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REVIEW

Oxytocin, brain physiology, and functional connectivity: A review of intranasal oxytocin fMRI studies

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Summary In recent years the neuropeptide oxytocin (OT) has become one of the most studied peptides of the human neuroendocrine system. Research has shown widespread behavioural effects and numerous potential therapeutic benefits. However, little is known about how OT triggers these effects in the brain. Here, we discuss some of the physiological properties of OT in the human brain including the long half-life of neuropeptides, the diffuse projections of OT throughout the brain and interactions with other systems such as the dopaminergic system. These properties indicate that OT acts without clear spatial and temporal specificity. Therefore, it is likely to have widespread effects on the brain's intrinsic functioning. Additionally, we review studies that have used functional magnetic resonance imaging (fMRI) concurrently with OT administration. These studies reveal a specific set of 'social' brain regions that are likely to be the strongest targets for OT's potential to influence human behaviour. On the basis of the fMRI literature and the physiological properties of the neuropeptide, we argue that OT has the potential to not only modulate activity in a set of specific brain regions, but also the functional connectivity between these regions. In light of the increasing knowledge of the behavioural effects of OT in humans, studies of the effects of OT administration on brain function can contribute to our understanding of the neural networks in the social brain.

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Contents

The word oxytocin originates from the Greek word okytokine, which literally translates as 'quick birth'. This refers to the effect oxytocin has on inducing labour and uterine-contractions. This mammalian hormone has received a lot of recent attention for its potential to positively influence social behaviour (Striepens et al., 2011). Oxytocin (OT) was synthesized soon after its discovery in 1953 by Vincent du Vigneaud (Du Vigneaud et al., 1953) and evidence later emerged for its ability to influence behaviour (Buijs, 1983; Kendrick et al., 1986, 1987; Pedersen and Prange, 1979; Zimmerman et al., 1974). Most early studies examined how OT influences the formation of social bonds (Carter et al., 1995) and maternal behaviour (Kendrick et al., 1987; Keverne et al., 1983; Pedersen and Prange, 1979). This work also showed that the effects of OT are at least partly modulated by gonadal hormones such as oestrogen.

While initial research into the effects of OT focused mainly on social bonding, animal research also provided the first indications of specific brain regions that might be affected by OT. For instance, in prairie-voles, Insel and Shapiro showed that the OT receptor is localized in the pre-limbic circuit, the nucleus accumbens, midline nuclei of the thalamus and lateral aspects of the amygdala (Insel and Shapiro, 1992a,b). Driven by these findings, the focus shifted to research into the effect that OT administration has on human behaviour; specifically, the effect on psychological processes such as trust, morality, self-perception and social emotional behaviour (Atzil et al., 2011; Bartz et al., 2011; Bos et al., 2012; Carter et al., 2008; Heinrichs et al., 2009; Ishak et al., 2011; Meyer-Lindenberg et al., 2011; Ross and Young, 2009; Striepens et al., 2011). Research indicates that OT has more widespread effects than its original meaning suggests. The increased availability of a synthesized variant of the hormone has led to a large body of research into the effects of OT on behaviour, with a special emphasis on social behaviour (Gordon et al., 2011; Lee et al., 2009).

The aim of the current review is to discuss some of these effects and to provide a selective overview of the current status of research involving two main methods: physiological research and neuroimaging. Oxytocin's physiological properties show that it has potential to have effects on neural communication, particularly in regions related to socio-emotional processing. This review focuses on the effects of OT on functional connectivity, which is the correlation between the temporal signal fluctuations of two brain regions (van den Heuvel and Hulshoff Pol, 2010) and as such is an approximation of neural communication. Emerging evidence suggests that OT modulates neuronal communication throughout brain areas that play a key role in social-emotional behaviour. As such OT affects the intrinsic dynamics of the brains neural network.

1. Physiological properties of oxytocin

Oxytocin is secreted by the pituitary gland and is triggered by projections from the hypothalamus, causing a wide range of bodily reactions (Ross and Young, 2009). However, most behavioural and brain related effects are not triggered directly by this secretion because of the blood—brain barrier. Instead, the behavioural effects of OT are believed to originate from centrally projecting neurons (Ross et al., 2009). These neurons are located in the paraventricular nuclei (PVN) and supraoptic nuclei (SON) of the hypothalamus, where the synthesis of OT takes place (Meyer-Lindenberg et al., 2011) (see Fig. 1a and b).

Early studies considered the PVN to be a key region in the formation of OT innervations to other brain regions (Buijs et al., 1983). Recent studies have also incorporated the SON as another important region, since most peptides that circulate in the plasma are synthesized in this area (Ludwig and Leng, 2006). Regarding the mechanism by which neuropeptides are dispersed across the brain, magnocellular neurons in the SON synthesize OT and project to the posterior pituitary (Fig. 1b). As Fig. 1a shows, smaller parvocellular neurons in the PVN secrete OT and axonal projections affect the amygdala, hippocampus, striatum and brainstem (Ludwig and Leng, 2006). In addition, dendritic release of OT into the extracellular space has a diffuse effect throughout the entire brain affecting a wide range of behaviours (Meyer-Lindenberg et al., 2011). This diffused dendritic release can

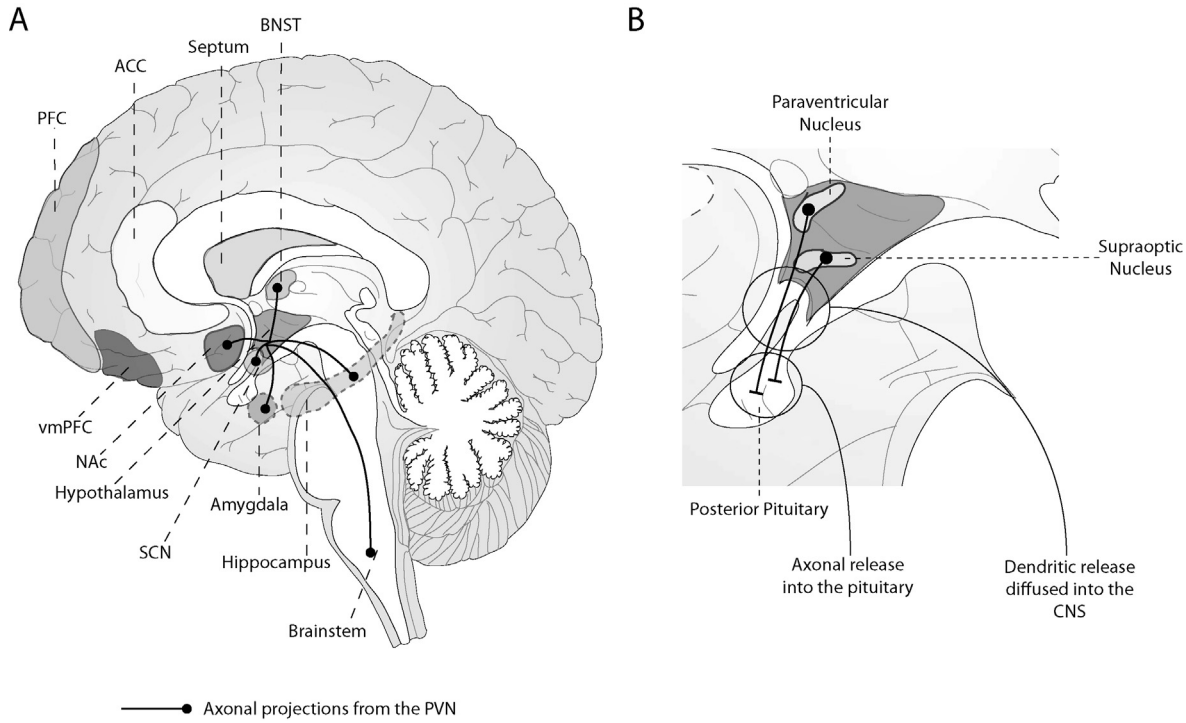

Figure 1 The neurophysiology of oxytocin adapted from Meyer-Lindenberg et al. (2011). Panel A shows axonal (parvocellular) projections from the PVN to several brain regions involved in socio-emotional processing. Panel B shows the extra hypothalamic projections from the SON and PVN to the posterior pituitary. Along these axonal projections there is also diffused dendritic release of peptide that can spread throughout the brain. *Abbreviations*: PFC = prefrontal cortex, ACC = anterior cingulate, BNST = bed nucleus of the stria terminalis, vmPFC = ventromedial prefrontal cortex, NAc = nucleus accumbens, SCN = suprachiasmic nucleus, PVN = paraventricular nucleus, CNS = central nervous system.

occur along the extra hypothalamic fibres projecting to the posterior pituitary (see Fig. 1b). The basic structure for these projections is sexually dimorphic and present at birth, as shown in animal research (de Vries, 2008; de Vries et al., 1981). This suggests the involvement of sex steroid hormones in the formation of the OT system.

1.1. Pharmacodynamics and wiring

Because peripheral administered OT does not cross the blood–brain-barrier, nasal administration is often used when investigating the effects of neuropeptides (Born et al., 2002). Born et al. (2002) have shown that peptides can directly access the cerebrospinal fluid (CSF) through the nasal pathway as it bypasses the blood–brain barrier. Oxytocin is considered to have similar pharmacodynamic properties as its closest cousin, arginine vasopressin (AVP). In their groundbreaking study, Born et al. (2002) showed that intranasal administration of AVP triggered a significant increase in AVP levels in both plasma and CSF beginning after approximately 10 min, continuing to rise up to 80 min after administration. This clearly demonstrated that intranasal administration of neuropeptides could potentially affect the central nervous system (CNS). They also found a significant increase in plasma levels after intranasal administration of a higher dose of 80 IU. This increase was not significantly correlated with the increase in CSF levels of AVP. However, some 'leakage' in blood–brain transport cannot be ruled out. This also points to the possibility that intranasal administration can have side effects in the peripheral nervous system (PNS).

The CSF levels of administered peptides remained elevated up to 80 min after administration. However, external or behavioural effects do not always last that long (Thompson et al., 2006). Thompson and colleagues showed that there were autonomic, motor and perceptual responses 15 min after vasopressin administration; after 50 min these effects disappeared. Although the effects of 20 IU might be too subtle to cause long-lasting motor effects such as facial mimicry, timing in administration studies needs to be considered.

1.2. Mechanism of action

The mechanism by which neuropeptides exert their effect is complex and not fully understood. A clear mapping of the OT receptor distribution in humans, the precise effect OT has on behaviour and its exact physiological effect in the CNS, all remain to be determined. It is clear that neuropeptides have the potential to influence neurotransmission, albeit not in the same fashion as classical neurotransmitters such as GABA, serotonin and dopamine.

Explicitly comparing neuropeptides to classical neurotransmitters reveals this potential (Ludwig and Leng, 2006). First, the half-life of peptides in general, and OT and vasopressin in

particular, is much longer (approximately 20 min) than that of neurotransmitters (Mens et al., 1983), which generally have a half-life of approximately 5 ms. The fact that peptides such as OT and vasopressin degrade much slower in the brain gives them the potential to have an effect over longer distances and dilute to different regions (Landgraf and Neumann, 2004; Ludwig and Leng, 2006). Second, neuropeptides are stored in large dense-core vesicles (LDCV's), whereas neurotransmitters are generally stored in small synaptic vesicles (SSV's). SSV's are selectively located at synaptic terminals in contrast to LDCV's, which are released from all parts of a neuron, specifically dendrites of magnocellular neurons (Morris and Pow, 1991). Neuropeptides thus also lack the spatial specificity of classical neurotransmitters, enabling them to act throughout the brain.

Neuropeptides may however also act in a comparable way to classic neurotransmission. Neuropeptidergic neurons also make synaptic connections with other neurons. There is thus a possibility that peptides can directly act as neurotransmitters at the axon terminals. However, caution is warranted as there is only indirect evidence for this mechanism of action. The assumption that OT can be released from axon terminals will need to be directly confirmed in future studies. Whether release occurs through direct synaptic and/or non-synaptic transmission, neural communication is affected.

1.2.1. Modes of communication: the dynamic concept

Landgraf and Neumann (2004) present a dynamic concept that considers multiple variable modes of communication exerted by neuropeptides. They propose that different areas in the brain use different modes of communication (e.g. axonal versus dendritic release). Exposure to certain stimuli might cause a shift from one form of peptide release to another. The exact mechanism and cascading effects of neuropeptide release would then be dependent on the stimulus and brain area(s) involved. This dynamic concept emphasizes task-dependency and incorporates the role of context and individual variability (Bartz et al., 2011). It would be interesting for future research to explore what happens in the brain at rest, as well as in specific contexts.

1.2.2. Modes of communication: volume transmission

Given the lack of spatial and temporal specificity of neuropeptides, they have also been hypothesized to play a key role in volume transmission (Torrealba and Carrasco, 2004). Volume transmission (as opposed to synaptic transmission) is characterized by its three-dimensional diffusion into the extracellular fluid and lack of obvious structural extracellular communication pathways (Agnati et al., 1995). The source of release may be very distant from the targeted cells. Dendritic release of OT would likely follow such a pattern. Because volume transmission is generally diffuse and can act over long distances it is hard to disentangle precise targets and key regions involved in the communication process. If neuropeptides do indeed influence neuronal communication in the brain by way of volume transmission or in a more dynamic fashion, as proposed by Landgraf and Neumann (2004), it will be hard to find precise targets or regions showing, for example, hyper-activation as a result of a specific neuropeptide.

1.2.3. Modes of communication: the priming hypothesis

Another hypothesis that aims to account for the diverse yet precise behavioural effects of OT is the priming hypothesis (Ludwig and Leng, 2006). This stems from the finding that, under normal conditions, dendritic release of OT is *not* activated by electrical activity. A peptidergic OT signal can trigger dendritic peptide release that is *independent* of electrical activity and prime the LDCV's to be released. Specifically, neuropeptides can discharge Ca^{2+} from thapsigargin intracellular stores independent of electrical activity, and thus trigger dendritic peptide release. This priming mechanism then causes a cascade that enables prolonged effects of OT, by creating a loop. Because more peptide is released from the dendrites, more Ca^{2+} is discharged from the intracellular stores and more LDCV's are primed for release. A feedback mechanism through the production of endocannabinoids, inhibiting glutamate release, counteracts this cascade (Hirasawa et al., 2004). This feedback mechanism prevents the OT system from ending up in an endless loop of neuropeptide secretion. This priming concept also provides a framework to study the stimulus-dependent effects of OT. Because priming initially occurs at sites that are sensitive to OT, the largest effect will first be in those regions. The prolonged effect enables a temporary functional neural rewiring that is most apparent in those regions expressing the strongest affinity for OT. The most likely candidates for such functional rewiring are in the limbic and pre-limbic areas, due to the density of OT receptors in these regions (Insel and Shapiro, 1992a,b).

1.3. Interaction with other systems

Given its widespread potential for affecting activity throughout the brain, it is unsurprising that OT also interacts with systems such as the dopaminergic system (Skuse and Gallagher, 2009; Smeltzer et al., 2006; Strathearn et al., 2009) and the gonadal hormone system (Bale and Dorsa, 1995b; Bale et al., 1995).

1.3.1. Interaction with dopamine and serotonin

The most obvious link between the dopamine (DA) and OT system stems from the fact that, at least in humans, social affiliative behaviour (which is modulated by OT) is accompanied by modulation of dopaminergic reward pathways (Skuse and Gallagher, 2009; Young and Wang, 2004). This by itself does not mean that interactions between OT and dopamine always take place in similar brain regions. Animal research has shown a great degree of overlap in OT and dopamine receptor binding sites (Baskerville et al., 2009; Liu and Wang, 2003; Smeltzer et al., 2006). Specifically, Liu and Wang (2003) demonstrated that blockade of either OT or DA-D2 receptors in voles abolished the effects of OT administration or the DA-D2 receptor agonist on partner preferences. Given the behaviourally relevant overlap in reward related processing between OT and DA, it is not surprising to see that this effect is localized in the nucleus accumbens. Furthermore, human studies have shown that OT can effectively modulate reward-related brain regions (Strathearn et al., 2009). Studies into the effects of OT using reward-related paradigms thus need take into account that the

measured effects might in part be modulated by this oxytocin—dopamine interaction. Additionally, animal research has shown that OT exerts its anxiolytic effect by regulating serotonin release (Yoshida et al., 2009). Indeed, OT has the potential to elevate serotonin levels (Pfister and Muir, 1989).

1.3.2. Interaction with gonadal hormones

As OT was originally associated with induction of labour, it is not surprising to find interactions with gonadal or sex steroid hormones. Evidence from animal research shows that, following OT administration, oestrogen modulates maternal behaviour (Kendrick et al., 1987; Pedersen and Prange, 1979). In addition, regulation of OT receptor mRNA in the hypothalamus is partly regulated by testosterone (Bale and Dorsa, 1995a; Johnson et al., 1991) and oestrogen (Bale and Dorsa, 1995b). The precise interaction between these different neuroendocrine systems remains unknown. Two reviews have discussed how both of these neuroendocrine systems (testosterone and OT) play a role in social-emotional behaviour (Bos et al., 2012; Gabor et al., 2012). Bos et al. (2012) show how steroid hormones and neuropeptides influence different and overlapping aspects of social-emotional behaviour. They provide a model of brain regions for this group of behaviours. The interaction between hormones and peptides is reflected in a balance in brain activity patterns. Testosterone, by acting on vasopressin, shifts the balance towards the lower brainstem regions. Oestrogen, by acting on OT, shifts the balance more towards prefrontal brain regions.

As discussed above, OT has effects in the brain that are not necessarily limited to a specific spatial location because of its release mechanism, and is not restricted to a temporal scale because of its long half-life and potential to influence other systems. It is therefore hard to predict what the specific behavioural effects of OT are purely from its physiological properties.

2. Imaging oxytocin

Human studies have shown that OT has modulatory effects on trust (Kosfeld et al., 2005), in-group bias (De Dreu et al., 2010, 2011, 2012), emotion recognition (Domes et al., 2007b) and anxiety (Labuschagne et al., 2010, 2011). Kosfeld et al. (2005) showed that intranasal administration of OT makes people more willing to take social risks in social-economic interactions. Other authors have hypothesized and shown that the 'trust-effect' might be better explained in terms of empathy (Domes et al., 2007b). Domes et al. (2007b) showed that OT improves people's ability to accurately infer emotions in others. The increased prosocial behaviour reported by Kosfeld et al. (2005) is partly mediated by the fact that people empathise more strongly under increased OT. However, De Dreu et al. (2010, 2011, 2012) have shown that OT does not always have positive effects on social behaviour: OT may also promote ethnocentrism (preferring to help and support the in-group). Although this seems paradoxical, that OT can be both an empathogen and make people more in-group focused, this may reflect that empathy is likely to have first evolved in the context of kinship relationships.

Bartz et al. (2011) have further questioned the pro-social nature of the psychological effects of OT. They show that most behavioural studies fail to demonstrate a main effect and suggest that context and individual differences are equally important mediators of the effects of OT. They describe three mechanisms that might be used to explain the effects, or lack of effects, of OT. One mechanism, studied in animal research in relation to modulation of amygdala activation, is anxiety reduction. The idea is that OT reduces anxiety, thereby causing prosocial behaviour. Another mechanism by which OT might act on behaviour is through affiliative motivation. This is based on the early animal findings on pair bonding, discussed earlier. It is possible that OT stimulates behaviour in a certain context by modulating affiliation for specific types of stimuli. This type of explanation would also fit with oxytocin—dopamine interactions and amygdala modulation. The third mechanism is that of perceptual selectivity or social salience, where OT alters the perception and salience of social cues, based on the evidence that OT modulates 'social' perception (Bartz et al., 2011). It is likely that these mechanisms interact and overlap, both behaviourally and in terms of the brain areas involved. Clearly the effects of OT are rather widespread, ranging from increasing trust to decreasing stress. Furthermore, the mechanism by which a certain behavioural outcome is attained might differ depending on the stimulus. Generalizatons about any specific effects of OT should thus be made with caution.

Nevertheless, the common theme is that OT modulates social behaviour (Bartz et al., 2011; Striepens et al., 2011), whether through increasing empathy, trust and pair bonding or by reducing (social) stress and anxiety. The precise outcome of this is likely to be mediated by context and individual variation (Norman et al., 2012; Saphire-Bernstein et al., 2011; Strathearn et al., 2009; Walum et al., 2012). Knowing which brain regions are affected by OT might elucidate a neural underpinning for this common theme and differentiate between the mechanisms involved in a specific context. Most importantly, knowing which brain regions are involved during a specific experimental paradigm could provide a top-down indication of task-dependent modulation resulting from OT administration. This knowledge is vital if we want to understand the relationship between an OT 'primed' brain and the resulting behaviour. In recent years several studies have shown altered activation patterns of specific brain regions in response to OT using fMRI. Most studies have used paradigms investigating emotional processing. However, some main themes can be distinguished and are directly or indirectly related to the amygdala; see Table 1 for an overview.

The amygdala is a key brain region in fear regulation, anxiety and emotion regulation in general (Adolphs et al., 1998; LeDoux, 2000; Whalen et al., 1998). Behavioural studies and animal models indicate reductions in anxiety, extinction of fear conditioning and increase in trust in relation to OT, which has led to special attention to the role of the amygdala. Work in rodents has shown OT-specific modulation of the central amygdala (Huber et al., 2005). This still does not elucidate which of the mechanisms proposed by Bartz et al. (2011) might be affected by OT, as all are directly or indirectly related to amygdala activity. As follows from the priming hypothesis and dynamic concept discussed

Table 1 Summary of functional imaging studies in oxytocin.

Reference	Design	Paradigm/stimulus	Dose[a]	Timing[b]	Subjects	Main findings
Kirsch et al. (2005)	CO	Fearful and threatening scenes and faces	27 IU	50 min	15	↓ AMYG (for threatening stimuli) ↓ FC: AMYG-BST
Domes et al. (2007a)	CO	Emotional faces	24 IU	45–75 min	13	↓ AMYG (for valenced stimuli)
Petrovic et al. (2008)	BS	Fear conditioning, emotional faces	32 IU	45 min	27	↓ AMYG, FG (for aversively conditioned faces)
Gamer et al. (2010)	BS	Emotional faces	24 IU	45 min	46	↓ AMYG (for angry faces) ↑ AMYG (for happy faces)
Domes et al. (2010)	CO	Emotional faces	24 IU	45–60 min	16[d]	↑ left AMYG, FG, STG (for fearful faces) ↓ IFG (for angry and happy faces)
Labuschagne et al. (2010)	CO	Emotional faces	24 IU	45 min	36[e]	↓ AMYG (for fearful stimuli in patients with GSAD)
Labuschagne et al. (2011)	CO	Sad, happy and neutral faces	24 IU	50 min	36[e]	↓ mPFC, ACC (for sad faces in patients with GSAD)
Baumgartner et al. (2008)	BS	Trust game	24 IU	50 min	49	↓ AMYG, mid-brain, DS (for sustained trust)
Singer et al. (2008)	CO	Pain exposure (self-experiences or observed)	32 IU	45 min	20	↓ AMYG (for experienced pain in selfish individuals)
Pincus et al. (2010)	WS	RMET	40 IU	10 min[c]	20[f]	↑ smFG, INS (in depressed patients. ↑ ventral regions (in controls)
Rilling et al. (2012)	BS	Iterated prisoners dillema	24 IU	42 min	91[g]	↑ left AMYG, CN (for reciprocated cooperation) ↑ FC: AMYG-aINS
Riem et al. (2011)	BS	Response to infant crying	24 IU	36 min	42[h]	↓ AMYG ↑ INS, IFG
Riem et al. (2012)	BS	Response to infant laughter	24 IU	40 min	42[h]	↓ AMYG ↑ FC: AMYG-OFC-ACC-Hipp-Prec-SMG-MTG
Lischke et al., 2012	CO	Threatening and non-threatening scenes	24 IU	45 min	14[d]	↑ right AMYG (for negative relative to neutral scenes)
Wittfoth-Schardt et al., 2012	CO	Viewing of pictures from own (oC), familiar (fC) and unfamiliar children (ufC)	24 IU	30 min	19	↓ left GP (for oC and ufC) ↓ FC: left GP-right GP-left Hipp-FPC (for oC > fC)

Abbreviations: CO = cross-over, BS = between subjects, WS = within subjects, AMYG = amygdala, BST = brain stem, FG = fusiform gyrus, STG = superior temporal gyrus, IFG = inferior frontal gyrus, DS = dorsal striatum, GSAD = generalized social anxiety disorder, mPFC = medial prefrontal cortex, ACC = anterior cingulate cortex, smFG = superior middle frontal gyrus, INS = insula, CN = caudate nucleus, aINS = anterior insula, RMET = reading the mind in the eyes task, FC = functional connectivity, OFC = orbitofrontal cortex, Hipp = hippocampus, Prec = precuneus, SMG = supramarginal gyrus, MTG = middle temporal gyrus, GP = globus pallidus, FPC = frontopolar cortex.

[a] Total dose, not per nostril.

[b] Time from intranasal administration until the start of the experiment.

[c] NB; this study scanned before and after inhalation, contrary to a cross-over design the scanning procedure for both conditions (placebo vs. oxytocin) were thus done in a single sessions.

[d] NB; this study exclusively tested women.

[e] 18 people with generalized anxiety disorder and 18 controls.

[f] 10 people with depression (unmedicated) and 10 controls.

[g] NB; this study also tested the effect of vasopressin, 27 of the 91 participants received vasopressin.

[h] NB; this study exclusively tested (nulliparous) women.

previously, the exact effect OT has on amygdala activation is likely to be task-dependant (Bartz et al., 2011). It is also likely that effects are mediated by interaction with other brain regions and with sex steroid hormones (Bos et al., 2012). It is of interest to note that the neurodevelopmental condition of autism involves some key aspects discussed here: social deficits (DSM, 1994), reduced OT levels (Modahl et al., 1998), and amygdala dysfunction (Ashwin et al., 2006; Baron-Cohen et al., 2000; Welchew et al., 2005).

2.1. Fear and emotion regulation

Kirsch et al. (2005) were the first to show that OT reduces amygdala activation in response to fear inducing stimuli using

a task that normally engages the amygdala (Hariri et al., 2002). They further showed that, using seed-based connectivity analysis approach (Friston et al., 1993), OT reduces amygdala brain-stem coupling. This study provides a first indication of OT modulating connectivity in regions related to cognitive emotional processing. It is noteworthy that OT administration did not significantly affect self-reported mood. Subsequently, other studies have partly replicated this attenuating effect of OT on amygdala activation in response to emotional faces in general (Domes et al., 2007a), to conditioned emotional faces (Petrovic et al., 2008) and to fearful faces (Gamer et al., 2010). Domes et al. (2007a) showed that compared to neutral expressions, OT reduces amygdala activation for angry, fearful as well as happy faces. In contrast to other studies (Kirsch et al., 2005) they report the strongest effects on the right amygdala when comparing placebo and OT conditions. Domes et al. (2007a) also report changes in frontal, temporal and brainstem areas when comparing OT to placebo conditions.

Using a fear-conditioning paradigm Petrovic et al. (2008) have shown OT effects in the anterior cingulate and an effect in the amygdala for direct gaze. This group also reported OT induced activation changes in left inferior orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (vmPFC) when comparing the conditioned and unconditioned stimuli. OT also appeared to attenuate activity in these regions. These results suggest that the modulatory effects of OT on the amygdala are strongest when the stimuli either represent 'stronger' or more socially relevant cues. Consequently the authors argue that OT differentially affects social versus non-social cues. Specifically, OT might be more prone to modulate amygdala activity in situations where the amygdala might already be more strongly activated. This also suggests that the effect of OT is specific for 'social' brain areas and further modulated by the specific context or stimulus.

More recent studies suggest a difference in the effect of OT on amygdala activation that is related to the valence of emotional stimuli (Gamer et al., 2010). Gamer et al. (2010) found that different sub-regions of the amygdala respond differently to OT depending on the valence of presented faces. They report attenuated amygdala activity for fearful faces (specifically in the lateral and dorsal regions of the anterior amygdala) and enhanced activity for happy faces. They report no general suppression or uplifting effect of OT on amygdala activation when valence is disregarded. It has to be noted however that, in contrast to other studies mentioned in this section, Gamer et al. (2010) used a between-subjects design. There is some evidence to suggest that there are individual differences in how OT affects the brain possibly due to individual variation in pharmacodynamics (Born et al., 2002). In addition, prenatal sex hormone differences might have an influence on the formation of the OT system, causing individual differences later in life (de Vries et al., 1981).

The reported findings regarding effects on the amygdala do not always overlap. For example, the study by Domes et al. (2007a) reports an attenuated amygdala response to emotional faces regardless of valence. Later studies show an opposite activation pattern for fearful compares to neutral faces (Domes et al., 2010; Gamer et al., 2010), but also for angry and happy faces compared to neutral (Domes et al., 2010). Interestingly, Domes et al. (2010) only tested women. Another recent study by Lischke et al. (2012) also reports increased amygdala activation in females in response to threatening stimuli following OT administration. Sexual dimorphism should thus be considered an important aspect of OT's modulatory capacity. This is strengthened by the idea of interaction with gonadal sex steroid hormones previously described (de Vries, 2008). This reinforces the notion of taking into account individual differences of OT's effects (Bartz et al., 2011). Regardless of the sexually dimorphic directionality of OT's effect on neural activity it is clear that the amygdala is an important target of OT modulation.

2.2. Anxiety

Building on the early animal research showing possible anxiolytic properties of OT (McCarthy et al., 1996; Windle et al., 1997), some imaging studies have focused on anxiety. Labuschagne et al. (2010, 2011) examined cortical activation in people with generalized social anxiety disorder (GSAD). People with GSAD have heightened amygdala activity in response to threatening stimuli. Labuschagne et al. (2010) show that OT attenuates this heightened activity using the same paradigm as Domes et al. (2007a,b) and Kirsch et al. (2005). In contrast to the imaging studies mentioned earlier they report no significant effects of OT on amygdala activation in the control group. The authors mainly describe this difference by pointing towards design, group size and individual variability. The fact that there is a sex difference in amygdala activity in relation to OT and fearful faces (Domes et al., 2010) and that different sub-regions of the amygdala respond differently to OT administration (Gamer et al., 2010) point to the possibility of individual differences.

Born et al. (2002) have also reported individual variation in the CSF peptide level increase following intranasal administration. The attenuated amygdala activity reported by Labuschagne et al. (2010) also indicates the possibility that OT moderates or normalizes baseline hyperactivity. OT might act, in part, to maintain a certain homeostasis. A follow-up study by the same group further supports this idea (Labuschagne et al., 2011). They also reported modulatory effects of OT in the bilateral mPFC and ACC. For both regions there was an exaggerated baseline response in GSAD that appeared to be attenuated by OT. These findings fit with the idea that there is large variability in how OT affects cognition (Bartz et al., 2011). Depending on an individual's specific predisposition (such as their generalized anxiety), OT will have different effects.

2.3. Other oxytocin modulations

Other findings of imaging OT include increases in trust (Baumgartner et al., 2008), reaction to pain (Singer et al., 2008), mental state attributions to others (Pincus et al., 2010), reciprocal cooperation (Rilling et al., 2012) and response to infant crying (Riem et al., 2011). Singer et al. (2008) report effects of OT mostly on amygdala and mPFC areas. Attenuating effects of OT on the amygdala, assessed with an economic trust game, seemed to be driven by the prior level of selfishness. This fits with the notion of individual variability in the effects of OT (Bartz et al., 2011). This could support the hypothesis suggested by Labuschagne et al. (2010, 2011) that OT modulates the 'extremes'. Furthermore, Wittfoth-Schardt et al.

(2012) showed that OT reduces activation in the left globus pallidus in response to passive viewing of pictures of fathers' own children and unfamiliar children, but not for familiar children. This study provides evidence for OT's social facilitation effect through attenuation of the more 'extreme' socially salient cues.

In one of the first fMRI studies looking at effects of OT in a clinical population, OT differentially affected depressed people versus controls (Pincus et al., 2010). Using the 'Reading the Mind in the Eyes' Test (RMET) (Baron-Cohen et al., 2001) Pincus et al. (2010) showed differential activation patterns when comparing depressed patients to controls. In typical controls OT was associated with increased activation of amygdala, ventromedial, parahippocampal and semantic associative areas. In depressed individuals, OT caused increased activity in higher order brain regions and the insula. These findings again suggest that the effects of OT are dependent on the type of paradigm used. They also give indirect support to the notion that OT effects varies depending on individual predispositions. Riem et al. (2011) also report OT induced reduced right amygdala activation in response to infant crying, in line with earlier findings using a different paradigm (Domes et al., 2007a). They also found increased activation in the insula and the inferior frontal gyrus.

3. Functional connectivity

A neural correlate for the effects of OT on social behaviour is not evident from the studies reviewed here. Although the amygdala is one of the nodes affected by OT administration, several studies report involvement of other areas (Domes et al., 2007a; Kirsch et al., 2005; Petrovic et al., 2008; Pincus et al., 2010; Riem et al., 2011; Rilling et al., 2012; Singer et al., 2008). These imaging studies provide an indication for task dependent modulatory effects of OT. Unfortunately, they rarely provide an account of how these systems interact. Different brain regions do not function in isolation but instead make up a network of interconnected nodes (van den Heuvel and Hulshoff Pol, 2010). How this network deals with a certain exogenous stimuli depends not only on the nodes involved but also on how these nodes interact. Functional connectivity analysis is one way to investigate interactions in a network of multiple brain regions. In fMRI this means a temporal correlation in the BOLD fluctuations of either single voxels, or groups of voxels, defined as regions of interest (ROI's). Surprisingly, this alteration in functional connectivity has not been systematically investigated. A literature search revealed few imaging studies using any type of functional connectivity analysis to investigate the dynamics of OT in the human brain (Domes et al., 2007a; Kirsch et al., 2005; Riem et al., 2012; Sripada et al., 2012). Without exception, these studies all used a hypothesis-driven approach, taking the amygdala as a seed or ROI, and focusing only on functional relations with that region. Rilling et al. (2012), for example, adopted a paradigm that shows involvement of multiple areas. They report increased functional connectivity between the amygdala and the anterior insula and enhanced caudate nucleus and left amygdala activation in a decision-making paradigm.

Additionally, following their study on the effects of OT on infant crying, Riem et al. (2012) explicitly investigated the effects of OT on functional connectivity in the paradigm used earlier (Riem et al., 2011). They report enhanced functional connectivity between the amygdala and the orbitofrontal cortex (OFC), anterior cingulate (ACC), hippocampus, precuneus, supramarginal gyri and the middle temporal sulcus. This is the first direct evidence of the influence of OT on communication within a broad emotion regulatory network. Interestingly, these regions largely overlap with the model of social-emotional processing proposed by Bos et al. (2012). That study also predicted changes in a network of regions comprising the amygdala, OFC and the ACC. They also include the thalamus, brainstem, septum and superior temporal sulcus as brain areas that might be modulated by neuropeptides. Another study that explored functional connectivity differences in a task-based design reported attenuating effects of oxytocin (Wittfoth-Schardt et al., 2012). Specifically, they report decreased functional connectivity in response to socially salient stimuli in fronto-pallido-hippocampal networks following OT administration. This reduced functional coupling need not be contradictory to the previously reported increases in functional coupling. As the authors state, it is likely that OT's facilitation effects on bond formation operates by increasing approach tendencies and decreasing social avoidance.

The only study that has explored what happens during rest also found a decreased coupling of the amygdala with frontal regions (Sripada et al., 2012). This study reported enhanced functional coupling between the right amygdala and rostral medial frontal cortex. This confirms the idea that OT can influence functional coupling in a baseline condition, independent of specific contexts. A lead for expecting such functional connectivity changes as a result of OT administration comes from the priming hypothesis (Ludwig and Leng, 2006). As stated earlier, a prolonged priming effect of OT can elicit functional rewiring of neuronal networks. This functional rewiring is a temporary alteration of the way the network is configured and how it responds to an exogenous signal or stimulus. This pattern of temporary strengthening or weakening of functional connections can occur after a single peptidergic signal, as is the case in an OT administration study.

4. Discussion and future directions

A network of interconnected regions may be the basis of behavioural effects observed with OT administration. Although the amygdala is one of the most important regions, the effects of OT are likely to affect areas beyond the amygdala. Changes in one node of the network will affect the functioning of the network. Bos et al. (2012), for example, also mention OFC, ACC, STS and thalamic regions as part of a functionally connected neural network that can be influenced by OT (and testosterone). The studies reviewed here find enhanced connectivity in some of these regions (Kirsch et al., 2005; Riem et al., 2012; Sripada et al., 2012). They report enhanced functional connectivity between the amygdala and the orbitofrontal cortex, anterior cingulate, hippocampus, precuneus, supramarginal gyri and the middle temporal sulcus. However, they also find reduced functional coupling between the amygdala and the brainstem (Kirsch et al., 2005).

Future research will need to disentangle whether this alteration of the social brain circuitry is task-dependent or if there is already an effect during resting-state, as Sripada et al. (2012) have shown. Using a seed-based hypothesis-driven approach, any changes in regions that have an indirect effect will likely have been missed. The imaging studies reviewed here also mention a number of other regions such as the insula and superior middle frontal gyrus (Pincus et al., 2010), the globus pallidus (Wittfoth-Schardt et al., 2012), as well as the mPFC (Labuschagne et al., 2011; Singer et al., 2008). It is possible that OT modulates functional connectivity in this specific subset of social brain regions without directly affecting the amygdala, or indirectly through modulation of the amygdala functional connectedness.

We hypothesize that OT causes changes in the baseline activity and resting-state coupling of certain brain regions (Fig. 2a and b). These baseline conditions are likely to differ between individuals, which in part could account for the large interpersonal variability in the effects of OT (see Fig. 2a). The changes from this baseline brought about by OT administration or release predispose a network of 'social' brain regions towards a certain response, the eventual outcome of which is dependent on the stimulus encountered. This network is likely to consist of regions shown in Fig. 2b.

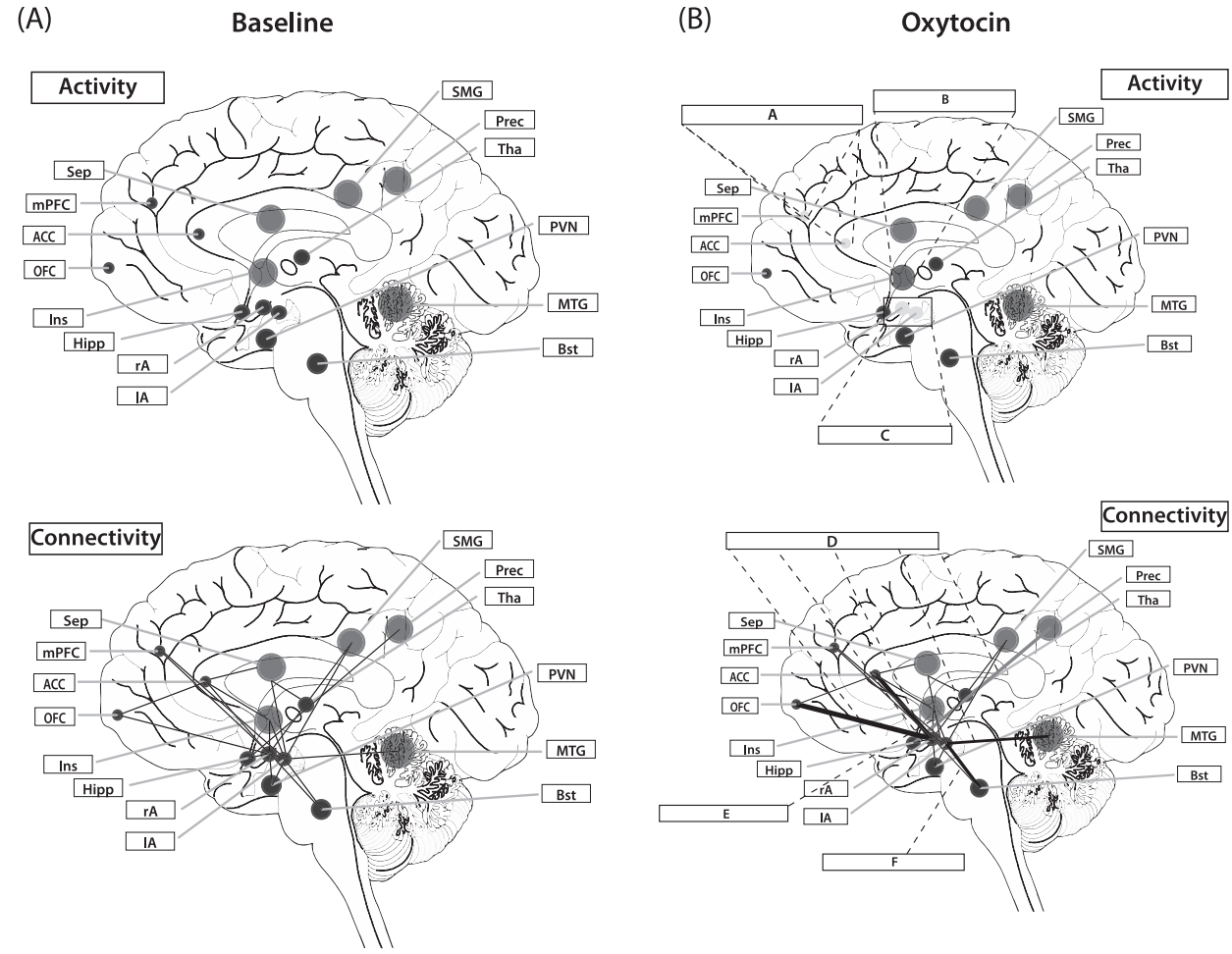

Figure 2 (a) Graphical representation of the proposed framework. During baseline resting state the brain is in a so-called default mode in terms of activity and connectivity. Regions important for social-emotional behaviour show spontaneous BOLD fluctuations that synchronize to different degrees. (b) Oxytocin modulates both regional activity as well as connectivity between different regions. How this results in a specific behaviour will depend on the interaction between context and oxytocin modulation of the neural network. Context by itself can also stimulate oxytocin release and thus initiate modulation in similar fashion. (A) mPFC and ACC hypo-activation for sad faces in patients with GSAD (Labuschagne et al., 2011). (B) Insula hyper-activation depressed patients (Pincus et al., 2010). (C) Amygdala deactivation for fearful or angry stimuli (Domes et al., 2007a; Gamer et al., 2010; Kirsch et al., 2005). (D) Increased functional connectivity between amygdala—OFC—ACC—precuneus—MTG—hippocampus and SMG in response to infant laughter (Riem et al., 2012). (E) Enhanced functional connectivity for amygdala and anterior insula in an iterated prisoners dilemma (Rilling et al., 2012). (F) Reduced functional coupling between amygdala and brainstem (Kirsch et al., 2005). *Abbreviations in this figure*: SEP = septum, mPFC = medial prefrontal cortex, ACC = anterior cingulate, OFC = orbitofrontal cortex, INS = insula, Hipp = hippocampus, rA = right amygdala, lA = left amygdala, SMG = supramarginal gyrus, Prec = precuneus, Tha = thalamus, PVN = paraventricular nucleus, MTG = middle temporal gyrus, Bst = brainstem.

Exploring parallels with animal research into receptor localization and molecular targeting might lead to the inclusion of more brain regions in the model. This will lead to a more precise account of the OT system and how it exerts its effect throughout the brain. It might also reveal more structural pathways underlying a functional connectivity account. For example, recent work in rodents has identified pathways through which OT can exert effects on the amygdala and forebrain regions (Knobloch et al., 2012; Viviani et al., 2011). Knobloch et al. (2012) clearly demonstrate widespread central projections of hypothalamic OT neurons. Additionally, they also demonstrate how axonal release from these neurons might be involved in behaviour linked to specific brain regions. Such efforts will constitute a bottom-up approach in localizing the specific targeting of OT.

Reviewing behavioural and imaging studies of OT administration also leads to a number of caveats that complicate between-study comparisons. First, the time between administration and the first scan may be one variable. Most studies use an interval of approximately 45 min between administration and testing. As stated earlier, there is reason to believe that effects decline after the peak CSF level, leading to no external effects after 50 min (Thompson et al., 2006). Given the peak levels in CSF and plasma after about 10 min (Born et al., 2002) it would be interesting to assess shorter intervals. Some studies have successfully used this timing in a clinical population (Pincus et al., 2010). Secondly, sex differences in general, and in functional connectivity in particular, have not been reported extensively in the case of humans. The studies that have done so report differential effects in the amygdala (Domes et al., 2007a, 2010; Lischke et al., 2012). These studies show opposite activation patterns in males and females in response to emotionally relevant stimuli as a result of OT administration. Sex differences in the effects of OT on brain activation are thus an important factor to consider. Third, few studies in humans have explored dose-dependency; most reported studies have used a single dose of approximately 24 IU. Some behavioural studies have used much higher dosages (Marsh et al., 2010), but dosage effects have not been reported. Initial work does show a slight difference in pharmacodynamic properties following intranasal administration of different dosages (Born et al., 2002). All these caveats are important targets for future research.

The most important difference across studies is the slight difference in experimental paradigms that may affect aspects of social behaviour. Thus, caution is warranted when speaking about prosocial effects of OT in general. These experimental paradigms likely trigger a response in specific parts of a 'social brain' network. They thus adopt a 'context of interest' approach. Combined with a 'region of interest' approach, focusing on the brain regions that are activated in a specific context, interactions between other regions that may comprise this network might be missed. The study of functional connectivity in the social brain that is affected by OT will help us understand how different systems that underlie responses in different contexts may interact.

In sum, the interaction between OT, neural network and the environment has not been thoroughly studied. We hypothesize that OT affects functional connectivity both between and within regions of the 'social brain'. Also, we expect that the precise modulation of this network by OT will vary both between different individuals and different contexts, in line with the effects of the peptide on social behaviour (Bartz et al., 2011). OT fMRI studies should also take into account context, for example, by looking at resting-state effects and the differences in different behavioural paradigms. These studies should also be aware of individual predispositions towards any specific outcome; using within-subject designs is in this respect the preferred option. More extensive psychosocial assessments would be a second way to improve our understanding of the varying effects of oxytocin, taking into account individual differences. Finally, the use of OT as a potential 'treatment' for clinical conditions such as autism, borderline personality disorder, and social anxiety disorder, and an examination of the brain changes that underlie any behavioural change, is an important target for future research.

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Conflict of interest

The authors declare no competing financial interests.

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