A Review of Oxytocin's Effects on the Positive, Negative and Cognitive Domains of Schizophrenia

Supplemental Information

COGNITIVE DEFICITS (Note: Please see Main text for references in this section)

To facilitate research and drug discovery into the cognitive abnormalities associated with schizophrenia (SCZ), the NIH-funded Measurement and Treatment Research to Improve Cognition in SCZ (MATRICS) initiative identified 7 specific domains of cognitive impairment in patients with this debilitating disorder; visual and verbal learning and memory, attention/vigilance, working memory, reasoning and problem solving, information processing speed and social cognition (1).

Preclinical Studies of OT's Effects on Cognitive-Like Deficits

Numerous reports have implicated oxytocin (OT) in social cognition deficits (see (60, 61) for recent reviews). The majority of these studies are consistent with the facilitation of social recognition by OT in rodents and non-human primates. For example, Popik *et al.* found that OT infusion into the rat medial preoptic area facilitated social recognition (62). A seminal finding in this area showed that OT knockout (KO) mice failed to recognize familiar conspecifics even after repeated encounters (63-65) and this deficit was remediated by infusion of OT into the medial amygdala (66). Consistent with OT KOs, oxytocin receptor (OXTR) KO mice also exhibited social recognition deficits (67, 68). Most recently, Feifel *et al.* found that acute peripheral administration of OT restored social recognition in a strain of rats that display a natural deficit in this behavior (unpublished data). In non-human primates, intranasal (IN) OT attenuated attention to negative facial expression in rhesus monkeys (69).

There have been only a few reports on OT's effects in MATRICS-relevant animal models of non-social cognition. For example, Tomizawa *et al.* reported that OT improved long-lasting spatial memory in mice through a mitogen-activated protein kinase (MAP) cascade (70). On the other hand, OT infused into the rat nucleus basalis of Meynert inhibited spatial learning (71). Most recently, Feifel *et al.* discovered that peripheral OT facilitated latent inhibition (LI) in Brown Norway rats that exhibit a natural deficit in this parameter (72). Importantly, LI is considered by MATRICS to be a good candidate animal model for the attention/vigilance domain impaired in SCZ (73).

Along these lines, the Cognitive Neuroscience Treatment Research to Improve Cognition in SCZ (CNTRICS) initiative has chosen baseline prepulse inhibition (PPI) as a candidate model for gain control: an important construct of perception (1). In this respect, Feifel *et al.* reported peripherally administered OT attenuated natural PPI deficits in the Brown Norway rat (74). In an earlier study, this group found that the second generation antipsychotic drug clozapine—but not the first generation antipsychotic drug haloperidol—improved PPI in Brown Norway rats suggesting that OT's facilitation of PPI is not related to its inhibition of dopamine functioning (75). In contrast to findings consistent with therapeutic-like effects of OT on PPI, Huang *et al.* recently reported that 21 days of IN OT had no effect on PPI in male mice (46); however this finding is difficult to interpret since it was not determined whether a single dose of OT facilitates PPI in mice.

Aside from effects on the above-mentioned cognitive-like domains, numerous studies over the last four decades suggest that OT modulates memory processes in a variety of species including rats, and mice (76, 77). These memory effects, notably, vary based on the paradigm studied. For example, in rodents acute OT improves memory consolidation in a passive avoidance paradigm. However, it has long-term inhibitory effects on acquisition, retention, consolidation and retrieval (see (78) for review).

Exogenous OT Effects on Cognitive Deficits

Social Cognition Deficits

The effects of IN OT on social cognition in healthy subjects are reviewed in Evans *et al.* (79). In toto, these studies have consistently shown that a single administration of IN OT acutely enhanced the processing of social stimuli. Similarly, in SCZ patients, a single dose of IN OT enhanced recognition of emotion, sarcasm, deception and empathy (80-84).

Regarding the effects of chronic OT treatment on social cognition in patients with SCZ, IN OT twice a day for 2 - 6 weeks improved social perception and theory of mind (35) as well as fear recognition and the perspective-taking component of empathy (38). Similarly, Davis *et al.* (41) found that administering IN OT just prior to twice weekly social cognitive training for six weeks in patients with SCZ significantly enhanced the training's benefit on a subject's ability to detect empathic accuracy, an effect that lasted at least one month. In contrast, Cacciotti-Salja *et al.* found no benefit when OT was administered twice a day to SCZ subjects while they underwent 6 weeks of social cognitive training (40). The inconsistent effects of OT on the benefits of social cognitive training may have been due to differences in training methods employed by the two studies (40, 41).

Very recently, Shin *et al.* (85) produced the first report of effects of OT on neural activity associated with social cognition (facial emotion recognition) in SCZ. This group found a single dose of IN OT decreased amygdala activity for fearful faces and increased activity (fMRI) for happy faces, a result consistent with numerous other reports of changes in amygdala activity during emotional recognition tasks in normal controls (86). Putative brain circuits implicated in OT's effects on social cognition are displayed in Figure 1 (Main text).

Non-Social Cognitive Deficits

There is an overall dearth of reports on the therapeutic effects of OT on non-social cognitive deficits. In one study, OT improved a measure of learning and verbal memory (the California Verbal Learning Test) but not a test of working memory (Letter Number Sequence) in patients with SCZ (87). On the other hand, Michalopoulou *et al.* recently reported that a single dose of OT improved the "executive" component of working memory in patients with SCZ (88). As in all the studies reviewed, these contrasting results may be due to different dosages or duration of OT treatment employed (see study details in Table 2, main section), highlighting the important reality that optimal dose and dosing of OT are understudied.

ENDOGENOUS OT AND SCHIZOPHRENIA

(Note: Please see Supplemental References, below, for references in this section)

The Endogenous OT System and Positive Symptoms

Only a few reports have examined a relationship between pOT and positive symptoms in patients with SCZ (Table S1). For example, Rubin *et al.* reported female patients with higher pOT had less severe positive symptoms and overall psychopathology (1). In contrast, a more recent study by the same group found that higher pOT levels related to more severe positive symptoms (2).

It is important to note here that substantial evidence suggests that pOT levels may not reliably reflect CSF OT concentrations, and therefore may not be relevant to the behaviors of interest (3, 4), but see (5).

The Endogenous OT System and Negative Symptoms

Converging evidence is consistent with an inverse relationship between endogenous OT levels and negative symptoms of SCZ. For example, studies have shown that both pOT (6) and cerebrospinal fluid (7) levels of OT exhibit a negative correlation with PANSS negative subscale scores in male patients with SCZ. More recently, Strauss *et al.* also found that low pOT levels predict the severity of asociality in SCZ patients (8). Similarly, decreased pOT levels measured after trust-related interactions were associated with negative symptoms of SCZ, suggesting that decreased trust-related OT release may be associated with social withdrawal, isolation, and flattened affect in this disorder (9). As part of a growing literature on the clinical import of OT and OXTR gene variants (10), several genomic studies have found evidence for an association of OXTR and OT gene variants with the negative symptoms of SCZ. In this respect, OXTR gene variants rs237902 and rs53576 were significantly associated with PANSS negative symptoms scores (11) and emotional withdrawal (12), respectively. In addition, Souza *et al.* found that the OT gene variant (rs2740204) was nominally associated with negative symptoms (13).

The Endogenous OT System and Cognitive Deficits

Higher pOT levels in SCZ have been related to several parameters related to the cognitive domains discussed above: larger anterior hippocampal volumes, superior emotion recognition (14), more prosocial behavior in males & females and perception of faces as happier by females and controls but not males (15). In an approach-avoidance task, patients with SCZ with higher pOT levels exhibited increased avoidance of angry faces (16) suggesting that elevated levels of endogenous OT increased social awareness in patients with SCZ. Most recently, Strauss *et al.* reported higher that pOT levels were associated with better emotion recognition in controls and SCZ (female only) (17) and more accurate encoding of socially relevant information in SCZ Strauss *et al.* (18). On the other hand, Rubin *et al.* (2, 19) reported no difference in pOT levels between SCZ and control subjects and found that patients' OT levels were not related to clinical

symptoms or cognition. In genetic studies, the OXTR variants rs22544298 and rs2268493 were significantly associated with empathic concern (20) and poorer performance on a social cognition index, mentalizing and social perception in patients with SCZ (21), respectively.

Regarding non-social cognitive deficits, Frost *et al.* failed to find differences between pOT levels in SCZ and control subjects. However, in both groups, higher pOT levels were associated with superior processing speed, working memory, and social cognition (22).

Table S1. The Endogenous Oxytocin System in Patients with Schizophrenia: Relation to Symptom Domains

Authors	*N*	OT Parameter	Main Findings	Implications
Positive Symptoms				
Rubin *et al.* 2010 (1)	50 SCZ (27 M, 23 F) 58 CTL	pOT	Female patients with higher pOT levels had less severe positive symptoms and overall psychopathology	Sex differences in clinical course of SCZ (23, 24). Estrogen and prolactin regulate OT and OXTR expression (25-28)
Souza *et al.* 2010 (13)	140 M and F SCZ	OT and OXTR SNPs	Variants in the OXTR (rs237887) were nominally associated with positive symptoms	Supports a role for OT system in regulating positive symptoms
Rubin *et al.* 2013 (19)	38 SCZ (24 M, 14 F) 38 CTL	pOT	pOT did not differ between patients and CTL and were unrelated to severity of positive symptoms	Discrepant with (1)
Rubin *et al.* 2014 (2)	57 SCZ (M 35 F 22) 34 SCZA (M 15, F 19) 75 BP (M 24, F 8) 42 CTL	pOT	pOT did not differ between patients and CTL and were unrelated to severity of positive symptoms	Does not support a role of endogenous OT in manifestation of positive symptoms
Negative Symptoms				
Keri *et al.* 2009 (9)	50 SCZ (16 M, 34 F) 50 CTL	pOT	Low pOT after trust-related interactions were associated with negative symptom	Suggests endogenous OT counteracts negative symptoms
Souza *et al.* 2010 (13)	Vide supra	OT and OXTR SNPs	An OT gene variant (rs2740204) was associated with clozapine response and was nominally associated with negative symptoms	The endogenous OT system may mediate the effects of APDs (29, 30)
Sasayama *et al.* 2012 (7)	27 M SCZ, 17 M MDD 21 CTL	cOT	More severe negative symptoms (PANSS) related to lower cOT	
Montag *et al.* 2013 (11)	406 SCZ (285 M, 121 F) 406 CTL	OT and OXTR genes	Significant association between OXTR variant rs237902 and negative symptoms scores (PANSS), and OXTR variants rs53576 and rs237885 and SCZ	

Authors	*N*	OT Parameter	Main Findings	Implications
Haram *et al.* 2015 (12)	265 SCZ (Sex not indicated) 412 CTL	OT, OXTR, AVP, CD38 genes	Significant association between OXTR variant rs53576 and emotional withdrawal No significant associations between OT pathway gene variants and SCZ	Consistent with (11), suggesting a role for OXTR variant rs53576 in the negative symptoms of SCZ
Strauss *et al.* 2015 (8)	39 SCZ (28 M, 11 F) 21 CTL	pOT	pOT levels higher in SCZ compared to controls. Lower OT levels associated with greater severity of asociality in SCZ	
Jobst *et al.* 2015 (6)	41 M SCZ 45 CTL	pOT	More severe negative symptoms, e.g., emotional and social withdrawal (PANSS), related to lower pOT	
Cognitive Deficits				
Goldman *et al.* 2008 (14)	15 SCZ (6 PHS, 4 PNS, 5 NNS), 7 CTL	pOT	pOT increased in PHS patients compared to PNS or NNSA or controls, and higher pOT associated with greater accuracy in rating facial emotions pOT inversely correlated with anterior hippocampal volume	Along with (31), indicates potential of differential role of OT in various subtypes, especially PHS. PHS also exhibit impaired hippocampal function and structural pathology in amygdala, and anterior and lateral hippocampus
Keri *et al.* 2009 (9)	Vide supra	pOT	CTL subjects exhibited elevated pOT after trust related interactions, whereas subjects with SCZ did not	Suggests a defect in OT systems ability to respond to interactions promoting trust consistent with OT effects on facial affect recognition (31-36)
Rubin *et al.* 2010 (1)	Vide supra	pOT	In both sexes, patients with higher pOT exhibited more prosocial behaviors (PANSS)	Suggests endogenous OT promotes pro-social behavior
Rubin *et al.* 2011 (15)	48 SCZ (26 M, 22 F) 57 CTL	pOT	Higher pOT related to perceiving faces as happier in both female patients and CTL	Sex differences reported in other studies of pOT (37, 38) and in (39) but not other studies of IN OT (40, 41)
Montag *et al.* 2012 (20)	145 SCZ (91 M, 54 F) 145 CTL	OXTR gene	OXTR variant rs22544298 significantly associated with empathic concern	

Authors	*N*	OT Parameter	Main Findings	Implications
Rubin *et al.* 2013 (19)	Vide supra	pOT	pOT unrelated to cognition in SCZ	Association of endogenous AVP and worse cognition in untreated female but not male patients
Walss-Bass *et al*. 2013 (42)	60 SCZ (45 M, 15 F) 20 CTL	pOT	Significant correlations between social cognitive bias and pOT in control group and patients with SCZ with delusions. Social cognitive capacity only correlated with pOT in patients with SCZ exhibiting delusions	
Rubin *et al.* 2014 (2)	Vide supra	pOT	Higher pOT associated with better emotion recognition in healthy controls but not in proband or relative group	
Davis *et al*. 2014 (21)	74 SCZ (M 53, F 21)	OXTR gene	OXTR variant (rs2268493) was significantly associated with poorer performance on a social cognition index, as well as tests of mentalizing and social perception	
Frost *et al.* 2014 (22)	31 SCZ (sex not specified) 21 CTL	pOT	Higher pOT associated with superior processing speed, working memory, and social cognition	
Brown *et al.* 2014 (16)	28 M SCZ	pOT	In an approach-avoidance task, patients with SCZ with higher pOT levels exhibited increased avoidance of angry faces	Suggested elevated levels of endogenous OT increased social awareness in patients with SCZ
Strauss *et al.* 2015 (17)	41 SCZ (sex not specified) 22 CTL	pOT	Higher pOT levels associated with better emotion recognition in CTL and SCZ (female only)	Individual differences in endogenous OT predict emotion perception accuracy
Strauss *et al.* 2015 (18)	40 SCZ (28 M, 12 F) 22 CTL	pOT	SCZ had higher pOT compared to CTL. Fewer false positives for concrete items on SCRT associated with higher pOT in SCZ	In SCZ, accurate encoding of socially relevant information predicted by pOT

Authors	*N*	OT Parameter	Main Findings	Implications
Domain Not Specified				
Linkowski *et al.* 1984 (43)	12 SCZ (9 M, 3 F) 12 CTL	Plasma Np1	Basal NpI levels were decreased compared to CTL	
Beckman *et al.* 1985 (44)	28 M SCZ, 15 CTL	cOT	cOT increased in patients with SCZ and higher in patients on APDs (butyrophenones)	Relevance of cOT to central function in patients on APDs - see (45)
Legros *et al.* 1992 (45)	9 M SCZ, 14 M CTL	Plasma Np1	Basal NpI levels were decreased compared to CTL	
Mai *et al.* 1993 (46)	11 SCZ (sex not indicated), 10 CTL	Neurophysin staining in post mortem brain samples	Altered neurophysin staining in PVN, globus pallidus, substantia nigra in SCZ vs. CTL	Primarily untreated patients so not due to effects of medication
Glovinsky *et al.* 1994 (47)	40 SCZ (31 M, 9 F) 15 CTL	cOT	cOT levels did not differ within subjects based on APD status (treated or withdrawn), nor between SCZ and CTL	
Souza *et al.* 2010 (48)	179 SCZ (sex not indicated), 358 CTL	OT, OXTR genes	OT variants rs4813625 and rs3761248 nominally associated with SCZ	
Watanabe *et al.* 2012 (49)	1) 544 SCZ (290 M, 254 F), 674 CTL 2) 105 family based trios consisting of patients (59 M, 46 F) and both parents	OXTR gene	No significant associations in either the case control or trio study. Meta analysis detected nominal significance between OXTR variant (rs9840864) and SCZ	
Teltsh *et al.* 2012 (50)	1) Extended pedigree 25 SCZ spectrum, 31 unaffected family members 2) 52 families (90 SCZ, 96 unaffected) 3) 272 SCZ (177 M, 95 F), 273 CTL	OT, AVP genes	1) Two OT variants (rs4813626), (rs2740204) and one AVP variant (AVP3011589) significantly associated with SCZ 2) One OT variant (rs4813626) significantly associated with SCZ 3) One OT variant (rs4813626) significantly associated with male SCZ	One SNP (rs4813626) in OT gene significantly associated with SCZ in all three samples. However, its minor and major alleles in samples 2 and 3 were opposite to the extended pedigree in sample 1.

APD, antipsychotic drug; AVP, arginine vasopressin; CTL, controls; MDD, major depressive disorder; NNS, nonpolydipsic normonatremic schizophrenia; NP1, neurophysin for oxytocin; OT, oxytocin; cOT, cerebrospinal fluid oxytocin; pOT, plasma oxytocin; OXTR, oxytocin receptor; PANSS, Positive and Negative Syndrome Scale; PHS, polydipsic hyponatremic schizophrenia; PNS, polydipsic normonatremic schizophrenia; PVN, paraventricular nucleus; SCZ, schizophrenia; SCRT, Social Cue Recognition Test.

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