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Oxytocin and the social brain: Neural mechanisms and perspectives in human research

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ABSTRACT

The present paper summarizes functional imaging studies investigating the effects of intranasal oxytocin (OT) on brain responses to social stimuli. We aim to integrate previous research, point to unresolved issues and highlight perspectives for future studies. The studies so far have focused on identifying neural circuits underlying social information processing which are particularly sensitive to modulations by exogenous OT. Most consistently, stimulus-related responses of the amygdala and associated areas within the prefrontal and temporal cortices have been found to be modulated by OT administration. However, there are a number of unresolved issues related to the possible role of sex differences and hormonal status, genetic variability, and individual differences in socio-cognitive functioning. Future studies focusing on these open questions are expected to contribute to a more nuanced understanding of the role of the central OT system in humans and may provide the basis for novel treatment approaches for mental disorders characterized by social deficits.

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1. Introduction

1.1. *The role of oxytocin in human social cognition and behavior*

Within the last decade, the neuropeptide oxytocin (OT) has attracted increasing attention. Its importance for species-specific social functioning was first revealed by animal studies demonstrating that central OT receptor distribution critically determines several aspects of social behavior such as pair bonding and parental care (e.g. Insel and Young, 2001; Young and Wang, 2004).

In humans, most studies investigating the behavioral and neural effects of OT have used placebo-controlled intranasal application. The rationale for this approach is based on findings that neuropeptides are capable of reaching the central nervous system following intranasal administration (Born et al., 2002). An actual increase in central OT levels following intranasal OT administration was recently confirmed by microdialysis in relevant brain regions of rats and

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mice (Neumann et al., in press). Studies that have explored associations of peripheral OT levels with social stimulus processing are highly controversial regarding the validity of the assessment and interpretation with respect to CNS availability of the neuropeptide and need further investigation (Anderson, 2006; Horvat-Gordon et al., 2005; Landgraf and Neumann, 2004; Carter et al., 2007; for an overview, see Heinrichs et al., 2009).

To date, effects of OT on human social cognition and behavior have been summarized in several reviews and meta-analyses (e.g. Heinrichs and Domes, 2008; Heinrichs et al., 2009; Shahrestani et al., 2013; Striepens et al., 2011). The main body of empirical evidence so far suggests beneficial effects of intranasal OT on several aspects of social information processing and social behavior including eye gaze, facial emotion recognition, social reward processing and trust (for recent reviews, see Guastella and MacLeod, 2012; Meyer-Lindenberg et al., 2011; Shahrestani et al., 2013; Van IJzendoorn and Bakermans-Kranenburg, 2012). Together with results from animal studies, these findings point to the therapeutic potential of interventions in the central nervous OT system for the treatment of mental disorders characterized by social impairments like social anxiety, schizophrenia or autism spectrum disorders (for recent reviews, see Meyer-Lindenberg et al., 2011; Modi and Young, 2012; Striepens et al., 2011). Despite substantial evidence for beneficial effects of OT on social behavior, the neural mechanisms underlying these effects are still not well understood in humans.

1.2. *The oxytocin system in the human brain*

In rats, OT receptors are highly expressed in olfactory and hypothalamic regions, structures of the limbic system (e.g. amygdala), the thalamus, basal ganglia, as well as in the brain stem and spinal cord (for a review, see Gimpl and Fahrenholz, 2001). OT binding sites in humans, however, remain rather elusive. Preliminary results suggest that OT receptor distribution in the human brain differs substantially from other species with higher densities in dopaminergic neurons of the substantia nigra and the cholinergic nucleus basalis of Meynert (Loup et al., 1991). However, Gimpl and Fahrenholz (2001) point to the possibility that high levels of OT in one region might decrease local OT receptor expression to an extent that does not allow for detection by common methods like radioligand-based autoradiography. Thus, radioligands for in vivo PET studies in humans are still needed to provide a better understanding of OT receptor distribution in the human brain.

While mapping of OT receptors in the human brain is still in its infancy, functional brain imaging techniques allow for mapping of brain regions potentially mediating the effects of OT on human cognition and behavior. Some studies have explored OT effects on brain activation using EEG or MEG (Bick et al., 2013; Herzmann et al., in press; Hirosawa et al., 2012; Huffmeijer et al., 2013, 2012; Perry et al., 2010; Sheng et al., 2013). These methods have high temporal but rather low spatial resolution, which complicates localization of neural networks associated with the cognitive process under study, especially if the brain areas of interest are located subcortically. In comparison, spatial resolution is much higher in functional magnetic resonance imaging (fMRI), the most commonly used brain imaging tool in human OT research.

1.3. *Aims and structure of this article*

Here, we aim to provide a critical reflection on the current state of fMRI findings in OT research and highlight methodological challenges and open questions that should be addressed by future studies. We will start with a short review of selected fMRI studies integrating most of the previous evidence for effects of intranasal OT on neural correlates of social cognition and behavior (Table 1). In the majority of these studies, a single dose of OT was administered to healthy individuals following a randomized, placebo-controlled, experimental protocol. The cognitive functions under study included face perception and emotion processing (Domes et al., 2010a, 2007; Gamer et al., 2010; Kirsch et al., 2005; Lischke et al., 2012; Petrovic et al., 2008; Rupp et al., 2012), proxies of parental sensitivity and attachment (Riem et al., 2012, 2011; Rupp et al., 2013; Wittfoth-Schardt et al., 2012), as well as different aspects of social feedback processing (Baumgartner et al., 2008; Groppe et al., 2013; Rilling et al., 2012). So far, few studies have focused on potential effects of intranasal OT on brain responses in clinical samples characterized by social deficits such as social anxiety (Labuschagne et al., 2011, 2010), borderline personality disorder (Bertsch et al., in press), or autism spectrum disorders (Domes et al., 2013a, in press; Watanabe et al., in press).

2. Effects of OT on neural correlates of face perception and emotion processing

2.1. *The neural basis of social threat processing and anxiolytic effects of OT*

Results from both animal studies and human behavioral studies have consistently indicated anxiolytic effects of OT (e.g. Bale et al., 2001; Heinrichs et al., 2003; Huber et al., 2005; Viviani et al., 2011). An initial fMRI study therefore focused on OT effects on neural responses to threatening scenes and facial expressions (Kirsch et al., 2005). Compared to placebo, intranasal administration of OT dampened amygdala reactivity to negative social cues and reduced functional coupling of the amygdala with brainstem regions. These results correspond to recent findings from animal studies indicating that OT decreases behavioral fear responses by modulating amygdala signaling to brainstem regions (Knobloch et al., 2012; Viviani et al., 2011).

To gain a better understanding of potential anxiolytic OT effects in humans, a later fMRI study combined intranasal OT administration with a fear-conditioning paradigm in which neutral facial expressions were paired with electric shocks (Petrovic et al., 2008). After conditioning, participants were administered a single dose of OT and underwent fMRI scanning during which they viewed the same faces with shock electrodes applied. OT attenuated changes in affective stimulus ratings following fear conditioning and reduced neural responses to conditioned as compared to unconditioned stimuli in the amygdala, the medial temporal gyrus and the anterior cingulate cortex. These structures are discussed as part of a neural alarm

Table 1 – Effects of intranasal oxytocin administration on brain responses to positive and negative stimulus exposure in healthy men and women.

	Negative valence			Positive valence		
Sample	Stimuli	OT effects	References	Stimuli	OT effects	References
Male						
	Faces and scenes	↓ACC, **AMY**, CER, dlPFC, FG, ITL, MED, MTL, OFC, PAC, POC, PRC, THAL, vlPFC	Kirsch et al. (2005), Domes et al. (2007), Petrovic et al. (2008), Gamer et al. (2010), Striepens et al. (2012), Sauer et al. (2013)	Faces and scenes	↓**AMY**	Domes et al. (2007)
					↑**AMY**	Gamer et al. (2010)
		FC: **AMY**–BS, **AMY**–INS				
		↑INS	Striepens et al. (2012)			
	Social feedback	↓ACC, **AMY**, BS, CAU, INS, MB, POC	Baumgartner et al. (2008), Rilling et al. (2012)	Social feedback	↑**AMY**, CAU	Rilling et al. (2012)
		↑vlPFC, vmPFC	Rilling et al. (2012)			
		FC: INS-**AMY**, INS-IFG				
	Physical pain	↓**AMY**, MB, STRIA	Singer et al. (2008)			
		↑OFC	Singer et al. (2008)			
Female						
	Faces and scenes	↓**AMY**, dlPFC	Domes et al. (2010a, 2010b), Rupp et al. (2012)	Faces and scenes	↓SMA	Lischke et al. (2012)
		↑**AMY**, ATL, BS, CER, dlPFC, FG, HIPP, INS, MTL, POC, ROL, STG, vlPFC	Domes et al. (2010a, 2010b), Lischke et al. (2012)		↑CER, FG, HIPP, INS, MTG, ROL, STG	Domes et al. (2010a, 2010b)
	Social feedback	↓CUN, POC, PRC	Groppe et al. (2013)	Social feedback	↑VTA, MTL, OCC	Groppe et al. (2013)
		↑VTA	Groppe et al. (2013)			
	Infant crying	↓**AMY**	Riem et al. (2011)	Infant laughter	↓**AMY** FC: **AMY**–OCC	Riem et al. (2012)
		↑IFG, INS	Riem et al. (2011)		↑FC: **AMY**–ACC, **AMY**-ANG, **AMY**–HIPP, **AMY**–MTL, **AMY**–OFC, **AMY**–PREC	Riem et al. (2012)

↑=increased brain activity, ↓=decreased brain activity, ACC=anterior cingulate cortex, AMY=amygdala, ANG=angular gyrus, ATL=anterior temporal lobe, BS=brainstem, CAU=caudate nucleus, CER=cerebellum, CUN=cuneus, dlPFC=dorsolateral prefrontal cortex, FC=functional connectivity, FG=fusiform gyrus, HIPP=hippocampus, IFL=inferior frontal lobe, INS=insula, ITL=inferior temporal lobe, MB=midbrain, MTL=medial temporal lobe, MED=medulla, OCC=occipital cortex, OFC=orbitofrontal cortex, PAC=paracentral lobe, POC=postcentral lobe, PRC=precentral lobe, PREC=precuneus, ROL=rolandic operculum, SMA=supplementary motor area, STG=superior temporal gyrus, STRIA=striatum, THAL=thalamus, vlPFC=ventrolateral prefrontal cortex, vmPFC=ventromedial prefrontal cortex, and VTA=ventral tegmental area.

system in the context of threat processing (Liddell et al., 2005) suggesting mitigation of the conditioned fear response following OT administration. Taken together, the studies by Kirsch et al. (2005) and Petrovic et al. (2008) suggest that dampening effects of OT on neural reactivity to threat-related social stimuli might mediate its anxiolytic effects on human social behavior (Acheson et al., 2013; Heinrichs et al., 2003).

2.2. *Differential effects of OT on emotional valence processing and social attention*

OT effects within the amygdala, however, may not exclusively be driven by negative stimuli. Within a passive-viewing task, OT reduced amygdala responses to emotional faces irrespective of valence (Domes et al., 2007), a result which is at odds with the assumption that OT attenuates amygdala responses specifically for threatening cues. Instead, the dampening effects of OT on amygdala reactivity to emotional faces as found in our study may reflect a broader mechanism such as decreased vigilance or uncertainty towards social events.

Such inconsistencies could also be explained by differential interactions of emotion processing with visual attention processes. Accordingly, another study demonstrated that the amygdala mediates OT effects on both social attention and emotional valence processing in a healthy male sample

(Gamer et al., 2010). More specifically, OT increased the likelihood of reflexive saccades towards the eye regions of faces independent of the displayed emotional expression. This main effect was associated with an increase in posterior amygdala activity. Discrimination of different emotional expressions, on the other hand, was found to be associated with anterior amygdala activity: OT attenuated activity for fearful faces but increased activity for happy faces. A recent study employing the same experimental paradigm in female patients with borderline personality disorder showed that OT reduced patients' hypervigilance for threat cues and associated abnormal amygdala reactivity (Bertsch et al., in press). Taken together, these results illustrate that OT effects on visual attention should be taken into account when studying its effects on social stimulus processing in the amygdala.

2.3. *Effects of oxytocin on emotion processing in women*

In an initial study, a sample of healthy women received intranasal OT or a placebo before viewing emotional or neutral face stimuli in an MRI scanner (Domes et al., 2010a). Compared to placebo, OT increased reactivity to fearful facial expressions in brain areas involved in emotion processing, including the medial temporal lobe, amygdala, fusiform gyrus, superior temporal gyrus, and brainstem, but reduced activation in the prefrontal cortex. Increased amygdala reactivity to negative stimuli after OT treatment in healthy women was confirmed in studies using threat-related scenes (Lischke et al., 2012) and briefly presented facial expressions of anger (Bertsch et al., in press). The increased amygdala reactivity under OT found in women contrasts with earlier studies in men which consistently reported attenuated amygdala responses following OT treatment. This leads to the hypothesis that OT may exert opposing effects on amygdala reactivity in healthy men and women.

Moreover, effects of exogenous OT may differ depending on individuals' endogenous OT levels, which are known to be elevated in postpartum women (Drewett et al., 1982; Uvnäs-Moberg et al., 1990). This hypothesis is supported by a recent fMRI study showing differential effects of OT on amygdala activation in response to negative pictures in nulliparous and postpartum women (Rupp et al., 2012): nulliparous women had higher amygdala reactivity to negative stimuli than postpartum women under placebo; however, their amygdala reactivity was significantly reduced by a single dose of intranasal OT, thereby making their neural responses comparable to those observed in postpartum women. Thus, OT-induced attenuation of amygdala reactivity to arousing stimuli in women may reflect the neural basis for the stress-buffering effects of breastfeeding in postpartum women (Mezzacappa and Katkin, 2002; for a review, see Heinrichs et al., 2002) and known associations between breastfeeding, mother-infant-bonding, and maternal care (Bosch and Neumann, 2012; Feldman et al., 2010, 2007; for a recent review, see Galbally et al., 2011).

3. Effects of OT on brain responses to infant and sexual cues

Several fMRI experiments examined effects of OT on responsiveness to infant cues as a proxy of parental sensitivity and attachment. Healthy women were exposed to infant cry and laughter sounds (Riem et al., 2012, 2011) and infant pictures (Rupp et al., 2013) following intranasal OT treatment. Under placebo, exposure to infant crying elicited significant activation in the bilateral superior and middle temporal gyrus as well as the right amygdala (Riem et al., 2011). Intranasal OT reduced activation in the right amygdala but increased activation within the insula and the inferior frontal gyrus. During exposure to infant laughter, OT once again attenuated amygdala reactivity to emotional infant sounds, suggesting a mechanism that generalizes across positive and negative acoustic infant cues (Riem et al., 2012). OT also enhanced functional coupling of the amygdala with several brain regions associated with emotion processing and regulation, including the orbitofrontal cortex, anterior cingulate cortex, hippocampus, and middle temporal gyrus. The results suggest that OT might modulate fronto-cortical regulation of amygdala activation. In addition, decreased amygdala reactivity in postpartum women was also shown for the processing of infant and sexual pictures (Rupp et al., 2013). A recent study on OT-induced modulation of fathers' brain response to pictures of infants shows different results (Wittfoth-Schardt et al., 2012): intranasal OT administration decreased left globus pallidus (GP) reactivity to pictures of the father's own child, and reduced functional coupling of the left GP with the right GP, the left hippocampus and the left middle frontal gyrus, whereas amygdala activity appeared to be unaffected.

4. Modulation of neural activity by OT during social feedback processing

4.1. *Effects of OT on neural circuitry of trust and reciprocity*

In initial studies, OT was found to increase human trust behavior (Kosfeld et al., 2005), to maintain trust behavior following social betrayal, and to reduce neural responses associated with the experience of breached trust (Baumgartner et al., 2008). Specifically, feedback of social betrayal increased activation within the amygdala and caudate nucleus under normal conditions but not following OT administration (Baumgartner et al., 2008). Another study focused on reciprocal social cooperation in the context of a prisoner's dilemma game (Rilling et al., 2012). Participants played with a putative human partner or a computer partner who could either reciprocate or defect on their cooperation. Compared to placebo, intranasal OT increased reactivity of the left caudate nucleus and the left amygdala when participants' cooperative behavior was mirrored by a putative human partner as compared to a computer partner. Activation in both regions was highly correlated, suggesting that OT increased the reward value of experienced cooperation or enhanced the association of cooperative behavior with the

human partner. Together, these results support the hypothesis that OT shapes the processing of social cues in a prosocial direction by increasing the reward value of positive social cues while buffering against experiences of negative emotionality.

4.2. *Effects of OT on neural correlates of social reward and punishment processing*

A recent study directly tested whether OT influences the neural circuitry of social saliency and reward in the context of social feedback processing (Groppe et al., 2013). Female participants performed a social incentive delay task within the scanner in which they had to respond as quickly as possible to a cued target stimulus in order to receive social reward (happy facial expressions) or avoid social punishment (angry facial expressions). Under placebo, activation in the ventral tegmental area positively predicted correct responses in the social reward condition. OT increased activation in this area during anticipation of both rewarding and punishing social cues. This result is in line with the hypothesis that OT increases the motivational salience of social stimuli by modulating neural correlates of reward and punishment processing.

5. Studies targeting clinical conditions and individual differences

Several mental disorders with impairments in social information processing and social interaction are characterized by alterations in brain activation and connectivity. Such alterations have recently been reviewed for schizophrenia (Fitzsimmons et al., 2013), autism (Philip et al., 2012), and social anxiety (Freitas-Ferrari et al., 2010). While beneficial effects of OT on social cognition and behavior have been described for all of the above-mentioned neuropsychiatric disorders, recent meta-analytic results suggest that OT treatment may be specifically effective in autism spectrum disorders (Bakermans-Kranenburg and van IJzendoorn, 2013a). Overall, only few studies have explored the neural mechanisms that might mediate effects of intranasal OT on social cognition and behavior in clinical samples. Clearly, pre-existing differences in neural response patterns of clinical samples and healthy controls as well as individual drug medication need to be factored in when studying potential therapeutic effects of OT.

5.1. *OT-induced restoration of social cognition in autism*

Autism spectrum disorders (ASD) are characterized by several socio-cognitive impairments, including difficulties in recognizing faces or appropriately interpreting emotional cues of others. Previous evidence from behavioral studies suggests that OT exerts beneficial effects on social cognition and behavior in autism (Anagnostou et al., 2012; Andari et al., 2010; Guastella et al., 2010). Based on these findings, recent imaging studies focused on OT modulation of activity in the social brain in autism. A first study tested for OT effects on neural correlates of face processing in individuals with Asperger Syndrome (AS) and typically developed controls (Domes et al., 2013a). Intranasal OT administration induced preferential processing of faces within the amygdala in AS individuals which mirrored amygdala responses observed in neurotypical controls under placebo. In another study, OT improved emotion recognition performance and heightened amygdala reactivity to emotional facial features (eyes and mouths) in autistic individuals but not in typically developed controls (Domes et al., in press).

A recent study examined effects of intranasal OT on socio-communicational impairments in autism that stem from problems in interpreting nonverbal social cues (Watanabe et al., in press). When simultaneously-presented verbal and nonverbal information was in conflict, OT increased the number of judgments based on nonverbal as compared to verbal information. For judgments based on nonverbal information, OT enhanced activity in anterior cingulate and dorsal medial prefrontal cortex – regions that were previously found to display reduced activity in autistic individuals as compared to typically developed controls (Watanabe et al., 2012). Although a typically developed control sample was missing in the study of Watanabe et al. (in press), the increase in medial prefrontal cortex activity under OT may reflect hormone-induced normalization of neural responses in autistic individuals. In sum, preliminary evidence suggests that OT may be capable of restoring neural correlates of social cognition in autism.

5.2. *Normalizing effects of OT on neural hyperreactivity in social anxiety*

Socially anxious individuals typically show enhanced orienting towards socially threatening cues (Bar-Haim et al., 2007) and facilitated social threat conditioning (Pejic et al., 2013). These behavioral findings are mirrored in a neural hyperreactivity during social threat processing with a prominent role of the amygdala (Freitas-Ferrari et al., 2010; Pejic et al., 2013; Sladky et al., 2013). So far, two studies report modulating effects of OT on neural responses to emotional stimuli in social anxiety disorder (SAD) (Labuschagne et al., 2011, 2010): under placebo, individuals with clinical social anxiety as compared to healthy controls displayed a hyper-reactivity of the amygdala when processing facial expressions of fear and an increased activity in the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC) when viewing sad faces. Administration of OT reduced this neural hyperreactivity in social anxiety, supporting the assumption that OT may reduce stress reactivity and exert anxiolytic effects by modulating activation in neural correlates of threat processing (Labuschagne et al., 2011, 2010).

5.3. *Influences of individual differences on reactivity to intranasal OT*

Evidence from several studies in healthy individuals suggests that OT effects may be generally moderated by individual levels of social functioning. For example, individuals with higher autistic traits indicative of poorer socio-cognitive functioning seem to show stronger beneficial effects of OT on empathic accuracy (Bartz et al., 2010). In female patients

with borderline personality disorder, OT was found to decrease interpersonal trust and social cooperation preferentially in individuals with anxious attachment style and high sensitivity towards social rejection (Bartz et al., 2011a). In autistic individuals, an OT-induced increase in amygdala reactivity was predictive of individual improvements in behavioral performance (Domes et al., in press), suggesting that individual differences in social functioning may generally account for differences in neural reactivity to intranasal OT within the social brain. Together, these findings illustrate the necessity of considering individual-related variables when studying effects of intranasal OT on behavioral and neural measures of socio-cognitive processing (compare Bartz et al., 2011b; Guastella and MacLeod, 2012; Kemp and Guastella, 2011).

6. Methodological considerations for fMRI studies with pharmacological OT protocol

Imaging OT effects on brain activity associated with social stimulus processing has revealed several neural substrates that may mediate its behavioral effects. Still, results from fMRI studies remain heterogeneous, and caution is warranted in theorizing about oxytocinergic modulation of neural transmission in humans. Functional MRI does not measure neural activity per se, but instead measures alterations of magnetic susceptibility in a brain area induced by temporary changes of cerebral metabolism associated with neural activation. This fact has some important implications.

6.1. *Choosing an appropriate experimental design*

First, the size of experimental effects on the measured BOLD response is generally low, and signal changes depend crucially on the experimental paradigm. Inconsistent results on OT effects in the human brain as revealed by functional imaging may therefore arise from differences in task characteristics. These may include task demands (e.g. cognitive load, implicit vs. explicit emotion processing), stimulus characteristics (e.g. stimulus size, emotional intensity), timing issues (e.g. blocked vs. event-related design) and appropriate contrasting to an adequate control condition. In addition, neural responses to intranasally-administered OT may depend on the dosage used in a particular study. The systematic exploration of dose–response characteristics of intranasal OT administration should therefore be considered an important next step in human OT research.

Especially if complex cognitive processes (such as trust) and their modulation by OT are under study, interactions with other cognitive processes are likely induced by an experimental task. As the amygdala was shown to display functional segregation, caution is warranted when interpreting OT effects in this brain region, as these can be mediated by different cognitive processes such as valence processing and attention orienting (see Gamer et al., 2010). In order to address potential confounding effects of OT on social attention, eye movements can be assessed as a physiological correlate of visual attention processes during MRI scanning (Domes et al., 2013b; Gamer et al., 2010; Guastella et al., 2008). However, OT research would generally benefit from a more thorough understanding of the neural networks that underlie fundamental cognitive processes that are assumed to be modulated by exogenous OT.

6.2. *Accounting for connectivity within social brain networks*

To date, it remains unclear whether modulation of socio-cognitive functions by OT is specifically or predominantly mediated by the amygdala. The studies so far simply suggest that paradigms which are sensitive to modulations of amygdala activity seem to be particularly sensitive to changes in central OT levels. Observed changes in amygdala responses following OT administration may therefore reflect local OT effects on other brain areas that exert modulatory influence on amygdala activation.

This assumption addresses a crucial limitation of classic functional imaging. Functional MRI usually aims at identifying brain areas involved in specific perceptual and cognitive processes. However, a purely localizing approach does not account for the existence of complex neural networks in which functions and performances arise from dynamic interactions between brain areas. Statistical tools for the analysis of connectivity measures allow for exploration of such regional interactions and usually focus either on modulations of functional vs. effective connectivity by an experimental stimulation (Friston, 1994).

Two recent studies explored OT-induced alterations in functional connectivity between brain regions using resting state fMRI in men and women (Riem et al., in press; Sripada et al., 2013). In men, OT increased resting-state connectivity of the amygdala with anterior cingulate and medial prefrontal cortex while reducing amygdala coupling with brainstem regions (Sripada et al., 2013). In women, resting state connectivity of the precuneus with the brainstem and the cerebellum was shifted in a positive direction following OT administration (Riem et al., in press). Together, preliminary evidence from resting state fMRI points to modulatory effects of OT on brain networks involved in social cognition and stress reduction.

Indeed, there is growing evidence for the assumption that OT effects on social cognition and behavior are mediated by transregional communication in the brain (for a recent review on OT effects on functional connectivity, see Bethlehem et al., 2013). For example, increased attention to the eye region of faces following OT administration has been reported by both behavioral and neuroimaging studies (Domes et al., 2013b; Gamer et al., 2010; Guastella et al., 2008). This increased eye gaze seems to be mediated by enhanced functional coupling of the posterior amygdala with the superior colliculus under OT (Gamer et al., 2010). OT was also found to increase functional coupling of the amygdala with prefrontal and temporal regions as well as the hippocampus during processing of infant laughter (Riem et al., 2012) suggesting enhancing effects of OT on the neural processing of positive stimulus valence (Iidaka et al., 2001; Whalen et al., 2013). In contrast, reduced functional coupling of the amygdala with brainstem regions for aversive social stimulation may reflect

protective effects of OT against negative emotionality and stress reactivity (Kirsch et al., 2005; Rilling et al., 2012).

It should be noted, however, that functional connectivity analyses describe statistical dependencies between the time-series of the measured BOLD response in different brain areas and therefore represent mere correlations. To address the question of causality within neural network communication and its modulation by OT, analysis of effective connectivity should be included in future research on OT effects on human brain functioning (Friston et al., 2003; Stephan et al., 2010).

7. Sexual dimorphisms in neural correlates of social cognition and implications for OT research

7.1. *Sex differences in social processing and sexually dimorphic effects of OT*

So far, results from fMRI studies exploring a modulation of social-stimulus related brain activity have suggested differential OT effects in men and women. These differences have mainly been observed in the context of amygdala responses. Studies in men have consistently reported attenuated amygdala responses following OT administration. In women, OT was found to increase amygdala reactivity to emotional cues in some studies (Domes et al., 2010a; Lischke et al., 2012) and to dampen amygdala activity in other studies (Riem et al., 2012, 2011; Rupp et al., 2012). The reasons for such differences may be manifold and no fMRI study has so far systematically addressed the question of differential effects of OT on brain activity in men and women within a single experimental protocol.

However, there is substantial evidence that men and women differ in terms of brain anatomy and neural processing. For example, women have larger volumes of the orbitofrontal cortex, the caudate and parts of the mirror-neuron system (Cheng et al., 2009; Filipek et al., 1994; Sowell et al., 2002); whereas size of the hypothalamus, angular gyrus, and amygdala is larger in men than in women (Goldstein et al., 2001). Notably, brain activity of men and women was found to differ on all domains of socio-cognitive functioning that show modulation by exogenous OT, e.g. emotion processing and regulation (Domes et al., 2010b; for recent reviews, see Stevens and Hamann, 2012; Whittle et al., 2011).

7.2. *Effects of gonadal hormones on social stimulus processing and potential interactions with OT*

These sex differences are likely mediated by the early influence of gonadal hormones on differentiation and morphology of the central nervous system (Ahmed et al., 2008; Schwarz and McCarthy, 2008; Sisk and Zehr, 2005) as well as their short-term modulation of neural transmission during rest and cognitive processing (Maki and Resnick, 2001). It is important to note that differences in gonadal hormone levels in men and women (especially estrogens) are not stable but change with age as well as across the female menstrual cycle. Menstrual cycle related changes were found to affect activity in brain networks underlying social stimulus processing (Derntl et al., 2008; Dreher et al., 2007; Marečková et al., 2012) and preliminary evidence suggests that brain morphology itself may change across the menstrual cycle and following oral contraceptive use (Ossewaarde et al., 2013; Pletzer et al., 2010).

Evidence from animal studies indicates that the OT system is strongly influenced by gonadal hormones (Champagne et al., 2001; De Kloet et al., 1986; Gabor et al., 2012; McCarthy, 1995; Tribollet et al., 1990). Although corresponding evidence for molecular cross-talk of steroid hormones with OT is lacking in humans, it seems likely that OT effects on human brain activity may interact with central actions of gonadal hormones. Studies investigating OT effects on brain activity in women therefore accounted for the menstrual cycle phase (Bertsch et al., in press; Domes et al., 2010a; Lischke et al., 2012; Rupp et al., 2012). To date, a systematic exploration of potential effects of hormonal changes associated with the female menstrual cycle on reactivity to intranasal OT administration is missing. Future studies addressing this issue may contribute to a better understanding of the amount of variance in OT effects that might be explained by gonadal hormones. In sum, there is pressing need of considering sex hormone influences and menstrual cycle associated hormonal changes in the study of central OT effects.

8. OT and neurogenetics

8.1. *Association studies on the oxytocin receptor gene*

Given the high variance in behavioral and neural effects observed after OT application in most studies, one promising approach aims at identifying variations in specific genes which contribute to individual differences in social behavior and social cognition, including vulnerability for neuropsychiatric or developmental disorders characterized by social deficits (Ebstein et al., 2010). Several studies investigated associations between the gene coding for the oxytocin receptor (*OXTR*) and individual differences in social behavior (for a review, see Kumsta and Heinrichs, 2013).

The neurobiology underlying such associations between *OXTR* variants and social behavior phenotypes is addressed by the imaging genetics approach which relates genetic variants to brain structure and function (Meyer-Lindenberg et al., 2011). Specifically, imaging genetics aims at identifying endophenotypes (or intermediate phenotypes) such as alterations in brain activity and morphometry that may bridge the gap between genotype and interpersonal variance in social behavior. Several neurogenetic studies showed that genetic variation of *OXTR* affects a limbic circuit involving the amygdala, the hypothalamus and the cingulate gyrus (e.g. Tost et al., 2011, 2010). Although preliminary data suggest that *OXTR* single nucleotide polymorphisms (SNPs) may affect social cognition and behavior by modulating anatomy and functioning of the social brain (Kumsta and Heinrichs, 2013; Meyer-Lindenberg and Tost, 2012), meta-analytic evidence for a direct impact of the two most frequently tested SNPs on human social behavior is missing (Bakermans-Kranenburg and van Ijzendoorn, 2013b).

8.2. *Epigenetic and dopaminergic influences on central OT signaling*

In addition to these structural changes, the importance of epigenetic mechanisms that regulate genetic function and expression without affecting DNA structure was recently reviewed (Kumsta et al., 2013). In particular, methylation of the *OXTR* promoter region is assumed to differentially influence activity in brain regions associated with social perception. Epigenetic states of genes are known to be modified by experiences, especially those occurring in sensitive periods early in life (e.g., traumatic experiences), forming the basis for a potential neurodevelopmental role of the OT system. More precisely, the influence of early adverse experiences on individual socio-emotional functioning may be mediated by epigenetically determined alterations of central oxytocin signaling (Kumsta et al., 2013).

Finally, two recent studies suggest that structural variations in genes regulating oxytocin and dopaminergic signaling in the brain may interact with exogenous OT administration (Sauer et al., 2013, 2012). It should be noted, that the demand for large sample sizes to ensure reliability of observed interactions between genetic factors and exogenous OT sets a severe restriction to such investigations. Still, future fMRI studies may benefit from a neuropharmacogenetic approach as it surely helps to clarify the amount of variance observed in measures of neuroanatomy and neural signaling that may be attributable to individual differences in genetic factors.

9. Conclusions and desiderata for future research

In the past eight years, more than two dozen experimental fMRI studies have been published regarding the effects of OT on regional brain activity during social information processing, with many more currently underway. The studies so far show some variability in regard to the experimental task and the populations studied; nevertheless, most of the published studies have reported modulations of amygdala reactivity in response to emotional as compared to neutral, or social compared to non-social, stimuli. The few fMRI studies in clinical samples suggest that this modulation depends on baseline socio-cognitive functioning of the population under study or differences in endogenous oxytocin signaling. In addition, some studies have provided evidence for OT-induced modulations of functional coupling between the amygdala and down-stream brain areas such as the brainstem, as well as areas implicated in the regulation of amygdala reactivity such as parts of the prefrontal cortex.

Presumably, differences between the studies summarized above stem from two major sources of variance: (i) differences between the populations under study (e.g. male vs. female and healthy vs. clinical samples) and (ii) differences in regard to the primary cognitive processes involved in a task. With regard to population characteristics, the issue of possible sex differences could be elucidated in future studies by directly comparing the effects of intranasal OT on male and female brain functions within the same study. These studies should further take variations of hormonal status over the female menstrual cycle into account. In addition, systematic use of structural and functional genetic information may contribute to explain individual variance in brain responses to exogenous OT. Differences in experimental design and the underlying cognitive processes addressed by a task add further variability to fMRI findings on OT effects in the human brain. This issue relates to the fact that complex social stimulus processing involves a number of basic cognitive processes (perception, attention, memory, etc.). Future imaging studies would benefit from a clear a priori definition of the basic cognitive processes under study and specifically tailored experimental tasks.

In addition, there is still a general lack of basic knowledge regarding the distribution of OT receptors and the molecular and cellular mechanisms of OT in the human brain. These issues are expected to be resolved as basic research into the genetic mechanisms of neuropeptides and receptor mapping moves forward. As previous approaches to explore effects of OT on brain connectivity were merely correlational, localizing the primary brain areas which are modulated by exogenous OT may benefit from advanced methods for analyzing effective connectivity using fMRI. Additionally, other neuroimaging techniques, such as source-localization with high-density EEG may be employed. Together, these methods will broaden our search from a single brain area to functionally integrated brain circuits underlying complex cognitive processes, such as the recognition of an emotion from a facial expression.

In sum, advances made in functional and structural imaging techniques and neurogenetics over the past years have revealed a yet-incomplete picture of the acute effects of OT on brain function. However, future studies focusing on some of the issues highlighted in the present paper will undoubtedly help to reveal the neural functions of OT in the context of social information processing and might pave the way to develop improved treatment strategies for mental disorders characterized by social dysfunction.

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