AWARD NUMBER: W81XWH-12-1-0543

TITLE: A randomized controlled trial of intranasal oxytocin as an adjunct to behavioral therapy for autism spectrum disorder

PRINCIPAL INVESTIGATOR: John Gabrieli, PhD

CONTRACTING ORGANIZATION: Massachusetts General Hospital
Boston, MA 02114

REPORT DATE: December 2017

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
December 2017	Final	30Sep2012 - 29Sep2017

4. TITLE AND SUBTITLE

A Randomized, Controlled Trial of Intranasal Oxytocin as an Adjunct to Behavioral Therapy for Autism Spectrum Disorder.

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-12-1-0543

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Aude Henin, Ph.D. and John Gabrieli, Ph.D.

E-Mail: ahenin@partners.org

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESSES
Massachusetts General Hospital, Boston, MA 02114

Massachusetts Institute of Technology,
Cambridge, MA 02138

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The aim of this study was to conduct a double-blind, placebo controlled trial to examine the feasibility and efficacy of cognitive behavioral therapy (CBT) for young men with autism spectrum disorder. In addition, the study examined whether oxytocin administration prior to CBT sessions can enhance treatment effects. To examine these questions, we recruited 57 male participants (ages 18-40 years) with a primary diagnosis of autism spectrum disorder. Participants were randomized to receive 12 weeks of individualized social skills training, with or without oxytocin augmentation, or a 12-week stress management intervention (plus placebo drug). Participants were assessed at baseline and every 4 weeks during treatment, as well as at post-treatment by an evaluator who was blind to treatment condition. Assessments included clinician-, self-, and parent reports of autism spectrum disorder symptoms, anxiety, depression, social skills, and overall functioning. In addition, we performed functional (fMRI) and structural (MRI) imaging with participants prior to treatment, to examine whether neuroimaging measures of brain function and structure can predict CBT treatment responsiveness. Data analyses are ongoing with results

15. SUBJECT TERMS
Cognitive-behavioral therapy, oxytocin, neuroimaging, emerging adults, autism

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	11	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

INTRODUCTION:

The primary objectives of this clinical study were to test the two hypotheses that (1) cognitive behavioral therapy (CBT) aimed at core social dysfunctions and (2) oxytocin (OT) administration prior to CBT sessions will each enhance social function in young adults with autism spectrum disorders (ASD). A third objective was to examine whether neuroimaging measures of brain function and structure can predict CBT treatment responsiveness.

To examine these questions, we recruited 57 men, ages 18-40, with ASD into this study. All participants were high-functioning patients with IQ scores in the average-to-above average range (90 and higher). Participants were randomly and blindly assigned into one of three groups, with stratification on age, ASD severity (ADOS score), and IQ:
(1) Group 1 (*All Placebo*), who received an active placebo behavioral treatment of 12 sessions of relaxation training, and placebo medication;
(2) Group 2 (*CBT/placebo*), who received the experimental CBT 12-session treatment, and placebo medication; and
(3) Group 3 (*CBT/OT*), who received the experimental treatment, and OT before 12 sessions of CBT treatment.

Participants were assessed at baseline and every 4 weeks during treatment, as well as at post-treatment by an evaluator who was blind to treatment condition. Assessments included clinician report, self-report, and parent reports of autism spectrum disorder symptoms, anxiety, depression, social skills, and overall functioning. In addition, we performed functional (fMRI) and structural (MRI) imaging with participants prior to treatment, to examine possible relationships between measures of brain function and structure and improvements on outcome measures to discover whether there are neural characteristics that can identify which ASD patients are most likely to respond to behavioral intervention.

BODY:

Progress To-Date (As per Statement of Work)

Task 1. IRB approval

Submit clinical trial description documents to local IRBs and HRPO.

1a. Update consent forms to reflect local IRB and HRPO regulations (months 1) MIT+MGH

1b. Apply for MIT IRB approval (months 1-3) MIT

- **We initially submitted the application for IRB approval in May 2013, initial approval was given in October 2013.**
- **Approval for the most recent continuing review at the MGH IRB was received on July 28th, 2017.**

1c. Apply for MGH IRB approval (months 1-3) MGH

1d. Apply United States Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO) approval (months 2-5) MGH+MIT

- We received an IND from the FDA for the use of oxytocin in the study
- We submitted the protocol to the HRPO upon preliminary approval from MGH and MIT IRB and received approval from HRPO on April 4, 2014 for the MIT Site and on April 7th 2014 for the MGH Site.
- We created a CT.gov account for the study and have updated this account regularly, as per the CT.gov requirements.
- Both MIT and MGH received access to NDAR (National Database for Autism Research) and completed an initial submission in July 2015. Both sites are currently preparing data for the January 2018 submission.

Task 2. Staff recruitment and preparation of testing materials, initial pilot study
This task involves setting up the system for subject recruitment, randomization and tracking. As well as setting up a system for continuously adding assessment results.

- **The study staff is as follows:**
Principal Investigators:
o John Gabrieli, Ph.D. (PI)
o Aude Henin, Ph.D. (co-PI)

MGH Staff:
o Dina Hirshfeld-Becker, Ph.D. (independent evaluator at MGH)
o Angela Utschig, Ph.D. (study therapist at MGH)
o Jamie Micco, Ph.D. (study therapist at MGH)
o Jennifer Park, Ph.D. (independent evaluator at MGH)
o Christine Cooper-Vince, MA (study therapist at MGH)
o Ben Shapero, MA (study therapist at MGH)
o Tim Soto, MA (study therapist at MGH)
o Gagan Joshi, MD (study physician)
o Janet Wozniak, MD (study physician)
o Tanishia Choice, MD (study physician)
o Sophie Baron, B.A. (research assistant)
o Christian Hoover, B.A. (research assistant)
o Flavia Vaz De Souza, B.A. (research assistant)
o Carrie Vaudreuil, M.D. (study physician)
o Anthony Debenedetto (intern/student)
o Carrie Vaudreuil, M.D. (study physician)
o Anthony Debenedetto (intern/student)

MIT Staff:
o Satrajit Ghosh, Ph.D. (MIT PI, neuroimager and statistician, MIT)
o Susan Whitfield-Gabrieli (Research Scientist, MIT)
o Dorit Kliemann, Dr. (neuroimager and project coordinator, MIT)
o Annie Cardinaux, Ph.D. (independent assessor at MIT)
o Caitlin Malloy, Ph.D. (independent assessor at MIT)
o AJ Haskins (independent assessor at MIT)
o Thomas Quartieri (data analyst of voice data, MIT)

- Greg Ciccarelli (data analyst of voice data, MIT)
- Mathias Goncalves (technical research assistant, MIT)
- Yoel Sanchez Araujo (technical research assistant, MIT)

- **We have trained study clinicians on the CBT therapy protocol, and the independent evaluators on the study measures**

- **We have initiated regular meeting with MIT and MGH staff to jointly coordinate ongoing steps and topics.**

- **MIT and MGH staff have completed the work on developing a data entry system that will facilitate cross-site sharing of data**

2a. Prepare stimuli and scanner protocol (months 1-3) MIT
We will create a setup for stimulus presentation using the Psychophysics Toolbox for MATLAB. The setup will include stimulus presentation for functional localizers used in the imaging sessions as well as tests for attention during the pre and post periods. Prepare stimuli and presentation for RMET and Social cooperation task.

Sequences for functional and structural neuroimaging prior to treatment have been tested for study eligibility (all with whole-brain coverage in a higher resolution 32-channel coil):

- ***Resting State:*** **2x2x2 mm, TR=1.09s, TE=30 (2x- PA and AP phaseencoding)**
- ***Structural:*** **MEMPRAGE: 1x1x1mm, Multi-echo (withpossiblemotioncorrection)**
- ***T2 SPACE:*** **1x1x1mm, bandwidthmatchedto T1-weighted MEMPRAGE**
- ***Diffusion weighted:*** **5mXXs, 2x2x2 mm, 61 directions, b=1000, 9 b=0 values (2x, PA, AP)**
- ***Functional tasks:*** **3x3x3mm TR=2.5s, TE=30ms**

- These tasks have been successfully piloted and are functioning as expected
2b. Setup software for behavioral testing (months 1-3) MGH+MIT
The research coordinator will install the study software on the study purchased laptops.

- We worked with developers of behavioral tasks to implement several behavioral tasks in the study

- The behavioral tasks have been implemented as part of the assessment protocols and are working as expected

2c. Run pilot experiments (months 5-7) MGH+MIT
Run the initial pilot study to ensure all components are operational.

- **The imaging protocol was piloted with several participants at MIT and is operating as expected.**

2d. Setup contract with pharmacy to supply drug and placebo after IRB approval.

- **We worked with the MGH pharmacy, MGH mailroom, and the oxytocin distributor to obtain the oxytocin and placebo for the study. We successfully ordered and had shipped the oxytocin and placebo from the manufacturer, set up and implemented the blinding and randomization procedures with the MGH pharmacy, and administered the drug/placebo to participants during the treatment phase.**

Task 3. Begin recruitment of 150 subjects (Specific Aim 1,2)
We will start recruiting subjects for the study in an ongoing basis, taking care to balance enrollment subject to characterization by clinical assessment.

3a. Announce study to clinics, referral sources (months 5-34) MGH

- **We created advertising materials including clinician and patient letters, advertisements to be posted on the subway and other public locations, and internet advertisements. We posted an ad on the local subway in July 2014 and have reposted this ad several times since then. In addition, we have posted the ad on Craigslist, the MGH clinical trials website, and the MGH research website. We have also posted paper versions of the ad at local colleges and other public places.**

- **We met with local individuals and agencies (e.g., Lurie center, Child Psychiatry Department, and Bressler center) to inform them of our study and facilitate recruitment.**

- **We developed and implemented, with the MGH pharmacy, a blocked randomization schedule that takes into account potential confounds such as level of autism severity, IQ, participant age, and current medication status.**

Task 4. Subject workflow (months 5-34)

After consenting, all subjects will undergo characterization by the clinician and if admitted to the study will be scheduled for imaging sessions and will be given directives on how to use the software.

4a. Telephone screen MGH

- **We developed the telephone screen and received MGH IRB Approval for its use.**
- We screened a total of 127 potential participants.

4b. Characterization by clinician (Specific Aim 1) The characterization of subjects

will include a formal clinical neurological examination and symptom assessment as described in Specific Aim 1, and a neuroimaging exam (Specific Aim 3). MGH + MIT

- The independent evaluators were trained and received ongoing supervision to ensure reliability.

- We consented and conducted baseline characterization with 57 participants and 35 of their parents. Twelve of these participants were found ineligible at baseline for the following reasons

- **Long QT interval on EKG (1 participant)**
- **Significant psychotic symptoms (2 participants)**
- **Severe mood and sleep problems (1 participant)**
- **Did not meet diagnostic criteria for ASD (3 participants)**
- **Significant medical illness (COPD 1 participant)**
- **Suicidality (1 participant)**
- **Homicidality with need for immediate hospitalization (1 participant)**
- **IQ below cutoff (1 participant)**
- **Age above cutoff (1 participant reported that he was age 40 but then was found to be in his 50's)**

-Two participants were withdrawn during treatment. The first was withdrawn after the therapist uncovered that he had psychosis, an exclusion criteria. The other participant was withdrawn during treatment due to a severe adverse event that we could not definitively determine was unrelated to study treatment.

-Six participants dropped out voluntarily during the study due to scheduling difficulties and/or moving out of state. Four of these were post-randomization.

4c. Schedule imaging session. MIT
- **We completed baseline neuroimaging sessions with 36 participants.**

4d. Schedule CBT. MGH

Task 5. Perform neuroimaging, pre-treatment assessment and CBT(Specific Aim 2, 3; months 5-34) MGH + MIT
During this phase all subject data are collected. Each subject participates in the study for approximately 60 days.

5a. Collect imaging data during pre-treatment visit. MIT
Visit 1 (pre-treatment) consist of structural and functional brain measures requiring 1 hour in the scanner per visit. Diffusion, structural and functional data will be collected.

- **Neuroimaging sessions and pre-scanning ADOS-assessments were implemented without issue.**

5b. Perform CBT for 12 weeks (12 sessions) MGH
- **We completed treatment with 29 participants.**

5c. Safety Review
Data collected for the proposed research will be stored in secure physical files, and password protected electronic files. All measures will be taken to protect the identity of participants. The files from this study may be available for review by USAMRAA, the Institutional Review Board (IRB) at MIT and MGH, and by representatives of other governmental agencies as part of their normal duties. All records will be kept in a form. Otherwise, only the members of the research team conducting this study will have access to the study records. Information gained from this study may be used as part of a scientific publication; however, participants will in no way be personally identified. We will keep completely de-identified data wherever possible so that sharing of data is easiest and available for submission into the NDAR.

- **We held DSMB meetings and received approval from our committee with no safety concerns.**
- **Both MIT and MGH received NDAR approval**

Task 6. Analysis of data (Specific Aim 2,3; months 5-34) MIT + MGH
The data will be analyzed at both MIT and MGH. The focus at MIT will be on the analysis of the imaging data, while the focus at MGH will be to analyze the clinical assessment data

6a. Analysis of imaging data
We started analysis of the individual imaging data will using the NiPyPE imaging analysis framework and using tools from well-established neuroimaging analysis packages (SPM, FSL and FreeSurfer).

6b. Analysis of behavioral data
When each participant completes the study, the research coordinator will download the participants data from the secure web portal. Research coordinator will transcribe these data into the centralized study database for statistical analysis as described in the full research proposal. We have started work to extract, visualize, and analyze the clinical and behavioral information stored in the RedCap database.
Data analysis of behavioral tasks is ongoing

Task 7. Preparation and publication of results (Specific Aim 3,4; months 34-36)
Once sufficient data has been prediction models will be prepared in order to determine which form of treatment is most effective for a particular case characterization.
Data analysis is ongoing and results are not yet available.

7a. Preparation of treatment prediction models MIT

7b. Preparation of manuscripts MIT+MGH

We are currently working on analyzing study data and will work on manuscript preparation in the near future.

7c. Submission of curated data into NDAR.

- **Initial submission was completed in July 2015.**
- **January 2018 submission is currently in preparation.**

List of acronyms:
DTI – Diffusion tensor imaging
fMRI – Functional magnetic resonance imaging
MGH – Massachusetts General Hospital
MIT - Massachusetts Institute of Technology
RCT – Randomized control trial

KEY RESEARCH ACCOMPLISHMENTS:

- Obtained comprehensive clinical information on 57 men with autism spectrum disorder
- Obtained fMRI, MRI, and DTI data on 36 men with autism spectrum disorder
- Completed a randomized clinical trial with 29 men with autism spectrum disorder

REPORTABLE OUTCOMES:
Presentations:

Henin, A. Cognitive Behavior Therapy for Autism Spectrum Disorders. Presented as part of an MGH Psychiatry Academy Course in 2012, 2015, and 2016.

Henin, A. (2016) The Promise of Oxytocin as an Intervention for Individuals with Autism Spectrum Disorders. Presented at the Annual Meeting of the Association for Behavioral and Cognitive Therapies, New York, NY.

Manuscripts:

Henin A., Berman N. The promise and peril of emerging adulthood: Introduction to the special series. Cognitive and Behavioral Practice. 2016 Aug 23(3): 263-412.

Park, J.M., Baron, S, Hoover, C.S., and Henin, A. Cognitive Behavioral Therapy. In the Sage Encyclopedia of Intellectual and Developmental Disorders (Ellen Braaten, editor). In press.

Employment and Research Opportunities:

Sophie Baron, B.A., a research assistant on this project, went on to graduate studies in social work at Boston University.

Noah Berman, Ph.D., study clinician, accepted a position as an Assistant Professor of Psychology at the College of the Holy Cross, Worcester, MA.

Dorit Kliemann, Ph.D., a postdoctoral fellow on the project, accepted a postdoctoral scholarship in Cognitive Neuroscience at Caltech, Pasadena, CA.

Jennifer Park, Ph.D., a postdoctoral fellow on this project subsequently accepted a position as Clinical Director of Rogers Behavioral Health-San Francisco East Bay, San Francisco, CA.

CONCLUSIONS: The current study offers important information about the feasibility, acceptability, and efficacy of social skills training in young men with autism spectrum disorders. The study highlights the extensive comorbidity and functional difficulties in these young men, as well as their treatment needs. There are specific challenges when

implementing cognitive-behavioral treatment protocols in this population, including heterogeneity of presenting symptoms, cognitive strengths and vulnerabilities, and functional impairment. Therefore, treatment protocols need to be sufficiently flexible to address these varying treatment needs while maintaining fidelity to underlying treatment principles. The current study is one of the first to examine these questions and as such, will yield important information to guide psychosocial interventions with this vulnerable population at high need for efficacious treatment. In addition, the study will examine whether predictors of treatment response (both psychosocial and neurobiological) can guide the selection of treatment strategies.

REFERENCES: N/A

APPENDICES: N/A

SUPPORTING DATA: N/A