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Oxytocin receptor polymorphism and childhood social experiences shape adult personality, brain structure and neural correlates of mentalizing

H. Schneider-Hassloff [a,*,1], B. Straube [a], A. Jansen [a], B. Nuscheler [a], G. Wemken [b], S.H. Witt [c], M. Rietschel [c], T. Kircher [a]

[a] Department of Psychiatry and Psychotherapy, Philipps University Marburg, Germany
[b] Institute of Psychology, Social Psychology, Philipps University Marburg, Germany
[c] Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Germany

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ABSTRACT

Introduction: The oxytocin system is involved in human social behavior and social cognition such as attachment, emotion recognition and mentalizing (i.e. the ability to represent mental states of oneself and others). It is shaped by social experiences in early life, especially by parent–infant interactions. The single nucleotid polymorphism rs53576 in the oxytocin receptor (OXTR) gene has been linked to social behavioral phenotypes.
Method: In 195 adult healthy subjects we investigated the interaction of OXTR rs53576 and childhood attachment security (CAS) on the personality traits "adult attachment style" and "alexithymia" (i.e. emotional self-awareness), on brain structure (voxel-based morphometry) and neural activation (fMRI) during an interactive mentalizing paradigm (prisoner's dilemma game; subgroup: n = 163).
Results: We found that in GG-homozygotes, but not in A-allele carriers, insecure childhood attachment is - in adulthood - associated with a) higher attachment-related anxiety and alexithymia, b) higher brain gray matter volume of left amygdala and lower volumes in right superior parietal lobule (SPL), left temporal pole (TP), and bilateral frontal regions, and c) higher mentalizing-related neural activity in bilateral TP and precunei, and right middle and superior frontal gyri. Interaction effects of genotype and CAS on brain volume and/or function were associated with individual differences in alexithymia and attachment-related anxiety. Interactive effects were in part sexually dimorphic.
Conclusion: The interaction of OXTR genotype and CAS modulates adult personality as well as brain structure and function of areas implicated in salience processing and mentalizing. Rs53576 GG-homozygotes are partially more susceptible to childhood attachment experiences than A-allele carriers.

1. Introduction

Investigating the neural underpinnings of human social cognition and behavior, the neuropeptide oxytocin (OXT) has received considerable attention. OXT is involved in complex social behavior and social cognition in humans such as attachment (attachment security and the tendency to share emotions with friends) [Buchheim et al., 2009; Tops et al., 2007], social memory [Bartz et al., 2011], emotion recognition [Shahrestani et al., 2013] and mentalizing [Domes et al., 2007]. Mentalizing is the ability to represent mental states such as beliefs, intentions and emotions of oneself and others. Mentalizing proficiency is considered as crucial for successful human social interactions [Premack and Woodruff, 1978].

OXT and its receptor are expressed in the central nervous system and in peripheral tissues. In the central nervous system OXT is primarily produced in the hypothalamic paraventricular and supraoptic nuclei and released into the neurohypophysis and into a variety of extrahypothalamic brain areas (for a review see e.g. Gimpl and Fahrenholz (2001)). The regional distribution of the OXT receptor (OXTR) varies between species, and in humans the OXTR is present e.g. in the limbic system including amygdala, in the dorsal ACC, striatum and hypothalamus [Boccia et al., 2013; Gimpl and Fahrenholz, 2001; Skuse and Gallagher, 2009]. The oxytocin system is regulated by gonadal steroids and is partly sexually dimorphic; e.g. animal studies showed that OXTR density in medial prefrontal cortex and plasma OXT tend to be higher in females, and that pair bonding is more dependent on OXT in females than in males [Carter, 2007; Carter et al., 2009; Gimpl and Fahrenholz, 2001; Insel and Hulihan, 1995; Kramer et al., 2004; Smeltzer et al., 2006]. Animal and

* Corresponding author at: Department of Psychiatry and Psychotherapy, Philipps University Marburg, Rudolf-Bultmann St 8, 35039, Marburg, Germany.
E-mail address: schneid5@staff.uni-marburg.de (H. Schneider-Hassloff).
[1] Present Address: ZNL TransferCenter for Neuroscience and Learning Ulm University Park St. 11 89073 Ulm Germany.

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neuroimaging studies' in humans have revealed that the amygdala, a brain structure implicated in responses to motivationally salient stimuli [Lindquist et al., 2012], is involved in the effects of OXT on social cue processing [Bethlehem et al., 2013; Gabor et al., 2012; Gamer et al., 2010]. It has been put forward that OXT alters the perceived salience of social cues as a possible mechanism of action [Bartz et al., 2011].

Neurogenetic approaches in humans have explored how variations in the oxytocin receptor gene modulate human social behavior and related brain functions [Donaldson and Young, 2008; Ebstein et al., 2012]. The single nucleotid polymorphism (SNP) rs53576 (G/A), located in the third intron of the OXT receptor gene (OXTR), has been linked to social behavior phenotypes in humans, but its functionality remains elusive. GG-homozygotes of rs53576 were shown to be more sensitive to social cues: They displayed higher affective empathy [Rodrigues et al., 2009], more sensitive parenting [Bakermans-Kranenburg and van Ijzendoorn, 2008], higher trust behavior [Krueger et al., 2012] and higher reward dependence [Tost et al., 2010]. GG-homozygotes activated the amygdala to a greater extent during face processing, and genotype-related alterations in reward dependence (i.e. reliance on social approval) negatively correlated with structural changes in local gray matter volume of the amygdala [Tost et al., 2010]. Behavioral findings regarding mentalizing have shown that rs53576 is significantly associated with performance in affective mentalizing (measured by the "Reading the mind in the eyes test" = RMET) [Lucht et al., 2013; Rodrigues et al., 2009], but risk-alleles differed. Attachment security in depressed [Costa et al., 2009], but not in healthy adults [Bradley et al., 2011; Gillath et al., 2008; Rodrigues et al., 2009] was modulated by rs53576.

To elucidate these findings further, gene-by-environment (GxE) approaches have emerged to be promising. Results from animal and human studies suggest that the OXT system is shaped by social experiences in early life, especially by parent–infant interactions [Bales and Perkeybile, 2012; Ross and Young, 2009]:

Studies in rats showed that variations in maternal care induced long-term changes in the OXT receptor expression (e.g. in the amygdala) and in social behavior in the adult offspring [Champagne et al., 2001; Francis et al., 2002; Lukas et al., 2010]. Epigenetic modulations might account for this effect of maternal care on gene expression as was shown for the glucocorticoid receptor in the rat hippocampus ([Weaver et al., 2004]; for a review see e.g. [Champagne and Curley, 2009; Kumsta et al., 2013; Zhang and Meaney, 2010]).

In humans child maltreatment was associated with alterations in peripheral OXT levels in response to physical contact in children [Fries et al., 2005], in adult women with alterations of cerebospinal fluid OXT levels [Heim et al., 2009] and with OXT-induced modulations of functional connectivity between brain regions implicated in social cognition in an fMRI resting state experiment [Riem et al., 2013].

Interestingly childhood experiences like child maltreatment and infant attachment security were shown to modulate adult attachment security/style, emotion regulation and internalizing symptoms in GG-homozygotes, but not in A-allele carriers of rs53576 [Bradley et al., 2011; Hostinar et al., 2014; Raby et al., 2013]. Similarly G-allele carriers of rs53576, in contrast to AA-homozygotes, were susceptible to the quality of the childhood family environment [Bradley et al., 2013] resp. childhood maltreatment [McQuaid et al., 2013] with regard to resilient coping and positive affect resp. depressive symptomatology. Therefore variation in OXTR rs53576 seems to convey different susceptibility to long-term effects of childhood experiences on social phenotypes, with higher susceptibility in G-allele carriers.

As mentalizing - a crucial faculty during social interaction - is modulated by the OXT system, a comparable susceptibility effect of rs53576 with regard to mentalizing can be surmised. A recent quantitative meta-analysis identified a core neural network implicated in mentalizing, consisting of the bilateral medial prefrontal cortex, temporoparietal junction, superior temporal sulcus, temporal poles, anterior temporal lobes, posterior cingulate cortex, precuneus, the left inferior frontal gyrus and possibly the amygdala [Mar, 2011]. Using implicit mentalizing tasks neural activation in middle and superior frontal gyri and in superior parietal cortex was also shown to be linked to mentalizing [Kircher et al., 2009; Krach et al., 2008].

To our knowledge, the interaction effects of genetic variation in OXTR and early environmental factors on the neural correlates of mentalizing and on brain structure are still unknown. With this study we tested the hypothesis that the SNP rs53576 in OXTR and the early environmental factor childhood attachment security (CAS) interact to modulate social behavior, structure and function of the brain in adulthood. Childhood attachment describes the emotional bond between child and caregiver. It can be classified as either secure or insecure [Bowlby, 1969]. Childhood attachment security – prospectively or retrospectively assessed – is significantly related to mentalizing ability in childhood as well as to emotional regulation, social competence and psychopathology across the lifespan [Meins et al., 1998; Sroufe, 2005; Symons and Clark, 2000; Ward et al., 2006]. It therefore represents an important environmental factor during development. The interaction of OXTR genotype and childhood attachment on adult brain structure and function are yet unknown.

1.1. Hypotheses

In our study, we firstly examined the interaction effects of rs53576 and childhood attachment security (CAS) on personality traits relevant to attachment and emotion recognition, i.e. adult attachment style (AAS) and alexithymia. We assessed the AAS with the Relationship Scales Questionnaire (RSQ), using the two subscales that measure avoidance of attachment (AV) and attachment-related anxiety (ANX). Alexithymia is characterized by difficulties in identifying and describing one's own emotions and is associated with affective [Luminet et al., 2011] and cognitive mentalizing [Moriguchi et al., 2006]. It was assessed using the questionnaire Toronto Alexithymia Scale 20. We hypothesized that GG-homozygotes are more susceptible to CAS than A-allele carriers with regard to adult attachment style and alexithymia (hypothesis 1).

We secondly investigated the interaction effect of rs53576 and reported childhood attachment security (CAS) on brain gray matter volume using voxel-based morphometry (VBM). We expected interaction effects of rs53576 and CAS in brain regions related to social salience (amygdala) and social cognition (i.e. mentalizing-associated network) (hypothesis 2).

We thirdly investigated the interaction effect of rs53576 and CAS on the neural correlates of mentalizing using fMRI. Subjects performed a socially interactive game (Prisoner's Dilemma Game) that triggers implicit mentalizing processes [Kircher et al., 2009; Rilling et al., 2012]. We expected GxE-modulation in mentalizing-related brain areas [Kircher et al., 2009; Krach et al., 2008; Mar, 2011] (hypothesis 3).

Finally we assumed an association between brain morphology and function. We therefore explored brain regional overlaps of structural (VBM) and functional (fMRI) genotype-by-CAS interaction effects. We also explored whether GxE effects on brain structure are associated with GxE effects on mentalizing-related neural activity and whether GxE effects on both brain structure and mentalizing-related neural activity are associated with social adult behavior (adult attachment style and alexithymia).

2. Methods

2.1. Participants

195 subjects (97 female = 49.7%; mean age = 24.0 years, SD = 3.2, range 19–38) were included in the analysis of adult attachment style, alexithymia (RSQ/TAS) and in the structural MRI study (sMRI). A subsample of these, i.e. 163 subjects (77 female = 47.2%; mean age = 24.0 years, SD = 3.1, range 19–35), were included in the functional MRI study (fMRI). Inclusion criteria were student status, age (18–40 years), right-handedness (as assessed by the Edinburgh