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

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PROTOCOL

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Intranasal oxytocin (OT) has shown promise as an agent that can effective ly improve social processing in disorders that are characterized by impairments in social behaviors, in cluding schizophrenia. However, important gaps in our understanding of OT's effects on the brain have greatly limited its development as a therapeutic agent and made it difficult to interpret mixed research findings. One very important therapeutic function of OT may be its ability to enhance learning of social information. The proposed research will evaluate, in sequential steps, OT's effects on learning social cognitive skills in psychotic patients within a manualized training program that we have developed. The initial step (R21) is to demonstrate target engagement (i.e., that OT is getting to the brain and influencing social processes) and to establish optimal dosing of OT. Promising neurophysiological measures of target engagement for OT include EEG mu suppression while observing biological motion, and pupillary dilation during an emotion recognition task.

The R21 phase will determine the dose-response curve to OT for proposed measures of target engagement (i.e., mu suppression and pupillary dilation). The proposed study will use a single administration, within-subjects, crossover design to model the dose-response to OT across a large range of doses. Subjects with schizophrenia will be randomized to either: 8, 12, 24, 36, 48, 60, 72, or 84 IU OT (6 subjects to each dose). Each subject will receive OT and placebo in a dministrations separated by one week in randomized order. 30 minutes following OT administration, mu suppression and pupillary response will be assessed. We will also collect data on two measures of social salience (operationally defined here as behavioral tasks of social preference) to examine their correlations with measure of target engagement.

Specific Aims

R21 Specific Aims: This phase will determine the dose-response curve to OT for proposed measures of target engagement (i.e., mu suppression and pupillary dilation). The proposed study will use a single administration, within-subjects, crossover design to model the dose-response to OT across a large range of doses. Subjects with schizophrenia will be randomized to either: 8, 12, 24, 36, 48, 60, 72, or 84 IU OT (6 subjects to each dose). Each subject will receive OT and placebo in administrations separated by one week in randomized order. 30 minutes following OT administration, mu suppression and pupillary response will be assessed. We will also collect data on two measures of social salience (operationally defined here as behavioral tasks of social preference) to examine their correlations with measure of target engagement.

Aim 1. To determine the dose-response relationship OT versus placebo for measures of target engagement.
H1: At the optimal level of OT we will observe significant effects on □-suppression.
H2: At the optimal level of OT we will observe significant effects on pulillary dilation.

A Go/No GO decision will be based on Specific Aim 1. If either hypothesis is sup ported we will decide to go to the R33. Specific Aim 2 is exploratory and the results of the analysis will not be used for a Go/No Go decision.

Aim 2. To evaluate the relationship between target engagement and measures of social salience.

Background

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 imp ediment 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. How ever, 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 conclude d – 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 acti vation 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 st udy 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.

We hope to have 48 subjects complete the study with valid and useable data. In order to reach that number while allowing for screen failures and subject attrion, we may enroll as many as 100 subjects. Subjects may participate in one or both locations (the VA and UCLA), so we cannot estimate how many subjects will participate in one location versus the other.

Duration of Research:

The R21 is a two year study that could be extended for three more years as an R33 based on the results of the first two years of the study. That would involve a new IRB submission for the R33. We estimate the R21 will take approximately 2.5 – 3 years.

Recruitment of Subjects:

To meet our recruitment goals, patients with schizophrenia will be recruited from five sources: previous participants who have asked to be contacted for future studies by initialing this preference in a consent form from another study, participants of the MIRECC Treatment and Clinical Neuroscience Repository (Marder #0042), outpatient mental health clinics within the VA Greater Los Angeles Healthcare System (VAGLAHS), the UCLA Psychosis Clinic; and local board and care facilities. Patients will include persons who meet DSM-5 criteria for schizophrenia. We have well-established connections to several VA clinics and local board and care facilities. These relationships have been built on a demonstrated respect of their policies. We only recruit at locations where the staff members have been fully informed about the type of research we perform, the associated risks and benefits, and have approved our recruiter's presence. The main recruitment locations we might visit for this study are the following within the VA: DDTP, 206 Mental Health Clinic, MHICM, Day Tx, the Domiciliary, Exodus Lodge, and the following board and care facilities: The Manor, Golden Manor, Ocean View Manor, Brentwood Manor, Beverlywood Manor, the Graduate House, and Step Up on 2nd.

Any patient with schizophrenia who is not already part of the Repository will be asked to review and sign the MIRECC Treatment and Clinical Neuroscience Repository (Marder, #0042) consent form and HIPAA authorization for initial screening purposes prior to consenting for this study. Patients who agree will be asked to respond to a brief screening interview which includes questions about their mental health, medical and educational history, residence, past hospitalizations (if any), past or current drug use (if any), and current medications (if any). We will also ask for permission to review medical records and contact their primary care provider (PCP) or other responsible clinician to help determine mental health diagnosis or other general eligibility questions. If, after joining the repository, the patient continues to appear eligible for this study, the participant will be asked to review and sign the consent and HIPAA form for this study. The information from the repository combined with details provided in the diagnostic interview and rating scales will be reviewed during the weekly lab case review and the final determination of eligibility will occur at that time. No telephone screening will be performed for this study. All screening procedures will occur in person with our recruiter or Drs. Marder, Dunn, or Yang.

Patients who are not willing to join the repository will be asked to review and sign the consent and HIPAA form for this study only and proceed to the diagnostic interview to determine study eligibility.

Study Locations

We have lab space in two places that we will use for this study: offices at the VA Greater Los Angeles Healthcare System MIRECC in Building 210 and the UCLA Translational Research Center for Neuropsychiatry (TRCN), which is located at the UCLA Semel Institute. Subjects' participation in this study may occur at one or both locations (meaning all activities will be conducted in both locations, and individual subjects may participate in one or both places). All subjects will be asked to sign the VA consent form and HIPAA authorization since all data will be stored in our VA lab space, and if they are a UCLA patient, then they will also be asked to sign the UCLA HIPAA authorization.

We acknowledge that the use of multiple testing sites always requires some additional consideration. In this case, we are fortunate in that we are involved in setting up performance-based and EEG labs in the new space on the 2nd floor of Semel. The rooms will be dedicated testing rooms, and very similar (in size and arrangement of furniture) as our lab space at the VA. In addition, the testing conditions will be similar, with, most importantly, the same EEG system used at both sites. For personnel, we will be using the same staff at both locations for all aspects of the study, and the lab staff who will administer the EEG and pupillometry tasks have all been trained by Dr. Wynn on the Biosemi system. The testing parameters between the two sites will also be similar (same size monitors, distances from screen, room lighting, etc.). All staff have current VA appointments and are up-to-date on trainings.

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 venipuncture (CBC and basic metabolic panel), urine specimen for urinalysis, and urine 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)

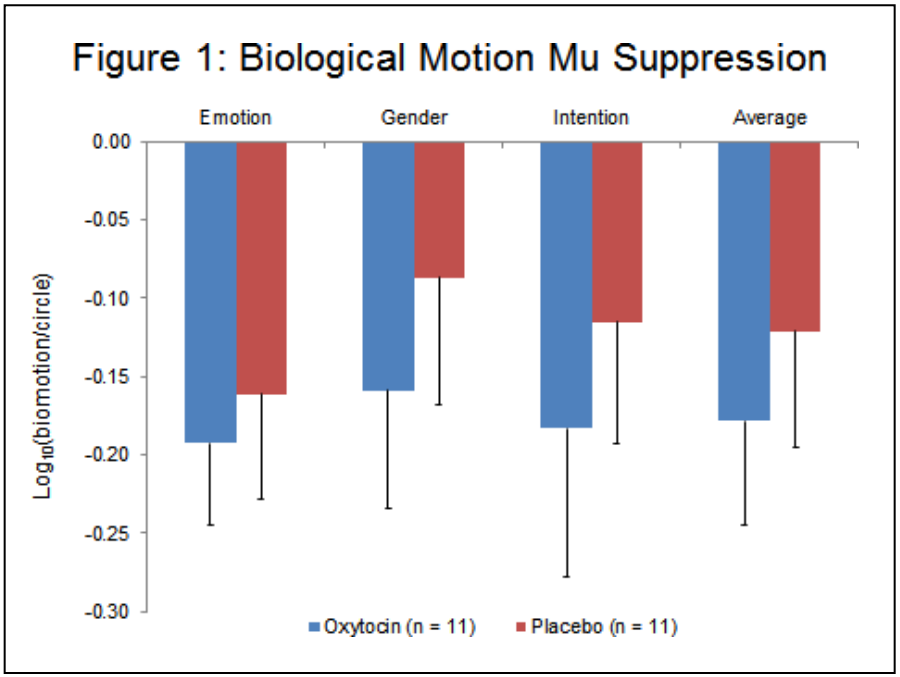
Table1: Study Events	Screening	Visit 1 (1 wk post screening)	Visit 2 (2 wk post screening)
Screening, SCID, demographics, consent	X		
OT Challenge		X	X

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.

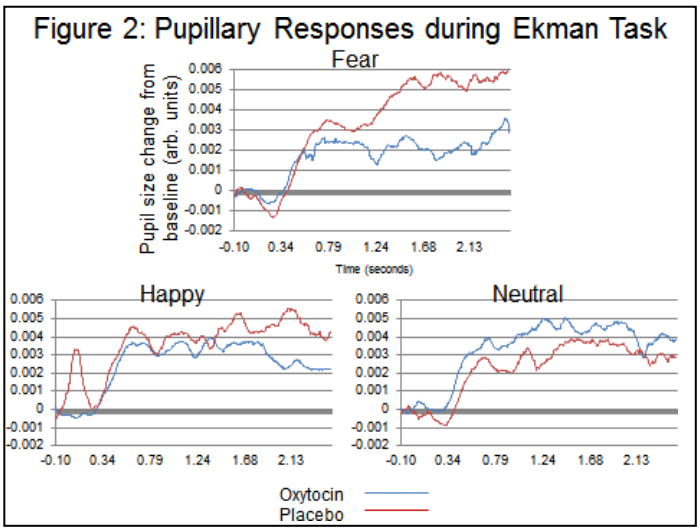
EEG data will be initially filtered with a 0.5 Hz high-pass filter and re-referenced to the mastoids. Eyeblinks will be corrected using standard algorithms [38]. Artifacts exceeding +/- 100 μV in amplitude at any electrode site will be rejected. As in prior studies the first 10 s of each block will not 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

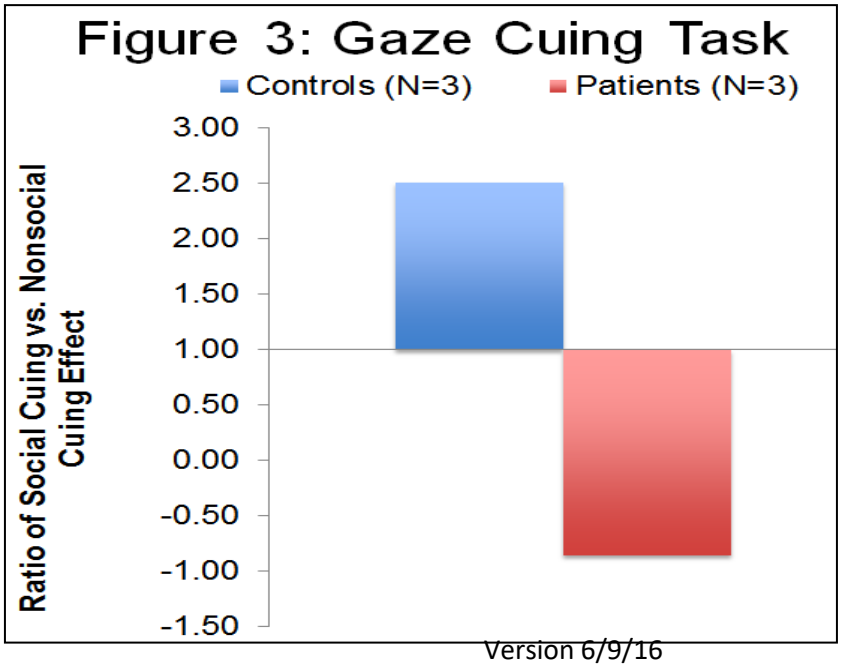
cross and stimulus. Once the choice screen appears they are instructed to identify which stimulus type was shown and they can blink freely. They can then initiate the next trial when they feel they will not need to blink. This task will take approximately 20 minutes to complete.

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

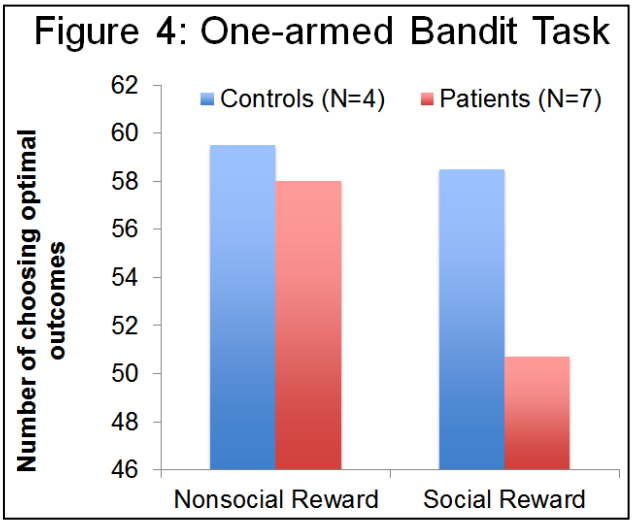


recorded. We will use 4 stimulus onset asynchronies (SOAs) between the cue and the target (i.e., SOA of 150, 250, 350, and 700 ms) to examine the time course of social orienting across SZ patients and controls as a function of the SOA. There will be 100 trials for each SOA per type of cue (social or 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.

Risks and Safety:

Oxytocin is a hormone that is secreted by the pituitary gland. The safety of raising OT by a nasal spray has been supported by numerous trials. The doses of OT that will be used in the R21 phase do not exceed the doses that have been used in a number of trials. This study will use a maximum dose of 84 IU administered once whereas studies have administered as much as 320 IU in a single day [1]. David Feifel (personal communication) has administered 84 IU twice daily and did not find adverse effects. We do not anticipate side effects at this dose although nasal irritation and headache are possible.

Since hyponatremia is a possible effect of OT we will exclude subjects with hyponatremia. Trials of chronic OT in schizophrenia indicate that it may improve symptoms of psychosis. The most serious side effects would occur in pregnant women since OT can increase tone in the pregnant uterus. It can also promote lactation. We will avoid these effects by screening women with pregnancy tests and excluding those who are pregnant.

Other Possible Oxytocin (intranasal) Risks: Stinging in the nose, runny nose, or tearing of the eyes. There is also a very small chance (1 report in the scientific literature each) of the development of psychotic thinking. Other possible risks may include: increased heart rate, increased or decreased blood pressure, abnormal heart rate, flushing, headache, allergic reaction that can be severe, and seizure for patients with a history of epilepsy. One of the study psychiatrists will briefly assess each subject before they leave after a study visit to make certain they are not experiencing any ongoing side effects that might require treatment.

Psychiatric interviews: It is possible that some of the questions may lead participants to think of upsetting experiences. They may refuse to answer any question they wish, and this will not affect participation.

Social Cognitive Testing: These tests may be challenging for participants and may lead to feelings of frustration at times. If a participant tires, they can receive additional rest periods or testing can be continued on another day.

EEG tasks: Preparation for application of EEG electrodes involves cleansing the skin with a mild abrasive for the purpose of obtaining a clean, low impedance signal. Participants are informed during preparation that if they feel any discomfort to let the tester know and they will reduce or cease cleansing. Slight flushing where the electrodes were applied to the skin may occur in a very few cases which disappears after a couple of days (similar to receiving a professional facial cleansing).

Blood draws: As with any blood draw, there are limited risks of infection, excessive bleeding, nerve injury, blood clots, allergic reaction, nausea, vomiting, dizziness, fainting, or need for blood transfusion.

Urine Tox Screens: If a participant tests positive for any illegal drugs, there is a remote possibility that someone outside this research lab may learn of this result, however, the researcher staff will not release this information to anyone and the researchers will obtain a Certificate of Confidentiality, which protects subjects' privacy. Both the urine sample and the results will be identified only by a code number, and the urine sample will be destroyed immediately after the results are obtained.

Although this protocol does not contain procedures that would be expected to increase suicidal ideation or suicide risk, it is not uncommon for patients with schizophrenia to have periods of suicidal ideation. Some of the measurement procedures may identify such suicidal ideation. If suicidal ideation or other evidence of suicide risk is identified during the course of this protocol, one of the clinically trained staff members of this study (i.e., Stephen Marder, M.D., Walter Dunn, M.D., Ph.D., Yvonne Yang, M.D., Ph.D., Amy Jimenez, Ph.D., or Lena Reddy, Ph.D.) will gather additional information to evaluate lethality and any imminent danger to self and to guide appropriate intervention. Information such as the specific thoughts regarding suicide, any plans to harm oneself, accessibility of means, relevant psychiatric history, use of medications and illicit substances, and availability of support systems will be considered. For lower levels of suicidal ideation, interventions will include notification of the participant’s key support persons, such as their treating psychiatrist, psychotherapist, and/or

family members. For imminent suicide risk, hospitalization will be arranged. The limitations on confidentiality regarding disclosures that a participant is having suicidal thoughts are also described in the relevant consent forms.

Potential Benefits:

The R21 may result in a better understanding of the relationship between OT dose and the response of a brain network associated with social information processing. This could result in a more scientific approach to making decisions about the dose of intranasal OT.

Risk / Benefit Ratio:

As discussed previously, there is a great need to develop treatments for social cognitive deficits in patients with psychosis, given their important role in functional recovery. Due to the nature of the study, patients who agree to participate will not derive a lasting benefit from the experimental treatment after the study is complete. However, the knowledge gained from the study will contribute to research which may lead to future improved treatments. Due to the minimal safety risks of the study treatment and procedures, the risks are deemed small and justifiable in relation to the benefits.

Informed Consent Process and Comprehension:

The consent process will take place one-on-one in a private room at the research project offices at the VA. The study coordinator will explain the purpose of the study and all interviewing and testing procedures in detail and then one of the study psychiatrists (Drs. Marder, Yang or Dunn) will meet with the subject to review the procedures, risks, and benefits more thoroughly, answer questions, and sign the consent form. We have several procedures in place to ensure that prospective participants fully understand the procedures, risks, and protections of the study. First, the consent form is written in easy to understand language. Second, the researcher reads the form to and with the potential subject, and invites questions after each section of the form. Third, the researcher asks the subject a series of questions about the study, such as what they are to do if they no longer want to participate, or what they would do if they experience any stress during the protocol.

All subjects in this study will have the capacity to give informed consent. Comprehension of information specific to the study (i.e. purpose, procedures, risks, protections) will be assessed by the researcher during the informed consent process using the form “Evaluation of Capacity to Sign Consent.” Subjects who do not have the capacity to give informed consent (those who cannot successfully understand the consent form and respond to the questions in the Evaluation of Capacity to Sign Consent will not be included. We may include subjects who are under conservatorship who can demonstrate clear understanding of the consent form and research procedures as evidenced by their response to the Evaluation of Capacity to Sign Consent. Subjects will be informed that participation in research is voluntary and refusal to participate will not jeopardize their care at their institution. There are no waivers or modifications of treatment for research purposes.

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.

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.

As part of the conditions of the grant from NIMH which funds this study, we have been informed that we are required to submit de-identified subject data to the National Institute of Mental Health Data Archive (NDA). The types of data we will submit include the following: demographic data, data from diagnostic and symptom assessments, and social salience / social cognition performance data, and EEG task data

Participant Name:_____ **Date:** _____

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

Principal Investigator: **Stephen R. Marder, M.D.** Phone: 310-268-3647

INTRODUCTION

You are being invited to take part in a research study at the VA Greater Los Angeles Healthcare System and UCLA under the direction of Stephen R. Marder, M.D. and his research team because you are 18 to 55 years of age and have no history of serious head injury or significant medical diseases, understand spoken English, and you are diagnosed with schizophrenia, schizoaffective disorder, or delusional disorder. Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits to you and/or to the future population of individuals you represent.

Read the information below closely, and discuss it with family and friends if you wish. Ask one of the study staff if there is anything that is not clear or if you would like more details. Take your time to decide. If you do decide to take part, your signature on this consent form will show that you received all of the information below, and that you were able to discuss any questions and concerns you had with a member of the study team.

Your participation in this study is voluntary. If you don't take part, you can still receive all usual care that is available to you. Your decision not to take part will not affect the relationship you have with your doctor or other staff, and it will not affect the usual care that you receive as a patient. If you decide to take part, you may still withdraw at any time. If you do not wish to be in this study or leave the study early, you will not lose any benefits to which you are entitled.

BACKGROUND AND PURPOSE

People with psychosis often experience difficulties in the areas of living independently, working, and social relationships. These difficulties seem to be associated with problems in thinking (referred to as cognition) such as difficulties in memory or attention. They also include problems in perceiving how others are feeling. There are no approved medication treatments available for these problems and other types of treatments are very limited in their availability. With this research, we hope to learn whether administration of a medication, oxytocin, which is also a hormone and neurotransmitter in your body, will improve different aspects of your ability to perceive and respond to people.

This experimental medication (oxytocin) is being tested while you are taking your usual psychiatric medication. Thus, this study is researching a treatment that is different from your usual standard of care.

Because this is a research study, the study drug will only be given to you during this study and not after the study is over.

INVESTIGATOR DISCLOSURE

This study is being funded by the National Institute of Mental Health (NIMH). NIMH is providing financial support for this study.

DURATION OF THE RESEARCH:

This is a two year study that could be extended for three more years based on the results of the first two years of the study. This study will involve three visits. The first visit will include the screening and interview procedures and will last about 2 hours. If, based on the results of that visit, you are eligible to participate in the study, then there will be two more visits spaced one week apart. Both of these visits will last about 3 hours and include receiving the study medication, or placebo, before assessments (on one week you will receive either oxytocin or placebo, and for the following week, you will receive the one you did not receive the first time).

This study is designed to enroll 48 participants. In order to allow for people who drop out of the study or are determined to be ineligible after the screening visit, we plan on enrolling up to 100 subjects.

STUDY PROCEDURES

We have lab space in two places that we will use for this study: offices at the VA Greater Los Angeles Healthcare System MIRECC in Building 210 and the Translational Research Center for Neuropsychiatry (TRCN), which is located at the UCLA Semel Institute. Your participation in this study may occur in one or both locations. All participants will be asked to sign the VA consent form and HIPAA authorization since all study data will be stored in our lab space at the VA, and if you are a UCLA patient, then you will also be asked to sign the UCLA HIPAA authorization. As part of this HIPAA authorization, you will be asked to provide your permission to allow our research staff to review your medical records and contact your primary mental health care provider as part of this study. We sometimes need to review your medical records and contact your provider to help determine your eligibility and suitability for participating in the study.

If you decide to take part in this study, this is what will happen:

Screening Visit:

As part of this study, you will be interviewed about your personal life experiences and emotional well-being by a specially-trained interviewer. The interview will include a Psychiatric and Social History Schedule, which is a brief interview that includes questions about your occupational and educational history, your residence, past hospitalizations (if any), and current medications (if any). It will also include a verification of psychiatric diagnoses with the Structured Clinical Interview for DSM-V (SCID I). You may at any time refuse to answer any questions. The psychiatric interview you will receive is not, and does not take the place of, a full psychiatric evaluation.

You will also receive a brief medical exam, and have blood drawn for basic lab assessments (CBC and metabolic panel) and a urine samples for urinalysis. If you are female, you will be asked to provide a urine sample for a pregnancy test to ensure that you are not pregnant. These samples will all be coded and destroyed after analysis.

If you are already a participant in the MIRECC Treatment and Clinical Neuroscience Repository (Marder, 0042), we will be using some of the information about you stored in this repository in addition to these interviews to determine if you are eligible for this study.

If you are not eligible for this study based on the information provided in your clinical interviews, medical records (if applicable), and primary care provider (if applicable), your participation will end at this time.

Oxytocin or Placebo (Visit 1 and Visit 2):

You will be assigned by chance (like flipping a coin) to receive either nasal spray containing oxytocin or nasal spray without oxytocin for your first visit. You will be randomly assigned to one of 8 dosing groups: 8, 12, 24, 36, 48, 60, 72, and 84 IU of oxytocin. One half of participants will receive oxytocin nasal spray for the first visit and one half will receive nasal spray without oxytocin. For your second visit, you will receive the spray that you did not receive the first time (either oxytocin or placebo). So, for one visit you will receive the oxytocin nasal spray and the other you will receive the placebo spray. The clinical interviewers and testers will not know whether you are receiving oxytocin or the placebo but the primary investigator, Dr. Marder, will know.

Thirty minutes before each of the two assessment visits, you will be given a nasal spray containing either oxytocin or placebo.

Assessments (Visit 1 and Visit 2):

a) Prior to participating in study assessments, you will be asked to provide a specimen of urine to test for the presence of drugs (legal and illegal), which may affect the results of this study. The drugs classes that will be screened for include: benzodiazepines (drugs typically given as a sedative or to reduce anxiety), barbiturates (drugs which cause reduced activity in the brain, ranging from mild to heavy sedation), amphetamines (drugs which act as stimulants), opiates (drugs which are used to treat pain), PCP (phencyclidine, a drug which induces hallucinatory effects), cocaine, and THC (tetrahydrocannabinol, the psychoactive chemical in marijuana). If the urine screen is positive for substance use, you will not be able to participate in the study that day. You will not be disqualified from the study, but instead you will be asked to come back on a different day. However, if you test positive for drugs on multiple occasions (i.e., more than 4 times), you may be disqualified from the study. If you test positive for intoxicants, you will be offered referrals to treatment facilities (community or VA-based as appropriate). If you are noticeably intoxicated during assessment, you will be offered transportation back to your residence for your safety and that of others.

b) After receiving the nasal spray containing either oxytocin or placebo, you will be asked to receive standard measures of brain activity (EEG) while looking at briefly presented people and objects as well as a series of moving dots resembling human movements on a computer screen. EEG is a technique that detects and records electrical activity generated by the brain. Electrical activity is measured by placing small recording electrodes on the surface or your scalp, forehead, and ear lobes. Electrodes are small silver discs (about the size of an eraser on a pencil) that detect very low levels of electrical activity. Small recording electrodes will also be placed near your eyelids to record eye movement. The electrodes will be filled with a gel containing salt. The EEG recording will take approximately 1 hour.

c) You will also be asked to have measurements of your pupil and eye movements recorded while looking at pictures of faces and a series of moving dots resembling human movements on a computer screen. The method of recording your pupil and eye movements is called pupillography and is a safe, non-invasive measure. You will rest your chin and forehead in a chin rest device so as to limit your head movements. A small camera is placed about 12 inches away from your eye to record only your pupil and eye movements; your face will not be recorded at any time. A small infrared light, that is harmless and invisible to the human eye, will be directed at your eye in order for the camera to detect your pupil. This task will take approximately 45 minutes to complete.

d) You will be asked to take two tests that measure your interest in social versus non-social cues and rewards. For the first task, you will be asked to indicate the location of a target (the

letter X in one of two peripheral boxes) following a central cue that contains either social information (such as a pair of eyes gazing left or right), or nonsocial information (an arrow pointing left or right). After cue offset, the target will appear and remain on the screen until a response is made. You will be asked to detect the location of the target as quickly and accurately as possible. The second task, a motivation task, involves several scenarios in which two slot machines will appear: a "neutral" machine paired either with a "good" slot machine or a "bad" slot machine. You will have a few seconds to choose the slot machine that will give the optimal outcome. Then, the reward outcome will be presented for a few seconds. The type of reward presented will be social or nonsocial. Examples of social rewards include color photographs of faces showing happy (positive outcome), angry (negative outcome) or neutral (neutral outcome) emotional expressions. Examples of nonsocial rewards include 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). Together, these tasks will take about 1 hour to complete.

e) You will be examined briefly by a study doctor before you leave after each of these two visits to make sure that you are not experiencing any side effects from the oxytocin or placebo that might require treatment.

Your involvement in this research project will in no way affect any other treatment you are currently receiving.

Responsibilities and expectations of you as a participant in the study include:

- Take the study medication as instructed at study visits.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the investigator or research study staff to reschedule as soon as you know you will miss the appointment.
- Complete the testing to the best of your ability.
- Ask questions as you think of them.
- Tell the investigator or research staff if you change your mind about staying in the study.

POSSIBLE RISKS OR DISCOMFORTS

Any procedure has possible risks and discomforts. The procedures in this study may cause all, some or none of the risks or side effects listed. Rare, unknown, or unforeseeable (unexpected) risks also may occur.

Risks of study drug

Oxytocin is a hormone which has effects on reproductive and social behavior. In women, naturally secreted oxytocin leads to contraction of the womb (uterus) during childbirth and the production of milk for breastfeeding. Manufactured oxytocin is sometimes given to induce labor if it has not started naturally or it can be used to strengthen contractions to aid childbirth. In addition, manufactured oxytocin is often given to speed up delivery of the placenta and reduce the risk of heavy bleeding by contracting the uterus. Therefore, female participants who are pregnant, planning to become pregnant or are breastfeeding cannot participate in this study.

Possible Oxytocin (intranasal) Risks: Stinging in your nose, runny nose, or tearing of your eyes. There is also a very small chance (1 report in the scientific literature each) of the development of psychotic thinking. Other possible risks may include: increased heart rate, increased or decreased blood pressure, abnormal heart rate, flushing, headache, allergic reaction that can be severe, and seizure for patients with a history of epilepsy.

Psychiatric interviews and questionnaires: it is possible that some of the questions may lead you to think of upsetting experiences. You are free to not answer any question you wish, and this will not affect your participation.

Testing for use of legal and illegal drugs: If you test positive for any illegal drugs, there is a remote possibility that someone outside this research lab may learn of this result, however, the researcher staff will not release this information to anyone and the researchers have obtained a Certificate of Confidentiality, which protects your privacy. Both your urine sample and the results will be identified only by a code number, and the urine sample will be destroyed immediately after the results are obtained.

Measures of social cognition: These tests may be challenging for you and may make you feel frustrated at times. You can stop the taking the test at any time by telling the staff that you want to stop. It is also possible that you may find some tests boring. If you get tired taking the tests, you can ask for more breaks or take the tests on another day. During the measures of your pupil and eye movements, you might become slightly restless having to hold your head still.

Measures of brain activity (EEG) while looking at briefly presented objects on a computer screen: when the recording disks are applied to your eyelids and scalp, your skin will first be cleaned with rubbing alcohol which might cause some slight skin irritation.

Blood draws: As with any blood draw, there are limited risks of infection, excessive bleeding, nerve injury, blood clots, allergic reaction, nausea, vomiting, dizziness, fainting, or need for blood transfusion.

As in any research study, it is possible that personal information about you could become known to other people. The investigators will take precautions to prevent this from happening. Your name will not appear on any questionnaires or test that you complete during the study. Instead, all questionnaires and tests you complete will be coded with a study ID.

Risks of the usual care you receive are not risks of the research. Those risks are not included in this consent form. You should talk with your health care providers if you have any questions about the risks of usual care.

POTENTIAL BENEFITS

There is no certain direct benefit to you from your participation in the study, although you may briefly experience an improvement in social perception and understanding after receiving the oxytocin nasal spray. However, the information we get from this study may help us treat future patients.

ALTERNATIVES TO PARTICIPATING IN THIS RESEARCH

You may choose not to participate in this study. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. You may discuss these options with your doctor.

There are no currently available FDA-approved medications for the treatment of cognitive problems in schizophrenia. The alternative to participation is to continue with the care you are already receiving. You can also ask your psychiatrist if there are any cognitive training programs (non medication-based treatment) available for you to participate in.

CONFIDENTIALITY

Taking part in this study will involve collecting private data about you. This data will be protected in the following ways:

Your research data in this study will be identified only by an assigned study number. All hard copy data collected (interviews, assessments) will be coded where possible, and original documents with sensitive information will be stored separately from coded data. All hard copy data will be stored in locked drawers in locked offices. Electronic data with identifiers will be password protected, encrypted and stored on the secure VA network, and no data with

identifiers collected at the VA will leave the VA lab space. The blood and urine samples and results of the lab tests will be coded, and the samples destroyed immediately after results are obtained. Data collected at the UCLA TRCN, if applicable, will be securely transmitted to the VA, and hard copy source documents will be securely transported back to our VA lab space for storage.

We will not share your records or identify you unless we have to. There are times when we may have to show your records to other people. For example, someone from State or Federal Regulatory Agencies, UCLA Office of the Human Research Protection Program, the Office of Human Research Protection (OHRP), the Government Accountability Office (GAO), the VA Office of Research Oversight (ORO), the Institutional Review Board – VAGLAHS and any of its delegated subcommittees, our local Research and Development Committee, the Research Compliance Officer and other study monitors may look at portions of records that identify you. The information collected in this study will be processed to meet the purpose of the clinical study. It may also be used in reports of the study, scientific presentations, and/or publications, but your identity will not be disclosed.

This research is covered by a Certificate of Confidentiality issued by the Department of Health and Human Services (DHHS). This Certificate will protect the investigators from being forced to release any research data in which you are identified, even under a court order or subpoena. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

This protection, however, is not absolute. A Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. Note however, that if an insurer or employer, learns about your participation, and obtains your consent to receive research information, then the investigator may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your own privacy.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in a research project under the following circumstances. The Certificate of Confidentiality will not be used to prevent disclosure to local authorities of child abuse and neglect, or harm to self or others.

As just mentioned above, we may not be able to keep confidential any disclosure or endorsement of thoughts to harm yourself. In the event that you tell the research staff that you are thinking about killing yourself or you answer yes to a question about having thoughts about

suicide, the research staff will ask you more questions about the thoughts. Depending on how intense your thoughts are or how much you feel like hurting yourself, your treating psychiatrist, case manager, family and/or friends will be notified of your thoughts and will be asked to work with you on a plan to keep you safe. If your thoughts of harming yourself are very strong, the research staff will help get you to a hospital for safety.

Data from this study may be submitted to the National Institute of Mental Health Data Archive (NDA). NDA is a data repository run by the National Institute of Mental Health (NIMH) that allows researchers studying mental illness to collect and share deidentified information with each other. A data repository is a large database where information from many studies is stored and managed. Deidentified information means that all personal information about research participants such as name, address, and phone number is removed and replaced with a code number. With an easier way to share, researchers hope to learn new and important things about mental illnesses more quickly than before.

During and after the study, the researchers will send deidentified information about your health and behavior and in some cases, your genetic information, to NDA. Other researchers nationwide can then file an application with the NIMH to obtain access to your deidentified study data for research purposes. Experts at the NIMH who know how to protect health and science information will look at every request carefully to minimize risks to your privacy.

You may not benefit directly from allowing your information to be shared with NDA. The information provided to NDA may help researchers around the world treat future children and adults with mental illnesses so that they have better outcomes. NIMH will also report to Congress and on its web site about the different studies that researchers are conducting using NDA data. However, you will not be contacted directly about the data you contributed to NDA.

You may decide now or later that you do not want to share your information using NDA. If so, contact the researchers who conducted this study, and they will tell NDA, which can stop sharing the research information. However, NDA cannot take back information that was shared before you changed your mind. If you would like more information about NDA, this is available on-line at http://data-archive.nimh.gov.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

COSTS TO PARTICIPANTS AND PAYMENT

Costs to Participants:
You will not be charged for any treatments or procedures that are part of this research study. If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications that are not part of this study.

PAYMENT OFFERED FOR PARTICIPATION

You will be paid $50 for each of the study visits. You will also be reimbursed for any study related travel expenses. You will receive payment in cash at the end of each day of participation.

MEDICAL TREATMENT AND COMPENSATION FOR INJURY

Every reasonable safety measure will be used to protect your well-being. Since you may participate in more than one location for this study, if you are injured as a result of taking part in this study, the institution where you are injured, UCLA or the VA, will provide necessary medical treatment at no cost to you.

If you should have a medical concern or get hurt or sick as a result of taking part in this study, call:

DURING THE DAY:

Dr. Marder at 310-268-3647 or Dr. Yvonne Yang at 203-887-7674 or Dr. Walter Dunn at 310-478-3711 49234.
AFTER HOURS:

You can also call the UCLA Page Operator at (310) 825-6301 to reach Dr. Marder, or one of the study psychiatrists Dr. Yvonne Yang, or Dr. Walter Dunn 24 hours a day, 7 days week.

Emergency and ongoing medical treatment will be provided as needed at the VA for a study-related injury. If you are injured as a result of being in this study at UCLA, the University will provide all necessary emergency medical treatment and any additional necessary care to the extent of your insurance coverage. UCLA and the VA do not normally provide any other form of compensation for injury.

You do not give up any of your legal rights and you do not release the VA from any liability by signing this form.

YOUR RIGHT TO TERMINATE PARTICIPATION

It is up to you to decide whether or not to take part in this study. If you decide to take part you may still withdraw at any time. If you do not wish to be in this study or leave the study early, you will not lose any benefits to which you are otherwise entitled. If you don't take part, you can still receive all usual care that is available to you. Your decision not to take part will not affect the relationship you have with your doctor or other staff and it will not affect the usual care that you receive as a patient.

RIGHT OF INVESTIGATOR TO TERMINATE YOUR PARTICIPATION

The study doctor has the right to end your participation in this study for any of the following reasons*:* if it would be dangerous for you to continue; you do not follow study procedures as directed by the study doctors; or if you become ill during the research. The investigator, Dr. Marder, will make this decision. If your participation is discontinued, it will not affect your relationship with the VA or the care you may receive here. In addition, your study doctor may end your participation without regard to your consent.

PERSONS TO CONTACT ABOUT THIS STUDY

If you have questions about your rights as a study participant, or you want to make sure this is a valid VA study, you may contact the VA Greater Los Angeles Institutional Review Board (IRB). This is the Board that is responsible for overseeing the safety of human participants in this study. You may call the VA Greater Los Angeles IRB at 1-310-268-4437 if you have questions, complaints or concerns about the study, or if you would like to obtain information or offer input.

SIGNIFICANT NEW FINDINGS

Sometimes during the course of a research study, new information becomes available about the study drug that is being studied that might change a person's decision to stay in the study. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw from the study, your research doctor will arranges for your medical care to continue. If you decide to continue in the study, you might be asked to sign an updated informed consent form. Your research doctor could also decide it to be in your best interests to withdraw you from the study. If so, he or she will explain the reasons and arrange for your usual medical care to continue.

AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

Dr. Marder or an approved member of his research team has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You

have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.

You voluntarily consent to participate in this study. You also confirm that you have read this consent, or it has been read to you. You will receive a copy of this consent after you sign it. A copy of this signed consent will also be put in your medical record if applicable.

I agree to participate in this research study as has been explained in this document.		
_____ Participant's Name	_____ Participant's Signature	_____ Date

_____ Name of person obtaining consent	_____ Signature of person obtaining consent	_____ Date

It is likely that there will be related studies in the future that may interest you. Please initial the section below indicating whether you agree to allow us to contact you with information about future related studies. Your decision will not affect your medical care or your participation in the current study.

_____ I agree to allow the investigators to contact me about future studies.

_____ I DO NOT agree to allow the investigators to contact me about future studies.

RIGHTS OF HUMAN SUBJECTS IN MEDICAL EXPERIMENTS

Any person who is requested to consent to participate as a subject in a research study involving a medical experiment or who is requested to consent on behalf of another has the right to:

1. Be informed of the nature and purpose of the experiment.

2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.

3. Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment.

4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.

5. Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits.

6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.

7. Be given an opportunity to ask any questions concerning the experiment or the procedure involved.

8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.

9. Be given a copy of any signed and dated written consent form used in relation to the experiment.

10. Be given an opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.