Oxytocin Improves "Mind-Reading" in Humans

Gregor Domes, Markus Heinrichs, Andre Michel, Christoph Berger, and Sabine C. Herpertz

Background: The ability to "read the mind" of other individuals, that is, to infer their mental state by interpreting subtle social cues, is indispensable in human social interaction. The neuropeptide oxytocin plays a central role in social approach behavior in nonhuman mammals.

Methods: In a double-blind, placebo-controlled, within-subject design, 30 healthy male volunteers were tested for their ability to infer the affective mental state of others using the Reading the Mind in the Eyes Test (RMET) after intranasal administration of 24 IU oxytocin.

Results: Oxytocin improved performance on the RMET compared with placebo. This effect was pronounced for difficult compared with easy items.

Conclusions: Our data suggest that oxytocin improves the ability to infer the mental state of others from social cues of the eye region. Oxytocin might play a role in the pathogenesis of autism spectrum disorder, which is characterized by severe social impairment.

Key Words: Emotion, oxytocin, peptide, social cognition, theory of mind

The ability to infer the internal state of another person to adapt one's own behavior is a cornerstone of all human social interactions. Humans have to infer internal states from external cues such as facial expressions in order to make sense of or predict another person's behavior, an ability that is referred to as "mind-reading" (Siegal and Varley 2002; Stone et al 1998). In particular, individuals with autism have distinct difficulties in interpreting social cues such as facial expressions, leading to severe social impairment (Hill and Frith 2003).

The neurohypophyseal peptide oxytocin is well known for its physiological functions in labor and lactation. In addition, oxytocin receptors are distributed in various brain areas (Landgraf and Neumann 2004) that are associated with social behavior, including reproductive and parenting behaviors, affiliation and attachment, social memory, and reactivity to social stress in nonhuman mammals (Carter 1998; Ferguson et al 2000; Young and Wang 2004). Neuropeptides have been shown to cross the blood–brain barrier after intranasal administration (Born et al 2002), with several studies reporting direct effects on human behavior (Heinrichs et al 2003, 2004; Kosfeld et al 2005). In particular, oxytocin appears to reduce responses to social stress and to increase trust in social interaction (Heinrichs et al 2003; Kosfeld et al 2005). Because mind-reading is an essential basis of human social interaction and oxytocin has been shown to modulate social approach behavior, we hypothesized that oxytocin might also promote mind-reading in humans. Specifically, oxytocin was expected to improve performance in a task testing the ability to infer the affective mental state of others from subtle facial cues.

Methods and Materials

In this study, we used a double-blind placebo-controlled within-subject design to investigate the effects of a single dose of intranasal oxytocin on the performance of inferring mental states from the eye region, measured with the "Reading the Mind in the Eyes Test" (RMET; Baron-Cohen et al 2001). It should be noted that the RMET tests a specific facet of mind-reading, that is, inference of the internal state from subtle affective facial expressions rather than mind-reading in general. Because the RMET was originally developed to measure severe impairments in mind-reading capability in adults with autism spectrum disorders, we circumvented possible ceiling effects in healthy subjects by dividing the 36 items into two subsets of easy and difficult items. These subsets were generated based on the median of item difficulty derived from a pilot study comprising 80 male volunteers.

Participants were 30 healthy male volunteers aged 21 to 30 years (mean ± SD, 25.3 ± 2.2). The study protocol was approved by the ethics committee of the Medical Faculty of the University of Rostock. All participants gave written informed consent before participation. Exclusion criteria were medical or psychiatric illness, use of medication, substance abuse, and smoking. A single dose of 24 IU oxytocin (Syntocinon spray, Novartis, Basel, Switzerland) or placebo was administered intranasally 45 min before the start of the RMET . The placebo contained all inactive ingredients except for the neuropeptide (for details see Heinrichs et al 2003). Participants underwent both the oxytocin and the placebo conditions with a 1-week interval in a balanced within-subject design. In the RMET, 36 pictures of the eye regions of different persons were presented to the participants on a computer screen with four alternative labels describing what the person displayed might be thinking or feeling at the moment. To minimize simple memory effects across test sessions, the RMET was adapted to presentation on a personal computer that enabled randomization of picture order and label position.

Drug and session effects were statistically tested using paired *t* tests. The sequence effect of treatment was tested using analysis of variance for repeated measures. The significance level was always set at $p < .05$. Statistical analyses were carried out using SPSS (Statistical Package for the Social Sciences) 12.0 for Windows.

Results

Compared with placebo, oxytocin improved performance on the RMET in 20 of the 30 participants. This resulted in a significant mean increase of approximately 3% correct responses (mean ± SD: placebo: 69.4 ± 8.1; oxytocin: 72.4 ± 8.6; $t = -2.18$, $df = 29$, $p = .019$, one-sided; see Figure 1). We hypothesized that oxytocin would particularly improve the performance on those pictures that represent highly subtle social cues by showing eye

From the Department of Psychiatry and Psychotherapy (GD, AM, CB, SCH), Rostock University, Rostock, Germany; Institute of Psychology (MH), Department of Clinical Psychology and Psychotherapy, University of Zürich, Zürich, Switzerland.

Address reprint requests to Gregor Domes, Department of Psychiatry and Psychotherapy, Rostock University, Gehlsheimer Strasse 20, 18147 Rostock, Germany; E-mail: gregor.domes@med.uni-rostock.de.

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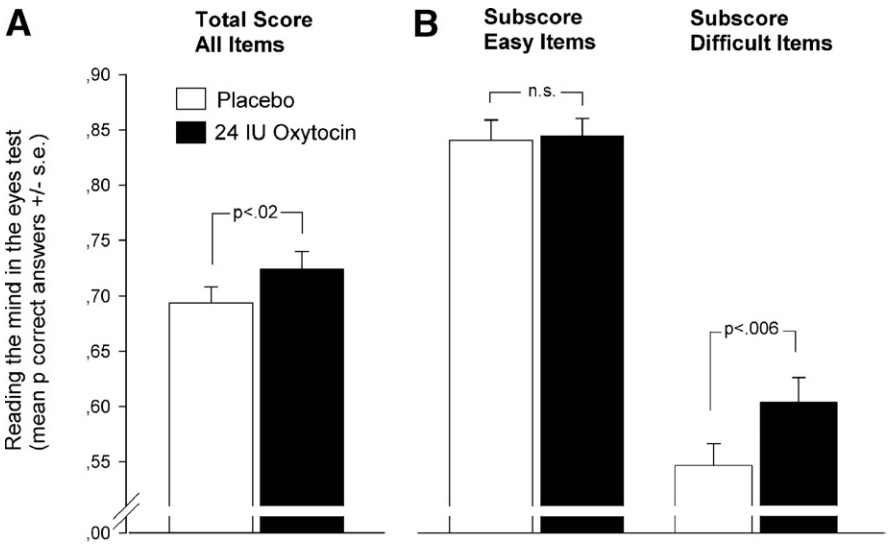

Figure 1. (A) Oxytocin improved performance in the Reading the Mind in the Eyes Test (RMET) compared with placebo ($t = -2.18$, $df = 29$, $p = .019$, single-sided). **(B)** Performance in the RMET as a function of item difficulty: oxytocin improved performance on the difficult items ($t = -2.68$, $df = 29$, $p < .006$, single-sided), whereas no effect was detected on the easy items ($t = -.20$, $df = 29$, *ns*, single-sided).

regions that are difficult to interpret in terms of the affective mental state. Indeed, our data show that oxytocin significantly improved mind-reading for difficult items ($t = -2.68$, $df = 29$, $p < .006$, single-sided; see Figure 1). As expected, oxytocin did not influence performance for easy items in our sample of healthy participants ($t = -.20$, $df = 29$, $p = .421$, one-sided).

To control for nonspecific effects of oxytocin on arousal, wakefulness, and mood, we assessed these variables directly before the RMET by means of a suitable questionnaire (Steyer et al 1994). There were no substantial differences between the oxytocin and the placebo condition for arousal (mean ± SD: 34.3 ± 4.7 vs. 34.0 ± 4.8; $t = .37$; $df = 29$; $p = .717$; two-sided), wakefulness (mean ± SD: 28.8 ± 6.8 vs. 28.2 ± 7.1; $t = .50$; $df = 29$; $p = .619$, two-sided), and mood (mean ± SD: 35.6 ± 4.1 vs. 34.2 ± 4.5; $t = 1.55$; $df = 29$; $p = .131$; two-sided). To test for possible sequence effects of treatment on test performance, we conducted a two-way repeated-measures analysis of variance (drug × sequence). Neither the main effect of sequence of treatment ($F = .06$; $df = 1,28$; $p = .816$) nor the sequence by drug interaction was statistically significant ($F = 1.62$; $df = 1,28$; $p = .214$). Moreover, the simple practice effect between the first and the second session was not significant ($t = -1.19$; $df = 29$; $p = .242$).

Discussion

In sum, this study shows that a single dose of intranasally administered oxytocin is sufficient to cause a substantial increase in the ability in affective mind-reading and therefore in interpreting subtle social cues from the eye region of other individuals. The ability of mind-reading is involved in almost all kinds of human social interactions. Evidence for the key role of oxytocin in prosocial behavior and affiliation has come primarily from studies in animals (Bartz and Hollander, in press; Carter 1998; Ferguson et al 2000; Young and Wang 2004). Recent studies in humans suggest that oxytocin improves trust and stress-protective effects of positive social interaction (Heinrichs et al 2003; Kosfeld et al 2005). The capability of oxytocin to ease inference of the affective mental state of others might reduce ambiguity in social situations and in this way encourage social approach, affiliation, and trusting behavior.

What neurobiological mechanisms might underlie the observed effect of oxytocin on affective mind-reading? First, the RMET comprises face processing, which involves a distributed network of brain regions including sections of the fusiform gyrus (fusiform face area [FFA]), the superior temporal sulcus, and limbic structures including the amygdala (Haxby et al 2000). Interestingly, the most consistently replicated neurofunctional finding in autistic patients is FFA hypoactivation to face perception (Pierce et al 2004; Schultz et al 2003). A recent study showed a strong and positive association between activation of the FFA and the amygdala and the amount of time spent fixating on the eye region of emotional faces in autistic patients (Dalton et al 2005), pointing to the particular role of the eye region in affective mind-reading. Oxytocin might have modulated the face perception network at different levels, resulting in a more accurate inference about affective mental states. In addition, various brain regions that are important for social memory may be involved, because the participant needs to retrieve previously stored experiences of others' mental states and their associated facial expressions and match them to the particular stimuli presented. Notably, prominent oxytocin receptor binding has been found in respective brain regions, in particular, the hippocampus and the septum (Gimpl and Fahrenholz 2001).

A large body of evidence shows that the amygdala and its cortical projections is crucially involved in the processing of emotional facial stimuli (Phan et al 2002). Kirsch and colleagues (2005) conducted a functional magnetic resonance imaging (fMRI) study and found reduced reactivity of the left amygdala to negative facial stimuli after a single dose of oxytocin and reduced coupling of the amygdala with brainstem regions that are involved in autonomic fear reactivity. Accordingly, oxytocin has been shown to excite inhibitory neuronal populations within the amygdala in vitro (Huber et al 2005). In our study, stimuli were neither aversive nor fear-inducing. Therefore, notions about the underlying neural mechanisms of the reported effect have to be treated with caution. Evidence from lesion studies, however, does corroborate the assumption that mind-reading also involves the amygdala network as a core circuitry (Siegal and Varley 2002; Stone et al 2003). Additionally, Baron-Cohen and colleagues (1999) showed amygdala activation in response to the RMET using fMRI. Consequently, oxytocin might have modulated emotional reactivity of the amygdala, facilitating deeper processing of the presented stimuli and thus enhancing task performance.

It has been put forward that oxytocin enhances the reward of social encounters, promoting the motivation to engage in social interactions (Insel and Young 2001). Consistent with this, highly social species have high densities of oxytocin receptors in brain circuits that play a crucial role in reward processing, the nucleus accumbens, and the prelimbic cortex (Lim et al 2004). In our study, oxytocin might have enhanced motivation to engage in this particular task on social attribution.

In light of these alternative explanations, further research is still needed to specify the effects of oxytocin on social cognition and its underlying neuroanatomic structures and processes.

Our results may have clinical implications for individuals with severe social impairment, especially patients with autism who show diminished plasma levels of oxytocin (Green et al 2001; Modahl et al 1998). Additional evidence for a link between oxytocin and autism comes from genetic studies, which suggest an association between the oxytocin receptor gene and susceptibility to autism (Auranen et al 2002; Shao et al 2002; Wu et al 2005). Because autism spectrum disorder is characterized by distinct impairments in mind-reading, oxytocin should be considered a significant factor in the pathogenesis and treatment of autism.

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