Oxytocin and Schizophrenia Spectrum Disorders

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Abstract  In this chapter, we present an overview of studies of oxytocin (OXT) in schizophrenia and the schizophrenia spectrum. We first outline the current state of pharmacological treatment of the symptoms of schizophrenia and point to unmet clinical needs. These relate particularly to the debilitating negative symptoms and social cognitive deficits that are frequently observed in patients suffering from schizophrenia. We argue that new treatments are needed to alleviate these impairments. As OXT has been proposed and investigated as a putative treatment, we will then summarise evidence from studies in patients with schizophrenia that have investigated the effects of OXT at several levels, i.e. at the levels of clinical symptoms, social cognitive function as assessed with experimental and neuropsychological tasks, and brain function as assessed using functional magnetic resonance imaging (fMRI). Finally, we will introduce the concept of the schizophrenia spectrum and highlight the importance of studying OXT effects in subclinical spectrum samples, such as in people with high levels of schizotypal personality. We conclude that the evidence of beneficial effects of OXT in schizophrenia is inconsistent, calling for further research in this field.
Keywords  Brain function • Negative symptoms • Oxytocin • Schizophrenia • Schizotypy • Social cognition

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1 Schizophrenia: Current Pharmacological Treatments and Unmet Clinical Needs

Schizophrenia is a severe neurodevelopmental disorder that occurs in 0.7–1% of the general population and carries a huge economic burden worldwide (Wittchen et al. 2011). Schizophrenia is a syndrome of unknown aetiology that consists of a heterogeneous constellation of signs and symptoms (Insel 2010). The most common form of schizophrenia entails positive symptoms such as paranoid delusions and auditory hallucinations that arise in late adolescence or early adulthood (Insel 2010). Additionally, negative symptoms such as anhedonia and amotivation have long been considered a cardinal feature of schizophrenia (Kring et al. 2013; Kring and Barch 2014).

Despite the fact that the conventional system for establishing a proper clinical diagnosis of schizophrenia leans heavily on positive symptoms such as delusions and hallucinations, it is ultimately the negative symptoms that predict prognosis as well as functional and occupational outcome in this patient group (Brüne et al. 2011; Rabinowitz et al. 2012). The stress brought on by negative symptoms such as social withdrawal and isolation can lead to drug-seeking and self-medication attempts to alleviate social deficits, presenting a kind of downward spiral into greater social and economic ruin (for a review, see Millan et al. 2016). Despite considerable advances of pharmacological treatment in schizophrenia with third-generation antipsychotics such as aripiprazole, negative symptoms, particularly anhedonia and amotivation, have remained largely treatment-refractory (Mucci et al. 2016) and often develop early in the course of the disorder, several years before the onset of the first psychotic episode (Fusar-Poli et al. 2013).

Patients with schizophrenia furthermore exhibit a wide range of social cognition impairments including emotional perception, empathy, theory of mind, and cognitive biases (Penn et al. 2008; Green et al. 2015). Social cognition deficits have been shown to contribute to 25% of the variance mediating the functional outcome in schizophrenia (Schmidt et al. 2011). Frustratingly, despite often being able to control the positive symptoms of schizophrenia, negative symptoms, especially...
anhedonia and amotivation, and (social) cognition deficits remain a great challenge to treat, with only limited available treatments to significantly impact prognosis (Carpenter and Koenig 2008; Insel 2010).

2 Oxytocin Effects on the Clinical Symptoms of Schizophrenia

Recent advances in affective and cognitive neuroscience suggest that OXT, a neuropeptide that interacts with key neuromodulators such as dopamine and serotonin, may be effective in enhancing social and affective functions in healthy people and could have prosocial effects in patients with schizophrenia (Bukovskaya and Shmukler 2016; Shilling and Feifel 2016). OXT is a nine-amino-acid peptide hormone and neurotransmitter that is now widely recognised as having an important role in social bonding, social interaction, and fear extinction in both animals and humans (Meyer-Lindenberg et al. 2011; Kirsch 2015). On the one hand, OXT is peripherally (hormonally) active following its synthesis in the hypothalamus and release from the posterior pituitary into the blood. Additionally, OXT functions centrally as a neuropeptide at OXT receptors in subcortical regions such as amygdala, olfactory nucleus, globus pallidus, and ventral pallidum, as well as cortical regions such as anterior cingulate cortex, regions known to be associated with both the social brain system and the reward-related system (Boccia et al. 2013; Kirsch 2015).

Despite the anticipated potential of OXT in treating the negative symptoms and social cognitive deficits of schizophrenia (Shilling and Feifel 2016), recent meta-analyses of the therapeutic effects of OXT on clinical symptoms and social cognition in schizophrenia have shown somewhat conflicting results (Hofmann et al. 2015; Oya et al. 2016; Williams and Bürkner 2017a; see also Williams and Bürkner 2017b). This inconsistent state of the literature could be due at least in part to differences in methodology. Whereas OXT was moderately more effective in alleviating psychiatric symptoms versus placebo when using conventional univariate meta-analytic methods (Hofmann et al. 2015; Oya et al. 2016), this was not the case in a further meta-analysis (Williams and Bürkner 2017a). When using multivariate meta-analytical methods, clinical symptoms did not significantly differ following OXT administration and there was moderate evidence that intranasal OXT had no effect on negative symptoms (Williams and Bürkner 2017a).

However, in addition to differences in statistical methodology, it could be that the effect of OXT is difficult to quantify due to how it shapes the course of schizophrenia. The spectrum of neurotransmitters is extremely wide throughout the course of disease development and progression, and complex interactions are present between neurotransmission and environmental and genetic factors (for a review, see Millan et al. 2016). OXT most likely plays a role in both disease formation at a very early stage prior to diagnosis via abnormal signalling but also...
at a later, more comprehensive stage of social cognition and the individual’s interaction with his or her social environment (see Fig. 1; from Millan et al. 2016). Therefore, the effects of OXT on clinical features of schizophrenia could be more dependent on an interactive and global context, perhaps shaping an individual’s overall perception and reaction to social environment in the long term and as a mediator of more function-specific neurotransmission via other peptides. Indeed, the meta-analyses using conventional univariate methods found that OXT’s effect on negative symptoms was dependent on administration interval (i.e. daily versus on the day of training) (Hofmann et al. 2015; Oya et al. 2016), whereas the analysis by Williams and Bürkner (2017a) did not include the interval time as a moderator in their multivariate meta-analysis. The dependence of OXT effects on administration interval supports the notion that OXT plays a more complex role than an effecter of acute change in specific clinical symptoms, instead likely acting as a mediator of further neurotransmission.

Importantly, however, most of the studies included in the meta-analyses adopted traditional clinical ratings that did not incorporate the most recent two-faceted construct of negative symptoms, i.e. anhedonia/motivational and expression (Blanchard and Cohen 2006). The Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al. 2013) was specifically designed in accordance with the current state in the affective neuroscience of anhedonia and addresses the limitations of conventional clinical tools for assessing negative symptoms in schizophrenia (Blanchard et al. 2011; Kring et al. 2013). As mentioned above, social cognition is a crucial realm in which patients with schizophrenia commonly struggle and for which there is a lack of effective treatments, and OXT could present an adjunct to further pharmacological or psychotherapeutic treatment. Future work drawing upon recent developments in clinical neuroscience and appropriate assessment tools is needed.

3 Oxytocin Effects on Social Cognition in Schizophrenia

It is well documented that social cognitive deficits contribute to social dysfunction in patients with schizophrenia (Couture et al. 2006, 2008; Schmidt et al. 2011; Ho et al. 2015). Specific facets of social cognition identified as impaired include emotion perception, empathy, theory of mind, and cognitive biases (Penn et al. 2008; Green et al. 2015). Alterations in activation patterns in medial prefrontal cortex, superior temporal sulcus, and temporo-parietal junction have been observed in patients during theory of mind tasks (Brunet-Gouet and Decety 2006; Bosia et al. 2012). In empathy tasks, patients with schizophrenia have also shown reduced activation of middle/inferior frontal gyrus and insula (Russell et al. 2000) as well as left medial prefrontal cortex (Lee et al. 2006).

Recent findings have shown that theory of mind and empathy comprise both cognitive and affective components (Shamay-Tsoory et al. 2007; Sebastian et al. 2012). For theory of mind, cognitive components include making inferences about
Fig. 1 Model of mechanisms implicated in the development of schizophrenia. **Note:** The figure is taken from Millan et al. (2016) and depicts the core pathophysiological mechanisms postulated by Millan and colleagues to underlie the development of schizophrenia. Figure reprinted with permission. **Abbreviations:** CRT cognitive-remediation therapy, DA dopamine, DCS direct current stimulation, DISC1 disrupted in schizophrenia 1, E–I excitatory–inhibitory, Glu glutamate, HPA hypothalamic–pituitary–adrenocorticotrophic, miRNA microRNA, mGluR metabolic Glu receptor, mTOR mammalian target of rapamycin, NCAM neural cell adhesion molecule, PAMs positive allosteric modulators, rTMS rapid transcranial magnetic stimulation, SHANK3 SH3 and multiple ankyrin repeat domains protein 3. *Signalling molecules include cannabinoids, serotonin, oxytocin and neurosteroids.*
others’ beliefs and intentions, whereas affective components include making inferences about others’ emotions (Shamay-Tsoory et al. 2007). In terms of psychological processing, affective theory of mind is similar to the cognitive component of empathy, as both require inferring the emotions of others (Sebastian et al. 2012). Benedetti et al. (2009) adopted a comic script task (Völlm et al. 2006) that captured both theory of mind and empathy in patients with chronic schizophrenia and found impaired activations in left temporo-parietal junction and temporal pole.

There is also growing evidence for olfactory dysfunction in people with schizophrenia (Cohen et al. 2012; Moberg et al. 2014). This is relevant to the study of OXT effects in schizophrenia, as socio-affective and interpersonal deficits in schizophrenia may express themselves not only in clinically detectable negative symptoms, but may also become apparent as relatively subtle alterations in basic communicative-perceptual functions that underlie social interactions and their disturbances. One such alteration is that of the olfactory system, an evolutionarily ancient mechanism that is a foundation for various aspects of interpersonal relations and social perception.

A recent meta-analysis (Moberg et al. 2014) found that patients with schizophrenia demonstrated significant deficits of medium-to-large effect size across a wide variety of olfactory tasks. Schizophrenia patients had lower odour identification accuracy, lower odour detection threshold sensitivity, poorer odour discrimination and odour memory, and impaired odour hedonic judgements compared with healthy individuals (see also Brewer et al. 2001, 2003; Malaspina et al. 2002; Malaspina and Coleman 2003; Szeszko et al. 2004; Moberg et al. 2006; Strauss et al. 2010). A structural neuroimaging study (Turetsky et al. 2003) reported that poorer odour identification correlated with reduced volume of the entorhinal cortex. Schizophrenia patients with olfactory agnosia were also found to display hypo-activation of thalamic regions (Clark et al. 1991) and right-sided hypo-metabolism of frontal and medial temporal regions when they performed olfactory identification tasks (Malaspina et al. 1998).

In healthy humans, one-off administration of exogenous OXT has been shown to improve fundamental social and affective functions, including social stress, anxiety, memory, interpersonal affiliation and bonding, the ability to recognise emotions, trust, and empathy (for review, see Kirsch 2015). In schizophrenia, a number of studies have investigated the effects of OXT on olfaction. Lee et al. (2013) conducted a randomised, double-blind, placebo-controlled pilot study to examine the effect of intranasal OXT on olfactory identification as well as positive and negative symptoms in schizophrenia. After receiving adjunctive intranasal OXT 20 IU or placebo twice daily over 3 weeks, the patients receiving OXT showed significant improvement in odour identification on the University of Pennsylvania Smell Identification Test (UPSIT) relative to patients receiving placebo. Improvement was driven largely by improvement in the identification of pleasant odours.

Woolley et al. (2015) adopted a randomised, double-blind, cross-over design to investigate therapeutic effects of intranasal OXT 40 IU on olfactory detection for lyral (a pleasant odour) and anise (specifically sensitive to menstrual cycle phase in women) in out-patients with schizophrenia and healthy controls. Whilst patients did
not differ significantly from controls in detection of either odour when given the
placebo, OXT administration significantly and selectively improved olfactory
detection thresholds for lyral but not for anise in patients. These findings again
support the important role of OXT in olfactory hedonic processing of pleasant
odours in schizophrenia.

Incorporating a wider range of measures to specifically capture hedonic identi-
fication and judgment, Strauss et al. (2015) examined the association between
plasma OXT levels and measures of olfaction and social outcomes in out-patients
with schizophrenia and healthy controls. Patients had higher plasma OXT levels
and lower overall UPSIT accuracy than controls. Patients experienced significantly
more negative emotionality than controls in response to olfactory stimuli. Lastly,
lower plasma OXT levels were associated with poorer accuracy for pleasant and
unpleasant odours and with greater severity of asociality in schizophrenia patients.

In a systematic review of OXT effects on social cognition in schizophrenia
(Bukovskaya and Shmukler 2016), plasma OXT levels were found to correlate
with schizophrenia patients’ ability to identify facial emotion (Goldman et al.
2008), social cognition (Averbeck et al. 2012), and social withdrawal (Kéri et al.
2009). Intranasal OXT has also been associated with fear recognition (Goldman

While these findings are important in improving our understanding of both OXT
effects and the pathophysiology of social cognitive deficits in schizophrenia, many
of the previous studies were limited either by only collecting behavioural data (see
below section on brain function), often with relatively small sample sizes, or only
including patients with chronic schizophrenia, and none have examined the neural
mechanisms of OXT effects on theory of mind and empathy in schizophrenia.

4 Oxytocin Effects on Brain Function in Schizophrenia

Despite the evidence of beneficial effects of exogenous OXT on behavioural,
emotional, and social cognitive functions in healthy individuals and schizophrenia
patients (Kirsch 2015), surprisingly little is known about the effects on brain
function in schizophrenia. At the time of writing, only one published fMRI study
on the impact of OXT on brain function in schizophrenia patients seems to be
available (Shin et al. 2015).

The study by Shin and colleagues observed OXT effects in the amygdala that
depended on both task (negative or positive emotional stimuli) and group (patients
or controls). Although it provided important first evidence in this field, the study
employed a relatively small sample size (\(N = 16\) patients, \(N = 16\) controls) with
variable disease status in the patients, introducing clinical heterogeneity, and did
not focus on other aspects of socio-affective processing. Thus, much more remains
to be found with regard to the effects of exogenous OXT on brain function in
schizophrenia. Relevant clues come from studies of healthy individuals. A number
of studies have shown that OXT administration reduces amygdala activation,
although group- and task-dependent effects in other areas of the “social brain” may also be observed (Bartholomeusz et al. 2015; Kirsch 2015).

Overall, it is apparent that more research is desperately needed to elucidate the neural effects of OXT during social cognitive and affective functions, but also during the resting state (Smucny et al. 2014; Sheffield and Barch 2016), in patients with schizophrenia.

5 Oxytocin and the Schizophrenia Spectrum

A growing body of work from both clinical and non-clinical scientists has shown that schizophrenia is not, despite its clinically important and reliable categorical diagnosis according to ICD and DSM, a binary phenotype (present, absent). Instead, there is substantial agreement that intra- and inter-individual continua play an important role in improving our understanding of the aetiology of the disorder (van Os et al. 2009; David 2010; Insel 2010; Nelson et al. 2013). One prominent approach to the inter-individual continuum of schizophrenia is found in the field of schizotypy research (Nelson et al. 2013; Ettinger et al. 2014).

Schizotypy refers to a constellation of personality traits that resemble the phenotypic expression of the symptoms of schizophrenia at a subclinical level. Schizotypal traits cluster into three dimensions, including the cognitive-perceptual (positive), disorganised, and interpersonal (negative) dimensions (Raine 2006), similar to the symptom structure of schizophrenia (Liddle 1987). Social and interpersonal difficulties represent a prominent dimension of dysfunction in schizotypy and likely reflect core neurobiological processes genetically related to schizophrenia (Tarbox and Pogue-Geile 2011).

In addition to the apparent phenomenological overlap with schizophrenia, there is substantial evidence of overlap of schizotypy with schizophrenia in terms of (1) genetic and non-genetic aetiological influences, (2) cognitive, perceptual, and (oculo-)motor disturbances, (3) brain structural and functional alterations, and (4) pharmacological response (Nelson et al. 2013; Ettinger et al. 2014).

However, despite this overlap between schizophrenia and schizotypy and the acknowledged importance of the spectrum approach (van Os et al. 2009; David 2010; Nelson et al. 2013), no published evidence is available on the effects of exogenous OXT in schizotypy, indicating that future studies in this area are sorely needed.

Indirect evidence for a potential role of OXT in schizotypy comes from findings that blood levels of OXT positively correlated with overall and negative dimension schizotypy scores in healthy females (Tseng et al. 2014). While OXT levels may negatively correlate with symptom scores in schizophrenia patients (Rubin et al. 2010), positive correlations with schizotypy scores are compatible with higher OXT levels in association with depression, especially in combination with interpersonal deficits (Parker et al. 2010) and social anxiety (Hoge et al. 2008). Of note, measures of both anxiety and depression traits are closely related to schizotypy (Macare et al.
and are of relevance to negative symptoms and social cognition. However, there may be discrepancies between peripheral and central OXT levels (Kirsch 2015), thus direct OXCT challenge studies in schizotypy are urgently needed.

### 6 Conclusions

In this chapter we have provided an overview of the possible role of oxytocin in the adjunctive treatment of schizophrenia. Due to limitations of space, this review should not be considered to be exhaustive. The conclusions that may be drawn from this overview are given below.

First, it is apparent that the treatment options for schizophrenia need improving. OXT has been dealt as a promising candidate for improving the social cognitive deficits of this disorder. However, evidence from clinical studies is inconsistent at present. We have acknowledged the complexity of interactions between the disease process, genetics, and environmental factors that any (pharmacological) treatment of schizophrenia encounters. Future studies using refined methods drawing upon neuroscientifically informed clinical assessments are needed. Second, social cognitive functions are reduced in schizophrenia, causing significant impairment in everyday life. There is evidence that OXT improves social and affective functions both in healthy individuals and in people with a diagnosis of schizophrenia. Third, the neural mechanisms mediating effects of OXT on social cognitive or affective processes in schizophrenia are essentially unknown, with more research needed. Finally, while there is good evidence of a continuum between schizophrenia and schizotypy, no evidence is available on OXT’s effects on psychological or neural processes in individuals with high levels of schizotypy. Again, more work is needed.

Future studies of OXT effects in schizophrenia may also benefit from incorporating genetics. Specifically, the inconsistencies in the clinical literature on OXT effects in schizophrenia may be in part due to differences in genetic makeup, which may affect the response to OXT (Bartholomeusz et al. 2015). Thus, pharmacogenetic designs may be important in order to explain variance in OXT response.

Finally, future studies should also address in detail to what extent sex mediates response to OXT. Biological sex is a primary domain of variation to consider in biomedical research. However, much preclinical and clinical research has typically included only male humans or animals, or has failed to identify the biological sex of the subjects (Tannenbaum et al. 2016; Brooks and Clayton 2017). The importance of sex differences in biomedical research has recently been acknowledged by the National Institutes of Health (US) in their notice on “Consideration of Sex as a Biological Variable in NIH-funded Research” (notice number NOT-OD-15-102).

To conclude, there is evidence, albeit inconsistent, of beneficial effects of OXT on the symptoms and social cognitive deficits in schizophrenia. Although this evidence can be considered promising, more work is clearly needed to provide a
more detailed and comprehensive picture of OXT effects in the schizophrenia spectrum.

References


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