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Dissertations-Kurzfassung

Influence of autism-associated and other genetic variants in the oxytocin system on neural correlates of social processing in an oxytocin challenge study

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The oxytocin (OT) system has been implicated in a wide range of social behaviors for more than two decades now. While early studies primarily focused on animals, oxytocin challenge studies in humans have gained increasing importance during the last years and yielded mainly positive effects of an OT administration on social behavior. On the neural level, these effects have been found to be mediated via OT induced changes in social brain activation. However, it seems reasonable to assume genetic variants in the OT system to influence these OT effects on social brain activation. Although there are studies that report associations between genetic variations in the OT system and social phenotypes on the behavioral and on the neural level, no one has ever combined an imaging genetics approach with an OT challenge.

Due to its role in the regulation of social behavior, OT has also been discussed in the context of Autism Spectrum Disorders (ASD). Indeed, there is first evidence for an improvement of social deficits after OT administration and also for associations between ASD and genetic variants in the OT system. Accordingly, we combined an imaging genetics approach with an OT challenge under special consideration of autism associated genetic variants in the OT system to gain some deeper insight into the complex role of OT for human social behavior.

For this purpose, we investigated 55 healthy young men with functional magnetic resonance imaging (fMRI) in a double-blind, placebo-controlled, cross-over design. During the fMRI scan, two different paradigms on processing of social stimuli were applied. The first paradigm, a simple matching task, addressed basic processing of positive and negative social scenes as well as emotional faces. The second one focused on processing of direct vs. averted eye-gaze. Based on this dataset, we performed three different studies on the influence of different genetic variants in the OT system on social brain activation and their interaction with intranasally administered OT.

The first study explored the effect of an autism-associated single nucleotide polymorphism (SNP), rs3796863, in the gene coding for CD38, a transmembrane protein which is involved in OT secretion. Our analyses revealed a significantly higher activation of the left fusiform gyrus in homozygotic risk allele carriers, which was particularly increased after OT administration. Furthermore, we found slower reaction times for homozygotic risk allele carriers, which were recovered under OT. We interpret the altered brain activation and reaction times in homozygotic risk allele carriers as a potential intermediate phenotype for autism.

In the second study, we concentrated on interactions between the oxytocin and the dopamine (DA) system via investigation of the CD38 SNP and the catechol-O-methyltransferase (COMT) val158met polymorphism. However, our results provide evidence for a significant gene x gene interaction effect in the amygdala during basic social processing that was only present under PLA and completely abolished after OT treatment. While homozygotic risk allele carriers of the CD38 SNP had strongest amygdala activation when they were also carriers of two COMT met alleles and lowest for two val alleles, the opposite pattern was found for the heterozygotic CD38 genotype. Since both SNPs affect the availability of the specific substance, our results suggest that the effect of circulating OT on social processing depends on DA availability.

The third study aimed to explore the influence of three SNPs in the promoter region of the oxytocin receptor gene (OXTR). We observed a significant effect for one SNP (rs401015) on amygdala activation for the processing of direct vs. averted eye gaze. However, this effect was only present under OT treatment. The heterozygous genotype showed increased activation of the left amygdala for

direct eye gaze and decreased activation for averted eye gaze. We believe this finding to reflect an OT induced increase in salience signaling during the processing of direct eye gaze.
Besides specific implications of each single study, all three studies have in common that they provide evidence for an interaction between genetic variants in the OT system and an OT treatment during neural processing of social stimuli. Therefore, we gained some deeper insight into the highly complex regulation of OT effects on human social behavior. Finally, our results can also be translated to ASD and have important implications for future research, especially intervention studies.