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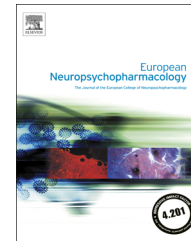Muldoon, Glennis
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SHORT COMMUNICATION

Effects of intranasal oxytocin on neural processing within a socially relevant neural circuit

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Abstract
Dysregulation of the Mirror Neuron System (MNS) in schizophrenia (SCZ) may underlie the cognitive and behavioral manifestations of social dysfunction associated with that disorder. In healthy subjects intranasal (IN) oxytocin (OT) improves neural processing in the MNS and is associated with improved social cognition. OT's brain effects can be measured through its modulation of the MNS by suppressing EEG mu-band electrical activity (8–13 Hz) in response to motion perception. Although IN OT's effects on social cognition have been tested in SCZ, OT's impact on the MNS has not been evaluated to date. Therefore, we designed a study to investigate the effects of two different OT doses on biological motion-induced mu suppression in SCZ and healthy subjects. EEG recordings were taken after each subject received a single IN administration of placebo, OT-24IU and OT-48IU in randomized order in a double-blind crossover design. The results provide support for OT's regulation of the MNS in both healthy and SCZ subjects, with the optimal dose dependent on diagnostic group and sex of subject. A statistically significant response was seen in SCZ males only, indicating a heightened sensitivity to those effects, although sex hormone related effects cannot be ruled out. In general, OT appears to have positive effects on neural circuitry that supports social cognition and socially adaptive behaviors.
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1. Introduction

The Mirror Neuron System (MNS), a neural circuit comprised of interconnections between inferior frontal cortex, inferior parietal lobule and superior temporal sulcus is implicated in supporting social functioning (Iacoboni and Mazziotta, 2007). Recent emphasis on connecting neuropsychiatric disorders with brain networks (Research Doman Criteria- RDoCs initiative) (Cuthbert and Insel, 2010; Singh and Feifel, 2013) has generated interest in studying the MNS in disorders with prominent social cognition and behavioral deficits.

Under controlled conditions, the MNS modulates 8–13 Hz oscillations over sensorimotor cortex (Keuken et al., 2011), such that exposing a subject to motion generated by a biological agent desynchronizes these baseline rhythms. This event related desynchronization or "mu suppression" (MS) is considered an operational measure of MNS function (Singh et al., 2011; Ulloa and Pineda, 2007). One experimental approach to interrogate MNS involves presenting subjects with point light animation videos (sparse visual representations of motion) that require filling in of context by the subject in order for the animated object to be perceived. Videos with biological motion (e.g. a person running) elicit greater MS than those with non-biological motion (e.g. moving circle) (Singh et al., 2011; Ulloa and Pineda, 2007).

Social dysfunction is a core feature of schizophrenia (SCZ). Recent studies have shown that SCZ subjects with poor social functioning exhibit weaker MS to biological motion, but not to other stimuli (Mehta et al., 2014), suggesting that a dysregulated MNS may underlie the social dysfunction of the disorder. Current antipsychotic drugs are unable to adequately reverse social dysfunction (Kucharska-Pietura and Mortimer, 2013), or MS abnormalities in SCZ despite demonstrated improvement in psychotic symptoms (Mitra et al., 2014). This underscores the need for treatments that regulate MNS activity in schizophrenia and other disorders associated with MNS dysfunction.

Oxytocin (OT) is a neurohormone with important effects on social behavior in mammals, including increasing trust, reducing fear, improving theory of mind and social memory (Meyer-Lindenberg et al., 2011). OT appears to affect biological motion detection (Keri and Benedek, 2009), and improves MS as shown in a study by Perry et al. (2010), in which a single 24IU dose of intranasal (IN) OT enhanced MS to biological motion in healthy controls (HC). Thus, it appears OT may sharpen the detection of socially relevant stimuli via regulation of the MNS. Though OT's effects on MNS function in SCZ patients has, thus far, not been directly investigated, we hypothesize that OT can remediate MNS dysregulation associated with this disorder. The current pilot study, therefore, investigated whether IN OT could enhance MS in response to biological motion in SCZ patients. Since both previously reported studies tested only 24IU-OT, (Keri and Benedek, 2009; Perry et al., 2010), we compared the effects of 24IU-OT and 48IU-OT to explore whether higher doses induce greater MS in HC and SCZ. The study was designed for efficient pilot testing using the National Institutes of Mental Health (NIMH) (http://www.nimh.nih.gov/funding/opportunities-announcements/clinical-trials-foas/index.shtml) guide lines to support "go/no-go" decisions on whether a larger study is justified for rapid translation. This approach allows for pilot testing to obtain an estimate of effect size to design and implement adequately powered studies. Therefore, a total of 32 subjects were recruited (detailed demographic information presented in the next section).

2. Experimental procedures

2.1. Participants

Men and women 18 years of age or older who met DSM-IV criteria for SCZ based on SCID interview were included. Subjects were on a therapeutic dose of an antipsychotic medication, with no changes in the 4 weeks prior to testing and were at least moderately ill (severity scores on PANSS and CGI-S). The mean daily chlorpromazine equivalent dose for subjects' antipsychotics was 201.8 +175.7 mg. A history of substance abuse or dependence in full remission and negative urine toxicology at screening was allowed but not other axis 1 disorders. HC subjects without any psychiatric disorders were included.

2.2. Medication administration

In a randomized, double-blind, cross-over design, all participants were pretreated with a single administration of IN placebo, low-dose OT (24IU) and high-dose OT (48IU) (compounded by UCSD investigational pharmacy) prior to viewing videos of biological and non-biological motion. Subjects received each drug condition in randomized order, separated by one OT-free week. Patients were maintained on their pre-enrollment antipsychotic regimen. OT or placebo was administered at $t=0$ and timer started for 45 min. During the first 10–15 min, EEG cap and electrodes were applied for testing. Subjects remained in a quiet room free of social stimulation until five minutes prior to end of timer. At this time, subjects were alerted to the fact that testing would begin soon. Presentation and stimuli were cued and testing started at 45 min post OT administration in all subjects.

2.3. EEG methods

After each IN medication administration a 32-electrode Biosemi EEG cap, 2 reference electrodes and 2 pairs of electrodes for eye movement (EOG) monitoring was applied to the subject's scalp (10-20 system), mastoid processes and eye region, respectively.

Subjects viewed 60–80 s videos of biological motion (person jumping rope), non-biological motion (rotating circle) and baseline condition (two moving balls) presented in random order (Detailed description (Singh et al., 2011). Both EEG and EOG were digitally amplified and sampled at 1024 Hz using the Biosemi Active II system. EEG data were processed with Brain Vision Analyzer (www.brainproducts.com) using 0.5 Hz high-pass filter (24 dB), artifact removal ($\pm100\,\mu V$ oscillations and first and terminal 10 s of recording); Remaining artifact-free segment was used to compute mu power in 8–13 Hz frequency using Fast Fourier Transform (FFT). FFT was performed at 0.5 Hz intervals, 2048 points per segment using a Hanning window. EEG data from 1 HC and 1 SCZ subject was not included in statistical analysis due to a mechanical failure that precipitated incomplete data collection.

EEG recordings from left (C3) and right (C4) sensorimotor cortex were used to calculate MS for each condition using the equation: log 10 (mu power of experimental condition/mu power during baseline condition) (Oberman et al., 2007; Singh et al., 2011). A log-transformed ratio was used to control for variability in absolute mu power due to individual differences in scalp thickness and electrode impedance. Mu suppression social index (MSSI) was calculated to obtain a quantitative measure that reflected OT's

specific effect on social motion processing (biological motion video) versus non-specific motion processing (non-biological motion video) by subtracting MS during non-biological condition from MS during biological motion condition. An MSSI$>$1 represented greater effect in MS on social vs. non-social motion processing.

2.4. Statistical analysis

MSSI data were analyzed using repeated measures analysis of variance (RM-ANOVA) with treatment (placebo, 24IU OT or 48IU OT) and electrode site (C3, C4) as within-subject variables and diagnostic group (HC, SCZ) and sex (male, female) as between-subject variables. SPSS Version 22 was used to calculate η^2 or Cohen's d to obtain estimates of effect sizes for RM-ANOVAs or t-tests, respectively. Significant omnibus results were followed by appropriate post-hoc testing. Correlations between daily chlorpromazine equivalents (antipsychotic dose) and OT induced MSSI over left and right sensorimotor cortex were investigated using parametric and non-parametric equations for each OT dose.

3. Results and discussion

3.1. Demographics

Fifteen HC (6 Males, 9 females) and 17 SCZ subjects (9 Male, 8 females) were enrolled. All subjects were able to self-administer nasal spray after receiving instruction, and completed all three visits. The only side effect reported was nasal congestion in one subject after treatment that resolved within 24 h. Sex ((χ^2 (1, $N=32$)=0.290, $p=0.6$) and age (CTRL- 37 years$\pm$15; SCZ- 47 years$\pm$16 (t, 30=3.0, $p=0.09$)) were not significantly different between groups. SCZ subjects had significantly fewer years of education

(13.9$\pm$2; (t, 25=4.0, $p\leq$ 0.01)), compared to HC (17$\pm$1 years of education), respectively.

3.2. Data analysis

There was a significant three-way interaction between treatment $\times$ sex $\times$ diagnostic group (F (2, 54)=4.1, $p\leq0.05$, $\eta^2=0.13$]), but no main effect of treatment (F (2, 54)=1.9, $p=0.16$, $\eta^2=0.07$) or electrode site (F (1, 27) =0.132, $p=0.7$, $\eta^2=0.01$). Treatment $\times$ sex $\times$ diagnostic group interaction, followed up by 2 factor RM-ANOVAs (treatment $\times$ diagnostic group) in males (F (2, 30)=2.2, $p=0.1$, $\eta^2=0.14$]) and females (F (2, 24)=2.0, $p=0.1$, $\eta^2=0.13$]) demonstrated medium effect sizes, though did not reach significance. Similarly, 2 factor RM-ANOVA for treatment $\times$ sex in HC (F (2, 24)=1.6, $p=0.2$, $\eta^2=0.12$) and SCZ subjects (F (2, 30)=2.7, $p=0.08$, $\eta^2=0.15$) also demonstrated medium effect sizes, but was statistically non-significant. Exploratory single factor RM-ANOVAs were carried out to parse out treatment effects in HC males, SCZ males, HC females and SCZ females separately (Figure 1). These tests revealed a significant treatment effect in SCZ males (F (2, 16)=3.6, $p<0.05$, $\eta^2=0.3$) with a large effect size. Single factor RM-ANOVAs in HC males (F (2, 8)=0.6, $p=0.5$, $\eta^2=0.15$), HC females (F (2, 16)=2, $p=0.2$, $\eta^2=0.2$) and SCZ females (F (2, 14)=1.1, $p=0.4$, $\eta^2=0.14$), revealed medium effect sizes, though did not reach statistical significance. Follow-up paired samples t-tests in SCZ males comparing placebo to 24IU (t (8)=1.0, $p=0.3$, Cohen's $d=0.4$) and 48IU OT (t (8)= -1.7, $p=0.1$, Cohen's $d=1.3$) revealed a large effect size at the higher dose, although
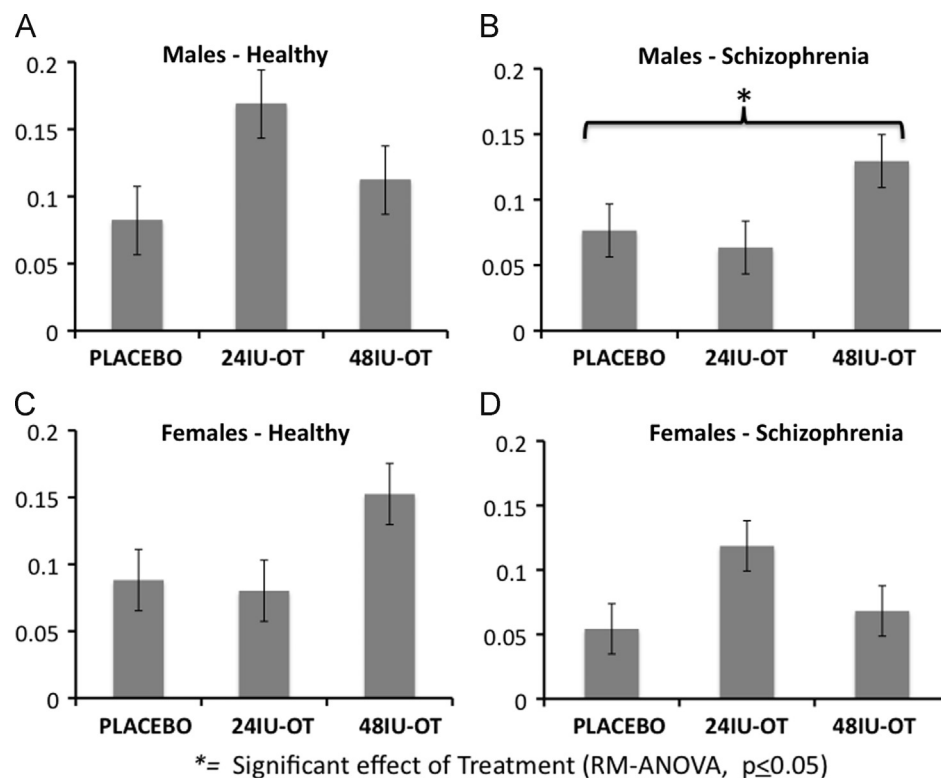

Figure 1   Mu Suppression Social Index (MSSI) As a Function of Oxytocin Treatment: This graph illustrates change in MSSI in response to single doses of IN Placebo, IN 24IU OT or 48IU OT in HC males, HC females, SCZ males and SCZ females.

statistical significance was not reached. Parametric correlations between daily chlorpromazine dose and OT induced MSSI over left and right sensorimotor cortex, respectively, to placebo, $(r(17)=0.12, p=0.6; r(17)=-0.35, p=0.2)$, 24IU OT $(r(17)=0.09, p=0.7; r(17)=-0.16, p=0.5)$ or 48IU $(r(17)=-0.2, p=0.4; r(17)=-0.26, p=0.3)$ did not reveal any significant correlations. Similarly, nonparametric correlations between antipsychotic dose and OT induced MSSI over left and right sensorimotor cortex, respectively, to placebo $(r_s(17)=0.04, p=0.9, r_s(17)=-0.2, p=0.4)$, 24IU OT $(r_s(17)=0.03, p=0.2, r_s(17)=-0.27, p=0.3)$ or 48IU OT $(r_s(17)=-0.26, p=0.3, r_s(17)=-0.37, p=0.1)$ did not reach statistical significance.

3.3. Conclusions

This is the first study to compare the effect of different OT doses on MS and the first to test the effects of OT on MS in individuals with SCZ. The results suggest that single doses of IN OT affect neural processing of socially-relevant information, and that the effects are influenced by gender and diagnostic group. OT's enhancement of MSSI reached statistical significance in SCZ males only, suggesting that this subgroup may be the most sensitive to OT's influence. Nonetheless, the lack of statistical significance in the other subgroups must be viewed in context of the highly limited power produced by dividing the sample in four sex/diagnosis subgroups. The medium treatment effect sizes in the three subgroups where treatment did not reach statistical significance supports the notion that small subgroup sample size contributed to the lack of statistical significance.

Perry et al. (2010) found that a single IN administration of 24IU OT can improve MNS function in healthy males (Perry et al, 2010) and in our study that dose (24IU) also produced a trend toward increased socially specific MS, but 48IU was less effective, indicating that higher doses do not produce a stronger effect (see Fig. 1). In contrast, healthy females' response trended towards greatest change in MSSI with 48IU-OT indicating a lower sensitivity to OT-induced enhancement of MNS function. In SCZ subjects the dose-sex relationship appears to be reversed, with women trending towards greatest biologically specific MNS facilitation in response to 24IU-OT, whereas men had the strongest response to 48IU.

3.4. Discussion

OT appears to influence men and women differently at the level of brain function and behavioral response. For instance, OT administration increases amygdala activation in women (Kanat et al., 2014; Riem et al., 2011; Rupp et al., 2014), but decreases it in men. In a small sample of patients with generalized anxiety disorder, men showed decreased anxiety with 3-week OT treatment, whereas women showed increased levels of anxiety (Olff et al., 2013). Differential responses to OT in men and women are particularly interesting, since women have higher prevalence of anxiety disorders (Schulte-Ruther et al., 2008), whereas men are at higher risk for autism and schizophrenia (Kanat et al., 2014) perhaps due to structural and anatomical differences in male and female mirror-neuron regions (Cheng et al., 2009). In addition, varying concentrations of endogenous sex hormones in male

vs. female, and premenopausal vs. postmenopausal women may also influence the presence and severity of SCZ symptoms. For instance, in premenopausal SCZ women, estrogens are associated with improved positive and negative symptoms (Heringa et al., 2015), whereas testosterone is associated with improved negative symptoms in SCZ males (Heringa et al., 2015). Additional considerations in women include differential responsiveness of the OT system depending on the stage of a woman's menstrual cycle. This was not controlled in the present study; therefore, it is plausible that differential EEG responses in the present study may have been modulated by sex hormones in addition to the influence of OT treatment.

In addition to sex specific effects, OT appears to have differential effects in clinical vs. healthy populations, such that clinical samples with pretreatment MNS deficits show a greater response than healthy subjects with intact MNS function. This is consistent with other findings, for example, IN OT improved subjective stress response and cortisol levels in a stress paradigm only in those subjects who had reduced coping and emotion regulation abilities, but not in subjects with normal function in these domains (Kanat et al., 2014). Similarly, IN OT had no effect in subjects with normal pretreatment empathic accuracy but improved empathic accuracy in less socially proficient individuals (Kanat et al., 2014).

Thus, the present study supports the growing body of literature on OTs differential brain effects. IN OT appears to increase socially-specific MS in SCZ subjects, particularly males, and therefore, provides preliminary support for the notion that it can remediate deficits in MNS-mediated social processing, in contrast to established antipsychotics (Mitra et al, 2014). Several studies have reported that IN OT enhances social cognition in patients with SCZ (Kanat et al., 2014) and enhancement of MNS function may underlie that effect. Limitations of this study include a small sample size, which limits the generalizability of our results. Building upon this work, additional studies with larger sample sizes will need to explore the effects of chronic OT administration on MNS function, social cognition and socially adaptive behaviors in disorders with social deficits. Special attention will need to be focused on effects of sex and endogenous sex hormone concentrations and their potential additive antipsychotic effects on OT.

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