde der Einfluss von AVP auf das Kooperationsverhalten beim Menschen untersucht. In einem spieltheoretischen Paradigma, das der Hirschjagd von Jean Jacques Rousseau nachempfunden war, war es die Aufgabe der Probanden zwischen einer kooperativen Strategie A und einer nicht-kooperativen Strategie B zu wählen. Dabei zeigte sich eine selektive Wirkung von AVP auf das Kooperationsverhalten beim Menschen: AVP erhöhte die Wahl der kooperativen Strategie A in Abhängigkeit vom monetärem Anreiz zu kooperieren. In solchen Spielen, in denen die Wahl der kooperativen Strategie sehr attraktiv war, erhöhte AVP das Kooperationsverhalten. Dagegen konnte in Spielen mit geringem Anreiz zur Kooperation kein Einfluss von AVP festgestellt werden. Auf neuronaler Ebene zeigte sich in Abhängigkeit der Wahl der kooperativen Strategie eine vasopressininduzierte Verminderung der neuronalen Aktivität im linken dorsolateralen präfrontalen Kortex (dlPFC), sowie eine durch AVP induzierte Erhöhung der neuronalen Aktivität während der Wahl der nicht-kooperativen Strategie. Zusätzlich konnte unter AVP Einfluss eine erhöhte funktionelle Konnektivität des linken dlPFC und einer Hirnregion des Belohnungssystems, dem Pallidum, während der Wahl der kooperativen Strategie gezeigt werden. Aufgrund der vielfachen Evidenz, dass der dlPFC bei der Risikowahrnehmung des Menschen eine wichtige Rolle spielt, läßt sich schließen, dass AVP möglicherweise Kooperationsverhalten durch eine Verminderung der Wahrnehmung für soziales Risiko erhöht.

Die dritte fMRT-Studie diente der Untersuchung des modulierenden Einflusses von AVP auf die behavioralen und neurophysiologischen Korrelate von reaktiv-aggressivem Verhalten. Dazu wurde eine modifizierte Version des Aggressionsparadigmas nach Taylor genutzt, bei dem der Proband gegen einen vermeintlichen Gegenspieler in einem Reaktionszeitwettstreit antrat. Dieser vermeintliche Gegenspieler war ein Konföderierter der Versuchsleiterin, wodurch der gesamte Ablauf des Experiments von der Versuchsleiterin kontrolliert wurde. In der verwendeten Version des Taylor Aggressionsparadigma lösten sich aktive und passive Abschnitte ab. In aktiven Abschnitten konnte der Proband bei Gewinn der Reaktionszeitaufgabe den Gegenspieler mit einem lauten Ton bestrafen, jedoch bei Verlieren der Reaktionszeitaufgabe nicht vom Gegner bestraft werden. In passiven Abschnitten hingegen wurde der Proband bei Verlieren der Reaktionszeitaufgabe mit einem lauten Ton bestraft und konnte den Gegenspieler aber nicht bei Gewinn der Reaktionszeitaufgabe bestrafen. Die Lautstärke des Strafreizes wurde zu Beginn eines jeden Versuchs vom Proband festgesetzt. In diesem fMRT-Experiment zeigte sich während der Wahl des Bestrafungslevels in passiven Abschnitten eine vasopressininduzierte Erhöhung der neuronalen Aktivität im

superioren temporalen Sulcus (STS). Dabei erreichte die BOLD Antwort des rechten STS unter AVP Einfluss in passiven Abschnitten dasselbe Niveau, wie in aktiven Abschnitten beider Medikationsgruppen. Dieses Ergebnis wurde dahingehend interpretiert, dass die Probanden in passiven Abschnitten unter dem Einfluss von AVP ihre Wahl des Bestrafungslevels stärker reflektieren, sowie deren Konsequenzen auf die Wahl des Bestrafungslevels besser antizipieren, möglicherweise um das Risiko einer hohen Bestrafung im Falle des Verlierens der Reaktionszeitaufgabe zu vermindern. Des Weiteren deutet dieses Ergebnis darauf hin, dass AVP möglicherweise die Salienz von weniger bedeutungsvollen sozialen Interaktionen erhöht.

Abstract

The neuropeptide vasopressin (AVP) has a key role in the regulation of social behavior in humans and in a wide range of other mammalian species. In various investigations using voles or golden hamsters, for example, the influence of AVP on diverse forms of social behavior has been documented. However, up to now the knowledge about AVP's role in human social behavior is still limited. The present thesis attempts to provide insight into AVP's role in human social behavior by investigating three distinct social interactions using functional magnetic resonance imaging (fMRI) combined with intranasally administered AVP.

The first fMRI experiment addresses the modulatory impact of AVP on the neural correlates of automatically elicited emotional empathy and mentalizing processes. Based on the assumption that observing the emotional state of another person activates the same representations in the observer, a paradigm was used, in which pictures were presented showing either a social interaction or a situation with only a single person. In addition, these pictures were either of negative or neutral content. The variation of emotional and social content enabled a differentiated examination of emotional empathy as well as mentalizing processes and further allowed to analyze how the corresponding neural substrates are modulated by intranasal AVP.

The main finding of this study was that AVP modulates the neural activity in the right amygdala during the observation of pictures that illustrated a socially threatening scene. In addition, the functional connections between the right amygdala and the medial prefrontal cortex were strengthened when subjects watched the socially threatening scenes. Together with the findings from the study by Zink et al. (2010), the present study suggests that AVP attenuates inhibitory inputs of the medial prefrontal cortex, which are usually present to regulate the amygdala fear response. The AVP induced inhibition of the negative feedback loop from the medial prefrontal cortex to the amygdala might result in more sustained activity in the amygdala, which could be important for our survival by increasing the sensitivity for a faster reaction to socially threatening stimuli.

In a second fMRI study the impact of AVP on human cooperative behavior was investigated by using a two player's stag hunt game, which is based on a parable of Jean Jacques Rousseau. A task design with distinct cooperation incentives allowed to disentangle AVP's influence on behavior during high and low cooperation incentive levels. Participants were asked to choose between a cooperative strategy A and a non-cooperative strategy B.

The findings at the behavioral level indicate that AVP is acting selectively as it only increased cooperative behavior when the incentive to cooperate was high, but showed no impact in games with low incentive levels. At the neural level, AVP reduced the BOLD signal in the left dorsolateral prefrontal cortex (dlPFC) during the choice of the cooperative strategy and increased the BOLD signal during non-cooperative choices. Furthermore, AVP strengthened the functional connectivity of the left dlPFC and the left pallidum. As a recent meta-analysis by Mohr et al. (2010) highlighted the dlPFC as crucial brain site during risky decision-making, the present findings suggest that AVP promotes human cooperative behavior by decreasing the perception of social risk.

The third fMRI study asked for the moderating impact of AVP on reactive aggressive behavior in humans. In a modified version of the Taylor aggression paradigm (TAP) that comprised “active” and “passive” blocks, the participant played a reaction time task against another player who in fact was a confederate of the experimenter. In “active” blocks participants could punish the “opponent” with a loud polystyrene scratching noise in case of winning the trial, whereas the participant did not receive such a punishment when losing the trial. In “passive” trials participants were punished when loosing the reaction time task, but the “opponent” could not be punished by the participant when he won the reaction time task. The volume level of the punishment level was adjusted at the beginning of each trial, independently of whether it was an “active” or a “passive” trial, and served as an index of reactive aggression.

At the neural level the main AVP effect was found in the superior temporal cortex, namely in the right superior temporal sulcus. A modulation was found in “passive” trials during the selection of the punishment level for the opponent which reached a level comparable to that in “active” trials for both groups. These findings may indicate that under AVP influence the participants reflect more on their choice of punishment level selection by more strongly anticipating its possible consequences on the opponents’ punishment level selection, possibly to avoid the risk of receiving a high punishment in case of losing the reaction time task in “passive” trials. Results from the aggression task might also be taken as evidence that AVP might increase the salience of less meaningful social situations.

Chapter 1

Introduction

1.1 Outline of the thesis

Besides its well-known peripheral effect to increase water absorption in the collecting ducts of the kidney nephron, the neuropeptide vasopressin (AVP) has also been shown to act on the central nervous system in diverse mammalian species. Here, AVP is a key mediator of complex social behaviors such as pair bond formation (Bielsky and Young, 2004; Goodson and Bass, 2001; Lim and Young, 2006), social recognition (Zink et al., 2011), and aggressive behavior (Bos et al., 2012; Caldwell et al., 2008; Goodson and Bass, 2001). In the majority of AVP studies, animal models like voles or Syrian hamsters were used to explore AVP's mediating impact on distinct forms of social behavior, while little effort has been made to study AVP's impact on social behavior in humans. Human work so far has been mostly directed to AVP's sister hormone oxytocin, which also has effects on social behavior that are partially orthogonal to those of AVP (Meyer-Lindenberg et al., 2011).

The present thesis focuses on AVP and its modulation of social behavior in humans. Three fMRI studies that involve centrally administered AVP are presented. In study 1 (chapter 2) the influence of AVP on automatic aspects of emotional empathy and mentalizing processes will be illustrated in detail. The second experiment (chapter 3) demonstrates the mediating role of AVP in human cooperative behavior, whereas the third study (chapter 4) focuses on how AVP modulates behavioral and neurophysiological underpinnings of reactive aggressive behavior in humans. An integrated general discussion of the findings of the three studies with suggestions for future studies comprises chapter 5.

This introduction will first provide a detailed overview on the structure and functions of the neuropeptide AVP with a special focus on its role in the regulation of social behavior. This is followed by a summary of theoretical approaches and empirical evidence related to empathy, mentalizing, cooperative behavior and human aggressive behavior. Finally, a brief introduction to the functional magnetic resonance imaging method will be given.

1.2 Vasopressin

1.2.1 Structure and physiology

The neuropeptide AVP is synthesized in the nucleus supraopticus and the nucleus paraventricularis of the hypothalamus whose magnocellular neurons project to the posterior pituitary where AVP is stored and released into the bloodstream to exert its peripheral effects. It consists of 9 amino acids with the following sequence: Cys – Tyr – Phe – Gln – Asn – Cys – Pro – Arg – Gly – NH_2 with cysteine residues forming a sulfur bridge. The most well-known function of AVP is to regulate the retention of water in the kidneys. During dehydration AVP is released from the posterior pituitary into the bloodstream and acts on the AVP2 receptors of the kidneys to conserve more water, mediated by increasing the water permeability of the distal tubules. Aside from its role as antidiuretic hormone, AVP has a crucial function in the regulation of blood pressure, which is promoted by enhancing the peripheral vascular resistance.
There is ample evidence that AVP is also acting centrally (Meyer-Lindenberg et al., 2011). Axons of AVP neurons of the nucleus supraopticus and the nucleus paraventricularis project directly to the amygdala, the hippocampus, lateral septum, the nucleus accumbens and some brain stem regions (ventral tegmental area and the solitary tract nuclei down to the spinal cord; Bos et al., 2012). AVP1a receptors (AVPR1a) in mammals have been localized in the hippocampus, amygdala, hypothalamus, bed nucleus of the stria terminalis, brainstem, lateral septum and in the prefrontal and cingulate cortex of monkeys (Loup et al., 1991; Young et al., 1999), whereas AVP2 receptors, that are important for the water regulation, were found to have a higher density in the kidneys.

How AVP impacts neurobehavioral functions in humans can be effectively studied by intranasal administration of this neuropeptide. Earlier studies could demonstrate a clear advantage of transnasal administration over an intravenous treatment, because the latter method allowed only a small quantity of injected AVP to cross the blood brain barrier (Banks et al., 1987; Ermisch et al., 1985; Mens et al., 1983; Zlokovic et al., 1990). By contrast, Born et al. (2002) showed that intranasal administration of AVP resulted in a high level of AVP in the cerebrospinal fluid (CSF) within 10 min, with a further increase for up to 80 min after administration.
How AVP enters the human brain after intranasal administration is still a matter of debate: Via an intraneuronal pathway AVP might be transported in the axons of olfactory neurons to the human brain. However, proteolysis of AVP might occur and transport via this

pathway may take hours for the peptide to reach the human brain (Illum, 2000; Thorne et al., 1995). Thus, an extraneuronal pathway might rather account for a fast transport to the CSF and brain. Using this pathway, AVP molecules may pass via diffusion the intercellular clefts in the olfactory epithelium to the subarachnoid space (Illum, 2000; Thorne et al., 1995).

1.2.2 Vasopressin and social behavior

1.2.2.1 The role of Vasopressin in social bonding and affiliative behavior

AVP appears to regulate social bonding behavior in different mammalian species (Bielsky and Young, 2004; Goodson and Bass, 2001; Lim and Young, 2006). Voles represent optimal models to study the role of AVP in social pair bonding due to differences in social behavior and social organization in closely related species (Aragona and Wang, 2004; Carter et al., 1995; Insel, 2010; Lim et al., 2005; McGraw and Young, 2010). Prairie voles and pine voles are monogamous species while montane and meadow voles usually have multiple sexual partners (Insel, 2010). The partner preference test is an established method to study pair bonding behavior in voles by initially mating a male and female who get isolated from each other afterwards. The male is then placed into the middle of a three chamber apparatus and the partner female and a novel female are seated in the other chambers. The partner preference is usually assessed by the amount of time that the male spends close to the chambers of the partner female and the novel female (Caldwell et al., 2008; Carter and Getz, 1993; Carter et al., 1995; Williams et al., 1994). It has been suggested that a partner preference is present in the case that the male spends twice as much time with the partner female than with the novel female (Insel, 2010). Young et al. (1999) revealed a higher partner preference in social prairie voles after a central infusion of AVP, whereas this effect could not be seen for non-social montane voles. In addition, a central infusion of AVPR1a antagonists inhibited these behaviors in social prairie vole males, but no impact was observed when administering these antagonists to non-social montane voles (Insel et al., 1993; Insel, 2010; Young et al., 1999). Similar results have been seen in mice that were genetically engineered to express additional AVP receptors and who also increased the amount of social interactions between males (Young et al., 1999).

In humans, genetic studies clearly implicate a specific influence of AVP on social bonding and affiliative behavior. Variations in the AVPR1a locus are thought to be responsible for

differences in personality traits associated with social interactions and the onset of reproduction (Donaldson et al., 2008; Israel et al., 2008; Prichard et al., 2007). For example, AVPR1a genetic variability accounted for differences in human pair bonding in a study that tested 552 Swedish twin pairs, all of them living in a relationship with a partner. Males who were homozygous for a specific allele of AVPR1a more often suffered from marital problems or threat of divorce (Donaldson et al., 2008; Walum et al., 2008).

The effect of the AVP system on human social bonding behavior has up to now solely been shown by means of behavioral genetics studies. How AVP impacts the neural circuits underlying human social bonding behavior has not been established yet. The only attempt in this direction comes from Zink et al. (2011) who investigated a process that is essential for the formation of social bonds: social recognition – the ability to recognize other people. By using fMRI and an intranasal application of 40 International Units (IU) of AVP, Zink et al. (2011) revealed activity in the left temporo-parietal junction (TPJ) related to social recognition. The authors thus argued that AVP modulates the processing of unfamiliar faces such that these are more easily transferred to a familiar categorization.

1.2.2.2 Vasopressin as a modulatory factor in aggressive behavior

A growing body of evidence points to a key role of AVP in social forms of aggressive behavior primarily in male-male aggression (Caldwell et al., 2008; Goodson and Bass, 2001). Investigations on male rodents and Syrian hamsters revealed increased aggressive interactions after injections of AVP in the anterior hypothalamus (AH) and the lateral septum (Bos et al., 2012; Caldwell and Albers 2004b; Ferris et al., 1997). This effect was further pronounced when AVPR1a antagonists were microinjected into the AH of Syrian hamsters eliciting an inhibition of aggressive behavior against intruders (Ferris and Potegal, 1988). A complementary effect was reported by Veenema et al. (2010) who observed an increase in aggressive behavior when AVP acted on the lateral septum, but a decrease in aggressive behavior when AVP acted on the bed nucleus of the stria terminalis. This might indicate a crucial role of AVP in up- but also in down-regulating aggressive behavior (Bos et al., 2012).

Besides its mediating function in intermale aggression, AVP also showed to mediate aggression in females. It had an impact on maternal aggression to protect the offspring against intruders. For example, in rats that were treated with AVP receptor antagonists in the amygdala, maternal aggression was down-regulated (Bosch and Neumann, 2010),

while the opposite effect appeared in low anxious rats that received microinjections of synthetic AVP in the central nucleus of the amygdala.

As with social bonding, most of the knowledge on AVP effects on aggression is based on animal studies, while there is little evidence in humans yet. Coccaro et al. (1998) determined the relation between the AVP concentration in the cerebrospinal fluid and life histories of aggressive behavior in personality-disordered persons. They found a positive relationship that was stronger for males than for females. Based on findings from animal studies pinpointing to a modulatory role of AVP in aggression-related species specific signals such as flank marking in hamsters (Ferris et al., 1984; Ferris et al., 1985) and scent-marking in squirrel monkeys (Winslow and Insel, 1991), Thompson et al. (2004) predicted that AVP would similarly influence the processing of social stimuli necessary for human social communication. Moreover, they expected that AVP would equally affect agonistic communication signals in response to these stimuli. Contrary to expectations, AVP did not influence the attention toward happy or angry facial expressions in healthy young men. The same applies for arousal measures related to latter experimental conditions. By using electromyographic (EMG) measures, Thompson et al. (2004) could demonstrate in young men, however, that under AVP-influence EMG-responses induced by neutral facial expressions, had the same amplitude as EMG-responses evoked by angry facial expressions under placebo. Such a finding implies that AVP impacts aggressive behavior in human males such that harmless social stimuli are interpreted as threatening (Thompson et al., 2004). In a second study, Thompson et al. (2006) found that AVP increased an agonistic EMG-pattern with regard to faces of unfamiliar men in male subjects. It also promoted a reduction of the perception of the friendliness of those faces. Interestingly, in women AVP stimulated affiliative EMG patterns during the presentation of faces of unfamiliar women and increased the perception of the friendliness of those faces.

In conclusion, human and animal studies suggest an influence of AVP on aggressive behavior, but it remains to be investigated how possible target structures, involved in human aggressive behavior, are modulated by AVP.

1.3 The concept of empathy

The ability to decipher and predict the emotional state of others is essential for every day social interactions. The philosopher David Hume once argued that the processes, by which one person can infer the internal state of another and adjust their response accordingly, are the basis for social perception and interactions in human life (Hume,

1740/1896). The capacity to share the feelings of another person is called empathy. Different empathy concepts have been developed with remarkable disagreement regarding its definition (De Vignemont and Singer, 2006; Eslinger, 1998; Gordon, 1995; Hoffman, 2000; Meltzoff and Moore, 1983; Preston and de Waal, 2002; Wispé, 1986; Zahn-Waxler et al., 1992). A widely accepted definition of empathy comes from De Vignemont and Singer (2006), who stated that we empathize with others when we have: "(1) an affective state, (2) which is isomorphic to another person's affective state, (3) which was elicited by observing or imagining another person's affective state, and (4) when we know that the other person's affective state is the source of our own affective state". Other researchers have referred to empathy as being simply an adoption of the posture or expression of the other person, signified as "motor mimicry" or "imitation" (Dimberg et al., 2000; Hoffman, 2000). An investigation by Meltzoff and Moore (1983) revealed that preverbal children already actively mimic and imitate other children and there is ample evidence that the imitation of others, like footshaking or touching one's hair, is a highly automatic and unconscious process (Decety and Ickes, 2009). Blair (2005) suggested that empathy comprises an *affective* and a *cognitive* component. The *affective* component refers to the ability to share the feelings of others, while its *cognitive* counterpart maintains the cognitive representation of the mental states of others without feeling them in one's own body. The *cognitive* component is also termed mentalizing or "Theory of Mind" (ToM). Different models have been suggested that tried to integrate the different components of empathy (Decety and Ickes, 2009). Preston and de Waal (2002) in their perception-action model claimed that we automatically match another person's neural state during perception due to an automatic activation of our own representations of that observed state, situation and person. These latter representations in turn activate respective responses, which can be either emotional, cognitive, behavioral or a combination of all of these. The processes are viewed as being automatic, unconscious and uneffortful, but can be controlled and inhibited (Glimcher et al., 2009).

1.3.1 The neural basis of Theory of Mind

Neuroimaging studies have advanced the understanding of ToM processes by revealing the neural substrates that underlie human's ability to infer the beliefs and intentions of other people. In experimental settings ToM processes are usually induced by telling participants stories or exposing them to cartoons and by instructing participants to reason about the beliefs and intentions of the protagonists of the stories. Neuroimaging and lesion studies identified a neural circuit that comprises the medial prefrontal cortex

(mPFC), the superior temporal sulcus (STS), the temporo-parietal junction (TPJ) and the temporal poles (TP; Baron-Cohen et al., 1994, 1999; Brunet et al., 2000; Calder et al., 2002; Castelli et al., 2000; Fletcher et al., 1995; Gallagher et al., 2000; Gobbini et al., 2007; Goel et al., 1995; Krämer et al., 2010; Marjoram et al., 2006; McCabe et al., 2001; Mitchell et al., 2005; Rilling et al., 2004; Saxe and Kanwisher et al., 2003; Vogeley et al., 2001; Völlm et al., 2006). In a meta-analysis on ToM processing, mPFC activity was identified in thirty-five of fourty fMRI studies that investigated neural correlates of ToM processing (Carrington and Bailey, 2009). Additionally, lesion studies have underpinned the unique role of the mPFC in ToM processing during first- and second order false belief tasks (Rowe et al., 2001). More specifically, Saxe and Wexler (2005) argued that subcomponents of ToM are associated with distinct brain regions, such that the mPFC is involved in the understanding of desires, goals and feelings of others, whereas the TPJ region is implicated in the ability to infer more abstract contents of mental states, such as beliefs. In a recent fMRI study by Krämer et al. (2010), the neural basis of automatic mentalizing and emotional empathy processing was assessed and revealed ToM-related neural activity in classical mentalizing brain regions: the mPFC and in the STS region. Several neuroimaging studies have converged in a role of the STS region during ToM processing. Völlm et al. (2006) for instance detected increased activity in the superior temporal gyrus when participants were presented with comic strips in a “Theory of Mind” condition.

Understanding the neural mechanism of the ability to represent others’ beliefs, intentions and desires has also become a research target in the field of neuroeconomics. Human decision-making assumes the capacity to construct a “Theory of Mind” of the other in order to optimally predict the action of one’s vis-à-vis. To study the relation between these mechanisms and human decision-making, data on the ultimatum game or the prisoner’s dilemma provide a good empirical framework. Rilling et al. (2004) implemented these two economic paradigms to determine whether neural correlates of ToM processing are active during the reasoning about intentions of others and could identify increased neural activity in the posterior STS that was associated with partner decisions in the ultimatum game and also in the prisoner’s dilemma. However, up to now, little is still known about how exactly ToM processes interact with economic decision-making.

1.3.2 A neural circuit of emotional empathy

Emotional empathy has mostly been studied with relation to observation of pain (Bufalari et al., 2007; Gu et al., 2010; Jackson et al., 2005, 2006; Lamm et al., 2007; Singer et al., 2004). For example, in the study by Singer et al. (2004) empathy for pain was elicited in couples with the observing female partner lying in the fMRI-scanner. A painful stimulation of the right hand was applied to either the female partner herself or to her male partner. A mirror allowed the female partner to see the execution of the painful stimulation on her own hand and on the hand of her partner. A neural network comprising the bilateral anterior insula (AI), the rostral anterior cingulate cortex (ACC), the brainstem and the cerebellum was activated during the reception of the painful stimulation on her own hand, but also during the observation of the painful stimulus execution on the partner's hand. This finding implies that the pain circuit is active during the self-experience of pain, but also when observing the own partner suffering from pain. These results specifically underpin the suggestion made by Preston and de Waal (2002), who claimed an automatic activation of neural representations in response to an observed emotional state of another person. Similar activity in the so-called pain matrix has also been reported using painful facial expressions (Lamm et al., 2007), a painful pinprick stimulus to the fingertips (Morrison et al., 2004) or films with painful situations (Jackson et al., 2005, 2006). The AI and the ACC are the most commonly replicated brain regions linked to empathy for pain (De Vignemont and Singer, 2006; Jackson et al., 2005; Lamm et al., 2007; Morrison et al., 2004; Singer et al., 2006). Both regions have also been highlighted regarding the representation of internal body states (Craig, 2002; Critchley et al., 2001, 2004; Damasio, 1994). Based on this knowledge, Singer et al. (2004) advanced an interoceptive model of emotions by extending it into the empathy domain. They claimed that bodily states that are represented in these latter brain regions provide two distinct functions. Firstly, they allow the generation of subjective representations of feelings and also the prediction of autonomic responses related to anticipated emotional stimuli. Additionally, they enable an empathic simulation of the internal state of other's.

Besides the AI and the ACC, neuroimaging studies have also identified the amygdala (Meyer-Lindenberg et al., 2009; Völlm et al., 2006) and the inferior frontal gyrus (Krämer et al., 2010; Schulte-Rüther et al., 2007) as key brain sites for emotional empathy processes. Moreover, Krämer et al. (2010) associated the left STS to automatically elicited emotional empathy processes.

As already outlined in the previous chapter with regard to ToM processing, affective empathy processing may also interfere with action selection in economic decision-making. Evidence for this assumption comes from Singer et al. (2006). In a trust game Singer et al. (2006) have introduced a fair and an unfair partner to the participant and incorporated these players in a further pain experiment similar to that from Singer et al. (2004). This time the participant could observe the painful stimulation on the hand of the fair or the unfair player. In line with previous results, increased activity emerged in empathy-related brain regions (AI and ACC) when observing the fair player receiving a painful stimulation. Interestingly, this pain-related activity was absent in male participants when observing the unfair player suffering from pain, whereas female participants still showed neural activity in the aforementioned pain-related brain regions. Male participants showed increased neural activity in the nucleus accumbens instead, a key brain site in reward processing (Hamann et al., 2004; Knutson et al., 2001; Preuschoff et al., 2006; Sabatinelli et al., 2007). Moreover, the activity in the nucleus accumbens correlated positively with male participants' desire for revenge. These findings point to an interaction between fairness and emotional empathy responses.

1.4 Human cooperative behavior

It is often more advantageous to cooperate with others, than to take matters only into one's own hands. For instance, success may be more easily achieved through collectively working in a group. In social neuroscience and neuroeconomic research, laboratory experimental games such as the stag hunt game, the coordination game or the prisoner's dilemma game have been used to characterize cooperative behavior in humans (Declerck et al., 2010; Liebrand et al., 1986; Rilling et al., 2012; Skyrms, 2004; Wiltermuth and Heath, 2009; Yoshida et al., 2010).

In the stag hunt game, which is based on a parable of Jean Jacques Rousseau, each player has to make her or his own decision by taking the anticipated decision of the other player into account and has to make a choice between a payoff-dominant strategy and a risk-dominant strategy. The terms "payoff-dominant" and "risk-dominant" are related to the distinct Nash-equilibria incorporated in the stag hunt game: a "payoff-dominant" Nash equilibrium (see figure 1.1 at the top left of the payoff-matrix) and a "risk-dominant" Nash equilibrium (see figure 1.1 at the bottom right of the payoff-matrix). A Nash equilibrium is a solution concept where no player would be better off when changing the strategy (Nash, 1950).

As illustrated in figure 1.1, to go for the “payoff-dominant” strategy A as row player would only make sense, if one expected the column player to also cooperate by choosing the payoff-dominant strategy A as well. In this case both players would receive the highest payoff. On the other hand, if the column player would decide to go for the risk-dominant strategy B, then the row player would receive no payoff in the present example (see figure 1.1 at the top right of the payoff-matrix). If the row player is willing to go for the risk-dominant strategy B, because he expects the column player to defect mutual cooperation, the row player would earn 3 Euros in the case that the column player would have gone for the payoff-dominant strategy A or 5 Euros if the column player would have preferred the risk-dominant strategy B.

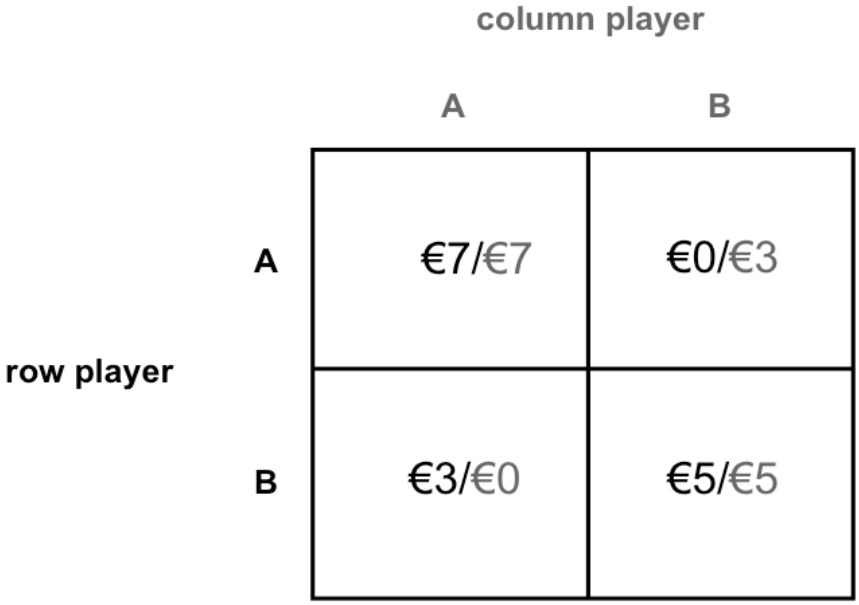

Figure 1.1 Payoff matrix of a stag hunt game

As the stag hunt game, the prisoner’s dilemma game (PD) has been used to study human cooperative behavior. The PD entails a dilemma between a strategy, which is benefical for both players, and a more self-interested strategy (see figure 1.2). If both players go for the self-interested strategy, a worse payoff would be the result for both players (see figure 1.2 at the bottom right of the payoff-matrix). Indeed, while mutual cooperation is the most efficient choice for both players in the PD, one can always achieve an even higher payoff,

when choosing the self-interested strategy which only pays off, however, when the other player decides against the self-interested strategy.

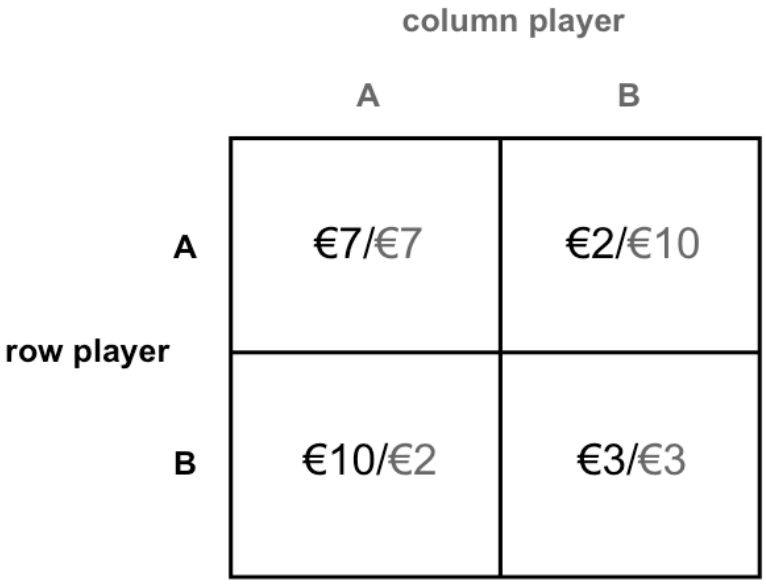

Figure 1.2 Payoff matrix of a Prisoner's dilemma game

A crucial component which might facilitate the formation of cooperative behavior is the ability to cognitively represent the mental states of the other, which is also termed "Theory of Mind" or mentalizing (see chapter 1.3 for more details). If one can anticipate the behavior of the other person better, by understanding his or her mental states such as desires, intentions and beliefs, cooperative behavior with the other person might occur. In addition, executive functions, such as the ability to decide for an action during a novel situation, as well as the monitoring of an ongoing action, may also contribute to the formation of human cooperative behavior.

1.4.1 The neural foundation of human cooperative behavior

In recent years, neuroimaging studies have revealed the neural network underlying human cooperative behavior by measuring brain activity during strategic decision-making in economic games (Decety et al., 2004; Rilling et al., 2002, 2004, 2012; Yoshida et al., 2010) or mentalizing and emotional empathy tasks (Calder et al., 2002; Gallagher et al.,

2000; Gobbini et al., 2007; Grattan et al., 1994; Grattan and Eslinger, 1989; Heberlein et al., 2004; Krämer et al., 2010; Narumoto et al., 2001; Rowe et al., 2001; Vogeley et al., 2001; Völlm et al., 2006). Moreover, neuroendocrine research, mostly employing the social neuropeptide oxytocin (OT), examined the effects of hormones on behavior and brain activity during human cooperation (Declerck et al., 2010; Rilling et al., 2012). Neuroimaging studies as well as lesion studies shed light onto the neural circuit of processes that crucially shape human cooperative behavior: In such experimental settings employing economic games, the participants were introduced to another player, who was (in most of the studies) a confederate of the experimenter, and the participant was made believe that the interactive character of the game would be achieved via a computer network.

An fMRI study by Rilling et al. (2002) incorporated the prisoner's dilemma game and observed that activity changes in ventromedial prefrontal cortex and anterior cingulate cortex were associated with the degree of cooperation. The ventromedial prefrontal cortex was also engaged in a further study by Rilling et al. (2012), but this time the increased activity pattern was based on subjects' reciprocated cooperation with a human partner when compared to a computer partner. Decety et al. (2004) reported activations in the orbitofrontal cortex (OFC) when comparing cooperative vs. competitive trials. From the known role of the OFC in reward processing (Gottfried et al., 2003; O'Doherty et al., 2001; Rolls, 2000), Decety et al. deduced that cooperation might be a socially rewarding process, reflected by an increase in the recruitment of the OFC.

Yoshida et al. (2010) investigated how belief inference during cooperative interactions is neurobiologically represented and provided first evidence for a role of the rostral mPFC in the encoding of the uncertainty of inference about the strategic choice of the other player. Yoshida et al. (2010) could thus extend the role of the rostral mPFC to the ToM subcomponent "belief inference". Additionally, they reported the dorsolateral prefrontal cortex to be crucial for the encoding of the depth of recursion in relation to the strategic choice.

With regard to social neuropeptides, intranasal OT increased cooperation in a coordination game, but its action was critically dependent on prior social contact and extrinsic cooperative incentives (Declerck et al., 2010). In addition, Declerck et al. (2010) suggested that OT may increase the willingness to cooperate by reducing fear (Kirsch et al., 2005) and enhancing reward (Depue and Morrone-Strupinsky, 2005), but only if the context is such that one would benefit from social approach. In dangerous and uncertain

situations an opposite effect might occur: OT would rather increase avoidance behavior such as risk aversion. This should result in defection rather than in cooperation.

In a further investigation using the prisoner's dilemma game to examine the effects of OT and AVP on human cooperative behavior, Rilling et al. (2012) revealed an OT dependent increase of cooperative behavior (relative to AVP) for those rounds that were preceded by unreciprocated cooperation. On the neural level, OT enhanced neural activity in the nucleus caudatus during reciprocated cooperation, which was linked to increased reward and trust from reciprocated cooperation. Moreover, OT also modulated neural activity in the left amygdala in response to reciprocated cooperation. Intranasal AVP also enhanced cooperative behavior in this study, but its effect was strongly dependent on a cooperative gesture by the other player.

In addition to OT and AVP, the neurotransmitter serotonin has recently been thought to modulate cooperative behavior in humans (Wood et al., 2006). Based on previous findings that have linked mutual cooperation to reward-related brain structures (Rilling et al., 2002, 2004) and the known role of serotonin in various aspects of reward processing (Aronson et al., 1995; Redgrave and Horrell, 1976; Sasaki-Adams and Kelley, 2001), Wood et al. (2006) predicted that a reduction of serotonin (realized by dietary tryptophan depletion) would decrease cooperative interactions while promoting defection in the prisoner's dilemma. Indeed, a reduction of serotonin level significantly decreased cooperative behavior, albeit only for the first but not the second day of the study.

1.5 Human aggressive behavior

The experience of being provoked motivates impulses for revenge. This so-called reactive aggression is in contrast to the rather cold-blooded and goal-directed instrumental aggression.

Substantial research has stressed critical factors that promote aggressive behavior and points to an interaction of genetic and environmental influences (Ghodsian-Carpey and Baker, 1987; Miles and Carey, 1997). Distinct domain-specific theories of aggression have been developed in the past (Anderson and Bushman, 2002; Bandura and Barab, 1973; Berkowitz, 1993; Mischel, 1973; Tedeschi and Felson, 1994; van Honk et al., 2010). One approach that has dominated psychological research for several decades was the frustration-aggression hypothesis (Dollard et al., 1939). According to this theoretical

approach, frustration always predicts aggressive behavior in an individual. Thus, whenever frustration occurs, it will lead to aggressive behavior in this individual, and also the occurence of aggression is always mediated by frustration. The cognitive neoassociation theory by Berkowitz (1993) later provided an update of the frustration-aggression hypothesis by stating that aggressive behavior is not only elicited by frustration, but is also caused by the presence of further unpleasant situational cues, like provocation or the experience of uncomfortable temperatures, leading to unpleasant emotions and feelings such as anxiety, anger or pain which might trigger “fight” or “flight” tendencies.

Recently, the general aggression model (GAM; Anderson and Bushman, 2002) posits that aggressive behavior is promoted by situational and personal factors, which enhance aggressive affect, aggressive cognition and arousal. Situational factors are for instance frustration, provocation, pain or the use of drugs, while personal factors could be traits, gender, beliefs and attitudes. Affective and cognitive processes mediate appraisal and decision processes that finally cause impulsive or thoughtful actions (Anderson and Bushman, 2002; Krämer et al., 2007).

Aggressive behavior can be quantified in various ways, using aggression questionnaires, behavioral ratings and neurophysiological approaches like fMRI or electroencephalography (EEG; Grafman et al., 1996; Krämer et al., 2007, 2008, 2011; Lotze et al., 2007; Mathiak and Weber, 2006; Wiswede et al., 2011). To capture the reactive character of aggression, many investigations introduced an opponent to the participant under study, which is in fact a confederate of the experimenter. Established paradigms that have frequently been used to elicit and measure aggressive behavior in the laboratory are the Taylor aggression paradigm (TAP; Taylor, 1967), the Buss aggression machine (Buss, 1966), the Point subtraction aggression paradigm (Cherek, 1981) and the Hot sauce aggression paradigm (Lieberman et al., 1999).

In the TAP, for which convergent and discriminant validity has been demonstrated (Anderson et al., 1999; Bernstein et al. 1987; Giancola and Zeichner, 1995b), reactive aggressive behavior is elicited by provoking the participant in the course of a competitive reaction time task. In winning trials participants can punish the “opponent” for instance with a loud noise or an electric shock, while they get punished by the “opponent” when losing the trial. Due to a separation of the distinct phases of the aggressive interaction into a decision phase (selection of punishment level for the opponent player) and an outcome phase (punishment is applied or received), the paradigm allows the separate consideration of the distinct emotional and cognitive processes that contribute to human aggressive behavior.

1.5.1 Neural structures and neurotransmitter systems underlying aggressive behavior

Research in humans (Blair and Cipolotti, 2000; Damasio et al., 1994; Dougherty et al., 1999; Harlow, 1848; Pietrini et al., 2000) and animals (Emery et al., 2001; Gregg and Siegel, 2001; Machado and Bachevalier, 2006; Panksepp, 1998) identified a number of brain areas important for aggression including the medial amygdala, the hypothalamus, the periaqueductal grey, the bed nucleus of the stria terminalis and the OFC. Brain imaging and brain-lesion studies specifically linked increased aggressive behavior to lesions/decreased activity in the frontal cortex (Anderson et al., 1999; Coccaro et al., 1997; Nelson and Trainor, 2007). For example, neural activation of the frontal cortex was significantly lower compared to the average baseline in those individuals scoring high on measures of reactive aggression (Soloff et al., 2003; Volkow et al., 1995). In healthy individuals, neural sites important for aggression, specifically the amygdala and the hypothalamus, receive sufficient inhibitory inputs from frontal areas. A diminished functioning of this regulation pathway may result in reduced cognitive control of aggressive behavior (Brower and Price, 2001). Individuals high in reactive aggression, for instance, demonstrated reduced activity in the OFC and exaggerated activity in the amygdala during the exposure to emotional faces, while these findings could not be seen for healthy controls (Coccaro et al., 2007). In particular the OFC has been linked to reactive aggressive behavior in an extensive line of functional and structural imaging studies involving patients with neurological alterations and healthy individuals (Anderson et al., 1999; Blair, 2004; Brower and Price, 2001; Davidson et al., 2000; Grafman et al., 1996; Raine and Yang, 2006). Besides the OFC, the mPFC has been shown to be engaged in reactive aggressive behavior (Lotze et al., 2007). Lotze et al. (2007) found specifically the dorsal part of the mPFC to be activated during participants' selection of the punishment level for the "opponent" and could further demonstrate a positive correlation with the intensity of the selected punishment. The ventral part of the mPFC in turn was activated during the exposure of videos illustrating the opponent suffering, which suggests that this part of the mPFC is more involved in emotional processes like compassion and empathy (Krämer et al., 2007; Lotze et al., 2007). Krämer et al. (2007) used a version of the TAP separating the aggressive interaction into a decision phase and an outcome phase, which allowed to study the neural events related to these phases. Moreover, the introduction of two players - an unfair (highly provocative) and a fair (low provocative) opponent - allowed the authors to disentangle neural correlates associated with general social interaction processes from those which are related to reactive aggressive behavior.

With regard to the decision phase, enhanced emotional involvement and cognitive demands after provocation were linked to a higher recruitment of brain regions previously found to be involved in negative emotions like anger or disgust: the bilateral AI and the rostral part of the ACC (Damasio et al., 2000; Dougherty et al., 1999; Phillips et al., 1997). Regarding neural activity directly linked to aggression, Krämer et al. (2007) revealed neural activations in the dorsal striatum, a brain region consistently associated with reward processing (Balleine et al., 2007; O'Doherty et al., 2004) and found a neural correlate of conflict monitoring and cognitive control, namely the ACC, to be engaged in aggression (Botvinick et al., 1999; Carter and Van Veen, 2007; Cohen et al., 2000; Milham et al., 2001; Nelson et al., 2003; Van Veen et al., 2001). For the outcome phase, the ventral striatum was linked to win vs. loss trials and it was argued that it might be rewarding for the participants to be able to avoid the opponents' punishment. Win trials against the unfair player compared to win trials against the fair player were associated with increased activity in the left amygdala, the right anterior insula and rostral and dorsal parts of the ACC. Specifically for the amygdala a growing body of evidence has emerged regarding its role in aggressive behavior stemming from studies with healthy individuals, but also neurological patients, such as psychopaths (Blair, 1995, 2001; Blair et al., 1997; Wiswede et al., 2011). Krämer et al. (2008) recently suggested that the role of the amygdala in aggressive behavior needs to be considered from two distinct perspectives. On the one hand, exaggerated amygdala activity, due to dysregulations of this brain structure, may have relevance for reactive aggressive behavior, while on the other hand a reduction of amygdala functioning may result in impaired ability of moral socializing as seen in psychopaths (Blair, 2004).

The social neuropeptides AVP and OT may play a significant (but complementary) role in aggressive behavior. Substantial work points to a promoting role of AVP in aggressive interactions (see chapter 1.2.2.2 for a detailed overview to the role of AVP in aggressive behavior) while OT seems to down-regulate aggressive behavior (DeVries et al., 1997; Harmon et al., 2002; Lee et al., 2009; Ragnauth et al., 2004, 2005; Takayanagi et al., 2005; Winslow et al., 2000). Lee et al. (2009) recently provided the first human data on the role of OT in aggressive behavior by determining the relationship between cerebrospinal fluid levels of OT and life histories of general aggression and aggression against other persons and revealed a negative correlation. Findings from recent studies point to a facilatory role of OT in affiliative behavior, by increasing trust (Kosfeld et al., 2005) and suppressing stress reactivity (Heinrichs et al., 2003), and thus may also account for OT's aggression-reducing role.

A further key role in the modulation of aggressive behavior is played by the neurotransmitter serotonin (Asberg et al., 1976; de Boer et al., 1999; Higely et al., 1996; Mehlman et al., 1994; Saudou et al., 1994; Yanowitch et al., 2011). A reduction of serotonergic activity in neural substrates of the emotional circuit, namely the prefrontal cortex and the ACC, is related to impulsive aggressiveness (New et al., 2002; Parsey et al., 2002; Seo et al., 2008; Siever et al., 1999). Although the majority of studies point to a prominent role of serotonin in aggressive behavior, controverse effects have been reported as well (Coccaro et al., 1997; Krämer et al., 2011; Manuck et al., 2006; Moss et al., 1990). For example, Krämer et al. (2011), using the TAP and an acute tryptophan depletion to assess the role of serotonin in reactive aggressive behavior, found that serotonin reduced reactive aggression in low trait-aggressive participants and showed no effect in high trait-aggressive participants. These findings in line with earlier results (Coccaro et al., 1997; Manuck et al., 2006; Moss et al., 1990) question the suggested inverse relationship between serotonin levels and aggressive behavior.

1.6 Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) is a noninvasive neuroimaging method, which allows hemodynamic changes to be visualized by using a natural contrast medium – the hemoglobin. Given that in consequence to enhanced neural activity the concentration of desoxyglobin in venous blood vessels decreases, a dephasing of the spins depending on the blood oxygenation level occurs. This contrast mechanism is called blood oxygenation level dependant (BOLD) effect (Ogawa et al., 1990). In more detail, the BOLD effect reflects a complex interaction of blood flow, blood volume and the oxygenation of the hemoglobin (Detre and Floyd, 2001). Since the augmentation of neural activity causes a local vasodilatation (elongation of blood vessels), an increase in blood flow is initiated that in turn leads, on the one hand, to an increase of the oxygenized hemoglobin over the metabolic need and, on the other hand, to a diminution of the desoxyhemoglobin. The resulting decrease of desoxyhemoglobin in the blood vessels provokes a change in the magnet field resulting in an increase in BOLD signal in T2*-weighted imaging sequences (Bandettini and Wong, 1997). The BOLD signal can be described with the hemodynamic response function (HRF), which is subdivided into three different components. The first is the “initial dip”, a reduction of the signal based upon an increase of the desoxyhemoglobin caused by an increase of oxygen consumption of active neurons. This is followed by an “overshoot” – a strong increase of the BOLD signal,

imposed by an increase of the oxyhemoglobin over the metabolic need. This overshoot is finally followed by a slow decline of the BOLD signal up to its initial value, which is reached after approximately 24 s (Heeger and Ress, 2002). Moreover, Friston et al. (1998) observed a minor undershooting of the HRF before reaching the base level. It has been proven that the activations identified with fMRI are directly related to neural activity and reflect the synaptic information flow that arises before neurons increase their fire rate (Logothetis et al., 2001, 2002, 2003).

The major advantage of fMRI is the high spatial resolution that can be reached dependent on the used magnetic field strength (Jäncke, 2005). However, in contrast to the EEG that allows a high temporal precision, a limitation of fMRI is the relatively poor temporal resolution due to the latency of the neurovascular coupling (Matthews, 2001).

1.7 Research aims

The present thesis aims to investigate the role of AVP in modulating various forms of human social behavior with a particular emphasis on the neural level measured by fMRI. In the first study, the effect of intranasally administered AVP on the neural basis of automatic emotional empathy and mentalizing processes is studied (chapter 2), which is realized by a presentation of pictures that are varied in their emotional and social content. It is predicted that AVP would increase mentalizing processes in humans based on its known role to modulate social bonding behavior. A successful relationship presumes that we are able to predict and understand the mental states of our partner. This might be, amongst other factors, mediated by AVP acting on brain sites belonging to the traditional mentalizing circuit comprising the medial prefrontal cortex, the superior temporal sulcus and the precuneus. Furthermore, it is hypothesized that AVP would increase neural activity in brain sites that have been related to emotional empathy, namely the ventrolateral- and the ventromedial prefrontal cortex. A functional connectivity analysis using a method introduced by Rissman (Rissman et al., 2004), is used to delineate neural correlates of empathy and mentalizing on a network level. In a second study (chapter 3), the effect of AVP on behavioral and neurophysiological correlates of human cooperative behavior is studied in a stag hunt game, which required a decision between a cooperative and a non-cooperative strategy. Here, it was predicted that AVP would increase human cooperative behavior based on its known role in social bonding behavior. Furthermore, it was hypothesized that AVP would only increase human cooperative behavior when the incentive to cooperate is high and the individual can thus benefit from it. The third

experiment (chapter 4) addresses the impact of AVP on reactive aggressive behavior and its neural correlates. In light of AVP's characteristic role in aggressive behavior evidenced by studies with animal models, it was hypothesized that AVP would also promote human aggressive behavior by increasing the selection of higher punishments in response to a provoking opponent. On the neural level, this effect might be reflected by enhanced activity of brain sites previously related to anger, namely the AI and the ACC.

Chapter 2

Vasopressin modulates neural responses related to emotional stimuli in the right amygdala

2.1 Introduction

Social cognitions are an essential precondition for smooth social interactions in humans (Decety, 2010; Decety and Ickes, 2009; Frith and Frith, 2012). They enable us to predict and understand the feelings, intentions and motivations of others (Bernhard and Singer, 2012), a set of abilities often conceptualized as empathy. Eisenberg et al. (1998, p.702) defined empathy as "an affective reaction that results from the apprehension or comprehension of another's emotional state or condition that is identical or very similar to what the other person is feeling or would be expected to feel". Empathy involves an affective and a cognitive component (Goubert et al., 2009). The affective component pertains to shared feelings, whereas the cognitive component refers to the explicit reasoning about another individual's emotional state while maintaining the distinction between oneself and others (Decety and Ickes, 2009). The cognitive component may be referred to as mentalizing and is related to the "ToM" concept. It enables humans to cognitively represent the mental states of others, including their emotional states, without becoming emotionally involved. A theoretical framework that integrates the emotional and cognitive component of empathy is the perception-action model (PAM) by Preston and de Waal (2002). Based on previous research showing that perception and action rely on shared cortical networks, the PAM postulates that the perception of another person's emotional state activates one's own representation of that observed state, situation and person automatically. In a recent investigation, Krämer et al. (2010) provided evidence for the PAM's predictions regarding the involvement of cortical brain sites in automatically elicited empathic processes. In their study, emotional empathy led to increased BOLD-responses in ventromedial and ventrolateral prefrontal cortical areas. Lesion studies (Blair and Cipolotti, 2000; Hornack et al., 2003) and investigations using functional MRI (Baron-Cohen et al., 1994) have already shown an involvement of these brain regions in emotional processing. In contrast to other studies (Meyer-Lindenberg et al., 2009; Völlm et al., 2006), Krämer et al. found no activations in the amygdala related to emotional empathy. A possible reason for the missing amygdala response might have been that the stimuli of Krämer et al. lacked internal facial features in order to give room for the individual subject's interpretation. This fact might have made the stimuli less emotionally salient, even though such stimuli are used to elicit emotional responses related to

attachment in psychotherapy (George and West, 2001). Krämer et al. (2010) further reported that cognitive aspects of empathy led to enhanced activations in areas previously linked to mentalizing, namely the STS, precuneus and mPFC. These brain sites are known to be active during the observation of social interactions (Iacoboni et al., 2004), when thinking about social relations (Abraham et al., 2008; Kumaran and Maguire, 2005), or, in case of the STS, when putting oneself into other people's shoes (Baron-Cohen et al., 1994; Fletcher et al., 1995; Gallagher et al., 2000; Hynes et al., 2006; Marjoram et al., 2006; Rilling et al., 2004; Saxe and Kanwisher, 2003; Saxe and Powell, 2006; Völlm et al., 2006; Wolf et al., 2010).

In diverse mammalian species the neuropeptide AVP is of importance for the regulation of social behavior. It is mainly synthesized in the paraventricular and supraoptic nuclei of the hypothalamus (Bos et al., 2012; Meyer-Lindenberg et al., 2011). It is known from studies in monkeys that a high density of Vasopressin V1 receptors can be found in the hypothalamus itself, the brain stem, the lateral septum, and the nucleus accumbens, but also in the hippocampus, the amygdala, and in parts of the extended amygdala complex, the bed nucleus of the stria terminalis (Loup et al., 1991; Young et al., 1999). At the behavioral level, AVP is linked to the formation of social bonds (Bielsky and Young, 2004; Goodson and Bass, 2001; Lim and Young, 2006), social recognition (Bielsky and Young, 2004; Dantzer et al., 1987), social communication (Albers et al., 1992; Ferris et al., 1984; Winslow and Insel, 1991), and protective aggression (Bosch, 2011). In humans, the mechanisms of AVP action are poorly understood (McCall and Singer, 2012; Meyer-Lindenberg et al., 2011). However, there is increasing evidence that AVP, together with the neuropeptide oxytocin and the steroids testosterone and estradiol, mediates the regulation of complex human social behavior (Bos et al., 2012; van Anders et al., 2011). For example, several studies have shown a relationship between polymorphisms of the human AVP receptor gene AVPR1a and social behavior (Ebstein et al., 2010) like pair bonding in men, altruistic behavior (Avinun et al., 2011), or prosocial decisions in economic games (Knafo et al., 2008). Moreover, Coccaro et al. (1998) reported a positive correlation between cerebrospinal fluid AVP levels and life histories of general aggression and aggression against other persons, an effect more pronounced in men than women. AVP seems to act as the "prerequisites" for social interaction, affecting cognitive processes like social perception, social recognition, and social communication (Albers, 2012; Bos et al., 2012). In their initial study, Thompson et al. (2004) investigated processes related to emotional social communication. In male participants, intranasally administered AVP led to an increase of EMG responses to neutral faces to a level comparable to that observed for angry faces in the placebo group, indicating that AVP alters the interpretation of social stimuli, which are taken as if they were threatening. In a

subsequent investigation (Thompson et al., 2006), AVP enhanced agonistic men's facial motor patterns in response to faces of unfamiliar men and decreased the perception of the friendliness of those faces. In women, however, AVP stimulated affiliative facial motor patterns in response to faces of unfamiliar women and increased perceptions of the friendliness of those faces. By contrast, men treated with AVP showed impairments in the recognition of negative emotions while the perception of positive emotions was unaffected (Uzefosky et al., 2012). Guastella et al. (2010, 2011) reported enhanced encoding under AVP treatment for social-emotional and sexual stimuli. This effect was found for stimuli of negative and positive valence, suggesting that AVP enhances the processing of social information independent of the stimulus valence.

An important structure in the processing of socially and emotionally relevant information, that harbors abundant vasopressin V1 receptors (Huber et al., 2005; Veinante and Freund-Mercier, 1997), is the amygdala. AVP may thus have an indirect influence on cortical structures via the amygdala's strong connections with the ACC, the ventral part of the prefrontal cortex and the OFC, all of which have been associated with socio-emotional functions. The OFC is also connected to the ACC and the superior temporal cortex, forming a network crucial for the processing of higher order emotions, like empathizing and mind-reading (Bos et al., 2012; Hein and Knight, 2008; Singer et al., 2004).

By combining the application of AVP and functional MRI, Zink et al. (2010) provided first insights regarding the target structures of AVP during the processing of negatively valenced social stimuli in humans. Although they did not reveal a direct impact of AVP on amygdala activity during the processing of fearful faces, Zink et al. (2010) reported an altered functional connectivity between the amygdala and prefrontal brain regions under AVP treatment. Moreover, AVP also neutralized a deactivation of the ACC during the processing of fearful faces, which was seen in the placebo condition. In a second investigation, Zink et al. (2011) described an effect of AVP on activations of the TPJ, a brain site related to social recognition. They deduced that AVP seems to shift the meaning of socially relevant information such that unfamiliar social information is more readily categorized. In Rilling et al. (2012), intranasally administered AVP resulted in enhanced cooperation in response to cooperative signs by the partner. These behavioral effects were accompanied by increased activations in the extended amygdala, namely the bed nucleus of the stria terminalis.

To further investigate the impact of AVP on the amygdala and related neural networks involved in the processing of social cognitions and emotion, we used the stimuli of Krämer et al. (2010) in an fMRI study with male participants, who received either intranasal AVP or a Placebo in a randomized, double-blind manner. In order to disentangle, whether AVP's impact is more related to the processing of social or to emotional information, our

stimuli comprised pictures illustrating either a social interaction or a single person and were additionally varied in their emotional valence (negative and neutral content). Thus, the used picture set resulted in 4 different categories: EMOT-TWO (social interaction, emotionally valenced), NEUT-TWO (social interaction, emotionally neutral), EMOT-ONE (single person, emotionally valenced), NEUT-ONE (single person, emotionally neutral). In order to enhance participants' thinking about the presented stimuli, it was their task to think about how they would feel in the situation depicted on the picture. In case of pictures depicting two persons, they had to choose one person.

In light of the purported function of AVP in social bonding behavior and AVP's known involvement in the processing of social and emotional information, we predicted that AVP would increase neural activity in "mentalizing" related brain regions, such as the mPFC, the STS and the precuneus. We also predicted that AVP will strengthen the functional connectivity of these neural circuits. Since the processing of socially relevant information implies to comprehend emotional cues, we assumed AVP to influence brain sites related to the processing of affective relevant information. Based on the reported hypothesis (Bos et al., 2012), that AVP's influence on human behavior is mediated via the amygdala, we expected to find increased activations during the processing of emotional information under AVP treatment in the amygdala, but also in brain sites related to emotional empathy, e.g., the ventromedial and ventrolateral prefrontal cortex.

2.2 Methods

2.2.1 Participants

Fourty-two healthy men (age=19-39 years, mean=25.8 (AVP: age=21-39, mean=26.4; Placebo: age=19-37 and mean=25.2)) participated in the study after giving informed consent. Statistical comparison revealed no age difference between groups ($t(37)=0.921$, $p=0.363$). All participants were right-handed and reported to be free of any psychiatric and neurological disorder, kidney disease, cardiovascular problems, asthma and migraine. Three subjects had to be excluded from further analysis because of extensive head movements in the scanner (2) or cardiovascular problems while lying in the scanner (1), leaving 39 subjects (21/18 in the AVP/Placebo-groups) for the analyses. The study was approved by the ethical committee of the University of Magdeburg.

2.2.2 Drug administration

Subjects received either a nasal spray with 20 IU's of AVP or placebo in a double-blind manner. Nasal sprays were randomly assigned and self-administered by the subjects. According to previous investigations examining the time course of cerebrospinal fluid vasopressin levels (Born et al., 2002), AVP was given 15 min before the experiment. Subjects did not report alterations in water retention at the end of the experiment. All scanning sessions were performed between 8 am and 6 pm.

2.2.3 Stimulus presentation

Black-and-white drawings from Krämer et al. (2010) without facial features to avoid neural activity elicited by facial expressions (Adolphs et al., 1999; Adolphs and Tranel, 2003; Sprengelmeyer et al., 1998) were presented. Two of the four conditions comprised social situations (two persons) having either a negative or neutral emotional connotation (EMOT-TWO and NEUT-TWO; figure 2.1). In the other two conditions either one person in an emotionally negative (EMOT-ONE) or in an emotionally neutral situation (NEUT-ONE; figure 2.1) were shown. Depicted emotions comprised anger, sadness, pain and anxiety. Pictures were presented in pseudo-randomized order in four runs. Each run comprised 24 pictures (six pictures per condition) with no more than two successive instances of a particular condition. Trial duration was 16 s with a picture presentation of 6 s followed by a fixation cross (10 s). Subjects were instructed to watch the pictures carefully and to think about how they would feel in the depicted situation. In the case of two persons on a picture, they were instructed to choose one of the persons and to put themselves into the shoes of this person. After each run and without concurrent scanning, eight of the twenty-four pictures, that had been presented during the previous run, were shown again to the subjects. Participants had to describe in one sentence how they would feel in the situation of the person(s) illustrated on the pictures. Again, in case of pictures with two persons, they had to pick one person and describe their feelings pertaining that person's situation.

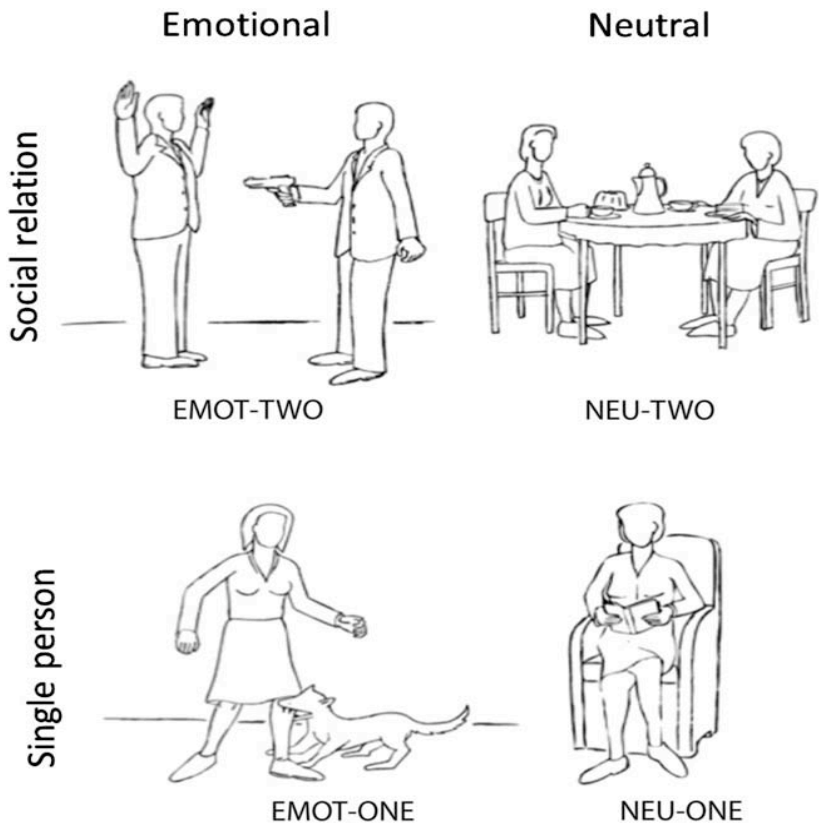

Figure 2.1 Example stimuli for the four experimental conditions.

2.2.4 Questionnaire

In order to control for potential trait differences regarding interpersonal reactivity, participants completed the German version of the Interpersonal Reactivity Index (IRI; Paulus, 2009) after scanning, i.e. about 120 minutes after administration of AVP or placebo. At this time, plasma AVP levels have returned to baseline according to Pietrowsky et al. (1996), and thus the IRI results were taken as an index of the stable (trait) interpersonal reactivity of the participants. The IRI comprises four 7-item subscales: *Perspective taking* is the ability to capture the psychological perspective of another person and is thought to involve several cognitive, but not affective, empathic processes. The *fantasy* scale reflects the tendency to put oneself into the role and behavior of characters from novels or movies. The third subscale - *empathic concern* - measures the sympathy and care for others, whereas the *personal distress* scale taps into feelings of inner restlessness and uneasiness when confronted with extreme situations such as an

emergency. Statistical testing revealed no difference between groups for all subscales of the interpersonal reactivity index (all $t<0.2$ and $p>0.27$). The mean [SD] scores of the normative/AVP/placebo groups were: *Perspective taking* subscale: 16.78 [4.72]/19.7 [3.6]/19.4 [3.4]; *Fantasy* subscale: 15.73 [5.6]/15.3 [3.9]/16.5 [4.3]; *Empathic concern* subscale: 19.04 [4.21]/18.3 [2.1]/18.8 [4.3]; *Personal distress* subscale: 9.46 [4.55]/9.6 [3.1]/10.7 [4.1].

2.2.5 fMRI-data acquisition

Functional (Gradient-Echo-EPI-sequence; TR=2000 ms; TE=30 ms; FOV=224 mm; flip angle=80°; matrix=64x64; slice thickness=3.5 mm; interslice gap=0 mm) and structural images (T1-weighted MPRage: 256 x 256 matrix; FOV=256 mm; 192 1mm sagittal slices) were recorded with a 3-T Siemens Magnetom Trio syngo MR 2004A Scanner. In each of the four runs, 384 volumes were obtained, each comprising 32 transversal slices (3.5 x 3.5 x 3.5 mm^3) parallel to the anterior and posterior commissure (AC-PC).

2.2.6 fMRI-data analysis

Standard fMRI analysis

Data were analyzed using SPM5 (Wellcome Department of Imaging Neuroscience, University College London). Preprocessing comprised slice time correction, motion correction, coregistration, spatial normalization, high pass temporal filtering (128 s), and spatial smoothing (Gaussian Kernel=8 mm FWHM). In order to minimize signal-correlated movement effects, estimated movement parameters (x, y, z, pitch, roll, and yaw) were included in the statistical analysis. In an event-related design the hemodynamic responses were modeled on the basis of a GLM with the standard hemodynamic response function for each subject. The events EMOT-TWO, EMOT-ONE, NEUT-TWO, and NEUT-ONE were specified time-locked to their onsets. In order to identify the main effects of the pictures' emotional and social content, contrast maps were calculated comprising the following comparisons: the emotional conditions (EMOT-TWO and EMOT-ONE) were contrasted against the neutral conditions (NEUT-TWO and NEUT-ONE) and the social conditions (EMOT-TWO and NEUT-TWO) against the single conditions (EMOT-ONE and NEUT-ONE). These contrasts were finally entered into one-sample t-tests for AVP and Placebo groups separately. The significance level for these contrasts was set to $p<0.01$ (false discovery rate corrected, FDR; except for the negative vs. neutral contrast in the Placebo group: $p<0.05$ (FDR)) and a voxel level threshold of 10 was applied to the data. To reveal the interaction of AVP treatment and automatic emotional empathy and

mentalizing processes, between group comparisons were performed by conducting two-sample-t-tests with the contrasts social > single and negative > neutral. Regarding the contrast negative > neutral, the between-group comparison AVP > Placebo revealed increased activity in the right amygdala and the right parahippocampal gyrus when lowering the voxel level threshold to 5. Since the amygdala is a target region for AVP and of crucial importance for the processing of emotional and social information, the interaction of the right amygdala was further investigated by a Region-of-interest (ROI)-analysis using the functional cluster from the negative > neutral contrast of this latter brain site. Percent signal changes were extracted for each participant using rfx-plot (Gläscher, 2009). The resulting percent signal changes were entered into a 2x2x2 repeated-measures ANOVA with the three factors drug (AVP, Placebo), emotion (negative, neutral drawings), and social relation (two persons, single person).

Functional connectivity analyses

The functional connectivity method proposed by Rissman et al. (2004) was applied to examine how the interaction between the amygdala and other brain regions were changed under AVP treatment when processing emotionally relevant visual information. The analytical procedure based on the assumption, that if two regions interact within a cortical network, their activation patterns should be strongly correlated. This analysis was implemented on the basis of another GLM using separate covariates to model BOLD responses of a particular stage (pictures) in each single trial. For each participant, parameter estimates (beta values) of cues were extracted to form a set of cue-specific beta-series. Initially, a beta-series was calculated for the functional cluster of the right amygdala from the between-group comparison AVP > Placebo (negative vs. neutral condition). Afterwards, the beta-series averaged across the functional amygdala ROI voxels were correlated with the beta values of every other voxel in the brain (see Camara et al., 2011; Ye et al., 2010). Correlation maps were calculated for every condition and for each subject of both groups separately and finally normalized by means of an arc-hyperbolic tangent transform. The subsequent statistical test for this normalized correlation maps was performed similar to the standard SPM BOLD analysis. The normalized maps were entered into a flexible factorial design matrix of SPM5 (factors: subjects, group (AVP, Placebo) and condition (EMOT-TWO, NEUT-TWO, EMOT-ONE, NEUT-ONE)). Statistical threshold was set to $p<0.001$ (uncorr.). In order to further investigate the group differences within significant cluster, subsequent ROI-analyses were performed. Accordingly, correlation values of the functional cluster in the medial prefrontal

cortex and the inferior parietal lobule were extracted for each participant and entered into a 2x2x2 repeated-measures ANOVA with the three factors drug (AVP, Placebo), emotion (negative drawings, neutral drawings) and social relation (drawings depicting a social relation, drawings showing a single person). Regarding the mPFC, both functional clusters were initially combined by means of marsbar (Brett et al., 2002) before extracting the correlation values.

2.3 Results

2.3.1 fMRI-data

In both groups the contrast two > single person (table 2.1; figure 2.2, left column) revealed increased activation in the superior and the middle temporal cortex and the precuneus. These regions have previously been associated with social cognitive processes and ToM. Furthermore, both groups showed increased activity in the middle frontal gyrus. By decreasing the significance level to $p<0.05$ (FDR), the medial frontal cortex, an area associated to ToM, was revealed in the AVP group as well as in the placebo group (table 2.1).

Whilst the contrast two > single person revealed many similar activations in the AVP and placebo group, differences emerged for the emotion contrast (negative > neutral). In general, the activations for the AVP group were statistically stronger (table 2.2; figure 2.2, right column) and significant differences between the negative and neutral condition were seen in the inferior parietal lobule, the middle temporal gyrus, the supramarginal gyrus, the inferior and middle frontal gyrus and the insula. The AVP group showed an enhanced activation of the amygdala, which was not seen in the placebo group, not even when lowering the significance level to $p<0.005$ (uncorr.). For the negative > neutral contrast, the middle temporal cortex, the supramarginal gyrus and the middle frontal gyrus showed increased neural activity in the placebo group as well. In contrast to the AVP group, increased neural activity was also observed in the fusiform gyrus, the cuneus and the inferior temporal gyrus. To delineate the impact of AVP on the processing of social information, between-group comparisons for the contrast social > single were calculated. This revealed increased neural activity for AVP in the insula and the inferior and middle frontal gyrus, the posterior cingulate gyrus and the precentral cortex (see figure 2.3 and table 2.3). No brain region survived the threshold $p<0.001$ (uncorr.) for the reverse contrast (Placebo > AVP).

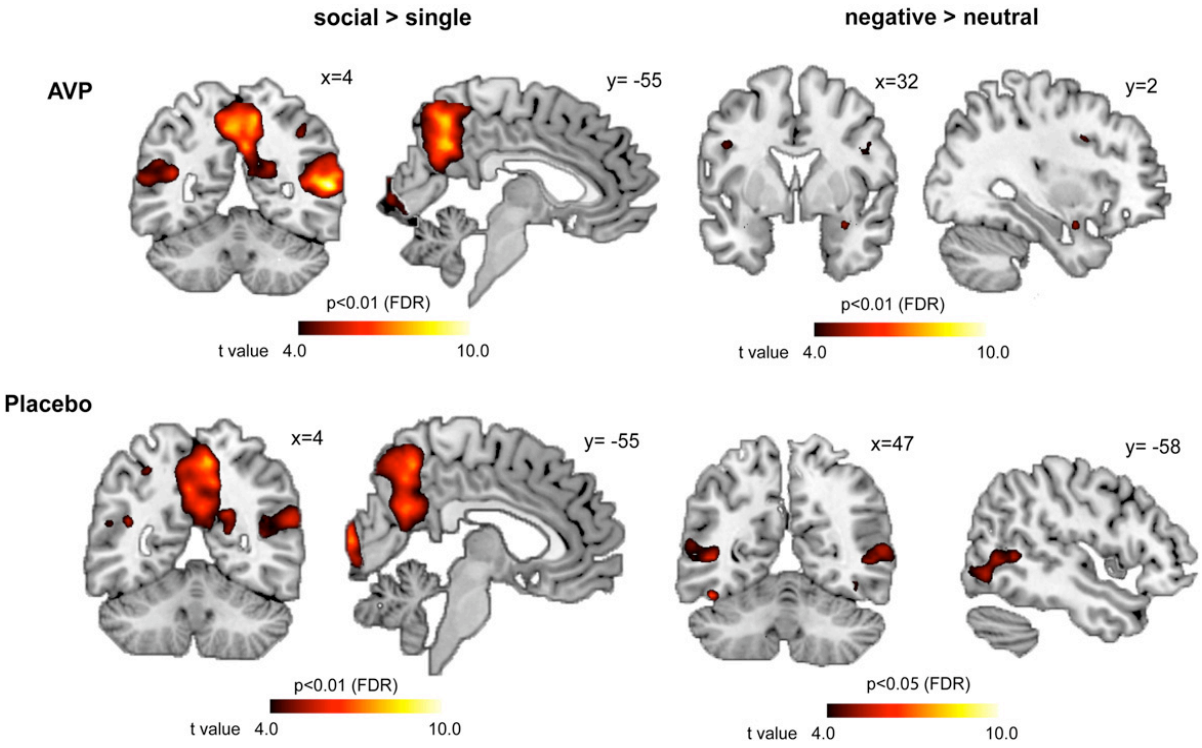

Figure 2.2 Brain activations in the contrast two persons > single person and negative > neutral for the AVP and placebo group, respectively. Contrasts for the AVP group and the placebo group were FDR-corrected p<0.01, the placebo group's contrast negative > neutral was FDR-corrected p<0.05; for all groups cluster threshold=10 voxel; Contrast social > single: increased activations in the cuneus and the superior and mid-temporal gyrus in both groups. Contrast negative > neutral: increased activation in the parietal cortex and the amygdala under AVP-treatment; under placebo increased activations in the middle temporal gyrus.

Table 2.1. Brain regions indicating increased activity when contrasting drawings showing a social relation vs. drawings illustrating a single person. Hem=hemisphere, BA=Brodmann area, xyz=MNI-coordinates, T=t-values, size=cluster size. Cluster threshold=10.

		social > single					
Hem		**BA**	**x**	**y**	**z**	**T**	**size**
AVP p<0.01 (FDR)							
L	Calcarine	17	-6	-94	-4	14.88	2297
L	Superior occipital gyrus	18	-14	-92	2	10.15	
L	Superior occipital gyrus	17	-10	-98	8	9.94	
R	Middle temporal gyrus	39	54	-56	10	10.60	2287

R	Middle temporal gyrus	37	54	-64	14	8.97	
R	Superior temporal gyrus		58	-50	16	7.96	
L	Middle temporal gyrus		-50	-72	14	9.16	1511
L	Middle temporal gyrus		-46	-66	20	8.10	
L	Superior temporal gyrus	22	-38	-56	18	6.3	
L	Precuneus		-6	-60	50	9.11	3396
R	Precuneus	7	10	-56	52	8.89	
R	Precuenus	7	4	-58	36	8.2	
R	Middle frontal gyrus	9	36	20	34	6.78	
R	Middle frontal gyrus		36	8	44	5.89	
L	Precentral gyrus	6	-30	-6	54	5.87	145
L	Precentral gyrus	6	-30	-8	46	5.21	
R	Angular gyrus	7	40	-62	50	5.17	158
R	Inferior parietal gyrus		38	-54	42	5.13	
R	Angular gyrus		40	-70	52	4.72	
R	Supramarginal gyrus	40	46	-46	42	4.74	21
L	Superior temporal gyrus		-64	-40	12	4.2	10
R	Middle frontal gyrus		32	32	44	4.16	12
p<0.05 (FDR)							
R	Medial prefrontal cortex	25	0	26	-2	4.53	22
R	Medial prefrontal cortex	10	20	58	4	4.14	39
Placebo p<0.01 (FDR)							
R	Lingual gyrus		12	-82	-10	10.98	1367
R	Cuneus		8	-94	6	9.62	
L	Cuneus	18	-16	-96	18	8.39	
R	Superior temporal gyrus	13	46	-46	20	9.18	991
R	Superior temporal gyrus		46	-54	18	7.43	
R	Superior temporal gyrus		56	-46	20	7.31	
R	Precuneus		12	-60	42	8.74	2233
R	Precuneus	7	8	-54	54	8.30	
R	Precuneus	7	10	-62	50	7.86	
L	Middle temporal gyrus		-46	-72	14	7.01	405
L	Middle temporal gyrus	19	-54	-76	14	6.99	
L	Superior temporal gyrus	22	-40	-56	20	5.66	
L	Superior parietal lobule	7	-30	-58	50	5.63	27
R	Middle temporal gyrus		56	-12	-18	5.18	12
p<0.05 (FDR)							
R	Medial prefrontal cortex	11	4	60	-14	3.94	30
R	Medial prefrontal cortex	10	8	62	30	3.55	22
R	Medial prefrontal cortex		4	62	38	3.52	

Table 2.2. Brain regions showing increased activity when contrasting negative vs. neutral drawings. Hem=hemisphere, BA=Brodmann area, xyz=MNI-coordinates, T=t-values, size=cluster size. Cluster threshold=10.

		negative > neutral					
Hem	**Brain region**	**BA**	**x**	**y**	**z**	**T**	**size**
AVP p<0.01 (FDR)							
L	Inferior parietal lobule	40	-60	-28	32	9.46	549
L	Inferior parietal lobule		-62	-42	26	7.50	
L	Supramarginal gyrus		-60	-50	28	6.93	
R	Inferior parietal lobule	40	64	-44	24	9.01	1414
R	Middle temporal gyrus		48	-62	10	7.91	
R	Middle occipital gyrus		48	-70	6	7.59	
R	Amygdala		32	2	-18	5.29	80
R	Middle frontal gyrus	17	40	14	32	7.10	
R	Middle frontal gyrus		34	8	34	5.55	277
L	Superior temporal sulcus		-56	-56	10	6.93	545
L	Middle temporal gyrus	39	-54	-70	8	6.60	
L	Superior temporal sulcus		-46	-66	4	6.51	
L	Insula		-40	-6	-6	6.25	80
L	Insula		-30	10	-16	6.14	34
L	Inferior frontal gyrus		-48	8	18	6.06	41
L	Precentral gyrus	6	-46	0	30	4.99	14
Placebo p<0.05 (FDR)							
L	Fusiform gyrus	37	-42	-54	-18	8.16	93
L	Middle temporal gyrus		-44	-54	4	6.91	412
L	Middle temporal gyrus	39	-46	-70	8	5.14	
L	Middle temporal gyrus		-50	-62	4	5.09	
R	Cuneus	18	10	-92	12	6.02	92
R	Middle temporal gyrus		52	-60	4	5.85	503
R	Middle temporal gyrus		56	-52	4	5.74	
R	Inferior temporal gyrus	37	48	-68	-4	5.71	
R	Inferior temporal gyrus		40	-52	-12	5.71	90
L	Superior occipital gyrus	18	-6	-100	8	5.36	44
R	Lingual gyrus	18	20	-74	-8	5.27	20
L	Precentral gyrus	6	-42	0	50	5.23	23
L	Middle frontal gyrus		-26	-4	52	4.91	11
L	Middle occipital gyrus		-20	-82	16	4.88	14
L	Inferior frontal gyrus		-40	14	32	4.67	13
L	Supramarginal gyrus	21	-66	-26	30	4.59	17
L	Supramarginal gyrus	40	-64	-36	28	4.23	
L	Supramarginal gyrus		-58	-50	26	4.36	11

AVP > Placebo social > single

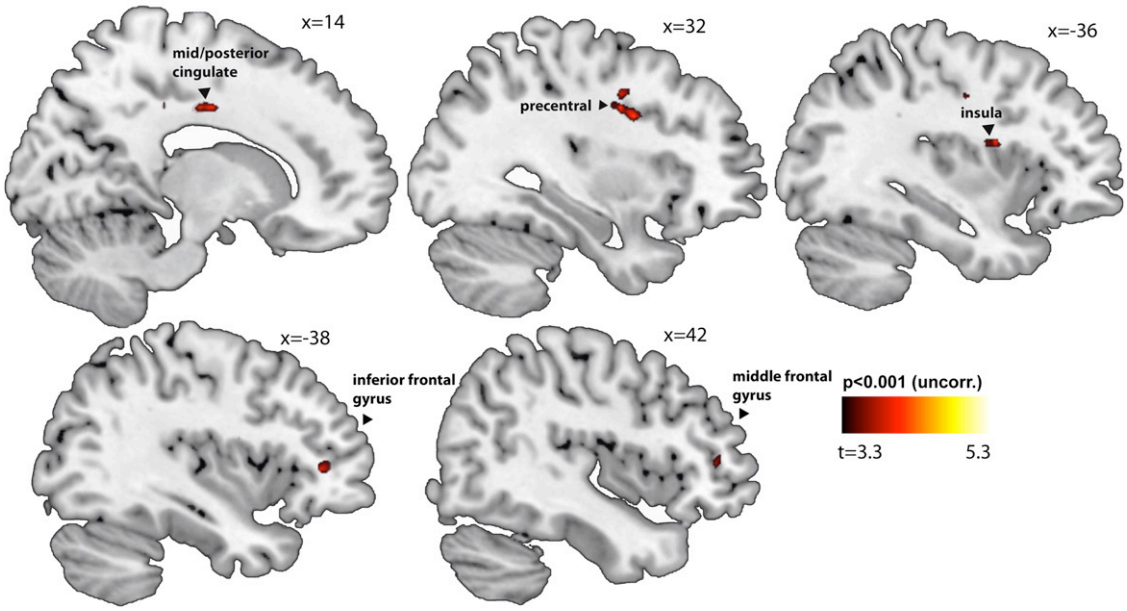

Figure 2.3 Between-groups comparison AVP > Placebo revealed for the first level main effect contrast social > single increased hemodynamic response in the depicted cortical brain sites. p<0.001 (uncorr.); cluster threshold=10 voxel.

With regard to AVP effects on emotional empathy processes, a between group comparison (AVP > Placebo) indicated increased activity in limbic structures such as the right amygdala and the right parahippocampal cortex (see table 2.4). The between-group comparison Placebo > AVP revealed no brain region surviving a significance level of p<0.001 (uncorr.). A ROI-analysis of the functional cluster in the right amygdala employing a 2 (AVP vs. placebo) x 2 (emotion vs. neutral) x 2 (social vs. single) ANOVA, revealed a significant drug x emotion interaction [F(1,39)=13.4, p=0.001; figure 2.4] and a significant emotion effect [F(1,39)=4.45, p=0.042], but no social main effect [F(1,39)=0.64, p=0.428] or drug x social [F(1,39)=0.62, p=0.435] and drug x emotion x social interaction [F(1,39)=0.06, p=0.802]. A similar ROI analysis for the right parahippocampal gyrus resulted in a main effect of emotion [F(1,39)=10.36, p=0.003] and a drug x emotion interaction [F(1,39)=13.27, p=0.001]. Additionally, the drug x social interaction [F(1,39)=1.12, p<0.001] became also significant. The main effect social [F(1,39)=1.15, p=0.29] and the 3-way interaction [F(1,39)=1.12, p=0.297] were not statistically significant. As illustrated in figure 2.4, the interaction plot indicates that AVP acts on the processing of emotional content, as the largest signal changes were seen for pictures with negative content.

Table 2.3. Brain regions showing increased activity for the comparison AVP > Placebo with regard to the contrast social > single. Hem=hemisphere, BA=Brodmann area, xyz=MNI-coordinates, T=t-values, size=cluster size. Cluster threshold=10.

		AVP > Placebo	**social > single**				
Hem	**Brain region**	**BA**	**x**	**y**	**z**	**T**	**size**
p<0.001 (uncorr.)							
R	Posterior cingulate gyrus	24/31	16	-14	38	5.61	80
L	Precentral gyrus	6	-28	-14	38	4.55	42
R	Precentral gyrus	6	32	-2	34	4.47	69
L	Insula		-36	4	18	4.32	10
L	Inferior frontal gyrus		-46	10	8	4.29	13
L	Inferior frontal gyrus		-38	36	4	4.23	45
L	Inferior frontal gyrus		-44	42	6	4.05	
L	Insula		-30	28	14	3.99	22
R	Middle frontal gyrus		42	40	6	3.71	12
R	Middle frontal gyrus	46	46	44	12	3.44	16

Table 2.4. Neural correlates indicating increased activity for the comparison AVP > Placebo and the contrast negative > neutral. Hem=hemisphere, BA=Brodmann area, xyz=MNI-coordinates, T=t-values, size=cluster size. Cluster threshold=5.

		AVP > Placebo	**negative > neutral**				
Hem	**Brain region**	**BA**	**x**	**y**	**z**	**T**	**size**
p<0.001 (uncorr.)							
R	Parahippocampal gyrus		32	-40	8	3.63	5
R	Amygdala		32	2	-18	3.57	6

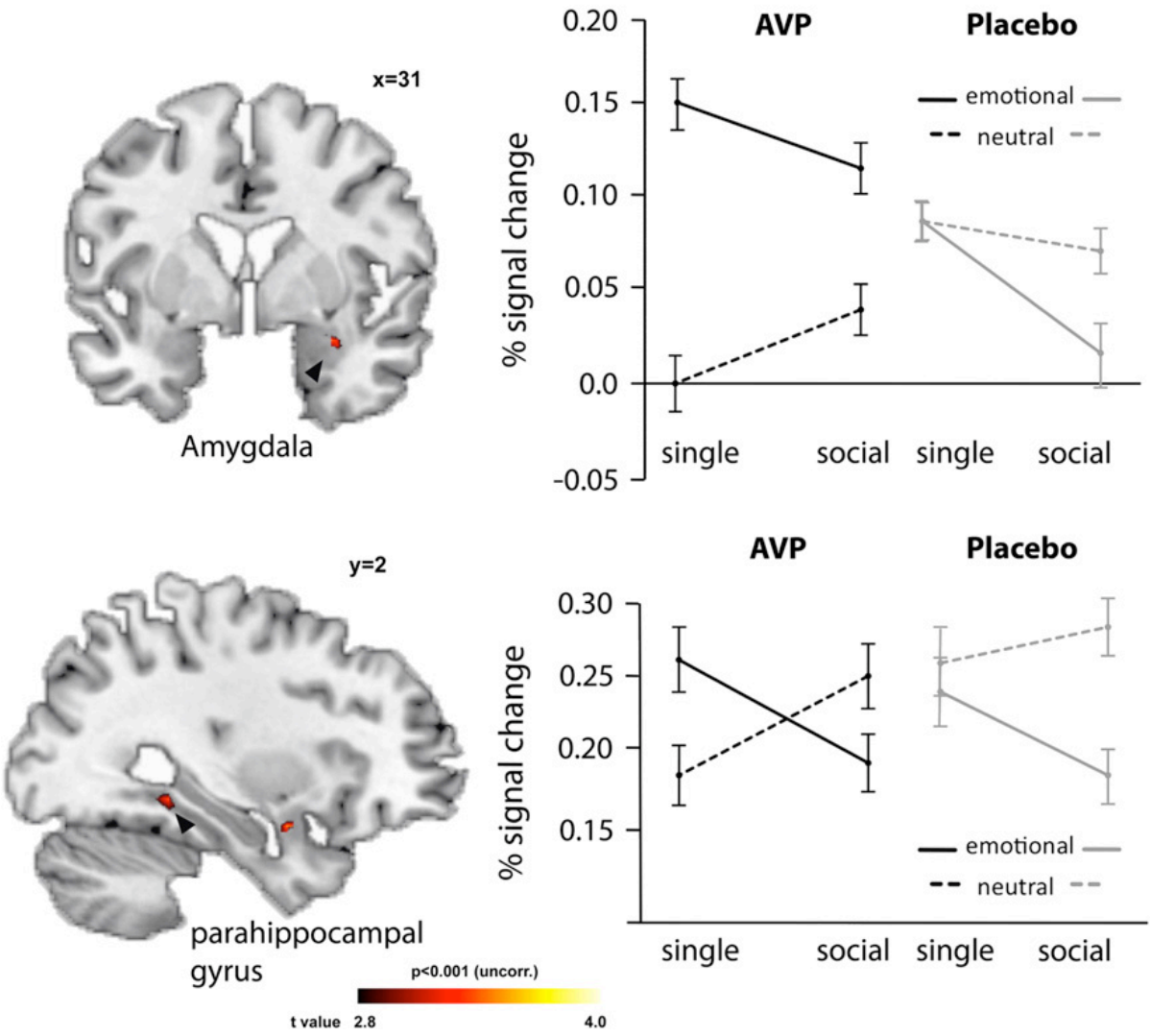

Figure 2.4 Active brain sites for the between-groups contrast AVP > Placebo of the first level main effect negative > neutral. The interaction plots depict the percent signal changes of the functional ROIs in the amygdala and the parahippocampal gyrus. p<0.001 (uncorr.); cluster threshold=5 voxel.

Table 2.5. Brain regions indicating different functional connectivity with the right amygdala for the main effects social > single and negative > neutral in the AVP group. Hem=hemisphere, BA=Brodmann area, xyz=MNI-coordinates, T=t-values, size=cluster size. Cluster threshold=10.

social > single

Hem	Brain region	BA	x	y	z	T	size
AVP p<0.001 (uncorr.)							
R	Inferior parietal lobule		50	-42	26	4.20	13
R	Cuneus	18	10	-76	12	4.07	94
R	Cuneus	30	16	-70	10	3.32	
R	Precuneus		-8	-56	58	3.52	13

negative > neutral

Hem	Brain region	BA	x	y	z	T	size
AVP p<0.001 (uncorr.)							
R	Cerebellum		28	-68	-36	4.75	268
R	Cerebellum		24	-80	-38	4.44	
R	Cerebellum		26	-60	-38	4.11	
R	Middle temporal gyrus		46	-34	-4	4.43	157
R	Superior temporal gyrus		48	-36	8	4.12	
L	Superior frontal gyrus	10	-6	62	28	4.38	97
R	Superior frontal gyrus	9	6	56	28	3.78	
R	Cerebellum		6	-60	-24	4.14	94
R	Cerebellum		6	-58	-36	3.88	
R	Cerebellum		10	-52	-22	3.58	
L	Middle temporal gyrus		-42	-46	0	3.95	13
L	Middle frontal gyrus	47	-52	38	-2	3.75	12
R	Cerebellum		20	-60	-26	3.60	13
L	Inferior frontal gyrus	45	-58	26	18	3.59	16

The right amygdala ROI was used as a seed region for a functional connectivity analysis (Rissman et al., 2004). While for the placebo group the comparisons social > single and negative > neutral revealed no differences regarding amygdala connectivity, AVP treatment led to stronger connections of the amygdala to the inferior parietal lobule, the cuneus and the precuneus for the social > single contrast. Moreover, AVP was associated with increased amygdala connectivity with the superior temporal gyrus, the middle frontal and inferior frontal cortex and the cerebellum for the negative > neutral contrast (see table 2.5).

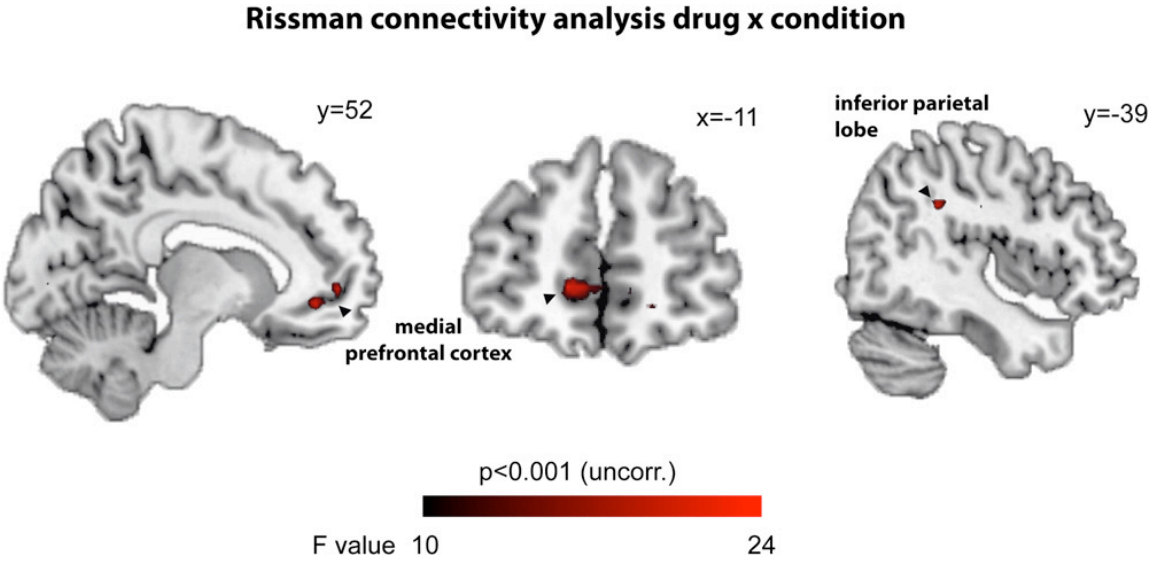

Figure 2.5 Brain regions from the drug x condition contrast showing drug-treatment dependent functional connectivity with the right amygdala for the four experimental conditions (EMOT-TWO, NEUT-TWO, EMOT-ONE and NEUT-ONE). p<0.001 (uncorr.); cluster threshold=10 voxel.

The interaction drug (AVP, placebo) x condition (EMOT-TWO, NEUT-TWO, EMOT-ONE, NEUT-ONE) indicated altered functional connectivity of the right amygdala with two clusters in the medial prefrontal cortex, the inferior parietal lobule and the occipital gyrus (see table 2.6 and figure 2.5). An ANOVA on the extracted normalized correlation coefficients of this medial prefrontal cortex region resulted in a significant drug x emotion [$F(1,39)=10.4$, $p=0.003$], drug x social [$F(1,39)=6.7$, $p=0.014$], and emotion x social [$F(1,39)=4.9$, $p=0.033$] interaction. Thus, AVP impacts functional connectivity of the amygdala to the medial prefrontal cortex during the processing of emotional and social content (see figure 2.6). Follow-up between-group comparisons were significant for the EMOT-TWO ($p=0.017$) and the NEUT-ONE condition ($p=0.004$). A similar ANOVA on the normalized correlation coefficients from the inferior parietal lobule resulted in a significant drug x social interaction [$F(1,39)=7.6$, $p=0.009$]. As illustrated in figure 2.7, AVP influences the connectivity of the amygdala to the inferior parietal lobule during the processing of social content. Follow-up between-group comparisons indicated significant differences regarding the EMOT-TWO ($p=0.019$) and the NEUT-ONE condition ($p=0.005$).

Table 2.6. Brain regions showing drug-treatment dependent altered connectivity with the right amygdala. Hem=hemisphere, BA=Brodmann area, xyz=MNI-coordinates, T=t-values, size= cluster size. Cluster threshold=10.

drug x condition

Hem	Brain region	BA	x	y	z	F	size
p<0.001 (uncorr.)							
L	Cuneus		-22	-86	2	23.56	39
L	Middle occipital gyrus		-22	-84	12	16.34	12
R	Inferior parietal lobule		42	-40	30	15.04	11
L	Medial prefrontal cortex		-12	40	-6	14.65	22
L	Medial prefrontal cortex	10	-12	52	0	14.50	22

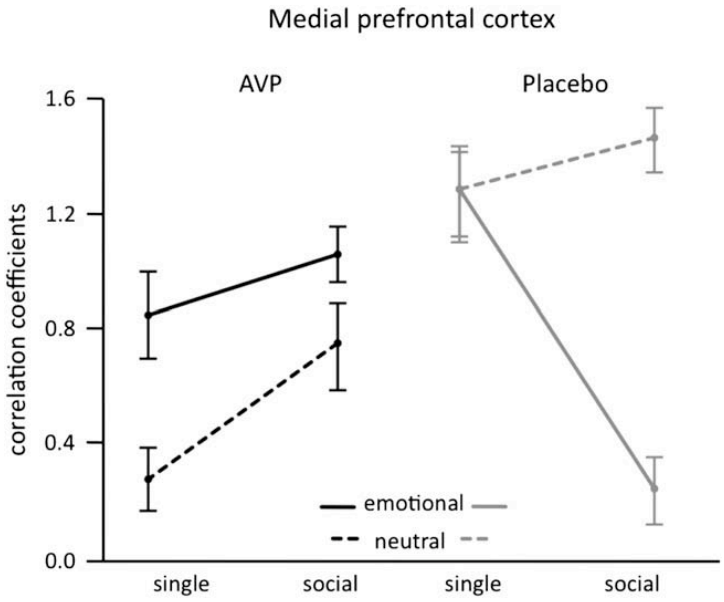

Figure 2.6 Mean normalized correlation coefficients for the four experimental conditions (EMOT-TWO, NEUT-TWO, EMOT-ONE and NEUT-ONE) from the functional ROI located at the medial prefrontal cortex. Functional ROI is defined by the voxels surviving p<0.001 (uncorr.) in the drug x condition interaction (see legend Figure 2.5).

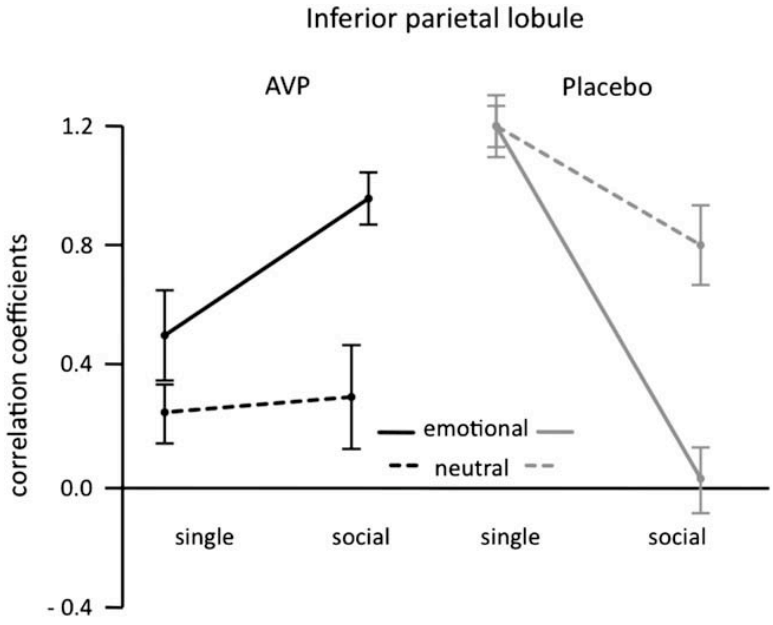

Figure 2.7 Mean normalized correlation coefficients for the four experimental conditions (EMOT-TWO, NEUT-TWO, EMOT-ONE and NEUT-ONE) from the functional ROI located at the inferior parietal lobule. Functional ROI is defined by the voxels surviving $p<0.001$ (uncorr.) in the drug x condition interaction (see legend Figure 2.5).

2.4 Discussion

The present investigation revealed an impact of AVP on the neural activity in the amygdala and the parahippocampal cortex during the processing of emotional information. AVP increases activity in the right amygdala for pictures with negative valence. The pictures' social content, i.e. the number of persons' depicted, does not affect the activation in the right amygdala. Previous reports without any drug treatment (Calder et al., 2002; Castelli et al., 2000; Gobbini et al., 2007; Heberlein et al., 2004; Krämer et al., 2010; Meyer-Lindenberg et al., 2009; Narumoto et al., 2001; Vogeley et al., 2001; Völlm et al., 2006) indicated the amygdala to be selectively involved in the processing of the emotional component of empathy, but not in the processing of socially relevant, "ToM" related information (Völlm et al., 2006). Along with the known vasopressin V1 receptor density in the amygdala, the present finding provides a first insight in the neural mechanisms by which AVP is influencing the processing of emotionally relevant information. This modulation of amygdala activity is noteworthy, since previous AVP studies on social and affective processing have failed to reveal effects in the amygdala (Rilling et al., 2012; Zink et al., 2010, 2011).

Moreover, AVP significantly increased functional connectivity of the amygdala with regions in the mPFC during the processing of the EMOT-TWO condition and significantly decreased functional connectivity between both latter regions regarding the NEUT-ONE condition. Similar changes of functional connectivity of the amygdala were also found for the inferior parietal lobule.

The connection between the amygdala and the prefrontal cortex is well known in the context of decision making processes (Gupta et al., 2011), risk taking behavior (Minati et al., 2012), loss aversion (Basten et al., 2010), and future thinking (Laufer and Paz, 2012; Peters and Büchel, 2010). The maladaptive interplay of these brain sites is assumed to be related to addictive behavior (Gu et al., 2010; Ma et al., 2010; Noori et al., 2012) and several psychiatric affective disorders (Cisler et al., 2012; Li and Sinha, 2008; Passarotti et al., 2012; Prater et al., 2012; Tang et al., 2012). It has been suggested that the medial part of the PFC is an important regulator of neural activity in the amygdala (Pezawas et al., 2005; Quirk et al., 2003; Stein et al., 2007). According to Quirk et al. (2003), the mPFC inhibits neural activity in the central amygdala by reducing responsiveness of central amygdala output neurons to basolateral amygdala input. Zink et al. (2010) argued that the negative feedback loop between the mPFC and the amygdala might be attenuated under AVP administration resulting in more sustained neural activity in the amygdala in response to threatening stimuli. The current findings are in line with this suggestion. The connectivity analysis used here, is based on a correlation of beta-series. Thus, the finding of increased functional connectivity between the mPFC and the amygdala implies that increased mPFC activation is related to increased amygdala activation. This finding contradicts the normal inhibitory feedback loop from the mPFC to the amygdala and implies that AVP reduces the suppressive effects of the mPFC on amygdala activity. In this regard it should be noted that this AVP effect was seen in response to pictures illustrating social situations with negative emotional connotation (EMOT-TWO condition). From an evolutionary point of view, increased amygdala activity (resulting from a diminished negative regulatory feedback) might be important for our survival, because it might trigger a faster reaction to socially threatening stimuli.

How do these AVP effects come about in the brain? According to Bos et al. (2012), AVP may act directly on the Vasopressin V1 receptors in the amygdala which may then also result in effects in distant brain regions such as the mPFC. However, when the present findings are considered together with those by Zink et al. (2010), it seems more likely that AVP exerts its effect via Vasopressin V1 receptors in the mPFC with the amygdala modulation being a secondary event. In fact, a high density of Vasopressin V1 receptors has been found in the prefrontal cortex of monkeys (Young et al., 1999). The fMRI technique is not suited to decide between these two alternatives. Therefore, future

research, using different approaches, is necessary to mechanistically explain AVP effects. Besides these AVP effects on emotional processing, our analyses revealed also effects on cognitive processes related to social, non-emotional information. Contrasting pictures with two vs. pictures with one person, AVP increased activation in brain regions belonging to previously described networks involved in the processing of social information. For example, the mid/posterior cingulate cortex is known to be engaged by mentalizing processes (Denny et al., 2012). This is also true for the inferior frontal and the mid-frontal gyrus (Bernhardt and Singer, 2012; Spunt et al., 2011). A recent meta-analysis (Molenberghs et al., 2012) revealed that all cortical areas which were active in the present social>single contrast have “mirror” properties, i.e. are involved when actions, action intentions, or goals of others are processed (Gobbini et al., 2007). For example, Becchio et al. (2012) reported an increased activation in the inferior and medial prefrontal cortex during the observation of social intended action. Hooker et al. (2010) showed a correlation of precentral cortex activation when watching social actions and self-reported empathy. In the present investigation AVP resulted in an increase of activation in brain sites with mirror properties. This may be the neural basis for AVP’s impact on social cognition.

It should be noted that the present study, as well as that by Zink et al. (2010), involved only healthy men. Since the present and the Krämer et al. (2010) study used the same emotional stimuli, but the Krämer et al. (2010) study investigated men (11) and women (17), a cursory comparison of the results can be used as a hint for potential sex differences in the used paradigm. While the processing of social information reveals no serious differences between Krämer et al. (2010) and the results of the placebo group, the emotion effect resulted in different cortical activations, particularly in the temporal and the inferior frontal gyrus. Thus, it is unclear whether similar findings would be obtained in women. A gender difference regarding AVP’s impact on emotional processing might be expected because of the known sexually dimorphic distributions of AVP receptors in humans (Decety and Ickes, 2009) and the fact that women are generally more empathic than men (Chakrabarti and Baron-Cohen, 2006). Future investigations should therefore also investigate women with due consideration of the female hormonal cycle. Finally, as there were no group differences in the interpersonal reactivity index, the AVP effects in the present fMRI study cannot be attributed to a pre-existing difference in empathy between the both groups.

Chapter 3

Vasopressin increases human risky cooperation by enhancing the functional coupling of the dlPFC and pallidum

3.1 Introduction

No other species shows the level of cooperative behavior that humans do. From the construction of pyramids to spice trading to international response to catastrophes, the history of mankind is marked by an ever-increasing scale of cooperation. However, collaboration is often a risky behavior, as its outcomes depend on the actions of others; therefore, engaging in cooperation is likely to depend on the possible gains from joint effort and the belief that other parties will cooperate as well (Axelrod, 2006; Gintis et al., 2005).

Understanding the neurobiological processes that drive cooperation in humans is of major interest in social neuroscience and in the field of neuroeconomics (Decety et al., 2004; Declerck et al., 2010; Rilling et al., 2002, 2004, 2012; Yoshida et al., 2010). Rilling et al. (2002), for instance, scrutinized the neurobiological underpinnings of human cooperative behavior by combining functional magnetic resonance imaging with an iterated prisoner's dilemma game and reported a relationship between the degree of cooperation and neural activity in the ventromedial prefrontal cortex and anterior cingulate cortex. Decety et al. (2004) delineated a brain site often engaged in reward processing, namely the orbitofrontal cortex (Gottfried et al., 2003; O'Doherty et al., 2001; Rolls, 2000) with regard to human cooperative behavior. The authors argued that this finding might be a hint that cooperative behavior reflects a socially rewarding process. Yoshida et al. (2010) analyzed the neural basis of belief inference, which is a key process of cooperative interactions, and found the rostral medial prefrontal (paracingulate) cortex to be crucial for encoding the uncertainty of inference about the other's strategy during cooperative games. In addition, they associated the dorsolateral prefrontal cortex with the encoding of the depth of recursion of the strategy being used (Yoshida et al., 2010).

Recently, the modulatory impact of the neuropeptides AVP and OT on cooperative behavior came into the focus of interest (Declerck et al., 2010; Israel et al., 2012; Rilling et al., 2012). However, little is still known about how these "social bonding chemicals" mediate cooperative behavior in humans. The present study focuses on AVP that has been linked to complex social behaviors such as pair bonding (Goodson and Bass, 2001; Lim and Young, 2004), affiliative behavior (Jarcho et al., 2011; Pitkow et al., 2001) and social recognition (Bielsky and Young, 2004; Dantzer et al., 1987).

Indeed, two previous investigations already analyzed the role of AVP in human cooperative behavior (Israel et al., 2012; Rilling et al., 2012). Using a social dilemma task, Israel et al. (2012) found that OT enhanced the cooperation rate in their study, but they did not see any effect for AVP. In the study by Rilling et al. (2012), AVP only increased cooperative behavior in a prisoner's dilemma game, when participants saw that their partner chose the cooperative strategy. This effect was related to enhanced neural activity in the bed nucleus of the stria terminalis. Interestingly, Rilling et al. (2012) and Israel et al. (2012) used an economic task design, where the incentive to cooperate is relatively low, because higher payoffs can be achieved when defecting cooperation. In the prisoner's dilemma (PD) game for instance, a player can always get a higher payoff if s/he decides to defect and the partner chooses the cooperative strategy.

We hypothesized that the incentive to cooperate in PD games was not strong enough for AVP administration to have robust behavioral effects. We therefore turned to a different social value structure - called the "stag hunt" (SH) game. In SH, the benefit of risky mutual effort is high enough to make cooperation privately beneficial when others cooperate too (unlike in PDs). We used SH games with varying cooperation incentives by presenting games with high incentives to cooperate, but also with low incentives to cooperate. Furthermore, we used functional brain imaging to illuminate AVP's target brain regions during human cooperative behavior. In the games, players had to choose between cooperative ("stag") and non-cooperative ("rabbit") actions (see figure 3.1), where their payoffs depended on both, their own and their partner's decisions. The game has two Nash equilibria: a payoff-dominant (see figure 3.1 at the top left of the payoff-matrix), and a risk-dominant (see figure 3.1 at the bottom right of the payoff-matrix). A Nash equilibrium is a solution concept where no single player can obtain a higher payoff by deviating unilaterally from this profile (Nash, 1950).

If the partner cooperates, choosing "stag" is optimal, as mutual cooperation yields the highest possible payoff in the SH. Yet, "stag" incorporates a strategic risk, as it would yield the lowest possible payoff if the partner defected. Therefore, in the absence of a belief that the other player would cooperate, it is optimal to choose the non-cooperative (but less risky) "rabbit" action that yields a higher certain minimal payoff.

As previous AVP studies highlighted the amygdala and the functional connections of this region as possible targets for centrally acting AVP (Brunnlieb et al., 2013a; Rilling et al., 2011, Zink et al., 2010), we hypothesized that the amygdala would play a key role in AVP's mediating effects on cooperative behavior in the SH. Indeed, a high density of Vasopressin V1 receptors have been localized in the central amygdala (Huber et al., 2005; Veinante and Freund-Mercier, 1997). Bos et al. (2012) recently argued that human

social behavior is mediated by a direct binding of AVP to the receptor binding sites in the amygdala, which then, over an indirect pathway activate brain regions that show strong functional connectivity with this cerebral structure. The amygdala complex has strong connections with the medial prefrontal cortex, the orbitofrontal cortex and the anterior cingulate cortex, but also with regions in the lateral prefrontal cortex, which might be possible target regions of AVP during human cooperative behavior (Boss et al., 2012; Hein and Knight, 2008; Sartre and Markowitz, 2004; Singer et al., 2004).

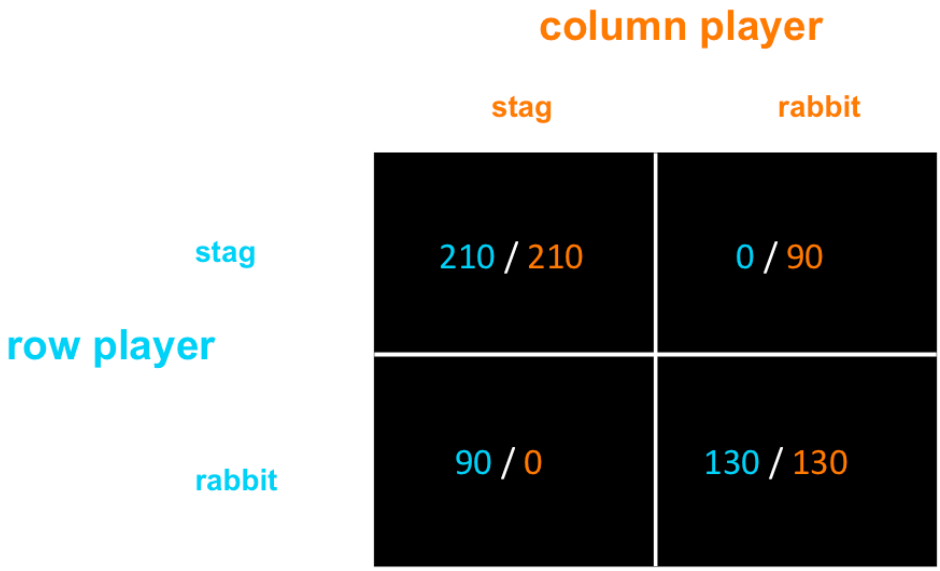

Figure 3.1 Payoff-matrix of the stag hunt game (210/210 is the payoff-dominant equilibrium and 130/130 is the risk-dominant equilibrium).

3.2 Methods

3.2.1 Participants

Thirty-four healthy adult male participants (age=19-34, mean=25.6, SD=4.2; AVP: mean=25.7, SD=2.9 / Placebo: mean=25.5, SD=5.3 / t=0.121, p=0.905, df=32) were involved in the study. Participants were right-handed and reported no psychiatric or neurological disorder, kidney disease, cardiovascular problems, asthma or migraine. Four participants were excluded from further analysis because of extensive head movements during scanning (3) and cardiovascular problems (1). Thus, thirty participants were included in data analyses (15/15 in the AVP/Placebo group). Each participant gave

informed consent and was paid for his participation. The study was approved by the ethical committee of the University of Magdeburg and conducted in accordance with the Declaration of Helsinki.

3.2.2 Drug administration

In this double-blind placebo controlled fMRI study, participants were randomly assigned to the placebo or verum condition. In the verum condition participants received a nasal spray with 20 IU of AVP, whereas participants in the placebo condition received 0.9 % NaCl spray. The verum/placebo was self-administered 15 min before starting the behavioral task. Participants did not report any alterations in water retention or any other side effects at the end of the experiment. The investigation was performed between 8 am and 6 pm.

3.2.3 Experimental procedure

Prior to the experiment each participant was introduced to another “player” who was a confederate of the experimenter. Participants were told that the other player would sit in another room next to the scanner and that both players would interact via a network computer. Participants were instructed to act as row player (see figure 3.1 in blue) and were told that the other player would act as the column player (see figure 3.1 in orange). Outside the scanner the participants were familiarized with the rules of the stag hunt game. Only after the experimenter was completely convinced that participants had fully understood the task, the scanning procedure was started. In total 105 different stag hunt games were presented. Participants were asked to indicate their choice of strategy (“stag”, “rabbit”) by button press.

Importantly, participants received no feedback about the choice of the other player in order to avoid that participants adjust their beliefs during the course of the experiment in response to the choices of the other player.

The study comprised 7 different basis games which differed in their incentive to cooperate (see figure 3.2). This was realized by increasing the value C (see figure 3.2). The higher the C value, the less attractive it was to cooperate. For instance, in basis games 1 and 2 the incentive to cooperate is high, whereas in the basis games 6 and 7 it is more attractive for the individual not to cooperate. Each of the 7 basis stag hunt games was varied 14 times, which was realized by an increase of each payoff by 10 Euro cents (see figure 3.3 demonstrating the variation of basis game 1).

Basis games	A / A	B / C	C / B	D / D
1	210 / 210	0 / 40	40 / 0	130 / 130
2	210 / 210	0 / 50	50 / 0	130 / 130
3	210 / 210	0 / 70	70 / 0	130 / 130
4	210 / 210	0 / 80	80 / 0	130 / 130
5	210 / 210	0 / 90	90 / 0	130 / 130
6	210 / 210	0 / 110	110 / 0	130 / 130
7	210 / 210	0 / 120	120 / 0	130 / 130

Figure 3.2 Seven different basis stag hunt games were varied in their incentive to cooperate (parameter C). With higher C it is less attractive to collaborate, as the risk-dominant strategy becomes more attractive.

Figure 3.3 The payoffs of the 7 basis stag hunt games were varied 14 times by increasing each payoff by 10 Euro cents (here presented for basis game 1).

The payoffs from the equilibrium A/A (see figure 3.2) ranged between 210 and 350 Euro cents and the payoffs from the equilibrium D/D between 130 Euro cents and 270 Euro cents.

3.2.4 fMRI-data acquisition

Scanning was performed using a 3-T Siemens Magnetom Trio syngo MR 2004A Scanner. In each of the 5 runs, 168 volumes (32 transversal slices (3.5 x 3.5 x 3.5)) were recorded parallel to the anterior-posterior commissure line (AC-PC). Functional images comprised the following parameters: Gradient-Echo-EPI-sequence; TR=2000 ms; TE=30 ms; FOV=224 mm; flip angle=80 °; matrix=64x64; slice thickness=3.5 mm; interslice gap=0 and for the structural images: T1-weighted MPRage: 256 x 256 matrix; FOV=256 mm; 192 1mm sagittal slices.

3.2.5 Behavioral data analysis

For the choice data, a logistic linear regression model, where the dependent variable was the choice of strategy (1=stag, 0=rabbit) and the independent variables were drug (1=AVP, 0=Placebo), incentive level (parameter C) and the interaction between them, was calculated by controlling for subject fixed effects. For the response times, a linear regression model was calculated separately for each group, where the independent variables were the choice made (1=stag, 0=rabbit) and the incentive level, controlling for subject fixed effects.

3.2.6 fMRI-analyses

Standard fMRI-analysis

Analyses of fMRI-data were conducted using SPM8 (Wellcome Department of Imaging Neuroscience, University College London) and comprised a preprocessing which included slice time correction, motion correction, coregistration, spatial normalization and spatial smoothing (Kernel=8mm FWHM). Furthermore, a high pass temporal filtering (128 s) was applied to the data. A GLM was estimated that included the regressors for the choices of “stag”, “rabbit” and estimated movement parameters (x, y, z, pitch, roll, and yaw) to minimize signal-correlated movement effects. At the first level, all choices of “stag” were weighted against all choices of “rabbit” to reveal brain activity related to human cooperative behavior. Neural correlates associated with non-cooperative behavior were

assessed by contrasting all choices of “rabbit” vs. all choices of “stag”. In a further step, these t-contrasts from the first-level analysis were entered into one-sample t-tests for both groups separately. These contrasts were considered at a significance level of $p<0.005$ (uncorr.) and a cluster threshold of 10 voxels. In order to tap into the interaction of treatment and human cooperative behavior, first-level contrasts were used to calculate two-sample t-tests. These contrasts were considered at a threshold of $p<0.001$ (uncorr.) and a voxel level of 10. As the between-group comparison Placebo > AVP for the contrast “stag” > “rabbit” choices revealed increased neural activity in the left dorsolateral prefrontal cortex (dlPFC), a functional region-of-interest analysis was conducted with the functional cluster of latter brain region by means of the toolbox rfx-plot (Gläscher, 2009). Percent signal changes were subjected to a 2x2 repeated-measures ANOVA with the factors: drug (AVP, Placebo) and choice of strategy (stag, rabbit).

Functional connectivity analyses

Functional connectivity analyses were accomplished by means of the method by Rissman (Rissman et al., 2004) using parameter estimates obtained in the context of the general linear model. According to this functional connectivity approach, those brain regions should indicate a functional relation whose beta-series are correlated in a given condition. The left dlPFC was chosen as seed region. An additional GLM was calculated and beta-values of both experimental conditions were used to calculate condition-specific beta-series for each single participant. Beta-series were also calculated within the functional cluster of the left dlPFC from fMRI standard analyses and were further averaged across voxels. A correlation of the beta-series from the left dlPFC with the beta-series of every other voxel in the brain was conducted (see Camara et al., 2008, Ye et al., 2010). The resulting correlation maps of “stag” and “rabbit” choices were normalized using an arc-hyperbolic tangent transform and entered into paired t-tests for both groups separately. The significance level was set at $p<0.001$ (uncorr.; cluster level=10). In order to tap into the impact of AVP on the functional connectivity of the left dlPFC and other regions in the brain, normalized correlation maps were also entered into two-sample-t-tests. The comparison AVP > Placebo for “stag” choices were considered at a significance level of $p<0.001$ (uncorr.; cluster level=10), while for the reverse contrast (Placebo > AVP) no brain region survived the chosen threshold. Regarding “rabbit” choices, the comparison AVP > Placebo were considered at $p<0.001$ (uncorr.; cluster level=10). For the comparison Placebo > AVP, no brain region survived the latter threshold.

3.3 Results

3.3.1 Behavioral data

3.3.1.1 Choice data

The logistic regression (see table 3.1) showed a significant incentive effect (t=-0.69, p<0.001), drug effect (t=1.73, p<0.09) and drug x incentive interaction (t=-0.06, p<0.04). This implies that the AVP group was significantly more likely to choose "stag", and significantly more responsive to incentives; when the value of C was lowered (leading to increased incentive to cooperate), the AVP group's likelihood of choosing "stag" increases significantly relative to the placebo group (see also figure 3.4).

3.3.1.2 Reaction times

The linear regression analysis indicates that the placebo group responded significantly slower during "stag" choices relative to "rabbit" choices (t=2.615, p<0.01; see table 3.3 and figure 3.5). This effect disappeared in the AVP group (t=-0.23, p>0.81), where reaction times
for "stag" and "rabbit" did not significantly differed from each other (see table 3.2 and figure 3.5).

Table 3.1 Logistic regression: dependent variable = "stag" choice.

	Beta	**Marginal effect**	**T value**	**p value**
Constant	0.794*** (0.257)	0.197***	3.0873	0.0020
Drug (AVP = 1)	0.633* (0.365)	0.157*	1.7330	0.0831
Incentive level (C value)	-0.014*** (0.002)	-0.0035***	-6.9328	0.0000
Drug x Incentive level Interaction	-0.006** (0.003)	-0.0015**	-2.0676	0.0387
Subject fixed effects dummies	Yes			
Observations	3150			
Pseudo R-square	0.90			

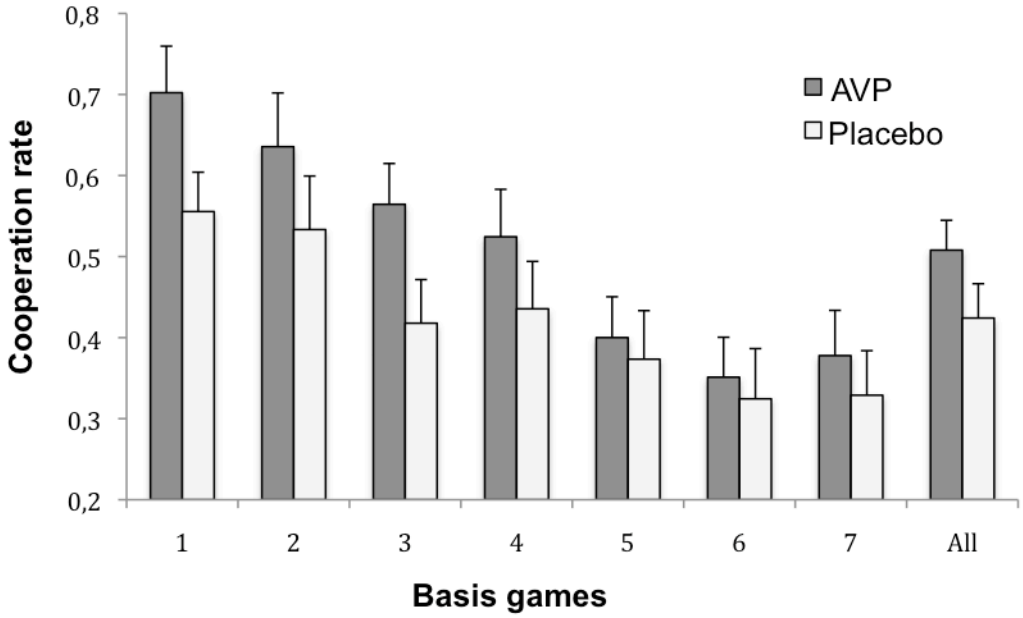

Figure 3.4 Cooperation rates are presented for each subgame and for both groups separately. In those games, where the incentive is high to cooperate (see for instance basis games 1 and 2), AVP increased cooperative choices. In games with low incentives to cooperate (see for instance basis games 6 and 7), there was no difference between both groups.

Table 3.2 Regression analysis: dependent variable: reaction times (AVP group).

	Beta	**T value**	**p value**
Constant	5.248*** (0.002)	20.925	0.000
Choice (stag = 1)	-0.024 (0.001)	-0.230	0.818
Incentive level (C value)	-0.008*** (0.001)	-4.191	0.000
Subject fixed effects dummies	Yes		
Observations	1575		
R-square	0.25		

Table 3.3 Regression analysis: dependent variable: reaction times (Placebo group).

	Beta	**T value**	**p value**
Constant	6.51*** (0.002)	22.832	0.000
Choice (stag = 1)	0.32*** (0.001)	2.615	0.009
Incentive level (C value)	-0.006*** (0.000)	-2.676	0.008
Subject fixed effects dummies	Yes		
Observations	1575		
R-square	0.33		

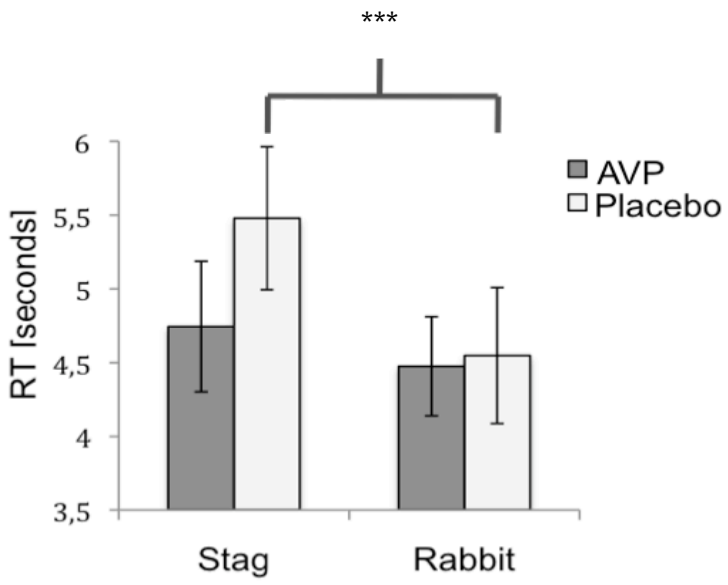

Figure 3.5 Mean reaction times of “stag” and “rabbit” choices are presented for both groups separately.

3.3.2 fMRI-data

3.3.2.1 fMRI standard analyses

For the contrast “stag” vs. “rabbit” choices, increased activation in the medial prefrontal cortex and in the superior frontal gyrus was seen in both groups (see table 3.4). In the placebo group, increased neural activity was also found in reward-related brain regions (caudate, pallidum, putamen) and in the right amygdala. Furthermore, the placebo group showed also increased activation pattern in the anterior cingulate gyrus, the middle cingulate gyrus and the inferior and middle frontal gyrus. With regard to the contrast “rabbit” vs. “stag” choices, the AVP group showed increased neural activity in the middle frontal gyrus and in the cerebellum, while in the placebo group the precuneus and in the postcentral gyrus showed greater activity (see table 3.5).

The between-group comparison Placebo vs. AVP for the contrast “stag” vs. “rabbit” choices revealed increased neural activity in the left dlPFC (see figure 3.6 and table 3.6). A region-of-interest analysis of the functional cluster in the left dlPFC showed a significant drug (AVP, Placebo) x choice (stag, rabbit) interaction [$F(1,28)=21.2$, $p<0.001$; see figure 3.7]. AVP decreased the BOLD signal in the left dlPFC during “stag” choices, whilst the opposite pattern appeared during “rabbit” choices.

3.3.2.2 Connectivity analyses

For the contrast “stag” vs. “rabbit” choices, in the AVP group increased functional connectivity of the left dlPFC was seen with the right anterior cingulate gyrus and the right caudate, while in the placebo group enhanced functional connections of the left dlPFC were found with the ventrolateral prefrontal cortex, the right caudate and the left middle occipital gyrus (see figure 3.10 and table 3.7). For the inverse contrast (“rabbit” vs. “stag” choices), in the AVP group, the left dlPFC indicated enhanced functional connectivity with the left amygdala, the left insula and the left angular gyrus (see figure 3.8 and table 3.8). In the placebo group, by contrast, the medial prefrontal cortex and the superior frontal cortex showed enhanced functional connections with the left dlPFC for “rabbit” vs. “stag” choices (see figure 3.9 and table 3.8). Furthermore, there was increased functional connectivity between the left dlPFC and the left insula, the right cingulate gyrus and the calcarine for the latter contrast.

Table 3.4 Brain regions indicating increased neural activity for "stag" > "rabbit" choices. Hem=hemisphere, BA = Brodmann area, xyz=MNI-coordinates, T=t-values, size= cluster size. Cluster threshold=10.

"stag" > "rabbit" choices

Hem	Brain region	BA	x	y	z	T	size
AVP p<0.005 (uncorr.)							
L	Superior occipital gyrus	17	-14	-94	14	4.90	152
L	Middle occipital gyrus	18	-24	-88	14	4.25	
L	Superior occipital gyrus	18	-16	-96	24	3.80	
R	Medial frontal gyrus		14	-20	60	4.17	13
R	Superior occipital gyrus	18	20	-92	18	4.13	15
R	Medial prefrontal cortex	10	0	64	0	3.80	18
R	Medial prefrontal cortex	10	4	62	-8	3.21	
R	Precentral gyrus	6	34	-6	54	3.68	16
R	Medial prefrontal cortex	6	8	-2	58	3.66	20
R	Superior frontal gyrus	6	16	-10	60	3.03	
Placebo p<0.005 (uncorr.)							
L	Caudate		-10	10	10	6.24	32
L	Caudate		-10	14	2	3.48	
L	Pallidum	48	-14	6	-4	4.99	60
L	Pallidum	48	-14	-2	-6	3.43	
R	Medial prefrontal cortex		8	30	-14	4.69	30
L	Inferior frontal gyrus	44	-54	18	34	4.59	50
R	Thalamus		8	-22	4	4.54	55
R	Superior frontal gyrus	11	22	52	-2	4.44	107
R	Superior frontal gyrus	10	26	60	16	4.13	
R	Superior frontal gyrus	6	24	56	6	4.04	
R	Anterior cingulate gyrus	32	12	46	6	4.35	10
R	Medial prefrontal cortex	10	12	54	2	3.37	
L	Postcentral gyrus	3	-34	-16	34	3.94	10
R	Middle Cingulum	32	8	32	36	3.94	11
R	Superior frontal gyrus	8	20	34	40	3.86	23
R	Middle frontal gyrus	9	22	28	46	3.09	
R	Putamen		18	4	-12	3.76	30
R	Amygdala		24	-4	-12	3.32	
R	Inferior frontal gyrus	45	50	36	4	3.69	18

Table 3.5 Brain regions showing enhanced neural activation patterns for "rabbit" > "stag" choices. Hem=hemisphere, BA=Brodmann area, xyz=MNI-coordinates, T=t-values, size= cluster size. Cluster threshold=10.

"rabbit" > "stag" choices

Hem	Brain region	BA	x	y	z	T	size
AVP p<0.005 (uncorr.)							
L	Middle frontal gyrus	44	-50	18	40	3.67	10
R	Cerebellum		8	-36	-20	3.34	10
Placebo p<0.005 (uncorr.)							
R	Precuneus	37	36	-48	4	4.65	18
L	Postcentral gyrus	4	-38	-24	56	3.48	23

Table 3.6 Brain regions that showed increased neural activity for the comparison Placebo > AVP and the contrast "stag" vs. "rabbit". Hem=hemisphere, BA=Brodmann area, xyz=MNI-coordinates, T=t-values, size=cluster size. Cluster threshold=10.

Placebo > AVP "stag" > "rabbit" choices

Hem	Brain region	BA	x	y	z	T	size
p<0.001 (uncorr.)							
L	Dorsolateral prefrontal cortex	44	-54	18	34	5.1	62

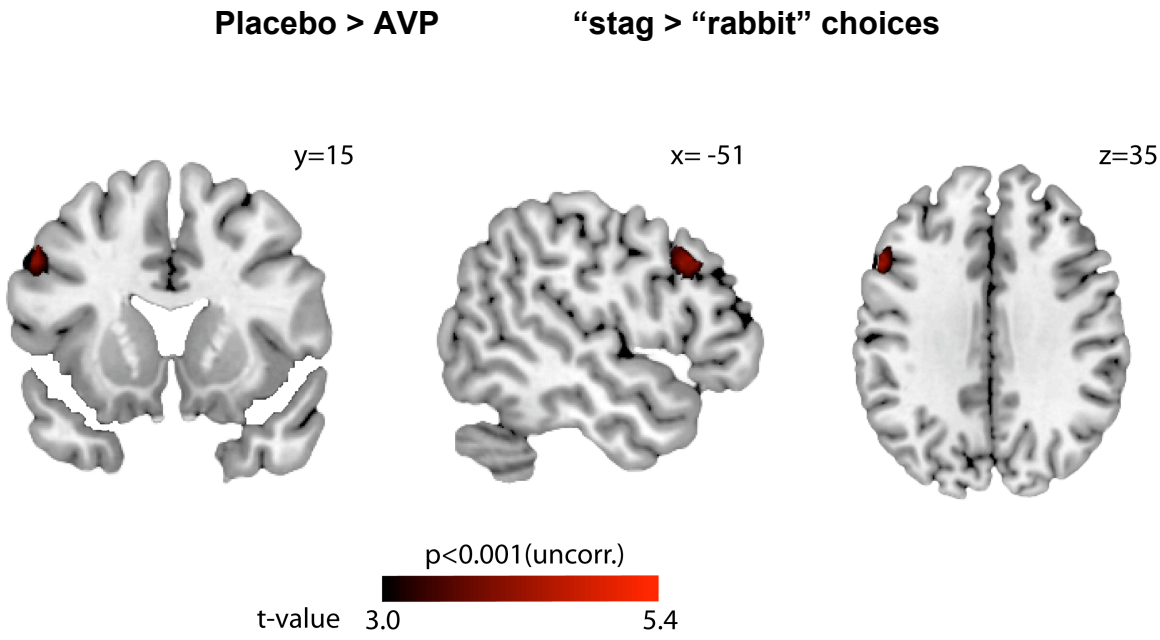

Figure 3.6 Increased neural activity in the left dlPFC for the comparison Placebo > AVP and "stag" > "rabbit" choices (cluster threshold=10).

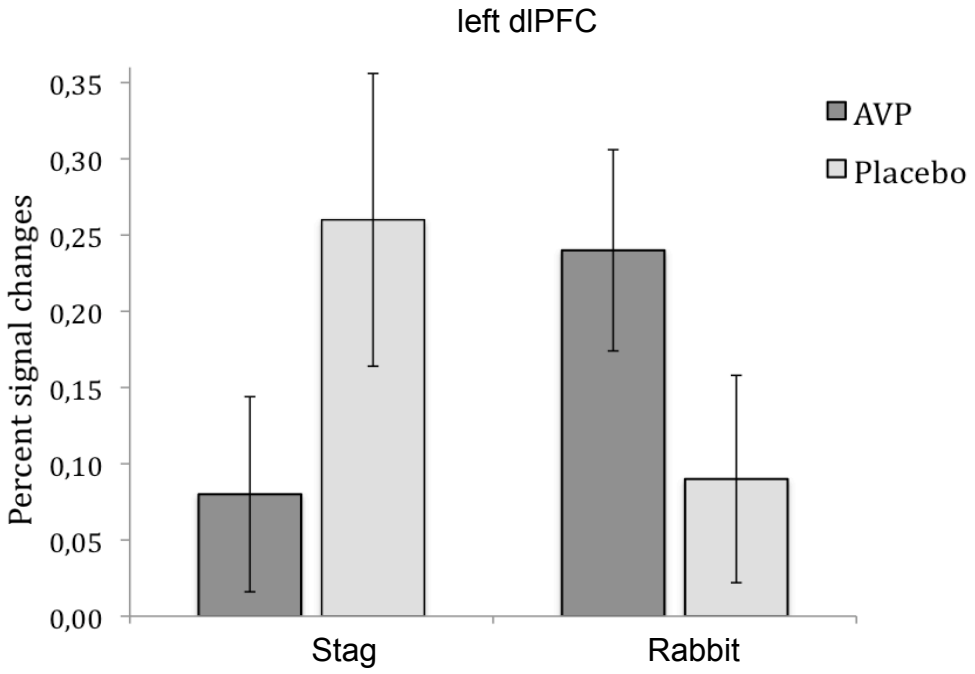

Figure 3.7 Percent signal changes of the left dlPFC are illustrated for "stag" and "rabbit" choices and for both groups separately.

Table 3.7 Brain regions that showed increased functional connectivity with the left dlPFC for "stag" > "rabbit" choices are presented for both groups separately. Hem=hemisphere, BA=Brodmann area, xyz=MNI-coordinates, T=t-values, size=cluster size. Cluster threshold=10.

Rissman connectivity analysis "stag" > "rabbit" choices

Hem	Brain region	BA	x	y	z	T	size
AVP p<0.001 (uncorr.)							
R	Anterior cingulate gyrus	32	20	28	20	5.17	26
R	Caudate		10	20	18	5.10	
Placebo p<0.001 (uncorr.)							
R	Ventrolateral prefrontal cortex	47	40	30	-12	6.21	43
L	Ventrolateral prefrontal cortex	47	-34	32	-16	5.98	37
L	Ventrolateral prefrontal cortex	38	-42	28	-14	4.45	
L	Middle occipital gyrus	19	-36	-76	6	5.10	12
R	Caudate		20	14	20	4.72	18
R	Caudate		14	16	14	4.63	

The between-group comparison AVP > Placebo for "stag" choices revealed increased functional connectivity of the left dlPFC with the left pallidum, the cingulate gyrus, the right medial frontal gyrus and the right superior frontal gyrus (see figure 3.11 and table 3.9) under AVP treatment. For the reverse contrast no brain region survived a threshold of p<0.001 (uncorr.).

Regarding "rabbit" choices, the comparison AVP > Placebo indicated increased functional connectivity with the left parahippocampal gyrus, the left calcarine, the left amygdala, the right middle cingulum and the right anterior cingulate gyrus and the right inferior and middle frontal gyrus as well as the middle temporal gyrus (see figure 3.12 and table 3.10). For the contrast Placebo > AVP and "rabbit" choices, no brain region could be seen at a threshold of p<0.001 (uncorr.).

Functional connectivity analysis: AVP "rabbit" > "stag" choices

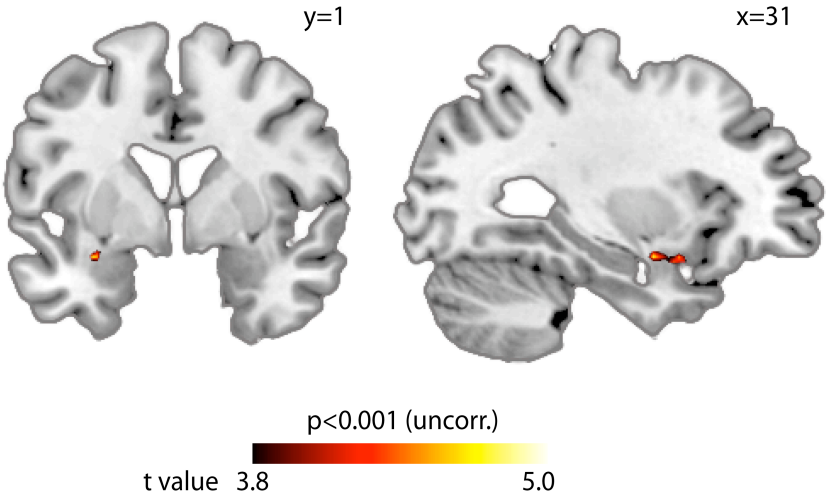

Figure 3.8 In the AVP group the contrast "rabbit" > "stag" choices indicated increased functional connectivity between the seed region (left dlPFC) and the left amygdala and the left anterior insula (cluster threshold=10).

Functional connectivity analysis: Placebo "rabbit" > "stag" choices

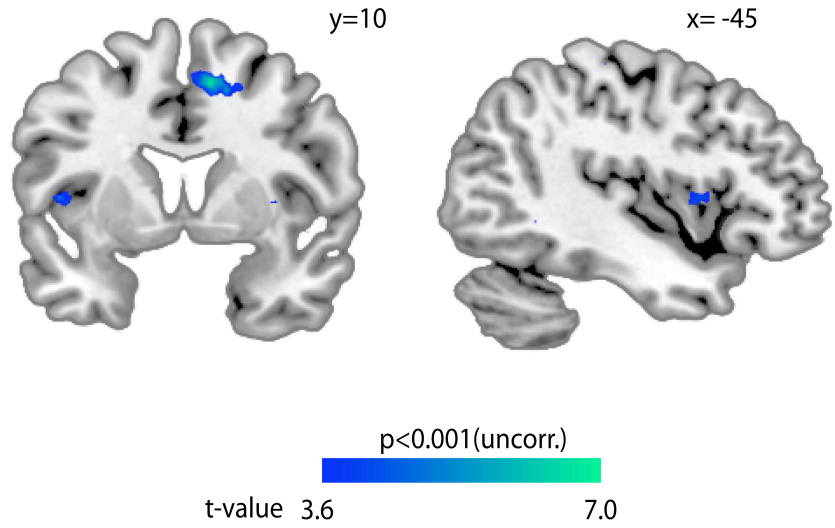

Figure 3.9 In the placebo group the left anterior insula, the right cingulate gyrus and the left medial frontal gyrus showed enhanced functional connectivity with the left dlPFC for "rabbit" > "stag" choices (cluster threshold=10).

Functional connectivity analysis: Placebo "stag" > "rabbit" choices

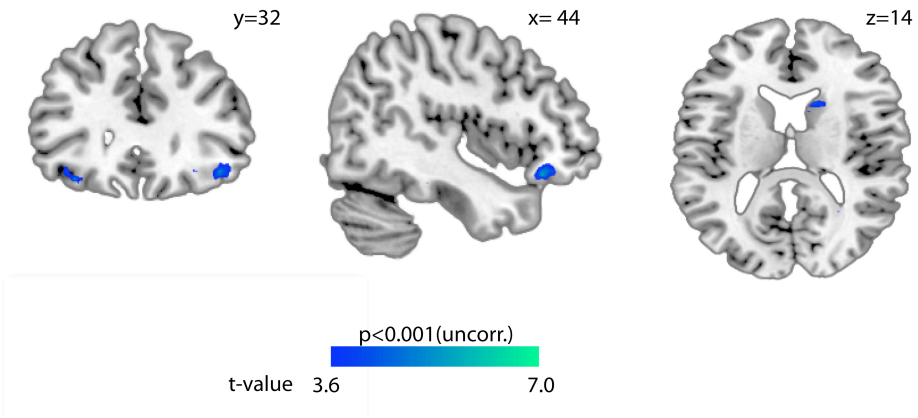

Figure 3.10 In the placebo group there was increased functional connectivity between the left dlPFC and the bilateral ventrolateral prefrontal cortex and the right caudate for "stag" > "rabbit" choices (cluster threshold=10).

Table 3.8 Brain regions that show enhanced functional connectivity with the left dlPFC for "rabbit" > "stag" choices are presented for both groups separately. Hem=hemisphere, BA=Brodmann area, xyz=MNI-coordinates, T=t-values, size=cluster size. Cluster threshold=10.

Rissman connectivity analysis "rabbit" > "stag" choices

Hem	Brain region	BA	x	y	z	T	size
AVP p<0.001 (uncorr.)							
L	Amygdala	34	-30	0	-16	4.85	25
L	Anterior Insula	38	-30	10	-16	4.77	
L	Angular gyrus	39	-54	-60	26	4.37	12
Placebo p<0.001 (uncorr.)							
R	Cingulate gyrus	6	10	6	50	6.89	71
R	Superior frontal gyrus	6	2	4	52	3.92	
R	Cerebellum	37	16	-48	-18	5.05	10
R	Calcarine	17	14	-56	-18	4.07	
L	Anterior Insula	48	-46	6	6	4.90	12
L	Medial frontal gyrus	6	-2	-4	56	4.67	21
L	Medial frontal gyrus	6	-4	-10	62	4.18	

Table 3.9 Brain regions indicating enhanced functional connectivity with the left dlPFC for AVP > Placebo regarding "stag" choices. Hem=hemisphere, BA = Brodmann area, xyz=MNI-coordinates, T=t-values, size= cluster size. Cluster threshold=10.

AVP > Placebo "stag" choices

Hem	Brain region	BA	x	y	z	T	size
p<0.001 (uncorr.)							
L	Pallidum	48	-22	-2	-2	4.29	15
R	Cingulate gyrus		10	6	50	4.28	70
L	Cingulate gyrus	24	-2	0	48	3.72	
R	Medial frontal gyrus	6	4	-2	54	3.48	
R	Superior frontal gyrus	6	16	-2	62	3.75	12

Table 3.10 Brain regions indicating enhanced functional connectivity with the left dlPFC for AVP > Placebo regarding "stag" choices. Hem=hemisphere, BA = Brodmann area, xyz=MNI-coordinates, T=t-values, size= cluster size. Cluster threshold=10.

AVP > Placebo "rabbit" choices

Hem	Brain region	BA	x	y	z	T	size
p<0.001 (uncorr.)							
L	Parahippocampal gyrus	30	-22	-34	-14	5.82	111
L	Parahippocampal gyrus	37	-24	-42	-14	4.10	
L	Parahippocampal gyrus	37	-32	-38	-12	3.97	
L	Calcarine	17	-18	-60	8	4.43	24
L	Amygdala	34	-28	2	-14	4.31	27
R	Middle Cingulum	23	4	-4	34	4.30	78
R	Anterior cingulate gyrus	24	4	12	30	4.06	
R	Middle Cingulum	32	10	16	36	3.65	
R	Inferior frontal gyrus	45	54	40	0	4.23	12
R	Middle frontal gyrus	46	50	48	4	3.64	
L	Middle occipital gyrus	19	-40	-80	14	4.15	17
L	Middle occipital gyrus	19	-34	-86	14	3.93	
L	Middle temporal gyrus	20	-58	-22	-14	3.94	14
L	Lingual gyrus	19	-18	-50	-2	3.87	12
R	Middle temporal gyrus	21	64	-22	-12	3.82	11

Functional connectivity analysis: AVP > Placebo "stag" choices

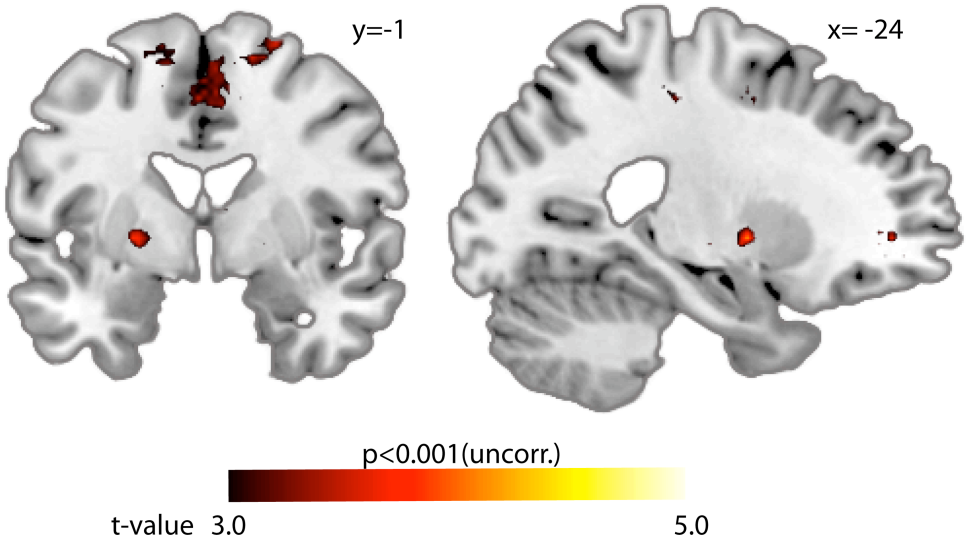

Figure 3.11 The left dlPFC showed increased functional connectivity with the left pallidum, the cingulate gyrus and the right medial and superior frontal gyrus for the comparison AVP > Placebo and "stag" choices (cluster threshold=10).

Functional connectivity analysis: AVP > Placebo "rabbit" choices

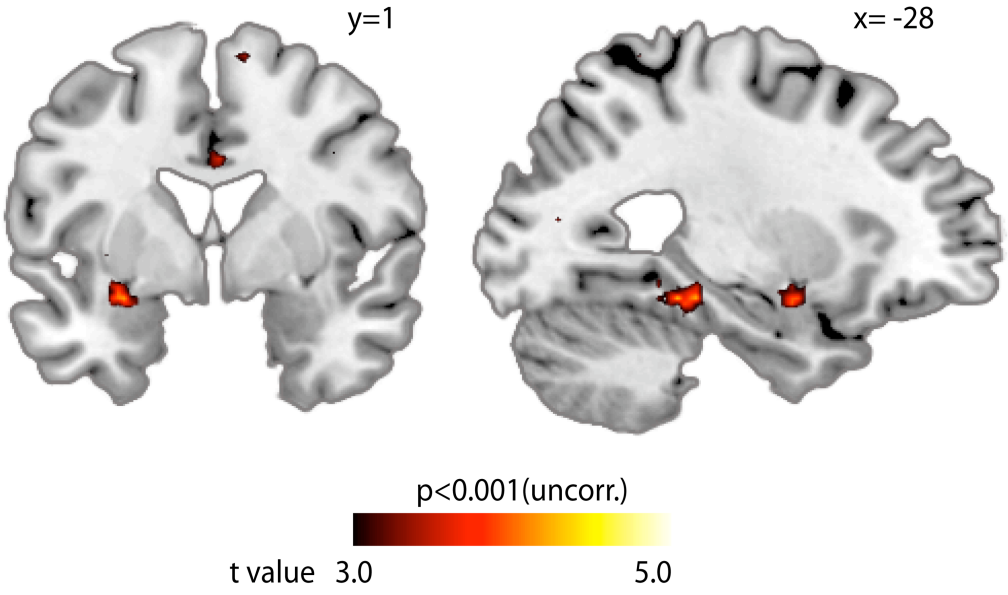

Figure 3.12 The left dlPFC indicated enhanced functional connectivity with the left amygdala, the left parahippocampal gyrus and anterior cingulate gyrus for the comparison AVP > Placebo and "rabbit" choices (cluster threshold=10).

3.4 Discussion

In the present study it was shown that the impact of AVP on cooperative behavior depends on the incentive to cooperate. In games where the incentive to cooperate was high, AVP substantially increased the choice of the cooperative strategy, whereas in games with weak incentives to cooperate, no impact of AVP could be seen. Thus, it seems that AVP action is context dependent, as it facilitated cooperation only in the games in which collaboration was an attractive option. This finding is in line with results from previous AVP studies that used a task design with low incentives to cooperate and failed to find a substantial impact of AVP on human cooperative behavior (Israel et al., 2012; Rilling et al., 2012).

AVP-related increase of cooperative behavior was associated with decreased neural activity in the left dlPFC, while defection was related to an AVP-promoted increase in BOLD signal in the left dlPFC. Previous studies have pointed to a role of the dlPFC in cognitive control (Braver et al., 2001; Carter et al., 2007; Hare et al., 2009; Miller and Cohen, 2001; Roberts and Hall, 2008), working memory (Duncan and Owen, 2000; Watanabe et al., 2005) and emotion regulation (Ochsner and Gross, 2005). For instance, Hare et al. (2009) found that neural activity in the left dlPFC increased when participants exercised self-control. A study by Yoshida et al. (2010) observed a positive relationship between neural activity in the left dlPFC and the level of strategic thinking during a stag hunt game, while Coricelli and Nagel (2009) associated increased dlPFC activation with high- versus low-level reasoning in a beauty contest game. A meta-analysis by Mohr et al. (2010) scrutinized 30 fMRI studies on risky decision-making and found the dlPFC as one of the most consistently engaged brain region in human risky choices. In light of the literature reviewed above, it is possible that the dampening effect of AVP on the activity in the left dlPFC reduced the perception of social risk based on diminished cognitive control, which in turn elicited the increased selection of cooperative (more risky) choices under AVP administration. Further, this behavioral effect can be explained in light of AVP's modulatory impact on the dlPFC's functional connectivity with other brain regions. In the present study, AVP strengthened the functional connectivity between the left dlPFC and the pallidum, a brain region critical for pair bonding, when participants chose the cooperative strategy. The pallidum is a crucial part of the reward circuitry and comprises a high quantity of Vasopressin V1 receptors (Donaldson et al., 2008; Insel and Young, 2001; Lim and Young, 2004; Pittkow et al., 2001). Lim and Young (2004), for instance, found that a selective blockade of Vasopressin V1 receptors in the ventral pallidum prevented specific partner preference in male prairie voles; in humans, neural activity in

the ventral pallidum was positively correlated with the length of a relationship, when participants were exposed to pictures of their beloved (Aron et al., 2005). According to Lim and Young (2004), social bonding in males is mediated by a binding of AVP to Vasopressin V1 receptors in the ventral pallidum, such that the social interaction itself becomes pleasant for the individual. Accordingly, the increase of the functional connectivity of the left dlPFC and the left pallidum might lead to a preference for the cooperative strategy.

Another interesting finding that might contribute to our understanding of AVP's role in human cooperative behavior is the following: during the defection of cooperation, AVP enhanced the functional connectivity of the left dlPFC with the left amygdala, the left parahippocampal gyrus and the ACC. The amygdala, in particular, is a known target region of AVP, because of its high density of Vasopressin V1 receptors (Huber et al., 2005; Veinante and Freund-Mercier, 1997). Moreover, according to Bos et al. (2012), effects of AVP on human social behavior are mediated by a direct binding of AVP to Vasopressin V1 receptors in the amygdala. In line with this assumption, it is reasonable that AVP acted on the Vasopressin V1 receptors in the amygdala, which resulted in excitatory inputs to the left dlPFC giving rise to the increased BOLD-signal in the left dlPFC (during defection of cooperation). The amygdala might thereby act as a warning or alarm system, since defecting cooperation is related to a sure (but lower) payoff than the amount of money participants could receive when both parties cooperate. Increased functional connections with the parahippocampal gyrus might thereby facilitate memory storage of this negative event by interacting with the amygdala. This is consistent with Phelps (2004) and Kilpatrick and Cahill (2003) that found dense interconnectivity of the amygdala and the hippocampal complex (including the parahippocampal gyrus) to subserve the formation of emotional memories.

As there are no known direct anatomical connections between the amygdala and the dlPFC (Ghashghaei and Barbas, 2002; Siegle et al., 2007), it is likely that the AVP induced BOLD signal increase in the left dlPFC (during defection of cooperation) is mediated via the ACC, that also indicated increased functional connectivity with the left dlPFC in the present study. Evidence for this hypothesis comes from studies that reported strong connections of the ACC with both, the dlPFC and the amygdala (Amaral and Price, 1984; Ghashghaei and Barbas, 2002; Ghashghaei et al., 2007; Ray and Price, 1993). Furthermore, the study by Zink et al. (2010) found AVP-induced altered functional connectivity between the ACC and the amygdala. It is thus possible that AVP-related increased activity in the left dlPFC during defection of mutual cooperation is possibly mediated by excitatory inputs from the amygdala via the ACC to the dlPFC. On the other hand, it could also well be that AVP bound directly on Vasopressin V1 receptors in the left

dlPFC: a study by Young et al. (1999) could localize Vasopressin V1 receptors in the prefrontal cortex of non-human primates. The fMRI method is not suited to distinguish whether the AVP effect in the left dlPFC is a primary or secondary event (mediated via the amygdala). This issue remains to be investigated by future research.

As a final cautionary note, it has to be mentioned that this study only involved healthy male volunteers. Therefore, it is necessary that future AVP studies also consider female participants in order to see whether the effects found in this study can be generalized to women. Given the known gender differences in risk-taking behavior (Byrnes et al., 1999; Powell and Ansic, 1997) and a sexual dimorphism regarding the distribution of Vasopressin V1 receptors (Decety and Ickes, 2009), a gender effect has to be assumed in terms of AVP's impact on human cooperative behavior.

3.5 Conclusions

The findings of the present study suggest that AVP increases cooperative behavior only when it is advantageous for the individual to cooperate. AVP had no impact on cooperation, when the incentive to cooperate is low. This effect is possibly mediated by a reduced perception of social risk, promoted by an AVP induced BOLD signal reduction in a brain region typically activated during risky decision-making: the dorsolateral prefrontal cortex. The selective acting of AVP in human cooperative behavior might have an evolutionary value for survival. Further, it supports AVP's known role as a social bonding chemical.

Chapter 4

Vasopressin modulates neural activity in the right superior temporal cortex during human reactive aggression

4.1 Introduction

Reactive aggression is defined as a direct retaliating response to a perceived threat or provocation. According to Dodge and Coie, “perceptions of threat and experiences of anger push the reactively aggressive individual to retaliate” (Dodge and Coie, 1987 p.1147). In contrast, proactive aggressive behavior is characterized as calculated and goal-directed acting with the intention to harm another person.

The general Aggression Model (GAM) by Anderson and Bushman (2002) provides a theoretical framework for human aggressive behavior and posits that situational and personal variables influence aggressive behavior via the moderating impact of affect, cognition, and arousal. Situational variables include the provocation by another person, frustration, pain and drugs, while personal variables comprise (among others) personality traits, sex, beliefs and attitudes. According to the GAM, these feed into appraisal and decision processes that finally cause impulsive or thoughtful actions (Anderson and Bushman, 2002; Krämer et al., 2007).

An established paradigm in social psychology is the Taylor Aggression Paradigm (TAP), which elicits reactive aggression in the laboratory by provoking the participant during a competitive reaction time task. During winning trials, participants are allowed to punish their opponent player, for example, with a loud noise or an electric shock of variable intensity, whereas during losing trials participants get punished by their opponent player. Since the aggressive interaction in the TAP is separated into a decision phase (selection of punishment level for the opponent player) and an outcome phase (punishment is applied or received), the paradigm is attractive for neuroscientific research as it allows to disentangle the neural underpinnings of different emotional and cognitive processes during reactive aggressive interaction. For example, Krämer et al. (2007) used functional magnetic resonance imaging (fMRI) and a version of the TAP in which healthy participants played in alternating trials against an unfair (high provocation) and a fair (low provocation) opponent in a competitive reaction time task with the punishment comprising aversive noise of different intensities as punishment. For the decision phase, provocation-dependent activations were seen in the bilateral AI and the rostral part of the ACC, brain regions that have been previously associated with negative emotions like anger or disgust (Damasio et al., 2000; Dougherty et al., 1999; Phillips et al., 1997). Aggressive behavior,

as a direct response to provocations of the unfair opponent, was linked to enhanced neural activity within the dorsal striatum, which according to previous neuroimaging studies is involved in reward processing (Balleine et al., 2007; de Ouervain et al., 2004; O'Doherty et al., 2004), but is also known to be active during effective punishment (de Quervain et al., 2004). Krämer et al. (2007) argued that this activation probably reflects the participants' anticipation to receive less provocations by their opponent player in the following trials. Besides the dorsal striatum, reactive aggressive behavior was further linked to increased activations in the dorsal part of the ACC, a brain site that has been associated with conflict monitoring and cognitive control in numerous previous studies (e.g., Botvinick et al., 1999; Carter and Van Veen, 2007; Cohen et al., 2000; Milham et al., 2001; Nelson et al., 2003; Van Veen and Carter, 2002).
For the outcome phase, Krämer et al. (2007) reported enhanced neural activity in the ventral striatum / nucleus accumbens associated for win compared to loss trials, which might reflect the rewarding properties of the avoidance of the opponents' punishment.

The question arises to what extent reactive aggression is modulated by neurotransmitter systems and / or neuropeptide hormones. With regard to the former, serotonin has been implicated by a wealth of studies in impulsive aggression (Bjork et al., 1999, 2000; Cleare and Bond, 1995; Coccaro and Kavoussi, 1997; Manuck et al., 2006; Moss et al., 1990; Pihl et al.,1995), even though a study using the TAP in conjunction with fMRI and an acute tryptophan depletion, a pharmacological manipulation known to reduce brain serotonin level, did not reveal any marked effects (Krämer et al., 2011). One suggested pathway of serotonin to control aggressive behavior and the motivation to act aggressive is via an antagonistic impact on brain sites related to the regulation of the social neuropeptide AVP (Ferris et al., 1997, 2008). Research on animal models have shown that AVP itself is a key player in the control of aggression and other "male-typical behaviors" (Heinrich and Domes, 2008) like pair-bond formation and stress-responsiveness (Bos et al., 2012; Caldwell and Albers, 2004a; Ferris and Delville, 1994; Ferris et al., 1997; Goodson and Bass, 2001). For example, in animals like male Golden and Syrian hamsters, microinjections of AVP into the anterior hypothalamus and the lateral septum increased the number of aggressive interactions, while microinjections of AVP receptor 1a (AVPR1a) antagonists into the anterior hypothalamus inhibited aggressive behavior against intruders (Bos et al., 2012; Caldwell and Albers, 2004a; Ferris and Delville, 1994; Ferris et al., 1997). In humans, there is actually little evidence for a direct link between AVP and reactive aggression. However, a first hint was given by Cocarro et al. (1998) reporting a positive correlation between cerebrospinal fluid AVP levels and life histories of general aggression, which was more pronounced for men than

for women. Research by Thompson et al. (2004) suggested that AVP acts on processes related to emotional social communication, which in turn could promote reactive aggressive behavior. In their initial study, they investigated facial EMG, while male participants watched facial expressions. Intranasally administered AVP led to an increase of EMG responses to neutral faces to a level comparable to that observed for angry faces in the placebo group. Thompson et al. (2004) argued that AVP alters the interpretation of social stimuli that are taken as if they were threatening. In a consecutive investigation, Thompson et al. (2006) described that, in men, AVP enhances agonistic facial motor patterns in response to faces of unfamiliar men and decreases the perception of the friendliness of those faces. In women, however, AVP stimulated affiliative facial motor patterns in response to faces of unfamiliar women and increased perceptions of those faces' friendliness. In a recent study, Uzefosky et al. (2012) reported an inverse pattern of results. Their study revealed for men treated with AVP an impairment in the recognition of negative emotions while leaving the perception of positive emotions unaffected. According to work by Guastella et al. (2010) and Guastella et al. (2011), the impact of AVP on the processing of social and interpersonal information is less specific. Instead, AVP seems to enhance the processing of social information generally, irrespective of the stimulus category's valence. Up to now, just a few studies using functional MRI have tried to elucidate the neural underpinnings of AVP's impact on the processing of social information. Zink et al. (2010) and Zink et al. (2011) reported in men an impact of AVP administration on the brain's fear regulatory system (Zink et al., 2010) during an emotional-face matching task and also changes in the activity of the TPJ, a brain area known to be a key site in the theory of mind network, when processing socially relevant familiarity information (Meyer-Lindenberg et al., 2011). Additional evidence for AVP's modulatory influence on social behavior is given by Rilling et al. (2012). In their prisoner's dilemma paradigm, they reported for men treated with AVP, but not for men treated with oxytocin or placebo, increased cooperation in response to cooperative signs by the partner. In AVP-treated men who initiated such a cooperative interaction, the processing of the cooperative interaction's outcome resulted in increased activations in brain sites belonging to the vasopressin circuitry like the stria terminalis, the bed nucleus of the stria terminalis, and the lateral septum. In contrast to Rilling's behavioral results, Israel et al. (2012) failed to find significant evidence for an impact of AVP on cooperative behavior. However, their nested social dilemma paradigm does not comprise any kind of reciprocity between acting persons, which might explain the missing impact of AVP on cooperative behavior. These findings imply that AVP influences processes linked to social communication.

Even though previous fMRI studies on the TAP have not revealed differential activations of the amygdala (Krämer et al., 2007, 2011; Lotze et al., 2007), this group of nuclei is involved undoubtedly in the appraisal of threat and the regulation of aggressive behavior (Dougherty et al., 1999, Nelson et al., 2003). Interestingly, the central amygdala harbours high quantities of Vasopressin V1 receptors (Huber et al., 2005; Veinante and Freund-Mercier, 1997). The amygdala is connected to a widespread network of brain regions involved in the regulation of aggressive behavior (e.g. Passamonti et al., 2008, 2012) and these connections may allow AVP to exert a modulatory influence on aggressive behavior.

By using fMRI and the TAP, the current study tries to delineate the impact of AVP on the neural basis of the distinct stages of human reactive aggression. Following Wiswede et al. (2011), a modified version of the TAP was used in which participants played against just one opponent who selected relatively high punishments. As previous investigations were ambiguous with regard to the meaning of certain brain activations (e.g., a particular activation on win trials might have been due to the possibility to punish the opponent or due to the fact that punishment by the opponent had been avoided), “passive” and “active” blocks were introduced. In “passive” blocks, participants were punished by a loud aversive tone on loss trials but could not administer a punishment to the opponent player on win trials, whereas in “active” blocks the participant could punish the opponent player on win trials but did not get punished on loss trials.

In light of the evidence linking AVP to enhanced aggressive behavior (Bos et al., 2012; Caldwell and Albers, 2004a; Coccaro et al., 1998; Ferris and Delville, 1994; Ferris et al., 1997; Thompson et al., 2004, 2006), it was predicted that AVP would lead to the selection of higher punishment levels during the decision phase compared to placebo. In addition, this effect should be more pronounced during trials of the “active” block, where participants can punish the opponent when winning the trial. On the neural level, AVP was expected to modulate activity in the AI and the ACC during the decision phase, as these have been revealed in previous studies using the TAP. In addition, the predicted AVP-related increase in negative affect in response to the relatively high provoking opponent might also elicit an increased feeling of reward when being able to punish the opponent in “active” trials, which should be associated with an increase in BOLD signal in the ventral striatum during “active” trials for the comparison of win trials versus loss trials. As the amygdala was not modulated in previous studies using the TAP, we had no expectations with regard to this structure.

4.2 Methods

4.2.1 Participants

Thirty-six healthy adult male volunteers (age=19-32, mean=25.8, SD=3.4) were recruited from a volunteers' database at the Department of Neurology of the University of Magdeburg. The groups did not significantly differ in their age (the AVP group: mean=26.5, SD=4.3 and the placebo group: mean=25.0, SD=4.0). Participants of both the groups were students of the University of Magdeburg to assure a uniform education level. Subjects were right-handed and reported to be free of any psychiatric and neurological disorder, kidney disease, cardiovascular problems, asthma, and migraine. Two subjects were removed from further analysis, because of extensive movement artifacts and three were excluded, because during the debriefing it became apparent that they had not been completely deceived by the experimental set-up. Thus, data analyses are based on 31 participants (16 treated with AVP) using a between-subjects design. All subjects gave written informed consent and were paid for participation. The study had been approved by the ethical committee of the University of Magdeburg and conducted in accordance with the Declaration of Helsinki.

4.2.2 Drug administration

Participants randomly received either an intranasal dose of 20 IU of AVP or a placebo in a double-blind manner. As in Born et al. (2002), nasal sprays were self-administered by the participants under the supervision of the experimenter. Each subject self-administered four sprays. The original 1 ml synthetic vasopressin solution (Goldshield Pharmaceutical Ltd., Croydon, UK) contained 0.5 % chlorobutanol, while the only active substance was argipressin. In order to get 20 IU AVP per four sprays, the solution was filled up with 0.9 % saline solution. In the placebo condition, four sprays of 0.9 % saline solution were administered. Ten minutes before entering the scanner, AVP was self-administered by the subjects under the supervision of the experimenter. After 5 minutes of premeasures (T1 and IR-EPI image) and a further task lasting 20 minutes, participants started with the TAP 35 minutes after AVP administration. The entire duration of the experimental procedure was 24 minutes (12 minutes per run). Subsequently to the TAP, a diffusion tensor imaging protocol (14 min) was performed. Finally, 120 minutes after AVP administration, subjects filled out the Buss and Perry Aggression Questionnaire (AQ) and the interpersonal reactivity index (IRI). The questionnaires were presented at the end of the session in order to avoid any hint to the main target of this paradigm's intention to induce aggression.

There was no report of altered water retention or any other side effects when subjects were debriefed at the end of the experiment. Scanning sessions took place between 8 am and 6 pm.

4.2.3 Experimental procedure

Participants were told that they would play a reaction time task against another male player who unbeknownst to them was a confederate of the experimenter. They were informed that they have won a trial, whenever they responded faster than the opponent, but lost a trial, when the opponent responded faster. In the TAP's experimental procedure, it was predefined that, in two-third of the trials, the participant loses the competitive reaction time task. Prior to the experiment, the participant and the confederate were introduced to each other. The confederate was introduced as the other "player" the participant had to play against and was a male, 26-year-old student. The confederate was not acquainted with anybody of the participants. Before the participant entered the scanner, he had to complete eight test trials outside the scanner. After being convinced that the participant understood the task, the confederate was brought to another room and the participant was told that they would be interconnected via a network computer during the game. At the end of the experimental procedure, participants were debriefed by explaining the experimental set-up and the investigation aims.

Aggression paradigm

A modified version of the TAP was used in two runs. Each run consisted of six "passive'" blocks and six "active" blocks. Each "passive" and "active" block comprised four trials and blocks were presented alternately. In "passive" blocks, the participant was punished when he lost the reaction time competition, while in "active" blocks the participant could administer a punishment to the opponent player in the case that he won during the reaction time task. The punishment was a loud polystyrene scratching noise presented at four different levels. The adjustment of the volume was accomplished prior to the experiment such that participants judged level 4 as unpleasant but not painful. Each trial started with a fixation phase which was followed by a decision phase during which the participant received an indication whether the actual trial was a "passive" or an "active" one, by presenting either the German word for threat (in passive trials) or punish (in active trials; see figure 4.1 illustrating the experimental procedure). In both, "active" and "passive" blocks, participants had to select the magnitude of the punishment (four different levels) during the decision phase. The selection of the punishment level was done by a

button press on a keyboard with key 1 reflecting the lowest and key 4 reflecting the highest punishment level. The decision phase was followed by a "!", which cued the participant for the upcoming reaction time task. For the reaction time task, a visual cue (a bird from a computer game) was presented on the screen and participants were instructed to press a button as fast as possible when the visual cue appeared on the screen. The duration of the visual cues appearance was similar for all trials, irrespective of the participant's reaction time (see figure 4.1). Directly after the reaction time task, participants were presented with the opponents' selection of the punishment level.

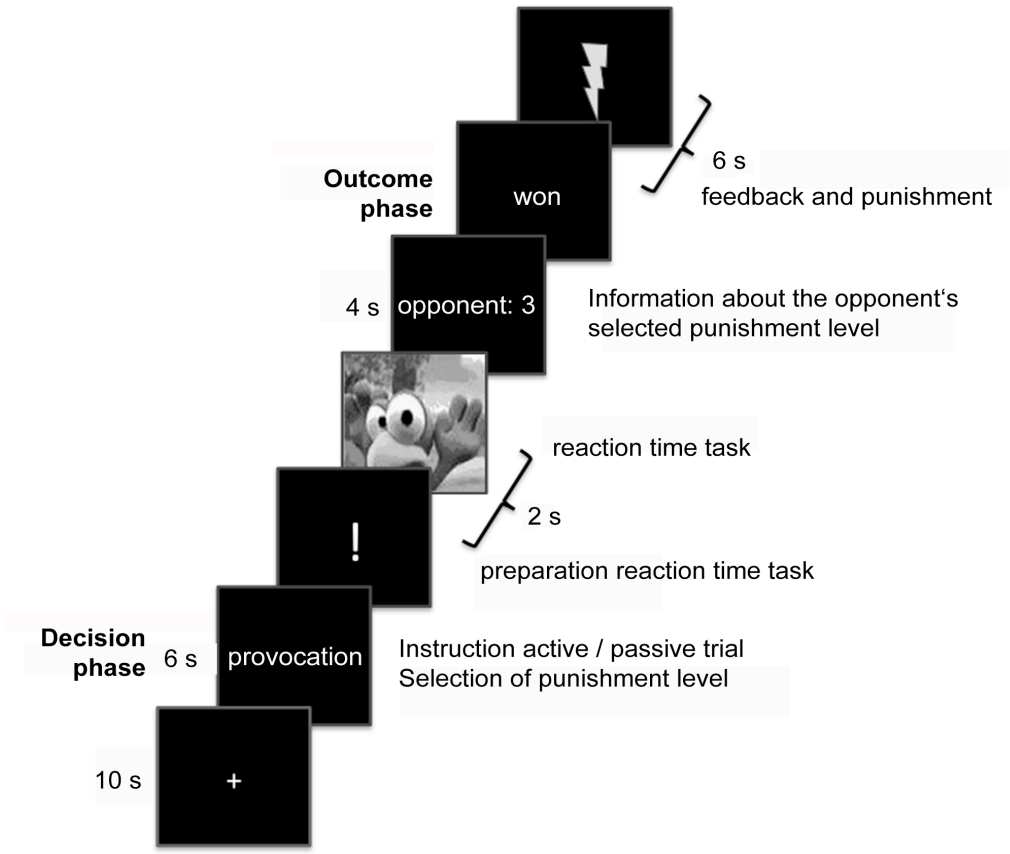

Figure 4.1. Trials of the experiment comprised a decision phase, the reaction time task, and an outcome phase. During the decision phase, participants made the selection of punishment level for the opponent (strength 1-4). This was then followed by the reaction time task where participants had to react as fast as possible when a chicken appeared on the screen. Directly after the reaction time task, they received feedback about the punishment level chosen by their "opponent player". In the upcoming outcome phase, participants were informed about whether they have won or lost the trial and either could punish the "opponent player" or received the punishment by the "opponent player". In "active" trials, participants could punish the opponent in case of winning the trial, whereas the participant received no punishment when losing the trial. On the contrary, in "passive" trials, participants could get punished when losing the reaction time task, but the "opponent player" received no punishment when losing the reaction time task.

Feedback of the opponents' punishment level selection was given in every single trial, no matter if it was an "active" or a "passive" one. They were also informed that feedback regarding their selection of punishment magnitude, was given to the opponent as well, serving as a threat for the opponent. Subsequently, the information whether they had won or lost the trial was given by presenting the German words for "won" or "lost". At the end of the trial, the punishment was administered depending on the actual block.

4.2.4 Questionnaires

Following the scanning session, participants completed the Buss and Perry AQ (Buss and Perry, 1992) and the German version of the IRI (Paulus, 2009). The AQ comprises 29 items scored from 1 ("extremely uncharacteristic of me") to 5 ("extremely characteristic of me") and assessed the four aggression dimensions physical aggression, verbal aggression, anger, and hostility. The IRI includes four 7-item subscales: *Perspective taking* is the ability to capture the psychological perspective of another person and is thought to involve several cognitive, but not affective, empathic processes. The *fantasy* scale reflects the tendency to put oneself into the role and behavior of characters from novels or movies. The third subscale - *empathic concern* - measures the sympathy and care for others, whereas the *personal distress* scale taps into feelings of inner restlessness and uneasiness when confronted with extreme situations such as an emergency. For the AQ, a total score was calculated by summing up the scores of the four aggression dimensions. To test for differences between the groups, one multivariate analysis of variance (MANOVA) per questionnaire was calculated comprising the between-factor group (AVP, placebo) and the within-subjects factor scale (AQ: physical aggression, verbal aggression, anger and hostility; IRI: perspective taking, fantasy scale, empathic concern, and personal distress).

4.2.5 fMRI-data acquisition

A 3-T Siemens Magnetom Trio syngo MR 2004A Scanner was used to record functional (Gradient-Echo-EPI-sequence; TR=2000 ms; TE=30 ms; FOV = 224 mm; flip angle = 80 °; matrix = 64x64; slice thickness=3.5 mm; interslice gap=0 mm) and structural images (T1-weighted MPRage: 256 x 256 matrix; FOV=256 mm; 192 1-mm sagittal slices). 388 volumes were recorded in each of the two runs. Each volume comprised 32 transversal slices (3.5 x 3.5 x 3.5 mm) recorded parallel to the anterior and posterior commissure (AC-PC).

fMRI analyses

FMRI data were analyzed using Statistical Parametric Mapping toolbox (SPM8, Wellcome Department of Imaging Neuroscience, University College London, London, UK). Preprocessing implemented slice time correction, motion correction, coregistration, spatial normalization and spatial smoothing (Gaussian Kernel, full width at half maximum (FWHM) 8 mm). A filter width of 128 s was used for temporal high pass filtering. Preprocessed data were entered into a random effects analysis. For the decision phase, the regressors “active” and “passive” blocks were defined (6s). For the outcome phase, the regressors “win” and “loss” were defined for active and passive blocks separately (6s). Regressors of noninterest regarding the target (2s), as well as the information about the opponents selected punishment level (4s), were included in the GLM. In addition, movement parameters (x, y, z, pitch, roll, and yaw) from movement correction were included in the statistical analysis to minimize signal-correlated movement effects. In order to control for serial correlations, the standard SPM autoregressive model was applied. The resulting regressors were convolved with the standard hemodynamic response function. Aggression-related effects during the decision phase were delineated by means of contrast maps calculated for each subject by comparing “active” trials vs. “passive” trials. This contrast was entered into a one-sample *t*-test for both groups separately. In order to test the influence of AVP treatment, two-sample *t*-test’s (AVP vs. placebo and vice versa) were conducted with the contrast images “active” trials vs. “passive” trials from the first-level analysis. This analysis essentially tests for an interaction of group and condition. In order to further investigate this interaction, the resulting active brain sites - the right STS, the ACC, and the fusiform gyrus - were used as a basis for post hoc functional region of interest (ROI) analyses. This was done by creating a 10-mm sphere centered at the peak voxel of the between-group comparison placebo versus AVP. In order to reveal this interaction’s direction, percent signal changes were extracted using rfx-plot (Gläscher, 2009) and finally entered into a 2x2 repeated-measures ANOVA implementing the following factors: drug (AVP and placebo) and block (active, passive).

For the outcome phase, win trials were contrasted against loss trials for each subject and entered into one-sample *t*-tests. Based on the hypothesis that it might be more rewarding for the AVP group relative to the placebo group to punish the opponent during active trials, a ventral striatum ROI was defined as a 5mm sphere centered at the peak voxel of the win trials versus loss trials contrast. This latter step was done separately for both the groups. Extracted percent signal changes were subjected to a 2x2 ANOVA with the factors block (“active” and “passive”) and outcome (win and loss) for both the groups separately. Between-group comparisons were conducted by entering the win trials versus loss trials contrast into a two-sample *t*-test.

4.2.6 Behavioral data

The average punishment level was calculated for each participant and "active" and "passive" trials separately. Data were subjected to a 2x2 ANOVA comprising the factors drug (AVP and placebo) and block condition ("active" blocks and "passive" blocks). In addition, the total number of high punishment level selections (levels 3 and 4) was calculated for each participant and for "active" and "passive" blocks separately and again entered to an ANOVA. Furthermore, the decision times for the participants' decision for high (levels 3 and 4) and low (levels 1 and 2) punishment levels were calculated for both the blocks separately. A 2x2x2 ANOVA with the factors drug (AVP and placebo), punishment level (low and high) and block condition ("active" and "passive") was conducted. Finally, the reaction times during the reaction time task (rtt) were calculated for both the blocks and entered into a 2x2 ANOVA with the factors drug (AVP and placebo) and block condition ("active" and "passive").

4.3 Results

4.3.1 Questionnaires

The mean AQ scores of AVP/placebo groups were (standard deviation in brackets) physical aggression scale, 27.5 (7.3)/27.1 (6.1); verbal aggression scale 12.8 (4.0)/11.0 (3.8); anger subscale 23.5 (4.8)/25.2 (3.7); hostility 26.8 (5.7)/27.3 (7.7). The statistical test revealed neither significant differences between the groups ($F<0.001$, $p>0.99$, $df=1.35$) nor a significant group x scale interaction ($F=1.63$, $p=0.2$, $df=3.33$). Only the main effect scale reached significance ($F=142.9$, $p<0.001$, $df=3.33$); however, for the current study's implication, this effect is of no interest. Mean IRI scores were perspective taking, 16.85 (4.02)/18.93 (3.37); fantasy, 15.0 (3.33)/16.47 (4.41); empathic concern, 17.5 (1.86)/18.13 (3.91) and personal distress, 9.25 (3.32)/10.27 (2.28). The pattern of statistical results was similar to the analysis of the AQ, showing a non-significant group ($F=1.33$; $p=0.25$; $df=1.29$) and group x scale test ($F=0.19$; $p>0.9$; $df=3.27$), but a significant scale effect ($F=37.07$, $p<0.001$; $df=3.27$).

4.3.2 TAP task: behavior

The average punishment level, the average of the total number of high punishment level selections, the decision times of punishment level selection and the reaction times to the bird stimulus did not differ between the groups (table 4.1).

Table 4.1 Average punishment level, average of the total number of high punishment level selection, mean reaction times of punishment level selection, and mean reaction times from the reaction time task are illustrated for both groups.

	AVP		Placebo	
	Active blocks	**Passive blocks**	**Active blocks**	**Passive blocks**
Average of punishment level selection	2.54 (SD=0.3)	2.38 (SD=0.5)	2.58 (SD=0.3)	2.54 (SD=0.48)
Average of the total number of high punishment selection	11.2 times (SD=6.9)	10.2 times (SD=6.6)	10.7 times (SD=4.5)	10.9 times (SD=4.8)
Mean reaction times (s) for high punishment selection	1.01 (SD=0.4)	1.11 (SD=0.4)	1.13 (SD=0.5)	1.11 (SD=0.48)
low punishment selection	1.0 (SD=0.33)	1.05 (SD=0.24)	1.14 (SD=0.38)	1.02 (SD=0.3)
Mean reaction times (s) of reaction time task	1.2 (SD=0.7)	1.18 (SD=0.56)	1.6 (SD=1.7)	1.38 (SD=0.84)

4.3.3 fMRI-data

In the whole brain analysis, the contrast “active” versus “passive” showed activity in the hippocampus during the decision phase in both the groups, which extended to the amygdala in the AVP group only (figure 4.2). Activation was also observed in the fusiform gyrus in both the groups (see table 4.2). Whereas the placebo group showed enhanced activity for active trials in the medial frontal gyrus, the temporal cortex (STS, superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, figure 4.2, left column), and the ACC, these activations were not present in the AVP group (see table 4.2). “Passive” trials, on the other hand, showed more pronounced activity in the lingual gyrus in both the groups. Additionally, the AVP group showed activations in the parahippocampal gyrus, the precuneus, the precentral gyrus, and the superior parietal gyrus (see table 4.3). Thus, whereas in the AVP group the contrast “passive” versus “active” trials comprised more activated brain sites, the placebo group showed more activated brain regions in the “active” versus “passive” trials contrast.

Table 4.2 Brain regions indicating increased activity in active trials compared with passive trials. Hem=hemisphere, BA=Brodmann area, xyz=MNI-coordinates, T=t-values, size=cluster size. Cluster threshold=10.

Active trials vs. Passive trials

Hem	Brain region	BA	x	y	z	T	size
AVP p<0.001 (uncorr.)							
L	Fusiform gyrus	20	-36	-10	-24	5.12	98
L	Hippocampus and partly the amygdala		-26	-8	-12	3.91	
R	Middle occipital gyrus	18	34	-96	-2	5.12	88
L	Lingual gyrus	18	-26	-94	-12	4.36	19
Placebo p<0.001 (uncorr.)							
L	Anterior cingulate gyrus	32	-2	50	12	6.40	1297
R	Anterior cingulate gyrus	32	8	44	12	6.29	
L	Anterior cingulate gyrus	24	-6	38	10	5.50	
L	Middle occipital gyrus	39	-42	-70	22	5.85	61
R	Medial frontal gyrus	9	6	54	40	5.54	172
L	Medial frontal gyrus	9	-6	44	44	4.41	
L	Medial frontal gyrus	9	-2	52	42	4.31	
R	Superior temporal sulcus	21	50	-42	6	5.37	334
R	Superior temporal gyrus	48	48	-22	4	4.60	
R	Superior temporal gyrus	41	48	-30	10	4.56	
L	Superior temporal gyrus	41	-42	-30	10	5.36	379
L	Middle temporal gyrus	20	-38	-24	-4	5.27	
R	Middle occipital gyrus	18	38	-88	4	5.31	232
R	Inferior occipital gyrus	19	34	-84	-2	4.50	
R	Inferior occipital gyrus	18	24	-100	0	4.42	
L	Medial frontal gyrus	11	-6	52	-14	5.26	86
R	Medial frontal gyrus	11	2	50	-16	4.20	
R	Middle temporal pole	20	42	14	-40	4.87	38
L	Cerebellum		-20	-86	-30	4.75	49
L	Cerebellum		-20	-84	-38	3.94	
R	Hippocampus	20	32	-8	-24	4.11	28
R	Inferior temporal gyrus	37	52	-60	-14	4.43	15
L	Inferior temporal gyrus	20	-46	-16	-30	4.41	23
L	Fusiform gyrus	20	-34	-14	-24	4.17	
L	Cerebellum		-6	-54	-18	4.37	36
R	Middle temporal gyrus	21	58	-34	-4	4.24	11
L	Cerebellum		-4	-84	-22	4.24	11
L	Inferior frontal gyrus		-54	26	-2	4.21	13
L	Inferior occipital gyrus	18	-28	-94	-8	4.05	13

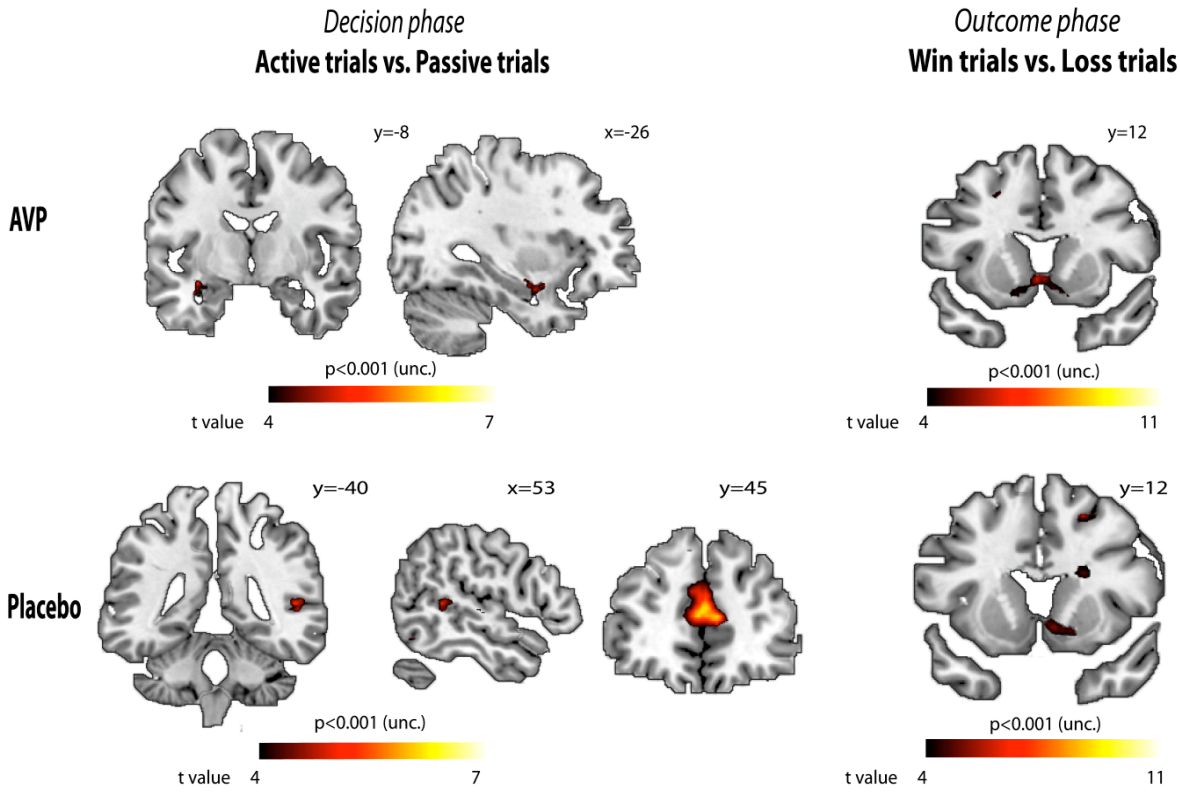

Figure 4.2 Neural activations are illustrated for the AVP group and placebo group for the contrast active trials versus passive trials from the decision phase and win trials versus loss trials from the outcome phase.

With regard to the between-group comparison and the contrast “active” trials versus “passive” trials, no brain region showed higher activity for AVP compared to placebo at the specified significance level ($p<0.001$ (uncorr.)). However, the reverse contrast (placebo > AVP) revealed increased activity in the right STS, the middle occipital gyrus, the anterior cingulate gyrus, and the fusiform gyrus (table 4.4, figure 4.3). The subsequent functional ROI analyses for the STS and the ACC revealed a main effect of block (STS: $F(1,29)=7.93$, $p=0.008$; ACC: $F(1,29)=23.98$, $p<0.001$) and a drug x block interaction (STS: $F(1,29)=13.52$, $p<0.001$; ACC: $F(1,29)=20.22$, $p<0.001$). In both functional ROIs, the interaction is driven by an increase of the BOLD signal for the condition “passive” trial in the AVP group that reached a level comparable to that for the condition “active” trial in both the groups (figure 4.4). The analysis of the FFG ROI revealed a significant drug x block interaction ($F(1,29)=9.77$, $p<0.004$), whereas the main effects failed to reach significance.

Table 4.3 Neural correlates showing enhanced activity for the passive trials versus active trials contrast. Hem=hemisphere, BA=Brodmann area, xyz=MNI-coordinates, T=t-values, size=cluster size. Cluster threshold=10.

Passive trials vs. Active trials

Hem	Brain region	BA	x	y	z	T	size
AVP p<0.001 (uncorr.)							
R	Lingual gyrus	17	8	-92	2	8.87	1787
L	Superior occipital gyrus	17	-14	-94	10	8.15	
R	Lingual gyrus	17	8	-90	4	7.02	
R	Superior occipital gyrus	19	24	-86	44	5.37	59
R	Superior occipital gyrus		10	-86	46	4.54	
R	Parahippocampal gyrus	20	34	-28	-16	5.03	14
L	Precentral gyrus	6	-44	2	54	4.71	10
R	Sulcus calcarinus	17	8	-70	8	4.46	11
R	Lingual gyrus	17	0	-72	8	3.95	
L	Precuneus	7	-8	-78	52	4.19	14
R	Superior parietal gyrus		22	-80	54	4.16	28
Placebo p<0.001 (uncorr.)							
L	Lingual gyrus	18	-14	-92	-4	5.56	116

In the outcome phase, the contrast win > loss trials showed activity in the ventral striatum in both the groups, which was present in both hemispheres in the AVP group and confined to the right hemisphere in the placebo group (figure 4.2, right column). Additional activity was seen in several frontal areas (medial frontal, middle frontal, and superior frontal gyrus) and in the fusiform and the lingual gyrus in both the groups. For the AVP group, additional increased activity was seen in the anterior cingulate gyrus and the supramarginal gyrus (SMG), whereas the placebo group showed activations in the precuneus, cuneus, hippocampus, precentral gyrus, inferior temporal gyrus, and thalamus (table 4.5).

In order to test the predicted differences in the ventral striatum, a functional ROI-analysis centered at the peak voxel of the ventral striatum revealed a main effect of outcome in both the groups (the AVP group: $F(1,29)=36.4$, $p<0.001$; the placebo group: $F(1,29)=15.5$, $p=0.002$). In both the groups, there was neither a main effect of block nor a significant interaction. Loss trials were associated with enhanced activity in the superior temporal pole and inferior parietal lobule in the AVP group (see table 4.6), whereas in the placebo group no brain region was activated at chosen statistical threshold and after decreasing the threshold to $p<0.005$ (uncorr.).

Table 4.4 Brain regions for the between-group comparison Placebo vs. AVP and the contrast Active trials vs. Passive trials are illustrated. Hem=hemisphere, BA=Brodmann area, xyz=MNI-coordinates,T=t-values, size=cluster size. Cluster threshold=10.

Placebo vs. AVP Active trials vs. Passive trials

Hem	Brain region	BA	x	y	z	T	size
p<0.001 (unc.)							
R	Superior temporal sulcus	42	48	-40	10	4.62	63
R	Middle occipital gyrus	19	36	-74	6	4.49	35
L	Anterior cingulate gyrus	24	-4	38	12	4.44	113
R	Anterior cingulate gyrus	24	4	38	10	4.22	
R	Anterior cingulate gyrus	32	4	44	16	3.59	
R	Fusiform gyrus	37	40	-48	-20	4.44	115

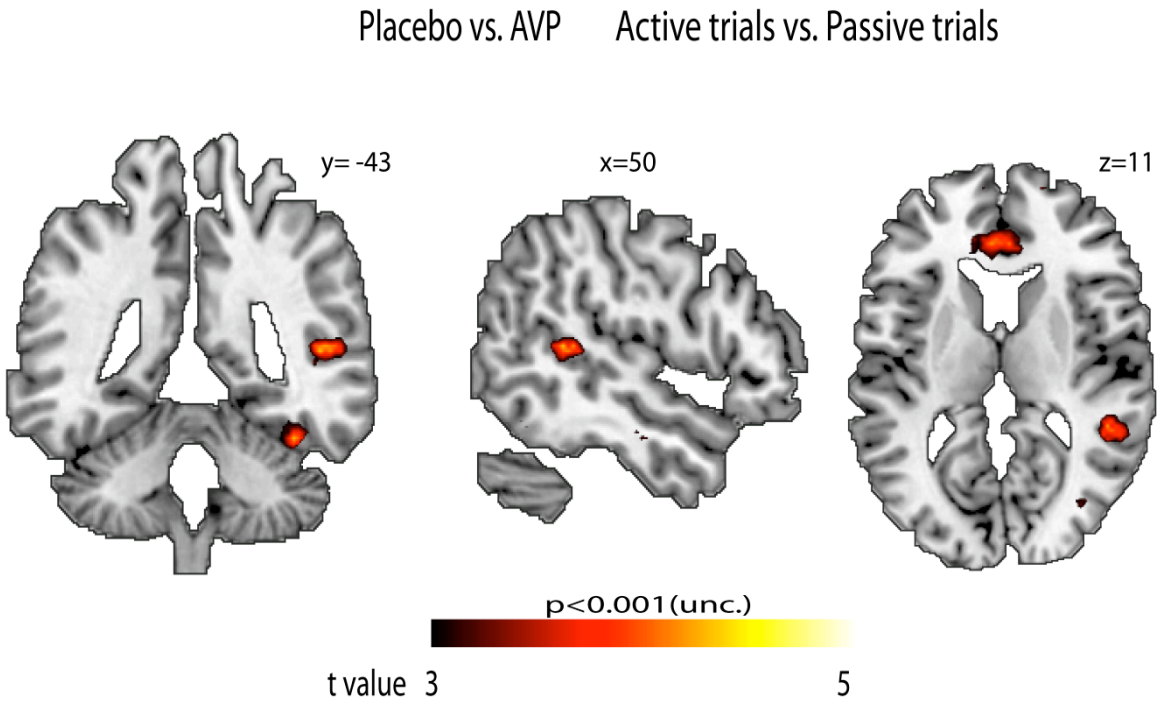

Figure 4.3. Between-group comparison (placebo vs. AVP) for the contrast active trials versus passive trials.

Table 4.5 Neural correlates for the comparison Win trials vs. Loss trials and Loss trials vs. Win trials. Hem=hemisphere, BA=Brodmann area, xyz=MNI-coordinates,T=t-values, size=cluster size. Cluster threshold=10.

Win trials vs. loss trials

Hem	Brain region	BA	x	y	z	T	size
AVP p<0.001 (uncorr.)							
R	Medial frontal gyrus	6	12	-16	54	7.73	86
R	Medial frontal gyrus		8	-26	58	4.75	
L	Middle frontal gyrus		-32	24	30	5.00	134
L	Middle frontal gyrus		-34	20	42	4.86	
L	Ventral striatum		-2	12	-4	6.18	1061
L	Anterior cingulate gyrus		-8	34	4	6.10	
R	Supramarginal gyrus		40	-44	34	5.72	13
R	Medial frontal gyrus	9	16	26	36	5.47	181
R	Middle frontal gyrus	9	32	22	38	5.43	
L	Middle occipital gyrus		-24	-80	6	5.06	207
L	Lingual gyrus		-24	-82	-10	5.04	
L	Fusiform gyrus	19	-26	-78	-18	4.47	
L	Superior frontal gyrus		-20	52	14	4.86	60
L	Middle frontal gyrus		-34	56	12	4.35	
R	Middle frontal gyrus		34	36	22	4.44	17
R	Superior frontal gyrus		16	46	42	4.33	21
R	Superior frontal gyrus		22	60	14	4.25	11
Placebo p<0.001 (uncorr.)							
L	Cuneus	18	-14	-88	16	10.31	10938
L	Cuneus	19	-4	-96	20	9.12	
L	Lingual gyrus	17	-10	-90	0	8.97	
L	Cerebellum		-8	-60	-46	6.87	226
L	Cerebellum		-14	-46	-50	6.41	
L	Cerebellum		-22	-58	-44	5.00	
R	Hippocampus		36	-24	-10	6.64	362
R	Fusiform gyrus	19	36	-46	-10	6.15	
R	Ventral striatum		18	22	-8	6.34	1345
R	Superior frontal gyrus		22	12	52	6.18	42
R	Superior frontal gyrus	10	12	64	24	5.84	430
R	Superior frontal gyrus		22	28	48	5.71	
R	Middle frontal gyrus		28	34	48	5.24	
R	Precentral gyrus		32	-18	54	5.41	71
R	Middle frontal gyrus		26	-12	54	4.07	
L	Inferior temporal gyrus		-52	-4	-36	5.11	45
L	Inferior temporal gyrus	20	-44	-6	-34	4.27	
L	Middle frontal gyrus		-16	46	-10	4.73	21
L	Thalamus		-14	-30	10	4.70	40
L	Thalamus		-22	-32	2	4.22	
R	Thalamus		4	-14	10	4.67	71
R	Precuneus		10	-60	56	4.57	24
R	Precuneus	7	14	-52	54	4.31	
L	Superior frontal gyrus		-10	56	2	4.30	32
L	Medial frontal gyrus	10	-6	60	14	4.27	34
R	Thalamus		10	-32	4	4.13	14

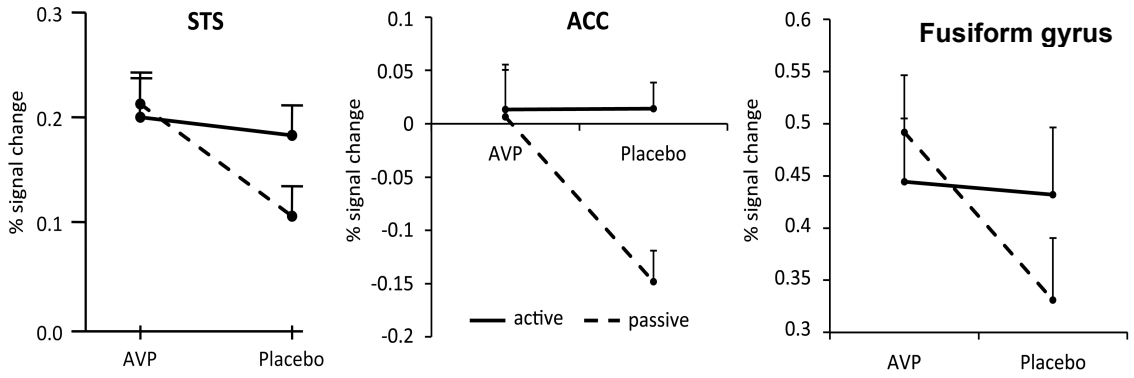

Figure 4.4 The interaction in the right STS, the ACC, and the fusiform gyrus is based upon an AVP-promoted increase in BOLD signal during the selection of punishment level in passive blocks.

With regard to the between-group comparison of win trials versus loss trials, for the comparison AVP > placebo no brain region survived the significance level ($p<0.001$ (uncorr.)), while for the placebo > AVP contrast the left SMG showed increased activity (see table 4.7). As can be seen from the subsequent ROI-analysis (figure 4.5), this effect is driven by an activation decrease under AVP treatment, while under placebo win outcome is associated with an activation increase. The statistical test of the extracted percent signal changes revealed a significant drug x outcome interaction ($F(1,29)=18.57$, $p<0.001$), but no significant main effect (drug $F(1,29)=1.32$, $p=0.25$; outcome $F(1,29)=3.98$, $p=0.055$).

Table 4.6 Results of the contrast loss trials > win trials. Hem=hemisphere, BA=Brodmann area, xyz=MNI-coordinates, T=t-values, size=cluster size. Cluster threshold=10.

Loss trials vs. Win trials

Hem	Brain region	BA	x	y	z	T	size
AVP p<0.001 (uncorr.)							
L	Superior temporal pole		-40	2	-20	5.04	92
L	Superior temporal pole		-38	-2	-10	4.74	
L	Inferior parietal lobule	40	-54	-34	22	4.68	126
L	Inferior parietal lobule	40	-62	-32	30	3.81	

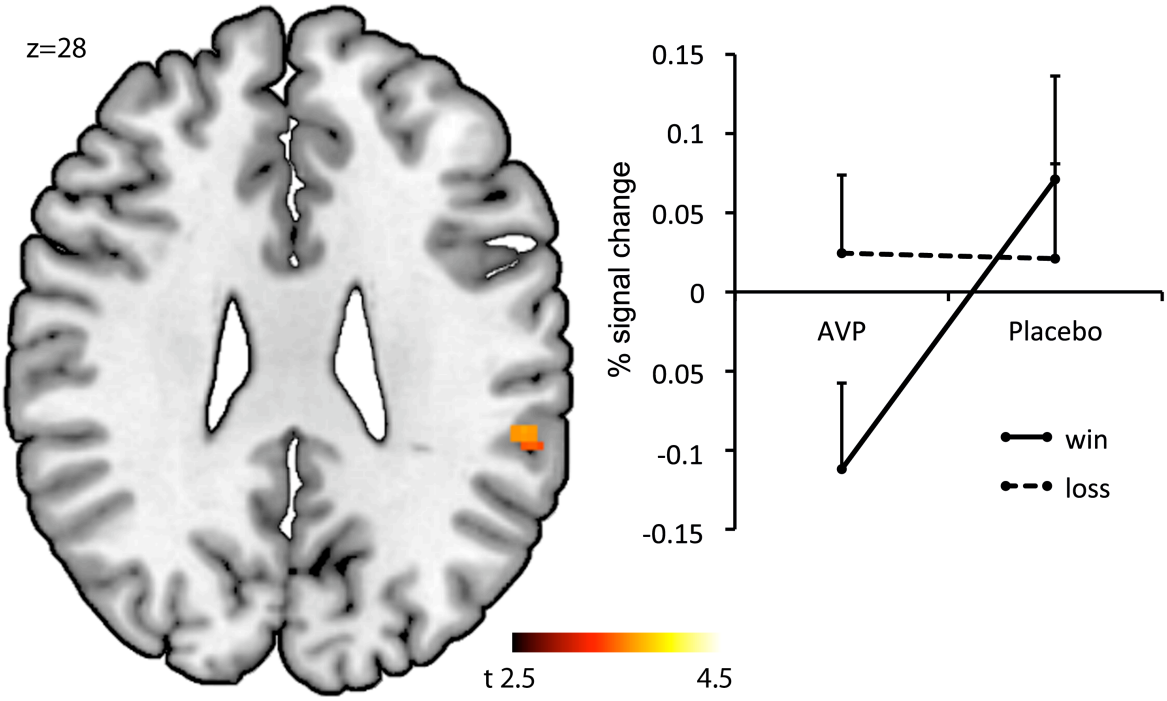

Figure 4.5. Between-group comparison (Placebo vs. AVP) for the contrast win trials versus loss trials.

Table 4.7 Results for the between-group comparison placebo > AVP and the contrast win trials > loss trials are illustrated. Hem=hemisphere, BA=Brodmann area, xyz=MNI-coordinates, T=t-values, size=cluster size. Cluster threshold=10.

Placebo > AVP Win trials vs. Loss trials

Hem	Brain region	BA	x	y	z	T	size
p<0.001 (uncorr.)							
L	Supramarginal gyrus	48	-56	-34	28	3.7	15

4.4 Discussion

The present fMRI study asked whether AVP, a neuropeptide that has previously been shown to modulate aggressive behavior in animals and humans, would influence behavior and neural responses in a laboratory task designed to study reactive aggression.

The present study used a between-groups design, as the nature of the TAP paradigm precludes repeated testing. It is therefore important to note that neither for AQ nor for the IRI significant differences between groups were found. However, we have to state, as it is already described in the “Methods” section, that the questionnaire data were collected at the end of our investigation. We did so in order to ensure that participants were not primed regarding the aim of the present investigation. Since the used questionnaires captured situation independent traits and a sufficient long lag was used between drug administration and collecting the questionnaire data, it is justified to assume that the questionnaire data were unaffected either by the TAP or by the drug administration. Thus, any group differences in aggressive behavior and/or neural responses in the TAP can be related to an effect of AVP rather than trait differences in aggressive behavior between both the groups.

Like in some other studies (Brunnlieb et al., 2013a; Pietrowski et al., 1996; Zink et al., 2010, 2011), we found AVP-related changes in brain activation patterns, but against our own hypothesis no AVP-related behavioral effects. Based on animal studies, showing that microinjections of AVP in the lateral septum or in the anterior hypothalamus led to increased aggression in male rodents (Bos et al., 2012; Caldwell and Albers, 2004a; Ferris and Delville, 1994; Ferris et al., 1997), and derived from investigations in humans, reporting an AVP-mediated bias in the perception and processing of social and emotional information, it had been expected that AVP would lead to higher punishment levels, whereas the selection of higher punishment levels was hypothesized to be more pronounced in “active” trials than in “passive” trials. In contrast to studies reporting an impact of AVP treatment on observable behavior (Guastella et al., 2010, 2011; Rilling et al., 2012; Thompson et al., 2004, 2006; Uzefosky et al., 2012), but in line with the above-cited investigations (Pietrowski et al., 1996; Zink et al., 2010, 2011) and a study by Israel et al. (2012), which also did not find an impact of AVP on social behavior, the expected behavioral effects did not show up. As AVP effects on behavior may be relatively small, one reason for these inconsistent findings might be the small group sizes in the present study and the studies by Zink et al. (2010, 2011). The study by Israel et al. (2012) investigated 96 male participants, however, rendering the sample size explanation for the

lack of behavioral effects insufficient. Therefore, there is a clear need for future research to identify additional factors moderating the impact of AVP on human social behavior.
Both, the reported brain activation patterns and the fact that after intranasal application of desglycinamide-arginine-vasopressin detectable levels of this analog to AVP can be found in the CSF as early as 5 minutes (Born et al., 2002; Riekkinen et al., 1987), suggest that the nasally applied AVP indeed reached the brain within the current protocol. The question arises whether the dosage used in the present investigation might have been too low to induce a behavioral effect. In several previous investigations, 20 IU AVP did induce a behavioral effect, although this was not the case in others. Also, in Zink et al. (2010, 2011), even 40 IU AVP did not cause a behavioral effect. Thus, there is no consistent relationship between dosage of AVP administration and behavioral effect. A similar phenomenon is already known regarding the influence of exogenous OT on social cognition and prosocial behavior. Inconsistencies in effects resulted in the assumption that prosocial behavior is not directly affected by exogenous OT, but rather is the result of OT's interaction with situational/contextual variables and situationally independent, individual stable personality traits (Bartz et al., 2011; Guastella and MacLeod, 2012).

Numerous variables are supposed to impact aggressive behavior in humans with each of these interacting factors contributing just a small fraction of the variance in order to prevent erratic aggressive responses and to stabilize behavior. This implies that the pharmacological impact of AVP can be present without behavioral effect, if other factors are able to even the neuropeptide's impact on overt aggressive behavior out. As Guastella and MacLeod (2012) already noted with respect to the varying impact of exogenous oxytocin on prosocial behavior, the impact of a neuropeptide is underestimated in case its influence on behavior is highly variable between subjects, but the neuropeptide's effect is pooled across subjects. This is usually the case in all between-subjects designs like in the present one. Thus, future research has to focus on the meaning of interindividual differences for the relationship between AVP treatment and aggressive behavior in humans.

The main finding on the neural level was that AVP modulated the activity in the right STS during the decision phase of "passive" trials during which participants could get punished by the opponent after losing the reaction time competition. In the present investigation, AVP enhanced the BOLD signal in the right STS during the decision phase of "passive" trials to a level comparable to that observed for "active" trials in both the groups. Previous work has linked the STS region to humans' ability to infer intentions and goal-directed behavior of other's referred to as mentalizing processes (Calder et al., 2002; Castelli et

al., 2000; Gallagher et al., 2000; Gobbini et al., 2007; Heberlein et al., 2004; Narumoto et al., 2001; Vogeley et al., 2001; Völlm et al., 2006). Accordingly, this suggests an AVP effect on neural processes supporting mentalizing/appraisal processes. The difference between "active" and "passive" trials is that only in "active" trials the punishment level selection had an instantaneous impact on the opponent. However, the opponent was also informed about the selected punishment level in "passive" trials, which indicated the player's intentions and could influence the opponent's behavior as well. The STS activation during "passive" trials can be interpreted as an indication, that under AVP these indirect consequences of punishment level selection were taken more into account. This explanation is supported by the increased activation for "passive" trials under AVP treatment in the ventral-rostral ACC and the fusiform gyrus, brain sites known to process social cognitions. The ventral-rostral ACC is involved in the integration of action monitoring and emotions (Bush et al., 2000; Etkin et al., 2011), but is also active during cooperation (Chaminade et al., 2012), mentalizing processes (Amodio and Frith, 2006; Camchong et al., 2011; Gilbert et al., 2010; Sommer et al., 2007), and theory of mind related tasks (Abu-Akel and Shamay-Tsoory, 2011; Apps et al., 2012; Weiland et al., 2012). The fusiform gyrus is involved in theory of mind tasks as well, but also in the appraisal of aggression-provoking situations (Krämer et al., 2007).

The interpretation of an increased involvement of mentalizing processes under AVP is corroborated by group differences in activation patterns for the comparison "passive" trials versus "active" trials. Whereas in the placebo group, only the lingual gyrus was found activated at the chosen statistical threshold, activations in the AVP group were found in a number of brain regions including the precuneus, a brain region previously associated with mentalizing processes as well (Döhnel et al., 2012; Krämer et al., 2010; Spreng et al., 2009). Although the results of the present investigation are in line with previous studies reporting that AVP moderates the processing of social-emotional information, the nature of AVP's impact on these processes is less clear. On the one hand, AVP treatment in men seems to promote the processing of emotional (Guastella et al., 2010), sexual (Guastella et al., 2011) and social information (Rilling et al., 2012), which results in increased activations of related brain sites (Rilling et al., 2012; Zink et al., 2010). On the other hand, studies by Thompson et al. (2004, 2006) have shown that AVP treatment resulted selectively in an aggressive/threatening interpretation of neutral, emotionally ambiguous information, while having no effect on the processing of positive or negative affective information. This effect seems to be similar to the reported activation pattern for "passive" trials in the present investigation. It is still an open question whether this effect is caused by an AVP-mediated increase of the salience of social/emotional information or by a more general affective relevant connotation of previous neutral stimuli under AVP treatment. At

least at the neural level, there is some evidence speaking against a global activation effect under AVP, since Zink et al. (2011) reported a decrease of the TPJ's activation under AVP when social-affective stimuli are processed.

Interestingly, an activation of the hippocampus extending to the amygdala was found for "active" trials (decision phase) in the AVP group. For the placebo group, a cluster in the hippocampus was identified as well, but did not extend to the amygdala. While this is a first hint at a direct influence of AVP on the amygdala, it needs to be interpreted with caution as it was only present when the activation patterns of the two groups were considered separately, but not on statistical comparison of the two groups. Similar to Krämer et al. (2007), the comparison of win trials versus loss trials (outcome phase) yielded increased activity in the ventral striatum, a key structure of reward processing. One of the hypotheses of the present study was that, under AVP, it might be more rewarding to punish the opponent, which should be reflected in a higher BOLD signal in the ventral striatum for win trials in "active" blocks. This hypothesis was not borne out, however, as a functional ROI-analysis for the ventral striatum did not show any interaction between the factors outcome and block in both the groups. Thus, AVP did not lead to an increase in reward-related activity in the ventral striatum when receiving the information to be allowed to punish a relatively highly provoking opponent. Instead, we found a differential effect in the outcome phase in the SMG. Several studies related the SMG to the processing of intentions (Osaka, et al., 2012) and the perception of social cooperation (Leube et al., 2012), but also to the processing of perspective taking (self vs. others, Morey et al., 2012). Indicated by the decreased activations for the win trials under AVP treatment, AVP seems to level such postdecisional processes. Together with the findings from the decision phase, one may conclude that AVP rather influences appraisal and mentalizing processes in emotional social exchange, but does not have a direct impact on processes related to the aggressive act per se.

Although the present investigation focuses on the impact of AVP on aggressive behavior, it is quite clear that AVP as well as OT modulate socially relevant behavior in a more general sense. In contrast to AVP, only two social situations have been described in the literature in which OT is associated with aggressive behavior: maternal aggression (Lee et al., 2009) and defensive aggression against competing outgroups in the context of parochial altruism (De Dreu et al., 2010). Apart from that, OT is closely related to bonding and prosocial behavior (McCall and Singer, 2012; Meyer-Lindenberg et al., 2011; Zink and Meyer-Lindenberg, 2012). It increases the ability to detect emotional and social signs in facial expressions, acts as an anxiolytic and, as a secondary effect, promotes trust in

other persons (Baumgartner et al., 2008). While functional imaging studies suggest that the amygdala is a key brain site for OT effects, only indirect support is available for the hypothesis that AVP acts via the amygdala as well. The dampening effect of OT on the amygdala is very often accompanied by decreased activations in the orbito- and medial prefrontal brain sites (Kirsch et al., 2005; Sripada et al., 2012). Just a few studies have reported increased activations in mentalizing-related brain sites, when processing social stimuli under OT treatment (Riem et al., 2011, 2012). However, the OT treatment related effects in the superior temporal cortex were found in women (Domes et al., 2010), while the present investigation and the study by Zink et al. (2011) found the AVP-treatment-related effect in men. To summarize, there is some evidence that exogeneous OT and AVP seem to act on overlapping brain circuitries. Future research has to disentangle the mechanisms of action and the potential differences between sexes.

As a final cautionary note, we would like to point to two limiting aspects of the reported results. As can be seen from other studies, the differential impact of AVP on BOLD responses related to cognitive functions seems to be relatively small. Accordingly, previous investigations have focused their analyses on a priori defined ROIs, i.e. BA 25/32 and the amygdala (Zink et al., 2010) or the amygdala alone (Rilling et al., 2012), and restricted corrections for multiple testing to these ROIs. In contrast, our results are based on a whole brain analysis. Since the reported *t*-values for between-group comparisons are at least as high as in the Zink et al. (2010) or Rilling et al. (2012) study (our study see table 4.4: t=4.62, Zink et al. (2010), table 1: Vasopressin>Placebo t=4.5; Rilling et al. (2011), supplementary table 3, AVP>PL t=3.1), but the criteria for a statistical test to survive a correction for multiple comparisons are more restrictive for a whole brain than for a ROI analysis, our statistical tests do not survive corrections for multiple comparisons. Due to the fact that the outcome of our statistical tests is similar to the effects of the cited studies, we regard these results as reliable. However, it is obvious that future research on AVP has to incorporate larger samples. Second, the present study only involved healthy men since in women an AVP treatment could interact with the hormonal cycle. Previous studies by Thompson et al. (2004; 2006) have revealed sex differences in AVP effects in humans. Moreover, it is known that AVP interacts with estrogen and OT (Akaishi and Sakuma, 1985; Gabor et al., 2012; Sarkar et al., 1992). Thus, further studies that also involve female participants at specific points of the hormonal cycle are needed to investigate, whether one can generalize the AVP effect seen in the current study also to women.

Chapter 5

General Discussion

The current thesis addresses the impact of AVP on various aspects of human social behavior. In a first study the role of AVP on empathy and mentalizing processes (chapter 2) was investigated, while in a second investigation the influence of this neuropeptide on human cooperative behavior (chapter 3) was illuminated. Third, the role of AVP in human reactive aggression (chapter 4) was examined. The series of current studies suggest a selective impact of AVP on human social behavior: during social situations that are affiliative (cooperative interaction), AVP seems to facilitate appropriate behavior, while in negative social situations such as an aggressive social interaction, AVP has no substantial influence on behavior. This may indicate a specific impact of AVP on human affiliative behavior and underpins the known role of AVP in social bonding as seen in several animal models (Caldwell et al., 2008; Carter et al., 1995; Insel, 2010; Young et al., 1999). Moreover, the present findings do not support the classical view of AVP as a modulator of aggressive behavior, as previously emphasized in human (Coccaro et al., 1998; Thompson et al., 2004; 2006) and animal studies (Bos et al., 2012; Caldwell and Albers, 2004a; Caldwell et al., 2008; Ferris et al., 1997; Goodson and Bass, 2001). It rather provides evidence for a prosocial action of AVP in humans. However, it should be noted at this point that the present thesis provides the first human data on AVP's impact during a reactive aggressive interaction. Thus, a larger data base is required to reveal more insight into the role of AVP in human aggressive behavior.

From an evolutionary point of view, a facilitated formation of social relationships might improve an organism's chance for survival and increase reproductive success. It is well known that people with strong social support, by living in happy social relationships with family and friends, have in most cases a longer life and can better cope with diseases than those people who suffer from loneliness and social isolation (Giles et al., 2005). The formation of social relationships also helps to establish security and thereby reduces stress and anxiety.

The known interactive character of central AVP with dopaminergic reward pathways also increases the rewarding nature of social relationships (Skuse and Gallagher, 2009; Young and Wang, 2004). The reward system, which is crucially linked to socially affiliative behavior, embodies a high quantity of AVP1a receptors in the ventral pallidum, the nucleus accumbens shell, the lateral septal nucleus and further regions in the dorsal striatum (Lim and Young, 2004; Skuse and Gallagher, 2009).

The present thesis found first evidence for a modulatory impact of AVP on human reward pathways. During cooperative behavior, AVP increased the functional coupling between the left dlPFC and a brain site often attributed to the reward system: the left pallidum. Previously, it has been reported that AVP1a receptors in this brain area are essential for pair bonding in prairie voles (Young et al., 2004). The author's argued that AVP acts on the ventral pallidum such that the social interaction becomes pleasant for the individual which in turn leads to an association of this pleasant, rewarding aspect with the other individual. As the present thesis found a first hint of an interaction between vasopressinergic and reward pathways, upcoming research might specifically focus on the interplay of both pathways. In the long run this could lead to the development of treatments for autism, borderline personality disorders, social anxiety disorders or schizophrenia; neuropsychiatric disorders that are characterized by strong social deficits (Meyer-Lindenberg et al., 2011).

For example, previous studies have linked social anxiety disorders to low dopamine levels (Schneier et al., 2000; Tiihonen et al., 1997). In addition, recent research found that AVP stimulates the release of dopamine in the reward system (Lim and Young, 2004; Nair and Young, 2006). According to this, intranasal AVP might be considered as possible treatment to stimulate the dopamine release in patients that suffer from social anxiety disorders. Additionally, it might have therapeutic value for people who suffer from attention deficit/hyperactive disorder which are similarly characterized by low dopamine levels (Iversen and Iversen, 2007; Swanson et al., 2007; Volkow et al., 2007).

In general, an important precondition for the development of novel treatments is to establish a better understanding of AVP's neural pathway and the neuroanatomical distribution of Vasopressin V1 receptors in the human brain. The series of current studies identified possible target regions of centrally acting AVP: the right amygdala during the processing of socially threatening scenes, the left dorsolateral prefrontal cortex during human cooperative behavior and the right superior temporal sulcus during a reactive aggressive interaction. Within this context, however, it should be noted that the functional magnetic resonance imaging method, which was used in all of the present studies, is not suited to distinguish whether the effects in latter brain regions are due to AVP's direct binding to specific receptors in these brain regions or are mediated via other brain sites. For example, previous studies did not localize any Vasopressin V1 receptors in the superior temporal cortex. Accordingly, it might well be that the AVP effect in the right superior temporal sulcus during human reactive aggression (see chapter 4) is based on excitatory influences of brain regions that comprise a high quantity of Vasopressin V1 receptors, such as the amygdala or the hippocampus. Bos et al. (2012) recently argued

that the effects of AVP in the human brain are mediated by a direct binding of AVP in the amygdala and that the effects of AVP on other brain sites are mediated via an indirect pathway from the amygdala. The findings of the present thesis might provide evidence for this assumption: (1) AVP significantly increased the BOLD signal in the right amygdala and altered it's functional connectivity with the medial prefrontal cortex during the processing of socially threatening scenes; (2) AVP enhanced the functional coupling between the left dlPFC and the left amygdala during the defection of cooperative behavior. This is consistent with Zink et al. (2010) who reported AVP induced alteration of the functional coupling between the amygdala and regions of the medial prefrontal cortex during the processing of fearful faces. However, given that previous work also localized Vasopressin V1 receptors in the prefrontal cortex (Young et al., 1999), it is also reasonable that AVP effects in the amygdala are modulated by influences from these distal regions. Connectivity approaches that allow insight into the direction of influence might bring more light into the discussion of a direct and indirect pathway of AVP's mediating effects in the socio-emotional network. In the present thesis functional connectivity according to Rissman (Rissman et al., 2004) was used to get insight into interregional interactions of the socio-emotional network and how these are affected by acutely administered AVP. Since the Rissman connectivity approach is based upon correlation analyses between beta-series, it does not provide any information regarding the direction of information transfer and the impact of centrally acting AVP on this information transfer. Therefore, effective connectivity approaches, such as Granger causality mapping or Dynamic causal modelling, should be considered for future research that allow to specify the causality between regions of the socio-emotional network.

The development of radioactively labeled AVP for PET studies might be a cornerstone for the understanding of the Vasopressin V1 receptor distribution in the human brain and could extent our knowledge, that we gained from receptor autoradiography and hybridization histochemistry in animal models, in various ways. Furthermore, since the intranasal pathway has been proven to bring a high level of AVP molecules into the human brain (Born et al., 2002), a better knowledge of the neurophysiology of AVP might help to establish treatments that mediate a long lasting effect of intranasally administered AVP.

Previous research showed similar effects of AVP and OT with regard to emotion recognition and memory encoding (Guastella et al., 2010, 2011) and found opposite effects of both neuropeptides in the context of social stress and cognitive performance (Ebstein et al., 2009; Kirschbaum et al., 1993; Meyer-Lindenberg et al., 2011; Shalev et al., 2011). The present thesis observed AVP effects during human cooperative behavior

that are similar to those reported for OT. AVP increased human cooperative behavior when the incentive to cooperate was high, but showed no substantial impact when the incentive to cooperate was low (see chapter 3). Similarly, in Declerck et al. (2010) OT increased cooperative behavior in a coordination game (high incentives to cooperate), whereas in the prisoner's dilemma game (low incentives to cooperate), no substantial impact of OT could be seen. Thus, the findings of the present thesis and those of Declerck et al. (2010) suggest that AVP and OT both increase cooperative behavior, when the situation is such that social approach is advantageous for the individual. Declerck et al. (2010) also reported that OT increased cooperative behavior strongly dependent on a prior social contact with the partner and surprisingly decreased cooperative behavior when participants were matched with anonymous partners. In the current AVP study, all participants had a prior social contact to the other player, which resulted in increased cooperation rates, just as observed in Declerck et al. (2010) for OT, where participants had to introduce each other by name, had to state their favorite hobby and shaked the hand of the other player. It is interesting to speculate whether AVP induces similar behavioral parameters like OT, when participants are matched with anonymous partners.
Rilling et al. (2012) compared both social neuropeptides and found that AVP increased human cooperative behavior, but only in response to a cooperative gesture of the other player. By contrast, OT increased cooperation following unreciprocated cooperation in the previous round.
To summarize the current findings and the work of Declerck et al. (2010) and Rilling et al. (2012), it appears that AVP and OT influence human cooperative behavior in dependence on the social context.

The present findings also suggest that AVP increases trust in humans, as previously reported for OT during a trust game (Kosfeld et al., 2005). Taking into account that AVP facilitated cooperative behavior in humans and cooperation requires a certain trust in your partner, it is reasonable that AVP promotes trust and might thus be used in future research to enhance psychotherapeutic interventions by the application of neuropeptides.

In general, research with animal models provided the view that OT and AVP have opposing roles (see e.g. Landgraf et al., 2008; Viviani and Stoop, 2008). For example, it has been suggested that AVP and OT have opposite effects on anxiety and fear (Viviani and Stoop, 2008). In humans, neuroimaging work found that intranasal OT reduced neural activity in the amygdala in response to threatening stimuli of different social valence (Kirsch et al., 2005). This dampening effect of OT on the amygdala has been replicated (Baumgartner et al., 2008; Domes et al., 2007; Petrovic et al., 2008; Singer et al., 2008).

By contrast, the present thesis found first evidence for an AVP promoted BOLD signal increase in the amygdala during the processing of socially threatening scenes (see chapter 2). This suggests opposing roles of both neuropeptides in humans' fear-related amygdala activity and is in agreement with the extant animal models (Viviani and Stoop, 2008). Nevertheless, as this is the first AVP study that found an AVP effect in the amygdala, future research is needed to provide more data.

A possible sexual dimorphism of central AVP effects and the anatomical distribution of Vasopressin V1 receptors within the socio-emotional network merit further consideration. The present thesis, as well as the majority of prior AVP studies, recruited only healthy males in order to avoid interactions with cyclic hormonal fluctuations in women. Accordingly, the effects demonstrated by the current thesis are limited to men and it is possible that for instance mentalizing and emotional empathy processes are differently affected by AVP in women. This is supported by Thompson et al. (2006) who found different AVP effects in women and men on socio-emotional communication patterns. Moreover, sex differences have also been demonstrated with regard to AVP's sister hormone OT (Domes et al., 2010; Gamer et al., 2010). These sex specific patterns might in turn lead to a completely different behavioral outcome in females from the one seen in males for cooperative behavior and reactive aggression.

The current work is based on administration of 20 IU of AVP in all studies which is a relatively low dose taking into account that the majority of previous AVP studies has used higher doses (e.g. Rilling et al., 2011, 2012; Zink et al., 2010, 2011). It is therefore possible that a higher dose of AVP would have led to AVP induced behavioral changes during the reactive aggressive interaction, as expected from the respective literature on animal models. Accordingly, future studies should compare different dosages of AVP.

In conclusion, we are still at the beginning of understanding AVP effects in the regulation of human social behavior and more research is needed, for example, on sex differences, AVP effects in clinical populations, and the neuroanatomical distribution of AVP receptors.

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Abbreviations

ACC	anterior cingulate cortex
AC-PC	anterior and posterior commissure
AH	anterior hypothalamus
AI	anterior insula
am	ante meridiem
ANOVA	analysis of variance
AQ	aggression questionnaire
Arg	arginine
Asp	aspartic acid
AVP	vasopressin
AVPR1a	AVP receptor 1a
AVPR2	AVP receptor 2
BA	brodmann area
BOLD	blood oxygen level dependant
CSF	cerebrospinal fluid
Cys	cysteine
Df	degrees of freedom
dlPFC	dorsolateral prefrontal cortex
EEG	electroencephalography
EMG	electromyography
ERP	event-related potential
F	F-value (ANOVA)
FDR	false discovery rate
FFG	fusiform gyrus
fMRI	functional magnetic resonance imaging
fMRT	funktionelle Magnetresonanztomographie
FOV	field of view
FWHM	full width half maximum
GAM	general aggression model
GLM	general linear model
Gln	glycine
Hem	hemisphere
HRF	hemodynamic response function
i.e.	(lat:id est) that is
IRI	interpersonal reactivity index
IU	international Units
L	left
MANOVA	multivariate analysis of variance
min	minutes
mm	milimetre
MNI	Montreal Neurological Institute
mPFC	medial prefrontal cortex
MR	magnetic resonance
MRI	magnetic resonance imaging
Ms	milisecond
OFC	orbitofrontal cortex
OT	oxytocin
PAM	perception-action model
PD	prisoner’s dilemma
PET	positron emission tomography
Phe	phenylalanine
pm	post meridiem

Pro	proline
R	right
ROI	region of interest
s	second
SD	standard deviation
Size	cluster size
SH	stag hunt
SMG	supramarginal gyrus
SPM	statistical parametric mapping
STS	superior temporal sulcus
t	t-values
TAP	taylor aggression paradigm
TE	echo time
ToM	theory of mind
TP	temporal poles
TPJ	temporo-parietal junction
TR	repetition time
Tyr	tyrosine
uncorr.	uncorrected
VOI	volume of interest

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Publications

Vasopressin modulates neural responses reated to emotional stimuli in the right amygdala (Brain research, 2013)

Vasopressin modulates neural activity in the right superior temporal cortex during human reactive aggression (Social neuroscience, 2013)

Androgens Modulate Brain Networks of Empathy in Female-to-Male Transsexuals: An fMRI Study (Zeitschrift für Neuropsychologie)