Adjunctive Effects of Acute and Chronic Administration of Intranasal Oxytocin on Cognitive Deficits in Schizophrenia

Irene J. Sue

University of Vermont
Adjunctive Effects of Acute and Chronic Administration of Intranasal Oxytocin on Cognitive Deficits in Schizophrenia

John Forbes Nash, Jr., one of the winners of the 1994 Nobel Memorial Prize in Economic Sciences, once wrote cautionary letters to embassies in Washington, D.C. with regards to his being pursued and conspired against by red-tied Communists. This conspiracy, entirely unfounded and untrue, was a result of paranoia: Nash suffers from schizophrenia — a chronic, severe, and significantly disabling neuropsychological disorder which affects approximately 1% of the general American population. While Nash was diagnosed at 33 years old, the average onset age of clinical symptoms of schizophrenia is approximately between the ages of 16 and 30. Such symptoms are generally categorized into positive, negative, and cognitive symptoms. The current discussion provides a brief overview of the psychopathology of schizophrenia, common pharmacological treatments for cognitive function deficits in the disorder, and emerging evidence for oxytocin’s potential role as an adjunctive pharmacological treatment for said deficits.

Psychopathology of Schizophrenia

The latest edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) exercises a dynamic approach which eliminates further differentiation of schizophrenia into subtypes (paranoid, disorganized, catatonic, undifferentiated, and residual) listed in DSM-IV, thereby accounting for the heterogeneity of symptom type and severity prominent in the disorder. According to DSM-5, clinical diagnosis of schizophrenia requires presentation of two or more of the following key symptoms: delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and negative symptoms (anhedonia, lack of motivation, social withdrawal, etc.). It is required that these symptoms to be continuously present for at least six months, during which one’s social and occupational functioning is severely compromised in comparison to that prior to the onset of the disorder. Additionally, the diagnosis is excluded if an individual presents
symptoms associated with schizoaffective and mood disorders, unless prominent delusions and/or hallucinations are present, or if such symptoms are a direct physiological consequence of recreational or clinical drug use.

Pharmacological Treatments

Traditionally, pharmacological treatments of schizophrenia have targeted general clinical symptoms and focused upon the central mechanisms of dopaminergic pathways. First-generation antipsychotics, commonly referred to as neuroleptics, were introduced in the early 1950’s. They included chlorpromazine (Thorazine) and haloperidol (Haldol), the former of which is no longer available in the United States. While both are dopamine (DA) D2 receptor-specific antagonists, these neuroleptics led to a wide range of central and peripheral side effects, such as dystonic reactions, Parkinsonian symptoms, and akathisia (citation removed). Second-generation antipsychotics, on the other hand, possess less D2 affinity, and therefore no longer solely utilize D2-receptor antagonism. Their usage has been found to demonstrate, relative to neuroleptics [section removed here] . . . .

The efficacy of these pharmacological treatments on negative symptoms of schizophrenia is similar to or exceeds that of neuroleptics; and the rate of relapse is likewise significantly decreased in comparison. In addition, while neuroleptics have been found to improve attention and short-term memory in 30% of patients with schizophrenia, second-generation antipsychotics have demonstrated significant enhancement in the same cognitive domains in 30% to 70% of patients with the disorder (Citations removed). It is this increased scope of pharmacological actions and effects that has encouraged researchers to explore and target other neurotransmitters and their actions; for example, oxytocin.

Oxytocin
Oxytocin (OXT) is a 9-amino acid peptide hormone which regulates lactation and uterine contraction in the periphery, and functions centrally as a neurotransmitter involved in multiple aspects of social behavior (Citations removed). It has been found that patients with schizophrenia demonstrate decreased baseline levels of OXT, which were then strongly associated with predictions of negative symptoms (Citations removed) and decreased ability in facial emotion identification (Citations removed). In addition, it has also been suggested that there exists a negative correlation between OXT levels in the cerebrospinal fluid and negative symptoms of male patients with schizophrenia (Citations removed).

OXT is therefore a potential candidate for treating clinical symptoms of schizophrenia. In a randomized, double-blind, and placebo-controlled study, clinically diagnosed schizophrenia patients were randomly assigned to receive intranasal OXT or matched placebo for 8 weeks (Citations removed). The treatment intervention consisted of 20 international units (IU) of the drug administered twice a day for the first week followed by 40 IU administered twice a day for the following 7 weeks. Additionally, the patients were also maintained on a stable dose of 5 or 6 mg/day of risperidone. During the 8-week treatment, the patients were assessed using the Positive and Negative Syndrome Scale (PANSS) at weeks 0, 2, 4, 6, and 8. Adverse side effects of the drug treatment were examined using the Extrapyramidal Symptom Rating Scale (ESRS) at baseline and at weeks 1, 2, 4, 6, and 8. It was found that . . . . The authors concluded that . . . .

Other studies with shorter treatment durations have also reported similar beneficial results on clinical symptoms and cognitive function deficits in schizophrenia. In a randomized, double-blind, crossover study, 15 patients with schizophrenia, in addition to their stable dose of at least one antipsychotic prescribed prior to the study, received 3 weeks of daily intranasal OXT at 20 IU and another 3 weeks of daily intranasal placebo at the same dose (Feifel et al., 2010). These two treatments were separated by a 1-week washout period, and their order (OXT-placebo vs.
placebo-OXT) was randomly assigned to each subject. During the 7-week total study duration, subjects were evaluated 7 times: They were assessed using the PANSS, Clinical Global Impressions-Severity (CGS-S), and Clinical Global Impressions-Improvement (CGS-I). It was found that the OXT treatment, compared to the placebo, led to significantly reduced scores on the CGI-I and positive and negative subscales of PANSS.

Extension of the above study further demonstrated that adjunctive intranasal OXT might improve verbal memory in patients with schizophrenia (Feifel, Macdonald, Cobb, & Minassian, 2012). In addition to PANSS, CGI-S, and CGI-I, two memory tasks, the California Verbal Learning Test (CVLT II) and Letter Number Sequencing (LNS) task, were used to measure subjects’ cognitive function. The results showed that the 3-week intranasal OXT treatment did not lead to significant effect of drug on LNS scores; however, it did lead to significantly improved performance on total recall trials, short delay free recall, and total recall discrimination on the CVLT II. These findings thus add to the evidence supporting . . . .

Social Cognition Deficit in Schizophrenia

In addition to general cognition deficits, patients with schizophrenia also exhibit social cognition deficits, which can manifest as impairments in functional outcomes such as social skill, social behavior in the milieu, community function, and social problem-solving (Citations removed)). These impairments are further significantly associated with neurocognitive functions including verbal fluency and processing speed, verbal/visual learning and memory, and reasoning and problem-solving (Citations removed).

More specifically, growing literature on social cognition deficits in schizophrenia has suggested emotional-processing impairments as an endophenotype of the disorder, especially with regards to facial emotion recognition, which is generally assessed by presenting Ekman and
Freisen’s pictures (Citations removed) and administering the Facial Emotion Identification Test (FEIT) and Facial Emotion Discrimination Test (FEDT). In the FEIT, subjects are instructed to recognize, or label, a presented facial expression; in the FEDT, they are instructed to discriminate, or differentiate between, two presented facial expressions. Patients with schizophrenia have been found to perform poorly on these and other tasks of similar nature. For example, in a study conducted by (citations removed), facial emotion recognition was examined in 50 patients with early-stage schizophrenia, 50 patients with chronic schizophrenia, and 50 healthy control subjects. All participants completed the Facial Emotion Recognition Test (FERT), which consisted of 36 still photographs of human faces displaying 9 fundamental emotions: excitement, joy, surprise, distress, disgust, contempt, anger, shame, and fear. It was found that patients with chronic schizophrenia, relative to other subject groups, demonstrated significantly greater difficulty in recognizing facial emotions, especially those representing negative affects.

This finding is furthered and somewhat contradicted by that found in a study conducted by (Citations removed). The study involved 79 ultra-high risk patients, 30 first-episode schizophrenia patients, and 30 healthy control subjects, all of whom completed a facial emotion recognition task which consisted of 21 posed photographs of faces representing 7 fundamental emotions: sadness, anger, happiness, disgust, surprise, fear, and neutrality. The authors found that both ultra-high risk and first-episode schizophrenia patient groups exhibited significantly greater facial emotion recognition deficit than did the healthy control group. Results from such studies thus lend support to the notion that facial emotion recognition deficit may be an endophenotype of schizophrenia; however, its independence from the stages of illness requires further investigation.

While facial emotion recognition and discrimination are primarily involved in bottom-up processing, there is also evidence which supports that top-down cognitive processing of emotions may also be impaired in schizophrenia. Theory of Mind (ToM), in context of the current disorder,
refers to impairment of one’s ability to relate his/her and others’ intentions with execution of behaviors (Citations removed). Deficits in ToM, therefore, may potentially lead to aforementioned psychopathology in schizophrenia (Citations removed). In a study which assessed ToM and emotion recognition, 23 patients with schizophrenia and 18 healthy control subjects completed several social cognition tasks and behavioral measures (Citations removed). The former assessed subjects’ performance on tasks related to ToM and facial emotion recognition. ToM was assessed by a series of 6 cartoon picture stories, and facial emotion recognition by 6 still photographs displaying 6 fundamental emotions: happiness, sadness, fear, surprise, anger, and disgust. The behavioral measures included the PANSS and Social Behavior Scale (SBS). It was found that patients with schizophrenia demonstrated significant impairment on all tasks related to social perception and cognition, and had much greater difficulty in recognizing deception and cheating detection and providing cogent answers to second- and third-order false belief questions. Such results contribute to the existing literature regarding social cognition deficits in schizophrenia.

Oxytocin and Social Cognition Deficits

In addition to alleviating symptoms of general cognitive deficits in schizophrenia, OXT has also been observed to provide beneficial effects on social cognition deficits in the disorder. In a randomized, double-blind, placebo-controlled trial conducted by (Citations removed), patients with schizophrenia self-administered 24 IU intranasal OXT or placebo twice daily for 14 days, during which they remained on their previously prescribed antipsychotic regimens. On the final treatment day, social cognition measures (the Brüne ToM Picture Stories Task and the Trustworthiness Task) and psychiatric measures (the PANSS and Paranoia Scale) were administered. It was found that the OXT group, consistent with previous findings reported previously, presented significantly reduced scores on PANSS. In addition, the results also
demonstrated that the OXT group performed significantly better in accurately identifying second-order false belief in the Brüne task.

Furthermore, it has also been shown that an acute, single dose of intranasal OXT may improve social cognition deficit in schizophrenia (Citations removed). In this randomized, double-blind, placebo-controlled, and crossover study, 48 healthy control subjects and 35 patients with schizophrenia, in addition to their prescribed antipsychotic regiments prior and unrelated to the study, received a single intranasal dose of OXT or placebo at 24 IU upon first administration, and the other treatment at the same dose upon second administration. 7 days later. The order of such treatments (OXT-placebo vs. placebo-OXT) was randomly assigned. Forty minutes proceeding the drug administration, the subjects were assessed using the Interpersonal Perception Task (IPT), which is a measure that assesses perception of nonverbal aspects of social exchange, such as facial expression, body language, and social meanings of statements. During the task, the subjects were presented with real-life scenes and situations, and instructed to make judgments about the relationship between individuals involved in 2 types of social interactions: kinship (familial relationships) and intimacy (romantic partnership). Subjects’ answers to questions posed after each scene constituted as measures of how accurately interpersonal judgments were made based on interpretation of verbal dialogues and nonverbal cues. The overall results showed that there was a significant effect of drug on recognition and judgment of both kinship and intimacy. However, when patients and control subjects were compared, such effect was only significant for the recognition of kinship in the patient group. The investigators thus concluded that an acute, single-dose administration of intranasal OXT might be instrumental in improving social cognition in schizophrenia.

A study conducted by (Citations removed) further investigated the effects of acute, single-dose administration of intranasal OXT. In this randomized, double-blind, placebo-controlled trial, 23 subjects on previously prescribed antipsychotic regimen received a dose of 40 IU intranasal
OXT or placebo, and were administered clinical and social cognition assessments. The clinical assessments included the PANSS, CGI-S, CGI-I, and MIRECC Global Assessment of Functioning (MIRECC GAF), the latter of which was used to specifically measure occupational and social functioning. Social cognition, in this particular study, was classified into lower- and higher-level processes, and assessed by 4 tests which represented 4 different social cognitive domains: ToM was measured by Part III of the Awareness of Social Inference Test (TASIT Part III: Social Inference-Enriched); empathy by the Emotional Perspective Taking Task (EPTT); social perception by the Half Profile of Nonverbal Sensitivity (Half-PONS); and facial affect recognition by FEIT. Lower-level social cognition included facial affect perception, social perception, and detection of lies; and higher-level social cognition involved empathy and detection of sarcasm and deception. The results showed that while this acute, single dose of intranasal OXT did not lead to improved performance on overall social cognitive function or clinical symptoms, there was a significant drug effect, relative to placebo, on higher-level social cognition. The authors therefore concluded that the effect of acute, single-dose administration of intranasal OXT might be specific to more complex social cognition.

While studies reviewed in the current paper have demonstrated beneficial effects of intranasal OXT on general and social cognitive functioning, it is crucial to remind oneself that specific mechanisms of drug interactions between OXT and typical antipsychotic drugs remain largely unknown. Long-term effects of adjunctive use likewise beg for further investigation. Additionally, while these studies have utilized PANSS as a standardized and reliable assessment of clinical symptoms of schizophrenia, there exists no similar behavioral measure in defining and identifying specific aspects of social cognition deficits in the disorder. Future studies should focus upon determining the potential drug interactions between OXT and currently available antipsychotics, and developing a standardized measure which can be utilized in evaluating social cognition deficits in patients with schizophrenia.
Work Cited


