# Enhancing Social Cognitive Training with Oxytocin: Linking Target Engagement to Clinical Effects

## NCT03245437

## Protocol

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## A. Significance -- R21 and R33

**A.1 Social Cognition as an Intervention Target** Serious mental illnesses such as schizophrenia are associated with impairments in the ability to process social information, referred to as social cognition. These impairments involve skills in detecting basic social cues, such as identifying emotions expressed in faces, as well as higher level skills involved in mentalizing, such as understanding the thoughts and feelings of others[1]. These impairments present an attractive target for intervention since they are associated with poor community functioning, including the ability to work, succeed in educational activities, and to sustain social relationships[2, 3]. In fact, social cognition is more closely related to daily function than non-social cognition in schizophrenia [2]. It is likely that improving social cognition with psychosocial or pharmacological approaches will have clinically important effects on the serious social disabilities that limit the potential of these individuals. Although research from a number of groups [4, 5] – including our own [6] – has had promising results with training interventions for social cognition, these approaches have limited efficacy. This has convinced us to develop a research program that focuses on strategies for improving the potency of social cognition training. As noted below (section C.2.1), our initial results with intranasal oxytocin (OT) showed promise [7] for enhancing the effects of social cognition training.

**A.2 Limitations of Social Cognition Training** Social cognition comprises a group of processes that can be applied to understanding and responding to social information[2]. A recent consensus process [8] identified four core domains: emotion processing, social perception, theory of mind/mental state attribution, and attributional style/bias. Studies of training interventions for social cognition in schizophrenia (reviewed in [9]) found that the such approaches are effective for improving social cue detection, such as facial emotion identification skills[6, 10]. However, these approaches were relatively ineffective for inferential processes such as mentalizing and theory of mind. Given the severe impairments in processing social information in schizophrenia and their impact on social functioning it is plausible that a medication that can improve the training of mentalizing would result in substantially better social functioning. As described below in C.2.1, we hypothesized that these higher order processes would be aided by a pharmacological agent that helped patients to allocate more neural resources to social information. In our pilot study [7], we administered intranasal OT or placebo thirty minutes prior to a social cognition skills training (SCST). The findings from that trial were mixed in that patients in both the OT and placebo groups improved in their abilities in social cue detection. This was not surprising since we previously found that these abilities responded well to our training intervention[6]. We did find an effect of OT on our measure of empathic accuracy (described in section C.2.2d ) but not on a measure of theory of mind (The Awareness of Social Inference Test /TASIT). Since the abbreviated form of training we used in that trial included training in empathy, but not theory of mind, we interpreted our findings as indicating that OT's effects were on the learning of mentalizing skills. Since the abbreviated form of the intervention we used in that trial included training in empathy, but not theory of mind, we interpret our findings as indicating that OT's effects were on the learning of mentalizing skills. This encourages us to systematically explore ways that we can pharmacologically improve the training of patients with impaired social cognition.

We emphasize that our approach focuses on the facilitation of learning that occurs during training sessions. There is already some evidence that intranasal OT in single doses [11] or with chronic dosing [12] can result in improved social cognition. However, here we chose a substantially different, and potentially valuable, approach. Specifically, we posit that OT can enhance learning and the resulting improvements will be sustained even when the subject is drug-free. In our pilot study we evaluated social cognition domains one week and one month after the last administration of OT. The advantages of OT on empathic accuracy were seen at both times supporting our interpretation that OT was improving learning.

**A.3 Oxytocin effects on brain** Oxytocin is a peptide hormone that plays an important role in regulating mammalian social behaviors [13]. In animals, OT has been shown to support the formation of attachment bonds [14]. These effects are paralleled in healthy humans for whom OT can have prosocial effects that include improving trust and cooperation [15]. These prosocial effects have encouraged a number of groups to explore exogenous OT as a therapeutic agent for psychiatric disorders that are associated with impairments in social behaviors, including autism and schizophrenia.

OT has very poor passage through the blood brain barrier. As a result, oral and intravenous administrations are not effective for increasing brain levels. Evidence from rodent studies supports a direct

pathway through which intranasally administered OT diffuses directly to the brain [16]. It is also plausible that OT affects behavior through an indirect route by causing central release through a peripheral mechanism [17]. Although the exact path from nose to brain is not clear, there is compelling evidence that intranasal OT has effects on areas of the brain that have been linked to social behaviors. For example, studies using functional MRI have shown that the administration of OT can have effects on socially-relevant brain areas including the amygdala [18] and the ventral tegmental area [19].

The inability to use peripheral blood to estimate brain levels of OT has been an important impediment for clinical research with OT. As a result, important decisions for clinical trials, including dose and duration of drug action, have been based on very limited information. This is a substantial problem since studies in animals indicate that the dose-response of OT differs for different behavioral effects with some showing inverted-U shaped dose responses[20]. In addition, it has been difficult to explain why some individuals respond to OT and others do not. The R21 phase of this proposal will evaluate promising indicators of OT's effects on the brain, specifically examining the dose-response relationship for our proposed psychophysiological target measures of neural engagement. If these responses are reliable and valid indicators of OT's brain activity, they have the potential for facilitating treatment development by providing information for dosage selection, duration of drug effects, and identification of non-responders. This proposal will not be able to link OT to a particular receptor – such an approach to target engagement will only be feasible when a PET ligand for the OT receptor is identified. However, our proposed approach can indicate that intranasally administered OT has entered the brain and engaged a social processing network.

**A.4 Oxytocin and Social Salience** The R21 and R33 phases are designed to improve our understanding of the neurobiology underlying one of OT's properties; that is, OT's ability to increase the salience of social information [19]. For the purposes of this proposal we define social salience as the bias of the individual toward allocating cognitive resources toward social information. If both social and non-social stimuli are present, greater social salience would lead the individual to demonstrate what appears to be a greater preference for social over non-social information. The evidence that OT increases social salience comes from a number of sources. In sheep, OT promotes the selective olfactory recognition of offspring [21]. In humans, administered OT increases gaze toward eye regions [22] which are probably the most socially communicative part of faces. Moreover, studies with fMRI [23] found that this tendency toward increasing gaze to the eye is associated with an increased coupling of amygdala and superior colliculi activity. This supports the view that OT biases an individual toward social visual information. OT also improves the encoding of positive social memories [24], and improves empathic accuracy [25]. The measures of target engagement in this proposal – EEG mu suppression during biological versus non-biological motion and pupil dilation while detecting social information – both reflect allocation of neural resources to social information. This proposed study also includes measures of social preference as indicators of social salience. By evaluating the relationship between OT target engagement and social preference, this research program may contribute to our understanding of how OT affects human social behavior.

**B. Innovation – R21 and R33**

**B.1 Novel methods for studying OT's target engagement** The selected measures of target engagement – EEG mu suppression while observing biological motion and pupil dilation during an emotion recognition task – are plausibly related to how the brain focuses attention on social information. These methods are supported by our pilot data (which is summarized below, C1.e-f) and, if validated in the R21, will represent a methodological advance for OT clinical research.

**B.2 Approach to Dose-Response of OT** Decisions about the dose of OT have been largely based on trial and error. The measures of target engagement provide a unique and innovative approach for modeling the dose-response of OT. Moreover, our use of multiple doses of OT in the R21 maximizes the information available for understanding dose-response.

**B.3 Focus on OT's effects on learning** Our innovative approach to studying OT is focused on how it can affect learning. First, we are focused on an acute effect of OT and not administering drug chronically. This addresses a concern from preclinical studies which indicate that the increases in social behaviors following acute administration of OT are lost with chronic administration [26]. Second, subjects in our study will only receive OT prior to training sessions and social cognition measures will only be assessed days after OT administration when the drug has washed out of the system. As a result, observed improvements will be attributable to OT's effects on learning rather than to direct drug effects on social cognition.

**B.4 OT and social salience** The design of the R33 has the potential to link OT's effects on social cognition training to our measures of target engagement in brain and to our proposed measures of social salience. This has the

potential to advance OT as a therapeutic agent for impaired social cognition. In particular, it would indicate that patients with impairments in a brain system related to the attribution of social salience may benefit from OT.

**B.5 Social salience as a mediator of improvement in social cognition** An exploratory component of this project is the inclusion of social preference paradigms as indicators of social salience. Although somewhat speculative, we will be able to test the intriguing possibility that improvements in social cognition in people with psychosis come about because of changes in the salience of social information in their environment. This possibility, if supported, would focus rehabilitation efforts on enhancing the engagement value of social stimuli for individuals with social processing deficits.

## C. Approach

### C.1. R21 Approach

**C.1.a Measures of Target Engagement** For the purposes of this study, we selected measures that were suitable for clinical trials. That is, their administration is relatively inexpensive and results in modest subject burden. We considered an fMRI measure of target engagement of OT, but concluded – because of cost and subject burden – that it would not be feasible to include this in the R33 phase of the program. The proposed measures, pupil dilation during an emotion recognition task and mu suppression while observing biological motion, measure brain responses that are plausibly related to OT's effect on how subjects process social information. That is, pupil dilation appears to measure the allocation of resources to detecting social information and EEG mu suppression appears to measure the activation of the mirror neuron system which is important for processing social information.

**Pupil dilation during an emotion recognition task** Pupillary responses have been used for decades to examine cognitive and social processing. The muscles responsible for constricting or dilating the pupil receive input from the parasympathetic and sympathetic nervous systems, respectively. Pupil dilation occurs in response to *increased* sympathetic activity as well as in response to *decreased* parasympathetic activity [27]. Phasic increases in pupil dilation can be stimulus- or task-driven, with larger pupil diameter reflecting greater processing demands [28]. Pupil diameter also increases in response to emotional arousal that is not valence-specific, reflecting sensitivity to processing of emotionally-laden stimuli [29]. Two recent studies have examined the effects of OT on pupillary responses to emotionally-laden stimuli. In the first, Leknes et al. [30] found that the administration of a single intranasal dose of OT to healthy volunteers resulted in greater pupil dilation than placebo when subjects were engaged in a task that required the recognition of emotional expressions. In the second, Prehn et al. [31] examined pupillary responses in healthy men when viewing faces depicting various emotions, and found that OT improved performance compared to placebo during a dynamic facial recognition task. Moreover, larger pupil dilation was correlated with better task performance. Both groups interpreted their findings as indicating that the pupil response indicated greater allocation of resources to social information.

**EEG mu suppression while observing biological motion** The mirror neuron system (MNS) is hypothesized to reflect the brain's ability to map visual representations of others' actions onto the motor representations in the observer of the same actions, an important mechanism underlying the capacity to understand and imitate social actions [32]. The MNS can be assessed in humans through EEG measurements of neural oscillations in the mu range (8-13 Hz). While mu rhythms overlap in frequency with the more commonly known alpha rhythms (most apparent when the brain is "at rest"), they can be distinguished from alpha based on where on the scalp they are seen. Mu rhythms are typically seen over central scalp sites, overlaying sensorimotor cortex, whereas alpha rhythms are typically seen over occipital scalp sites. Mu rhythm amplitudes are largest when a person is at rest and *decreases* in amplitude when that person moves, observes movement, or even simply imagines moving [33]. This decrease in amplitude is called mu suppression and reflects engagement of the MNS. Mu suppression has been seen in response to a variety of stimuli, including point-light walkers depicting biological motion [32, 34]. Given that OT has been shown to increase responding to social stimuli, Perry et al. [35] examined its effects on mu suppression in healthy students when viewing stimuli depicting biological motion. The results of this study found greater mu suppression within a narrower frequency band (8-10 Hz) when subjects viewed point light biological motion than when they viewed non-biological motion (consisting of moving dots depicting a circle). Perry et al. also found that single doses of OT led to greater suppression of mu oscillations than placebo while subjects observed a point light display of a human walking.

**C.1.b Social Processing in Psychiatric Disorders** Impairments in social cognition cross diagnostic boundaries. For this research program we elected to limit the sample to diagnostic groups that had been studied using social cognition training programs that were similar to the system we plan to employ. Such studies have focused mostly on schizophrenia and schizoaffective disorders. Previous work from our group

[36] found that many patients with bipolar illness had relatively preserved social cognition. As a result, we restricted the sample to include only non-affective psychotic disorders.

**C.1.c Study Subjects:** Subjects will be 48 outpatient men and women 18 to 55 years old with non-affective psychotic disorders (schizophrenia, schizoaffective disorder, and delusional disorder) who are in a stable condition on antipsychotic and other medications. Stability criteria will include no recent hospitalizations within the six months prior to study entry and no changes in psychiatric medication or dosage changes greater than 10% within the past three months. Inclusion criteria will also include ability to provide informed consent, without serious medical conditions, and without recent substance use disorder. Exclusion criteria will include a positive pregnancy test, unstable medical conditions, history of serious head injury, and hyponatremia. Women will be excluded who are sexually active and not using an effective form of contraception. We will recruit subjects from a number of sources including the UCLA Psychosis Clinic which is led by the PI, the West Los Angeles VA Healthcare Center, and community board and care facilities where we are able to distribute flyers describing the study. The VA site manages more than 2000 patients with schizophrenia and the UCLA Psychosis Clinic has approximately 120 patients. Including subjects with other non-affective psychotic disorders will increase the recruitment pool.

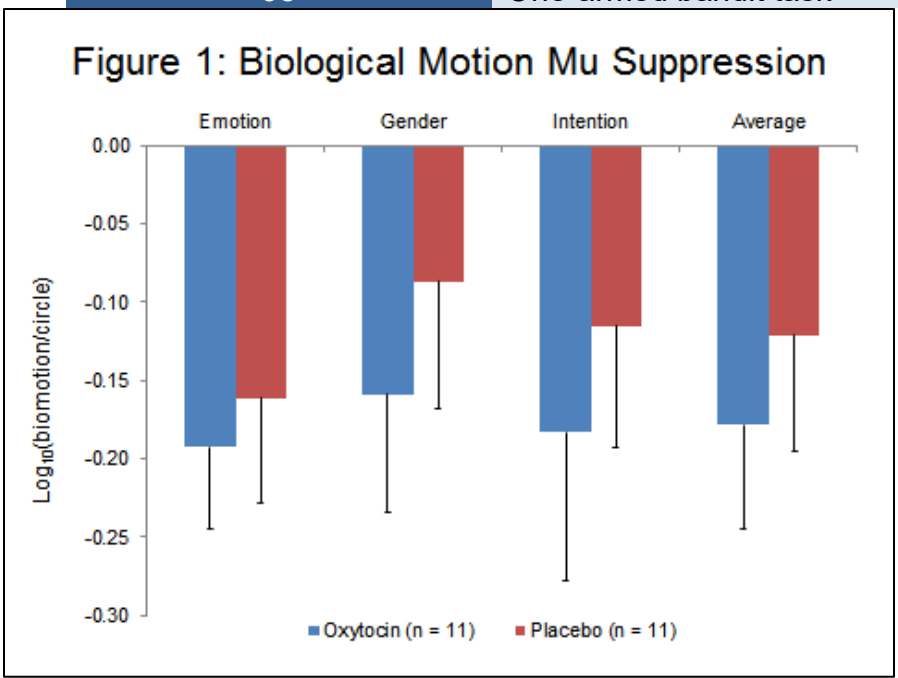
**C.1.d Study procedures:** Following an initial screening, subjects will be scheduled for a first visit during which informed consent will be obtained. Other assessments will include the Structured Clinical Interview for DSM-4 (SCID) modified for DSM-5 diagnostic criteria; a medical history; and a physical examination with laboratory tests including electrolytes and pregnancy tests for women. In addition, basic demographic information and a psychiatric history will be collected. One week later subjects will be randomly assigned to one of 8 dosing groups: 8, 12, 24, 36, 48, 60, 72, and 84 IU of oxytocin. (See Table 1)

| Table1: Study Events | Screening | Visit 1 (1 wk post screening) | Visit 2 (2 wk post screening) |
|---|---|---|---|
| **Screening, SCID, demographics, consent** | X | | |
| **OT Challenge** | | X | X |

**OT challenge** Each subject will participate in 2 OT challenges: one at the assigned dose and the other on placebo. The challenges will be separated by one week and will occur in randomized order. A single formulation of OT will be used and dose will be adjusted by the number of nasal sprays of OT or placebo. On the day of the challenge the study staff will observe the subject as he or she applies the assigned number of sprays of OT or placebo. We do not believe that subjects will be able to discriminate OT from placebo. In a prior study [11] subjects were unable to distinguish OT from placebo. The pupillometry, EEG, and social preference measures will be administered 30 minutes following OT or placebo administration in a standardized order (see Table 2).

**Table 2: Timeline of Oxytocin Challenge Procedures**

| Time (minutes) | Procedure |
|---|---|
| 0 | Drug administration, setting up of EEG electrodes |
| 30 | Biological Motion Mu Suppression |
| 45 | Pupillometry Task |
| 65 | Gaze-cuing task |
| 95 | One-armed bandit task |




**C.1.e. EEG Mu Suppression Task** To assess mu suppression, we will use a biological motion task in which subjects will be asked to identify either the gender, the emotion (happy or sad), or intention (moving towards or away) of a point-light walker. This paradigm has

been validated in a previous study to show greater mu suppression when viewing biological versus non-biological motion, and greater mu suppression when subjects were administered OT [37]. Stimuli consist of 5 s video clips. Each video clip contains all three dimensions, e.g. a clip can show a sad woman walking toward the observer, a happy man walking away, etc. Additionally, a non-biological motion clip will be used as a control stimulus, and consists of dots moving in a circle either to the left or right of the screen. Clips will be presented on a monitor approximately 70 cm from the participant. E-Prime will be used for stimulus presentation and for syncing of triggers with the EEG equipment.

Stimuli will be presented in four separate randomized blocks, with each block consisting of a separate task, requiring the subject to identify only one dimension (e.g., identify only gender, only emotion, only intention, direction of circle). A total of 23-26 clips per block will be administered. Twenty of the clips will be of one level of the dimension (e.g., male walkers) while 3-6 clips will be of the other level (e.g., female walkers). The participants are instructed to silently count the number of occurrences of the rare event and report this at the end of the block to ensure that they are attending to the task. This task will take approximately 15 minutes to complete.

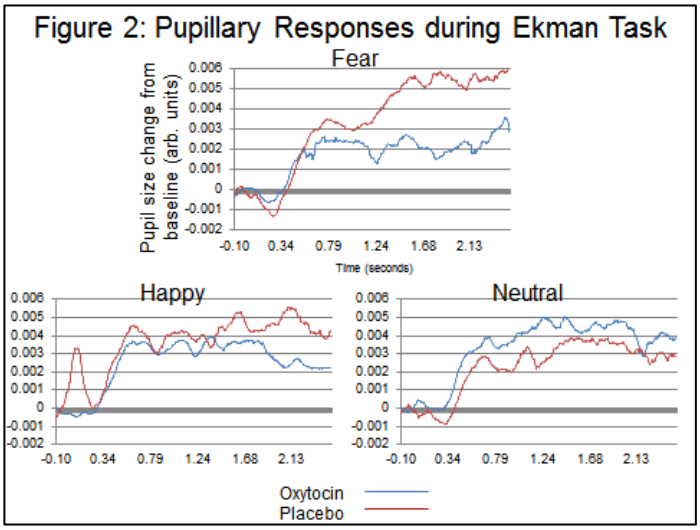
EEG data will be initially filtered with a 0.5 Hz high-pass filter and re-referenced to the mastoids. Eyeblinks will be corrected using standard algorithms [38]. Artifacts exceeding +/- 100 μV in amplitude at any electrode site will be rejected. As in prior studies the first 10 s of each block will not be analyzed to remove potential confounds of attentional shifts due to initiation of the stimuli [37, 39]. The first 2 s of each remaining 5 s clip will be analyzed [37]. A fast Fourier transform (FFT) using a Hanning window will be performed in 0.5 Hz intervals. Integrated power between 8-10, 10-12, and 15-25 Hz range will be assessed. Mu suppression will be calculated as the $\log_{10}$ ratio of the power during the biological motion clips relative to the moving circle clips. This ratio is intended to account for individual differences in EEG power as well as normalize ratio data that are not typically normally distributed. A negative number indicates mu suppression. Six electrode sites will be examined: C3, Cz, C4 (where mu suppression is expected), and O1, Oz, and O2 (where typical alpha modulation is seen).

EEG activity will be collected continuously throughout the session and amplified using a 64-channel BioSemi ActiveTwo amplifier (BioSemi, Germany). Data will be sampled at 1,024 Hz with filter settings of DC to 100 Hz. Sixty-four cap-mounted Ag-AgCl electrodes will be positioned using a modified international 10-20 system placement scheme. Additionally, four electrodes will be used to measure horizontal electrooculogram (EOG; placed on the outer canthus of the left and right eye) and vertical EOG (placed above and below the left eye). All electrodes will be referenced using common mode rejection during EEG recording and rereferenced offline to linked-mastoids. Data will be processed using Brain Vision Analyzer 2.

**Pilot Data:** We collected pilot data in 11 stable schizophrenia patients who were receiving an antipsychotic medication. After we obtained informed consent, subjects were administered 40 IU of OT or placebo in randomized order on 2 occasions separated by one week. The mu suppression paradigm was administered approximately 30 minutes following the nasal spray. As can be seen in Figure 1, mu suppression was greater than placebo in all three tasks, with an average effect size of d = 0.24.

**C.1.f Pupillometry Task** To assess pupil dilation to social stimuli, we will administer a facial affect identification task. This paradigm has been modified and adapted from previously published studies in healthy controls [40]. Stimuli will consist of male and female faces depicting happy, afraid, or neutral expressions, drawn from the Japanese and Caucasian Facial Expressions of Emotion and Neutral Faces dataset [41]. Additionally, the same stimuli have been scrambled to use as control stimuli. A dark grey background will be used throughout the experiment. Stimuli will be presented on a monitor approximately 70 cm from the participant. E-Prime will be used for stimulus presentation and for syncing with the pupillometry system.

Figure 2: Pupillary Responses during Ekman Task



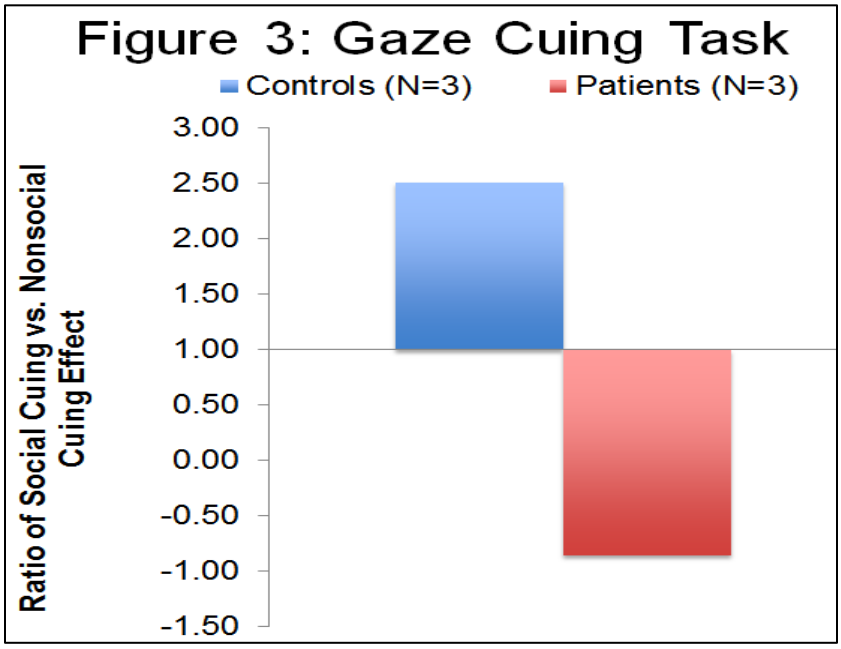

Sixteen of each stimulus type will be shown in a randomized order. Each trial begins with a 3 s fixation cross

followed by the presentation of the stimulus for 5 s. After stimulus offset, a screen will be shown with written options for type of stimulus. Participants will be instructed to not blink during the presentation of the fixation cross and stimulus. Once the choice screen appears they are instructed to identify which stimulus type was shown and they can blink freely. They can then initiate the next trial when they feel they will not need to blink. This task will take approximately 20 minutes to complete.

Pupillary responses from the right eye will be continuously recorded using a ViewPoint EyeTracker USB-220 (Arrington Research, AZ), using an infrared light source and infrared camera. The recording system will be connected to the presentation computer to synchronize trigger signals that indicate the beginning of a trial. Pupillometry data will be continuously recorded at 220 Hz and stored for offline data analysis. Pupillometry data will be analyzed with custom-written scripts in Matlab. Cleaning of data (e.g., removal of blinks) and data reduction will be accomplished following standard procedures [40, 42-44]. Briefly, data will be smoothed using a 20-point moving average filter. Eyeblinks, defined as changes in pupil size that are too large and rapid to represent actual pupil dilation or constriction, will be replaced by linear interpolation. Pupil diameter, measured as the average dilation over the 0.2 s preceding the onset of the stimulus, will be subtracted from pupil diameter after stimulus onset to produce a pupil dilation difference score: positive scores indicate dilation while negative scores indicate constriction. Stimulus-locked pupillary response will be averaged for each stimulus type. Data will be analyzed as the mean change in pupil size occurring between 0.8-2.5 s after stimulus presentation.

**Pilot Data:** Pilot data are available for 8 stable schizophrenia patients on antipsychotic medication who received double-blind 40 IU of intranasal OT or placebo administered a week apart. We assessed the effects of OT on pupillary responses using the paradigm described above. First, we found that greater pupil dilation was seen to faces, compared to a scrambled face (data not shown), consistent with prior studies. Second, as can be seen in Figure 2, OT reduced pupillary dilation to fearful faces in comparison to placebo (d=.81), consistent with OT down-regulating amygdala activation to fearful faces [18, 45] and consistent with the one previously published paper showing less dilation on OT to fearful faces [31]. While the sample size is small, these pilot data demonstrate the expected pupillary response to faces and the feasibility of OT to influence pupil size.

**C.1.g. Social Salience measures** For the purposes of the R21 and the R33 we will use behavioral measures of social preference to assess social salience. The two tasks, a gaze-cuing task and a one-armed bandit task, assess social orienting and social reward, respectively, and both are considered indices of social salience. As noted below, recent work in our laboratory indicates that individuals with schizophrenia are less likely than controls to show a preference for social cues.



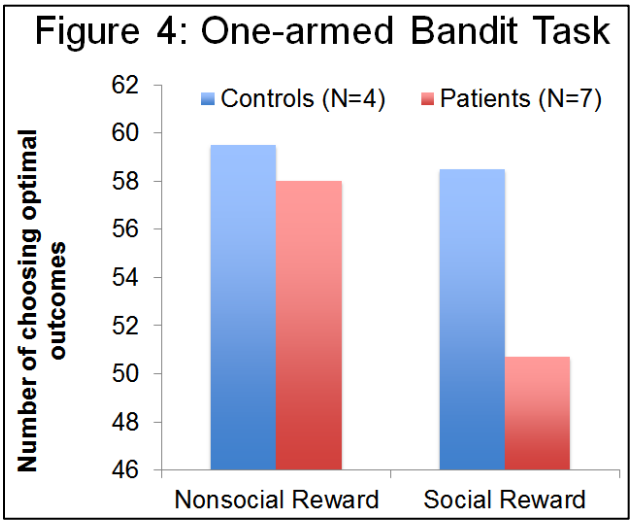

**Gaze-cuing task**: To assess social orienting, we will use a gaze-cuing task in which subjects will be asked to indicate the location of a target (the letter X in one of two peripheral boxes) following an uninformative central cue (either social or nonsocial) [46, 47]. The social cue will be a drawing of eyes gazing left or right; the nonsocial cue will be an arrow pointing left or right. On each trial a fixation cross will be presented for 700 ms along with two peripheral boxes (left and right), followed by the cue at the center of the screen for 150 ms. After cue offset, the target will appear and remain on the screen until a response is made. Subjects will be asked to detect the location of the target as quickly and accurately as possible; both accuracy and reaction time will be recorded. We will use 4 stimulus onset asynchronies (SOAs) between the cue and the target (i.e., SOA of 150, 250, 350, and 700 ms) to examine the time course of social orienting across SZ patients and controls as a function of the SOA. There will be 100 trials for each SOA per type of cue (social or nonsocial); there will also be 40 catch trials with a nondirectional cue to detect and exclude invalid

performance. Both social and nonsocial cues are uninformative, meaning that the direction of the cue will be consistent with the target location on half of the trials (congruent condition) and inconsistent on the other half (incongruent condition). The two types of cues will be randomly presented throughout the task. The difference between congruent and incongruent conditions is the cuing effect. The dependent measure typically used is the ratio of social and nonsocial cuing effects: a ratio greater than 1.0 shows preferential orienting towards social cues. This task will take 30 minutes to complete.

Pilot data: We adapted an existing task [46, 47] and collected pilot data with 3 controls and 3 schizophrenia patients who were stable on antipsychotic medication. As expected, controls showed a ratio greater than 1.0, indicating a preferential orienting for social cues. In contrast, patients showed a preference towards nonsocial stimuli (ratio <1.0) (Figure 3).

**One-armed bandit task**: To measure reactivity to social vs. nonsocial rewards, we will employ a one-armed bandit task [48, 49]. This task has two blocks with identical trial structures except for the type of reward (i.e., social or nonsocial). The order of the blocks will be counterbalanced across subjects. For the social reward block, we will use color photographs of unfamiliar faces from the NimStim collection [50], showing happy (positive outcome), angry (negative outcome) or neutral (neutral outcome) emotional expressions. For nonsocial reward, we will use: an image of a dollar bill (positive outcome), an image of a dollar bill crossed out (negative outcome), or an image of an empty rectangle (neutral outcome).

For each trial, after a fixation point (500 ms), two slot machines will appear: a "neutral" machine paired either with a "good" slot machine or a "bad" slot machine. A good slot machine has an 80% probability of a positive outcome and a 20% probability of neutral outcome; a bad slot machine has an 80% probability of negative outcome and a 20% probability of neutral outcome; and a neutral machine is always associated with neutral outcome. Subjects will have up to 2.5 seconds to choose the slot machine that will give them the optimal outcome. Then, the reward outcome will be presented for 1.5 s. The main dependent measure will be the total number of trials the subject chooses the machine with the optimal outcome (i.e., a good over a neutral machine; a neutral over a bad machine). Subjects will not be told the reward probabilities of each slot machine and need to learn them over the course of the task. All subjects will receive the same compensation regardless of their performance. This task takes 30 minutes to complete.




Pilot Data: We adapted an existing one-armed bandit task [48, 51] and piloted it with 4 controls and 7 stable schizophrenia patients on antipsychotic medication (Figure 4). For the social reward condition, the patients chose the optimal outcome much less frequently than the controls did; but the two groups did not differ on the nonsocial reward condition.

**C.1.h. Data Analysis:** The primary goal of the R21 phase is to determine the dose response curve to RT for mu suppression and pupillary response. Prior to modeling the form of the curves we will obtain descriptive statistics and graphical summaries for the measures of target engagement on placebo, at each of the active doses. We will also plot the within subject change scores and the overall dose-response curve. To formally determine whether there is target engagement we will fit a logistic dose response curve to the data for each of the outcome measures. We assume that the OT dose response curve can be adequately modeled using a 4-parameter model with a lower asymptote, slope, E50 (point of half of maximum response), and upper asymptote as the parameters. However, we will also fit a 5 parameter model that allows for an asymmetry in the acceleration and deceleration of the change slope to determine whether the additional parameter is necessary to represent the empirical dose response curve. Independent of which of the models for the dose response curve we finally choose we will determine whether there is target engagement by testing whether the upper asymptote is significantly different from zero using a z-test based on the parameter estimate and its standard error. Specifically this test allows us to determine whether there is a measurable change in the outcome variable of interest at the optimum dose of OT (where the upper asymptote is reached) while borrowing strength across all the measurement points. For the secondary aim, examining the relationship between target engagement and social salience we will use multiple linear regression models with the social salience measures as the outcomes and change in pupillary response and mu suppression in response (OT vs placebo) as the predictors, adjusted for OT dose.

Power: Calculations for the R21 Phase are based on the primary goal of detecting target engagement based on the OT dose response curves for mu suppression and pupillary response using a sample of size n=48. To estimate power we simulated 10000 replicate data sets following our study design (8 different doses of OT, with 6 observations at each dose) using the effect sizes from our pilot data on pupillary dilation and mu suppression, as well as the results reported in Prehn [31] for 47 normal participants on pupillary dilation, and the results reported in Perry [35] for mu suppression in 24 normal participants.. Specifically, the simulations conservatively assumed that the observed effect sizes represented the upper asymptote (i.e., that the optimal dose had been reached and observations at higher dosage levels than those employed in the respective studies would not show a stronger response). In addition, we assumed that the variances observed at 24, 36, 48, and 60 IU (the middle of the dose range where maximum change in the targets would be expected to occur) were as large as the variances reported in the studies, while the variances at the extreme ends of the range (8,12, 74 and 84 IU) were half of that. This is based on the patterns of variance heterogeneity common observed for dose response curves.

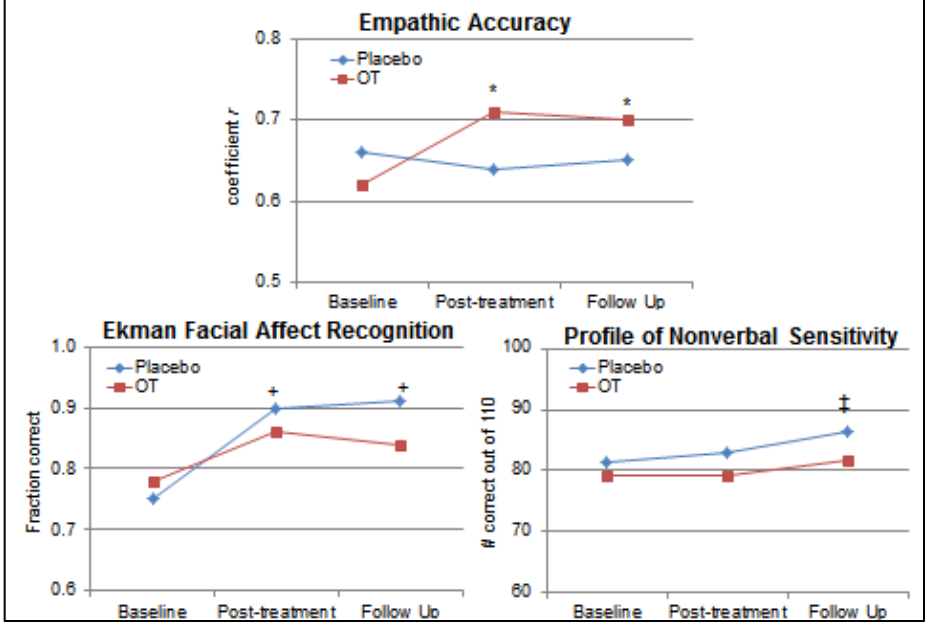
Under these assumptions the power for detecting a significant upper asymptote is 84% for pupillary response data that show an effect size of d = .81 at the optimal dose, equivalent to the results from our pilot data, and 92% using an effect size of d = 1.22, the average effect size reported in Prehn [31]. For mu suppression, the power is 89% for an effect size of d = 1.03 at the optimal dose, equivalent to the results in Perry (2010) and 45% for an effect of d = .24, the average effect seen across task conditions in our pilot data. These are extremely conservative estimates as we expect that these studies were not conducted at the optimal dose, and the estimate of measurement error is most likely inflated as it is based on observations in the steepest part of the dose response curve, where the response is least stable. The wide range of doses that is covered by our design ensures that we will be able to find a stable estimate for the optimal dose of OT.

**C.1.i. Go/No Go decision:** After all 48 subjects have completed the OT challenge, we will evaluate whether the dose response curves for pupillary response or EEG mu suppression show significant target engagement on OT relative to placebo. If there is a significant departure from placebo on either measure of target engagement, the R33 will be initiated.

### C.2. R33 Approach

**C.2.1 Background** A number of research groups – including our own [6] – have developed skills training methods for improving social cognition for individuals with psychotic disorders. We evaluated our approach in 68 subjects with psychotic disorders who were assigned to Social Cognition Skills Training (SCST) or control conditions. The SCST targeted emotional processing, social perception, attributional bias, and mentalizing (or Theory of Mind). Subjects were trained in groups of six to eight individuals twice weekly for 12 weeks. Subjects in SCST showed greater improvements in facial affect perception and emotion management.

Figure 5: Social Cognitive Performance – Measures Trained in SCST




As mentioned previously (A.2) this study is consistent with other trials – reviewed in [52] – which have found that social cognition training interventions are effective for improving cue detection, particularly emotion recognition. Training programs have been less successful for improving higher level inferential processes. We also evaluated a six week, 12 session version of SCST [7] in a study that included assigning schizophrenia subjects to either 40 IU of OT or placebo administered 30 minutes prior to each training session. The abbreviated form of SCST included sessions on facial affect recognition, social perception, and empathy. We did not find an effect of OT on measures of psychopathology or cognition. As mentioned earlier, we found that OT-treated subjects with schizophrenia demonstrated greater improvements on a measure of empathic accuracy compared with placebo following the training program (Figure 5). This advantage of OT subjects was

sustained one week and one month following the last dose of drug. Scores on the facial affect perception improved in both groups, indicating that cue identification responds well to training (i.e., learning), whether or not the subject has OT. Neither group showed improvement on a measure of social perception. These findings support a model in which individuals with an impaired ability for processing social information can use OT to enhance the salience of social information. This increase in salience then increases the ability of subjects to learn higher level social cognition skills.

### C.2.2 R33 Study Description

**C.2.2a Study Subjects:** Subjects will be 120 outpatient men and women 18 to 55 years old with non-affective psychotic disorders (schizophrenia, schizoaffective disorder, and delusional disorder) who are in a stable condition on antipsychotic and other medications. Stability criteria will include no recent hospitalizations within the six months prior to study entry and no changes in psychiatric medication or dosage changes greater than 10% within the past three months. Inclusion criteria will also include ability to provide informed consent, without serious medical conditions, and without recent substance use disorder. Exclusion criteria will include a positive pregnancy test, unstable medical conditions, history of serious head injury, and hyponatremia. Women will be excluded who are sexually active and not using an effective form of contraception. Subjects will be recruited from the sources described in the R21 (C1.c).

**C.2.2b Study Procedures:** Following a visit for eligibility screening and informed consent, subjects will receive the same OT challenge described in the R21 (see Figure 2). This will include a challenge with OT (using the optimal dose determined by the R21 study) or placebo separated by one week in counterbalanced order. Prior to randomization and at least one week after the last challenge, subjects will receive baseline ratings which include a performance battery of social cognition tasks, the MATRICS Consensus Cognitive Battery (MCCB) for non-social cognition, symptom assessments with the Brief Psychiatric Rating Scale (BPRS) and the Clinical Assessment Interview for Negative Symptoms (CAINS) [53], and safety assessments with the the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale [54] and the Columbia Suicide Severity Rating Scale (CSSRS)[55]. Subjects will be randomized to one of 4 groups: OT with Social Cognition Skills Training (SCST); Placebo with SCST; OT with Health Management (HM); placebo with HM. Both SCST and HM will take place in groups of 6-8 individuals and each will occur twice weekly for 12 weeks. OT will be administered at the optimal dose determined by the R21. Double-blind drug will be administered 30 minutes before the SCST or HM sessions and not at other times. Groups will include subjects who are assigned to both OT and placebo. The 6 and 12 week assessments will take place five to seven days after the most recent administration of double-blind medication. The 16 week assessment will be completed at least 28 days following the most recent training group and study drug administration. During the entire study subjects will continue to receive their current medications.

### C.2.2c Description of Training Interventions

Social Cognition Skills Training (SCST): SCST training methods are described in more detail elsewhere [6] and include: (a) breaking down complex training tasks into smaller components, (b) initially teaching skills at the most fundamental level and then gradually increasing task complexity and real-world relevance, and (c) repetitive practice to facilitate skill acquisition. Training and practice materials include picture, audio, and video stimuli from standardized sets, a collection of videos with racially diverse actors developed by our group, and interactive games and role-plays. Each session includes a review of the previous session, didactics on a new skill area, and interactive practice and games. Participants are trained to become better “social detectives” through 5 hierarchically ordered modules: (a) Emotional processing: focuses on defining 6 basic emotions (happy, sad, angry, disgusted, afraid, surprised), recognizing them on the face and in the voice, and identifying situations that typically lead to them. (b) Social perception: covers non-verbal social cues and social contexts which typically lead people to experience different emotions (e.g., eye contact, emotional intensity). (c) Attributional bias: conceptualizes suspiciousness as an emotion, and focuses on distinguishing among facts, guesses, and feelings, and avoiding “jumping to conclusions.” (d) Empathy: focuses on accurately identifying how other people are feeling and then using this information to communicate in an empathic, effective way. (e) Mentalizing: focuses on more complex communicative intentions by putting together the “5-W’s” of social situations (who, what, when, where, and why) to evaluate whether: (1) the clues “add up” to indicate that someone is sincere, or (2) mismatches among the clues point toward more complex intentions, e.g., sarcasm.

Health Management (HM) control condition: This condition is described in greater detail in a previous publication [56]. The purpose of the HM is to be used as a non-socially cognitive training task, focusing on teaching participants how to maintain mental health and to minimize personally-relevant symptoms by focusing on four skill areas: Identifying Warning Signs of Symptoms, Managing Warning Signs, Healthy Lifestyle Choices, and Avoiding Alcohol and Street Drugs. The format for training of each skill involves didactic

introduction, videotape demonstrations, resource problem solving, and outcome problem solving. In several prior RCT's we have found that this type of program is engaging and useful for patients, but unlikely to influence the key outcome variables under study.

Fidelity checks: For both interventions, investigators will provide weekly supervision to group leaders and attend sessions to conduct fidelity checks with standardized procedures.

**C.2.2d Assessments**

Each subject will receive assessments at baseline before starting the interventions, after 6 weeks, 12 weeks, and at 1-month following the last treatment group (Table 2).

**Social cognition assessments and outcomes:** We will assess social cognition in two subdomains: (1) social cue identification (Managing Emotions component of Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) branch 1, Ekman, Profile of Nonverbal Sensitivity (PONS); and (2) mentalizing (The Awareness of Social Inference Test (TASIT). and Empathic accuracy) (see below). The primary summary measure for each test will be mean-centered and standardized to create a Z-score. These Z-scores will be averaged to create a single composite score for social cognition that will serve as the primary outcome measure. If significant results are detected for the composite score, parallel follow-up analyses will be conducted on the individual components to determine which measures are most affected by treatment.

The measures of social cognition include:

1. *Managing Emotions component of Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT).* The MSCEIT [57] consists of 141 items and 8 ability subtests, which assess four components (branches) of emotional processing. For this application, we will focus on the *Managing Emotions* component. Managing Emotions has 2 subscales that examine the regulation of emotions in oneself and in one's relationships with others;
2. *Emotion Identification Test from Ekman Program.* This is a test of identification of facial emotion based on photographs from the software developed by Ekman [58];
3. *Profile of Nonverbal Sensitivity (PONS).* The PONS is used to assess social perception [59, 60]. Scenes of this videotape-based measure last two seconds and contain facial expressions, voice intonations, and/or bodily gestures of a Caucasian female;
4. *The Awareness of Social Inference Test (TASIT).* The TASIT [61] is a videotape test of theory of mind in various social contexts. The test includes 3 components and we plan to use only the third component, which assesses the ability to draw inferences about others' intentions and beliefs;
5. *Ambiguous Intentions Hostility Questionnaire (AIHQ).* The AIHQ is a new measure of attributional bias that was recently developed by Penn and colleagues [62]. We included this measure to specifically address attributional bias, which is a key component of the SCST intervention;
6. *The Empathic Accuracy Task.* This task (adapted by our lab from Zaki [63]) consists of video clips showing the head and shoulders of an individual while he / she discusses a positive or negative autobiographical event. Accuracy is defined as the correlation between the subject's ratings and the ratings of the individual in the video clip.

**Non-social cognition: MATRICS Consensus Cognitive Battery**. A secondary outcome measure will be a composite score of non-social cognition based on the MATRICS Consensus Cognitive Battery (MCCB). This battery is one of the key deliverables of the MATRICS Initiative and it has gone through extensive review and a detailed selection process [64-66]. It will take approximately 1.5 hours to administer this modified MCCB.

**Symptom and side effect rating scales:** Symptom rating scales (the expanded BPRS [67] and the CAINS [68]) will be included to enable us to characterize the clinical symptom state of the patients and to examine whether some symptoms act as moderating variables for success in the interventions. The UKU Side Effect Rating Scale and the CSSRS will be administered at baseline, and weeks 1, 4, 6 and 12.

**Target Engagement and Social Preference Measures:** See R21 Description

| Table 3 | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Study Events** | **Enrollment** | **Week-2** | **Week-1** | **Baseline Assess-ments** | **Week 6** | **Week 12** | **Week 16** |
| Screening, demographics, SCID, consent, Phys Exam | X | | | | | | |
| BPRS, CAINS, UKU, CSSRS | | | | X | X | X | X |
| MCCB | | | | X | | X | |
| MSCEIT | | | | X | X | X | X |
| Ekman | | | | X | X | X | X |
| PONS | | | | X | X | X | X |
| TASIT | | | | X | X | X | X |
| AIHQ | | | | X | X | X | X |
| Empathic Accuracy | | | | X | X | X | X |
| OT challenge | | X | X | | | | |

Symptom, cognition, and social cognition measures at weeks 6 and 12 occur one week following the previous OT or Placebo administration. Week 16 occurs one month following administration

**C.2.2e Data Analysis: :** Prior to performing the primary analyses, descriptive statistics and graphical summaries will be obtained for the key outcome and predictor variables to check for outliers, missing data and the need for transformations or non-parametric methods. Longitudinal trajectory plots will be used to examine change over time in the primary measures for each of the groups. To verify the success of randomization, the groups will be compared on baseline demographic, clinical and contextual variables using 2x2 ANOVAs or chi-squared tests. These factors (in particular symptoms) will also be considered as potential moderators of treatment effects.

The overall analytic approach for our 2x2 factorial design will be the generalized linear mixed model (GLMM). GLMMs allow for the comparison of the average change trajectories in the different groups while taking into account within subject autocorrelation and baseline differences between participants. They also accommodate the inclusion of both continuous and categorical subject level predictors as well as time-varying covariates and automatically handle missing data, producing unbiased parameter estimates as long as observations are missing at random. First we will test if there is a significant difference in the changes over time for participants in the SCST group vs. the control group (effect of interest: time x training group 2-way interaction (H3)). Then we will test whether the effect of SCST training is enhanced in the OT group (effect of interest: time x training group x OT group 3-way interaction (H4)). Additionally we will do post-hoc tests comparing the specific contrasts that make up this 3-way interaction to estimate how much OT increases the efficacy of cognitive training. These analyses will be conducted both from study entry to end of the study to estimate the treatment effect and from study entry to the follow-up point to determine stability of these treatment effects. Parallel models will be fit for the secondary measures (e.g. general cognition) and for independent components of the primary social cognition measures to see whether the treatments are more narrowly targeting specific subdomains.

For the mediation hypotheses in H5 and H6 we will adapt the Baron and Kenny approach to the GLMM. Specifically, we will determine whether social salience (H5) or target engagement (H6) are mediators by comparing their impact in hierarchical models that include and exclude them. To explore

potential treatment moderators, such as symptoms, we will add these terms and their interactions with the time and grouping variables to the primary models.

**Power:** Based on the 2 x 2 factorial longitudinal design of this study with a sample size of N=120 and assuming a moderate within subject correlation of r=.5 this study has 80% power to detect 3-way interactions with effect sizes as small as $f^2$=.023 (H4), and 2-way interactions with effect sizes as small as $f^2$=.016 (H3). Cohen (1988) describes an effect size of $f^2$=.02 as small.

**D. Milestones and Timeline**: As noted in the timeline, we anticipate that the start-up for the R21 will be accomplished in 3 months. We view this as feasible since all of the assessments – including the target engagement measures – have already been administered in our group. The 2 month start up of the R33 is also feasible since our group therapists are experienced in social cognition training. The rates of subject recruitment required for the R21 and the R33 are similar to recent studies completed by our group.

**Table 4**

| Year | 1, July 2015 | 2, July 2016 | 3, July 2017 | 4, July 2018 | 5, July 2019 |
|---|---|---|---|---|---|
| R21 start up, IRB, training | | | | | |
| R21 collection | | N = 48 | | | |
| R21 lock & analysis Go/No Go decision | | | | | |
| R33 start up | | | | | |
| R33 collection | | | | N = 120 | |
| R33 lock & analysis | | | | | |

**E. Resource Sharing Plan** The proposed study has a data sharing plan consistent with NIH policy. Final data that have not yet been published will be shared after acceptance of publication of the relevant paper. Data will be de-identified before sharing on a need to know basis, and on the agreement that once the data analysis is complete, the data will be returned or destroyed.

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