NeuroImage 149 (2017) 458–467

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Oxytocin differentially alters resting state functional connectivity between amygdala subregions and emotional control networks: Inverse correlation with depressive traits

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ARTICLE INFO

Keywords:
Basolateral amygdala
Superficial amygdala
Centromedial amygdala
Emotion
Oxytocin

ABSTRACT

The hypothalamic neuropeptide oxytocin (OT) has received increasing attention for its role in modulating social-emotional processes across species. Previous studies on using intranasal-OT in humans point to a crucial engagement of the amygdala in the observed neuromodulatory effects of OT under task and rest conditions. However, the amygdala is not a single homogenous structure, but rather a set of structurally and functionally heterogeneous nuclei that show distinct patterns of connectivity with limbic and frontal emotion-processing regions. To determine potential differential effects of OT on functional connectivity of the amygdala subregions, 79 male participants underwent resting-state fMRI following randomized intranasal-OT or placebo administration. In line with previous studies OT increased the connectivity of the total amygdala with dorso-medial prefrontal regions engaged in emotion regulation. In addition, OT enhanced coupling of the total amygdala with cerebellar regions. Importantly, OT differentially altered the connectivity of amygdala subregions with distinct up-stream cortical nodes, particularly prefrontal/parietal, and cerebellar down-stream regions. OT-induced increased connectivity with cerebellar regions were largely driven by effects on the centromedial and basolateral subregions, whereas increased connectivity with prefrontal regions were largely mediated by right superficial and basolateral subregions. OT decreased connectivity of the centromedial subregions with core hubs of the emotional face processing network in temporal, occipital and parietal regions. Preliminary findings suggest that effects on the superficial amygdala-prefrontal pathway were inversely associated with levels of subclinical depression, possibly indicating that OT modulation may be blunted in the context of increased pathological load. Together, the present findings suggest a subregional-specific modulatory role of OT on amygdala-centered emotion processing networks in humans.

Introduction

The hypothalamic neuropeptide oxytocin (OT) plays an important role in modulating social-cognitive and emotional behavior. Accumulating evidence from intranasal-OT (IN-OT) administration studies in healthy individuals suggests modulatory effects on emotional processing, including not only basal functional domains such as attention and emotional learning (Bartz et al., 2011; Eckstein et al., 2015a), but also complex emotion-cognition interactions, such as emotion regulation (Preckel et al., 2015), pair bonding and social interaction (Ditzen et al., 2012).

The amygdala, a subcortical structure with a pivotal role in emotion processing, has been defined as a key neural target of IN-OT effects. Studies that combined the administration of IN-OT with functional neuroimaging techniques consistently observed modulatory effects on neural activity in this region following OT (Wigton et al., 2015;

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http://dx.doi.org/10.1016/j.neuroimage.2017.01.078
Received 16 June 2016; Accepted 31 January 2017
Available online 01 February 2017

Rocchetti et al., 2014). Increasing evidence further suggests that IN-OT influences the functional interplay between the amygdala and frontal, striatal and brainstem regions during emotional task challenges (Kirsch et al., 2005; Striepens et al., 2012; Eckstein et al., 2015a). More recent studies employed functional MRI-based resting state functional connectivity (rsFC) and established effects of IN-OT on the intrinsic connectivity networks of the amygdala, with increased coupling between the amygdala and top-down regulatory hubs, particularly the medial prefrontal cortex (mPFC) and the anterior cingulate cortex (ACC), being most consistently reported (Riem et al., 2012; Sripada et al., 2013; Fan et al., 2014).

These previous rsFC studies generally treated the amygdala as a single homologous structure, while convergent neuroanatomical evidence from animal (Huber et al., 2005; Adhikari et al., 2015) and human (Amunts et al., 2005) studies, as well as accumulating human functional neuroimaging findings (Ball et al., 2007; Roy et al., 2009) emphasize the structural and functional heterogeneity of the amygdala. The human amygdala comprises at least three broad subdivisions (basolateral, superficial and centromedial amygdala subregion) with distinct functions and connectivity patterns (Roy et al., 2009; Bzdok et al., 2013). Prior neuroimaging research in humans suggests that the superficial subregion is particularly sensitive to social information (Goossens et al., 2009) and emotional tension (Lehne et al., 2014), whereas the basolateral subregion plays a pivotal role in higher-level sensory processing (Bzdok et al., 2013) and evaluation of potential threat (Onur et al., 2009). Initial findings have linked the centromedial subregion with motor responses and attentional allocation (Bzdok et al., 2013). The functional subdivision of the human amygdala is further corroborated by resting state functional MRI studies demonstrating distinct connectivity patterns across the three amygdala subregions: whereas spontaneous activity in the superficial subregion predicts activity in limbic regions, the basolateral subregion associates with temporal and frontal regions and the centromedial subregion primarily associates with striatal regions (Roy et al., 2009; Bzdok et al., 2013). The functional relevance of the distinct connectivity patterns is further emphasized by reports on subregion-specific associations with trait dimensions related to emotional processing such as harm avoidance (Li et al., 2012).

Studies in rodents have begun to examine selective effects of OT on the amygdala subregions and suggest differential effects in the domains of emotional learning and social interaction (Calcagnoli et al., 2015; Campbell-Smith et al., 2015). In humans, differential effects of IN-OT on the amygdala subregions have not been systematically examined. Initial evidence for subregion-specific effects of IN-OT on amygdala functioning in humans was provided by a task-based fMRI study reporting that the effects of IN-OT in the domains of valence and attention relate to subregion-specific activity changes in the anterior and posterior amygdala (Gamer et al., 2010). Moreover, a recent clinical study reported that IN-OT produced sex- and subregion-specific effects of the rsFC networks of the centromedial and basolateral amygdala in patients with post-traumatic stress disorder (PTSD) (Koch et al., 2016).

Together, these findings emphasize that examining the effects of IN-OT on the level of the whole amygdala might not fully account for the complex modulatory influence of OT on amygdala functioning. Given that a growing number of studies have begun to link subregion-specific amygdala rsFC networks with specific emotional functions (Papini et al., 2016) and neuropsychiatric disorders characterized by emotional deficits (Kleinhans et al., 2015; Aghajani et al., 2016), the examination of IN-OT effects on the subregion-specific amygdala networks might help to further disentangle the complex modulatory role of OT and inform future studies exploring its potential therapeutic application.

Against this background the present study combined IN-OT administration with fMRI-based rsFC and probabilistic amygdala subdivisions (Amunts et al., 2005) in healthy male participants to (1) characterize distinct effects of IN-OT on the subregion-specific amygdala networks, and to (2) evaluate whether the subregional analysis reveals more specific insights into the neural effects of IN-OT in comparison to the analysis on the level of the whole amygdala. Given the growing interest in the therapeutic application of OT in psychiatric disorders characterized by marked emotional dysfunctions, including depression and anxiety (McQuaid et al., 2014), the present study additionally explored associations between effects of IN-OT on the amygdala networks and sub-clinical levels of alexithymia, depression and trait anxiety. Previous findings in healthy individuals suggest that individual differences in these pathology relevant dimensions may moderate the effects of IN-OT (Alvares et al., 2012; Ellenbogen et al., 2013; Luminet et al., 2011). Moreover, individual variations in the sub-clinical range of these dimensions have been associated with both, impaired emotional functioning (e.g. Wiebking and Northoff, 2015) and amygdala integrity (Goerlich-Dobre et al., 2015).

Material and methods

Subjects and procedure

We recruited N=79 male participants (mean age M=24.27 years, SD=4.16 years) for the study that was registered as clinical trial (identifier NCT02689596) and conducted in accordance with the latest declaration of Helsinki. All participants were non-smokers and gave written consent (IRB Identifier 329/12). Intranasal oxytocin (24 IU; Syntocinon-Spray, Novartis; three puffs per nostril, each with 4 IU OT) or placebo (PL; 0.9% sodium chloride solution) was administered in a randomized double-blind between-group design according to current guidelines (Guastella et al., 2013). N=27 participants received OT, and N=52 participants received PL. Groups did not differ in age ($t(76)$ =−.111, p=.912), height ($t(75)$=−.595, p=.553), weight ($t(76)$=.062, p=.951), years of education ($t(71)$=.269, p=.788), sexual orientation (Chi square=1.591, p=.451), relationship status (Fisher's exact test, p=.340), or parental status (none of the participants had children, detailed group charateristics are given in Table 1). During a first screening session, participants were interviewed to ensure that none of the following exclusion criteria were met: Chronic physical or mental illness, regular nicotine or alcohol use, current or regular use of medication. In addition, the Beck's Depression Inventory (BDI; Kühner et al., 2007), Toronto Alexithymia Scale (TAS; Taylor et al.,

Table 1
Demographics and questionnaires.

	OT	PL	T	df	p	N(OT)	N(PL)
Age (years)	24.22 (± 3.89)	24.29 (± 4.32)	−.067	77	.947	27	52
Weight (kg)	79.11 (± 11.02)	78.94 (± 11.79)	.062	76	.951	27	51
Height (mm)	181.08 (± 6.83)	182.09 (± 7.05)	−.595	75	.553	26	51
Education (years)	16.33 (± 2.18)	16.20 (± 2.07)	.247	71	.788	27	46
BDI	3.17 (± 4.02)	2.90 (± 3.51)	.293	71	.771	24	49
TAS	48.50 (± 8.35)	50.48 (± 12.43)	−.704	70	.484	24	48
Trait Anxiety	43.58 (± 3.13)	44.06 (± 2.60)	−.689	70	.493	24	49

Abb.: OT, oxytocin; PL, placebo; BDI, Beck's Depression Inventory; TAS, Toronto Alexithymia Scale.