Oxytocin – not only a "social" neuropeptide

Implications from social and non-social task-based and task-free neuroimaging studies

Dissertation

zur Erlangung des mathematisch-naturwissenschaftlichen Doktorgrades

"Doctor rerum naturalium"

der Georg-August-Universität Göttingen

Im Promotionsprogramm Behaviour and Cognition

der Georg-August University School of Science (GAUSS)

vorgelegt von

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Göttingen, 2016

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Tag der mündlichen Prüfung: 24.10.2016

Summary

Research on the effects of oxytocin on social cognition and behavior is constantly growing. Moreover, oxytocin is already discussed to be used as a drug supporting common therapies for a range of disorders displaying deficits in social cognition. Although, the knowledge about its neurophysiological mechanisms lacks in particular regarding its functioning in the non-social domain of behavior, cognition and related brain responses. Therefore, the present thesis had the aim to explore whether the neuropeptide oxytocin has an effect on non-social cognitive processes and their underlying neural correlates, how the neural mechanisms of oxytocin are modulated by additional social input and which basal changes are driven by the effects of oxytocin. I addressed these questions by the use of functional magnetic resonance imaging (fMRI) with task-based and resting-state designs and with a neuroimaging genetics approach.

Oxytocin is synthesized in subnuclei of the hypothalamus and was originally known for its involvement in inducing labor. The oxytocin receptor is distributed largely across the brain, covering areas of the mesolimbic system such as the ventral striatum (vStr), the ventral tegmental area (VTA) and the amygdala, but also frontal areas and regions which are not prominently involved in social cognition. Generally, oxytocin is thought to affect social behavior and cognition, including parenting, affiliative behavior, but also emotion-regulation. It is also assumed to be sensitive for context, gender and personality characteristics. Whereas many studies explored the impact of oxytocin on socio-emotional actions such as on emotion-processing in the amygdala, only very few studies focused on the non-socioemotional domain, as for example memory processing or reward-related decision-making. With regard to the aims of this thesis, two of the three experiments employed a non-social decision making paradigm to reveal effects of oxytocin on non-social behavior and related brain activity. Indeed, oxytocin also modulated neural circuits during non-social tasks and even during the resting-state paradigm in the third experiment. This indicates that a social context might not be required to observe changes in neural activity and connectivity by oxytocin.

Several theories have been proposed to explain the mechanisms by which oxytocin might function. The social cognition theory suggests that oxytocin might modulate prosocial affiliative behaviors and self-referential processing, the fear/stress approach emphasized its anxiolytic and stress reducing effects, the general approach-avoidance hypothesis of oxytocin assumes that oxytocin acts on approach and avoidance motivation and the social salience hypothesis implies that oxytocin regulates the salience of social stimuli. In conclusion, currently there is no general theory accounting for all the social and non-social effects of oxytocin as described in the literature. In the same perspective, the overall results from the current thesis contradict aspects of each theory, while specific

patterns of effects may be best reconciliated with the framework of the approach-avoidance theory and the social salience hypothesis.

In the first study a neuroimaging genetics approach was applied to investigate whether common variants of the oxytocin receptor gene influenced behavior and neural responses in a non-social reward-based decision-making paradigm. Specifically, due to dopaminergic-oxytocinergic interactions oxytocin-induced changes were expected in bottom-up reward-related and in top-down cognitive control-related activity. Two of the three candidate single-nucleotide-polymorphism (SNP) of the oxytocin receptor gene (OXTR) were associated with a modulation of reward-related activity during desire and reason situations in the paradigm used. The desire context was formed by allowing to obtain a presented reward, whereas in the reason context the same reward had to be rejected. Participants who were homozygous for the major allele of the OXTR SNP rs1042778 expressed more bottom-up related activity in the vStr in the desire context. In contrast to this, minor allele carriers showed a greater suppression of the reward-related activity in the reason context. This might have led to better cognitive control and therefore to significantly better performance in the rejection of reward stimuli in reason situations. According to this, major allele carriers had a stronger coupling between the vStr and the VTA in desire contexts. Moreover, minor allele carriers displayed an enhanced connectivity between the vStr and the anteroventral prefrontal cortex (avPFC) in reason situations. For the OXTR SNP rs237897 an interaction of gender with the activity in the VTA could be detected. Female participants, homozygous for the major genotype, presented more activation in the left VTA compared to males. Altogether, this study could show that OXTR polymorphisms are able to modulate reward-related as well as control-related activity even in a non-social decision-making paradigm.

In study 2 a neuroimaging experiment was performed with the application of intranasal oxytocin and a modified reward-based decision-making paradigm including non-social as well as social stimuli. The main question was whether exogenous oxytocin alters behavioral and neural processes during the non-social condition in this task. Additionally, I was interested in possible changes of oxytocin effects by the presentation of emotional stimuli. Furthermore, by the additional use of both positive and fearful stimuli, I wanted to shed light on the ongoing discussion whether oxytocin acts valence-dependent or irrespective of valence on the activity of the amygdala. An opposite modulation of activity and functional connectivity regarding non-social compared with social context was shown after oxytocin treatment. In the non-social desire situation oxytocin reduced bottom-up activity within the vStr, probably by enhancing top-down control due to strengthening the negative coupling to a frontal region. In contrast, in non-social reason contexts the vStr was less deactivated, maybe due to decreased top-down control. By presenting fearful faces in the social condition, the

pattern of neural responses and functional connectivity reversed. In this condition, oxytocin increased the activation in the vStr in desire situations, while it reduced the activation in reason situations. This change in activity was paralleled by stronger positive coupling in the desire context and less coupling as well as negative coupling in the reason context. Furthermore, depending on valence oxytocin decreased amygdala activation for fearful faces and increased amygdala activation for positive faces. The altered activity within the reward system by oxytocin might be the reason for an impaired performance during both desire and reason trials. After oxytocin treatment participants were less accurate in selecting target stimuli than in rejecting the reward stimulus and vice versa for the placebo. This suggests rather an impaired working memory than disturbed stimulus-association learning. To sum up, the comparison between the effects of oxytocin in the non-social and social condition yielded that oxytocin influences corticomesolimbic regions in a context-sensitive manner.

The last study used a resting-state fMRI technique with additional administration of intranasal oxytocin. Of particular interest was the possible alteration of functional connectivity within and between large-scale networks by oxytocin. The analysis focused on functional networks indicated to play a major role in salience processing (the salience network - CO), social cognition and self-referential processing (the default mode network - DM) and attention processing (the ventral attentional network - VA). Thereby, basal changes by which oxytocin might influence neuronal responses were shown providing results for the ongoing debate on the underlying function of oxytocin. Although, I expected significant changes of functional connectivity within the DM network. The modulation of the CO and the VA networks were seen. Indeed, oxytocin changed the functional connectivity within and between large-scale networks even without engagement in a task. Oxytocin mainly influenced the VA by decreasing the cross-talk to regions typically part of the DM nodes; and oxytocin strengthened the functional connectivity to the edges of the CO, involving regions linked to salience processing. Additionally, oxytocin directly impacted the functional connectivity within the CO. Therefore, one basic effect of oxytocin might be to redirect attention (VA) from self-referential processing (DM) to the external environment, preparing for reception of salient information (CO).

Taken together, the purpose of the present thesis was to extend the knowledge about the effects of oxytocin as well as basic mechanisms of oxytocin's influence on cognition, behavior and neural activation and connectivity in non-social, social and task-free conditions. The results clearly demonstrated effects on neural activation, functional connectivity and on behavior in all three studies; supporting the claim that oxytocin does not only play an important role in socio-emotional processing.

Outline

Chapter 1

General Introduction

Someone skimming through the newspaper or online media in the last five years at some point came across the neuropeptide oxytocin. Whether it was hyped as the *love hormone*, *trust hormone*, *cuddle hormone* or *moral molecule*, it was clear for the public that scientists had identified a neuropeptide which was meant to be the glue for social interaction. Furthermore, oxytocin was handled as the miracle drug for diverse psychiatric disorders involving impaired skills in the socio-emotional domain as it showed promising positive impact on domains of social cognition such as emotion recognition and prosocial and altruistic behavior.

Scientific studies reporting experiments on oxytocin or at least publications referring to this neuropeptide accumulated over the last five years (Figure 1). It is worth mentioning that among these publications, the category of social-emotional processing increased especially. While between 1996 and 2001 only 5% of papers were published on this issue, in the last five years already 35% of all oxytocin publications included socio-emotional aspects. This bias reflects on the one side the public interest about the effects of this neuropeptide and on the other side the effort to use oxytocin as a drug for a wide range of disorders defined by social disabilities. By using more and more methods from neuroscience, as for example neuroimaging, the mechanisms behind oxytocin's social functions can be further explored.

However, a more detailed search on the scientific database pubmed revealed that the proportion of studies examining oxytocin's impact on cognition without social relations is stable with under 1% for clinical and neuroscience research in the years between 1996 and 2016. This issue is of potential concern as oxytocin is used in an increasing part of clinical research, but current theories and hypotheses about the function of oxytocin concentrate on its outcome mainly in the socio-emotional domain. When a neuropeptide is discussed to be used as a drug supporting common therapies it is imperative to study its consequences as a whole and not only in a limited domain. Oxytocin might also have an effect on cognitive functions such as executive control, reward-related decision-making or working memory in other than social situations, for example in economic situations. By focusing only on the socio-emotional aspects important effects of this neuropeptide on the living brain and organism could be missed and even the basic mechanisms and functions cannot be fully understood.

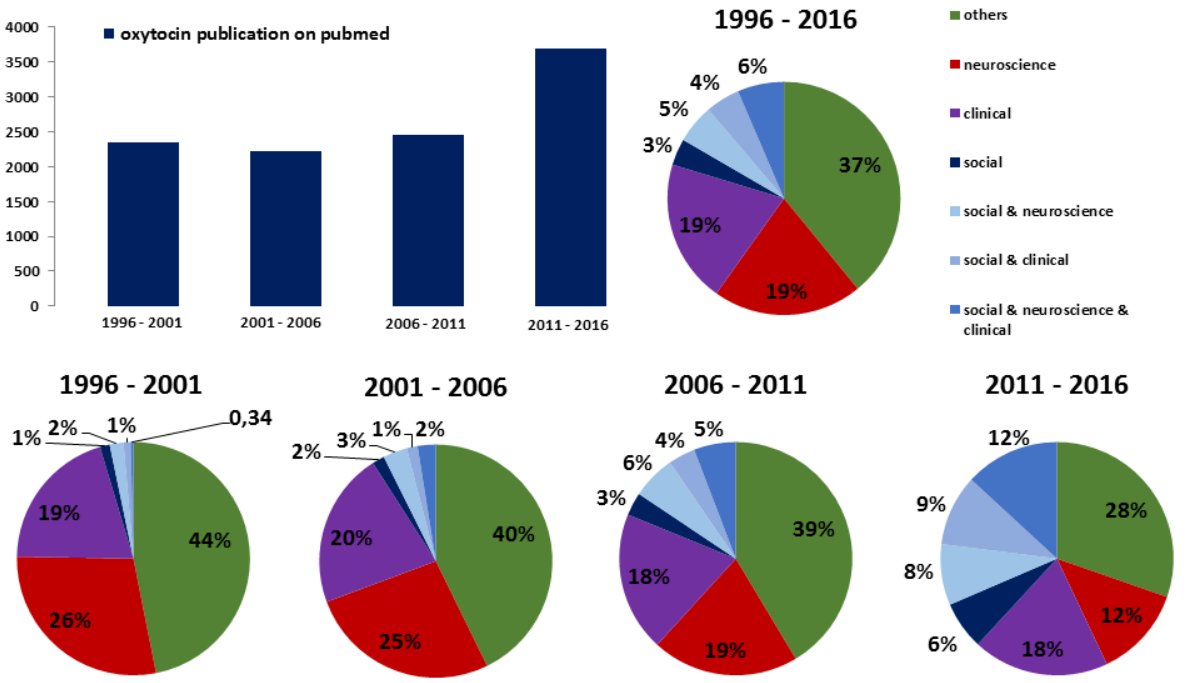


Figure 1: Publications referring to or dealing with oxytocin in the years between 1996 and 2001. Search on www.ncbi.nlm.nih.gov/pubmed for publications including the word "oxytocin" was performed on April 26th, 2016. Output was separated into papers published between 1996 - 2001, 2001 - 2006, 2006 - 2011 and 2011 - 2016. Further categories were formed by studies comprising terms referring to the neuroscience, clinical and social domain reclusive and combined. Top row: On the left side absolute quantities of oxytocin papers in 5 year steps between 1996 and 2016 are presented in a bar graph. Subcategories of oxytocin papers in percent are illustrated in a pie chart on the right side. Bottom row: Pie charts describe the proportion of subcategories of oxytocin papers in 5 year steps. Detailed information on pubmed search and forming of subcategories is specified in the appendix.

Therefore, the present thesis has the aim to explore whether oxytocin has an effect on non-social reward-related processes and their underlying neural correlates, how the neural mechanisms of oxytocin are modulated by additional social input and which basic neural mechanisms are underlying the function of oxytocin without non-social or social tasks. We addressed these questions by the use of functional magnetic resonance imaging (fMRI) with task-based and resting-state designs and with a neuroimaging genetics approach.

1.1. The neuropeptide oxytocin

Oxytocin was originally known for the induction of uterus contractions during labor or for the ejection of milk in mothers after birth, but it is also involved in parenting behavior in rodents and other mammalian species (for a detailed review see Insel, 1992). However, in the last twenty years more promising studies in voles implicated its role in pair- and mother-pup bonding by showing differences in the oxytocin pathway in polygamous and less parental montane voles compared with monogamous and highly parental prairie voles (for review see Insel, 2010). Since then a multitude of studies on human subjects was published exploring oxytocin's apparently unique effects on social and emotional processing (for review see Meyer-Lindenberg et al., 2011).

As oxytocin is highly suggested to play an important role on reward-related processes and behavior - described in the following subchapters - I chosed to investigate its non-social effects focusing on a reward-related decision-making paradigm. Although reviewing the assumed general effects of oxytocin on social-emotional cognition and behavior and related neural processes, I will emphasize mainly on its influences on reward-related behavior and the modulation of activity and functional connectivity in associated brain regions.

1.1.1. Neural pathways: oxytocin expression, distribution of receptors and fibers and suggested mechanism in the brain

The neuropeptide oxytocin is mainly synthetized and secreted by magnocellular neurons in two hypothalamic nuclei, the supraoptic (SON) and paraventricular (PVN) nuclei. To act as a hormone on peripheral targets outside the central nervous system, it is released by the posterior pituitary into the blood circulatory system (Gimpl and Fahrenholz, 2001; Insel, 1992). Besides, oxytocin is additionally released by dendritic transmissions or synaptic contacts into other regions of the central nervous system such as the limbic system and the autonomic systems of the brain stem (Insel, 1992; Knobloch et al., 2012; Ross et al., 2009). Moreover, it is hypothesized that oxytocin might be distributed by diffuse transmission into the extracellular space throughout the brain, allowing the neuromodulator to reach more distant targets (Gimpl and Fahrenholz, 2001; Knobloch et al., 2012). However, it must be pointed out that the central release of oxytocin might be independent of the pituitary release as the oxytocin levels in the cerebrospinal fluid and in plasma are not always correlated (Freeman et al., 2016; Kagerbauer et al., 2013; but see for positive results Born et al., 2002).

To date only one type of oxytocin receptor, a G protein-coupled receptor, has been identified (Gimpl et al., 2008; Gimpl and Fahrenholz, 2001). Recent histologic studies detected that the distribution pattern of the receptor is selective for species (Dumais and Veenema, 2016; Gimpl and

Fahrenholz, 2001; Insel, 1992). Histological studies performed in humans found staining in the ventrolateral septal nucleus, the amygdala, ventral striatum (vStr), the substantia nigra, the midbrain, the superior colliculus, the pontine tegmentum, the ventral pallidum, the globus pallidus, the cingulate cortex, the basal nucleus of Meynert, the hypothalamus, the olfactory bulb, postorbital gyrus, the vertical limb of the diagonal band of broca, hippocampus and in the subiculum (Boccia et al., 2013; Loup et al., 1991; Loup et al., 1989; for review see Stevens et al., 2014). Indeed, the distribution of oxytocin fibers and receptors might mismatch at different regions of the brain, but in general a similar pattern for oxytocin fibers and receptors is proposed (Knobloch et al., 2012; Stevens et al., 2014).

To my best knowledge, very few publications are available in the literature that address the issue of oxytocin's function on a molecular level which could be generalized to the human brain, despite the existent differences between species. An early experiment discovered that stimulation of neurons expressing oxytocin receptors facilitates gamma-aminobutyric acid (GABA) transmission, an inhibitory neurotransmitter, and therefore modulates the inhibitory network within the amygdala (Huber et al., 2005). Further support come from recently published experiments showing interactions between oxytocin and GABA receptors in stress (Smith et al., 2016) and fear responses (Knobloch et al., 2012). Other studies indicate that oxytocin receptors are mainly expressed by interneurons and that oxytocin might be important for the excitatory-inhibitory regulation by decreasing evoked inhibitory events (Mitre et al., 2016; Nakajima et al., 2014; Ninan, 2011). Mitre et al. (2016) suggested that this might be a mechanism by which oxytocin might enhance the processing of salient cues. Interestingly, the authors observed that oxytocin receptor activation in vivo was also evident for stimuli which were not defined as social, which is a main topic in the present thesis.

1.1.2. Effects of oxytocin on cognition and behavior

Generally, oxytocin is thought to affect social behavior and cognition. Early behavioral and pharmacological studies in animals could show its involvement in mother-pup bonding (Insel, 1992) and in pair formation especially in monogamous and polygamous types of species (Young et al., 2011). Further support emerged from genetic studies, indicating that an interruption of endogenous oxytocin synthesis or the prevention of oxytocin receptor binding would result in abnormal social cognition and behavior (Winslow and Insel, 2002) and in less social attachment and parental care (Keebaugh et al., 2015). Oxytocin is also known for its anxiolytic effects by facilitating regulation of emotion and stress responses after central release in response to stress inducing stimuli (for instance Nyuyki et al., 2011; for review see Neumann and Slattery, 2016).

The promising results obtained from these animal studies lead to the hypothesis that oxytocin might be mainly involved in socio-emotional processing and to the question whether it also applies to human social cognition and behavior (Meyer-Lindenberg et al., 2011). Due to the vast literature on this subject, I will concentrate on studies applying methods similar to the experiments reported here including neuroimaging genetics and intranasal administration of oxytocin, and excluding studies on endogenous oxytocin as measured in plasma.

The investigation of common variants of the oxytocin gene (OXT) and the oxytocin receptor gene (OXTR) and possible interactions provide evidence for its important role in social behaviors in humans (for review see Ebstein et al., 2009; Feldman et al., 2016; Kumsta et al., 2013; Meyer-Lindenberg et al., 2011). For example, genetic studies of OXTR single nucleotide polymorphisms (SNPs) revealed associations with empathy (Rodrigues et al., 2009; Schneiderman et al., 2014; Uzefovsky et al., 2015), theory of mind (Lucht et al., 2009), affect processing and emotion regulation (Haram et al., 2015; Melchers et al., 2013; Skuse et al., 2014; Tabak, 2013), prosocial decision making and social cooperation (Feng et al., 2015; Israel et al., 2009; but see for negative results Apicella et al., 2010), callous-unemotional traits and antisocial behavior (Beitchman et al., 2012), sensitive parenting (Feldman et al., 2012a), pair-bonding in adults and social childhood problems (Walum et al., 2012). Nevertheless, a meta-analysis could not find any link between two widely studied OXTR SNPs and social behavior measures (Bakermans-Kranenburg and van IJzendoorn, 2014).

Indeed, not only imaging genetic studies but also the application of intranasal oxytocin provides evidence for its important role in diverse social cognitions and behaviors. For instance it increases trust (Kosfeld et al., 2005; Mikolajczak et al., 2010; Zak et al., 2005), empathy (Abu-Akel et al., 2015; Bartz et al., 2010; Hurlemann et al., 2010), theory of mind and perspective taking (Domes et al., 2007b; Theodoridou et al., 2013b), self-referential processing (Liu et al., 2013), emotion processing and recognition (Di Simplicio et al., 2009; Fischer-Shofty et al., 2010; Lischke et al., 2012a; Schulze et al., 2011), social recognition memory (Rimmele et al., 2009; Unkelbach et al., 2008; Weigand et al., 2013), prosocial decision making (Hu et al., 2016), attentional gaze shifting to the eye region of emotional faces (Domes et al., 2007a; Ellenbogen et al., 2012; Gamer, 2010; Guastella et al., 2008; Lischke et al., 2012a; Tollenaar et al., 2013), social approach (Perry et al., 2015; Preckel et al., 2014; Scheele et al., 2012 but see for missing modulation Theodoridou et al., 2013a), sexual interest in women (Rupp et al., 2013), but also envy and gloating (Shamay-Tsoory et al., 2009) and aggressive behavior (Ne'eman et al., 2016). Moreover, exogenous oxytocin reduces anxiety and stress responses (de Oliveira et al., 2012; Ditzen et al., 2009; Heinrichs et al., 2003; Meinlschmidt and Heim, 2007), facilitates extinction of fear conditioning (Eckstein et al., 2015), and social reward learning depending on the valence of stimuli (Clark-Elford et al., 2014).

Whereas ample behavioral, neuroimaging and genetic studies in humans explored the impact of oxytocin on socio-emotional cognition and behavior, only very few studies focused on the non-social and non-emotional domain. Note that since the studies on stress response attenuation by oxytocin include mostly psychosocial or emotional stressors, these are covered by the socio-emotional section. One early study reported impaired learning performance for words in a verbal memory task in females and males after intranasal oxytocin administration (Bruins et al., 1992). Nevertheless, they did not detect any modulation of visual memory or attention. Moreover, it could be confirmed that oxytocin reduced the overall recall rate for social as well as for non-social words in comparison to a placebo condition (Heinrichs et al., 2004). However, in a further implicit recall test only the social words were affected. In contrast, a more recently published paper demonstrated that intranasal oxytocin impaired visual memory performance to both social and non-social stimuli (Herzmann et al., 2012). In an experiment exploring cooperative behavior, oxytocin increased cooperation when social information was presented, but decreased cooperation and lead to a risk-adverse strategy without social information in comparison to placebo (Declerck et al., 2010). Furthermore, studies on metabolic functioning and eating-disorders implicate that oxytocin also has an effect on the energy consumption and is related cognition, for instance a reduction of reward-related food intake was observed after intranasal oxytocin administration (Ott et al., 2013) and in addition it could be shown that oxytocin especially strengthened the top-down control over food intake (Striepens et al., 2016). Recently, more researchers became aware of the lack of studies on effects of non-social reward related behavior by oxytocin. However, neither a neuroimaging genetics study (Damiano et al., 2014) nor an intranasal oxytocin administration study on trauma-exposed participants (Nawijn et al., 2016) and on healthy subjects (Mickey et al., 2016) could observe any effects on behavior in a monetary incentive delay (MID) task (Knutson et al., 2000).

In contrast to studies examining the modulation of social and emotional processing and behavior by oxytocin, its possible effects on non-social cognitive functions are almost neglected in the research field. For this reason, the current doctoral thesis is dedicated to shed light also on the understudied functioning of oxytocin in these non-social domains, exploring those which were less popular in recent years.

1.1.3. Effects of oxytocin on neural activity and functional connectivity in humans

For clarity, only neuroimaging studies performed in humans are summarized here. Because of oxytocin's major role in socio-emotional processes, most task-based neuroimaging studies addressed its morphological and functional effects in neural circuits known to be involved in social cognition such as the amygdala and the hypothalamus. First, previous studies indicated that several

common OXTR polymorphisms impact the volume of the amygdala (Furman et al., 2011; Inoue et al., 2010; Marusak et al., 2015; Tost et al., 2010), the hypothalamus (Tost et al., 2011), the dorsal anterior cingulate cortex (ACC) and the posterior brain stem (Furman et al., 2011) as well as the insula (Saito et al., 2014) in different healthy populations. However, not only the volume of brain regions, but also reactivity and functional connectivity of the amygdala and the hypothalamus seem to be affected by certain OXTR SNPs. For instance, several studies found modulation of amygdala responses (Montag et al., 2013; Tost et al., 2010; Waller et al., 2016), its functional coupling to the hypothalamus (Tost et al., 2010) and also of the connectivity between the hypothalamus and the dorsolateral prefrontal cortex (dlPFC) (Wang et al., 2013).

Most of the fMRI studies exploring the effects of administered oxytocin on social cognition and emotion-related processes could find a suppression of the amygdala (Baumgartner et al., 2008; Eckstein et al., 2015; Kanat et al., 2015a, 2015b; Kirsch, 2005; Riem et al., 2014b, 2013). There are also studies showing a reduction of amygdala activation even without social context, for instance during painful stimulation (Singer et al., 2008) or after induction of acoustic startle responses (Striepens et al., 2012). Nevertheless, during positive reciprocated cooperation, the activity in the amygdala was found to become enhanced by oxytocin (Rilling et al., 2012). Additional to the modulation of activity within the amygdala, oxytocin decreased its functional connectivity with other regions involved in autonomic and behavioral responses in fear, such as brain stem regions (Kirsch, 2005), with regions involved in reward-related processes, such as the dorsal striatum and the midbrain (Baumgartner et al., 2008). However, functional connectivity between the amygdala and reward-related regions as well as regions involved in social cognition was also seen to be increased by oxytocin, to the orbitofrontal cortex, the ACC, the hippocampus, the precuneus, the supramarginal gyru and the middle temporal gyrus during infant laughter (Riem et al., 2012). Moreover, oxytocin increases the coupling between the amygdala and regions belonging to the salience network, such as the anterior insula and the left inferior frontal gyrus in memory performance after startle responses (Striepens et al., 2012) and during infant crying (Riem et al., 2011). Mixed results were obtained from neuroimaging studies using a resting-state paradigm. Contrary to task-based studies, intranasally applied oxytocin significantly increased the connectivity between the amygdala and the medial frontal cortex (Sripada et al., 2013) and reduced the coupling between the bilateral amygdalae and the right precuneus (Kumar et al., 2015).

Additionally, to its effects on the key region of the limbic system outlined above, there are more neural regions affected by oxytocin or oxytocin receptor genotypes. For instance, a paper reported increased activation in the inferior frontal gyrus, the middle temporal gyrus and the superior temporal gyrus in a theory of mind task; but this was accompanied by decreased

performance in the experiment (Voorthuis et al., 2014). In contrast, others found an improvement in accuracy of theory of mind together with enhanced neural activation in the superior temporal gyrus and the insula after oxytocin treatment (Riem et al., 2014a). Another newly published study on perspective taking detected that oxytocin enhanced activity in the temporo-partietal junction (TPJ) (Hu et al., 2016). Recently, a self- and other trait judgements task was used and demonstrated that oxytocin reduced responses in the dorsal and ventral medial prefrontal cortex (vmPFC) and in connectivity with the ACC (Zhao et al., 2016). In a resting-state paradigm by Riem et al. (2013) a decrease in functional connectivity between the posterior cingulate cortex and the brainstem was observed following oxytocin treatment. However, a recently published voxel-based meta-analysis observed only a hyperactivation of the left insula after oxytocin administration (Wigton et al., 2015). Then again, they included only eleven studies and did not check for confounding factors such as gender. It should be noted that the pattern of brain regions affected by oxytocin are largely overlapping with the social brain (for review see Norman et al., 2012).

Nonetheless, despite the extensive research on the amygdala reactivity after oxytocin treatment, there is still a discussion regarding the direction and the function of this modulation. On the one hand, Domes et al. (2007a) observed that oxytocin attenuated the neural activity in the amygdala during emotion processing regardless of the shown valence. In contrast to this, there is data pointing to a valence dependent regulation of the amygdala activity by oxytocin (Gamer et al., 2010; Shin et al., 2015). For instance, Gamer et al. (2010) reported that different subregions of the amygdala were involved in both valence-related and attentional effects. Whereas the activity was increased during presentation of positive emotional stimuli in a dorsal part of the amygdala, a more ventral subregion exhibited decreased activity during the presentation of negative emotional expressions. One of the more surprising results was that oxytocin increased the activation of the amygdala in females instead of reducing it as seen in males during presentation of fearful faces (Domes et al., 2010). Further evidence supporting the sex-specific modulation may lie in a study reporting enhanced amygdala reactivity during presentation of threatening scenes in women (Lischke et al., 2012b). However, extenuated amygdala reactivity by oxytocin were found in females diagnosed with generalized social anxiety disorder (Labuschagne et al., 2010).

Taken together, the most compelling piece of evidence from this large number of studies with regard to the aims of this thesis is that oxytocin also modulated neural circuits during non-social tasks and even during a resting-state paradigm. This indicates that a social context might not be required to observe changes in neural activity and connectivity by oxytocin. Additionally, the described neuroimaging studies on the impact of oxytocin on amygdala activation and connectivity seem to be insufficient to reveal the true underlying mechanism. As I will describe later, there is

growing support of the claim that gender, context and personal factors might influence the way in which oxytocin acts on neural and behavioral processes (Bartz et al., 2011). Therefore, further research on the specific effects of oxytocin on amygdala activity and connectivity and on neural regions involved in non-social tasks is required. The present thesis is an attempt to bridge this knowledge gap.

1.1.4. Oxytocin and dopamine interactions in the reward system

Due to the fact that two of the imaging studies presented in this thesis emphasizes the effects of oxytocin on the dopaminergic reward system, I summarize the relevant literature in an extra paragraph. Since I applied a decision-making paradigm recruiting mainly the key regions of the reward system, including the vStr (specifically the nucleus accumbens), the ventral tegmental area (VTA) and the PFC (Breiter and Rosen, 1999; Haber and Knutson, 2010), I will focus on these and related structures in the following section. The key regions studied in this study are illustrated in Figure 2.

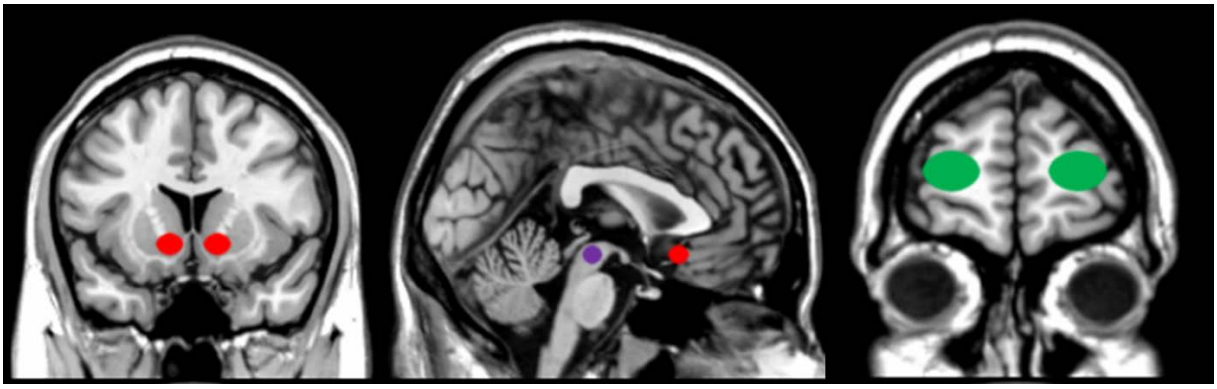


Figure 2: Key regions of the reward system studied in the task-based studies of the thesis. The bilateral vStr (including the NAcc) is shown in red, the midbrain/VTA is illustrated in pink and the avPFC is displayed by the green color.

vStr = ventral striatum, NAcc = Nucleus accumbens, VTA = ventral tegmental area, avPFC = anteroventral prefrontal cortex

The dopaminergic reward system is particularly involved in stimulus–association learning in which incentive salience is allocated to rewarding stimuli (Berridge, 2007; Flagel et al., 2011). Whereas the nucleus accumbens (NAcc) is suggested to play a major role in incentive salience processing as well as in reward anticipation and consumption (Berridge et al., 2009), the VTA is proposed to be involved mainly in salience processing (Bunzeck et al., 2006; Menon et al., 2015).

Moreover, the PFC is assumed to exert top-down control and to regulate, if necessary, the reward-related behavior (for example Ferenczi et al., 2016) as well as to be responsive to the magnitude of different rewards during reward receipt (Diekhof et al., 2012a).

Again, there are ample genetic and pharmacological studies performed in animals, highlighting the importance of key regions of the reward system involved in the modulation of social cognition by oxytocin. As the current thesis only involves studies conducted in humans, I will only mention a few of them. Above all, it could be shown that oxytocin interacts with the neurotransmitter dopamine in the reward system, especially in the NAcc and the VTA during pair-bonding (for review see Young et al., 2004), social cognition and behavior (Skuse and Gallagher, 2009) and during sexual behavior (for review see Melis and Argiolas, 2011). Moreover, it has even been postulated that oxytocin-dopamine receptor heteromers might exists in the NAcc, which also facilitates receptor-receptor interactions (Romero-Fernandez et al., 2013). Much research on maternal behavior and its modulation by oxytocin in the reward system has been done so far (for review see Bosch and Neumann, 2012), indicating that inhibiting oxytocin receptors in the NAcc and the VTA disrupts maternal behavior (D'Cunha et al., 2011; Olazábal and Young, 2006; Shahrokh et al., 2010). Additionally, knockdown of oxytocin receptor RNA in the NAcc (Keebaugh et al., 2015) and knocking out CD38 (Akther et al., 2013), which is engaged in oxytocin secretion (see for review Lopatina et al., 2013), results in aberrant parental behavior. An fMRI study by (Febo, 2005) investigating mother-pup bonding in rats could demonstrate that oxytocin administration as well as an oxytocin receptor antagonist modulated mainly regions which are known for their contribution to maternal behavior including the NAcc, the PFC, the VTA and the amygdala.

Finally, research on interactions between the dopaminergic and the oxytocinergic system as well as the modulation of reward-related structures by oxytocin becomes more popular regarding studies dealing with social cognition and behavior in humans. Parental behavior in mothers was examined, showing a correlation between oxytocin plasma levels and activation of brain regions related to the dopaminergic reward system, including the vStr (Atzil et al., 2012; Strathearn et al., 2009). Moreover, it was recently observed that oxytocin increased the response in the VTA during presentation of rewarding infant stimuli but also of sexual stimuli in women (Gregory et al., 2015). In two studies from the same group an increase of activation in the nucleus caudatus during reciprocated cooperation was described (Feng et al., 2015; Rilling et al., 2012). Moreover, one OXTR SNP influenced the activity in the dorsal striatum during a similar task (Feng et al., 2015). It should be noted that the change of activation was in the opposite direction for females and males. A likewise modulation of the dorsal striatum by oxytocin was also observed during a trust game (Baumgartner et al., 2008). By using positron emission tomography measuring stress induced dopamine release by

receptor availability, an oxytocin gene polymorphism was associated with greater stress-induced dopamine release in the ventromedial caudatus in females but not in males (Love et al., 2012). Wittforth-Schardt et al. (2012) suggested that oxytocin might affect the salience processing of social cues in the reward system as they found diminished activation and functional connectivity of the left globus pallidus with other reward- and attachment-related regions after oxytocin administration. In line with this, intranasally administered oxytocin led to an increase in the processing of socially relevant cues irrespective of valence in the VTA during a social incentive delay task which was assumed to might reflect the increase in salience of the anticipated social feedback by oxytocin (Groppe et al., 2013). Moreover, Hu et al. (2015) could show that oxytocin selectively increased responses in the amygdala, the extended hippocampus and putamen and functional coupling between the amygdala, insula and caudate during social feedback in the same task as used in the previous mentioned experiment.

Also, pair-boding in humans was considered to be influenced by oxytocin. Scheele et al. (2013) demonstrated in males an increased response in the VTA and the NAcc related to higher perception of the attractiveness of their own female partner. Moreover, they found an augmentation of the neural response in the left NAcc to their own partner compared with a familiar woman, indicating a partner-bond specific effect. However, in a positron emission tomography study altered binding of dopamine in the striatum or pallidum were not observed although attractiveness ratings for unfamiliar women were increased after intranasally applied oxytocin (Striepens et al., 2014). Instead there was an increased dopamine binding and reduced activity in the right dorsomedial PFC and superior parietal gyrus. Therefore, the authors concluded that oxytocin might alter attractiveness perception without dopaminergic contributions. A further lack of dopaminergic-oxytocinergic interaction was described by Sauer et al. (2013). They tested whether variants of the CD38 gene and a common catechol-o-methyltransferase (COMT) enzyme, known to be involved in the degradation of dopamine, interacted with the pharmacological intervention of oxytocin in response to social stimuli. While they found a modulation of the fusiform gyrus and a significant gene x gene x substance interaction in the amygdala, no significant effects for the vStr or the VTA were seen.

Nevertheless, oxytocin is also involved in dopaminergic-based but non-social behaviors, such as addictive behaviors (for review see McGregor and Bowen, 2012) and reward-related food intake. For instance, oxytocin's reduction of reward-related food intake was accompanied by a suppression of activation in the putamen, nucleus caudatus and midbrain regions (Striepens et al., 2016). In contrast, activity in the ACC, the precuneus and frontal regions was augmented indicating that oxytocin modulates mainly regions related to top-down control. Therefore, the authors suggested

that oxytocin might suppress the desire for rewarding food intake by strengthening cognitive control. Similar to my first study in this thesis, Damiano et al. (2014) published an imaging genetics study, in which they detected an association between a common polymorphism in OXTR and mesolimbic responses to rewards in a non-social MID paradigm. Recently, the same task was applied to participants suffering from post-traumatic stress disorder (PTSD) and traumatized controls uncovering enhanced neural processing of monetary reward and loss after oxytocin administration but not in the meso-limbic pathway (Nawijn et al., 2016). Another recently published paper applying the same paradigm to healthy controls found an increase of activation in the VTA during the presentation of incentive rewards (Mickey et al., 2016).

Despite the already existent neuroimaging studies on the impact of oxytocin on non-social behavior and related neural activation, there is still a profound lack of knowledge in this domain. For instance, Damiano et al. (2014) explored only three OXTR SNPs, which were not all identified as functional variants in previous literature. Additionally, the authors did not consider possible alteration of functional connectivity between reward related regions, which may be modulated by oxytocin. Neither Nawjin et al. (2016) nor Mickey et al. (2016) did explore functional coupling after oxytocin administration. Moreover, they included non-social stimuli only and therefore were not able to examine differences between social and non-social processing after oxytocin treatment. Importantly, the paradigm used in the first two studies of the present thesis differs from the MID task as it not only explores bottom-up related activation but also top-down processes or action control involved in suppressing impulsive decisions respectively.

1.1.5. Context, gender and personal characteristics are modulators of oxytocin's functionality

As already mentioned previously, in addition to its species selectivity, the behavioral and neural modulation by oxytocin seems to be sensitive for context and environment, gender and personality characteristics (for review see Bartz et al., 2011 or Olff et al., 2013).

Environmental factors appear to have a high impact on the distribution pattern of oxytocin receptors as seen in monogamous rodents living in an enriched environment in contrast to the oxytocin receptor distribution pattern in polygamous rodents in a poor environment (Insel, 1992). Furthermore, domesticated mice and rats exhibited higher densities of neurons expressing oxytocin than wild strains (Ruan and Zhang, 2015). Several publications in recent years documented sex-specific modulation by oxytocin. For instance, female laboratory rodents often possess higher oxytocin levels in contrast to males, who in turn show higher oxytocin receptor expression (Dumais et al., 2013). Moreover, behavioral effects related to oxytocin have been found to be gonadal

steroid-dependent in rats, since binding of oxytocin in some areas of the brain is estradiol-dependent in female rats (Insel, 1992). A detailed review of the interplay between oxytocin and gonadal hormones as well as further gender-specific effects by oxytocin in diverse species was published recently (Dumais and Veenema, 2016).

Yet, for humans the gender effects in oxytocin receptor distribution are lacking. Only Loup et al. (1991) were searching for sex differences. Because of a low female sample size (n=4) and insufficient sensitive staining for oxytocin receptors no gender-specific effects could be discovered in humans. But as opposite effects of intranasal oxytocin on behavior and neural activation in females and males were observed, as described subsequently, it is conceivable that humans also show sex specific distribution patterns. For instance, gender-specific effects under intranasally administered oxytocin were seen in perspective taking (Theodoridou et al., 2013b) and in social recognition memory (Herzmann et al., 2012). Higher concentrations of oxytocin in cerebrospinal fluid were detected in women compared to men suggesting that central release of oxytocin may be higher in females (as reviewed in Dumais and Veenema, 2016). OXTR SNP interactions with gender are thought to modulate amygdala volume (Furman et al., 2011; Tost et al., 2011), functional connectivity between the hypothalamus (Wang et al., 2013) and the dorsolateral PFC as well as amygdala reactivity to angry faces (Waller et al., 2016). Intranasally administered oxytocin reduced amygdala reactivity (for instance Kirsch et al., 2005) and diminished fusiform gyrus and superior temporalis gyrus activation (Domes et al., 2007a) evoked by several negative emotional stimuli in men but increased the activity in these areas to similar negative emotional stimuli in women (Domes et al., 2010; Lischke et al., 2012b). Similarly, an opposite sex-specific reactivity pattern elicited by oxytocin was found in the activation of the striatum and other reward-related areas during a social reciprocated cooperation paradigm (Feng et al., 2014; Rilling et al., 2014). Possible gonadal-hormone-oxytocin interactions were examined by Weisman et al. (2013) demonstrating that intranasally administered oxytocin altered testosterone levels and parenting behavior in fathers (Weisman et al., 2014). Further support comes from a recently published paper reporting a reduction in oxytocin-elicited reward-related activity in women using hormonal contraceptives (Scheele et al., 2016). Detailed reviews about gonadal-hormone-oxytocin interactions on social cognition and behavior are given by MacDonald (2013) and Dumais and Veenema (2016).

Furthermore, interactions with personality measures also account for variations in oxytocin's outcome on social behavior and neural responses (for review see Bartz et al., 2011). For instance, an interaction between an OXTR SNP and gender modulated the degree of self-reported harm avoidance (Stankova et al., 2012). Other common variants of the oxytocin gene were associated with stress-induced dopamine release linked to attachment anxiety, trait anxiety and lower well-being

depending on gender (Love et al., 2012), and with reward dependence in males only (Tost et al., 2010). Moreover, the environmental factor assessed by early life stress mediated the modulation of activity and functional connectivity within the limbic system by oxytocin (Fan et al., 2014; Grimm et al., 2014).

Overall, gender-specific effects were seen in neural and behavioral responses related to oxytocin and were also found in the decision-making paradigm used in this thesis (Diekhof et al., 2012). Therefore, I investigated the presence of gender-specific interaction effects with oxytocin in the neuroimaging genetics experiment as the sample was well-represented by including female and male participants. However, in the intranasal administration studies I included only male participants in order to avoid this possible confound. Moreover, potential inter-individual personality differences, measured by the Temperament Character Inventory (TCI) and the Barrett Impulsivity Scale (BIS), were also controlled for interaction with oxytocin outcome.

1.1.6. Common theories about oxytocin

Several theories have been proposed to explain the mechanisms by which oxytocin might act on social cognition, behavior and the underlying neural activity and functional connectivity. Due to the different outcomes in the socio-emotional domain, there is still an ongoing debate on the nature of its precise functioning. In the following section the main hypotheses will be shortly described.

Numerous experiments provide evidence for the influence of oxytocin on a broad range of social cognition and behavior and the underlying neural circuits as described in previous sections. Therefore, several researchers assume that a main oxytocin mechanism might lie in the enhancement of prosocial affiliative behaviors (Kosfeld et al., 2005; Zak et al., 2007). Nowadays, oxytocin is mainly suggested to influence neural circuits which are involved in social affective and self-referential processing (Kumar et al., 2015; Riem et al., 2013; Riem et al., 2011; Zhao et al., 2016). The major drawback of this social cognition theory is the fact that there is no common underlying mechanism which could explain all the consequences of oxytocin administration seen in different socio-affective processes, and non-social effects are totally neglected.

Along similar lines, the social-approach/withdrawal hypothesis by Kemp and Guastella (2010; 2011) infers that oxytocin mainly acts on the approach-avoidance system by upregulating the motivation for social approach such as in prosocial decision-making, and down-regulating social avoidance motivation such as by inhibition of negative emotional responses (Kemp and Guastella, 2010). Later, the theory was advanced into the general approach-avoidance hypothesis of oxytocin (GAAO) (Harari-Dahan and Bernstein, 2014) by claiming that oxytocin might act on a general level and not exclusive on social adaptive and maladaptive behaviors. Moreover, this theory specifies that

oxytocin might modify the reward system, including striatal, midbrain and frontal regions, leading to effects on approach motivation, and alters the cortico-amygdala circuitry for avoidance motivation. Although, the expanded version of the theory also considers non-social alterations by oxytocin, it is still a matter of debate why oxytocin also increases social behaviors which are defined as maladaptive in a particular context or depending on the gender of the tested sample.

The early fear/stress account mainly addressed the anxiolytic effects of oxytocin (Bartz et al., 2011) and according to it the anxiolytic function might be a basic mechanism by which oxytocin modulates several stress- and anxiety related responses. Therefore, this could also increase approaching behavior and salience processing, thereby affecting more complex social cognitions (Churchland and Winkielman, 2012). Indeed, the theory was extended by accounting additionally for stress and anxiety influences on social approach-related behavior (Heinrichs and Domes, 2008; MacDonald and Feifel, 2014), which was also supported by a paper reporting that the approach-related behavior elicited by oxytocin was modulated by social threat (Radke et al., 2013). Nowadays, oxytocin's involvement in stress reduction as well as in modulation of neural circuits for emotion regulation is considered (Neumann and Slattery, 2016). Therefore, this theory additionally considers oxytocin's non-social effects such as effects on stress responses. Nevertheless, it is still not successful in explaining oxytocin's influence on a variety of social cognitions and it is still neglecting non-social effects on memory or reward-related behavior.

The social salience hypothesis supposes that oxytocin may act primarily to regulate the salience of social stimuli and affiliative behaviors due to interactions with the dopaminergic system, including the VTA, the NAcc, the amygdala and areas of the PFC among other neural structures (Shamay-Tsoory and Abu-Akel, 2016). Major support for this hypothesis came from observed attentional shifts to salient features of social stimuli induced by oxytocin (for instance Gamer et al., 2010) or the increase in reward related activity linked to socially relevant stimuli (Groppe et al., 2013; Riem et al., 2011). A special focus is also placed on contextual and individual characteristics mediating the functioning of oxytocin (Bartz et al., 2011; Olff et al., 2013; Shamay-Tsoory and Abu-Akel, 2016). Further support arose from the observation that oxytocin seems to improve symptoms and to normalize neural activity and connectivity in patients suffering from disorders which are known to exhibit abnormal salience processing such as in PTSD (for review see Koch et al., 2014) or in generalized anxiety disorder (Gorka et al., 2015). In contrast to other theories the social salience hypothesis does not consider non-social effects of oxytocin.

Theodoridou et al. (2013a) performed a study in order to show which of the both most prominent theories, the approach-avoidance or the social salience hypothesis, accounts for an oxytocin mechanism. Interestingly, none of the two theories was supported by the results. Neither

an increased approach nor avoidance behavior – as suggested by the approach-withdrawal hypothesis - nor a stronger effect on social in comparison with non-social stimuli – as described by the social salience hypothesis - was found after oxytocin administration. In conclusion, currently there is no general theory accounting for all the effects of oxytocin on cognition, behavior and neural circuits in the literature.

1.2. Experimental methods used in the following studies

1.2.1. Functional magnetic resonance imaging (fMRI)

fMRI is a technique mainly used to explore cognitive function by utilizing the fact that active neurons spend energy that leads to an enhanced perfusion and blood oxygen level changes in involved neural structures. These local changes in blood oxygenation, which has been shown to be coupled with neural activity and is known as the blood oxygenation level dependent (BOLD) signal, can be detected by fMRI as oxygenated and deoxygenated blood exhibit different magnetic properties. The BOLD signal can be described in the hemodynamic response function, defined by a slow increase in blood flow reaching its maximum approximately 5 seconds after neural activation. As it is assumed that the hemodynamic response exhibits linear characteristics, general linear model can be used to compute statistical differences in time courses of the convolved BOLD signal. More detailed information regarding the fMRI technique is summarized in books for example by Huettel et al. (2009) or by Poldrack et al. (2011).

In the first two task-based neuroimaging studies reported in this thesis I used a rapid-event-related fMRI design and in the last one a resting-state fMRI paradigm. The task-based studies were used to investigate the effects of intranasal administered oxytocin and pre-selected OXTR SNPs on reward-based decision-making behavior and related mesocorticolimbic activation and functional connectivity. Previous neuroimaging studies provide evidence that by using the fMRI technique in tasks involving reward processing the neural underpinning of reward-related behavior can be investigated (Breiter and Rosen, 1999; McClure et al., 2004; O'Doherty, 2004). Therefore, I used a monetary reward-based decision-making paradigm which is called the Desire-Reason-Dilemma (DRD) paradigm and was developed in order to investigate neural activation and possible interactions between regions related to reward processing and impulse control (Diekhof et al., 2012; Diekhof et al., 2012b; Diekhof and Gruber, 2010). Contrary to the task-based studies, with the resting-paradigm I intended to examine the effects of oxytocin on neural connectivity during rest. I was especially interested in the modulation of large-scale networks by oxytocin. Large-scale networks are defined

by slow fluctuations (<.1 Hz) of coherent activity, consistent spatial topographic patterns and by involving brain regions known to play a role in sensor-motoric or cognitive systems (Betzel et al., 2014). Among other potential functioning they are suggested to reflect basic multiple states of the brain and to facilitate communication between regions far away from each other (Deco and Corbetta, 2011). As oxytocin exhibits a broad range of effects on neural activation depending on the particular experimental design, I was interested in investigating the underlying and basic mechanisms by which oxytocin might modulate neural connectivity irrespective of a task.

1.2.2. Statistical analysis used in the three fMRI experiments

Full factorial models in SPM (Wellcome Trust Centre for Neuroimaging, University College London, UK; http://www.fil.ion.ucl.ac.uk/spm) and MATLAB 2012a (The MathWorks, Inc., Natick, MA, USA) were used to analyze random effects on group level in the first two task-based studies. On the one hand, this enabled me to take all factors into account, including the particular contrast, genotype or treatment, and gender. Thus, to calculate within-subject-effects as well as between-subject-effects elicited by the experimental condition and oxytocin treatment or oxytocin receptor genotype depending on the reported experiment. Additionally, the full factorial model is known to be robust to different sample sizes by setting the variance parameter to unequal, which was of relevance for the imaging genetics study, and also for different amounts of events in the task-based intranasal administration study. Considering a recently published paper (Eklund et al., 2016) discussing the problem of false-positives in most of the neuroimaging studies using cluster-based-inference approaches, I report the main results of the first two task-based studies on a voxel-based-inference level, which was shown to be more conservative as applied by SPM, a software package for analyzing neuroimaging data.

Moreover, in both task-based studies I assessed the functional interaction between reward-related brain structures under oxytocin treatment by using psycho-physical interactions (PPI) (Friston et al., 1997). At first, individual BOLD signal time courses were extracted from so-called seed regions, defined by placing a sphere around preselected independent coordinates, which then served as physiological vectors in the analyses. The psycho-physiological vectors in the PPI analysis were formed by the specific contrasts of the DRD paradigm. Afterwards, the hemodynamic signals were deconvolved using a parametric empirical Bayesian formulation and mean-corrected to assess the underlying neural signal. Then the PPI interaction terms were built by multiplying the deconvolved physiological vector with the respective psychological vector, followed by convolution, mean correction, and orthogonalization. The three regressors (physiological vector, psychological vector and interaction term) went into the statistical analysis on single-subject-level. For group effects a

two-sample t-test was calculated for the single subject contrast images (PPI interaction term against baseline) of the oxytocin and the placebo treatment group.

In order to identify common large-scale networks, I applied a group independent component analysis (gICA) in the resting-state fMRI study. The gICA is a multivariate pattern approach across groups, dividing the neural signal into components (networks), which exhibit correlated signals within their elements but are independent from other components (Calhoun and Adali, 2012). The resulting components were individually back transformed to the single subject. After applying a GLM in SPM, the differences between oxytocin and placebo treatment groups were analyzed by the use of one-way ANOVAs. Further support for the observed changes by oxytocin was gathered by calculating Pearson correlation matrices to discover differences in the functional inter-network connectivity. The parallel analysis was conducted to account for the possible appearance of false-positives in the cluster-based analysis in SPM as described by Eklund et al. (2016).

1.2.3. Imaging genetics of oxytocin receptor gene polymorphisms

Although the approach of neuroimaging genetics applied to the oxytocin system is relatively new in oxytocin research, there is already ample evidence that common variants of the oxytocin receptor gene (OXTR) have an influence on the volume and the activation of neural structures involved in social cognition circuits (for review see Feldman et al., 2016; Israel, 2016; Kumsta and Heinrichs, 2013). Due to the fact that most of the imaging genetics studies focused on a modulation of social behavior and associated brain regions, there is a lack of evidence for potential effects also in non-social cognitions such as in reward-based decision-making. Indeed, a recently published paper found a link between an OXTR SNP and mesolimbic activation during reward anticipation in a monetary incentive delay task (Damiano et al., 2014). However, they did not investigate alterations of functional connectivity within the reward system. Additionally, in the imaging genetics study presented here I was also able to study possible influences on top-down control by OXTR polymorphism as the DRD paradigm offers situations eliciting bottom-up signals as well as situations in which action control is necessary (Diekhof and Gruber, 2010).

1.2.4. Intranasal application of oxytocin

The approach of intranasal application of oxytocin is widely-used since Born et al. (2002) provided evidence that intranasally administered vasopressin, a neuropeptide similar in structure to oxytocin, would reach the cerebrospinal fluid (CSF) within 30min (Born et al., 2002). In addition to the desired simple modulation of central oxytocin levels, there are no serious side-effects reported,

no subjective changes for the receiver and oxytocin application is not associated with adverse outcomes in a controlled setting (MacDonald et al., 2011).

Despite the growing number of studies on the effects of oxytocin on neural functioning, there is still an ongoing debate whether intranasally applied oxytocin reaches the central system or whether it is transported to the blood circuit (Guastella et al., 2013; Quintana et al., 2015). However, increased oxytocin levels within brain regions and in the extracellular fluid accompanied by increases in oxytocin plasma levels after intranasal oxytocin administration were reported for rodents (Neumann et al., 2013). Moreover, a study in nonhuman primates demonstrated an increase in CSF levels of oxytocin after intranasal application (Chang et al., 2012). So far, only one study performed in humans supplied evidence for the transportation of oxytocin to the brain by the use of arterial spin labeling in resting regional cerebral blood flow (rCBF) (Paloyelis et al., 2016). After oxytocin administration, they found increased rCBF in regions believed to become activated by oxytocin which sustained over the whole observation interval of 78min. Additionally, mixed results regarding the association between elevated oxytocin plasma levels and the central oxytocin pool were reported in the last decade. Although, Born et al. (2002) showed an association between plasma and CSF levels, others did not find such an association when investigating endogenous oxytocin (for instance Kagerbauer et al., 2013).

Until now, it is not clear which pathway from the nose to the brain is relevant for intranasally administered oxytocin. Therefore, different pathways have been suggested (Born et al., 2002; Guastella et al., 2013; Quintana et al., 2015) such as an intraneural pathway across the mucous layer to the olfactory bulb, a pathway by trigeminal nerve near the respiratory epithelium to the brainstem and last, via extracellular mechanisms or diffusion along paravascular or perineural spaces in the olfactory epithelium. Since it is assumed that taking the intraneural pathway might take at least hours, the extracellular pathway is more conceivable.

Chapter 2

Aims of the thesis

The main aim of the present thesis was to explore whether oxytocin modulates behavior and neural activity as well as connectivity even though no socio-emotional stimuli or context were presented. Despite existent evidence for non-social effects of oxytocin, there are still open questions of which behavior and neural structures are in particular influenced by oxytocin. Moreover, the current literature shows no consensus on the mechanisms by which oxytocin might affect social cognition, anxiety-, emotional and stress-related responses as well as non-social behavioral and cognitive patterns. The issue of finding a general and basic mechanism accounting for the diverse effects of oxytocin is still not solved to a sufficient degree. Therefore, this thesis addressed these core questions by applying different approaches such as the use of the fMRI technique with a non-social and social task-based decision-making paradigm, the use of a resting-state fMRI design providing no task, as well as intranasal administration of oxytocin and an investigation of an influence of common OXTR polymorphisms.

Chapter 3 describes a neuroimaging genetics approach to investigate whether common variants of the oxytocin receptor gene influenced behavior and neural responses in a non-social reward-based decision-making paradigm. Specifically, oxytocin-induced changes in bottom-up and in top-down processing were expected during desire and reason situations as the involved dopaminergic brain regions, namely the vStr, the VTA and the PFC, are known for its dense oxytocin receptor distribution and its modulation by oxytocin in studies on both animals and humans. Additionally, possible moderating effects such as gender and personality as well as impulsivity measures were proposed, since previous studies indicated an interaction with gender and individual characteristics in social reward-related behavior as well as associated brain regions by oxytocin.

Chapter 4 reports a neuroimaging study with the application of intranasal oxytocin and a modified reward-based decision-making paradigm including non-social as well as social stimuli. Again, the paramount question was whether exogenous oxytocin alters behavioral and neural processes during the non-social condition in this task. Additionally, I was interested whether and in which direction the observed pattern of effects would vary by presentation of emotional stimuli. Therefore, the focus was set to alterations of behavior and neural activation and functional connectivity by oxytocin during the decision-making task in the presence of non-social and emotional stimuli. The prediction was that in both conditions effects of oxytocin could be observed. Furthermore, by the use of positive and emotional stimuli during the social condition of the decision-making paradigm, I wanted to shed light on the ongoing discussion whether oxytocin acts valence dependent or irrespective of valence on the emotional-induced activity in the amygdala. On the basis

of previous published studies, I expected an influence of valence with opposite alteration of emotion processing by oxytocin.

Chapter 5 illustrates a resting-state fMRI study with additional administration of intranasal oxytocin. Of particular interest here was the possible alteration of functional connectivity within and between large-scale networks by oxytocin. The analysis concentrated on functional networks which mostly consist of neural regions indicated to play a major role in salience processing (the salience network), social cognition and self-referential processing (the default mode network) and attention processing (the ventral attentional network). Thereby, I supposed to find basic processes by which oxytocin might influence neuronal responses and to provide significant results for the ongoing debate on the underlying functioning of oxytocin. In detail, I expected significant changes of functional connectivity within the default mode network as previous studies as well as the social cognition theory and the approach-withdrawal hypothesis indicated a special role of oxytocin in social cognition. However, also a modulation of the salience network and the ventral attentional network were conceivable since the social salience theory proposed main effects in these functional networks.

Taken together, the purpose of the present thesis was to extend the knowledge about the effects of oxytocin as well as basic mechanisms of oxytocin's influence on cognition, behavior and neural activation and connectivity in non-social, social and task-free conditions.

Chapter 3

OXTR SNPs modulate the dopaminergic reward system in a non-social decision-making task

3.1 Abstract

Previously, it was shown that allelic variants of the OXTR impact behavior and its underlying reward-related neural response in social decision-making. However, although the research on the effects of oxytocin, its receptor and its genetically underpinning is escalated for the social-emotional domain, its impact on non-social cognition and behavior is mostly neglected. Therefore, we examined whether three single nucleotide polymorphisms of OXTR (rs1042778, rs237897, rs11131149) were associated with behavioral and neural responses in a monetary reward paradigm. For rs1042778 we found a main effect of genotype in the activation of the NAcc and a modulation of functional connectivity between this area, the VTA and the PFC. Additionally, the analysis revealed a gender x genotype interaction for rs237897. Moreover, impulsivity and personality scores correlated with the activation in reward related brain regions in both rs1042778 and rs237897 SNPs. We did not observe any significant impact of genotype on reward related behavior of rs1131149 nor on neural activation. Overall, we could show that allelic variation of OXTR, which is mainly studied in the social domain, is also involved in non-social decision-making by modulating the neural activity of the dopaminergic reward system.

3.2 Introduction

In everyday life, one has to take decisions in various contexts, such as in the management of financial conditions or in social interactions. Often the decision-making process is impeded when the possibility of gaining an immediate reward stands in contrast to the achievement of a prior defined long-term goal, which might offer higher benefits in the future. Therefore, cognitive mechanisms, such as self-control, are essential to overcome the impulse to select the proximate reward and in order to pursue the long-term plan.

It is assumed that at least two major systems are involved in these decision processes. Evidence comes especially from several animal studies (for instance Ferenczi et al., 2016) but also from human studies showing the recruitment of these systems occurring in reward related decision-making tasks (Clark et al., 2012; Ferenczi et al., 2016). For decisions favoring immediate or high rewards, parts of the mesolimbic dopamine system, the NAcc and the VTA, showed increased dopamine induced activation (Clark et al., 2012; Delgado, 2007; Haber and Knutson, 2010; Liu et al., 2011; McClure et al., 2004). In contrast, various regions of the PFC are associated with self-controlled behavior and decisions characterized by the ability to inhibit responses to manage goal-directed actions (Jimura et al., 2013; Kim and Lee, 2011; Knoch and Fehr, 2007). To investigate whether these two systems also interact in humans, a decision-making paradigm, called desire-reason-dilemma (DRD), was developed and applied in fMRI studies (Diekhof and Gruber, 2010). In situations in which participants were allowed to pursue their impulse and to collect immediate rewards, they found increased activation in the key regions, NAcc and VTA, but in situations in which the impulse for collecting the immediate reward had to be suppressed (desire-reason dilemma), they found reduced activation in NAcc and VTA and also a strengthened coupling between the NAcc and the anteroventral PFC (avPFC). Subsequent studies using the DRD paradigm demonstrated that gender (Diekhof et al., 2012), personality traits (Diekhof et al., 2012b), disorders such as depression (Goya-Maldonado et al., 2015) or bipolar disorder (Trost et al., 2014) and also allelic variation of a gene for encoding the cyclic AmP response element-binding protein (CREB) (Wolf et al., 2015) or of a gene (MADILI) associated with higher risk for bipolar disorder (Trost et al., 2016) could modulate the activation and connectivity between these systems.

In the current study, we explored whether allelic variation of the oxytocin receptor gene (OXTR) would also explain some variation in reward related activity during decision-making situations in the DRD paradigm. The functional and structural association of oxytocin with the neural reward system and related behavior is well studied at least in several animal studies on pair-bond-formation and mother-pup-bonding (Ross and Young, 2009; Young and Wang, 2004). Moreover, the oxytocin receptor is mainly distributed in mesolimbic and frontal areas, including the amygdala, hippocampus

and the anterior cingulate cortex but also the NAcc and medial PFC (Loup et al., 1989; Loup et al., 1991; Stevens et al., 2014). Several studies provide evidence for interactions between oxytocin and the neurotransmitter dopamine in reward-related regions (Baskerville and Douglas, 2010; Insel, 2010; Skuse and Gallagher, 2009) and evidence that dopamine-oxytocin receptor heteromers exists at least in the NAcc (Romero-Fernandez et al., 2013). Recently, also human studies start to focus more on the modulation of the reward system by oxytocin such as in romantic relationships (Scheele et al., 2013; Taylor et al., 2010), social learning (Hu et al., 2015), social memory (Herzmann et al., 2012) and social decision-making (Groppe et al., 2013; Hu et al., 2016). Even more interesting, SNPs of the OXTR show effects in social domains and underlying neural reward related processes, at least in prosocial decision-making (Israel et al., 2009) and pair-bonding (Walum et al., 2012). Moreover, interactions between OXTR genotypes and the neurotransmitter were observed during the processing of social stimuli (Sauer et al., 2013) and in stress responses with an additional effect of gender (Love et al., 2012). However, not only social reward processing might be affected by variations in OXTR. Indeed, a recent imaging genetics study showed even modulation of the mesolimbic reward circuit by an OXTR polymorphism in a monetary-incentive delay task without social context or stimuli (Damiano et al., 2014).

As there are fewer studies investigating the effects of oxytocin or OXTR in a non-social domain, it is still not clear whether the gene possess impact on the neural activation in further non-social cognitive tasks. This might be of special relevance as oxytocin is already used in trials with clinical populations which might benefit from its effects on social cognition (Koch et al., 2016; Shin et al., 2015; Watanabe et al., 2015). Though, not all daily tasks comprise a social context or social interactions as for example decision-making in financial or occupational affairs and dispensed oxytocin or a polymorphism in the OXTR might show also an effect on these non-social tasks. Therefore, the main research question of the present study was whether OXTR polymorphisms would also alter reward related activity and connectivity during the non-social DRD task. For the analysis, we mainly focused on key regions of the reward system, namely NAcc, VTA and avPFC, which have been shown to be strongly activated during the DRD paradigm (Diekhof and Gruber, 2010). We hypothesized to find an effect on neural activation and functional connectivity as the mentioned key regions are known to be modulated by oxytocin in a social context. Additionally, we were also interested if gender and OXTR genotypes would interact since the results of previous studies indicated that sex might affect both the dopaminergic (Diekhof et al., 2012) as well as the oxytocinergic (Feng et al., 2015) modulation. Moreover, as it is known that context and personality traits might modulates the effects of oxytocin, we wanted to explore whether this is also true for the OXTR polymorphism and non-social traits such as impulsivity and harm avoidance which was already found to modulate the activation during the DRD previously.

3.3 Methods

3.3.1 Participants

306 healthy male Caucasian subjects, recruited from the university environment, were included in this study. Participants were between 18 and 35 years old, had normal or corrected-to-normal vision, were free of any medical condition and were not suffering from psychiatric, neurological or any other diseases. In addition, they were screened for MRI contraindications and for drug or psychotropic use. Participants gave written informed consent and were paid for participation. All procedures were approved by the Ethics Committee of the University Medical Center Göttingen.

3.3.2 SNP selection, genotyping and analysis

We found 51 with OXTR associated SNPs after intensive search of common genetic data bases and review of published studies on OXTR effects in humans. From this sample, 10 SNPs were selected because of their effects on neural activity, anatomical structure and/or characterization as possible functional variants (Damiano et al., 2014; Feldman et al., 2013, 2012; Furman et al., 2011; Loth et al., 2014; Michalska et al., 2014; Montag et al., 2013; Tansey et al., 2010; Tost et al., 2011; Wang et al., 2013). Finally, 3 OXTR SNPs, rs1042778, rs237897 and rs11131149 were genotyped by using Illumina OmniExpress Chip. SNP rs11131149 was selected as proxy for rs13316193 because of their high association (R^2=1 and D'=1) according to SNAP (https://www.broadinstitute.org/mpg/snap/) and dbSNP-Q (https://cgsmd.isi.edu/dbsnpq/) data bases.

Minor allele frequencies of all selected OXTR SNPs were similar to values reported on public data bases and all SNPs were in Hardy-Weinberg-Equilibrium but not in linkage disequilibrium (Table1).

For genotyping, saliva was collected in Oragene saliva DNA kits (DNA Genotek) and human DNA was obtained by using the Gentra Puregene Blood kit (Qiagen). By using 400ng of DNA, SNP genotyping was performed with Illumina OmniExpress Genotyping BeadChips. Additionally, we checked for population stratification by the use of a principal component analysis included in EIGENSOFT (https://www.hsph.harvard.edu/alkes-price/software/). All subjects in this study were clustered together with HapMap3 European-descent populations.

We chose dominant models to explore the effects of OXTR SNPs on behavioral data and neural activity in the reward system by combining the homozygous minor allele groups (AA) with the

heterozygotes (AG) in comparison to the homozygous major allele groups (GG). This was done to minimize the number of between-subject comparisons and therefore to reduce the differences in sample sizes of the genotype groups. Furthermore, the minor carrier model account for the assumption that one minor risk allele is sufficient to modulate the reward related activity and it is known as a standard procedure for testing risk alleles on their impact on behavior or neural processes.

Table 1: Selected OXTR SNPs

SNP	Region	MAF	HWE ($\chi 2$)	Pairwise LD analysis ($D'/R^{2)}$		
				rs1042778	**rs11131149**	**rs237897**
rs1042778	intron	A = 0.43	1.64	-		
rs11131149	intron	A = 0.40	0.07	0.44 / 0.17	-	
rs237897	intron	A = 0.40	0.28	0.18 / 0.03	0.16 / 0.02	-

SNP = Single nucleotid polymorphism, MAF = minor allele frequency, HWE = Hardy-Weinberg-Equilibrium, LD = Linkage-Disequilibrium

3.3.3 The Desire-Reason-Dilemma paradigm

The DRD paradigm was developed to assess reward related activity in decision-making situations when a reward stimulus was allowed to be obtained or had to be rejected (Diekhof and Gruber, 2010). Prior to the fMRI experiment participants performed a conditioning task outside the scanner in which different colored squares were presented in a random order on a monitor and had to be accepted or declined by button press. Due to 20 repetitions for each of the 8 colors, participants learned that acceptance of two specific colors was associated with an immediate reward (bonus points) and the other 6 colors were associated with a neutral outcome. Afterwards, participants underwent a short training of the actual fMRI experiment. The event-related fMRI design consists of two sessions with 20 blocks respectively. Each block started with the presentation of two colored squares (cues) which had to be selected by button press in the following 4 or 8 trials to reach a superordinate goal of 50 points at the end. All other colors had to be rejected. Additionally, the reward associated colors from the conditioning task prior to scanning were presented. In half of the blocks, participants were allowed to select these colors to receive bonus points (desire context) and in the other half these colors had to be rejected to achieve the superordinate goal (reason context). Whether the participant had to abide by the rules of the desire or the reason context was indicated

by a letter prior to presentation of the cues, “B” (Bonus) for the desire and “Z” (Target) for the reason context. By missing or erroneous responses to target, non-target and bonus colors the current block was interrupted, the participant received zero points and a new block with new target colors started. In the end of each correctly finished block a feedback was given displaying the 50 points and additional selected bonus points. Again, a total feedback was presented at the end of each session. Finally, the amount of points was transferred into real money and payed to the participants (20-50€). The duration of a trial was about 1900ms including a blank screen (200ms), the color square (900ms), an immediate feedback (700ms) and again a blank screen (100ms). The total time to perform the 2 sessions of the DRD paradigm was approximately 12min. A more detailed description can be found in supplemental information (Figure S2).

3.3.4 Behavioral and personality measures and analysis

Behavioral data during scanning were acquired using Presentation software (Version 14.9, www.neurobs.com). In addition to demographic data, impulsivity scores and personality measures were obtained by applying the Temperament Character Inventory (TCI) and the Barratt Impulsiveness Scale (BIS). Normal distribution of performance data and personality measures were tested using the Kolmogorov-Smirnov test. Independent t-tests were used for differences between the groups of genotypes (two-tailed). When the normal distribution was violated the Mann-Whitney-U test was applied and for categorical parameters such as gender and handedness the Chi-squared test was used. To account for possible interaction effects with gender, we calculated separate ANOVAs for personality measures, performance and reaction time data including gender and genotype as between-subject factor. Analysis of behavioral and personality data were calculated using SPSS (IBM SPSS Statistics version 23, SPSS Inc., Chicago, Illinois, USA).

3.3.5 Imaging acquisition and analysis

MRI scans were conducted at a 3T scanner (Magnetom TRIO, Siemens Healthcare, Erlangen, Germany) by using a standard 8-channel phased array head coil. 31 axial slices (voxel size, 3x3x3mm^3; gap = 0.6 mm; matrix size = 96 x 96, field of view = 192 mm) were acquired in ascending direction using a T2*-weighted gradient echo-planar imaging sequence (interscan interval, 1.9 s; echo time, 33ms; flip angle, 70°). During each of the 2 functional sessions 185 volumes were obtained. FMRI data were preprocessed and analyzed using SPM5 (Wellcome Trust Centre for Neuroimaging, University College London, UK; http://www.fil.ion.ucl.ac.uk/spm). Preprocessing steps included coregistration, realignment to correct for head movements, slice-timing, normalization into standard

stereotactic space (MNI) with a resampling of 3 x 3 x3 mm^3, and spatial smoothing with an isotropic Gaussian kernel filter of 9 mm FWHM.

At the individual subject level, regressors were formed by convolving each experimental condition with the hemodynamic response function. Ultimately, the general linear model consists of 6 task conditions for correct trials in desire and reason context, 1 cue and 1 immediate feedback presentation, 2 block feedbacks for desire and reason respectively as well as 1 block abortion. Erroneous trials were excluded from the analysis.

First, a two-sample t-test was performed to assess brain activation effects elicited by the conditioned reward stimuli in the desire context and reason context for the entire sample independent from genotypes to confirm the reward related activation as hypothesized by previous studies using the DRD paradigm. For this reason, the desire and the reason contrasts were built by contrasting the conditions against baseline. To uncover the suppression of the reward related signal the desire-reason-dilemma was formed by comparing reward-related activity in the desire context versus reason context. For group inferences a full factorial model was calculated for each SNP with the factors genotype (AA + AG, GG), task condition (reward stimulus in desire context, reward stimulus in reason context) and gender (female, male) by using SPM8 (Wellcome Trust Centre for Neuroimaging, University College London, UK; http://www.fil.ion.ucl.ac.uk/spm). The task conditions were selected to reveal possible effects of the OXTR SNPs on reward related bottom-up activation in the desire context and on its suppression by top-down control in the reason context. Although, we did not find any interactions between gender and genotype on behavioral data, thought has been given to the fact, that intranasal oxytocin administration lead to heterogeneous neural effects between both sexes. As we had specific a priori hypothesis regarding task related neural activation based on previous observations *(*Diekhof and Gruber, 2010), we used small-volume-corrections for our regions of interests (ROI), namely NAcc and VTA, to correct for multiple testing. Coordinates from the original study were used to build spheres around the NAcc (x=±12 y=12 z=-4, 6mm) and the VTA (x=±8 y=-16 z=-16, 8mm). Activations are reported at a threshold of $p < 0.5/3 = 0.017$, corrected for family-wise error (FWE) as well as for multiple testing of all 3 SNPs. To illustrate the magnitude of change between the genotype groups, we plotted the means of the parameter estimates for desire and reason contrasts. For this purpose we extracted beta values with a sphere of 6mm around the reported peak levels by using the toolbox MarsBaR (Brett et al., 2002) and calculated the means and standard deviations for each group. Additional regions were reported in the supplemental information with a statistical threshold of $p<0.005$, uncorrected, with a minimum cluster size of k=10 voxels, if not otherwise indicated.

Furthermore, we assessed the functional interaction of significant ROI peaks to reveal the

impact of genotypes on the reward system by using psychophysiological interactions, PPI (Friston et al., 1996; 1997). Therefore, individual blood oxygenation level-dependent (BOLD) signal time courses were extracted from peak levels with a sphere of 8mm, which served as physiological vectors in the PPI analyses. The relative larger sphere of 8mm was selected to account for inter-individual differences regarding the exact localization of striatal activation and connectivity. The psychological vector consisted either of the desire, the reason or the dilemma contrasts. Then the PPI term was built separately for each of the regions by multiplying the deconvolved and mean-corrected BOLD signal with the respective psychological vector. The three regressors (PPI term, physiological and psychological vectors) went into the statistical analysis and genotype group comparisons were assessed by two-paired t-tests. Again, we used small volume corrections for previous defined ROIs and additionally included the avPFC as ROI. For the last region, we also used small-volume correction with a sphere of 6mm around coordinates (x=32 y=60 z=8) extracted from the original study. At last, we were interested in the influence of impulsivity and personality traits on differences in activation levels between genotype groups. Therefore, we correlated the subscales of the BIS and the subscale harm avoidance of the TCI questionnaires with the previously extracted beta values (Pearson's r correlation, two-tailed).

3.4 Results

3.4.1 Genotypic and sex effects on personality and behavioral data

228 participants were included in the final sample for all three selected SNPs. 77 participants were excluded because of missing imaging or genetic data, excessive head movements (more than 3.5mm) or absolute performance lower than 70% as well as voluntary abortion of the task. No statistical differences were seen in age, gender, handedness, TCI and BIS scores as well as in task performance between the genotype groups within SNP conditions except for the SNP rs1042778. The minor allele group was more accurate in rejection of the reward stimuli in the reason context (Table 2). The ANOVAs checking for interactions between genotype and gender regarding personality measures, performance and reaction time data yielded no significant effect (all $p > .017$).

Table 2. Mean values and standard deviation for demographic, personality and task performance data of selected SNPs and genotype groups

SNP	A/A + A/G	G/G	p–value
rs1042778			
Demographic data			
Gender	90 F, 58 M	47 F, 33 M	.76[a]
Handedness	139 R, 9 L	76 R, 4 L	.74[a]
Age (years)	24.10 ± 2.36	23.91 ± 2.64	.51[b]
Temperament and Character Inventory			
Novelty seeking	21.34 ± 5.82	21.38 ± 5.64	.97
Harm avoidance	13.53 ± 5.96	13.92 ± 6.50	.65
Reward dependence	16.75 ± 3.24	16.26 ± 3.71	.48[b]
Persistence	4.71 ± 2.20	4.70 ± 2.02	.91[b]
Barratt Impulsiveness Scale			
Attentional impulsivity	16.16 ± 3.06	16.23 ± 2.94	.94[b]
Motor-impulsivity	22.21 ± 3.60	22.53 ± 3.62	.51[b]
Non-planning Impulsivity	23.45 ± 4.02	24.00 ± 4.70	.56[b]
Total	61.82 ± 8.31	62.75 ± 8.77	.43
Performance and reaction time			
Goal failure (absolute value)	7.20 ± 3.94	7.75 ± 4.30	.43[b]
Desire context			
Acceptance of reward stimuli (%)	88.61 ± 12.15	89.61 ± 8.10	.60[b]
Reaction time (ms)	515.23 ± 49.77	520.05 ± 52.72	.49
Reason context			
Rejection of reward stimuli (%)	97.22 ± 4.01	95.84 ± 5.03	**.01[b*]**
Reaction time (ms)	500.78 ± 48.50	511.72 ± 57.29	.13
rs237897			
Demographic data			
Gender	85 F, 62 M	52 F, 29 M	.35[a]
Handedness	138 R, 9 L	77 R, 4 L	.71[a]
Age (years)	23.92 ± 2.42	24.25 ± 2.52	.42[b]
Temperament and Character Inventory			
Novelty seeking	21.49 ± 6.04	21.10 ± 5.12	.63
Harm avoidance	13.83 ± 6.33	13.38 ± 5.84	.60
Reward dependence	16.59 ± 3.52	16.54 ± 3.24	.87[b]
Persistence	4.78 ± 2.12	4.56 ± 2.01	.34[b]
Barratt Impulsiveness Scale			

Attentional impulsivity	16.43 ± 3.03	15.73 ± 2.94	.12[b]
Motor-impulsivity	22.56 ± 3.51	21.89 ± 3.74	.18
Non-planning Impulsivity	23.75 ± 4.22	23.46 ± 4.40	.62
Total	62.74 ± 8.30	61.08 ± 8.72	.10[b]
Performance and reaction time			
Goal failure (absolute value)	7.73 ± 4.15	6.78 ± 3.87	.13[b]
Desire context			
Acceptance of reward stimuli (%)	89.13 ± 10.03	88.65 ± 12.37	.62[b]
Reaction time (ms)	515.94 ± 49.02	518.67 ± 54.03	.70
Reason context			
Rejection of reward stimuli (%)	96.71 ± 3.99	96.78 ± 5.12	.13[b]
Reaction time (ms)	507.55 ± 54.76	499.30 ± 46.09	.25
rs11131149			
Demographic data			
Gender	87 F, 59 M	50 F, 32 M	.84[a]
Handedness	138 R, 8 L	77 R, 5 L	.85[a]
Age (years)	24.18 ± 2.64	23.78 ± 2.09	.33[b]
Temperament and Character Inventory			
Novelty seeking	21.07 ± 5.73	21.85 ± 5.76	.33
Harm avoidance	13.77 ± 6.08	13.49 ± 6.31	.75
Reward dependence	16.61 ± 3.24	16.52 ± 3.72	.77[b]
Persistence	4.78 ± 2.06	4.57 ± 2.26	.53[b]
Barratt Impulsiveness Scale			
Attentional impulsivity	16.17 ± 3.09	16.21 ± 2.88	.92
Motor-impulsivity	22.25 ± 3.57	22.44 ± 3.68	.61[b]
Non-planning Impulsivity	23.42 ± 4.04	24.05 ± 4.66	.29
Total	61.84 ± 8.27	62.70 ± 8.83	.46
Performance and reaction time			
Goal failure (absolute value)	7.53 ± 3.92	7.15 ± 4.33	.30[b]
Desire context			
Acceptance of reward stimuli (%)	88.40 ± 11.56	89.95 ± 9.57	.43[b]
Reaction time (ms)	521.18 ± 49.10	509.32 ± 53.04	.14[b]
Reason context			
Rejection of reward stimuli (%)	96.92 ± 4.16	96.41 ± 4.90	.54[b]
Reaction time (ms)	507.01 ± 48.07	500.35 ± 58.14	.38

p-values derived from t-tests between independent groups

[a] Chi-squared tests were used for handedness and gender

[b] Mann-Whitney-U tests were used for data violating the normal distribution

* p<.017, Bonferroni corrected to account for multiple testing

3.4.2 fMRI data

Entire sample

Replicating previous results (Diekhof et al., 2012; Diekhof et al., 2012b; Diekhof and Gruber, 2010), we found significantly stronger bottom-up activation in NAcc and VTA in the desire contrast and significant top-down suppression of the reward signal as revealed by the dilemma contrast (Table 3).

Table 3: Reward related activation and suppression in vStr and VTA during the DRD paradigm (MNI coordinates, t value)

Region	Desire	Reason	Desire-Reason-Dilemma
L/R vStr	-15 9 0 (15.33)	-15 9 0 (7.34)	-12 12 3 (13.17)
	15 9 0 (15.21)	15 9 0 (5.99)	12 12 3 (14.38)
L/R VTA	-6 -21 -18 (18.53)	-6 -21 -15 (8.83)	-3 -18 -18 (12.54)
	6 -21 -18 (18.78)	6 -21 -18 (8.48)	6 -18 -21 (12.83)

L/R = left/right, vStr = ventral striatum, VTA = ventral tegmental area. All values are significant at a threshold of FWE p<.000, svc corrected.

rs1042778

There was a main effect of genotype for the SNP rs1042778 in the activation of NAcc (x=-9 y=15 z=0, F=13.76, FWE_{svc} p=.004, Figure 1). Post hoc t-tests revealed that the genotype group with the major allele had more activation than the group with the minor allele (x=-9 y=15 z=0, t=3.71, FWE_{svc} p=.002). Indeed, plots of parameter estimates demonstrated that the major allele group showed in both desire and reason contrast more bottom-up related activation, but the difference in activation for the genotype groups was only at trend level for the reason contrast (x=-9 y=15 z=0, t=2.92, FWE_{svc} p=.018). The model including gender as additional between-subject factor showed no significant interaction between gender and genotype (all p>.017). The PPI analyses with the left NAcc as seed coordinate revealed changes in functional connectivity to other ROIs for allelic variation. In comparison to the minor genotype, participants belonging to the major genotype group showed a stronger functional coupling to the left VTA at trend level in the desire situation (x=-3 y=-12 z=-12,

t=2.53, FWE_{svc} p=.088), which is in line with the stronger bottom-up signal in the VS. In contrast, minor allele carriers exhibit a trend for a stronger coupling to the right avPFC in the reason situation (x=33 y=60 z=15, t=2.30, FWE_{svc} p=.082), which is in accordance with the stronger top-down suppression of the VS.

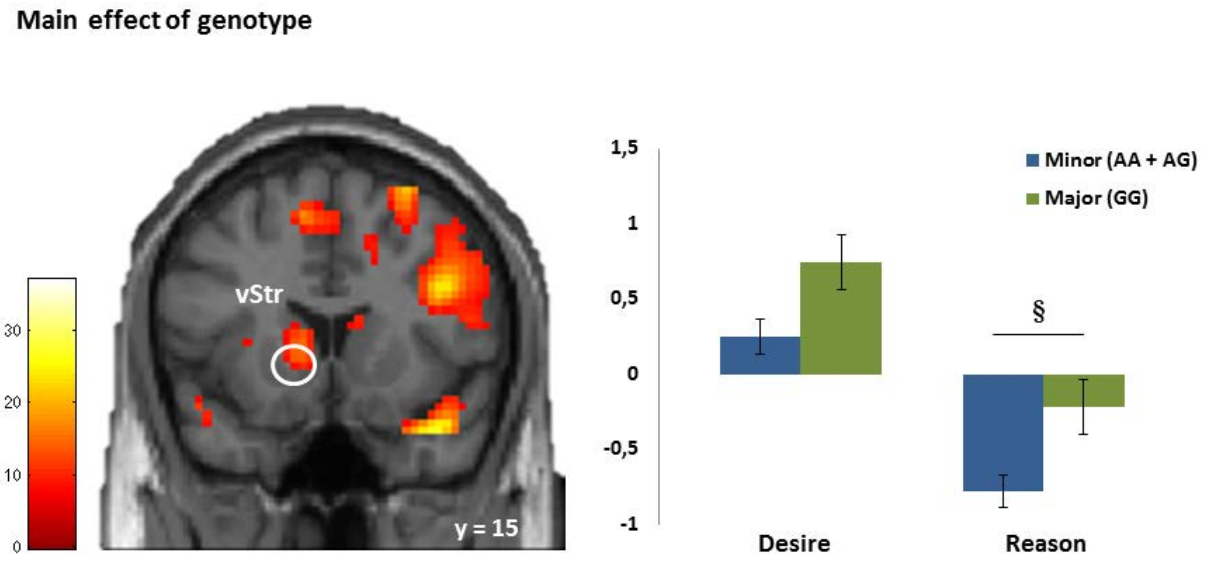


Figure 1: Effect of genotype for rs1042778 in the left ventral striatum. There was a significant effect for genotype in the left vStr (x=-9 y=15 z=0, FWE_{svc} p=.004). Among both conditions, the major allele group showed more bottom-up reward related activation than the minor allele group, but only for the reason contrast the difference was at trend level. For illustration purpose, differences in activation are shown at an uncorrected threshold of p<.005.
vStr = ventral striatum

rs237897

For SNP rs237897, the analysis showed no main effect of allele but an interaction effect between gender and genotype group in the left VTA (x=-6 y=-21 z=-15, F=11.58, FWE_{svc} p=.015, Figure 2). There was no difference in VTA activation level for the desire contrast. But in the reason contrast, female participants belonging to the major genotype group showed more activation in the left VTA compared to male participants with the major genotype (x=-6 y=-21 z=-12, t=6.63, FWE_{svc} p=.004). Additionally, plots of parameter estimates suggest that this activity pattern is reversed for the minor genotype groups in the reason contrast but the difference did not reach statistical

significance in posthoc t-test. Moreover, PPI analysis uncovered no significant allelic influence on functional connectivity to other regions of interest.

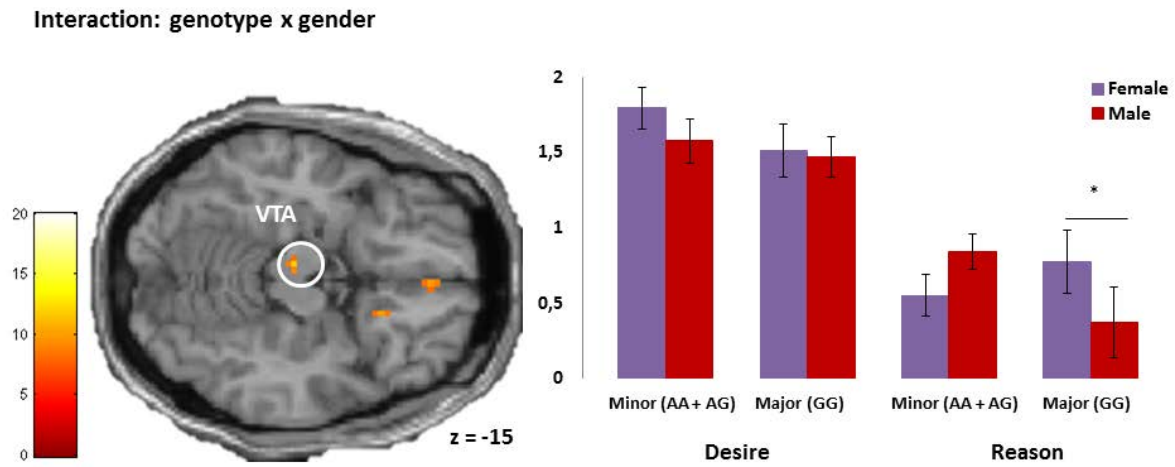


Figure 2: Effect of genotype x gender for rs237897 in the left VTA. There was a significant interaction effect for genotype x gender in the left VTA (x=-6 y=-21 z=-15, FWE_{svc} p=.015). For the reason contrast female participants with the major genotype showed more activation than male participants with the major genotype (x=-6 y=-21 z=-12, t=6.63, FWEsvc p=.004). For illustration purpose, differences in activation are shown at an uncorrected threshold of p<.005.
VTA = ventral tegmental area

rs11131149

For the rs11131149 OXTR SNP, allelic variation did not influence reward related signals in the NAcc or VTA. Also, the interaction with the factor gender showed no effect at all (p>.017).

Correlations of reward related activations with personality measures

Regarding OXTR SNP rs1042778, Pearson correlation illustrate that the BIS subscale attentional impulsivity is positively associated with the left NAcc activation in the major genotype group (r=.281, p=.011, two-tailed, Figure S6) but not in the minor genotype group and not for the other subscales and the total scale. Though, in the minor genotype group the TCI subscale harm avoidance was negatively correlated with the functional connectivity to the left VTA (r=-.216, p=.010, two-tailed, Figure S6) but not the other subscales. As a significant difference between genotype groups was found in performance regarding correct rejection of the reward stimulus in the reason context, a Pearson correlation was calculated to explore whether the performance data was

associated with differences in activation and functional connectivity. Nevertheless, the correlations did not reach statistical significance (all p>.017).

Pearson correlation for significant left VTA activation of OXTR SNP rs237897 in the desire contrast yielded a positive association for the BIS subscale attentional impulsivity in males with major genotype at a trend level (r=.452, p=.018, two-tailed, Figure S7) but not for the other subscales or the total scale. For the minor genotype group and for females no correlation reached statistical significance.

3.5 Discussion

In this study, we could demonstrate that two out of three a priori selected SNPs of the OXTR gene had an influence on the neural activation in NAcc and VTA during a decision-making task even in the absence of a social context. Additionally, we could also show that the coupling between regions associated with reward processing was affected by genotype and moreover, that impulsivity and personality scores correlated with activity depending on the particular genotype.

We found a main effect of genotype for the SNP rs1042778 independent from task context on reward related activity in the DRD paradigm. Participants with GG genotype exhibited greater activation in the left NAcc than carriers of the minor allele. A study on sensitive parenting found that major allele carrier of the same SNP exhibited higher oxytocin plasma level than carriers with the homozygous minor allele (Feldman et al., 2012a). Assuming a feedback loop between the OXTR and the oxytocin gene, it might be possible that the major allele of the OXTR SNP induces enhanced oxytocin synthetization which could be also mirrored in higher plasma oxytocin levels. Due to interaction of oxytocin with dopamine in the reward system this could result in enhanced activation during the present decision-making task. Though, the assumed feedback loop between the two genes as well as the interaction between dopamine and oxytocin are still to be investigated. Evidence for this suggested interaction comes from oxytocin administration studies which show an increased VTA and NAcc response under oxytocin when the male participant was presented pictures of the current female partner in contrast to unknown women (Scheele et al., 2013) or in a delayed reward task with social stimuli (Groppe et al., 2013). Additionally, in a social reward learning task participants learned better when social stimuli were presented and under oxytocin treatment. On the neural level, again activity in reward related regions was increased (Hu et al., 2015). Besides these previous fMRI studies, our finding demonstrates clearly that oxytocin changes the neural activation of the reward system also in the absence of a social context or social stimulation. Therefore, an induction of

oxytocin effects on neural activation and also decision-making behavior by a social content seems to be not always required. However, our finding is not in line with an fMRI study using a non-social monetary incentive delay task which did not observe a modulation of mesolimbic activation during reward anticipation or outcome by the SNP rs1042778 (Damiano et al., 2014). The difference between the findings of our and the previous study could rely on various aspects. First, we dealt with a much larger sample size resulting in a stronger statistical power in our analysis. Small effects of rs1042778 may not reach significance in the former study. Second, the design used by the authors was slightly different to the DRD paradigm applied in this study. The monetary incentive delay task enables investigation of reward anticipation and of reward outcome phases (Knutson et al., 2000), whereas these phases are not differentiated in the DRD. Therefore, the power to find a modulation of a particular OXTR SNP on the underlying signal might have been greater in our study. Our PPIs at trend level might shed light on the complex mechanisms behind the OXTR modulation of reward related activation. In the desire situation, the coupling between the left NAcc and the left VTA was stronger for GG carrier and might reflect a stronger bottom-up signal during the presentation of the immediate reward stimulus. This would be in accordance with the social salience hypothesis, a current theory about the function of oxytocin stating that oxytocin facilitates salience processing (Shamay-Tsoory and Abu-Akel, 2016). The bonus stimulus is perceived as salient in the DRD paradigm as it is associated with an extra reward and therefore, depending on the specific genotype, the coupling within the dopaminergic reward system is strengthened. Conversely, in the reason situation the functional connectivity to the avPFC was reduced for the major allele carrier which might result in a weaker top-down control and therefore in a less successful suppression of the reward related activity. Other neuroimaging studies found an attenuation of amygdala functional connectivity from subcortical regions to the PFC by oxytocin as well (Frijling et al., 2015; Wittfoth-Schardt et al., 2012) but see also (Riem et al., 2012; Sripada et al., 2013). Both the positive relationship of impulsivity with NAcc activity and the less accurate rejection of immediate reward during the reason context support the idea that the major genotype is more sensitive for bottom-up stimulation and reward processing respectively. Maybe due to this sensitivity, participants exhibit less self-control in intricate decision making situations such as the dilemma situations in the DRD paradigm in which participants with the major genotype failed to reject the desired bonus stimulus. Though, previous studies found that highly impulsive individuals who successfully solved the desire-reason dilemma compensated their lack of self-control by exhibiting diminished activation in the NAcc and increased connectivity to the avPFC (Diekhof et al., 2012b). OXTR effects on personality traits as harm avoidance were already previously reported (Stankova et al., 2012). However, here we could show an association between harm avoidance and genotype for the strength of functional connectivity. In AA/GA carriers harm avoidance was negatively correlated with the functional connectivity between NAcc and VTA. This

might indicate that A allele carriers do not only display stronger top-down control but also reduced bottom-up stimulation depending on their personality traits.

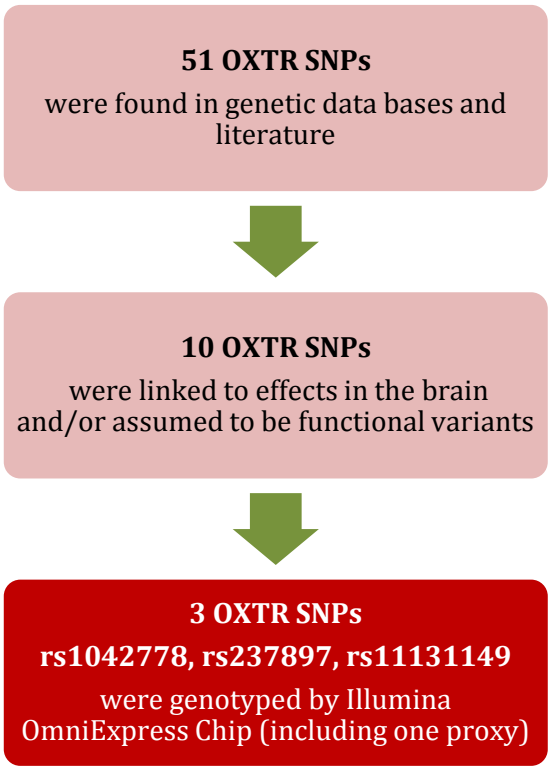
Analysis with the SNP rs237897 revealed an interaction between gender and genotype for the reward related activation in the VTA. Females with GG genotype displayed stronger activation of the VTA than male homozygous major allele carrier and vice versa for the minor allele genotype being significant for the reason situation. The OXTR SNP rs237897 was selected as it is implicated in transcriptional suppression of the gene and might be therefore a strong candidate for cis-acting variation, meaning that this SNP might have a genuine regulatory function in the gene (Tansey et al., 2010; Wade et al., 2014). Previous studies without oxytocin treatment or analysis of genotype reported already the impact of gonadal hormones on decision-making processes and indicated that reward related dopamine transmission might be modulated by gonadal hormones (Derntl et al., 2014; Diekhof et al., 2012). The observed sex differences in dopaminergic modulation by oxytocin in our study might be caused by the interplay between the neuropeptide with gonadal hormones as for example estrogen (Gabor et al., 2012; MacDonald, 2013). Indeed, neuroimaging studies with intranasal administration of oxytocin found an influence of gender on reward related activity. For example, during a reciprocated cooperation task responses in the caudate/putamen region were greater in males and reduced in females under oxytocin treatment (Feng et al., 2014). A further study using a Prisoner's Dilemma paradigm found in men increased brain activity in areas linked to reward processing, such as the striatum, whereas females showed no or reduced activity in these regions (Rilling et al., 2014). Another explanation would be a different pattern or density of oxytocin receptor distribution for gender as it was previously reported or indicated for several species including humans (Dumais et al., 2013; Dumais and Veenema, 2016; Smeltzer et al., 2006). Interestingly, in a positron emission tomography study the interaction between one allelic variant of the oxytocin gene and gender affected the stress-induced dopaminergic transmission in the ventromedial caudate. Only in female carriers of the minor allele but not in males the dopaminergic transmission was increased (Love et al., 2012).

The OXTR SNP rs11131149 was selected for this study as it was previously linked to ASD classification (Liu et al., 2010) and its major allele was associated with higher theory of mind as a function of cognitive sensitivity (Wade et al., 2014). More importantly, its proxy SNP rs13316193 is known as a functional variant as its minor allele has been linked to decreased expression of oxytocin receptors in the brain with weak correlation of total gene expression in the amygdala (Tansey et al., 2010). Nevertheless, under a dominant model we did not find any modulation of reward related regions by genotype.

3.6 Conclusion

In the decision-making process, current and future goals, rewards, consequences and contexts have to be evaluated and compared to select the optimal decision in the specific situation and for future success. Albeit the neuropeptide oxytocin and its receptor are suggested to effect mainly social cognition and behavior, our findings indicate that the allelic variation of OXTR might also contribute to individual differences in non-social reward based decision-making. Moreover, impulsivity traits and gender appeared to have selective influences on the extent of reward related neural activation and functional connectivity. More future studies should focus also on non-social cognitive processes and behavior to form a more comprehensive model of the neuropeptides function in humans.

3.7 Supplemental Information



With rs 1131149 as proxy for rs13316193 (R^2=1 and D'=1) according to SNAP (https://www.broadinstitute.org/mpg/snap/) and dbSNP-Q (https://cgsmd.isi.edu/dbsnpq/)

Figure S1: OXTR SNP selection process

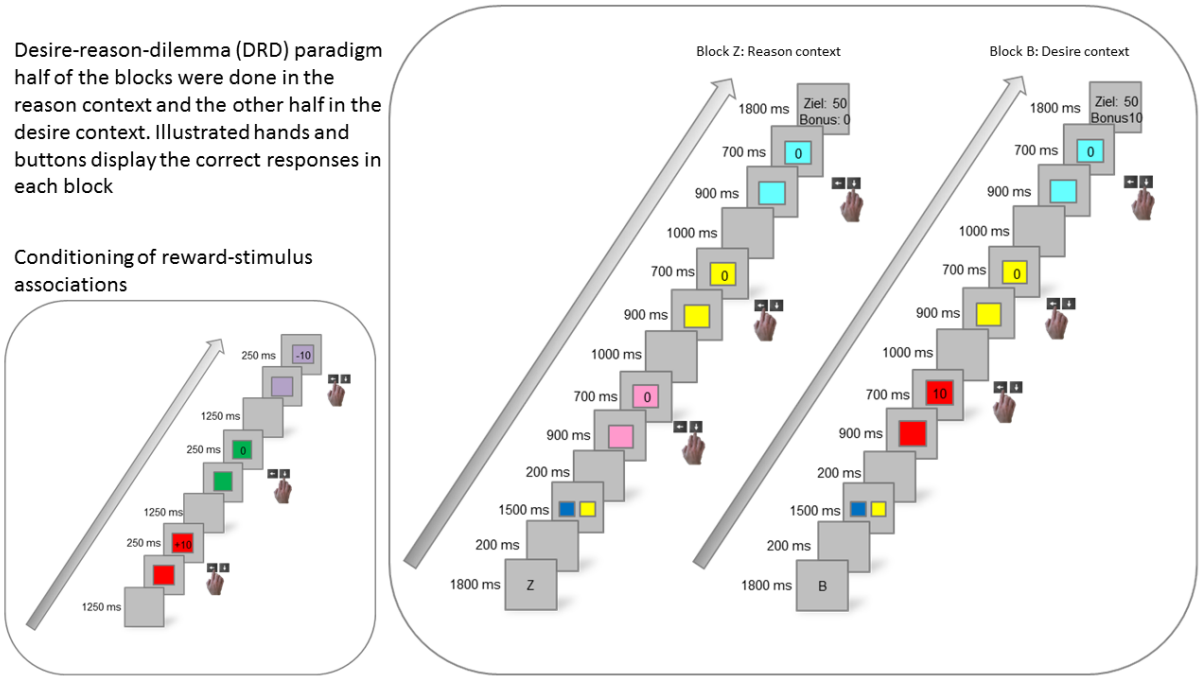


Figure S2: Desire-reason-dilemma paradigm (DRD)

Slightly modification of an artwork created by Maria Keil (2015).

Table S3: Whole brain differences in activation on cluster level between genotype groups of OXTR SNP rs1042778 (MNI, t values).

Region	MNI	k	t-value
Major (GG) > Minor (AA+AG)			
R/L Fronto median and SFG	12 30 42	2418	6.08*
	-24 21 63	21	3.78
R/L Temporal pole and mTG	39 15 -27	482	5.13*
	-48 12 -21	16	3.39
R/L SPL	45 -39 54	407	4.54*
	-21 -66 33	176	4.11
R/L OCC	15 -87 -3	301	4.41*
	-42 -87 -15	343	4.35*
L OFC	-42 48 -9	54	3.90
L IFG	-42 6 27	45	3.76
	-48 36 12	30	3.19
R/L pCC	0 -36 30	156	3.67
L iTG	-51 -63 -18	37	3.43
L Fusiform gyrus	-39 -36 -21	17	3.40
L AI	-30 18 6	52	3.39
Precuneus	0 -69 42	58	3.32
L avPFC	-30 48 15	17	3.03
R dPFC	24 51 24	22	2.98
L TPJ	-51 -51 30	10	2.83
Desire			
R Fronto median and SFG	12 30 42	369	4.78*
R/L IFG and MFG	45 12 27	367	4.06*
	-45 6 21	20	3.08
R/L SPL	45 -39 54	202	4.06
	-24 -69 39	38	3.10
R mTG and iTG	66 -36 -9	118	4.00
	51 -18 -24	56	3.47
R Temporal pole	39 15 -27	48	3.83
R/L OCC	36 -75 -3	121	3.42
	-33 -78 3	68	3.47
L Midbrain and Thalamus	-6 -12 -6	65	3.38
R/L Fusiform gyrus	33 -36 -27	12	3.27
	-39 -36 -21	10	3.37
L Occipital pole	-18 -99 -6	16	3.15
pCC	0 -36 30	39	3.10
R mOCC	42 -87 12	22	2.86
Reason			
R/L Fronto median and SFG	12 30 45	152	3.90
	27 18 63	14	2.96
R Temporale pole	45 15 -24	71	3.63
R/L Caudatus	-6 15 9	77	3.53
L OFC	-42 48 -9	18	3.23
R/L OCC	15 -90 -3	11	3.01

	-42 -90 12	10	3.13
R AI and IFG	33 30 9	63	3.08
	45 12 27	14	2.80
Major (GG) < Minor (AA+AG)			
L postcentral gyrus	-48 -18 51	10	3.09
Desire			
-	-	-	-
Reason			
-	**-**	**-**	**-**

Reported activations are significant at p<.005, uncorrected, with an extend threshold of k > 10.
R/L = right/left, SFG = superior frontal gyrus, mTG = middle temporal gyrus, SPL = superior parietal lobe, OCC = occipital cortex, OFC = orbito-frontal cortex, IFG = inferior frontal gyrus, pCC = posterior cingulate cortex, iTG = inferior temporal gyrus, AI = anterior insula, avPFC = anteroventral prefrontal cortex, dPFC = dorsal prefrontal cortex, TPJ = temporo-parietal junction, MFG = middle frontal gyrus, mOCC = middle occipital cortex.
clusters were significant at FWE p<.05 (whole-brain)

Table S4: Whole brain differences in activation on cluster level between genotype groups of OXTR SNP rs237897 (MNI, t values).

Region	MNI	k	t-value
Major (GG) > Minor (AA+AG)			
R SPL	60 -45 45	20	3.71
R IFG	51 39 12	25	3.61
R Angular gyrus	54 -69 33	12	3.20
R NAcc	15 18 -9	20	3.16
L ACC	-18 42 -3	16	3.09
Desire			
-	-	-	-
Reason			
-	-	-	-
Major (GG) < Minor (AA+AG)			
R/L OCC	6 -81 6	43	3.27
	-15 -84 30	35	3.69
R central operculum /MFG	54 -15 24	36	3.63
R SPL	18 -54 66	21	3.50
R/L fusiform and lingual gyrus	39 -66 -9	22	3.39
	-15 -66 0	22	2.91
R/L Cuneus	15 -72 30	46	3.36
	-6 -69 21	23	2.99
L avPFC	-18 54 -3	12	3.31
L OFC	-33 30 -9	17	3.28
R Amygdala	18 -6 -15	19	3.24
L IFG	-51 12 12	13	3.20
L Angular gyrus	-45 -60 36	10	2.99
R iTG	51 -48 -3	25	2.90
Desire			
-	-	-	-
Reason			
R central operculum /MFG	51 -18 27	27	3.31
L OFC	-33 33 -6	20	3.29
L OCC	-15 -84 30	12	3.17
R Amygdala	21 -6 -18	18	3.03
R Cuneus	15 -72 30	21	3.04
Precuneus	0 -57 27	37	2.95
Brain stem	0 -30 -3	13	2.91

Reported activations are significant at p<.005, uncorrected, with an extend threshold of k > 10.
R/L = right/left, SPL = superior parietal lobe, IFG = inferior frontal gyrus, NAcc = nucleus accumbens, ACC = anterior cingulate cortex, OCC = occipital cortex, MFG = middle frontal gyrus, avPFC = anteroventral prefrontal cortex, OFC = orbito-frontal cortex, iTG = inferior temporal gyrus.
* clusters were significant at FWE p<.05 (whole-brain)

Table S5: Whole brain differences in activation on cluster level between genotype groups of OXTR SNP rs11131149 (MNI, t values).

Region	MNI	k	t-value
Major (GG) > Minor (AA+AG)			
R/L precentral gyrus	60 9 36	30	3.41
	27 -6 63	22	3.24
	-24 -21 54	803	4.75*
R/L OCC	36 -75 15	317	4.68*
	-27 -81 15	56	3.78
R/L supramarginal gyrus	45 -36 48	161	3.92
	-54 -45 54	26	3.96
R/L iTG and MTL	48 -60 -9	94	3.53
	-39 -33 -6	27	3.32
R inferior OCC	39 -84 -15	14	3.28
R SPL	27 -42 54	35	3.10
L MFG	-30 36 30	14	3.09
R AI	33 12 12	15	3.06
L Caudatus	-18 15 18	19	2.88
Desire			
R OCC	36 -72 12	161	3.98
L precentral gyrus	-24 -21 54	212	3.76
R supramarginal gyrus	45 -36 48	37	3.10
R iTG	45 -57 -12	20	3.01
Reason			
L supramarginal gyrus	-54 -45 54	19	3.38
R OCC	39 -72 24	61	3.21
L SMA	-9 -3 51	11	3.00
L precentral gyrus	-24 -18 57	2.99	24
	-24 -21 33	2.84	13
	-39 -12 33	2.76	18
Major (GG) < Minor (AA+AG)			
R OFC, orbital gyrus	36 51 -12	12	3.63
	21 27 -15	36	3.14
L Angular gyrus, TPJ	-42 -51 15	26	3.50
R IFG	*54 33 18*	11	2.96
Desire			
-	-	-	-
Reason			
L Angular gyrus, TPJ	-42 -51 15	10	2.98

Reported activations are significant at p<.005, uncorrected, with an extend threshold of k > 10.
R/L = right/left, OCC = occipital cortex, iTG = inferior temporal gyrus, MTL = middle temporal lobe, SPL = superior parietal lobe, MFG = middle frontal gyrus, AI = anterior insula, SMA = supplemental motor area, OFC = orbito-frontal cortex, TPJ = temporo-parietal junction, IFG = inferior frontal gyrus.
* clusters were significant at FWE p<.05 (whole-brain)

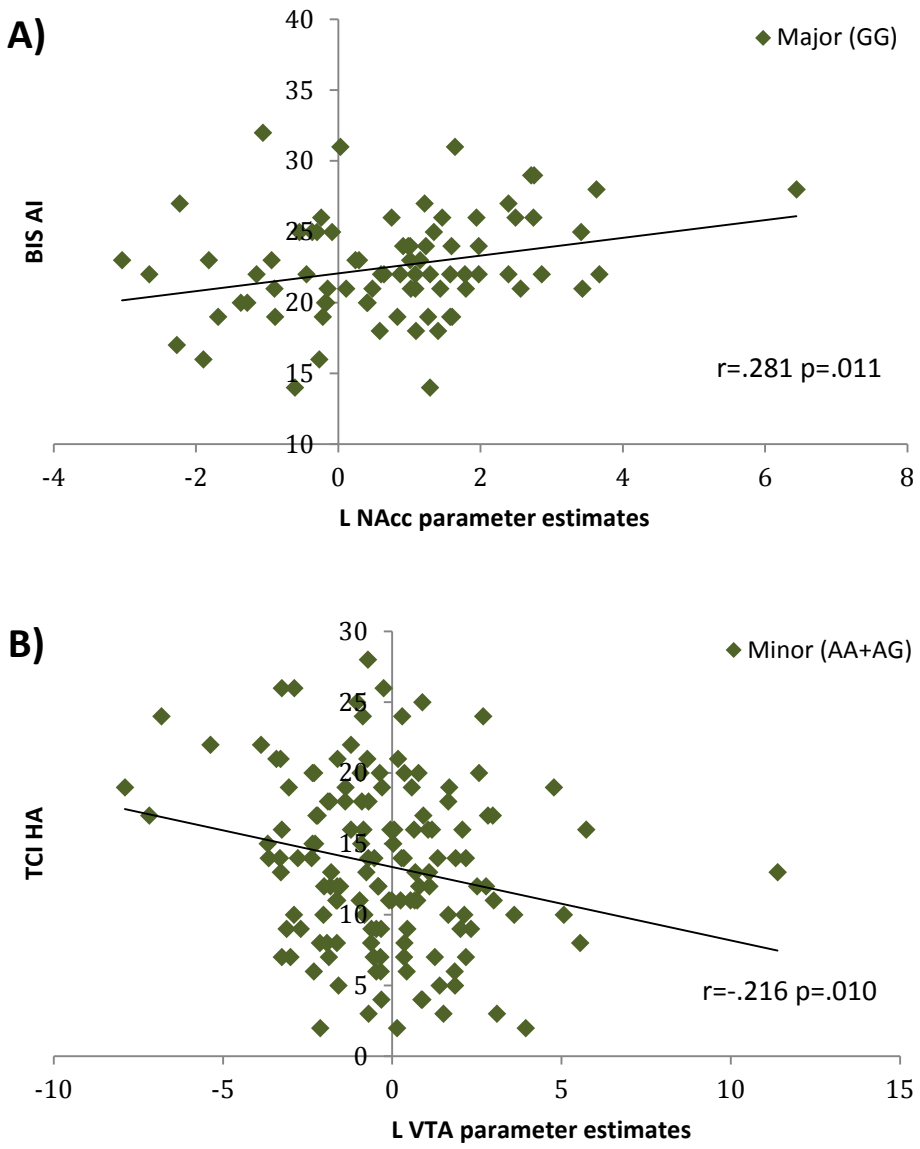


Figure S6: Effects of OXTR polymorphism rs1042778 on neural activity and connectivity correlated with raw scores of questionnaires. A) Correlation of major genotype (GG) activation of the left NAcc with the AI scale of the BIS. B) Correlation of the minor genotype (AA+AG) functional connectivity to the left VTA with the subscale harm avoidance of the TCI.

L = left, NAcc = nucleus accumbens, VTA = ventral tegmental area, BIS = Barrett Impulsivity Scale, AI = attentional impulsivity, TCI = Temperament Character Inventory, HA = harm avoidance.

Significance level: p<.017

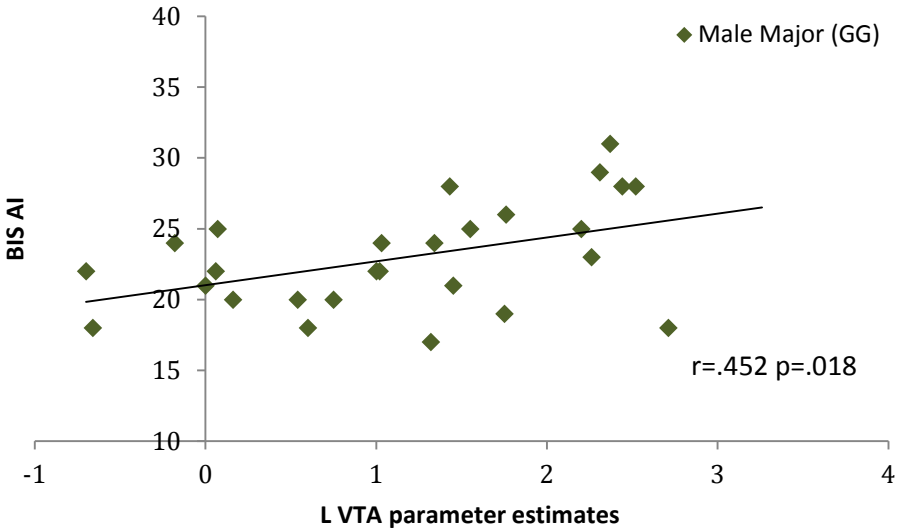


Figure S7: Effects of OXTR polymorphism rs237897 on neural activity correlated with raw score of questionnaire. Correlation of major genotype (GG) activation of the left VTA with the AI scale of the BIS in males.

L = left, VTA = ventral tegmental area, BIS = Barrett Impulsivity Scale, AI = attentional impulsivity, Significance level: p<.017

Chapter 4

Intranasal oxytocin influences the reward system during social and non-social decision-making

4.1 Abstract

Whereas a great amount of papers is published focusing on the impact of oxytocin on social decision-making situations, there is a profound lack in studies investigating the effects of intranasally administered oxytocin in non-social tasks. Therefore, the main aim of the present neuroimaging study was to explore whether oxytocin modulates behavioral and neural processes in a non-social reward-based decision-making task. Moreover, by introducing additional emotional faces as stimuli, it could be assessed how the effects of oxytocin on the reward system were moderated by emotional content. Lastly, we pursued whether the amygdala responds selectively under oxytocin treatment depending on the shown valence.

To address these questions, a modified version of the desire-reason-paradigm (DRD) was applied. In the "desire situation" a previously learned reward stimulus was featured together with a neutral stimulus and was free to be selected to obtain the offered reward. In the "dilemma situation" the reward stimulus was paired with a target and had to be rejected. Additionally, grey oval or emotional faces were presented. In this double-blind cross-over design 34 healthy male subjects received intranasal 24IU of oxytocin/placebo before fMRI scanning. fMRI data were analyzed by a full-factorial model and by calculating PPIs to assess the changes in functional connectivity between region of interests, especially VTA, NAcc as part of the vStr, and avPFC.

In the non-social desire situation oxytocin reduced bottom-up activity within the vStr and strengthened the negative coupling between frontal and mesostriatal regions. In contrast, in non-social reason situations the vStr was less suppressed under oxytocin and stronger positive coupling to the avPFC was observed. By introducing fearful faces in the social condition, the pattern of neural responses and functional connectivity reversed. While oxytocin increased the activation in the vStr in desire situations, it reduced the activation in reason situations. This change in activity was paralleled by stronger positive coupling in the desire as well as with negative coupling in the reason context. Moreover, depending on valence oxytocin decreased amygdala activation for fearful faces and increased amygdala activation for positive faces in non-reward trials. Oxytocin impaired performance during both desire and dilemma trials. Surprisingly, after oxytocin treatment participants were less accurate in selecting target stimuli than in rejecting the reward stimulus and vice versa for the placebo.

With this neuroimaging study, we could clarify that exogenous oxytocin modulates behavior and neural activation during non-social decision-making situations. Additionally, our findings give further insights into additional modulation by introducing emotional content. Currently oxytocin is used in various clinical trials and therefore it is even more important to examine the effects of oxytocin on neural activations also in non-social contexts.

4.2 Introduction

Many everyday decisions and actions are taken in social relevant situations. Whether someone behaves impulsively or self-controlled the resulting action might be strongly influenced by the situational social context. However, to what extent cerebral levels of neuropeptides modulate the underlying neural activation in such situations is still an open question. The neuropeptide oxytocin, functionally involved in social cognition and behavior (Ebstein et al., 2009; McCall and Singer, 2012), might be a good candidate for the investigation as it is known to act on regions of the reward system implicated also in decision making (Insel, 2010; Meyer-Lindenberg et al., 2011).

Although the original animal studies related oxytocin elicited behavior to the reward system, including the vStr and the VTA (Young et al., 2001, 2011; Olazábal and Young, 2006; Ross et al., 2009; Ross and Young, 2009b), most studies in humans focused on the amygdala and other regions associated with emotion processing and social cognition (Bethlehem et al., 2013; Ma et al., 2016; Zink and Meyer-Lindenberg, 2012). Despite the intensive research in this domain there is still a discussion about the neuropeptide's selectivity and its underlying mechanisms. Therefore, several hypotheses attempt to explain the functioning of oxytocin on a neural and a behavioral level. First, the social salience hypothesis (Shamay-Tsoory, 2010; Shamay-Tsoory and Abu-Akel, 2016) assumes that oxytocin increases the salience of social stimuli and conditions. The social approach/withdrawal hypothesis (Kemp and Guastella, 2010) focuses on oxytocin's up- and downregulating effects on approach and avoidance behavior and at last the fear/stress account (Neumann and Slattery, 2016) emphasizes the anxiolytic and stress reduction effects of oxytocin. Nevertheless, all accounts have the over-evaluation of the social component in oxytocin's mode of operation in common. Thus, they neglect possible non-social effects of oxytocin by setting their focus on social behavior and neural regions associated with emotion processing and social cognition. Only recently, Harari-Dahan and colleagues (Harari-Dahan and Bernstein, 2014) expand their general approach-avoidance hypothesis of oxytocin (GAAO) with the extension for non-social contexts and supposed that also the effects of oxytocin on neural and behavioral level in non-social conditions could be explained by approach and avoidance.

Currently, more research is done on oxytocin's impact on regions related to motivation and the reward system but they are still emphasizing the social-affective domain, as for example pair-bonding (Scheele et al., 2013), stressful life events (Loth et al., 2014), emotional memory as well as social reward anticipation (Hu et al., 2015) and emotion perception (Puglia et al., 2015). Only a few studies reported effects of oxytocin on behavioral and neural activity in non-social conditions. For instance, a behavioral study discovered that oxytocin could impair memory for both social and non-social visual objects (Herzmann et al., 2012), and an imaging genetic study implicated that the

oxytocin receptor gene is associated with mesolimbic activation during reward anticipation in a non-social MID task (Damiano et al., 2014). However, the mechanisms through which oxytocin might influence activation in the reward system with and without emotional information is an unsolved question yet.

Therefore, the first aim of the study was to explore whether oxytocin modulates the neural underpinnings and the behavioral outcome in a decision-making task even so no social context or stimuli are used. To address this question, we applied a modified version of the well-established desire-reason-dilemma-paradigm (DRD) (Diekhof et al., 2012b; Diekhof and Gruber, 2010; Trost et al., 2014). Thereby we focused mainly on the modulation of the reward system, especially on the VTA and on the NAcc as part of the vStr, and on the avPFC, a region associated with action control (Behan et al., 2015; Diekhof and Gruber, 2010). Furthermore, we pursued whether the amygdala responses selectively under oxytocin treatment to negative and positive valenced stimuli without the presence of a reward. And finally, we investigated how oxytocin moderates the activity in and the connectivity between regions in decision-making situations when both reward and emotion processes are involved.

4.3 Methods

4.3.1 Participants

40 male participants, students or with a completed tertiary education, were included in this double-blind, placebo-controlled and within-subject study. 6 participants were excluded afterwards. The remaining 34 participants (mean age 24.94±3.55y) reported to be right handed, free of any medication, not suffering from psychiatric, neurological or endocrine diseases and to have normal or corrected-to-normal vision. In addition, they were screened for MRI contraindications and for alcohol and drug use. Participants gave written informed consent and were paid for participation. All procedures were approved by the ethics committee of the medical faculty of the Georg-August-University of Göttingen.

4.3.2 Procedure

All participants underwent three testing sessions on three consecutive days. On the first day, they underwent a conditioning and training session at the test computer and on the second and third

day they performed the task in the MRT scanner. Before each fMRI scanning participants underwent again a short training of the subsequent experiment. 30min before start of the fMRT participants self-administered intranasal 24IU oxytocin (Syntocinon-Spray, Novartis, Basel, Switzerland) or placebo dependent on the session. The randomization order as well as the nasal sprays was prepared by the pharmacy of the Heidelberg University Hospital (InphaSol) whereby the placebo contained the same ingredients as the oxytocin nasal spray except for the neuropeptide. Once participants were positioned in the scanner and the structural scanning was completed they conducted three runs of the experiment during fMRI. At last participants underwent a 6min resting-state but the results of the resting-state are published elsewhere. Before each treatment and after scanning, participants had to complete the multidimensional mood questionnaire. There was no difference in the ratings between oxytocin or placebo treatment (p>.05, Table SI).

4.3.3 Stimuli

Task-relevant stimuli were formed by colored squares. 6 different colors were used in an equal frequency for every trial type. To form a social and emotional context in the decision-making task faces with different emotional expressions were presented within colored squares. 68 images of face identities (34 female/ 34 male) with neutral, fearful and happy expressions were taken from NimStim (Development of the MacBrain Face Stimulus Set was overseen by Nim Tottenham and supported by the John D. and Catherine T. MacArthur Foundation Research Network on Early Experience and Brain Development. Please contact Nim Tottenham at tott0006@tc.umn.edu for more information concerning the stimulus set), Radbout and ADFES databases. All faces were recorded from the front and with directed gaze. When the information was provided by the specific database only identities expressing emotions with validation ratings higher than 80% were used.

4.3.4 Desire-Reason-Dilemma paradigm

On the first day participants conducted a simple operant conditioning task outside the scanner. In 160 trials two out of six different colored squares were presented randomly and participants were free to select one of them by pressing a corresponding button, either the left one for the color presented on the left side of the monitor or the right one for the color presented on the right side of the monitor. Two of the colored squares were always immediately rewarded with 10 points (CR) and all others had a neutral outcome of 0 points. Presentation of colors was counterbalanced for both sides and responses for left or right button press, respectively. After participants learned the stimulus-response-reward contingencies they performed the actual experiment, a modified variant of the DRD (Diekhof and Gruber, 2010). In the novel paradigm task-

relevant stimuli (colors) were presented with social stimuli (neutral, happy and fearful faces) or with a control stimulus (grey oval) (see Fig. 1).

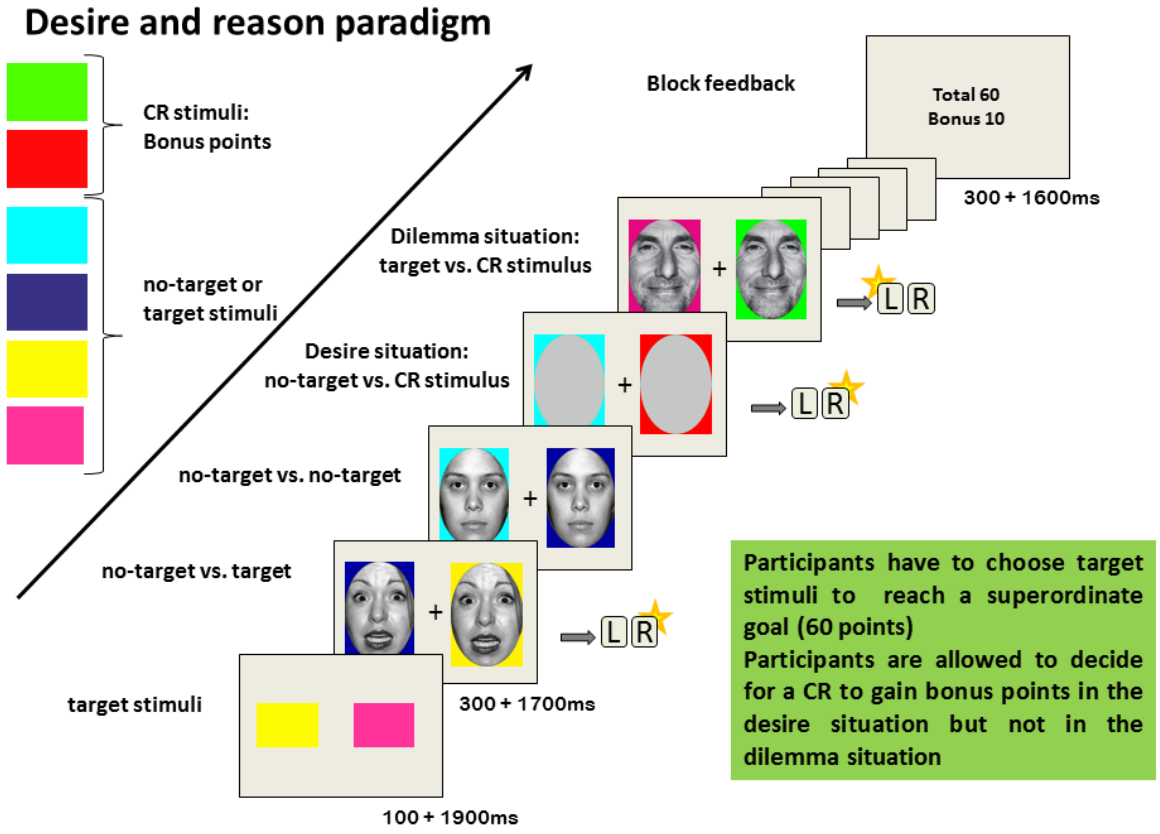


Figure 1: Experimental design of the Desire-Reason paradigm. In a prior conditioning phase participants learned that specific stimuli were associated with a reward (CR). In the main experiment, they had to select target stimuli to obtain points in the end of each block. Additionally, they were instructed to select the reward associated stimuli whenever it was not displayed together with a target color (desire vs. dilemma situation). When participants violated this rule, they did not receive the points in the end of the block. Stars indicate the best option to gain points by selecting targets and CR stimuli.

In the beginning of each block, two colors were defined as targets and participants had to choose them in the following trials. If the participants selected all presented target colors during a block, they gained 60 points in the end. But if the participant missed one target color or selected misleadingly the other color the outcome was zero at the end of a block. In addition, also the CR colors were presented during some of the trials. By collecting them the participants received bonus points (10 points each). Due to different combinations of colors the participant experienced different contexts or different trial types, respectively. In the "desire situation" the CR color was featured

together with a no-target color and was free to be selected to obtain the reward. In the "dilemma situation" the CR color was paired with a target color which had to be always selected to achieve the superordinate goal of 60 points in the end of the block. In this condition participants had to overcome the tendency to acquire the immediate reward stimuli to pursue the longtime goal. Control trials were defined by free selection of two no-target colors or by selection of the target color when it was paired with a no-target color. In all, participants completed 124 blocks over the course of three fMRI runs with 8 trials per block (for more information see SI). All experiments were conducted with the Presentation® software (Neurobehavioral Systems, Albany).

4.3.5 Statistical Analysis of Behavioral Data

Factorial repeated-measures ANOVAS for error rate and reaction time with the factors treatment (oxytocin, placebo), emotion (no, neutral, fear, happy), reward context (trials containing or missing the CR) and reason context (trials containing or missing the target color) were calculated with the software package SPSS (Version 19.0). To reveal effects in emotion and reward processing depending on treatment condition, separate ANOVAS for the emotions fear and happy were computed with the factors emotion (yes, no), treatment (oxytocin, placebo), reward context (trials containing or missing the CR) and reason context (trials containing or missing the target color). Afterwards dependent t-tests were calculated to uncover interactions within the ANOVAS.

4.3.6 fMRI Data Acquisition and Processing

MRI scans were conducted at a 3T Siemens TIM Trio scanner. 36 axial slices (voxel size, 3x3x3mm³; gap = 20%) were acquired in ascending direction using a T2*-sensitive echo planar imaging (EPI) sequence (interscan interval, 1.9 s; echo time, 30ms; flip angle, 70°). A total of 1382 volumes were obtained over the course of three functional sessions. In addition, a structural image was acquired by a three-dimensional, T1-weighted, gradient-echo (MPRAGE) sequence (1 x 1 x 1 mm^3). FMRI data were preprocessed and analyzed using SPM8 (Wellcome Trust Centre for Neuroimaging, University College London, UK; http://www.fil.ion.ucl.ac.uk/spm). Preprocessing steps included coregistration, realignment and unwarping, slice-timing, normalization into standard stereotactic space (skull-stripped EPI template by the Montreal Neurological Institute (MNI)), and spatial smoothing with an isotropic Gaussian kernel filter of 6 mm FWHM.

At the individual subject level, each experimental condition was convolved with the hemodynamic response function to form regressors for each trial type and emotion. The target cues and the block feedback were also modeled as regressors of no interest. Erroneous trials and trials in which the CR color was not selected in the desire situation were excluded from the analysis.

For group inferences a full factorial model was calculated with the factors treatment (oxytocin, placebo), emotion (no, neutral, fearful, happy) and trial type (no-target vs. no-target, no-target vs. target, desire situation, dilemma situation). As we were interested in revealing valence-related effects of oxytocin on amygdala activation without any interference by reward related activation, we composed the contrasts for negative valence (fearful vs. no face) and positive valence (happy vs. no face) merely of trials containing no CR stimulus. To identify reward related bottom-up activation in situations in which the subject was allowed to choose the desired CR stimulus, we calculated the desire contrast (CR vs. no-target > no-target vs. no-target). The reason contrast (CR vs. target > no-target vs. target) was built to demonstrate that bottom-up activation was missing in situations in which the subject was not allowed to select the CR stimulus, and the interaction contrast desire-reason-dilemma (desire contrast vs. reason contrast) uncovered the top-down associated suppression of reward related activation. The reward related contrasts were calculated for the no-face condition to discover the effects of oxytocin on the reward system without social context and also for the fearful face condition to explore the possible modulation of activation by emotional input. The standard statistical criterion for group statistics was $p < 0.005$, uncorrected, with a minimum cluster size of 10 voxels, if not otherwise indicated. As we had specific a priori hypothesis regarding task related neural activation based on previous observations (Diekhof and Gruber, 2010; Krämer and Gruber, 2015), we used small-volume-corrections (SI) to account for the multiple comparisons problem. Activations corrected for small volume are reported at a threshold of $p < 0.05$, corrected for family-wise error (FWE). Moreover, we used a very lenient statistical criterion of $p < 0.05$, uncorrected, to search also for minor signs of oxytocin's impact on reward related activation in regions related to our a priori hypothesis. To illustrate the magnitude of change in activation after oxytocin treatment, we plotted the means of the parameter estimates for both treatment conditions. For this purpose, we extracted the ßetas with a sphere of 4mm around the reported peak levels by using the toolbox MarsBaR (Brett et al., 2002) and calculated the means and standard deviations for each group.

Furthermore, we assessed the functional interaction between the vStr and the amygdala-hippocampus-complex to reveal the impact of emotion processing on the reward system under oxytocin treatment by using psycho-physical interactions, PPI (Friston et al., 1996; 1997). As seed region, we selected the local maxima of the left NAcc which showed a significant modulation of activation in the fearful vs. no face analysis under oxytocin in comparison to placebo treatment. For further information, please see SI or amendment.

4.4 Results

4.4.1 Behavioral Data

Accuracy: The ANOVA calculated for error rate revealed a significant main effect for treatment ($F_{(1,33)}$=7.17, p<.05) with more errors done under oxytocin treatment, for reward ($F_{(1,33)}$=60.55, p<.001) and for reason context ($F_{(1,33)}$=46.07, p<.001) with less accuracy in trials containing the CR or the target color. A significant interaction effect for treatment x reward ($F_{(1,33)}$=9.95, p<.005) and treatment x reason ($F_{(1,33)}$=15.76, p<.001) as well as a triple interaction treatment x reward x reason ($F_{(1,33)}$=5.23, p<.05) was also detected. Posthoc t-test discovered that all participants made more errors in trials containing the CR or target color in comparison to no-reward and no-target trials, but under oxytocin participants were significantly less accurate in reward ($T_{(33)}$=7.27, p<.001) and reason context ($T_{(33)}$=3.71, p<.001). Further contrasts revealed that in the oxytocin condition participants were less accurate not only in target trials in comparison to the placebo condition ($T_{(33)}$=6.94, p<.001). Also within the oxytocin condition participants made more errors in target than in desire trials ($T_{(33)}$=2.61, p<.05) and under placebo treatment vice versa ($T_{(33)}$=3.01, p=0.005). Both ANOVAs calculated for error rates specific for fear vs no emotion and happy vs. no emotion showed main effects for treatment ($F_{Fear(1,33)}$=4.805, p<.05; $F_{happy(1,33)}$=5.52, p<0.05), reward ($F_{Fear(1,33)}$=61.09, p<.001; $F_{happy(1,33)}$=41.45, p<.001) and reason context ($F_{Fear(1,33)}$=42.35, p<.001; $F_{happy(1,33)}$=52.2, p<.001). In general participants made more mistakes in trials containing a CR or target color compared to no-reward and no-target trials respectively. Under oxytocin treatment performance decreased regardless of context. Moreover, there were significant interaction effects in both analysis, between treatment x reward ($F_{Fear(1,33)}$=4.58, p<.05; $F_{Happy(1,33)}$=5.56, p<.05) and treatment x reason ($F_{Fear(1,33)}$=7.9, p<.01; $F_{Happy(1,33)}$=11.82, p<.005). Additionally, a significant triple interaction was found between treatment x reward x reason ($F_{Happy(1,33)}$=6.07, p<.05). In the fear analysis posthoc t-tests uncovered that participants under oxytocin treatment made significantly more errors in trials without a CR ($T_{(33)}$=4.85, p<.001) and in trials presenting a target color ($T_{(33)}$=3.05, p<.005) in contrast to the placebo treatment. The same pattern was found in the happy analysis with significantly less accuracy in trials without a CR ($T_{(33)}$=6.35, p<.001) and in trials with target colors ($T_{(33)}$=3.56, p=.001). There was no effect between treatment and emotion in any of the ANOVAS.

Reaction time: The ANOVAs calculated for reaction times yield no significant effects for treatment condition (p>.05).

4.4.2 Neuroimaging Data

Classical findings using experimental paradigms related to reward and emotion processing

We replicated the DRD effects (Diekhof and Gruber, 2010) in the absence of emotion and oxytocin treatment with higher bottom-up activation in reward related regions for the desire contrast, reduced bottom-up activation in the reason contrast and enhanced top-down control as shown in the dilemma contrast (SI, Table S2 & Figure S1). Additionally, we reproduced previous findings on the effects of emotion processing in the amygdala (Fusar-Poli et al., 2009; Sabatinelli et al., 2011). In the absence of reward and oxytocin application, emotion processing effects were seen in the amygdala with higher activation for positive and negative valenced stimuli in comparison to the non-social condition (SI, Table S3). The replications of these classical findings together confirm the proper functioning of the used paradigm.

Oxytocin effects on emotion processing in the amygdala

In the fearful vs no emotion condition without CR trials oxytocin reduced significantly the activation in the right amygdala-hippocampus-complex (x=20 y=-12 z=-20, t=3.26, FWE_{svc} p<.05) in comparison with placebo. Whereas in the happy vs no emotion condition without CR trials oxytocin increased the activation in the left amygdala (x=-14 y=-2 z=-16, t=3.02, FWE_{svc} p=.089) (SI, Table S3).

Oxytocin effects on bottom-up generation and top-down modulation of reward signals in NAcc and VTA

The comparison of the desire contrasts between the two treatment groups showed slightly reduced reward-related activation at the bilateral vStr (x=10 y= 16 z=-10, t=1.99, p<.05; x=-18 y= 16 z=-14, t=2.15, p<.05; Fig. 2a) but no difference in the bilateral VTA for the oxytocin condition. PPI analysis with the right NAcc as seed region gives evidence for strengthened negative coupling with the avPFC under oxytocin treatment (x=-32 y=46 z=14, t=3.37, FWE_{svc} p<.05; x=38 y=48 z=14, t=2.86, FWE_{svc} p<.05). Interestingly, the pattern of regions associated with increased connectivity to the bilateral NAcc partly overlapped with the pattern of negative connectivity in the reason contrast of the placebo condition (SI, Table S4), indicating oxytocin generated a dilemma in the desire contrast and a stronger top-down modulation of reward related activity, respectively. On the other hand, the reason contrast revealed higher activation at the ventral vStr (x=6 y=8 z=-10, t=2.93, p<.005; x=-8 y=16 z=-10, t=2.65, p<.005; Fig. 2b) and marginal reduced activation in the right VTA (x=4 y=-24 z=-22, t=2.02, p<.05) for oxytocin in comparison with the placebo condition. Therefore, the down-

regulation of reward-related striatal activation (x=8 y=14 z=-10, t=2.94, p<.005; x=-8 y=16 z=-10, t=2.62, p<.005; Fig. 2c) and of VTA activation (x=-12 y=-18 z=-10, t=2.04, p<.05) was attenuated by oxytocin in the desire-reason dilemma.

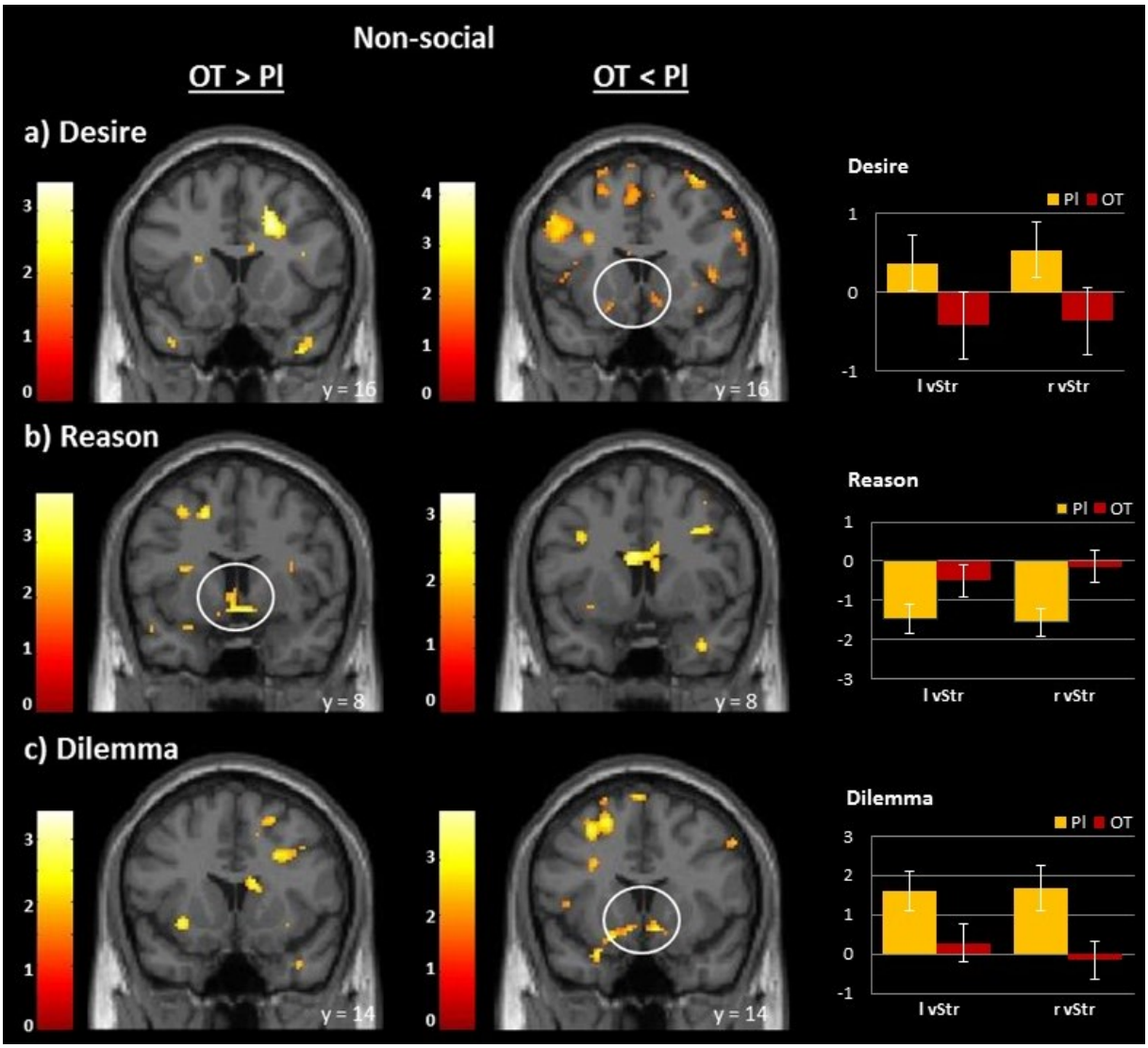


Figure 2: Oxytocin effects on bottom-up generation and top-down modulation of reward signals in vStr in a non-social context. a) Oxytocin suppressed the activation in the bilateral vStr in the desire contrast. b) Oxytocin increased activation in bilateral vStr in the reason contrast. c) Oxytocin reduced the down-regulation of the activation in bilateral vStr during a desire-reason dilemma. For illustration purposes a threshold of p < .05 uncor. was used. OT = Oxytocin, Pl = Placebo, vStr = ventral striatum, VTA = Ventral tegmental area.

Modulation of oxytocin effects on reward signals by additional emotion processing

Additionally, we were interested in examining whether the factors emotion and reward would interact under the influence of oxytocin in the vStr. As the modulation by oxytocin was similar but weaker for happy than for fearful we only describe here the DRD contrasts for the fearful vs no emotion condition. We found slightly more activation under oxytocin at the bilateral vStr and the VTA for the desire (NAcc: x=12 y=8 z=-8, t=1.78, p<0.05; x=-16 y=8 z=-6, t=1.82, p<.05; Fig. 3a; VTA: x=12 y=-16 z=-12, t=2.25, p<.05; x=-12 y=-14 z=-14, t=2.30, p<.05) and the dilemma contrast (NAcc: x=6 y=14 z=-10, t=1.78, p<.05; x=-8 y=16 z=-10, t=2.24, p<.05; Fig. 3c; VTA: x=18 y=-14 z=-14, t=2.03, p<.05; x=-12 y=-14 z=-14, t=1.89, p<.05). But for the reason contrast activation at the bilateral vStr was more strongly in the placebo condition (NAcc: x=4 y=16 z=-10, t=2.49, p<0.01; x=-8 y=6 z=-12, t=2.64, p<.005; Fig. 3a). There was no change in activation level for the VTA in the reason contrast. As shown in Figure 4a PPI analysis for oxytocin vs placebo in the desire contrast fearful vs no emotion discovered a significant strengthened coupling between the left NAcc (Seed: -16 8 -6), the bilateral amygdala-hippocampus-complex (x=-22 y=-8 z=-10, T=2.87 FWE_{svc} p<.05; x=34 y=-12 z=-22, T=3.52 p<0.000) and the VTA (x=0 y=-14 z=-18, T=3.02 FWE_{svc} p<.05). Contrary, we found a decreased coupling between the left NAcc (Seed: -8 6 -12) and the right amygdala-hippocampus-complex (x=24 y=4 z=-18, T=3.81 p<0.0005) in the reason contrast (Fig 4b).

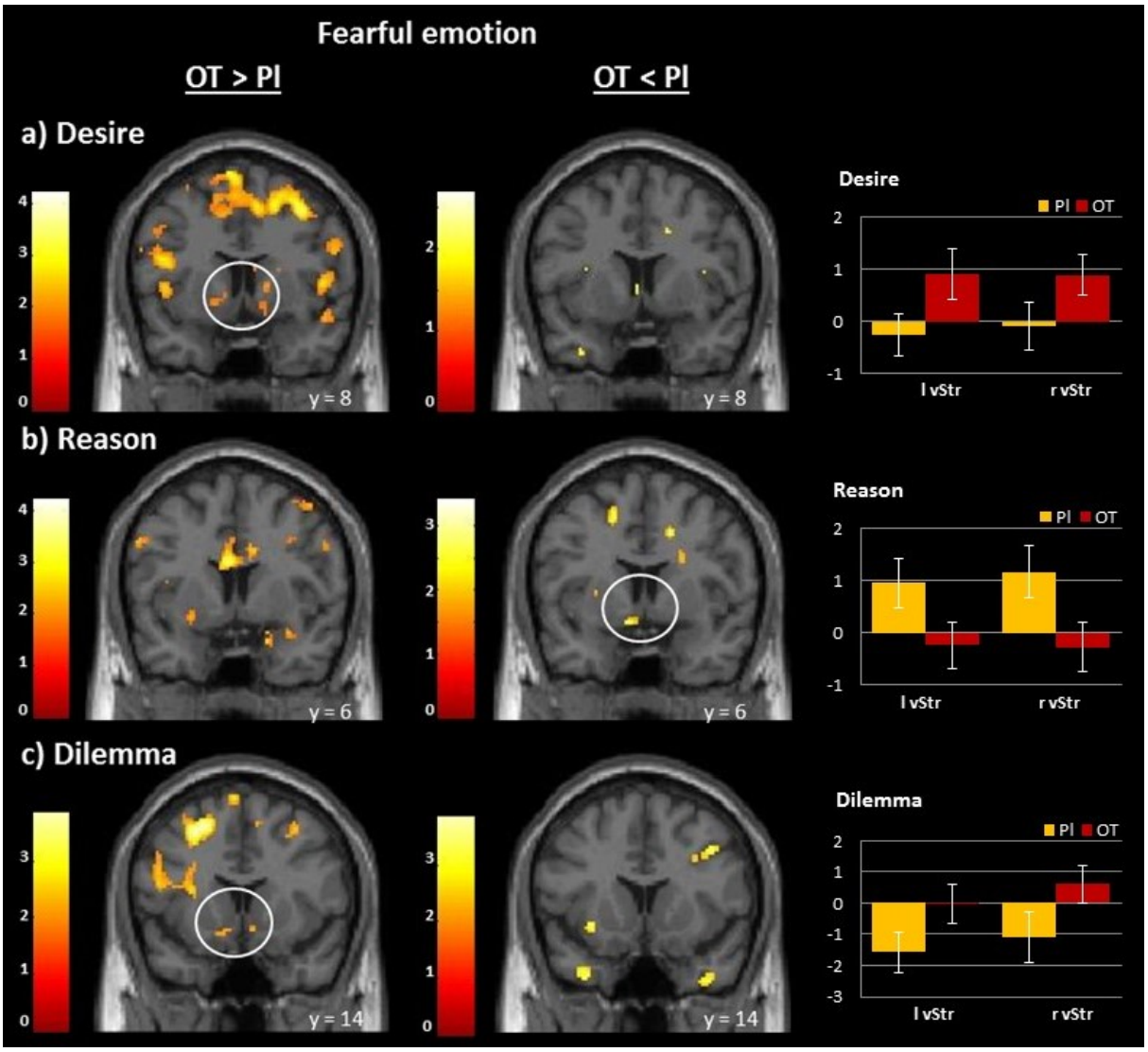


Figure 3: OT effects on bottom-up generation and top-down modulation of reward signals in vStr in a fearful context. a) Oxytocin increased the activation in the bilateral vStr in the desire contrast. b) Oxytocin suppressed activation in bilateral vStr in the reason contrast. c) Oxytocin increased the down-regulation of the activation in bilateral vStr during a desire-reason dilemma. For illustration purposes a threshold of $p < .05$ uncor. was used. OT = Oxytocin, Pl = Placebo, vStr = ventral striatum.

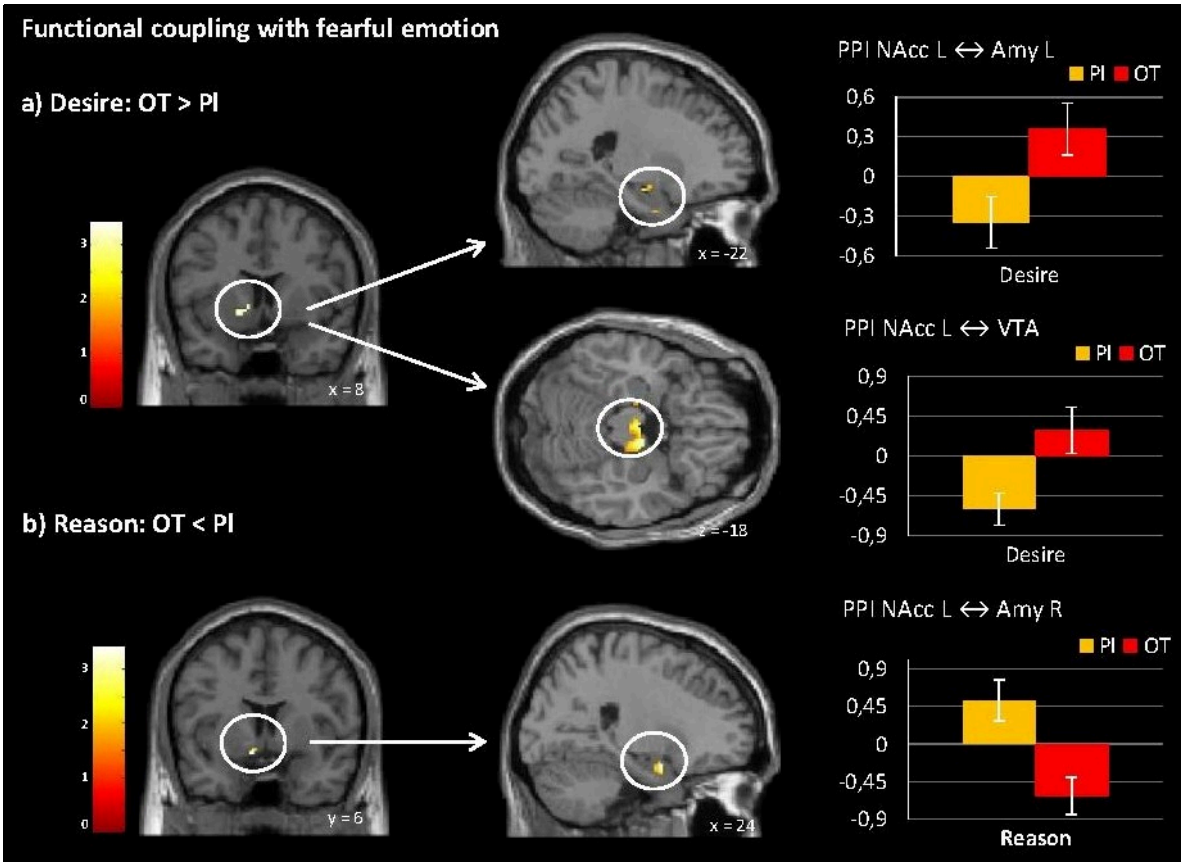


Figure 4: Oxytocin related changes in amygdala-striatal and reward related connectivity in the fearful face condition. a) Oxytocin increased the coupling between the left NAcc and the left amygdala-hippocampus-complex as well as the VTA in the desire contrast. b) Oxytocin decreased the coupling between the left NAcc and the right amygdala-hippocampus-complex in the reason contrast. For illustration purposes a threshold of $p < .05$ uncor. and an anatomical mask for the seed regions was used. OT = Oxytocin, Pl = Placebo, NAcc = Nucleus accumbens, VTA = Ventral tegmental area, Amy = Amygdala.

4.5 Discussion

To our knowledge this is the first neuroimaging study showing that exogenous administered oxytocin also modulated the neural activity in a decision-making task even though no social information was present. Both the bottom-up and the top-down signals were reduced by oxytocin. Previous animal (Baracz and Cornish, 2013; Mullis et al., 2013; Romero-Fernandez et al., 2013; Young et al., 2014), human neuroimaging (Riem et al., 2012, 2011; Strathearn, 2011; Strathearn et al., 2009) and genetic studies (Love et al., 2012; Sauer et al., 2013, 2012) implicated an interaction between dopamine and oxytocin in reward related behavior and its associated neural response (but see for missing associations Striepens et al., 2014). Contrary to studies finding an increase in reward-related

activity in vStr and VTA (Groppe et al., 2013b; Hu et al., 2015; Loth et al., 2014; Scheele et al., 2013), we could show a dampening of the reward-related activity under oxytocin treatment in the desire contrast during the non-social condition. The social salience hypothesis assumes that the dopamine-oxytocin interaction is necessary to assign salience to social stimuli and consequently that this interaction is the reason for the upregulation of activity (Shamay-Tsoory and Abu-Akel, 2016). As oxytocin decreased the reward related activity in non-social but salient trials, this hypothesis cannot account for the oxytocin effects observed in our study. The exploratory conjunction analysis for the bottom-up related connectivity in the desire contrast suggest a strengthened top-down control under oxytocin similar to the reason contrast under placebo. Following Wittfoth-Schardt and colleagues (2012) the underlying mechanism could rely on the attenuation of automatic neural responses. Moreover, Ninan (2011) found that oxytocin suppresses the glutamate release in the PFC but facilitate the activity-dependent strengthening of the glutamatergic synapses in the mPFC. The author suggests that the enhancement could result in downstream-inhibition of the amygdala by a feedforward inhibition of the central amygdala. It is possible that a similar mechanism for oxytocin is existent in the coupling between the avPFC and the vStr. As shown in the reason and the dilemma contrasts, the top-down signal is also decreased by oxytocin in situations in which cognitive control would be necessary to solve the task. Here again, oxytocin seems to inhibit prefrontal areas but in this situation, another neural circuit might have been affected and lead to a relief of top-down control on the vStr (Dembrow and Johnston, 2014; Richard and Berridge, 2013). In their review Bartz et al. (2011) discussed already the fact that the effects of oxytocin differ between individuals and experiments because of contextual and personal features but also due to diverse neural mechanisms. For instance, a study with exogenous oxytocin administration showed contrary behavioral adaptation depending on emotional content of stimuli and context (as reviewed in De Dreu, 2012). Therefore, it is not unlikely that depending on task context, desire or reason, the modulation of neural activation and connectivity by oxytocin might alter. For this reason, prospect studies should explore more intensely whether oxytocin modulates fronto-striatal circuits differently when a reward is present or absent.

Furthermore, by presenting a fearful face and introducing thereby a social context, the neural pattern of the reward system flipped with stronger bottom-up and top-down signals after oxytocin treatment. Connectivity analysis revealed that oxytocin strengthened the coupling between the NAcc, the amygdala-hippocampus-complex and the VTA in the desire contrast and decreased the coupling between the NAcc and the amygdala-hippocampus-complex in the reason contrast. Our findings are consistent with a previous neuroimaging study on the DRD paradigm which also showed an increased coupling between the amygdala and the vStr in the presence of reward and emotional information (Krämer and Gruber, 2015). According to a model by Bos et al (2012) oxytocin might

facilitate social behavior by enhancing cognitive control from prefrontal regions and by its effects on the reward system, respectively. On the one hand, oxytocin elicited its anxiolytic properties by boosting top-down control in trials presenting negative emotional information. This possible causes an attenuated amygdala reactivity as already seen in several studies before (Kirsch, 2005; Knobloch et al., 2012; Labuschagne et al., 2010; Neumann and Slattery, 2016). At the same time, the bottom-up activation in the VTA and the vStr amplifies due to the presence of a reward and a social stimulus. This is in line with findings of neuroimaging studies demonstrating an increase in reward-related activity by oxytocin (Groppe et al., 2013; Hu et al., 2015; Scheele et al., 2013). The oxytocin provoked reversal of the strong limbic-reward coupling and the decrease in striatal arousal in absence of reward demonstrate that the inhibition of top-down control together with the enhancement of bottom-up signal is essential for the effects observed in reward-related activity.

Besides, our fMRI data contribute to the discussion whether oxytocin attenuates the neural activity in the amygdala during emotion processing regardless of the shown valence (Domes et al., 2007a) or whether it acts with specificity on emotion processing (Gamer, 2010; Shin et al., 2015). As we found a reduction of activity in the amygdala for negative emotions and an increase in the activity for positive emotions, our results support the assumption of oxytocin's selectivity. But we did not observe any significant behavioral effect regarding the valence of the stimuli. According to the GAAO hypothesis (Harari-Dahan and Bernstein, 2014) oxytocin down-regulates the cortico-amygdala threat circuitry underlying avoidance/withdrawal, and up-regulates the dopaminergic reward circuitry underlying approach. Therefore, the behavioral outcome in the decision-making task might be the same for negative and positive valenced stimuli so that both emotional situations might entail approaching behavior under oxytocin treatment. In total, oxytocin worsened the overall performance in contrast to the placebo condition independent of emotional context. Interestingly, the impairment was stronger for trials containing no CR but the target stimulus. A behavioral study (Herzmann et al., 2012) found also amnesic effects of oxytocin on non-social stimuli. As the hippocampus and the amygdala are not only known for high oxytocin receptor distribution (Gimpl and Fahrenholz, 2001) but also for their major role in associative memory consolidation and memory recollection oxytocin might have affected the memory performance for target trials in the DRD paradigm.

To sum up, we could show that intranasally administered oxytocin attenuates the neural activation of the reward system in a non-social decision-making task. By presenting additionally emotional information oxytocin increased activation in reward related regions and strengthened the functional coupling between the NAcc and the amygdala-hippocampus-complex as well as the VTA. Since oxytocin is already seen as a potential target in the therapy of neuropsychiatric disorders or disorders leading to deficits in social cognition, as for example in drug addiction (McGregor and

Bowen, 2012), in autism spectrum disorder (Lin et al., 2014; Tachibana et al., 2013), in schizophrenia (Feifel et al., 2010; Pedersen et al., 2011) in general social anxiety disorder (Labuschagne et al., 2010) and in borderline personality disorder (Bertsch et al., 2013), it is even more important to examine the effects of oxytocin on neural activations and behavior also in non-social contexts. Future studies should focus more intensely on interactions between neural regions in different task contexts. This might reveal the diverse mechanisms and processes through which oxytocin modulates cognition and behavior and the newly obtained knowledge might enable the development of effective and save therapeutic approaches.

4.6 Amendment

Where does the observed flip in neural activity come from?

In the previous subchapters, analysis of neural activity in DRD contrasts revealed a flip in the direction of activation dependent on the socio-emotional content of the presented stimuli by oxytocin. While intranasally administered oxytocin reduced the activation of the vStr in the desire contrast and increased the reward-related activity in the reason contrast during the presentation of non-social stimuli (no face), it showed reverse effects during the presentation of socio-emotional stimuli (fearful face). Former connectivity analyses were calculated to explore the change of activity by oxytocin in comparison to placebo treatment within and between the respective conditions. Thereby, we could uncover that oxytocin might generate a dilemma situation in the non-social desire contrast. First, the negative coupling between the right NAcc and the avPFC was strengthened by oxytocin and second, a conjunction analysis indicated that the functional connectivity pattern of the desire contrast under oxytocin treatment overlapped to a great extent with the pattern usually observed in the reason contrast under placebo treatment. Additionally, we could demonstrate in the socio-emotional vs non-social condition that the functional connectivity between the NAcc and the amygdala-hippocampus-complex and the VTA was increased in the desire contrast and decreased in the reason contrast for oxytocin in comparison to placebo.

However, as we were interested whether the flip in activity would be mirrored in a direction change in the functional connectivity, we added more psycho-physiological interaction (PPI) analyses with focus on such regions which were recruited during the reward-based decision-making task for both conditions, namely as seed the bilateral NAcc and as ROIs the avPFC, the amygdala and the VTA.

Methods

Sample of subjects, task and procedure as well as the first and second level analysis of neuroimaging data were the same as reported in the previous paper.

Psycho-physiological interaction analysis (PPI)

We assessed the functional interaction between the vStr and the previous defined ROIs to reveal the impact of emotion processing on the reward system under oxytocin treatment by using psycho-physical interactions, PPI; (Friston et al., 1996; 1997). As seed regions, volumes of interest (VOI), we selected the local maxima of the bilateral NAcc which showed a significant modulation of activation by oxytocin in comparison to placebo in the desire, reason and dilemma contrasts in the

non-social and the socio-emotional condition (Table 1). The sphere for VOI dimensions was set to 8 x 8 x 8 mm^3 accounting for possible inter-individual functional-neuroanatomical differences. The extracted individual BOLD signal time courses of the VOIs served then as physiological vectors in the analyses. The psycho-physiological vectors in the PPI analysis were either formed by the desire contrast (CR vs. no-target > no-target vs. no-target), the reason contrast (CR vs. target > no-target vs. target) or the desire-reason-dilemma contrast (desire contrast > reason contrast). For the non-social condition, we only involved trials containing no face stimulus and for the socio-emotional condition we compared trials with fearful faces compared to trials without faces to correct for the non-social content. With the PPI toolbox of SPM8 the hemodynamic signals were deconvolved using a parametric empirical Bayesian formulation and mean-corrected to assess the underlying neural signal. Afterwards the PPI interaction terms were built by multiplying the deconvolved physiological vector with the respective psychological vector. Then again a convolution, mean correction, and orthogonalization were carried out and the three regressors (physiological vector, psychological vector and interaction term) went into the statistical analysis on single-level. For group effects a two-sample t-test was calculated between the single subject contrast images (PPI interaction term against baseline) of the oxytocin and the placebo treatment group. The following coordinates extracted from the literature were used for small volume correction for our previously defined ROIs VTA ± 4 -16 -20 (Diekhof et al., 2010), avPFC ± 36 48 12 (Trost et al., 2014) and amygdala 18 -6 -14 and -20 -6 -12 (meta-analysis by Fusar-Poli et al., 2009) with a sphere of 5mm. Additionally, we report functional connectivity to the a priori regions at an uncorrected threshold of p<.005 if it did not reach significance.

Table 1: Coordinates of the bilateral NAcc for VOI extraction.

Stimulus condition	**Contrast**		**NAcc Coordinates (MNI)**		
non-social	*Desire*	*Pl > OT*	10	16	-10
			-18	16	-14
	Reason	*OT > Pl*	6	8	-10
			-8	16	-10
Socio-emotional	*Desire*	*OT > Pl*	12	8	-8
			-16	8	-6
	Reason	*Pl > OT*	4	16	-10
			-8	6	-12

NAcc = nucleus accumbens, Pl = placebo, OT = oxytocin

Results

As we suggested, the flip in activity from reduction to enhancement by oxytocin and socio-emotional content is mirrored by the modulation of functional interaction between the NAcc and the amygdala, the VTA and the avPFC as reported in Table 2/3 for the right and left NAcc as seed regions.

Table 2: Functional interaction changes between the right NAcc and reward-related regions by OT during non-social and socio-emotional conditions.

Condition / Contrast	Region	MNI Coordinates (t-value)					
		OT		Pl		OT > Pl	Pl > OT
		pos FC	neg FC	pos FC	neg FC		
non-social							
Desire	avPFC		34 44 10 (3.17)				38 48 14 (2.86)
			-36 46 12 (3.72)				-32 46 14 (3.37)
	Amy-hippo		-16 -14 -20 (4.27)[a]				-20 -10 -12(2.93)
	VTA		-8 -18 -20 (4.63)				-6 -16 -20 (3.74)
	Caud/Ins		-24 4 14 (4.07)[a]	-24 4 14 (3.84)[a]			-24 4 14 (5.58)*
Reason	avPFC	30 48 10 (2.60)[c]				32 48 10 (2.94)	
	Amy				-22 2 -20 (2.49)[c]	-22 2 -20 (2.80)[b]	
Socio-emotional							
Desire	avPFC				22 54 10 (2.92)[b]	36 50 16 (2.80)[b]	
		-40 46 14 (3.29)				-34 44 12 (3.79)	
	Amy-hippo	36 -8 -20 (2.48)[c]			36 -6 -20 (3.54)[a]	36 -8 -20 (4.05)[b]	
		-14 -16 -12(3.27)[b]			-20 -12 -14 (2.66)[b]	-18 -10 -12(2.70)[b]	
	VTA				6 -12 -18 (3.98)	8 -16 -22 (2.91)	
	IFG	54 30 16 (4.53)[a]			54 32 16 (3.85)[a]	54 30 16 (5.78)*	
	Precuneus	4 -44 64 (4.72)[a]			8 -42 64 (3.95)[a]	8 -42 64 (5.85)*	
Reason	avPFC		-30 40 16 (2.54)[c]	-32 46 18 (2.66)[b]			-30 46 20 (3.12)[b]
	Amy		26 2 -22 (2.51)[c]				24 4 -20 (2.54)[c]
							-22 0 -24 (2.60)[c]
	VTA			-2 -10 -16 (2.93)[b]			-4 -12 -18 (2.79)

All reported coordinates are small volume corrected for family wise error if not otherwise indicated.
Pl = placebo, OT = oxytocin, pos FC = positive functional connectivity, neg FC = negative functional connectivity, NAcc = nucleus accumbens, avPFC = antero-ventral prefrontal cortex, Amy = amygdala, Amy-hippo = amygdala-hippocampus complex, VTA = ventral tegmental area, Caud/Ins = nucleus caudatus / insula, IFG = inferior frontal gyrus
* FWE-corrected on whole-brain level
[a] $p < .001$ (uncorrected)
[b] $p < .005$ (uncorrected)
[c] $p < .01$ (uncorrected)

Table 3: Functional interaction changes between the left NAcc and reward-related regions by oxytocin during non-social and socio-emotional conditions.

Stimulus condition / Contrast	Region	MNICoordinates (t-value)					
		OT		Pl		OT > Pl	Pl > OT
		pos FC	neg FC	pos FC	neg FC		
non-social							
Desire	Amy		-22 -4 -8 (2.80)				-22 -4 -8 (2.97)
Reason						–	
Socio-emotional							
Desire	Amy-hippo	32 -10 -22 (2.50)[c]			32 -14 -24 (3.13)[b]	34 -12 -22 (3.52)[b]	
		-22 -8 -10 (2.55)[c]			-22 -12 -14 (2.72)[b]	-22 -8 -10 (2.87)	
	VTA	–			4 -12 -18 (3.37)	0 -14 -18 (3.02)	
Reason	Amy		24 4 -18 (3.05)[b]	26 10 -18 (3.60)[a]			24 4 -18 (3.81)[b]
	Hypo		8 -6 -12 (4.41)[a]	6 -8 -12 (4.24)[a]			6 -8 -12 (6.10)*

All reported coordinates are small volume corrected for family wise error if not otherwise indicated.
Pl = placebo, OT = oxytocin, pos FC = positive functional connectivity, neg FC = negative functional connectivity, NAcc = nucleus accumbens, avPFC = antero-ventral prefrontal cortex, Amy = amygdala, VTA = ventral tegmental area, Hypo = hypothalamus
* FWE-corrected on a whole brain level
[a] $p < .001$ (uncorrected)
[b] $p < .005$ (uncorrected)
[c] $p < .01$ (uncorrected)

Interestingly, the reversed connectivity pattern is seen in the comparison between oxytocin and placebo treatment within and between the conditions, either non-social or socio-emotional (Figure 1). While there is more negative coupling between the NAcc and the other regions under oxytocin for the non-social condition in the desire contrast and for the reason contrast vice versa, there is the reversed connectivity pattern for the socio-emotional condition under oxytocin for both contrasts.

In the desire contrast with non-social stimuli oxytocin leads to a significantly strengthened negative functional connectivity between the bilateral NAcc and the left amygdala as well as between the right NAcc and the bilateral avPFC and the left VTA. Additionally, oxytocin reversed the functional coupling between the right NAcc and the left nucleus caudatus/anterior insula region from positive under placebo to negative, the difference is significant even on a whole-brain level. However, in the reason contrast oxytocin provokes a positive coupling between the right NAcc and the right avPFC and decouples the negative functional interaction between the right NAcc and the left amygdala.

In contrast, in the desire contrast with fearful faces oxytocin inverts the negative coupling between the bilateral NAcc and the bilateral amygdala and between the right NAcc and the right inferior frontal gyrus and the right precuneus into a positive coupling. Moreover, oxytocin decoupled the negative functional connectivity between the right NAcc and the right avPFC and the VTA and between the left NAcc and the right VTA. In the reason contrast with fearful faces the

functional connectivity pattern flipped again. Oxytocin reversed the positive coupling under placebo between the right NAcc and the avPFC as well as between the left NAcc and the right amygdala and the right hypothalamus. Additionally, oxytocin leads to a negative coupling between the right NAcc and the right amygdala and decouples the functional connectivity between the right NAcc and the left amygdala and the left VTA.

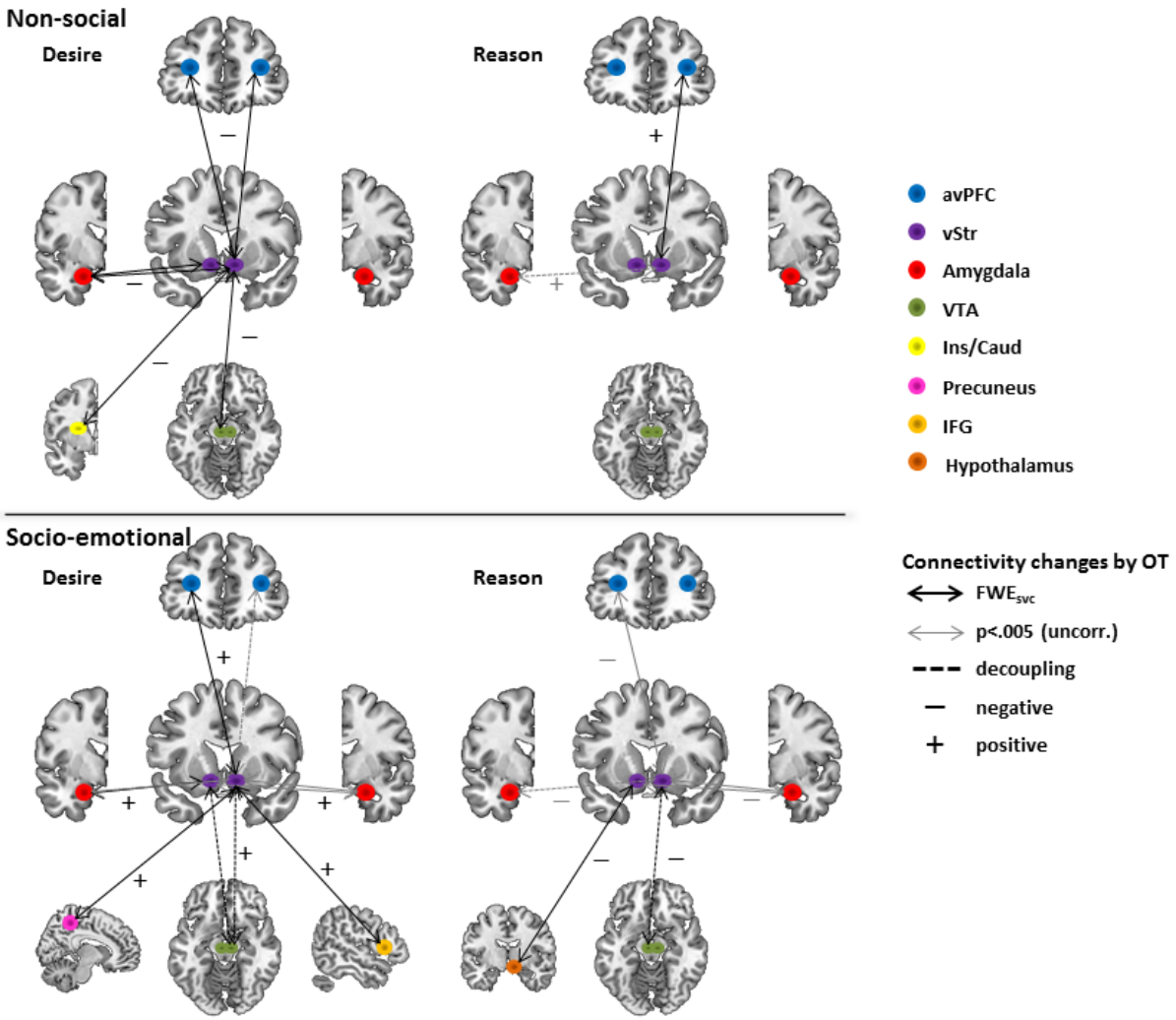


Figure 1: Functional connectivity changes by oxytocin.

Summary of results

To uncover the reason why both the bottom-up and the top-down signals were reduced by oxytocin in the previous neuroimaging study, we calculated additional PPIs between the bilateral NAcc as seed region and reward-related regions which are known to be activated during the DRD paradigm. As we suggested the reversed pattern in reward-related activation by oxytocin was mirrored by the modulation of functional connectivity within and between each socio-emotional context. In accordance with the previous calculated exploratory conjunction analysis in the desire contrast involving no faces we found an increased negative coupling between the NAcc and other reward-related regions by oxytocin. Additionally, to the strengthened top-down control implicated by the negative coupling between the NAcc and the avPFC, there was also a weakened bottom-up signaling to the NAcc by the VTA. Interestingly, although there was no socio-emotional content oxytocin leads also to a negative coupling between the left amygdala and the NAcc indicating that the amygdala is also involved in rewarding processes without emotional processes. Moreover, the functional connectivity pattern flipped with additional emotional input. Whereas there was a strengthened positive coupling between the NAcc and reward-related regions and additionally with the precuneus and the inferior frontal gyrus in the desire contrast, there was negative coupling up to decoupling between the NAcc and meso-cortico regions as well as an enhance negative coupling between the NAcc and the hypothalamus. Irrespective of emotional condition and task-context the right NAcc was more affected by the oxytocin induced modulation of functional connectivity than the left NAcc.

Therefore, the supplementary calculations of the functional connectivity between the conditions and task-context give essential insight into the mechanisms by which oxytocin might alter the meso-cortico circuit involved in reward processing. Not only bottom-up and top-down connectivity is changed by oxytocin but also the coupling between the NAcc and the amygdala independent whether emotional information was presented or not.

4.7 Supplemental Information

Participants

Participants were recruited via announcements at university facilities. 6 participants were excluded afterwards due to technical issues (n=2), extensive movement during scanning (n=2), performance under 75% in the task (n=1) and voluntarily abortion (n=1). The remaining participants were instructed were instructed not to take medication or to consume alcohol 24h before scanning and additionally not to drink coffee on the same day as scanning or two smoke or to eat 2h before the experiment.

SI Questionnaires and Measurements

Table S1: Means and standard deviations of the questionnaires

Questionnaires		**Mean**		**Standard deviation**
TCI				
Novelty seeking		21.44		5.95
Harm avoidance		9.71		6.37
Reward dependence		14.56		4.06
Persistence		4.32		1.71
Total		50.03		8.78
BAI		4.24		4.35
BDI-II		4.06		3.17
MWT-A		110.97		9.00
TAS-20		17.32		4.63
SPF		34.71		6.00
BIS				
Attention		16.24		2.82
Motor impulsivity		23.26		4.30
Non-planing impulsivity		23.29		4.38
Total		62.79		9.04
MDBF*	**Pl Mean**	**Standard deviation**	**OT Mean**	**Standard deviation**
GS*	-0.88	3.07	0.94	3.61
WM*	3.18	6.12	3.26	7.99
RU*	0.18	3.90	-0.03	4.52
Total*	2.47	9.24	4.18	13.10

*Subscores for MDBF were calculated by subtraction of scores before and after treatment.
TCI = Temperament and Character Inventory, BAI = Becks Anxiety Inventory, BDI-II = Becks Depression Inventory, MWT-A = Mehrfachwahl-Wortschatz-Intelligenztest, TAS-20 = Toronto Alexithymia Scale, SPF = Saarbrücker Persönlichkeits-Fragebogen, BIS = Barratt Impulsiveness Scale, MDBF = Mehrdimensionale Befindlichkeitsfragebogen, GS = Gute-Schlechte Stimmung, WM = Wachheit-Müdigkeit, RU = Ruhe-Unruhe.

Methods: Desire Reason Dilemma Paradigm

Over the course of three fMRI runs participants completed 124 blocks consisting of 8 trials each. The whole experiment contained 336 no-target trials presenting always two colors which were not with reward or target associated, 336 target trials presenting a target color paired with a no-target color, 160 desire trials presenting a CR with a no-target color and 160 dilemma trials presenting a CR with a target color. All different trials were presented pseudorandomly and counter-balanced for trial type transitions and positions within blocks. To equilibrate also the statistical analysis, only 160 of the 336 no-target trials and only 160 of the 336 target trials were considered in the calculated model. Every block started with a blank screen (duration: 100ms) followed by the presentation of two target-colors for the following block (duration: 1800ms). The target colors changed with every block. Each trial started with a blank screen (duration: 200ms) followed by the presentation of two colors (duration: 1700ms) from which the participants had to choose one and ended with a blank screen (duration: 100ms). After eight trials a blank screen was shown (200ms) followed by a feedback reporting whether all target colors were selected and the amount of the reward which was gained during the last block (duration: 1600ms). An additional blank screen (100ms) finished each block. A total feedback was always presented at the end of an fMRI run reporting the entire amount of target and reward points. All points acquired in the experiment were transferred into real money (max. 30€ per experiment) and added to the general reimbursement for participation (100€).

Methods: fMRI Data Acquisition and Processing

The following coordinates were used for small volume correction for regions with an a priori hypothesis: VTA ± 4 -16 -20 with a sphere of 10mm, NAcc ± 12 12 -4 with a sphere of 6mm (Diekhof et al., 2010), avPFC ± 36 48 12 with a sphere of 6mm (Trost et al., 2014) and amygdala 18 -6 -14 and -20 -6 -12 with a sphere of 10mm (Fusar-Poli et al., 2009).

We also calculated the functional connectivity between brain regions using PPI analysis. First, as we found an attenuating effect of oxytocin on the bilateral NAcc in the desire condition when no additional social information was given, we explored the functional interaction between the bilateral NAcc with other brain regions. Since we saw a pattern reminding us on the negative coupling in the reason contrast without pharmacological intervention (Diekhof and Gruber, 2010) we also conducted a PPI analysis for placebo treatment in the reason contrast. Afterwards we computed with both PPIs a conjunction analysis as included in SPM to explore which regions were found to be negatively coupled with the NAcc under oxytocin and placebo treatment in the different contrasts. Results are

described in the SI section. Additionally, we calculated PPIs from the left NAcc in the desire and the reason contrast to uncover the modulation of connectivity by oxytocin when a fearful face was presented. For a more detailed description of a PPI analysis see for example methods by (Krämer and Gruber, 2015) or read the Amendment section.

Behavioral data results

Further analysis: Further ANOVAS were calculated, but no differences were found for session order, bonus points or target points between the treatment conditions ($p<.05$).

fMRI results

Replication of previous findings under placebo treatment:

Table S2: Replication of previous findings under placebo treatment

Region of Interest	Bottom-up activation in desire contrast	Bottom-up activation in reason contrast	Downregulation of bottom-up activation in desire - reason dilemma
R/L NAcc	14 12 0 (2.74) -18 8 -2 (3.88)	NS NS	10 10 -6 (3.97) -10 10 -8 (4.09)
R/L VTA	8 -24 -16 (4.50)[a] -2 -24 -20 (3.68)	8 -24 -24 (2.46) NS	10 -26 -14 (2.91)[c] -8 -18 -8 (3.48)[b]

Reported activations are significant at $p<.05$, corrected for small volume, with an extend threshold of $k>10$. R/L = right/left, NAcc = nucleus accumbens, VTA = ventral tegmental area, NS = not significant.
[a] Voxels were significant at $p<.05$, corrected for false discovery rate (whole-brain correction).
[b] Voxels were significant at $p<.001$, uncorrected.
[c] Voxels were significant at $p<.005$, uncorrected.

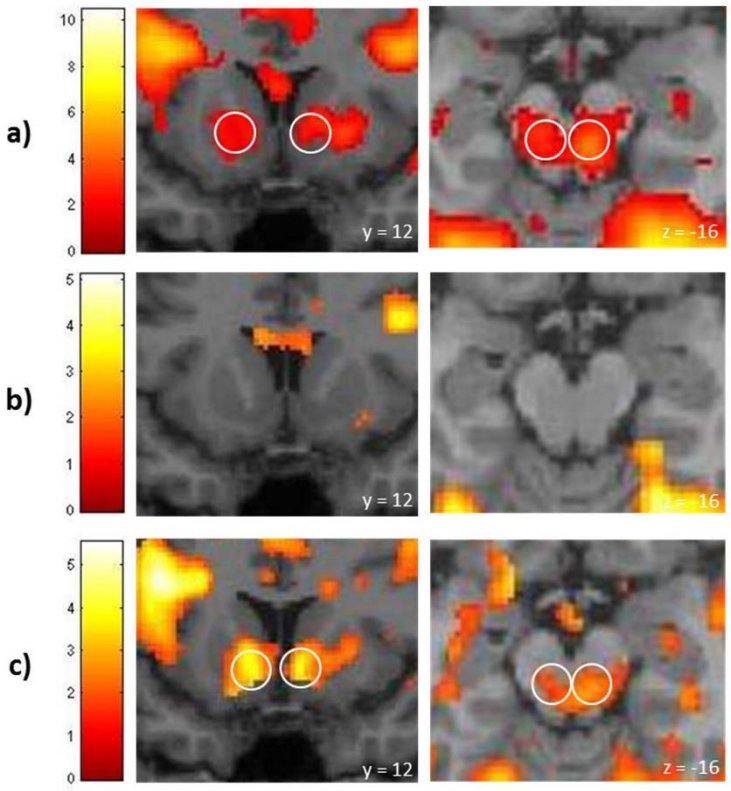


Figure S1: Replication of previous findings under placebo treatment. a) Significant bottom-up activation in bilateral NAcc and VTA in the desire contrast. b) No increased activation in bilateral NAcc and VTA in the reason contrast. c) Significant down-regulation of the activation in bilateral NAcc and VTA during a desire-reason dilemma. For illustration purposes a threshold of $p < .05$ uncor. was used. NAcc = Nucleus accumbens, VTA = Ventral tegmental area

Table S3: Emotion processing in the amygdala-hippocampus complex with and without oxytocin treatment

Table S3: Emotion processing in the amygdala-hippocampus complex with and without oxytocin treatment

Region of Interest	Fearful Faces vs. No Faces				Happy Faces vs. No Faces			
	PI	*OT*	*OT > PI*	*OT < PI*	*PI*	*OT*	*OT > PI*	*OT < PI*
R amygdala – hippocampus complex	20 -12 -20 (4.43)[a]	18 -6 -18 (2.77)	NS	20 -12 -20 (3.26)[b]	22 -6 -20 (3.06)	18 -6 -20 (3.04)	NS	NS
L amygdala – hippocampus complex	-18 -10 -20 (3.61)[a]	NS	NS	NS	NS	-18 -8 -20 (3.91)[b]	-14 -2 -16 (3.02)	NS

Reported activations are significant at p<.005, uncorrected, with an extend threshold of k>5. R/L = right/left, NS = not significant. The contrast Fearful Faces vs. No Faces was calculated with trials containing no reward associated stimuli. PI = Placebo; OT = Oxytocin.

[a] Voxels were significant at p<.05; corrected for FDR (whole-brain)

[b] Voxels were significant at p<.05, corrected for small volume.

Table S4: PPI results of oxytocin effects on negative coupling in desire contrast and of placebo effects on negative coupling in reason contrast as well as conjunction analysis of both PPIs.

Region	OT Desire	Pl Reason	Conjunction
Seed R NAcc (10 16 -10)			
R avPFC	40 40 8 (2.62)	38 36 10 (2.63)[c]	38 38 10 (2.31)[b]
R vmPFC	14 40 -8 (2.72)	16 50 -4 (3.12)	18 50 -4 (2.10)[b]
R frontomedian	4 44 50 (3.00)	12 32 48 (3.02)[b]	12 32 44 (1.93)
L frontomedian	-8 28 38 (2.93)	-10 30 34 (2.22)[c]	-10 30 34 (2.22)[b]
L postcentral gyrus	-50 -30 56 (2.81)	-50-32 60 (2.73)	-50 -30 58 (2.67)[b]
L middle cingulate gyrus	-12 18 28 (3.29)[b]	-12 14 24 (3.06)	-10 16 26 (2.61)[b]
L MFG	-42 48 20 (3.65)[b]	-38 44 24 (3.31)[b]	-42 44 24 (2.90)[a]
R central operculum	44 0 18 (2.88)	44 -4 20 (3.14)	44 -2 20 (2.53)[b]
L central operculum	-42 4 20 (4.21)[b]	-42 0 18 (2.80)[b]	-42 2 18 (2.79)[b]
R anterior Insula	38 10 -12 (2.62)[c]	36 10 -14 (2.84)	38 10 -12 (2.62)[b]
L anterior Insula	-38 8 -6 (3.20)	-40 4 -8 (3.07)	-38 6 -8 (2.38)[b]
L posterior Insula	40 -4 -8 (2.26)[c]	44 -4 -4 (3.42)[b]	40 -4 -8 (2.26)[b]
R angular gyrus	54 -46 40 (3.14)	52 -50 38 (2.81)	52 -48 38 (2.54)[b]
L IPL	-30 -56 32 (4.27)[b]	-34 -50 -30 (2.24)[c]	-34 -54 36 (1.98)
R superior occipital gyrus / occipital pole	18 -94 28 (3.29)	26 -92 18 (3.54)[b]	24 -92 28 (2.66)
L middle occipital gyrus	-28 -88 28 (3.37)[b]	-32 -86 20 (2.79)	-32 -86 24 (2.16)b
L thalamus	-12 -6 2 (3.96)[b]	-12 -4 4 (2.93)	-12 -4 4 (2.93)[b]
	-24 -22 10 (3.80)[b]	-24 -22 10 (2.24)[c]	-24 -22 10 (2.24)[b]
L nucleus caudatus	-8 20 6 (3.53)[b]	-10 16 14 (3.15)	-10 18 10 (2.77)[a]
R VTA	16 -18 -18 (2.82)	6 -8 -12 (3.00)	2 -18 -18 (1.99)
L VTA	-6 -16 -20 (4.92)[a]	-4 -12 -14 (2.74)	-4 -14 -16 (2.35)[b]
Seed L NAcc (-10 10 -8)			
L medial / anterior orbital gyrus	-16 42 -10 (4.47)[a]	-26 44 -8 (2.58)[c]	-24 42 -8 (2.04)
L central operculum	-38 0 24 (2.87)[b]	-42 4 14 (4.84)[b]	-40 0 22 (2.02)
L IPL	-34 -40 34 (3.55)	-32 -40 32 (3.23)	-32 -40 32 (3.01)[b]

Reported activations are significant at p<.005, uncorrected, with an extend threshold of k > 10 for PPIs and k > 5 for conjunction analysis. R/L = right/left, avPFC = anteroventral prefrontal cortex, vmPFC = ventromedial prefrontal cortex, MFG = medial frontal gyrus, IPL = intraparietal lobe, VTA = ventral tegmental area.

[a] Voxels were significant at p<.05, corrected family wise error (whole-brain).

[b] Voxels were significant at p<.001, uncorrected.

[c] Voxels were reported at p <.01, uncorrected.

Chapter 5

Intranasal oxytocin selectively modulates large-scale brain networks in humans

5.1 Abstract

A growing body of evidence indicates that the neuropeptide oxytocin alters the neural correlates of socio-emotional and salience processing. Yet the effects of oxytocin over the large-scale networks involved in socio-emotional and salience processing, namely the default mode (DM), ventral attention (VA) and cingulo-opercular (CO) networks, remain unknown. Therefore, we conducted a placebo-controlled crossover study with intranasal 24IU oxytocin in 38 healthy male subjects using a resting-state fMRI (rs-fMRI) paradigm to investigate these three network candidates. To fundamentally understand the underlying mechanisms of the neuropeptide, we compared the intra-network connectivity for each network candidate and also the inter-network connectivity across all networks between both treatment groups. Based on the relevance of inter-individual factors for oxytocin effects, we additionally correlated individual network changes with impulsivity scores. Our results show that oxytocin mainly alters the connectivity in the VA network, from one side reducing the coupling to regions that typically form the DM nodes, an introspective and self-referential network, and from the other side increasing the coupling to the edges of the CO network, which is involved in salience processing. The results of the inter-network analyses confirmed the specificity of the oxytocin effects. However, connectivity changes in key-regions of the reward system for each subject did not significantly correlated with the obtained impulsivity scores. Overall, our data supports that the modulation of functional connectivity within the VA network is a basic mechanism by which oxytocin directs attentional resources from internal to external cues, preparing the brain for contextual-dependent salience processing.

5.2 Introduction

The impact of the neuropeptide oxytocin on the neural correlates of social functioning is not fully understood and is of primary interest. Animal and human studies highlighted its critical role in approach-avoidance behavior (Calcagnoli et al., 2015; Scheele et al., 2012), pair-bonding (Johnson et al., 2016; Walum et al., 2012b) and mother-pup bonding (Elmadih et al., 2014; Shahrokh et al., 2010) and also in trust (Baumgartner et al., 2008), emotion recognition (Shahrestani et al., 2013), empathy and theory of mind (Hurlemann et al., 2010; Uzefovsky et al., 2015). One of the current hypotheses about the underlying neural processes of its function is that oxytocin might affect brain regions which are related to social cognition (Baribeau and Anagnostou, 2015; Skuse and Gallagher, 2009). It was found that oxytocin receptors are distributed in brain regions associated with emotion processing, self-referential processing and motivation, for instance in the amygdala, the prefrontal cortex and in the striatum, respectively (Insel, 1992; Loup et al., 1991; Stevens et al., 2014), and it is synthetized after social interactions such as sexual behavior (Waldherr and Neumann, 2007) or intimidation (Kéri and Kiss, 2011). Increasing interest on how oxytocin modulates networks associated with social processing has led to functional neuroimaging studies focusing on alterations in connectivity, with the amygdala as an a priori defined region of interest within resting-state (Kumar et al., 2015; Riem et al., 2012), but also within task-based studies (Hu et al., 2015; Kirsch, 2005) and in studies with clinical populations (Dodhia et al., 2014; Watanabe et al., 2015).

If oxytocin modulates the activity and connectivity in regions linked with social and emotional processing, it would also affect the default-mode network (DM) which is thought to represent or to largely overlap with the social brain (Mars et al., 2012; Schilbach et al., 2008). The DM nodes have been shown to be activated when the brain is at rest, mind-wandering or being concerned with one-self (Buckner et al., 2008; Raichle, 2015). This large-scale network includes the mPFC and ACC, the precuneus, the angular gyrus and the hippocampus, which are regions involved in several social cognitions (Li et al., 2014) and known to be modulated by oxytocin in task-based studies (Bethlehem et al., 2013; Zink and Meyer-Lindenberg, 2012). More recently, neuroimaging studies on trauma-exposed individuals (Frijling et al., 2015) or on anxiety disorder (Gorka et al., 2015; Labuschagne et al., 2010) indicate that oxytocin might alter social salience processing, thus involving the ventral attentional (VA) and the cingulo-opercular network (CO) (Koch et al., 2014; Shamay-Tsoory and Abu-Akel, 2016). The VA is thought to be involved in the redirection of attention and is defined by key nodes such as the temporoparietal junction (TPJ) and the ventrolateral prefrontal cortex (vlPFC). In contrast, the CO is more known for top-down control and altering cognitive control and is defined by the anterior insula (AI) and the dorsal ACC (Menon, 2015; Sheffield et al., 2015; Sylvester et al., 2012; Vossel et al., 2012). Previous resting-state studies support this assumption by determining that

oxytocin modulates the connectivity between central regions of the CO and the VA networks as for example the AI or the dorsal ACC and the vlPFC (Frijling et al., 2015; Koch et al., 2016).

The systematic investigation that considers the influence of oxytocin on the functional relationship across large-scale networks seems decisive for the comprehension of its modulatory effects over the neural correlates. Nonetheless, we are not aware of any resting-state fMRI (rs-fMRI) studies that explore whether oxytocin modulates the functional connectivity between and within large-scale networks. A resting-state paradigm was chosen due to an interest in exploring the basic mechanism by which oxytocin might alter neural systems. Moreover, several studies have already demonstrated that there exists a strong similarity between brain dynamics when the person is at rest or involved in a task (Smith et al., 2009). Therefore, we investigated all independent component-driven large-scale networks impacted by oxytocin in a counterbalanced crossover placebo-controlled design. Due to the strong influence of oxytocin on social behavior and its underlying neural connectivity, but also because of the latest effects seen on salience processing, we hypothesized that the DM, the CO and the VA networks would be majorly affected. Additionally, since oxytocin is thought to act differently on neural correlates and behavior depending on social contextual and inter-individual factors (Bartz et al., 2011; Olff et al., 2013), we further investigated, on an exploratory basis, whether individual functional connectivity modulations were associated with non-social personality and impulsivity scores.

5.3 Methods and Material

5.3.1 Participants

Forty healthy male participants from a university population were included in this double-blind, placebo-controlled, crossover study. Two participants were excluded because of voluntary drop-out and technical issues during scanning. Participants were right handed, between 18 and 35 years old, had normal or corrected-to-normal vision and German as a first language. They were medication free and were not suffering from psychiatric, neurological or any other diseases. In addition, they were screened for MRI contraindications and for alcohol and drug use. Participants gave written informed consent and were paid for participation. All procedures were approved by the Ethics Committee of the University Medical Center Göttingen.

5.3.2 Task and procedure

All participants underwent rs-fMRI scan under oxytocin and then placebo treatment, which occurred on two consecutive days. The day prior to the scanning session participants filled out a battery of self-rating questionnaires, including the Temperament and Character Inventory (TCI) and Barratt Impulsiveness Scale (BIS) (Supplementary Table 1). Approximately 75 min before the rs-fMRI scan, participants self-administered intranasal 24IU oxytocin (Syntocinon-Spray, Novartis, Basel, Switzerland) or placebo, according to a counterbalanced randomization order prepared by the Hospital Pharmacy of the Heidelberg University (InPhaSol). The placebo spray was produced to look identical and with the same content as the oxytocin spray, except for the absence of the neuropeptide. Studies investigating the oxytocin plasma concentration in saliva after intranasal administration demonstrated that the level returned to baseline not before 90min up to 4h post administration (Gossen et al., 2012; Weisman et al., 2012). Also, an early study exploring neuropeptides in cerebro spinal fluid (CSF) demonstrated that the vasopressin level, a related neuropeptide, did not reach baseline concentration within 80min after intranasal administration in humans (Born et al., 2002). Another recently rs-fMRI study showed an altered pattern in regional blood flow in humans within a 25-78min time measurement (Paloyelis et al., 2016). Based on these studies we can assume that oxytocin continues to act in the brain during the resting-state paradigm. During the rs-fMRI, participants were instructed to keep their eyes open and to focus on a fixation cross in the middle of the screen, to avoid attending to specific thoughts or to mind-wandering. Although not yet published, the fMRI study also comprised three runs of a decision-making experiment, which took place before the resting-state paradigm.

5.3.3 Image acquisition and preprocessing

MRI scans were conducted using a 3T scanner (Magnetom TRIO, Siemens Healthcare, Erlangen, Germany). Thirty-six axial slices (voxel size, 3x3x3mm³; gap = 20%) were acquired in ascending direction using a T2*-sensitive echo planar imaging (EPI) sequence (interscan interval, 1.9 s; echo time, 30ms; flip angle, 70°). A total of 188 volumes were obtained in the course of 6 min. In addition, a high-resolution (1x1x1mm^3) structural image was acquired by a three-dimensional, T1-weighted, gradient-echo (MPRAGE) sequence. Preprocessing of the fMRI data was performed with SPM8 (Wellcome Trust Centre for Neuroimaging, University College London, UK; http://www.fil.ion.ucl.ac.uk/spm) and included slice-timing, realignment and unwarping, co-registration and normalization into Montreal Neurological Institute (MNI) standard stereotactic space. To exclude whether differential functional connectivity of the treatment groups might be caused by unequal head motion, we applied the approach developed by Van Dijk and colleagues (Van

Dijk et al., 2012) and compared the individual root-mean-square of frame-by-frame displacements between treatment groups. Next, nuisance factors were removed to produce a clearer image by regressing out the 6 movement parameters, white matter and cerebrospinal fluid signals and their first temporal derivatives.

5.3.4 Independent component analysis and comparison of networks

The resulting images were given into temporal concatenation of group independent component analysis (gICA) in FSL MELODIC (Chen et al., 2008; Smith et al., 2009) to identify large-scale network components across treatment groups. The gICA resulted in 10 components from which 5 components were identified as DM, CO, VA, visual network (VS) and fronto-parietal network (FP), with the remaining components defined as artifacts. Large-scale networks are characterized by slow fluctuations (Deco and Corbetta, 2011), therefore, components were defined as artifacts when spikes of the powerband spectrum extended more than 0.1 Hz. Additionally, our output of 5 reliable resting-state networks remains in the typical range for standard resolution of 3 to 4mm in human neuroimaging studies that use a 1.5 to 3 tesla scanner (Deco and Corbetta, 2011). Individual back transformation was performed for each component with Butterworth band-filtered (0.01-0.1 Hz) first Eigenvariate time-courses and followed by GLM and Fisher's r-to-z transformation. The treatment group comparison of neural correlates in our a priori network candidates was performed in a one-way ANOVA at a statistical threshold of $p<.001$, cluster corrected ($k>13$) for multiple comparisons, based on the Monte Carlo simulation using the AlphaSim implementation in REST (Song et al., 2011). Cluster-wise analyses were run on within-network connectivity to explore which areas were more strongly or less strongly connected with a specific network. Large-scale networks for each treatment group, as well as the differences between them were visualized with MRIcron. Furthermore, scores of the personality and impulsivity questionnaires were included as covariates of interest in the group comparison to evaluate potential influences of individual characteristics over the functional connectivity changes. A separate model was run for each subscale or total. The existence of a modulation was determined by changes in functional connectivity within the network candidates at a more flexible exploratory threshold of $p<.005$. In this case, we extracted the parameter estimates with a sphere of 6mm of the main analysis (to avoid circularity) and correlated it with the specific scale (Pearson's r correlation, 2-tailed). We applied all 4 subscales, the total of the TCI, all 3 subscales and the total of the BIS for a sum total of 9 scores. Therefore, the p-value was set to $p < 0.5/9 = 0.006$ to correct for multiple testing. Lastly, Pearson's correlation coefficients were calculated to identify the differences across the large-scale networks within and between the two treatment groups and correlation matrices were produced by averaging correlations for each pair of network

over all subjects. The correlation maps were visualized with MATLAB 2012a (The MathWorks, Inc., Natick, MA, USA). To estimate treatment group differences in the matrices, correlation coefficients were r-to-z transformed and entered into a two-sample t-test with a p-value Bonferroni corrected for multiple testing (5 networks: $p < 0.5/5 = 0.01$). This inter-network analysis was done to support the results of the intra-network analysis and to account for the issue with the large degree of false positive results with SPM analysis, as demonstrated in a recent fMRI method paper (Eklund et al., 2016).

5.4 Results

The neural networks of 38 participants (mean age 24.95±3.39y) were analyzed in this study. The analysis of the mean displacement to evaluate whether head motion might contribute to the following results in functional connectivity showed no significant differences across treatment groups (placebo: M=1.29 SD=0.95; OT: M=1.34 SD=0.93; T=0.24, p=0.810). The gICA yielded 5 large-scale networks, namely the VS, the VA, the DM, the FP, and the CO networks, defined according to the spatiotemporal configuration presented in multiple studies (Deco and Corbetta, 2011; Finn et al., 2015; Sylvester et al., 2012; Vaidya and Gordon, 2013; Zhang et al., 2015). All networks were well represented in both treatment groups as shown in Figure 1 and in more detail in Supplementary Figure 1 and 2.

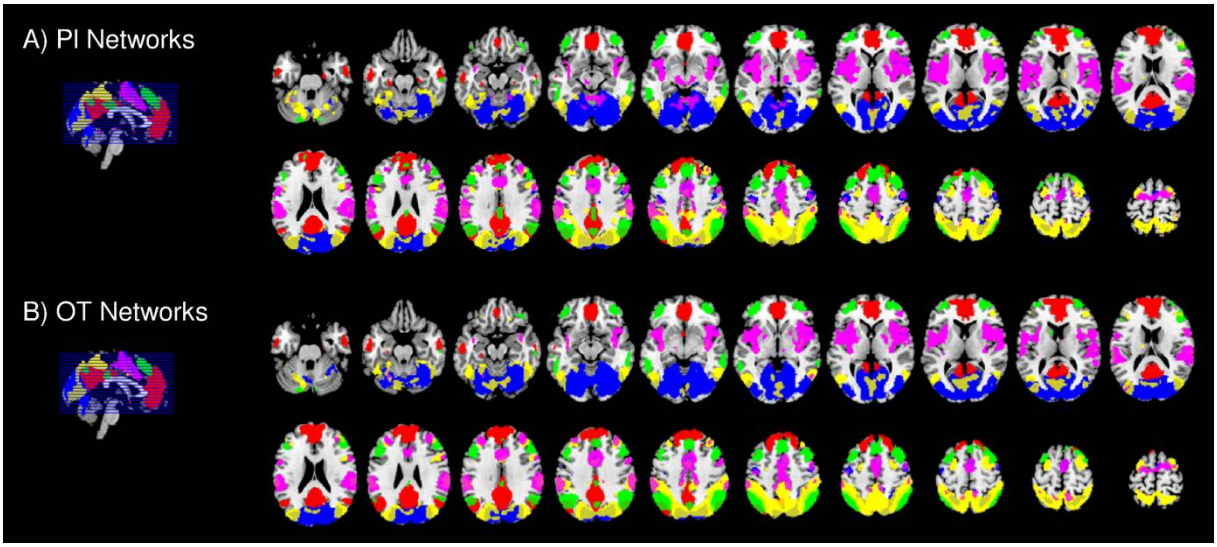


Figure 1: Functional connectivity across networks within Pl A) and OT B) treatment groups. Networks were identified after gICA: VS (blue), DM (red), VA (green), FP (yellow) and CO (pink).

gICA = group independent component analysis, Pl = placebo, OT = oxytocin, VS = visual network, DM = default mode network, VA = ventral attentional network, FP = fronto-parietal network, CO = cingulo-opercular network

5.4.1 Intra-network functional connectivity

At first, we identified differences in intrinsic functional network connectivity between both treatment groups (Supplementary Table 2). The strongest effect of oxytocin treatment concerned the functional connectivity within the VA (Figure 2A). Within the VA network, in contrast to placebo oxytocin significantly reduced the functional connectivity to regions typically belonging to the nodes of the DM, such as medial frontal, pregenual and subgenual ACC regions along with the precuneus, posterior inferior parietal lobe and hippocampus. In contrast, oxytocin significantly increased the functional connectivity to edges of the CO network, such as the superior AI, postcentral and superior parietal regions, medial septum, and inferior parietal lobe. Additionally, oxytocin decreased the functional connectivity within the ventral tegmental area (VTA), the central operculum, the inferior AI and the brain stem. The analysis of the CO network also revealed reduced functional connectivity in the VTA and cerebellum with the oxytocin versus placebo treatment (Figure 2B). Conversely, oxytocin strengthened functional connectivity within this network in the nucleus accumbens (NAcc) and supramarginal gyrus. Lastly, the analysis of the DM network showed that within this network no direct influence of oxytocin in contrast to placebo was statistically relevant (Figure 2C).

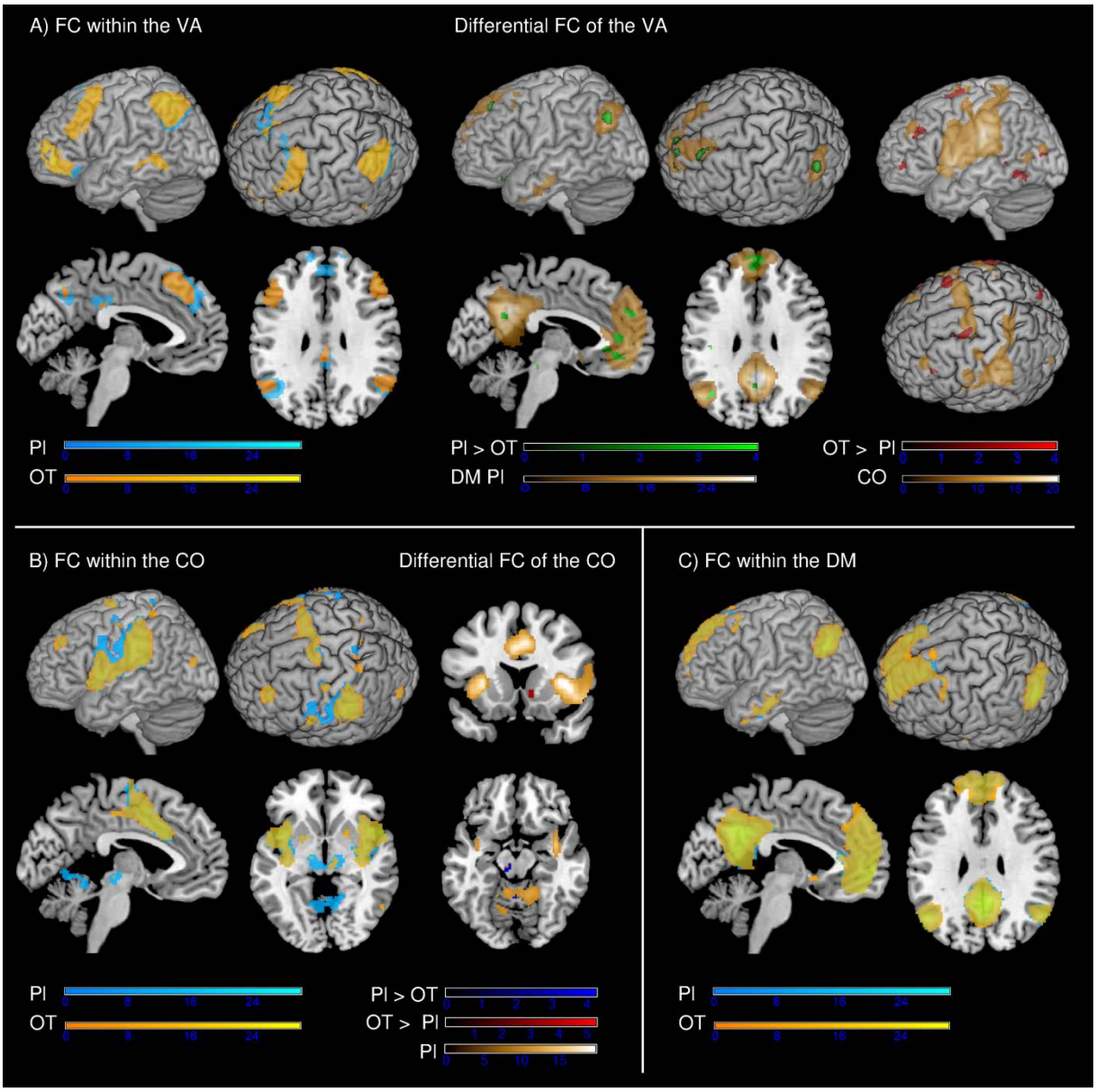


Figure 2: Influence of OT on functional connectivity within VA, CO and DM. A) FC within VA after Pl (blue) and OT (yellow) treatment. Analysis of VA revealed that OT reduced FC (green) to nodes of the DM (brown) and increased FC (red) to edges of CO (brown). B) FC within CO after Pl (blue) and OT (yellow) treatment. Analysis of CO (brown) revealed that OT increased FC (red) to the right NAcc and reduced FC (blue) to the VTA. C) FC within DM after Pl (blue) and OT (yellow) treatment. There were no statistical significant differences after treatment in FC within this network. For visualization purpose thresholded SPM maps of both treatment groups and networks were overlaid on MRIcron templates (AlphaSim correction at $p<.001$ with $k<13$ for treatment group comparisons). Color bars represent the intensity of t-values.

FC = functional connectivity, Pl = placebo, OT = oxytocin, VA = ventral attentional network, DM = default mode network, CO = cingulo-opercular network

5.4.2 Functional connectivity and impulsivity scores

In order to investigate whether non-social inter-individual factors have an influence on the effect of oxytocin over the candidate networks, we correlated the TCI and BIS scales with significant changes in functional connectivity under oxytocin treatment. However, we did not find any statistical significant correlations for TCI and BIS scales with significant changes in functional connectivity under oxytocin treatment.

5.4.3 Inter-network functional connectivity

At last, the inter-network functional connectivity in both treatment groups is shown for all networks with correlation matrices (Figure 3). Oxytocin significantly decreased the functional connectivity between the VA and the DM network (t=3.57, p<.001). There was also a trend-level decrease of the functional connectivity between the FP and the DM network, which did not survive correction for multiple testing (t=1.98, p=.055). Moreover, oxytocin slightly increased the functional connectivity between the VA and the FP as well as between the FP and the CO networks, but those findings were not significant (both p>.05).

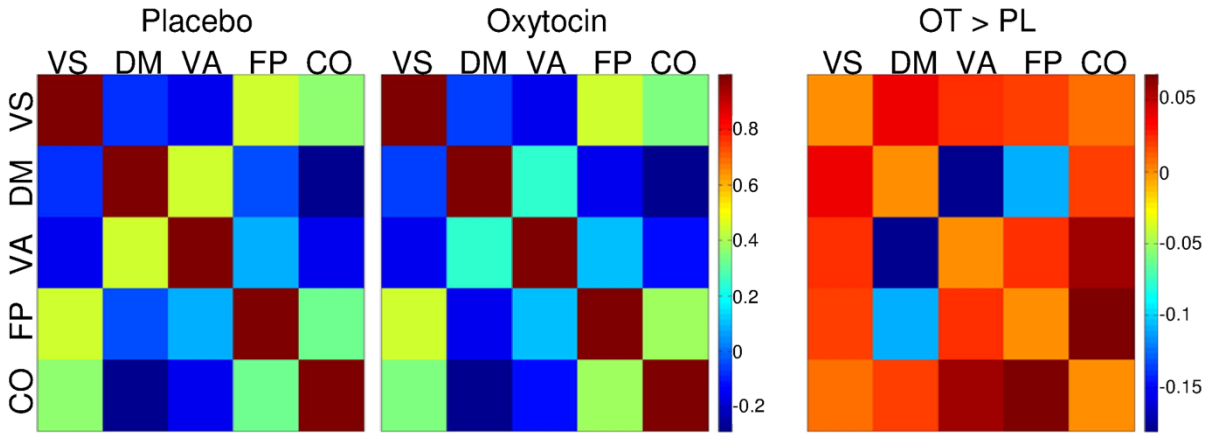


Figure 3: Inter-network functional connectivity matrices for Pl and OT treatment groups. Pairwise Pearson's correlations between time courses of networks are displayed for each treatment group. Change in network connectivity after OT treatment is displayed in an additional correlation matrix. Only the difference in FC between VA and DM network was significant (p<.01 Bonferroni corrected for multiple testing). The reduced connectivity between FP and DM networks was at a trend-level (p=.055). Colors of the matrices represent the intensity of the averaged z-scores.

Pl = placebo, OT = oxytocin, FC = functional connectivity, VS = visual network, DM = default mode network, VA = ventral attentional network, FP = fronto-parietal network, CO = cingulo-opercular network

5.5 Discussion

To the best of our knowledge, we have conducted the first resting-state study to systematically investigate the influence of exogenous oxytocin over the most representative networks for social cognition and salience processing, namely the DM, CO, and VA networks. Our findings show that oxytocin influenced the VA by decreasing the cross-talk to regions typically part of the DM nodes and strengthened the functional connectivity to the edges of the CO. Additionally; oxytocin directly impacted the functional connectivity within the CO, but not the functional connectivity within the DM. Furthermore, we show that inter-individual impulsivity scores were differentially correlated with oxytocin effects over CO and VA networks. This study sheds new light on the network mechanisms by which oxytocin might regulate the salience of social cues.

Based on our data, oxytocin seems to selectively modulate the DM and CO networks, with the functional connectivity of VA as the key player. The VA is called the 'circuit breaker' as it interrupts the top-down directed attention associated with the FP (Vossel et al., 2014), allowing the switch to reorient attentional resources to salient stimuli present in the external environment with the CO network (Corbetta et al., 2008; Corbetta and Shulman, 2002) and vice-versa. Building on this evidence, our results show that the VA under oxytocin has reduced access to break the DM circuit, but also increased access to potentiate attention reallocation to the CO network with an increased capacity of external salience processing. Unbalanced cross-talk between these three networks is in line with the social salience hypothesis of oxytocin, where an increased sensitivity to external contextual social cues (e.g. competitive vs. cooperative) environment can occur (Olff et al., 2013; Shamay-Tsoory and Abu-Akel, 2016). Further evidence for this assumption arises from other neuroimaging studies that display increased attentional effects in favor of relevant emotional or social stimuli after oxytocin use (Gamer et al., 2010; Tollenaar et al., 2013; Domes et al., 2016). For example, in a behavioral study the authors could observe that oxytocin increased the attention towards both positive and negative facial expressions in healthy male test subjects (Tollenaar et al., 2013). Whereas another study conducted in chronic depressed patients found that the attention was selectively redirected to happy faces and decreased towards angry facial expressions by the use of oxytocin (Domes et al., 2016). Additionally, a neuroimaging study focusing on the effects of oxytocin

on the neural activity in the amygdala could not only show that oxytocin modulated selectively the activation of different amygdala subregions depending on the valence of the presented emotional facial expressions, but also that oxytocin induced gaze shifts towards the eye region of a face irrespective of the presented emotional expression (Gamer et al., 2010). Another behavioral study performed in non-human primates found a decrease in allocation of attention towards negative emotional expressions (Parr et al., 2013). Despite the differences regarding oxytocins modulation of attention depending on the tested species, the presentation of specific emotion and whether the human sample was healthy or not, the results reveal that oxytocin might basically modulates attentional resources. One major hub for these switches and the reallocation of attention within the VA could be the TPJ, a region containing parts of the superior temporal sulcus, the angular gyrus, and the inferior parietal lobe, which has also been affected by oxytocin in a task-based study (Hu et al., 2016). The TPJ is assumed to be involved in perspective taking and is therefore implicated in switching between networks (Corbetta et al., 2008). However, there is evidence against the exclusive role of the TPJ reorientation of networks (DiQuattro et al., 2014), and some authors assume that the switch would rather rely on the insular cortex, which was also activated during tasks requiring reorientation and switching between networks (Sridharan et al., 2008). Under oxytocin treatment we found both a modulation of the superior temporal sulcus/angular gyrus and the AI, indicating that oxytocin might support the functional decoupling between internal processing to external cues, redirecting the attention, and switch between the large-scale networks.

According to the social salience theory by Shamay-Tsoory and Abu-Akel (Shamay-Tsoory and Abu-Akel, 2016), oxytocin regulates mainly the salience network. Through this modulation also the reorientation of attention to external cues might occur. The AI as a part of the VA or CO network, respectively, is not only implicated in network switching but seems to also have a prominent role in salience processing (Menon, 2015; Menon and Uddin, 2010). A meta-analysis by Wigton and colleagues (Wigton et al., 2015) demonstrated that oxytocin consistently enhanced the activation in the AI. Even though the authors interpreted this finding as a sign for increased emotion processing, a modulation of the salience network or of attention by oxytocin is just as well feasible. Moreover, we found alterations of connectivity within the CO network to other major hubs associated with salience and motivational behavior, such as the VTA and the vStr, including the NAcc (Menon, 2015). These structures are fundamentally involved in the dopaminergic reward system (Haber and Knutson, 2010), reinforcing in this context the idea of an interaction between salience processing and reward (Shamay-Tsoory and Abu-Akel, 2016). The effects of oxytocin on neural activity in VTA and NAcc has been shown in human studies using monetary and social reward learning tasks (Damiano et al., 2014; Groppe et al., 2013; Hu et al., 2015), and in non-human studies by an interaction between the neuropeptide and its receptor with the dopaminergic reward system (Romero-Fernandez et al., 2013;

Shahrokh et al., 2010; Young et al., 2014). Therefore, the significant attenuation of the coupling with the VTA and the increased connectivity to the NAcc within the CO shown in our results might also reflect a regulation mechanism of the reward and salience processing system by oxytocin.

Lastly, we could not show that non-social inter-individual factors (Bartz et al., 2011; Olff et al., 2013), such as impulsivity traits were associated with differential modulation of network connectivity after oxytocin treatment. Perhaps such associations are rather observed in task-based studies wherein neural regions are recruited and which are known to be correlated with impulsivity traits. The limitations of using an rs-fMRI approach must be considered. First, we cannot predict whether the modulation of networks in this study imply a subsequent modification of behavior. Also, as we did not include a task-based paradigm for comparison, we cannot draw direct conclusions regarding the regional activations driven by social and salience processing. Moreover, connectivity results cannot be generally translated to the activation findings in relevant regions (e.g. AI or VTA) seen in other studies. Therefore, we also cannot interpret the difference in connectivity to the NAcc and the VTA within the CO.

Although the mechanisms of how oxytocin influences behavior and its underlying neural activity in healthy subjects is still not clear, the neuropeptide has already been used in various experimental and clinical trials in autism (Watanabe et al., 2015), schizophrenia (Shin et al., 2015) and PTSD (Koch et al., 2016). Considering the development of exploring new possible biomarkers for psychiatric disorders using large-scale networks in patients (Goya-Maldonado et al., 2015; Sheffield et al., 2015; Sylvester et al., 2012), future rs-fMRI studies should focus to a greater extent on the modulation of large-scale networks by this neuropeptide in patient groups. Exploring the effects of oxytocin on large-scale networks could shed new light on the specific and selective action of the neuropeptide and might promote optimized pharmacological therapies based on specific dysfunctional networks. For example, disorders such as PTSD, which show deficits in salience processing or in reorientation of attention, might benefit from these new results.

All in all, our study contributes by showing the effects of the neuropeptide oxytocin in modulating the relationship between networks responsible for attentional (VA), emotional (DM) and salience (CO) processing. These results are in line with the social salience hypothesis, which proposes a framework of oxytocin increasing sensitivity to context-dependent social cues and therefore shifting resources towards social affiliations. Therefore, we conclude that oxytocin might prepare the subject for external information which demands attention and adaptive responses as seen, for example, in social interactions. As hypothesized, we also show in the VA and CO networks that inter-individual factors such as attentional and motor impulsivity scores are differentially modulated within the system by oxytocin.

5.6 Supplemental Information

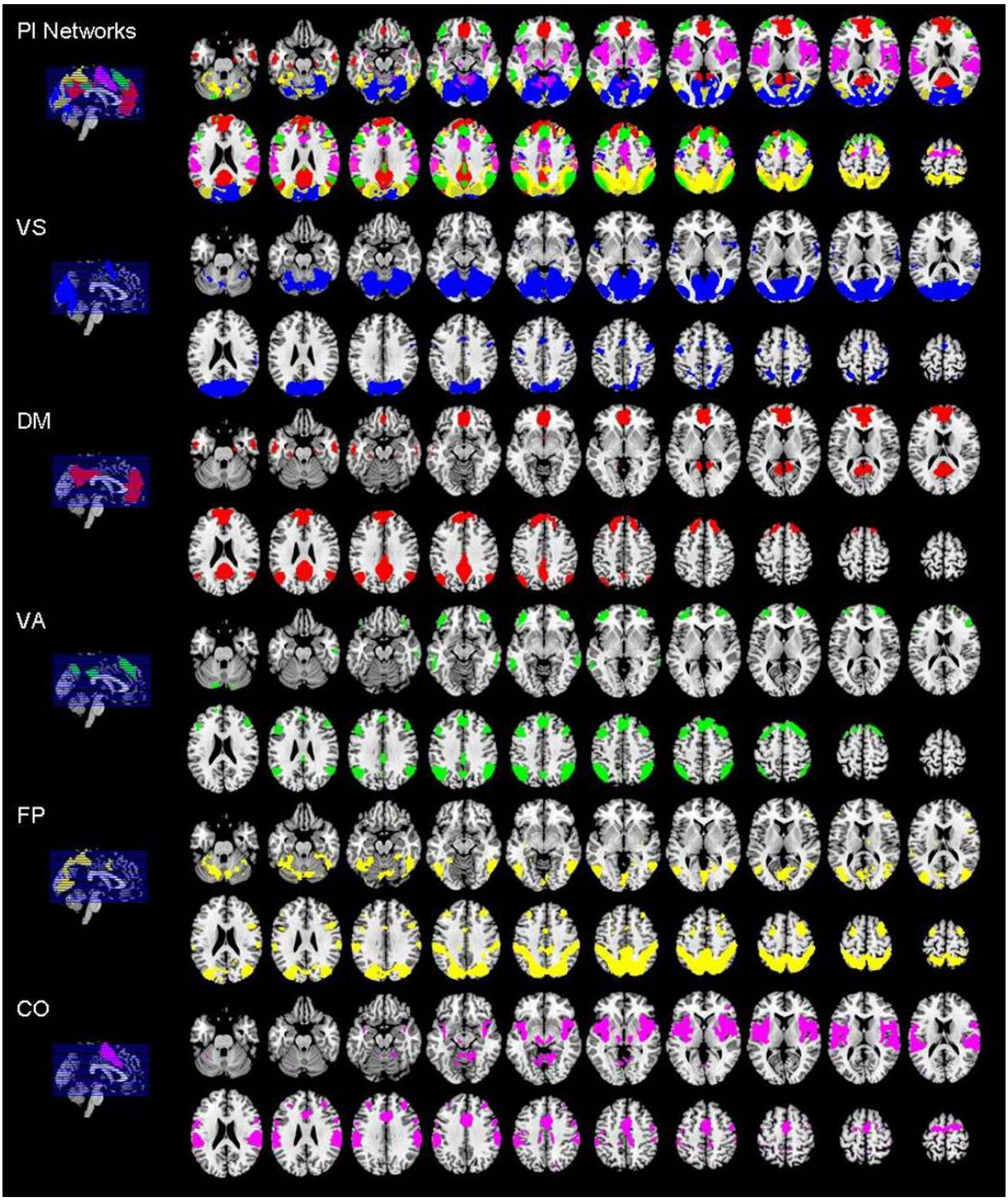
Supplementary Table 1: Means and standard deviations of the questionnaires

Questionnaires	Mean	Standard deviation
TCI		
Novelty seeking	21.44	5.95
Harm avoidance	9.71	6.37
Reward dependence	14.56	4.06
Persistence	4.32	1.71
Total	50.03	8.78
BIS		
Attention	16.24	2.82
Motor impulsivity	23.26	4.30
Non-planing impulsivity	23.29	4.38
Total	62.79	9.04

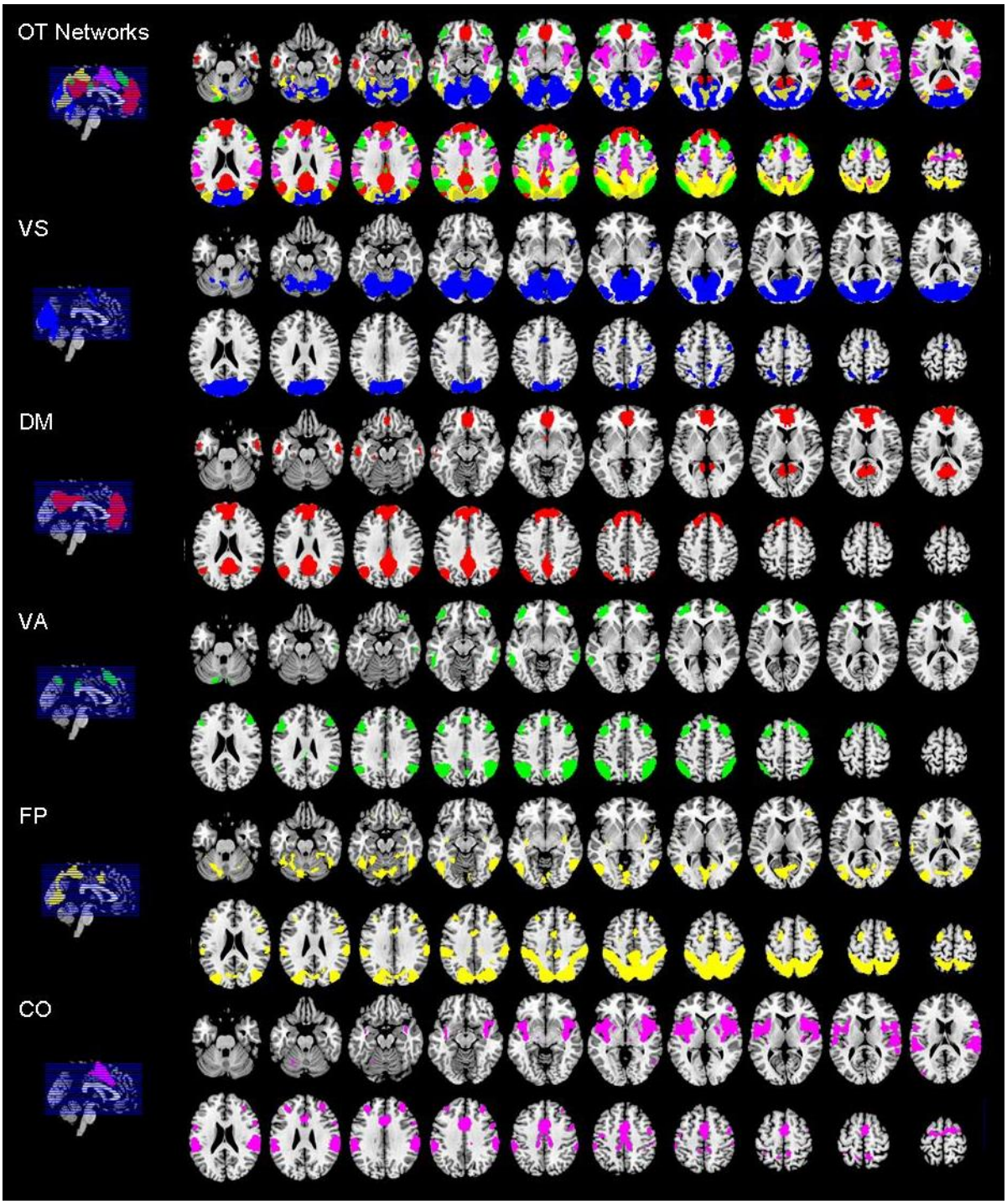
MDBF[a]	Pl Mean	Standard deviation	OT Mean	Standard deviation	T-Test
GS	-0.88	3.07	0.94	3.61	0.23
WM	3.18	6.12	3.26	7.99	0.62
RU	0.18	3.90	-0.03	4.52	0.32
Total	2.47	9.24	4.18	13.10	0.22

[a]Subscores for MDBF were calculated by subtraction of scores before and after treatment.

TCI = Temperament and Character Inventory, Pl = placebo, OT = oxytocin, MDBF = Mehrdimensionale Befindlichkeitsfragebogen, GS = Gute-Schlechte Stimmung (good-bad mood), WM = Wachheit-Müdigkeit (alertness-tiredness), RU = Ruhe-Unruhe (calm-restlessness).



Supplementary Figure 1: Functional connectivity across networks within Pl treatment group. Networks were identified after gICA: VS (blue), DM (red), VA (green), FP (yellow) and CO (pink).
gICA = group independent component analysis, Pl = placebo, VS = visual network, DM = default mode network, VA = ventral attentional network, FP = fronto-parietal network, CO = cingulo-opercular network



Supplementary Figure 2: Functional connectivity across networks within OT treatment group. Networks were identified after gICA: VS (blue), DM (red), VA (green), FP (yellow) and CO (pink).

gICA = group independent component analysis, OT = oxytocin, VS = visual network, DM = default mode network, VA = ventral attentional network, FP = fronto-parietal network, CO = cingulo-opercular network

Supplementary Table 2: Whole-brain table of effects of oxytocin on functional connectivity within networks (MNI coordinates/t-values).

Networks	OT > Pl	OT < Pl
VS		
L MTG	-	-60 -50 4 (4.08)
DM		
	-	-
VA		
L SFG	-	-8 50 26 (3.67)
R MFG	32 6 64 (3.59)	-
L mPFC	-	-8 56 6 (3.90)
L vmPFC	-	-6 46 -10 (3.39)
R vmPFC	-	8 50 -12 (3.47)
L ACC	-	-2 40 6 (3.64)
R ACC	-	2 32 -2 (3.94)
L posterior orbital gyrus	-	-32 26 -18 (4.28)
L inferior AI	-	-30 14 -20 (3.83)
L superior AI	-26 24 18 (4.20)	-
L central operculum	-	-34 -22 22 (3.75)
R posterior ITG	60 -54 -14 (3.68)	-
R postcentral gyrus	32 -30 42 (4.09)	-
L SPL	-28 -48 40 (3.99)	-
L precuneus	-	-2 -56 26 (3.64)
L supramarginal gyrus	-40 -38 38 (4.31)	-
L angular gyrus	-	-44 -66 36 (4.31)
R angular gyrus	50 -46 48 (4.03)	-
Septum	0 16 6 (3.96)	-
R Hippocampus	-	30 -8 -22 (3.51)
R VTA	-	8 -14 -12 (3.85)
L Brain stem	-	-2 -28 -18 (3.59)

FP		
R dorsal PFC	-	10 40 38 (4.38)
L FEF	-	-10 14 56 (4.41)
R FEF	-	16 22 52 (4.39)
R AI	-	26 16 -16 (4.18)
L STG	-	-60 -28 2 (3.57)
R STG	-	66 -24 -2 (3.55)
L parietal operculum	-	-28 -28 24 (4.11)
L SPL/angular gyrus	-	-28 -66 50 (4.48)
CO		
R supramarginal gyrus	62 -34 28 (3.67)	-
R NAcc	10 18 -4 (3.96)	-
L VTA	-	-8 -22 -10 (4.23)
R Cerebellum	**-**	**10 -48 -8 (4.22)**

Reported activations are significant with AlphaSim correction at p<.001 with an extended threshold of k=13. MNI coordinates. Pl = placebo, OT = oxytocin, R/L = right/left, VS = visual network, DM = default mode network, VA = ventral attentional network, FP = fronto-parietal network, CO = cingulo-opercular network, MTG = middle temporal gyrus, SFG = superior frontal gyrus, ITG = inferior temporal gyrus, MFG = medial frontal gyrus, mPFC = medial prefrontal cortex, vmPFC = ventromedial prefrontal cortex, ACC = anterior cingulate cortex, AI = anterior insula, SPL = superior parietal lobe, VTA = ventral tegmental area, FEF = frontal eye field, STG = superior temporal gyrus, NAcc = nucleus accumbens.

Chapter 6

General Discussion

6.1 Summary of results

This thesis presents three neuroimaging studies addressing the main question whether oxytocin also modulates neural activity, connectivity or task performance even when no social context or stimuli are presented. The results clearly demonstrated effects on neural activation, functional connectivity and on behavior. First, the contribution of OXTR SNPs in a non-social decision-making paradigm was evaluated by using an imaging genetics approach. Then the system was probed by using intranasal administration of oxytocin with both non-social and social stimuli. Lastly a resting-state fMRI without stating a task was applied to investigate the basic mechanism by oxytocin.

In the imaging genetics study, two of the three candidate OXTR SNPs were associated with a modulation of neural activity and functional connectivity in key regions of the reward system during the DRD paradigm. Alterations were seen for the desire context by modulation of the bottom-up related signal in trials receiving a reward, and for the reason context by modulation of top-down control in trials rejecting a reward. Participants who were homozygous for the major allele of the OXTR SNP rs1042778 expressed more bottom-up related activity in the vStr in the desire context which was positively correlated with attentional impulsivity. Conversely, minor allele carriers showed a greater suppression of the reward-related activity in the reason context. This was associated with better cognitive control and therefore to significantly better performance in the rejection of reward stimuli in reason situations. In accordance with this, *GG* carriers had a stronger coupling between the vStr and the VTA in desire situations which was negatively correlated with harm avoidance for the minor allele carriers. Moreover, *A* carriers displayed an enhanced connectivity between the vStr and the avPFC in reason situations. For the OXTR SNP rs237897 an interaction of gender with the activity in the VTA could be detected. Female participants, homozygous for the major genotype, presented more activation in the left VTA compared to male participants carrying two major alleles. Altogether, this results strongly suggest that OXTR polymorphisms are able to modulate reward-related as well as control-related activity even in a non-social decision-making paradigm.

With the administration of intranasal oxytocin, an opposite modulation of activity and functional connectivity regarding non-social compared with social context was shown. In the non-social desire situation oxytocin reduced bottom-up activity within the vStr, probably by enhancing top-down control due to strengthening the negative coupling between frontal and mesostriatal regions. In non-social reason situations, the vStr was less suppressed after oxytocin administration, possible due to decreased top-down control by stronger positive coupling to the avPFC. By inducing negative emotion by presenting fearful faces in the social condition, the pattern of neural responses and functional connectivity reversed. While oxytocin increased the activation in the vStr in desire situations, it reduced the activation in reason situations. This change in activity was paralleled by

stronger positive coupling in the desire context and less coupling as well as negative coupling in the reason context. In addition to the reward system also the interactions with the amygdala were examined. Depending on valence oxytocin decreased amygdala activation for fearful faces and increased amygdala activation for positive faces in trials containing no reward stimulus. The altered activity within the reward system by oxytocin might be the reason for an impaired performance during both desire and reason situations. Surprisingly, after oxytocin treatment participants were less accurate in selecting target stimuli than in rejecting the reward stimulus and vice versa for the placebo. This does not indicate disturbed stimulus-association learning as they were conditioned before treatment but rather than impaired working memory. To sum up, the comparison between the effects of oxytocin yielded that oxytocin influences corticomesolimbic regions in opposite direction depending on the condition, non-social or social. Whereas in the non-social condition both reward-related signals as well as top-down control related connectivity were inhibited by oxytocin, both bottom-up signals as well as suppression of these signals were increased by oxytocin in the social condition.

Lastly, in the resting-state fMRI study oxytocin changed the functional connectivity within and between large-scale networks even without engagement in a task. Surprisingly, oxytocin did not alter functional connectivity within the DM network. An alteration in the DM was expected as this network largely consists of regions known to be involved in social cognition and to be modulated by oxytocin (for instance Kumar et al., 2015). However, oxytocin mainly influenced the VA, including regions associated with attentional processing, by decreasing the cross-talk to regions typically part of the DM nodes and strengthened the functional connectivity to the edges of the CO, involving regions linked to salience processing. Additionally, oxytocin directly impacted the functional connectivity within the CO. Therefore, one basic mechanism of oxytocin might be to redirect attention (VA) from self-referential processing (DM) to the external environment, preparing for reception of salient information (CO). Overall, the impact of oxytocin might rely more broadly in changing the correlates of attention and salience processing than only in influencing social stimuli.

6.2 Oxytocin – not only a “social” neuropeptide

Although most of the current research concentrated on oxytocin’s role in emotion processing and social cognition, a few studies considered non-social effects as well. In the next section the findings of the present thesis will be discussed in the light of several major publications concerned with non-social effects.

The study by Damiano et al. (2014) is so far the only neuroimaging study focusing on modulations of OXTR SNPs on reward-related activation and associated behavior during a non-social monetary incentive delay task. Although they evaluated the same SNP as I have, they could not find any modulation by the OXTR SNP rs1042778. This might be due to their smaller sample size or due to differences between the applied paradigms. However, they found an association of the risk allele of OXTR SNP rs2268493 with decreases in activity in the NAcc, the ACC, the postcentral gyrus, the insula and the thalamus, indicating not only a modulation of the core reward-system but also of the reward-related areas.

Moreover, the intranasal oxytocin administration study by Nawijn et al. (2016), using the same task, found a modulation in PTSD patients and in trauma-exposed controls. They observed an increase in both groups of activity in the striatum, in the dACC and in the insula, but no effects on performance. Whereas the striatum is mainly suggested to be involved in reward-related processes (Diekhof et al., 2012), the dACC and the insula are known as key structures of the salience system (Menon, 2015). Interestingly, the observed increase in activity for control subjects is contrary to my findings. Considering a comparable sample size, the difference refers on the task as already suggested for the study by Damiano et al. (2014). This would suggest that the experimental context would be a much more powerful moderator on oxytocin function than previously assumed (Bartz et al., 2011; Olff et al., 2013). Oxytocin is known to normalize abnormal activity in the salience network in PTSD patients (Koch et al., 2016, 2014). A reason for the effects of oxytocin on neural activity in PTSD patients not to differ from the effects in controls, could be that the trauma-exposing events in the controls already entailed alterations in the neural correlates of salience processing.

Very recently, a modified version of the MID task was used in healthy participants under oxytocin treatment (Mickey et al., 2016). In contrast to my results, the authors do not find any impact of accuracy but an overall treatment effect on reaction time with lower times for oxytocin. In their region of interest analysis on the VTA and the NAcc a prolonged BOLD response for anticipation of incentive rewards was observed in the VTA but not in the NAcc. In a further whole-brain analysis they could show decreased activation of clusters belonging to the mPFC during the anticipation of monetary loss. As they report a main reason for missing detecting of any changes in the NAcc might rely on the sample size of 18 subjects. This might be too small to discover small to moderate effects as I found with the larger sample size used in the administration study. The main discrepancy between their findings and the results of the here described administration study again might be due to the application of different decision-making paradigms. Besides, since their lack any connectivity studies they were not able to investigate the modulation between their key regions.

Furthermore, Striepens et al. (2016) observed modulation of cognitive control by intranasal oxytocin in a reward-related food intake task. Indeed, the authors found decreased activity in the putamen, nucleus caudatus and midbrain regions indicating a suppressed reward-related bottom-up signal. Complementary to this, they reported activity in the ACC, precuneus and frontal regions possibly reflecting an increase in top-down related cognitive control. This pattern was shown in a condition which demanded cognitive control and was therefore comparable to the reason situation in the here described study. Contrarywise, I found an inhibition of top-down connectivity and an increase of activity in the reward system. Interestingly, the results in Striepens et al. (2016) were more in line with the results from the neuroimaging genetics study which found suppressed activity in the ventral striatum as well as enhanced coupling to the avPFC in minor allele carriers for the OXTR SNP rs1042778. Nevertheless, attention should be paid to two facts. First, the minor allele carriers were assumed to feature lower oxytocin levels in plasma (as shown in Feldman et al., 2012). Second, Striepens et al. (2016) studied the effects in women, whereas I studied both genders in the neuroimaging genetics study and only male participants in the intranasal oxytocin administration study. As described in the introduction, opposite sex-specific reactivity patterns elicited by oxytocin were also found in the activation of the striatum and other reward-related areas during a social reciprocated cooperation paradigm (Feng et al., 2014; Rilling et al., 2014). Therefore, the differences between the reward-related food intake study and my results seem to be based on moderation by gender.

In a behavioral study, oxytocin increased cooperation when social information was presented, but decreased cooperation and lead to a risk-adverse strategy without social information, in comparison to placebo (Declerck et al., 2010). In accordance to my results a behavioral effect in a non-social condition is reported. Moreover, similar to the observation of impaired memory effects after oxytocin administration, the behavioral effects after oxytocin administration in a non-social context may be categorized as maladaptive (Declerck et al., 2010). Nonetheless, my findings showed no difference between emotional and non-social conditions regarding behavioral outcome. Besides, there are some publications on the issue that oxytocin might impair memory in non-social conditions. For instance, Kim et al. (2016) could demonstrate that knockout of the CD38 gene in mice, which is involved in the secretion of oxytocin, led to impaired learning and memory in spatial as well in non-spatial tasks. As already mentioned in the introduction, impaired memory processes were also seen for social as well as for non-social words in a recall task (Heinrichs et al., 2004) and for social and non-social visual memory performance (Herzmann et al., 2012) in humans. This is in line with my results. I found a significant lower performance level in general in reward-based decision-making after oxytocin administration irrespective of social or non-social condition. Interestingly, the performance was disturbed for the target trials in particular and not for the desire trials. The target trials

contained stimuli which were shortly presented in the beginning of every block and the reward stimuli were operationally conditioned by stimulus-reward-association learning previous to the experiments. The more pronounced impairment for the memory of target trials leads to the assumption that merely the working memory in frontal areas was disturbed by oxytocin. The stimulus-reward-association which is based on the processes in the NAcc and VTA of the dopaminergic reward system (Jimura et al., 2013) was not significantly reduced.

Overall, all three of the approaches (the resting-state fMRI study will be discussed later) applied in this thesis could confirm the modulation of non-social effects by oxytocin (Figure 3).

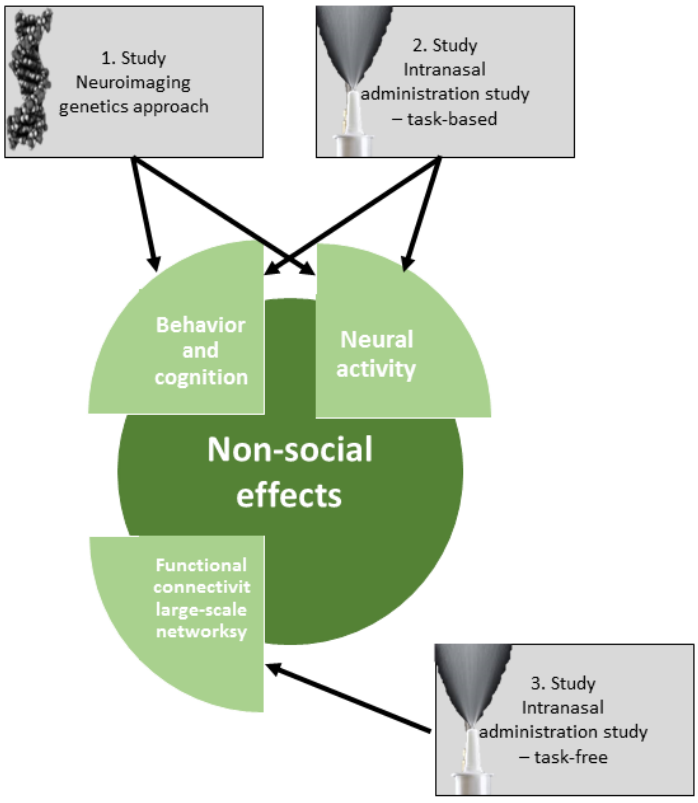


Figure 3: Investigating non-social effects of oxytocin by the use of three different approaches. Study 1 and 2 were tasked-based neuroimaging studies exploring the modulation of non-social effects by oxytocin in behavior and cognition (decision-making paradigm) as well as on a neural level. Study 1 applied a neuroimaging genetics approach, whereas study 2 used intranasal administration of oxytocin. Study 3 applied also intransal administration of oxytocin but in a task-free paradigm in order to investigate the functional connectivity changes of large-scale brain networks by oxytocin. Despite the use of the differerent approaches all three studies could show non-social effects of oxytocin either on a neural level or both on a behavioral and a neural level.

The findings of the increased reward related activity in the social desire situation after intranasal oxytocin administration are in accordance with other oxytocin studies showing an enhanced bottom-up signal in the striatum during reciprocated cooperation (Feng et al., 2014; Rilling et al., 2012) and trust adaptation (Baumgartner et al., 2008), in the VTA for socially reward-related stimuli (Gregory et al., 2015) and in a social reward-based decision making task (Groppe et al., 2013) and in the NAcc and the VTA for pair-bonding (Scheele et al., 2013). Moreover, the results replicated those of a previous neuroimaging study on the DRD paradigm which also showed an increased coupling between the amygdala and the vStr in the presence of reward and emotional information (Krämer and Gruber, 2015). According to a model by Bos et al. (2012), oxytocin might facilitate social behavior by enhancing cognitive control from prefrontal regions and by its effects on the reward system, respectively.

Besides, my fMRI data contribute to the discussion whether oxytocin attenuates the neural activity in the amygdala during emotion processing regardless of the shown valence (Domes et al., 2007a) or whether it acts with specificity on emotion processing (Gamer et al., 2010; Shin et al., 2015). As I found a reduction of activity in the amygdala for negative emotions and an increase in the activity for positive emotions, the results support the assumption of oxytocin's selectivity. Still no significant behavioral effect regarding the valence of the stimuli were observed. According to the GAAO hypothesis (Harari-Dahan and Bernstein, 2014) oxytocin down-regulates the cortico-amygdala threat circuitry underlying avoidance/withdrawal, and up-regulates the dopaminergic reward circuitry underlying approach. Therefore, the behavioral outcome in the decision-making task might be the same for negative and positive valenced stimuli in terms of salience so that both emotional situations might entail approaching behavior under oxytocin treatment.

The PFC is assumed to exert top-down control and to regulate reward-relating processing, especially in the vStr (for example Ferenczi et al., 2016) and although it is known that oxytocin modulates dopaminergic responses in the mesocorticolimbic circuit (for review see Love, 2014). The functional connectivity between the PFC and the vStr as displayed in both task-based studies has not been investigated yet. Nevertheless, several neuroimaging studies focused on the coupling between the PFC and the amygdala. For example, in a recently published neuroimaging study on extinction of fear conditioning, the authors observed that intranasal administered oxytocin increased reactivity in the PFC and inhibited activation in the amygdala (Eckstein et al., 2015), implying a top-down control on automatic limbic processing. Moreover, a neuroimaging genetics study applying resting-state fMRI reported that oxytocin reduced coupling between the PFC and the amygdala (Wang et al., 2013). A similar inhibitory modulation by oxytocin on coupling between the PFC and the NAcc or the VTA in

reward-based studies is conceivable, supported by the fact that both regions are known to express oxytocin receptors (for review see Stevens et al., 2014).

I performed a large-scale resting-state fMRI study with the aim to identify basal changes by oxytocin independently of a social or non-social context. Contrary to other studies investigating the influence of oxytocin on functional connectivity as I reviewed in the introduction, I applied an ICA. The ICA offers the advantage that the regions of interest (networks) are be separated automatically. Therefore, I could study the effects of oxytocin on several regions without being biased by choosing the seed regions. Yet the absence of modulation within the DM network was surprising. As I reviewed in the introduction, several behavioral and also neuroimaging studies suggest that oxytocin acts mainly on processes in neural structures belonging to social cognition circuits (for review see Zink and Meyer-Lindenberg, 2012). In a neuroimaging study on decision-making on judgements for self- and other traits (Zhao et al., 2016) oxytocin increased other traits judgements, which went along with reduced activation in the mPFC and its functional coupling with the precuneus and the ACC, indicating an inhibition of activity in the region of the DM network. In addition, several resting-state studies focusing on functional connectivity between regions underpinned this claim. For instance, in a resting-state paradigm by Riem et al. (Riem et al., 2013) a decrease in functional connectivity between the posterior cingulate cortex, which is a central node of the DM network (Li et al., 2014), and the brainstem was observed following oxytocin treatment. Another resting-state fMRI study found significantly reduced connectivity between the bilateral amygdala and the right precuneus, again a key node of the DM network and possessing an important role in social cognition (Kumar et al., 2015). However, I found that oxytocin administration in the resting-state fMRI paradigm modulated the VA and the CO networks, implicated in attention and salience processing, and thereby reduced also the connectivity between the VA and the DM networks. In comparison with the task-based studies I performed in order to investigate possible effects in a non-social task, this result is much more intriguing. Not only can a modulation of functional connectivity by oxytocin was observed without the presence of social stimuli or even a task. Moreover, the results indicate that the preselection of regions of interest belonging to the DM network in previous studies, might not have been the best option to study the basic effects of oxytocin. The finding supports the idea that the changes of functional connectivity within the VA network is a basic mechanism by which oxytocin redirects attentional resources from internal self-referencing processes (DM network) to external salient cues (CO network), possibly preparing the brain for contextual-dependent salience processing.

Altogether, a basal mechanism by which oxytocin might modulate neural responses may be through the allocation of attentional resources to salience processing networks. The task-based

administration study gives furher insight into the selective effects of oxytocin depending on the presence of socio-emotional context (Figure 4). However, as the resting-state study did not account for task-based effects, it is still an open question, whether non-social and social stimuli would additionally alter the effects of oxytocin on large-scale networks and lead to different outcomes during various tasks. Future studies should focus on the gaps of information between the assumed basic mechanism and the observed neural and behavioral changes during a task.

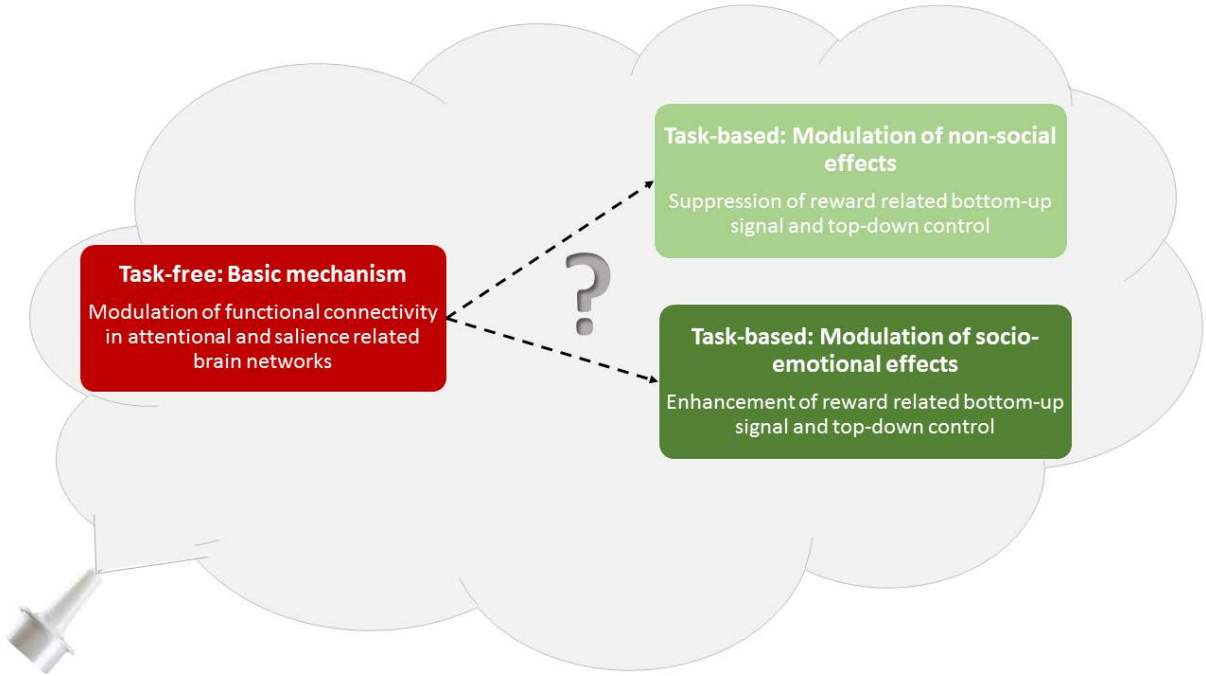


Figure 4: Summary and challenges of the neuroimaging studies applying intranasal administration of oxytocin. The resting-state fMRI study suggested a basal mechanism by which oxytocin might alter neural processing. The neuroimaging study applying a reward-related task showed contrary effects of oxytocin in the modulation of neural activity and connectivity depending on the socio-emotional content. Although, an influence on the functional connectivity within the salience network to regions of the reward system could be observed in the task-free paradigm, there is still the question on how this might be altered by additional tasks or emotional input.

To sum up, the neuroimaging studies presented in this thesis extended the current literature on oxytocin research. One the one hand, they represent a clear support for the claim that oxytocin does not act selectively on socio-emotional processes but also impacts non-social cognition and behavior as well as related brain activity. The results are in line with other findings supporting the broad range of cognitive and neural targets influenced by oxytocin. They give new and intriguing

insight into the changes in neural activation during non-social and social reward-based decision-making situations. Moreover, a new association of an OXTR SNP with neural activity and functional connectivity in a reward-based paradigm is reported which should be replicated and extended in the future. Furthermore, the findings of the resting-state fMRI study shed new light into the basic mechanisms of oxytocin – free of social, emotional and task-based influences.

6.3 Which theory could account for the observed effects of oxytocin?

I observed modulation of behavior and brain activity associated with intranasal oxytocin and with OXTR polymorphisms also in a non-social decision-making task behavior. Therefore, the social cognition theory is clearly not the one that best explains these findings. In addition to this, the results of the resting-state fMRI experiment demonstrate that the main changes in functional connectivity occur in networks associated with attentional and salience processing reaching the DM but not in the DM network itself, which overlaps to a great extent with the social brain (Li et al., 2014).

Due to the fact that the social salience hypothesis (Shamay-Tsoory and Abu-Akel, 2016) suggests that the amygdala is the key regulator in the process of salience-regulation and additionally that oxytocin only modulates social salience and not non-social salience, it is intricate to confirm this hypothesis on the findings of the neuroimaging genetics study. The experiment was not designed to optimally investigate amygdala reactivity and connectivity. Also, the task did not include social or emotional stimuli or contexts. The same is true for the fear/stress approach which is based on a presumed role of oxytocin for the regulation of the stress and emotion processing circuits (Neumann and Slattery, 2016). However, some aspects of the current findings may be interpreted within the theoretical framework of the social salience theory. For instance, the reward stimulus was perceived as salient due to its association with a reward and therefore, depending on the specific genotype, the coupling within the dopaminergic reward system was strengthened. Conversely, in the reason context the functional connectivity to the avPFC was reduced for the major allele carrier which might have resulted in a weaker top-down control and therefore in a less successful suppression of the reward related activity. As the salience of the reward stimulus remained unchanged the reward-related activity might have sustained. Now, in order to attend the salient stimulus, the cognitive control had to be inhibited by oxytocin. The interaction effect of OXTR SNP rs237897 with gender, associated with modified activation in the VTA during a reason contrast, might depend on the responsivity of the dopaminergic system. According to the theory the reactivity to a modulation associated with oxytocin might be based on factors such as gender (Shamay-Tsoory and Abu-Akel, 2016). Females carrying both major alleles could possess a more responsive dopaminergic system

which might induce a greater oxytocin-mediated modulation of the reward-related signal in the VTA. Here, the prefrontal circuit would not be involved. A potential reason could be that the responsiveness of the dopaminergic system could rely on denser distribution of OXTR specific to the VTA but not predominant prevalent in the PFC. It is important to mention that these are speculations and further investigations on the neurophysiological and neurobiological level are necessary.

In correspondence with the GAAO (Harari-Dahan and Bernstein, 2014) which assumes a modulation of reward-related areas to facilitate approach behavior, oxytocin carriers homozygous for the major allele of the OXTR SNP rs1042778 exhibited enhanced bottom-up related signal strength in the reward system, a stronger coupling between the vStr and the VTA in the desire context, and failed more often to reject the desired reward stimulus in dilemma trials in comparison with the minor allele carriers. Moreover, the major allele was associated with enhanced oxytocin plasma levels in a previous study (Feldman et al., 2012), indicating that in the current experiment, a higher amount of available oxytocin led to an increase in reward-related responses which in turn facilitated approach behavior in the dilemma situation. However, this approach behavior was not seen in the desire situation but in the reason situation which was accompanied by a relatively weaker coupling with the avPFC. This fact in turn leads to the assumption that the less accurate performance was not generated by a higher bottom-up signal but by a weaker top-down control of the avPFC, meaning that oxytocin might have modulated both desire as well as cognitive control linked to the avPFC. According to the GAAO the involvement of limbic-cortico circuits might modulate avoidance behavior (Harari-Dahan and Bernstein, 2014). In this framework oxytocin in the current experiment might have modulated both approach and avoidance circuits underlying approach-avoidance behavior to generate the effects seen on behavior and on the neural level. As the GAAO approach mainly focused on explaining behavioral effects, I do not discuss purely speculative links to the neural modulation by the interaction of gender and the OXTR SNP rs237897. Nevertheless, again as the DRD paradigm builds on the assumption that reward stimuli, learned by preceding reward-stimulus-associations, are desired by the participants, it is surprising that effects for both SNPs are mostly observed in the reason context and therefore in an avoidance situation rather than in a situation facilitating approaching motivation. This question remains to be addressed by further studies.

The effects on neural responses in the non-social decision-making condition under oxytocin administration is not addressed by any of the described theories of oxytocin function. Indeed, a stronger top-down control by enhanced negative coupling with the avPFC and the insula as well as with the amygdala and the VTA is observed in the non-social desire situation which led to suppressed bottom-up activation. Contrary, in the reason situation there is less positive coupling with the amygdala and strong positive coupling with the avPFC accompanied with an increase in the bottom-

up activity in the vStr. Regions related to the PFC are supposed to act in an opposite way on the vStr, which might explain the contrary functional couplings between the desire and the reason context (Jimura et al., 2013). However, the social salience theory would expect no modulation of the activity and functional connectivity in the absence of social stimuli, whereas the GAAO would assume the reversed neural pattern as the reward related stimulus should activate oxytocin-induced approach motivation. In contrast the social decision-making condition can be explained by nearly all of the approaches. On the one hand, according to the fear/stress account oxytocin elicited its anxiolytic properties by boosting top-down control in trials presenting negative emotional information. This possibly caused attenuated amygdala reactivity. Otherwise, the bottom-up activation in the VTA and the vStr amplified due to the presence of a reward and a social stimulus which is in accordance with the social salience theory as well as with the GAAO. The first one would interpret the boost in reward related activity as a sign for increased salience by oxytocin, which is supported by the enhanced functional coupling between the vStr, the amygdala and the VTA and the latter one would suggest that the increase of bottom-up activity reflected the motivation for approaching the desired stimulus, which in turn is underpinned by enhanced positive coupling with the IFG and the precuneus, structures involved in social cognition tasks (Kumar et al., 2015; Voorthuis et al., 2014; Zhao et al., 2016). However, the oxytocin provoked reversal of the strong limbic-reward coupling and the decrease in striatal arousal in absence of reward in the reason contrast, which cannot be explained by the fear/stress approach as the emotional content is still unchanged even though the reward related activity and the functional connectivity is altered. Because of the missing reward or salient stimulus respectively, the salience-processing in the reward system is diminished and only the cortico-limbic pathway is affected by oxytocin, which would lead to a stronger top-down control according to the social salience hypothesis. In the framework of the GAAO oxytocin acted on the avoidance pathway. Nevertheless, it is not clear why oxytocin would improve avoidance motivation by enhancing the top-down control, it is more likely that the negative coupling between hypothalamus and vStr resulted in the stronger reduced bottom-up signal in the reason context.

The basic mechanism by which oxytocin modulates neural processing and possibly subsequent behavioral responses and actions seems to be based on alterations in the functional connectivity within the VA network. Moreover, my results reveal that oxytocin modulated functional connectivity within and between the VA and CO networks, networks implicated in attentional processes and in salience processing respectively. This fits very well with the social salience hypothesis, which assumes that the basic mechanisms of oxytocin depend on dopaminergic-oxytocinergic interactions in the reward and salience system as well as on attention regulation mainly in the amygdala, frontal eye field and superior colliculi (Shamay-Tsoorie and Abu-Akel, 2016). Indeed, there were no significant functional seen in the amygdala or other mentioned regions.

However, oxytocin influenced the functional coupling of the CO network with the NAcc and the VTA, which might be the key player in the process of salience attribution (for review see Koch et al., 2014). Results suggest that the VA network is a basic mechanism by which oxytocin redirects attentional resources from internal self-referencing processes (DM network) to external salient cues (CO network), possibly preparing the brain for contextual-dependent salience processing. One major limitation is the fact, that the resting-state fMRI study not only did not involve social stimuli but also was performed completely task-free. The suggested oxytocin mechanisms in the social salience theory appear to presuppose an essential condition, the involvement of social stimulation. Overall, mounting evidence strongly suggests that oxytocin acts on activity as well as on the functional connectivity of the structures, therefore, the social salience theory should be revised. However, more research is needed before obtaining a definitive answer to the basic mechanism of oxytocin in the brain.

Until now, there is no present theory of oxytocin which could account for all the effects I observed in the studies reported in the present thesis. Indeed, the general approach-avoidance theory already attempted to account also for non-social effects, but only mainly considered effects concerning anxiety as well as stress or pain responses. Therefore, it is absolutely essential to expand current theories in order to also include non-social effects unrelated to stress or anxiety.

6.4 Relevance of the current thesis

First, the findings in the current thesis expand the knowledge on oxytocin's mechanisms and functioning in non-social cognition and reward-related behavior, such as action control, which is still a great gap in the current literature on oxytocin research. Moreover, the investigation of neural activation and functional connectivity underlying non-social and social situations in a reward-based decision-making task gives important insight into the way how oxytocin modulates neural reward processing depending on the social content. Furthermore, it highlights a basic mechanism on the neural level which might contribute in a significant way to the ongoing debate on the true effects of oxytocin.

Above all, I expect that the results will have a great impact on the application of intranasal oxytocin in clinical research. Due to its described enhancing influences on severely types of social behavior, the neuropeptide has been considered as a potential treatment for improving social cognitive deficits in several neuropsychiatric and developmental disorders. Indeed, improvement in social cognition by oxytocin treatment was seen in autism spectrum disorder (for review see

Guastella and Hickie, 2016), in schizophrenia (for review see Feifel et al., 2016), in drug addiction (McGregor and Bowen, 2012), in personality disorder (for review see Perez-Rodriguez et al., 2014) as well as in generalized social anxiety disorder (Gorka et al., 2015) and expected for PTSD (for review see Koch et al., 2014).

Additionally, I could demonstrate that exogenously administered oxytocin not only modulated behavioral and neural responses in a non-social reward-based decision-making experiment, but also that action-control and possibly parts of the working memory system were impaired in contrast to placebo treatment. This is in line with previous studies observing amnestic effects in non-social memory (Heinrichs et al., 2004; Herzmann et al., 2012) and also with an investigation of social working memory processing in highly social-anxious individuals exhibiting decreased performance after oxytocin treatment (Tabak et al., 2016). Enhanced cognitive control by oxytocin as well as diminished bottom-up signals were previously interpreted as beneficial in studies on non-social reward-based food intake (Ott et al., 2013; Striepens et al., 2016). In this thesis, however, the oxytocin-enhanced action-control in the desire situation and the reduced suppression of the reward-related signal in the reason situation led to less accurate performance. Additionally, the top-down suppression of the reward-related signal in the vStr was diminished in the reason context, though; in this situation, a stronger action control would increase the accuracy. Taken together, the behavioral consequences of oxytocin's neurophysiological effects on the reward-system and on areas responsible for cognitive control might differ depending on the context. More precisely, a behavioral outcome could be regarded as either adaptive or as dysfunctional in a given situation irrespective of the underlying processes, since a behavior's adaptivity is defined by the specific context and does not reflect a direct measure of the adaptivity of neuronal correlate. The disorders described above exhibit abnormal functioning of the reward and salience system even in non-social situations. For instance, the dopaminergic and salience system is suggested to be hyper-responsive in schizophrenia (for review see Grace, 2016), responses for social as well as non-social reward are disturbed in autism (Watson et al., 2015) and the salience system is assumed to work abnormally in PTSD (Koch et al., 2014, 2016). Based on these observations, it cannot be ruled out that oxytocin might also modulate reward and salience processing independently of a social context in patients receiving oxytocin as a potential treatment.

Therefore, major aim of the present thesis is to urge caution regarding the use of oxytocin as a potential treatment in the clinical research field. It would be of value to take heed of the possible non-social effects of oxytocin, which could highly and adversely affect the tested clinical population even outside social interactions and situations.

6.5 Limitations

There are some methodological limitations concerning the neuroimaging genetics approach. The analysis of dominant models did not enable me to determine whether there were recessive as well additive effects of the selected OXTR SNPs on brain activity or behavior. Carriers of heterozygous genotypes could mask effects of the minor allele by a major allele, which affects the outcome in a high degree. Generally, the most accurate way to investigate the effects of a single polymorphism might be the additive model accounting for effects of each possible genotype, homozygous for the minor allele, and heterozygous as well as homozygous for the major allele. However, I chose the minor carrier allele model for the following reasons. First, the sample size of participants who were homozygous for the minor allele was much smaller than the other two groups. Indeed, the full factorial model used in the analysis is able to account for unequal variances. Thus, within an additive model the minor allele group would have been undersized, rendering any additional investigations of gender interactions as well as personality and impulsivity interactions unfeasible. Second, as the minor alleles are also known as risk alleles for autism (for instance Damiano et al., 2014) or impaired empathy (Feldman et al., 2012) among other maladaptive effects, I focused on the advantages of using the standard model, which allows examining risk alleles for a comparison across different studies (Clarke et al., 2011). Furthermore, attempting a replication analysis was beyond the scope of this thesis. The replication of findings in general is very important for validating the results, but in neuroimaging studies dealing with common polymorphisms which display only low prevalence on the population level it is even more important to test for false-positives. Therefore, a replication study is still required and will be conducted soon. Moreover, the major allele of the OXTR SNP rs1042778, linked to elevated oxytocin plasma levels, facilitated bottom-up related activity in the desire situation and weakened top-down suppression in the reason situation of the non-social DRD paradigm. In contrast, enhanced oxytocin levels after intranasal administration suppressed reward-related activation in the desire contrast by stronger top-down control, and strengthened and increased the observed bottom-up signal in the reason contrast in the modified DRD paradigm with non-social conditions. There are several conceivable reasons for this. First, a measurement of elevated endogenous oxytocin in plasma does not prove that also central oxytocin is augmented (for instance, see review by Guastella et al., 2013). Nevertheless, as we did not measure oxytocin plasma level, we cannot be sure that the major allele carrier really exhibited elevated oxytocin level. Second, until now it was only suggested that the SNP rs1042778 might have functional variance since it is placed in the 3’ untranslated region of OXTR, and may lead to an increase in oxytocin synthesis, but it is still not proven by molecular studies. Third, genetic variation in sensitivity to exogenous oxytocin leading to an opposite pattern in brain activity has already shown for different haplotype blocks of the OXTR (Chen et al., 2015). Fourth, the effects in the non-social condition of the modified DRD paradigm

could rely on a carry-over-effect akin to overcompensation in the non-social condition following the over-regulation mediated by oxytocin in the presence of emotional stimuli. Fifth, differences in the experimental design parameters between both versions of the DRD paradigm could also account for the effects. Lastly, also unknown personality or environmental effects could confound the different outcomes. Hence, future research should pay more attention to these factors and the comparison between neuroimaging and imaging genetics studies should be performed very cautiously.

In retrospect, the analysis and interpretability of effects would have benefited from a simplification of the modified DRD design used in the intranasal oxytocin administration study. First, the design involved so many different conditions that the statistical power within the conditions was low due to reduced degrees of freedom. Moreover, due to the involvement of a large number of events the overall duration of the experiment was increased to a level where tiredness and fatigue as well as habituation concerning the experimental conditions during the task may have influenced neural processing. Second, the use of neutral emotional faces was not able to successfully serve as control stimulus for the emotional condition since they elicited no significant differences in the contrast with fearful or happy faces. Possibly based on the perceived salience effect or on the rewarding character of a viewed face, neutral expressions also increased activation in emotion-processing brain areas such as the reward system and the amygdala (see also Fusar-Poli et al., 2009, Derntl et al. 2009). Thus, the neutral face condition should have been omitted or replaced by another different carefully chosen control condition. For the current analyses, neutral faces could not be included in the GLM contrasts in an informative way. At last, I did not measure oxytocin plasma level to validate whether the intranasal application of oxytocin was absorbed and functional.

One major limitation of using a resting-state fMRI approach is clearly that this cannot predict whether the modulation of networks implies a subsequent modification of behavior. Also, as I did not include an additional task-based paradigm for comparison, I cannot draw direct conclusions regarding the regional activations driven by social and salience processing. However, the additional analysis of task-based data is in progress. Moreover, connectivity results from the resting state analysis cannot be generally translated to the activation findings in relevant regions (e.g. AI or VTA) seen in other studies. Therefore, it is impossible to interpret the difference in connectivity to the NAcc and the VTA within the CO beyond cautious speculation.

The neural effects seen in the studies are mostly very small and did not survive whole-brain correction for multiple testing. Along with this, only moderate differences in behavior were observed after oxytocin treatment. The here described studies were not designed to test the competing theories on the functioning of oxytocin. Indeed, I believe that the findings presented in this thesis may significantly contribute to the debate. Also, no theory could solely explain the effects of oxytocin

observed among all three studies. Therefore, future experiments on non-social cognition, behavior and brain activity should be performed to fill the missing gaps and to extend the current hypotheses.

6.6 Conclusion and Outlook

From the research that has been presented in this thesis, it is clear that oxytocin has an effect on behavior related to a reward-based decision-making paradigm using non-social stimuli. Except for the behavioral effect in the neuroimaging genetics study, intranasal oxytocin might in particular impair working memory rather than stimulus-condition learning. Distangling the specific mechanisms behind the impairments in memory performance could give further insight into the underlying biology. For instance, decreased reward-stimulus-association learning would indicate abnormal functioning of the reward system by oxytocin, whereas impairments in working memory would suggest a main target of oxytocin modulation in other brain regions. In addition, the knowledge about the timing of the mechanism occurrence, such as recognition, encoding, or recall, could lead to more attentive use of oxytocin in clinical trials. If the encoding is disturbed by oxytocin, recipients of oxytocin treatment should not take it within or shortly before a learning phase, for instance. By paying attention to these factors maladaptive side-effects could be avoided. Clearly, further studies exploring the effects of oxytocin on cognitive control in situations besides decision-making are required. Due to the fact that oxytocin may interact with dopamine on the corticolimbic or the mesolimbic pathways depending on context and personality factors discrepancies between studies are expected.

Moreover, oxytocin modulated neural activity and functional connectivity within the reward system during performance of this non-social paradigm. The pattern of modulation by oxytocin is preferentially inhibitory and depending on the given context, either the bottom-up related reward system or the top-down related cognitive control is suppressed. Interestingly, the review on the current literature yielded important differences between the results described here and other non-social investigations. In addition, the findings on the neural level are contrary to the expectations concerning the modulation of neural activity in the presence of social stimuli by current hypotheses of oxytocin pathways. Therefore, further research is required to investigate if the strong inhibition in the non-social condition is based on the characteristics of the used paradigm or if the dynamics on the neural level can be applied also to other situations. As I emphasized beforehand, it is still necessary to link the basal mechanism by which oxytocin changes neural processing in a task-free environement with the observed effects as seen in task-based studies. From major interest would be

how non-social and emotional input would influence additionally the modulation of large-scale networks by oxytocin.

Remarkably, the oxytocin-induced changes in activity and functional connectivity as seen in the non-social condition were completely reversed by emotion processing. In the presence of emotional content and depending on the context, either the bottom-up signal or the top-down signal were enhanced by oxytocin administration. Both increases could be explained in terms of some of the oxytocin hypotheses (Shamay-Tsoory and Abu-Akel, 2016; Harari-Dahan and Bernstein, 2014). However, the effects of oxytocin in a group comparison in such a complex design are too small to cover all involved neural regions on a whole-brain-level. Therefore, I had only insight into the oxytocin induced change in preselected regions of interest and therefore possibly missed true effects in regions assumed to be involved in these processes by the social salience hypothesis. In an attempt to gain more insight into the functional connectivity changes, I extended the functional connectivity analysis to further regions. A more effective approach for future analysis would be to apply dynamic causal modelling or multivariate pattern analysis. I expect that the underlying processes in the changes of neural activity would then become clearer.

I could demonstrate associations of two OXTR SNPs with behavior as well as brain activity and connectivity. As the effects of solely SNPs are in general very small, other approaches such as multilocus genetic composite analysis or haplotype analysis of diverse significant SNPs will be conducted in the future. Moreover, a combined analysis using candidate SNPs and intranasal application of oxytocin could account for oxytocin sensitivity modified by a particular genotype (Chen et al., 2015).

Lastly, the basic mechanism of oxytocin could be revealed by the investigation of oxytocin's effects on large-scale networks. The proposed mechanism is based on the oxytocin-induced changes in functional connectivity within the attentional network facilitating a switch between self-referential and salience processing. Furthermore, task performance could be evaluated in order to explore in which way the modulation of functional networks by oxytocin would change with environmental stimulation (for instance, simulating the context of a particular a task) non-invasive brain stimulation techniques, such as transcranial-magnetic stimulation (TMS), could be applied in the future. Depending on stimulation targets, one might be able to simulate engagements of regions in tasks in order to explore the response of oxytocin in the modulation of neural connectivity.

In general, the applied methods in the three studies successfully lead to findings addressing the main questions of the thesis. The combination of standard methods with new techniques or new experimental designs will broaden the understanding of the mechanisms behind oxytocin's effects on behavior, cognition and brain processes.

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List of abbreviations

ACC	anterior cingulate cortex
AI	anterior insula
ANOVA	analysis of variance
avPFC	anteroventral prefrontal cortex
BIS	Barrett Impulsivity Scale
BOLD	blood oxygenation level dependent
CD38	cluster of differentiation 38
CO	Cingulo-opercular network
COMT	catechol Omethyl transferase
CR	conditioned reward stimulus
CSF	cerebrospinal fluid
dlPFC	dorsolateral prefrontal cortex
DM	default mode network
DRD	Desire-Reason-Dilemma
fMRI	functional magnetic resonance imaging
FP	fronto-parieto network
GAAO	general approach-avoidance hypothesis of oxytocin
GABA	gamma-aminobutyric acid
gICA	group independent component analysis
GLM	general linear model
Hz	Hertz
MID	monetary incentive delay

min	minutes
mPFC	medial prefrontal cortex
NAcc	nucleus accumbens
OT	oxytocin
OXT	oxytocin gene
OXTR	oxytocin receptor gene
PCC	posterior cingulate cortex
PFC	prefrontal cortex
PPI	psycho-physical interaction
PTSD	post-traumatic stress disorder
PVN	paraventricular nucleus
rCBF	resting cerebral blood flow
RNA	ribonucleic acid
SNP	single nucleotide polymorphism
SON	supraoptic nucleus
SPM	Statistical Parametric Mapping
TCI	Temparament Character Inventory
TMS	transcranial magnetic stimulation
TPJ	temporo-parietal junction
VA	ventral attentional network
vlPFC	ventrolateral prefrontal cortex
vmPFC	ventromedial prefrontal cortex
vStr	ventral Striatum
VTA	ventral tegmental area

Appendix

Publications on oxytocin

Search on pubmed (www.ncbi.nlm.nih.gov/pubmed) was done on the 26.04.2016. First, all publications including the term "oxytocin" from the 26.04.1996 until the 26.04.2016 were listed. Then all of them were listed in 5years steps. Subcategories were formed by including additional terms.

Neuroscience: neuroimaging OR fMRI OR MRI OR BOLD OR neural OR neuronal OR neuron OR neurones OR neurons OR brain OR neuro

Clinical: clinical OR pathology OR clinic OR pathological OR psychiatric OR schizophrenic OR schizophrenia OR bipolar OR depression OR depressive OR affective OR disorder OR PTSD OR autism OR autistic

Social: social OR affective OR emotion OR emotional

The mixed categories were formed by searches combining (AND) the specific terms of each subcategory. All searches for a subcategory or a mixed category were done by excluding (NOT) the terms which should not be included in the lists. The subcategory others was formed by excluding all other terms except of the word oxytocin. The subcategory others contained mainly studies on labor and birth, but also molecular experiments and studies on cells which did not indicate a neuroscientific approach or research question. By applying ample of terms on psychiatric disorders we tried to minimize the possibility of including paper referring to neural issues in their experiments.

In a more detailed search, also the subcategory cognition was formed with the terms (cognition OR working memory OR executive control OR decision-making).

Acknowledgements

First, I like to acknowledge Prof. Dr. Oliver Gruber, who gave me the opportunity to work on one of my favorite subjects. I'm very grateful for your supervision and guidance whenever it was necessary and the encouragement during the partly frustrating analysis times.

Needless to say, I like to thank Dr. Igor Kagan and Prof. Dr. Julia Ostner for being part of my thesis-committee and all the helpful advice during my PhD. Along with this, I like to thank the rest of my examination committee Dr. Goya-Maldonado, Dr. Peter Dechent and Prof. Dr. Annekathrin Schacht (and Dr. Sergi Papiol), who were willing to examine my defense and to do everything for finding an appropriate date.

I had the fortune to work with smart and very friendly humans. Therefore, I like to give my gratitude to all of my former and actual lab colleagues - especially Anja, Bernd, Maria, Sarah T., Sarah W., Sören and Tracy. Thanks for all your professional help, smoker-breaks, (not only for the) apples, chocolates and coffees. I appreciate the great work and your friendship even outside the lab. Furthermore, I wish to acknowledge the colleagues from the MR-department, Ilona and Britta and all the persons who had participated in my studies.

In every academic career, there are particular individuals who influence one-self in a special way. Nadja F. und Roberto G.-M., thank you for sharing your excitement in science with me, for your advice and your friendship. I appreciated it a lot.

I like to thank the Göttinger connection Rebecca, Anna, Ingo, Caio and Adeelia for helping me to settle down in the city, for extending my view of the world and all the quiet times as well as the party times. I enjoyed them very much. Moreover, Rebecca, thanks for your excellent work in coordinating everything.

Anne and Nadine, to both of you goes my special gratitude. For your friendship and for being on the spot whenever it was necessary. Anne, you know that I would not be at this point without your generous help! Nadine, thanks for getting me always grounded again.

Special gratitude goes to my family. My parents (all three of you) who always supported my decisions during my personal and academic life. My dear siblings who always believed in me and had several times the chance to take an active part during my studies.