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Oxytocin administration enhances controlled social cognition in patients with schizophrenia

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Summary
Background: Individuals with schizophrenia have functionally significant deficits in automatic and controlled social cognition, but no currently available pharmacologic treatments reduce these deficits. The neuropeptide oxytocin has multiple prosocial effects when administered intranasally in humans and there is growing interest in its therapeutic potential in schizophrenia.
Methods: We administered 40 IU of oxytocin and saline placebo intranasally to 29 male subjects with schizophrenia and 31 age-matched, healthy controls in a randomized, double-blind, placebo-controlled, cross-over study. Social cognition was assessed with The Awareness of Social Inference Test (TASIT) and the Reading the Mind in the Eyes Test (RMET). We examined the effects of oxytocin administration on automatic social cognition (the ability to rapidly interpret and understand emotional cues from the voice, face, and body); controlled social cognition (the ability to comprehend indirectly expressed emotions, thoughts, and intentions through complex deliberations over longer time periods); and a control task (the ability to comprehend truthful dialog and perform general task procedures) in individuals with and without schizophrenia using mixed factorial analysis of variance models.
Results: Patients with schizophrenia showed significant impairments in automatic and controlled social cognition compared to healthy controls, and administration of oxytocin significantly improved their controlled, but not automatic, social cognition, $F(1, 58) = 8.75$; $p = 0.004$. Conversely, oxytocin administration had limited effects on social cognition in healthy

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participants. Patients and controls performed equally well and there were no effects of oxytocin administration on the control task.
Discussion: Intact social cognitive abilities are associated with better functional outcomes in individuals with schizophrenia. Our data highlight the potentially complex effects of oxytocin on some but not all aspects of social cognition, and support the exploration of intranasal oxytocin as a potential adjunct treatment to improve controlled social cognition in schizophrenia.
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1. Introduction

Social cognition, the ability to understand the thoughts and intentions of others, is critical for effectively navigating the social world. In fact, a range of social cognitive and affective operations are required to understand other people's mental states and behavior (Olsson and Ochsner, 2008), and these operations tend to be distinct from non-social cognition (Fett et al., 2011). Patients with schizophrenia (SZ) have widespread social cognitive deficits that interfere with social relationships and impair occupational functioning (Fett et al., 2011). Moreover, social cognitive deficits are more strongly associated with quality of life and functional outcomes than "positive" symptoms (e.g., hallucinations) or non-social cognition in SZ (Fett et al., 2011; Mancuso et al., 2011). Unfortunately, current antipsychotic treatments are ineffective in remediating social cognitive deficits (Kucharska-Pietura and Mortimer, 2013).

Previous studies attempting to examine social cognition in patients have often been hampered by the use of complex, multifaceted tests measuring multiple aspects of social cognition simultaneously. Advances in cognitive affective neuroscience have made it clear that understanding patient behavior in this domain requires the use of constructs that break social cognition down into subcomponents that reflect distinct neurologic systems. A clear distinction has been established during the past decade breaking socioemotional processing down into automatic, "reflexive" versus controlled, "reflective" dimensions (Lieberman, 2007). The automatic system operates quickly and unconsciously, is sensitive to subliminal cues, depends primarily on sensory processing, learns slowly, and is associated with basic person perception and immediate social cue detection (Bar et al., 2006) as measured by such tests as the Reading the Mind in the Eyes Test (RMET) (Bora et al., 2009). On the other hand, the higher-level, reflective controlled processing system operates on socioemotional information slowly and requires reflective consciousness, is insensitive to subliminal cues, depends on linguistic semantic processing, learns quickly, and makes more complex inferences based on deliberations performed over longer time periods (Lieberman, 2007).

Automatic social cognitive functions such as recognizing emotional cues and sarcasm, and making rapid personalized evaluations rely on anatomically discrete and phylogenetically ancient regions of the brain such as the medio-temporal salience structures including the amygdala and latero-temporal audiovisual integration areas (Rankin et al., 2009), as well as ventromedial orbitofrontal regions and the subcortical reward regions associated with them (Shany-Ur et al., 2012). In contrast, the higher-level, controlled system integrates social information collected over time from multiple modalities involving complex associative deliberations. Tests that measure these aspects of social cognition have traditionally involved making complicated, executively demanding deliberations about different perspectives in a social interaction and include higher-order theory of mind and *faux pas* tests, and moral reasoning deliberations (Chiong et al., 2013). In general, controlled social cognition requires more recently evolved higher-order cortical networks such as the dorsal executive-control networks and latero-anterior temporal structures, which mediate complex socioemotional semantics (Parker et al., 2005). Finally, this hierarchical separation of social cognition into separate neurologic systems has functional implications, as deficits in lower-level automatic and higher-level controlled social cognitive processing make independent contributions to functional outcomes in SZ (Mancuso et al., 2011; Sparks et al., 2010). Because of the neural and functional separation between automatic and controlled social cognitive processes, when investigating a pharmacological intervention to improve social cognition, it is important to test these processes separately.

The neuropeptide oxytocin (OT) has been implicated in bonding and sociality in mammals and when administered intranasally to humans has powerful prosocial effects (Macdonald and Macdonald, 2010). In patients with autism, a single dose of OT improves facial affect recognition (Guastella et al., 2010). There is also a burgeoning literature on the role of OT in SZ. In healthy subjects, peripheral OT levels increase after entrusting a secret to an experimenter. However, individuals with SZ do not show this increase and the severity of their negative symptoms predicts their OT response to the situation (Keri et al., 2009). Furthermore, in patients with SZ, plasma OT levels predict the ability to identify facial affect (Rubin et al., 2011), and cerebrospinal fluid (CSF) OT levels correlate with negative symptoms (Sasayama et al., 2012). Moreover, three recent clinical trials found that two (Pedersen et al., 2011), three (Feifel et al., 2010), and eight (Modabbernia et al., 2013) weeks of intranasal OT administration significantly decreased positive and negative symptoms, although one three-week clinical trial failed to find any effects of intranasal OT on positive or negative symptoms of schizophrenia (Lee et al., 2013). Together, this suggests that OT administration may be an effective treatment for schizophrenia.

In addition to these promising effects of OT on the clinical symptoms of schizophrenia, several studies have found that OT administration has positive effects on multiple aspects of social cognition in SZ, including automatic processes such as affect recognition (Averbeck et al., 2011; Goldman et al., 2011), and controlled processes such as theory of mind (Pedersen et al., 2011)). With regard to controlled social cognition, one study found that OT administration improved recognition of multiple emotions expressed on the face

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