OXYTOCIN AS ADJUNCTIVE TREATMENT OF SCHIZOPHRENIA

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SPECIFIC AIMS

The focus of the current project is to advance our understanding of the effects of oxytocin (OT) on components of social cognition in schizophrenia (SCZ). Despite the rapid increase in our understanding of the role of OT in rodent models of social behavior and an explosion of interest in the prosocial effects of OT in healthy controls, little work has been done to dissect the potential effects of OT on SCZ subjects with social deficits. Social deficits are a crucial aspect of the functional impairments that limit the rehabilitation of patients with SCZ. In particular, SCZ patients with enduring negative symptoms (deficit syndrome, Kirkpatrick et al. 1989) have prominent social deficits as a core feature of this subtype of the illness. Our currently available medications do very little to improve these social deficits. Hence it is of utmost public health importance to address the knowledge gap regarding the potential of OT to improve social function in this illness. Intact social function depends on the competent functioning of several cognitive domains that subserve perception of social cues and the generation of motivated social behavior. We propose to conduct a pharmacological challenge study of OT vs. placebo administration to study the effects of OT on specific components of social cognition in male deficit syndrome SCZ subjects.

Primary Hypothesis: Intranasal OT will improve social cognition in subjects with deficit syndrome SCZ.

Specific Aim 1: Administer OT intranasally vs. placebo in a parallel group double-blind design to 40 deficit syndrome SCZ subjects. Following OT or placebo (PBO) dosing, components of social cognition will be assessed as follows.

a. Evaluate the salience of social cues by the measurement of visual scan paths during gaze at pictures of faces.

b. Evaluate sensitivity to social reward by means of a computerized social reward ball-tossing task that assays social interactions in response to social reward.

c. Evaluate social cognition by means of testing the ability to correctly identify emotion from pictures of faces (Facial Emotion Identification Test, FEIT).

BACKGROUND

Impaired social functioning is an important symptom in SCZ

SCZ is a chronic severe psychotic illness that affects two to three million Americans, over 100,000 of whom are veterans (Owen et al. 2004). There are several key symptom domains that characterize the illness. Positive symptoms (such as hallucinations and delusions) are at least somewhat responsive to antipsychotic medication in a majority of patients. Negative symptoms such as poor motivation, anhedonia, poor social function, and poor occupational function are poorly responsive to medication or other currently available treatments. The deficit syndrome has been defined as a complex of these negative symptoms that endure throughout the course of a schizophrenia patient's disease (Kirkpatrick et al. 1989). The social impairments seen in these patients are core deficits that have been linked to poor functional outcomes (Couture et al. 2006; Fett et al.

2011). Furthermore, deficits in social cognition have been proposed to underlie and contribute significantly to impaired social functioning (Kern et al. 2008; Green et al. 2008). An underlying hypothesis of this work is that if social cognition could be effectively treated, these patients would improve their social and functional outcomes, potentially enabling them to achieve occupational competence, sustain stable independent living, and lead more fulfilling independent lives. Thus our understanding and treatment of the social impairments of SCZ is very important from a public health perspective.

OT effects on social cognition and behavior

Studies in rodents demonstrate a critical role for the neuropeptide OT in social bonding (Young et al. 2005). A large and rapidly growing translational literature indicates that this neuropeptide may also play a prosocial role in human behavior. The prosocial effects of OT adminstration have already been extensively reviewed in the literature (Striepens N et al., 2011). In the area of trust and altruism, studies utilizing a variety of economic and cooperation paradigms indicate that OT enhances trusting and social cooperation (Baumgartner T et al., 2008; De Dreu CK et al., 2010; Declerck CH et al., 2010; Kosfeld M et al., 2005; Mikolajczak M et al., 2010; Zak PJ et al., 2007). Feelings of empathy to others were enhanced with OT in three studies (Domes et al. 2007; Bartz et al. 2010; Hurlemann et al. 2010). Several studies indicate that OT increases the ability of healthy controls to identify emotion in faces (Di Simplicio et al. 2009; Fischer-Shofty et al. 2010, Marsh et al. 2010). There are reports using memory paradigms, in which OT administration induced enhanced recall of faces after OT (Savaskan et al. 2008; Rimmele et al. 2009), although an earlier study found no improvement (Ferrier et al. 1980). OT administration also increased recall of social words (Unkelbach et al. 2008). There is some indication that OT effects on recall are specific to emotional stimuli since several studies in healthy controls found that OT did not improve memory for nonsocial stimuli (Bruins J et al., 1992; Fehm-Wolfsdorf G et al., 1984; Geenen V et al., 1988; Kennett DJ et al., 1982).

OT as potential treatment in SCZ

Several lines of reasoning suggest that OT could be helpful as adjunct treatment of SCZ.
(1) Patients with SCZ have altered OT levels compared to healthy controls (Linkowski et al. 1984; Beckmann et al. 1985; Legros et al. 1992; Goldman et al. 2008; Keri et al. 2009).
(2) fMRI in concert with intranasal OT administration was associated with reduced blood-oxygen-level-dependent (BOLD) activation in the amygdala during presentation of fearful/threatening faces and scenes (Kirsch et al. 2005). This study gives indirect support to the idea that OT may ameliorate paranoia in patients with SCZ.
(3) The negative symptoms of SCZ include social isolation, autism, and amotivation for social engagement. There is face validity to the notion that OT could help with these symptoms in virtue of its pro-social action.
(4) To date there are three published placebo controlled trials of OT in SCZ. In the first study, OT was given in a placebo-controlled double-blind randomized crossover design (Feifel et al. 2010). In this study of fifteen completers, the Positive and Negative Symptom Scale (PANSS) and the Clinical Global Impressions scale (CGI) were used as outcome measures. OT added to antipsychotic treatment resulted in a significant improvement in positive symptoms, as measured by the PANSS total score, PANSS positive symptom subscale, PANSS negative symptom subscale, and the CGI. The effect size for these changes ranged from 0.40 for PANSS positive symptoms to 0.74 for the CGI. Furthermore, treatment with OT was well tolerated, with no significant differences between OT and placebo in rates of adverse effects nor in blood chemistry (Feifel et al. 2010). This same group published a second paper indicating an improvement in verbal memory in SCZ subjects following three weeks of twice daily OT (Feifel et al. 2012). The third study reports that two weeks of OT reduced psychotic symptoms and improved performance in a Theory of Mind task (Pedersen et al. 2011).

Dissecting components of social impairment in SCZ

Intact social competence depends on adequate function in several cognitive domains that subserve perception of social cues and motivated social behavior. We propose to interrogate these composite domains after administration of OT vs. placebo in this project.

i. *Eye tracking.* Relevant social cues must be of sufficient salience to command attention. This aspect of social cognition has been investigated by means of visual scan path paradigms that quantify the amount of time a subjects spends looking at the eyes and mouth regions of pictures of faces presented while the position of the eyes is tracked. The amount of eye gaze is predictive of a subject's ability to correctly identify emotions and meaning in others (Haxby et al. 2002). A single dose of OT significantly increases the amount of eye gaze in healthy controls (Guastella et al. 2008a) and in high functioning subjects with autism spectrum disorders (Andari et al. 2010). SCZ subjects have abnormalities in visual scan paths while viewing pictures of faces (Phillips and David 1997; Loughland et al. 2002a). *Thus we hypothesize that OT will increase gaze at the eyes in subjects with deficit syndrome SCZ (Specific Aim 2a).*
ii. *Social Reward Ball-Tossing Task.* Social stimuli must be sufficiently rewarding to motivate decision-making and behavior. This aspect of social function has been investigated with a computerized social interaction game that assays the effects of social reinforcement on decision-making. In a task developed by Andari et al. (2010) that was derived from an earlier task by Williams et al. (2000), subjects engage in a computerized version of a ball-toss game in which three fictional partners vary the proportion of times they throw the ball back to the subject. The outcome measure of interest was the choices made by the subject regarding to which fictional player they would throw the ball. In a study of high functioning autism spectrum subjects, OT administration selectively enhanced return of the ball to the most socially cooperative fictional partner (Andari et al. 2010). This result was interpreted as evidence that OT enhances appropriate behavioral responses to the social reward of reciprocity. *We hypothesize that OT administration will enhance socially reinforced behavior in subjects with deficit syndrome SCZ (Specific Aim 2b).*
iii. *Facial Emotion Identification Task (FEIT).* The socially competent person must be able to correctly identify the emotions in others in order to respond appropriately during social communication. The correct identification of emotions in others is a key aspect of social cognition that has been linked to functional outcomes in SCZ (Couture et al. 2006). This aspect of social cognition has been investigated in paradigms that query the subjects on identifying emotions displayed in pictures. Most studies in the literature report that patients with SCZ are deficient in the correct identification of emotions displayed in pictures of faces (Addington et al. 2006; Bigelow et al. 2006; van't Wout et al. 2007; Averbeck et al. 2012 and see review in Couture et al. 2006), although not all studies have found such impairments (de Achaval et al. 2010). The classic series of pictures of faces introduced by Eckman and Friesen (1976) have been used in many studies of affect recognition, but other series of pictures have also been utilized (Erwin et al. 1992; Kerr and Neale 1993). OT administration has been shown in two studies to increase the correct identification of emotions in faces in subjects with SCZ (Goldman et al. 2011; Averbeck et al. 2012). *We hypothesize that deficit syndrome SCZ subjects will exhibit improvement in facial emotion recognition after administration of OT (Specific Aim 2c).*

METHODS

1. Description of study population

Subjects for the study will be forty male patients with a diagnosis of SCZ. Diagnosis will be determined using the Structured Clinical Interview for DSM-IV Axis I Disorders/SCID-P (Spitzer et al. 1992). Subjects must be categorized as having a primary deficit syndrome on the Kirkpatrick Schedule for the Deficit Syndrome (Kirkpatrick et al. 1989).

Additional inclusion criteria:

1. Subjects must be between 18 and 65 years old at the time of study screening.
2. Subjects must demonstrate adequate decisional capacity, in the judgment of the consenting study staff member, to make a choice about participating in this research study.
3. Subjects must have been psychiatrically and medically stable for 8 weeks prior to consent in the judgment of the Principal Investigator.
4. Subjects must have been maintained on a stable treatment of antipsychotics and/or other concomitant psychotropic treatment for at least 6 weeks prior to consent.
5. Subjects must have no more than a moderate severity rating on hallucinations and unusual thought content as shown by a score of ≤ 4 on the Positive and Negative Symptoms Scale (PANSS).
6. Subjects must be able to validly complete the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB), in the judgment of the consenting study staff person.
7. Subjects must have the visual, auditory, and motor capacity to use the computer software in the judgment of the consenting study staff person. Visual acuity must be at least 20/30 corrected.
8. Subjects must have a minimal level of extrapyramidal symptoms as shown by a Simpson-Angus Scale total score ≤6.
9. Subjects must have a minimal level of depressive symptoms as shown by a Calgary Depression Scale (CDSS) total score ≤10.

Exclusion criteria:

1. Female sex
2. History of bipolar disorder
3. Active substance dependence within the prior 30 days (cigarette smoking is allowed)
4. Has had a psychiatric hospitalization in the 8 weeks prior to consent.
5. Suicidal or homicidal ideation in the previous six months
6. Subjects who have answered 'yes' to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the Columbia-Suicide Severity Rating Scale, C-SSRS, or who have answered 'yes' to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the C-SSRS "Suicidal Behavior" portion shall be excluded from the study if ideation or behavior occurred within one month of consent. Subjects excluded for this reason will be referred for appropriate treatment.
7. History of mental retardation or pervasive developmental disorder
8. History of neurological disorder (e.g., traumatic brain injury, seizure disorder, Parkinson's Disease, dementia), loss of consciousness for more than 10 minutes due to head trauma, known HIV infection, or AIDS
9. Treatment with a benzodiazepine in the two weeks prior to consent.

We will also be collecting data from up to twenty male participants, who have no psychiatric diagnosis and will be controls for this project. These controls will NOT receive oxytocin. They will only receive psychiatric screening interview, MCCB Consensus Cogntive Battery assessment, urine drug screen, vision testing, and the three social cognition tasks. For the control participants, the criteria is as follows:

Inclusion criteria:

- Male
- Ages 18 - 65

Exclusion criteria:

- Female
- History of a psychotic disorder, or depression requiring medication
- Active substance abuse or dependence within the prior 30 days
- Medical admission within the past six months

- Criteria to rule out subjects with medical problems likely to present a confound:

- Known HIV infection or AIDS
- History of TBI
- Seizure disorder
- Known Alzheimer's Disease or other dementia
- Minimal cognitive impairment (MCI)
- Parkinson's Disease
- Unstable medical condition

All subjects must provide informed consent as indicated by their signature on an Emory IRB-approved consent form and HIPAA authorization prior to participating in this study.

2. Study design

The study will be a double-blind placebo-controlled parallel group study of intranasal OT vs. intranasal placebo administered on a single test day.

3. Baseline evaluation

A diagnosis of schizophrenia will be confirmed by a structured diagnostic interview (SCID-patient version). Current symptoms will be rated by means of the Positive and Negative Symptom Scale (PANSS; Kay et al. 1987). The Kirkpatrick Schedule for the Deficit Syndrome will be used to confirm that subjects have a primary deficit syndrome (Kirkpatrick et al. 1989). As per new FDA requirements governing management of suicidality in clinical trials, the Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered on the Baseline day. As a safety precaution, subjects will receive a medical history, measurement of vital signs, a blood draw for chemistry, and a urinalysis to screen for unstable medical conditions. Subjects will also receive a urine toxicology screen to rule out active drug use at Baseline. Eye chart screening will be used to insure adequate visual acuity. The Simpson-Angus Scale (Simpson and Angus 1970) will be used to assess the extrapyramidal symptoms since clinically significant Parkinsonian side effects to antipsychotic medications could be a confound in our outcome measures. The Calgary Depression Scale (CDSS; Addington et al. 1992) will be performed to assess depressive symptoms since significant depressive symptoms could also be a confound in our outcome measures.

Because the social cognition measures rely in part on cognitive domains such as verbal memory, visual memory, and attention, these domains at Baseline will be assessed by means of the MCCB. The development of the MCCB was supported by the National Institute of Mental Health, and has emerged as the most respected battery of tests for understanding the cognitive functioning of people with SCZ. It is a standardized battery consisting of 10 individually administered tests that examine speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (Kern et al. 2008).

4. Description of pharmacological challenge

OT intervention will be administration of OT intranasally at a dose of three 4 IU puffs per nostril for a total dose of 24 IU. This dose has been used in a number of other similarly designed challenge

studies examining the effects of a single dose of OT (Kirsch et al. 2005; Kosfeld et al. 2005; Guastella et al. 2008a; Guastella et al. 2008b; Rimmele et al. 2009; Andari et al. 2010).

The PBO/control will consist of the OT vehicle only. Treatment assignment will be by random allocation in blocks of six. Both experimenters and subjects will be blind to the treatment they are receiving.

Thirty minutes after drug administration vital signs will be done. Testing of outcome measures for Specific Aims 1a - 1c will commence 45 minutes after administration of OT or placebo in the following order: Eye Tracking, Social Reward Ball-Tossing Task, and FEIT.

5. Social cognition outcome measures

a. Eye tracking. Methods will be similar to those used in Andari et al. (2010) and Guastella et al. (2008a). In order to assess the processing of social stimuli, subjects will be presented with a series of human faces of mixed sex and race showing neutral emotions and instructed to visually scan each face. There will be two face identification tasks used in the Eye Tracking session: *(i) Sex Identification Task.* After 2 seconds (sec) looking at each of 24 male and female faces from the NimStim set of facial expressions (Tottenheim et al. 2009), the subjects will indicate with a button press whether the face was male of female. *(ii) Gaze DirectionTask.* After 2 sec looking at each of 24 faces from the Wicker B database (Wicker et al. 2008) with gaze either averted or gaze looking straight ahead, the subjects will indicate with a button press whether the face was looking directly at them or looking away. Presentation software (Neurobehavioral Systems, Inc., Albany CA) will be used to present the visual stimuli and record the subjects' responses.

Subjects will be seated with their chin resting on a chin rest, their forehead resting against a bar, and head strap fastened to minimize head movements. The Applied Science Laboratories (ASL) Model 5000 Eye Tracking System will be used to track and quantify the eye movements of the subjects at a sampling rate of 50 Hz during the tasks. Calibration of eye position will be performed according to standard recommended procedures by ASL. Gaze position time in milliseconds (ms) and frequency saccades will be recorded by the ASL system.

Six regions of interest (ROIs) will be defined for each face stimulus: eyes, nose mouth, forehead, cheeks, and outside the contours of the face. The data will be processed off line for each face stimulus as the total time of fixation inside each of the ROIs and the number of saccades elicited by the face.

b. Reward Ball-Tossing Task. Methods will be adapted from Andari et al. (2010). In order to assess social reward sensitivity, subjects will perform a computerized Social Reward Ball-Tossing Task that consists of a modified version of Cyberball. Subjects will play an animated ball-tossing game with two fictional partners (A and B) who will be represented by their photos. Unbeknownst to subjects, the photos of the partners will be manipulated so that the photo of player A will display a smiling face (positive social reward) and the photo of player B will display an angry expression (negative social reward). These faces expressions will be presented on the screen in an animated fashion in order to enhance emotional responses in the subjects. The subject will commence playing a ball-tossing game in which the ball is tossed between the subject and his partners. The probability of ball-toss reciprocation will be randomly assigned between partners so that the subject has 50% of chance to receive the ball from A or B. These trials will be interleaved with neutral trials (neutral expressions) and non-social trials where subjects will play with random geometric shapes associated with positive and negative non-social rewards (green light versus red light).

c. Facial Emotion Identification Test (FEIT). The methods to be used are based on studies using this test in SCZ (Mueser et al. 1996; Wolwer et al. 1996; Penn and Combs 2000; Addington et al. 2006). The stimuli are19 standard black and white pictures of faces showing one of six different emotions (happy, sad, angry, surprise, disgusted, ashamed) that were developed by Ekman and Friesen (1976). The pictures are shown for 15 sec, with 10 sec between each face. After the presentation of each face

the subject is asked to choose which of the six emotions was displayed. The score on the test is the sum of correct responses.

Specific Aim 1a: Evaluate the salience of social cues by the measurement of eye tracking (visual scanpaths) during gaze at pictures of faces.

Hypothesis: Subjects receiving OT will exhibit more total gaze time within facial regions, and will have greater preference for gaze at the face area most salient for facial emotion decoding (eyes) than subjects receiving placebo. We hypothesize that during the Gaze Direction Task the OT group will have reduced saccades than the PBO group. This was seen in the Andari et al. (2010) study and interpreted as resulting from the subjects exploring the faces with multiple brief fixations separated by saccades indicating greater anxiety during this task that required examination of the eyes in order to make the judgment about gaze direction of the face stimuli.

Design and methods: 40 subjects with SCZ will randomized in a double-blind manner to receive a single dose of either OT or PBO, 45 minutes after which they will be tested on the Eye Tracking Tasks.

Statistical approach: The data will be analyzed separately for the Sex identification Task and the Gaze Direction Task. Within each of these tasks, the total fixation time in each of the ROIs and the total number of saccades will be computed for each face stimulus for each subject. Descriptive statistics in the OT and PBO groups will be computed for each of the face categories (male vs. female in the Face Identification Task or direct vs. averted gaze for the Gaze Direction Task). Mixed model ANOVAs will be constructed with a between-subjects factor of group (OT vs. PBO) and repeated measures factors of face (male vs. female or direct vs. averted gaze) and ROI. The initial analysis will use for the ROIs the areas within vs. outside the facial contours. Follow up ANOVAs will use all six ROIs (eyes, nose, mouth, forehead, cheeks, and outside the facial contours). The number of saccades will be analyzed in a similar manner. Should Baseline MATRICS total or subscale domain scores differ between the OT and PBO groups, those domain scores that differ significantly will be used as covariates in the ANOVAs. Significant main effects will be followed up by appropriate post-hoc tests.

Specific Aim 1b: Evaluate sensitivity to social reward by means of a computerized social reward ball-tossing task that assays social interactions in response to social reward.

Hypothesis: We predict that subjects in the PBO group will be insensitive to differences between the positive (socially rewarding) partner and the negative (socially non-rewarding) partner. Based on the results of previous literature on the social deficits of patients with SCZ, we predict that those subjects in the OT group will send more balls to the positive partner and decrease the latency in tossing the ball to the positive partner compared to the negative partner than will the subjects in the PBO group. We predict that the OT effect is likely to be selective for social trials as opposed to non-social trials.

Design and methods: 40 subjects randomized to receive a single dose of OT vs. placebo will perform the social reward ball-tossing task. Performance on the task will be compared between the OT and PBO groups.

Statistical approach: The number of balls sent to each of the partners, as well as the reaction time for each of the subjects' ball toss will be quantified to assess socially reinforced learning. An increase of number of balls sent to the positive player and a decrease in the reaction time to toss the ball to this player compared to the negative partner would indicate that social reward was affecting the subjects' behavior. The number of ball tosses to A and B within each block will be quantified. These data will

then be analyzed using a four-factor ANOVA (factors are OT vs. PBO; Player A vs. Player B; and block type [positive affect, negative affect, neutral affect, non-social reward]).

Specific Aim 1c: Evaluate social cognition by means of testing the ability to correctly identify emotion from pictures of faces as assessed by the FEIT.

Hypothesis: We hypothesize that the OT subjects will perform significantly better than the PBO on the FEIT.

Design and methods: 40 subjects randomized to receive a single dose of OT vs. PBO will perform the FEIT. Performance on the task will be compared between the OT and PBO groups.

Statistical approach: Descriptive statistics in the OT and PBO groups will be computed. The OT and PBO subjects' performance on the FEIT will be analyzed by means of a between-subjects ANOVA on the sum of correct responses. If Baseline MATRICS total or subscale scores differ between the OT and PBO groups, those subscale scores that differ significantly will be used as covariates in the ANOVAs.

6. Sample size determination

Sample size calculations are based on effect sizes (Cohen's d) in published studies of the social cognition tasks to be used. For all calculations alpha is set at 0.05.

Specific Aim 1a, Eye Tracking. For the eye tracking task, several studies reported abnormalities in eye tracking in SCZ compared to healthy controls. In two studies by Loughland et al. (2002a and 2002b), SCZ had reduced fixation on faces with an effect size of 0.74 and 0.73 respectively. The study by Green et al. (2003) reported a larger effect size of 1.12 for the reduction in the number of fixations on angry faces in SCZ subjects compared to controls. There is one study of OT administration in healthy controls in which the effect size for increased gaze to the eye region of face pictures after OT vs. PBO administration was 1.20 (Guastella et al. 2008a). If we conservatively assume that OT administration to our SCZ subjects will yield increased gaze to face stimuli with half the improvement reported in the Guastella et al. study, this would yield an effect size of approximately 1.0. Taken together, basing our sample size calculation for eye tracking on a conservatively anticipated effect size of 0.74, a sample size of **20 subjects per group** will be required to yield power of 0.80.

Specific Aim 1b, Social Reward Ball-Tossing Task. There are no published studies of this task in SCZ, so sample size calculations are based on the use of a similar task in high functioning autism subjects after OT or PBO (Andari et al. 2010). In that paper, the number of ball tosses to the "good" partner minus the ball tosses to the "bad" partner were significantly higher after OT than after PBO, with an effect size of 1.39. Assuming we see an improvement in this outcome measure in our SCZ at a more modest effect size of 0.8, a sample size of **18 subjects per group** will yield a power of 0.80 (one-tailed).

Specific Aim 1c, FEIT. The sample size determination for this task is based on several studies reporting reduced performance on this task in SCZ compared to healthy controls. In the Penn and Combs study (2000) a very large effect size of 2.2 was reported for this between-group difference. Addington et al. (2006) reported a between-group difference effect size of 0.82. An earlier study (Mueser et al. 1996) reported a between-group difference at an intermediate effect size of 1.79. We conservatively estimate that we will see the smallest of these three effect sizes, namely 0.82, for a difference between OT and PBO. This effects size will require a sample size of **19 subjects per group** (1-tailed) to yield a power of 0.80.

Summary of sample size determination. Based on the above calculations, we will plan to complete **20 subjects per group** or a total of 40 subjects. This number will enable us to detect significant between-group differences with power of 0.80 and alpha set at 0.05.

7. How this project will promote the goals of the CTSN and promote obtaining NIH funding

This project fits well within the area of interest of the CTSN since it represents a direct clinical translation of the preclinical neurobiology of OT. This project will provide necessary pilot data for a larger more definitively powered clinical trial of OT in SCZ that will be submitted to NIH. In that grant submission, in addition to the clinical trial component with social cognition outcome measures, a Specific Aim will be added to examine fMRI correlates of processing of social stimuli in the OT and PBO treated groups.

8. DSMB

The study will be closely monitored by the Principal Investigator, Dr. Erica Duncan, who is an attending psychiatrist at the Atlanta VA and an Associate Professor of Psychiatry at Emory University. In addition, the study will be monitored by the DSMB of the Department of Psychiatry and Behavioral Sciences at Emory University. This board is composed of Larry Tune MD, Boadie Dunlop MD, Bobbi Woolwine, LCSW, Tanja Mletkzo, Ray Tiyamiyu and Emeka Madubuike. Any unexpected or serious adverse events will be reported to the Emory University IRB in accord with the reporting requirements of the IRB.

9. Risk-benefit ratio

Subjects will receive a total of $100 to compensate for their time and effort to participate in the study. This is necessary in order to sustain motivation and engagement in the study and in order to compensate subjects for their time and travel expenses. As per the rules of our Institutional Review Board at Emory University, subjects will be compensated on a prorated basis on each of the two days that they come for study visits. Patients with schizophrenia may potentially benefit from knowledge gained in this study about OT as an adjunctive treatment option.

10. Risks

1. Phlebotomy: The risks are bleeding, infection at the blood draw site, and pain.
2. Measurement of vital signs: There are no risks.
Interviews for psychiatric history and symptom rating: The risk is that emotionally upsetting material may come up in the interviews.
3. Cognitive testing: The risk is one of frustration or boredom.
4. Loss of confidentiality: Collection of identifying information and information about psychiatric diagnosis and symptoms poses the risk of loss of confidentiality.
5. Intranasal OT administration: OT (Syntocinon) may trigger labor in pregnant women and milk ejection in women who recently gave birth. Since we will only enroll men, these side effects are not of concern for this study. In rare cases, nausea, vomiting, irregularities of the pulse, skin rashes and allergic reactions in combination with shortage of breath, blood pressure decreases or circulatory collapse have been reported **following the regular and repeated administration of Syntocinon**. However, it is important to note that no adverse side effects have been reported following the administration of OT in schizophrenia subjects for three weeks in the Feifel et al. (2010) study at twice the daily dose we will use.

11. Steps taken to minimize risks

1. Phlebotomy: The risks will be minimized by the use of standard sterile technique.
2. Measurement of vital signs: No steps necessary.

Interviews for psychiatric history and symptom rating: If emotionally upsetting material arises during interviews, the rater will redirect the interview into less emotionally laden areas and give the subject a chance to recover. Subjects will not be required to discuss material they are uncomfortable discussing.
3. Cognitive testing: Subjects will be guided through the cognitive testing with sensitivity to difficulties they may be having. They will be given the opportunity to rest if needed.
4. Loss of confidentiality: Study data and subject information will be stored in locked file cabinets in the research lab of Dr. Duncan, to which only research staff have keys and access. All electronic data containing HIPAA identifiers will be stored only on VA approved password approved computers located within the Duncan lab at the Atlanta VAMC, or backed up and password protected on VA research servers.
5. Intranasal OT administration: Prior to randomization, subjects will be screened with measurement of vital signs, SMA-12 (basic chemistry), and urinalysis. Subjects will be excluded for clinically significant abnormalities in these measures.

PLAN FOR DISCHARGE OF INVESTIGATOR/SPONSOR RESPONSIBILITIES TO THE FDA

The following responsibilities to the FDA will be performed by the PI with the assistance of the study team.

1. Responsibilities as the IND Sponsor:

a. Maintain an effective IND with respect to the investigations.
b. Submit annual reports on the progress of the investigation to the FDA.
c. Report essential information on the IND that is not within the scope of a protocol amendment, IND safety reports, or annual report, such as new toxicology, chemistry or technical information.
d. Submitting a protocol amendment to describe any change(s) in the protocol.
e. Selecting only qualified investigators by training and experience as appropriate experts to investigate the drug.
f. Providing each participating investigator with all information required to conduct the study properly.
g. Obtaining the following information from each participating investigator **before permitting them to begin any activity on the investigation**:
    i. Signed and completed investigator statement(s) – Form FDA 1572
    ii. Curriculum Vitae or other statements of qualification on file for all investigators
    iii. Clinical Protocol
    iv. Financial Disclosure Information (see next section)

2. Financial Disclosure:

Maintain current, complete and accurate records documenting the financial interests of all participating clinical investigators, including sponsor payments, for the duration of their participation in any covered studies under the IND, **plus 1 year** following the completion of the study.

3. Study Management:

a. Notify the FDA in written IND safety reports, of adverse events related to the drug that is both serious and unexpected.
b. Review and evaluate the evidence relating to the safety and effectiveness of the drug, and report serious and unexpected adverse events to FDA.
c. If the PI determines that the investigational drug presents unreasonable and significant risk to subjects, discontinue those investigations and notify the FDA and IRB. This notification would occur as soon as possible, and in no event later than 5 working days after making the determination.

4. Monitoring And Selection Of Study Monitors:

a. Arrange for the monitoring of the progress of all clinical investigations being conducted under the IND, to ensure that the investigation is conducted in accordance with approved investigational plan and protocol covered by the IND and in compliance with the signed FDA form 1572.
b. Select a monitor qualified by training and experience to monitor the progress of all clinical investigations conducted under its IND.

5. Receipt, Storage, Disposition, and Return of Investigational Drug:

Maintain adequate records showing receipt, shipment, or other disposition of the investigational drug. These records must include the name of the investigator to whom the drug is shipped, and the date, quantity, and the batch or code mark of each such shipment.

6. Current Good Manufacturing Practices (CGMP):

Ensure the minimum current good manufacturing practice for preparation of drug products for administration to humans in compliance with the requirements of § 501(a)(2)(B) of the FD&C Act.

7. Labeling and Representation of Investigational New Drug:

a. Immediate packaging of the IND intended for human use bears a label with the statement, "Caution: New Drug – Limited by Federal (or United States) law to investigational use".
b. Insure that the IND drug label does not bear any statement that is false or misleading, and does not represent the IND as safe or effective for the purpose it is being investigated.
c. Insure that the investigator does not represent the IND as safe or effective for the purposes for which it is under investigation.

8. ClinicalTrials.gov:

Insuring that the clinical trials is registered and results reported. The trial will be registered at trial initiation, but not later than 21 days after enrollment of first participant and to report summary results information for interventional studies of drugs within 1 year of completing data collection for the pre-specified primary outcome.

7. Budget

BUDGET SUMMARY		
		Year 1
Personnel:	$	36,288
Consultant:	$	-
Equipment:	$	-
Supplies	$	4,106
Other:	$	4,826
TOTAL:	**$**	**45,220**
DETAILS		
Supplies		
		Year 1
MATRICS test supplies @$30 each (45 tests)	$	1,350
OXY and placebo study drug	$	2,000
urine tox kits @ $6.25 each (45 kits)	$	281
Ekman stimuli	$	175
Custom cable for eye tracking	$	200
Screen converter for eye tracking	$	100
Supplies Total	**$**	**4,106**
Other		
		Year 1
VA lab CHEM 12 @ $12.39	$	558
VA lab urinalyses @ $2.63	$	118
Human Participant payment @ $100 per subject + $30 per screen failure	$	4,150
Other Total	**$**	**4,826**

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