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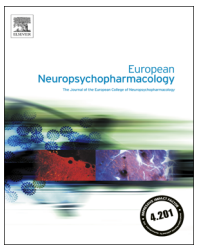

Oxytocin and social cognition in affective and psychotic disorders ☆

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Abstract
Impairments in social cognition are now recognized as core illness features in psychotic and affective disorders. Despite the significant disability caused by social cognitive abnormalities, treatments for this symptom dimension are lacking. Here, we describe the evidence demonstrating abnormalities in social cognition in schizophrenia, major depressive disorder, and bipolar disorder, as well as the neurobiology of social cognition including the role of oxytocin. We then review clinical trials of oxytocin administration in psychotic and affective disorders and the impact of this agent on social cognition. To date, several studies have demonstrated that oxytocin may improve social cognition in schizophrenia; too few studies have been conducted in affective disorders to determine the effect of oxytocin on social cognition in these disorders. Future work is needed to clarify which aspects of social cognition may be improved with oxytocin treatment in psychotic and affective disorders.

1. Introduction

Social cognitive abnormalities have recently been recognized as a core feature of mood and psychotic disorders (Billeke and Aboitiz, 2013; Cusi et al., 2013; Millan and Bales, 2013; Wolkenstein et al., 2011). Indeed, they are a critical obstacle to recovery and function (Brune et al., 2007) (Couture et al., 2006; Harvey and Bowie, 2012; Roncone et al., 2002), may cause more disability than

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psychosis (Doop and Park, 2009; Hooker and Park, 2002; Malaspina and Coleman, 2003; Perlick et al., 1992), and are only modestly improved by currently available medications (Goldberg et al., 2007; Green, 2006; Harvey and Bowie, 2012; Maat et al., 2014; Millan et al., 2014). Moreover, social cognitive impairments persist during remission (Inoue et al., 2004; Montag et al., 2010) and are present in those with subclinical symptoms (Cusi et al., 2013) as well as in drug-naïve patients (Wang et al., 2008). Evidence suggests that abnormalities in social cognition may be distinct from broader cognitive and perceptual deficits known to exist in affective and psychotic disorders (Billeke and Aboitiz, 2013; Harvey and Bowie, 2012; Lee et al., 2005; Montag et al., 2010).

Intact social cognition is critical for social functioning and interpersonal relationships (Tomasello et al., 2005). *In addition, social cognitive abilities are important for successful engagement in many psychological interventions* (Inoue et al., 2004). *Although social cognitive impairment has been found to persist during periods of remission, there is also evidence to suggest that this impairment may become worse as the illness progresses. For example,* social cognition impairment correlates with illness load (i.e., illness duration and symptom severity) (McKinnon et al., 2010), supporting the need for early intervention. It is also associated with lower social functioning (Couture et al., 2006; Inoue et al., 2006), higher disability (Cusi et al., 2013), and poor prognosis. Specifically, alterations in social cognition are associated with lower social adjustment (Couture et al., 2006) and global functioning, as well as higher relapse rates (Inoue et al., 2006). As these deficits are known to persist in the remitted state, patients may still have poor social adjustment due to impairments in social cognition even during symptomatic remission from affective or psychotic episodes (Inoue et al., 2004).

Despite the clinical significance of social cognitive impairment, pharmacological treatment for this core illness feature is not currently available. Several lines of evidence suggest that the neuropeptide oxytocin may be a potential treatment for social cognitive deficits across diagnoses (Bakermans-Kranenburg and van, 2013; Gumley et al., 2014). Here, we review the evidence for social cognitive abnormalities in mood and psychotic disorders as well as the clinical trials of intranasal oxytocin administration across diagnoses and evaluate the evidence for improvement of social cognition across disorders.

1.1. Definitions and components of social cognition

Social cognition may be defined as the "psychological processes that enable individuals to take advantage of being part of a social group" (Frith, 2008), and it is crucial for maintaining social relationships (Eisenberg and Miller, 1987). Therefore, it is not surprising that social cognitive abnormalities are associated with impaired social functioning, and, more broadly, decreased global functioning and disability. Social cognition can be conceptualized as a multidimensional construct encompassing different subcomponents which can be broadly summarized into five areas: theory of mind (ToM), social perception, social knowledge, emotion recognition and causal attribution style (Green and Leitman, 2008; van Hooren et al., 2008; Ochsner, 2008, Mancuso et al., 2011).

Theory of mind (*ToM*), also called mentalization or mentalizing, refers to the ability to represent others' mental states and to make inferences about others' intentions. It is a broad ability which involves the capacity to understand feelings, intentions, beliefs and metaphors (Brüne, 2005), and is closely related to the Research Domain Criteria (RDoC) (Insel et al., 2010) subconstruct "Understanding Mental States" within the Perception and Understanding of Others Construct in the Social Processes Domain.

Social perception refers to the ability to infer social roles as well as rules in complex and/or ambiguous situations from nonverbal and paraverbal social cues (Penn et al., 2002; Toomey et al., 2002). It also includes the capacity to determine the nature of the relationship between people such as professional, friendly, or romantic.

Partially overlapping with social perception, *social knowledge* refers to the awareness of rules and behaviors that are expected in social situations and/or interactions. Social perception and social knowledge are closely linked as a correct perception of social rules is necessary in order to determine what rules to adhere to in different social contexts (Green and Leitman, 2008).

Emotion recognition indicates the ability to perceive and identify emotion by facial expression and/or vocal prosody (Edwards et al., 2001). Emotion recognition closely overlaps with the RDoC (Insel et al., 2010) subconstruct "Reception of Facial Communication," within the Social Communication Construct in the Social Processes Domain.

Attributional style refers to the tendency of an individual to assign causality to events in his or her life, including whether this causality is internal or external. Healthy people usually have a self-serving bias in which they tend to attribute positive events to personal, internal factors and negative events to external causes (Miller and Ross, 1975).

Although these domains are generally accepted as representing the construct of social cognition, their boundaries cannot be considered absolute and considerable overlap exists between them (Green and Leitman, 2008). For example, the concept of empathy, which is considered to be a component of social cognition, is a complex multidimensional process that involves both cognitive and affective mechanisms (Achim et al., 2011) and taps into several of the above mentioned social cognitive domains.

Overlapping neural structures and systems subserve social cognitive processes. Primary sensory areas and more specialized structures (e.g. the fusiform face area) are involved in social perceptual processes (e.g. Sabatinelli et al., 2011). Emotion processing is regulated in part by the amygdala which, in turn, interacts with the insula and with the anterior cingulate cortex and the orbitofrontal cortex (e.g. Meyer-Lindenberg and Tost, 2012). Social attribution processes are partly mediated by the ventral premotor cortex, the superior temporal sulcus, the amygdala and the insula, whereas ToM abilities are subserved by the anterior medial prefrontal cortex and the temporoparietal junction (Meyer-Linderberg and Tost 2012). In addition to these somewhat distinct features, there are many more common structures and circuits that are involved in each