University of Nebraska Medical Center

DEPARTMENT OF PSYCHIATRY

RE: NCT 02824627

Please see the attached IRB approved application for study NCT02824627 (**IRB#321-16-FB: Investigating the impact of oxytocin on irritability/emotional dysregulation in children and adolescents with disruptive behavior and mood disorders, and the possible mediating role of amygdala activity.).**

This study was most recently IRB approved on 12/20/2021 (continuing review).

The application includes the protocol information and statistical analysis plan. There are not separate protocol and statistical analysis plan documents.

Please contact me at (402) 552-6239 if there are additional questions.

Sincerely,

Brigette Vaughan MSN, APRN
Lead Research Coordinator
UNMC Department of Psychiatry

985575 Nebraska Medical Center / Omaha, NE 68198-5575
402-559-6002 / FAX 402-559-6248 / www.unmc.edu/psychiatry

Pediatric Biomedical Research
SECTION I

1. Status:

♦ New Submission
Revised electronic IRB Application; IRB#
Initial electronic submission of an existing expedited IRB approved protocol; IRB#

2. Title of Protocol:

Investigating the impact of oxytocin on irritability/emotional dysregulation in children and adolescents with disruptive behavior and mood disorders, and the possible mediating role of amygdala activity

3. Responsible Personnel:

A. Principal Investigator (PI):

Hwang, Soonjo - Dept Of Psychiatry Home - 402-552-6351 - soonjo.hwang@unmc.edu - alt #: 402-552-6351 - degree: MD - address: PYH 3017 (Zip 5578) - phone: 405-552-6002

B. Secondary Investigator (SI):

Blair, Robert (James) J - Pharmacology/Exp Neuroscience - 301-496-5198 - - alt #: 402-498-1217 - degree: Ph.D. - address: 9000 ROCKVILLE PIKE RM 206 BETHESDA, MD (20892-0001) - phone: 301-496-5198

French, Jeffrey Alan - - - jfrench@unomaha.edu - alt #: 402-554-2558 - degree: Ph.D. - address: - phone:

Kratochvil, Christopher Jon - Vice Chancellor for Research - 402-559-8490 - ckratoch@unmc.edu - alt #: 402-552-6005 - degree: MD - address: ARS 2056 (Zip 7878) - phone: 9-6704

LeVan, Tricia D - COPH Epidemiology - 402-559-3985 - tlevan@unmc.edu - alt #: 402-995-3296 - degree: PhD - address: MCPH Room 3031 (Zip 4395) - phone: 9-3985

Wilson, Tony W - Pharmacology/Exp Neuroscience - 402-552-6431 - twwilson@unmc.edu - alt #: 402-552-6005 - degree: PhD - address: 378 BUCHER CIR BOYS TOWN (68010-7518) - phone: 402-214-5210

C. Participating Personnel:

Bohn, Alexandra C - Psychiatry - 402-552-6002 - alexandra.bohn@unmc.edu - alt #: 402-552-6007 - degree: BS - address: PYH (Zip 5575) - phone: 2-6002

Cordts, Katrina M - Psychiatry - 402-552-6002 - katrina.cordts@unmc.edu - alt #: 402-836-9910 - degree: PhD - address: PYH (68189-5575) - phone: 2-6002

Lerdahl, Arica A - Psychiatry - 402-552-6002 - arica.lerdahl@unmc.edu - alt #: 402-552-6101 - degree: BS - address: PYH 6009 (Zip 5575) - phone: 2-6002

Meffert, Harma - Pharmacology/Exp Neuroscience - 402-498-1053 - - alt #: 402-498-1053 - degree: Ph.D. - address: - phone:

Suk, Ji-Woo - Psychiatry - 402-552-6035 - jiwoo.suk@unmc.edu - alt #: 402-552-6230 - degree: PhD - address: PYH 6012 (Zip 5578) - phone: 2-6035

White, Stuart F - Pharmacology/Exp Neuroscience - 402-498-1235 - - alt #: 402-498-1235 - degree: Ph.D. - address: 5023 Sewar4d Street Omaha (68104)

D. Lead Coordinator:

Vaughan, Brigette Suzanne - - 402-891-0685 - bvaughan@unmc.edu - alt #: 402-552-6239 - degree: APRN - address: PYH Rm 3015, 5581 zip UNMC Psychiatry (Zip 5581) - phone: 2-6239

E. Coordinator(s):

Adams, Kathryn Opal - - - koa@5168@psu.edu - alt #: 402-498-1053 - degree: M.S. - address: - phone:

Killanin, Abraham Delanor - - 516-300-3329 - abraham.killanin@yale.edu - alt #: 402-498-1053 - degree: M.S. - address: 378 Bucher Circle (Zip 68010) - phone: 402-559-4044

Mobley, Alita - - - alita.mobley@boystown.org - alt #: 402-498-1053 - degree: M.S. - address: - phone:

Ternent, Elizabeth Charlotte - - 402-547-0909 - eternent248@yahoo.com - alt #: 402-498-1053 - degree: M.S. - address: - phone:

F. Data/Administrative Personnel:

G. Are you a student or house officer?
No

4. Funding Source:
Check all that apply and provide the source of the funding.
Cooperative Group:
♦ Grant - Provide Source: Intramural grant awarded to Dr. Soonjo Hwang by the department of psychiatry, UNMC
Commercial - Provide company name:
Department of Defense
Other - Provide Source:
Center for Clinical and Translations Research (CCTR)

5. Contract:
Is there a contract or agreement associated with this study?
No

6. Funding Agency Deadline for IRB Approval:
Yes
♦ No

7. Study Sites:
A. Provide the names and locations of all study sites where this research will be conducted under the oversight of the Joint Pediatric IRB.

1. The Department of Psychiatry, Child and Adolescent Psychiatry Division, University of Nebraska Medical Center
2. The department of pharmacology and experimental neuroscience, University of Nebraska Medical Center
3. Boys Town National Research Hospital

B. Is this a multi-site study?
No

C. Does this study involve any international sites where the PI will either conduct or supervise the study?
No

8. Principal Investigator Assurance

The PI understands and accepts the following obligations to protect the rights and welfare of research subjects in this study:

- I certify that I have carefully reviewed this application and all supporting documents. I have determined that the application is accurate, complete and ready for submission to the IRB.
- I certify that I, and all listed research personnel, have the necessary qualifications, expertise, and hospital credentials to conduct this study in a manner which fully protects the rights and welfare of research subjects.
- I certify that all listed research personnel will be given a copy of the final IRB approved application and any other relevant study-related documents in accordance with their defined responsibilities.
- I recognize that, as the PI, it is my responsibility to ensure that this research and the actions of all research personnel involved in conducting the study will comply fully with the IRB-approved protocol, all applicable federal regulations, state laws, and HRPP policies.
- I recognize that it is my responsibility to ensure that valid informed consent/assent has been obtained, as appropriate, from all research subjects or their legally authorized representative (LARs). I will ensure that all research personnel involved in the process of consent/assent are properly trained and are fully aware of their responsibilities relative to the obtainment of informed consent/assent according to federal regulations, state laws, and HRPP policies.
- I certify that the minimum amount of protected health information (PHI) or other identifiers necessary will be used and disclosed to conduct this research study (if applicable). I will implement reasonable safeguards to protect the PH/identifiers at all times.
- I will promptly inform the IRB of internal adverse events, as well as any unanticipated problems involving risk to the subjects or to others, as required within the time frame defined by HRPP policies. I will analyze each internal adverse event/reported problem to determine if it impacts the risk-benefit relationship of the study, the safety of the subjects, or informed consent.
- I will analyze each MedWatch/safety report to determine if it impacts the

risk/benefit relationship of the study, the safety of the subjects, or informed consent. I will promptly submit external adverse event reports in accordance with HRPP policies.

- I will promptly inform the IRB if I become aware of: 1) any complaints from research subjects, LARs, or others about research participation, 2) violations of federal regulations or state law, 3) violations of the HIPAA Rule, or 4) violations of HRPP policies.

- I will promptly inform the IRB of the results of external audits performed by sponsors, Contract Review Organizations (CROs), cooperative groups, FDA, or other external groups.

- I will not initiate any change in protocol without IRB approval except when it is necessary to reduce or eliminate a risk to the subject, in which case the IRB will be notified as soon as possible.

- I certify that there are, or will be, adequate resources and facilities to safely initiate, carry out and complete this research at the study sites specified in Section I.7. This includes sufficient staff, funding, space, record keeping capability, and resources necessary to address adverse events and any unanticipated problems involving risk to the subject or others. If the necessary resources become unavailable I will promptly notify the IRB.

- I will promptly inform the IRB of any significant negative change in the risk/benefit relationship of the research as originally presented in the protocol and approved by the IRB.

- I understand that continuing review by the IRB is required at least annually in order to maintain approval status. I will maintain IRB approval as long as this study is active.

- I understand that I am responsible for appropriate research billing in accordance with UNMC Clinical Trial Professional and Technical Fee Billing Policy #8008 or applicable Children s Hospital & Medical Center policy.

- I certify that I and all other personnel listed in Section I.3A-E of the IRB Application have disclosed all potential financial conflicts of interest as required and are in full compliance with the UNMC Conflict of Interest Policy #8010 and HRPP Policy. I further certify that all potential financial conflicts of interest are

appropriately managed in order to ensure protection of the rights and welfare of subjects.

- **I will maintain all required research records on file and I recognize that representatives from the IRB, OHRP, HHS, FDA, and other Federal Departments or Agencies may inspect these records in accordance with granted authority.**

- **I understand that failure to comply with the Common Rule, applicable Subparts B, C, and D of HHS regulations at 45 CFR 46, applicable FDA regulations, the HIPAA Rule, applicable state law, HRPP policies, and the provisions of the IRB-approved protocol may result in suspension or termination of IRB Approval of my research project and/or other administrative or legal actions.**

Hwang, Soonjo - 2020-11-12 15:17:18.366

9. Principal Investigator Financial Interest Disclosure
A. As the PI, I certify that I am in full compliance with UNMC Conflict of Interest Policy #8010 and I declare:
♦ I have no financial interest in this research.
I have a financial interest in this research. I have completed the UNMC Disclosure of Potential Conflict of Interest Form and obtained all required signatures. The original disclosure form is attached to this application.

B. As the PI,
♦ I understand that if there is any change in my financial interest during the course of this research, I will update and submit the UNMC Disclosure of Potential Conflict of Interest Form within five (5) business days from the time the change becomes known.

C. As the PI who is ultimately responsible for the proper conduct of this research, I also certify that:
♦ No Responsible Personnel have a financial interest in this research.
The Responsible Personnel listed below have informed me that they have a financial interest in this research.

D. I have informed all Responsible Personnel that if there is any change in their financial interests during the course of this study it must be disclosed by submitting or updating the required UNMC Disclosure of Potential Conflict of Interest Form.
Hwang, Soonjo - 2020-11-12 15:17:18.366

11. Scientific/Scholarly Merit and Resource Review Certification
A. Scientific Reviewer:
Fleisher, Mark Harry - Psychiatry - 402-552-6002 - mhfleish@unmc.edu - alt #: 402-552-6002 - degree: MD - address: 985575 NEBRASKA MEDICAL CTR OMAHA (Zip 5575) - phone: 2-6002

My signature certifies that this application has been reviewed for scientific/scholarly merit and available resources. I have determined that the application merits consideration by the IRB based upon the following:

- **1) The proposal has an acceptable level of scientific/scholarly merit which justifies the use of human subjects.**
- **2) The proposal has a sound research design in consideration of the stated objectives,**
- **3) The PI has the necessary qualifications, experience and credentials to conduct this research.**
- **4) The PI has or will have the necessary funding to support this research.**
- **5) There is or will be adequate physical space required for the research interventions at all study sites specified in Section 1.7. In addition, there is or will be adequate laboratory and clerical support, data storage capability, and any other resources necessary to complete this research.**
- **6) At all study sites specified in Section 1.7, there is emergency equipment, personnel, or services necessary to respond promptly to adverse events or unanticipated problems involving risk to the subject or others.**
- **7) I will promptly notify the IRB if the necessary resources to support this research become unavailable.**
- **8) I am not listed as study personnel in Section I of this application.**

Fleisher, Mark Harry - 2016-05-05 14:32:00.000

SECTION II

PROTOCOL ABSTRACT

1. Provide a brief (less than 400 words) abstract of the research protocol. This summary should include: 1) the title of the protocol, 2) a *brief* description of the purpose of the study, 3) eligibility criteria, 4) interventions and evaluations and 5) follow-up.

1. **Investigating the impact of oxytocin on irritability/emotional dysregulation in children and adolescents with disruptive behavior and mood disorders, and the possible mediating role of amygdala activity**
2. Irritability and emotional dysregulation are recognized as serious aspects of psychopathology seen in in pediatric psychiatric patients. While various behavioral as well as psychopharmacological interventions have shown some efficacy in improving irritability and emotional dysregulation, there are no data determining the neurobiological mechanism of effect at the neural level. Previous studies have demonstrated that heightened amygdala response to negative emotional stimuli is closely related to irritability and emotional dysregulation in children and adolescents. Also, there are studies showing administration of oxytocin can decrease the heightened amygdala response to negative emotional stimuli across various psychiatric diagnoses. This study is a double-blind randomized trial of oxytocin for irritability and emotional dysregulation in the pediatric population. Neuroimaging modalities of fMRI and MEG are employed to probe the neuro-circuitry changes occurring as a result of the oxytocin intervention, specifically including heightened amygdala response to negative emotional stimuli and dysfunctional fronto-amygdala connectivity. We will also investigate the genetic sequence of the oxytocin receptor in the study participants and its relationship with symptom profile and neural activity changes.
3. Children and adolescents (age 10-18) with a diagnosis of disruptive mood and/or behavior disorders (including Attention Deficit/Hyperactivity Disorder [ADHD], Oppositional Defiant Disorder [ODD], Conduct Disorder [CD], and Disruptive Mood Dysregulation Disorder [DMDD]), and clinically significant levels of irritability and emotional dysregulation as measured by the Affective Reactivity Index Scale (score>/= 4).
4. 2 weeks randomized, double-blind treatment with intranasal oxytocin (24 IU daily, or 12 IU daily if the weight is < 40kg) with assessment of diagnosis, symptom profiles (the Affective Reactivity Index [ARI], Inventory of Callous-Unemotional Trait [ICU], Behavior Assessment System for Children, third version [BASC-3], and Clinical Global Impression [CGI]) and pre- and post-oxytocin treatment neuroimaging (fMRI and MEG). The genetic sample will be obtained via buccal mucosa sampling.
5. Participant may receive outpatient clinically indicated follow-up care in the UNMC

department of psychiatry or other local community agency as appropriate.

PURPOSE OF THE STUDY AND BACKGROUND

2. Purpose of the Study

What are the specific scientific objectives of the research?

The primary objective of this research is to determine the impact of oxytocin on irritability and emotional dysregulation in children and adolescents with DSM-V disruptive mood and behavior disorders. It will also examine the impact of oxytocin on the neural response in the amygdala as well as fronto-amygdala connectivity dysfunction related to irritability and emotional dysregulation in children and adolescents, using fMRI and MEG. Changes in symptom profiles as a result of oxytocin treatment will be assessed for correlation with neural level changes. Differences in the magnitude of treatment responses to oxytocin as a function of polymorphisms in the oxytocin receptor (OTR) will also be assessed.

3. Background and Rationale

Describe the background of the study. Include a critical evaluation of existing knowledge, and specifically identify the information gaps that the project is intended to fill.

Irritability and emotional dysregulation in the pediatric population is defined as (1) excessive sensitivity to negative emotional stimuli, and (2) difficulty of behavioral and emotional control, resulting in displays of anger and reactive aggression (Leibenluft & Stoddard, 2013). Irritability and emotional dysregulation have been recognized as one of the most serious psychopathologies in children and adolescents (Krieger, Leibenluft, Stringaris, & Polanczyk, 2013). It is one of the most common reasons children and adolescents present for mental health services (Avenevoli, Blader, & Leibenluft, 2015). Irritability and emotional dysregulation can present across various psychiatric diagnoses in children and adolescents, including post-traumatic stress disorder (Diseth, 2005), depressive disorder (Stringaris, Maughan, Copeland, Costello, & Angold, 2013), bipolar disorder (Lagges & Dunn, 2003; Leibenluft, Charney, Towbin, Bhangoo, & Pine, 2003), and autism spectrum disorder (Lecavalier, 2006), to name a few. However, the most prominent group of children and adolescents whose main psychopathology is irritability and emotional dysregulation are those with disruptive behavior and disruptive mood dysregulation disorders, including Attention Deficit Hyperactivity Disorder (Karalunas et al., 2014), Oppositional Defiant Disorder (Herzhoff & Tackett, 2015), Conduct Disorder (Euler et al., 2015), and Disruptive Mood Dysregulation Disorder (Dougherty et al., 2014). In those disorders, it has been argued that dimensional/longitudinal characterization of irritability and emotional dysregulation across the conditions can predict clinical course and prognosis (Wakschlag et al., 2015). The dimensional approach to identifying irritability and emotional dysregulation across various diagnoses and the targeting of underlying biological mechanism associated

with symptom manifestation in a clinical trial is in line with the Research Domain Criteria (RDoC) agenda of National Institute of Mental Health (NIMH) (Insel et al., 2010; Leibenluft & Stoddard, 2013).

Neurobiological Mechanism of Irritability and Emotional Dysregulation in Disruptive Behavior and Mood Disorders of Children and Adolescents

There are several neurobiological mechanisms that may explain irritability and emotional dysregulation in these groups (Brotman et al., 2010; Deveney et al., 2013; Sebastian et al., 2014; Thomas et al., 2013; Viding et al., 2012). Increased amygdala reactivity to negative emotional stimuli (such as fearful faces, threat cues) is commonly related to irritability and emotional dysregulation in children and adolescents with disruptive behavior and mood disorders (Brotman et al., 2010; Sebastian et al., 2014; Thomas et al., 2013; Viding et al., 2012). In addition to this, dysfunctional fronto-amygdala connectivity has been suggested as a potential neurobiological mechanism of emotional dysregulation and irritability in children and adolescents by resting and task-based fMRI studies (Hulvershorn et al., 2014; Leibenluft & Stoddard, 2013), although there are very few studies investigating the potential role of fronto-amygdala connectivity in children and adolescents with disruptive behavior and mood disorders, and sometimes the result is inconsistent (Stoddard et al., 2015).
In this regard, it would be crucial to develop a treatment modality targeting the underlying neuro-biological mechanism of irritability and emotional regulation. Various psychopharmacological agents such as stimulants, mood stabilizers, antipsychotics, and antidepressants, as well as behavioral interventions such as parent management training have shown some efficacy in improving irritability and emotional dysregulation (Tourian et al., 2015), however, there are no data determining their mechanism of effect at the neural level.

Oxytocin for Treatment of Irritability and Emotional Dysregulation in Children and Adolescents, targeting Amygdala

One promising intervention is the neuropeptide oxytocin (OT). There is a growing body of data showing that intra-nasal administration of oxytocin has promise for treating a host of psychiatric disorders (Hofmann, Fang, & Brager, 2015). Further, it is well-established that differences in the structure and function of the oxytocin receptor (OTR) associated polymorphisms in the gene coding for the oxytocin receptor (*OXTR*) are associated with risk for, or resilience to, these psychiatric states (Aspé Sánchez, Moreno, Rivera, Rossi, & Ewer, 2015). The potential for interactions between OT treatments and OTR polymorphisms has been suggested as an important determinant of treatment outcome (MacDonald, 2015), but this interaction has not been widely tested in research or clinical contexts.
Considerable data indicates that oxytocin reduces amygdala response to negative stimuli in

patients with generalized anxiety disorder, borderline personality disorder, and post-traumatic stress disorder (Koch et al., 2015; Labuschagne et al., 2010). Given that (1) one of the potential underlying neuro-biological mechanisms of irritability and emotional dysregulation in pediatric population with disruptive behavior and mood disorder is the hyperactivity of amygdala to negative emotional stimuli, and that (2) oxytocin reduces this hyperactivity of amygdala to negative emotional stimuli, it is critical to determine the extent to which this intervention improves irritability and emotional dysregulation in children and adolescents with disruptive behavior and mood disorders, by reducing amygdala hyperactivity to negative emotional cues . This also will determine the extent to which treatment with oxytocin would improve other symptom manifestation related to irritability and emotional regulation (for example, reactive aggression) in this population.

Using Neuroimaging Techniques of Functional MRI and Magneto-Encephalography (MEG) in Clinical Trial of Oxytocin for Irritability and Emotional Dysregulation in Children and Adolescents

Functional MRI has been the main modality of neuroimaging to demonstrate neural areas related to irritability and emotional dysregulation in children and adolescents with disruptive behavior and mood disorders (Deveney et al., 2013; Hulvershorn et al., 2014; Leibenluft & Stoddard, 2013; Perlman et al., 2015). It is imperative to use adequate biomarker neuropsychological tasks to identify the neural areas related to the pathophysiology of irritability and emotional dysregulation, and to capture the impact of oxytocin on those neural substrates. Two fMRI biomarker tasks will be used in this project (i.e., the fearful expression processing task and the affective Stroop task), because they have been used successfully to identify the pathophysiology associated with irritability and emotional dysregulation, especially the heightened amygdala response to negative emotional stimuli/threat stimuli (Hwang et al., 2016; Hwang, White, Nolan, Sinclair, & Blair, 2014; Marsh et al., 2008). The two tasks that we will use to examine activation in amygdala and fronto-amygdala connectivity have been developed and studied by Dr. R.J.R. Blair and colleagues. (A) Research using the fearful expression processing task has shown that response to fearful emotional expression is associated with amygdala responses, and then symptom manifestation such as irritability (Wiggins et al., 2016), callous unemotional trait (Marsh et al., 2008), anxiety (K. Blair et al., 2008), and reactive aggression (Lozier, Cardinale, VanMeter, & Marsh, 2014). (B) The affective Stroop task has been used to demonstrated dysfunctional connectivity of amygdala in ADHD (Hwang et al., 2014) and disruptive behavior disorder (Hwang et al., 2016).
Magneto-encephalography (MEG) has a critical advantage of directly quantifying neural activity, with complete immunity to signal biases caused by aberrant neuro-vascular coupling (Hillebrand, Singh, Holliday, Furlong, & Barnes, 2005). Also MEG has an unique advantage that signal detection is practically unaffected by the inhomogeneous conductivity

and structure of skull and scalp tissue (Hironaga & Ioannides, 2007). By using MEG we aim to achieve better temporal resolution in detection of dysfunction in fronto-amygdala connectivity for children and adolescents with disruptive mood and behavior disorders, and the impact of oxytocin treatment on it. We will use the emotional Stroop task developed and used by Dr. Tony Wilson. It is designed to capture the fronto-amygdala connectivity related to irritability and emotional dysregulation, and has been used for patient population with Post-Traumatic Stress Disorder (Khanna et al., 2015). In short, fMRI and MEG are expected to be complementary to each other, in that the fMRI tasks will capture amygdala response to negative emotional stimuli with better spatial resolution of this neural area, whereas the MEG task will detect fronto-amygdala connectivity changes with better temporal resolution.

Sequencing analysis of oxytocin receptor gene by buccal mucosa sampling

Previous studies demonstrated that a common polymorphism in the gene encoding the oxytocin receptor is related to individual's social behavior, especially facial recognition ability (Skuse et al., 2014). Also this polymorphism may also impact an individual's response to various psychopharmacological and behavioral interventions (Chen et al., 2011).Thus, it is important to measure the presence of the polymorphism in the oxytocin receptor of children and adolescents with clinically significant irritability and emotional dysregulation to establish (1) a correlation between the presence of the polymorphism in the oxytocin gene and the level of neural dysfunction related to irritability and emotional dysregulation and (2) the correlation between the presence of the polymorphism in the oxytocin gene and response to oxytocin treatment on both neural and clinical levels.

CHARACTERISTICS OF THE SUBJECT POPULATION

4. Accrual
Is this study conducted <u>solely</u> at sites under the oversight of the Joint Pediatric IRB (e.g. UNMC, TNMC, CH&MC, UNO)?
Yes

A. What is the <u>total</u> number of subjects (per group, as applicable) needed to complete the research in order to achieve the scientific objectives of the research?
104 subjects are needed to complete the trial (52 per treatment group).

B. What is the statistical or other justification for the <u>total</u> number of subjects needed to complete the research in order to achieve the scientific objectives of the research?
The primary outcome is the change of Affective Reactivity Index (ARI) from the baseline to the last visit. A sample size of n=52 per group will provide 80% power to detect a difference between the group means of -4.0 in the change of ARI of -4.0 at the significance level of

0.05 using a two-sided two-sample t-test, assuming the mean of -4.0 and the standard deviation of 7.2 in the oxytocin group, and the mean of 0 and the standard deviation of 7.2 in the placebo group.

Sample size for the internal pilot study

Given the uncertainty regarding the parameter used to calculate the sample size, an internal pilot study will be conducted to obtain reliable estimate of standard deviation (SD) to recalculate the sample size and assess the retention rate. The minimum size for the internal pilot study, n=10 per group (19% of the pre-planned sample size) will be considered.

C. Based on the anticipated number of screen failures and/or subject withdrawals, what is the maximum number of subjects that will need to be consented in order to achieve the scientific objectives of the research?
A maximum of 140 subjects will be consented

5. Gender of the Subjects
A. Are there any enrollment restrictions based on gender?
No

6. Age Range of Subjects
A. What is the justification for inclusion of children in this research?
Childhood and adolescence is a vitally important period for the prevention of and early-intervention for disruptive behavior and mood disorders (Leibenluft & Stoddard, 2013). All of the disorders included in this protocol demonstrate an onset of symptoms in childhood and adolescence (American Psychiatric Association, 2013). In addition, working with children and adolescents provides more immediate access to the underlying pathophysiology of irritability and emotional dysregulation. In contrast, the pathophysiology seen in adults with chronic irritability and emotional dysregulation reflects not only the primary condition but also consequences of irritability and emotional dysregulation (e.g. anxiety disorder, borderline personality disorder, and especially, substance abuse/dependence). Children and adolescents have a lower risk of substance dependence, which is exclusionary.

B. What is the age range for the child subjects, and what is the justification for selecting this age range?
The age range for the child and adolescent subjects in this study is 10-18 years. The disorders included in this protocol have an onset of symptoms in childhood and adolescence

(American Psychiatric Association, 2013). The proposed age range in this protocol was also guided by our previous experience at National Institute of Mental Health conducting neuroimaging studies in youth with disruptive behavior disorders. In our experience, by age 10, 80-90% of participants can be successfully scanned and data are not often compromised by movement.

C. Will this study enroll wards of the state?
No

D. Will adults (19 years of age or older) be included in this research?
No

7. Race and Ethnicity
Are there any subject enrollment restrictions based upon race or ethnic origin?
No

8. Vulnerable Subjects
A. Will any of the following vulnerable populations be allowed to participate in this research? Check all that apply.
Pregnant individuals, fetuses or neonates (non-viable or of uncertain viability)
Prisoners
♦ None

B. Will any of the following vulnerable populations (Critically ill patients, Students of the investigator, Socially or economically disadvantaged individuals, Individuals with a stigmatizing illness or condition, Other) be specifically recruited for enrollment in this research?
No

9. Inclusion Criteria
What are the specific inclusion criteria?
Children/adolescents with disruptive behavior and mood disorders (ADHD, ODD, CD, DMDD)

1. 10-18 years of age
2. A current diagnosis of ADHD, ODD, CD, or DMDD as determined by the Kiddie-SADS, lifetime version
3. Clinically significant level of irritability as defined by a score of Ý4 on the Affective Reactivity Index (ARI) (Stringaris et al., 2012)
4. If currently on medication, medication treatment must be stable for at least 6 weeks

with a stimulant medication, alpha 2 agonist, atomoxetine, antipsychotics, mood stabilizers or antidepressant.

10. Exclusion Criteria

What are the specific exclusion criteria?

1. Comorbid psychotic, tic,or substance abuse disorders
2. Major medical illness that prohibits treatment by oxytocin (e.g., severe liver disease, seizure disorder, metabolic disorder)
3. Past history of allergic reaction to oxytocin and its nasal spray product
4. History of CNS disease (including history of seizure, epilepsy, CNS tumor, CNS hemorrhage, or serious CNS infection including meningitis or encephalitis)
5. Current use of anxiolytics (benzodiazepines and barbiturates).
6. A positive urine pregnancy test
7. A positive urine drug screen or any history of or currently active diagnosis of substance use disorder
8. Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II) (D. Wechsler, 2011) scores < 70
9. Metal in body (i.e., hearing aid, cardiac pacemaker, bone plates, braces, non-removable piercings/implants, etc), claustrophobia, or any other condition that would preclude fMRI scanning
10. Primary diagnosis of autism spectrum disorder with associated impairments in communication and significant behavioral disturbance.

11. Pregnancy and Contraception Requirements

A. Are non-pregnant females of childbearing potential included in this research?

Yes

1) Are there any specific contraception requirements?

No

1) Provide justification.

No interventions are likely to be of risk to a fetus (including Category A drugs)

♦ Other. Explain. We will exclude female participants with positive urine pregnancy test result.

B. Are pregnant females included in this research?

No

1) Provide justification for excluding pregnant females.

♦ Intervention includes a Category B, C, D or X drug
Intervention includes a procedure expected to be of risk to the fetus (e.g. exposure to ionizing radiation, maximal exercise test)
Research is not relevant to pregnant females (e.g. disease or condition rarely encountered in pregnant females)
Knowledge being sought in the research is already available for pregnant females or will be obtained from another ongoing study
A separate study in pregnant females is warranted and preferable
Physiology of pregnancy precludes generalization to other populations
Other. Explain.

2) Describe how pregnancy status will be assessed.
Self-report
Blood pregnancy test
♦ Urine pregnancy test
N/A study includes males only

C. Are breast feeding females excluded from participation?
Yes

1) Provide justification.
Oxytocin is released during lactation, however, the effect of administering additional oxytocin is not known. Also, the potential for mood changes during the post-partum period may impact results of the study.

METHODS AND PROCEDURES

12. Methods and Procedures Applied to Human Subjects
A. Are there any evaluations or tests that will be performed for the purpose of determining subject eligibility which would not be routinely conducted as part of standard clinical care of the prospective subject?
Yes

Describe the evaluations or tests to determine subject eligibility.
The participants and parent/guardian will be interviewed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS)(Kaufman et al., 1997) to confirm the diagnosis of ADHD/CD/ODD/DMDD, and to rule out any other potentially exclusionary psychiatric diagnoses. Their IQ will be measured by the Wechsler Abbreviated Scale of Intelligence, Second Edition (2-subtest

form)(Wechsler, 2011), to rule out intellectual disability. Urine drug screen will be done to rule out substance use disorder. Urine pregnancy test will be done to rule out pregnancy. Additional measures including the ARI, ICU, RPAQ, BASC-3, CGI-S, CGI-I, and CGAS will also be completed.

B. Describe sequentially all procedures, interventions, evaluations and tests.

Timeline of Research procedures

Research Procedures	Duration
Initial Research Assessment	2-4 hours
FMRI visit 1	2-3 hours
MEG visit 1	2-3 hours
Oxytocin/Placebo Treatment	14-21 days
FMRI visit 2	1-2 hours
MEG visit 2	1-2 hours
Final Research Assessment	2-3 hours

Evaluations

These evaluation measurements will be administered at the initial research assessment session as well as the final research assessment session, except the K-SADS and WASI which will be only administered at the initial research assessment session. A separate remote visit may be used to conduct K-SADS administration. All of these evaluations are solely performed for research purposes.

Initial evaluation:

Participants and their parent/guardian will complete a diagnostic assessment session following informed consent. This will be held at the outpatient clinic of the department of psychiatry, at University of Nebraska Medical Center. Participants and their parent/guaridan will be interviewed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS) (Kaufman et al., 1997) to confirm the diagnosis of ADHD/CD/ODD/DMDD, and to rule out any other psychiatric diagnoses listed in the exclusion criteria. K-SADS may be completed remotely by video call or phone. IQ will be measured by the Wechsler Abbreviated Scale of Intelligence, Second Edition (2-subtest form)(Wechsler, 2011). The WASI-II is standardized, well-established test for measurement of intelligence in adolescents population (David Wechsler, 2011). This will be used to rule out intellectual disability (I.Q. < 70)

Symptom Profile Assessment:

The Affective Reactivity Index (ARI) will be completed at the initial research assessment session and the final research assessment session. ARI is a 7 item inventory (self-report

and parent-report versions) specifically designed to measure irritability and emotional dysregulation (Stringaris et al., 2012). This will be used to measure the outcome of improvement in irritability by oxytocin treatment.

The Behavior Assessment System for Children, second version (BASC-3) will be completed at the initial research assessment session and the final research assessment session. BASC-3 is parent-reported, well-established scale for externalizing/internalizing problem of children and adolescents (Reynolds, 2015). This will be used to measure the outcome of improvement in emotional dysregulation and other related symptoms (externalizing behavior) by oxytocin treatment.

The Inventory of Callous Unemotional trait (ICU) will be completed at the initial research assessment session and the final research assessment session. ICU is a 24 item inventory specifically designed to measure callous-unemotional trait in children and adolescents (Berg et al., 2013; Frick, 2004). This will be used to measure outcome of improvement in callous-unemotional trait by oxytocin treatment. This will be also used to assess covariate function of callous-unemotional trait on treatment response.

The Reactive-Proactive Aggression Questionnaire (RPAQ) will be completed at the initial research assessment session and the final research assessment session. RPAQ is a 23 item inventory (self-report) specifically designed to measure two different types of aggressive behavior, i.e., reactive and proactive aggression (Raine et al., 2006). This will be used to measure outcome of improvement in related symptom of aggressive behavior by oxytocin treatment.

The Clinical Global Impression: Severity and Clinical Global Impression: Improvement scales (CGI-S and CGI-I) will be used at study entry and study completion to quantify, based on clinician's global assessment of the individual, the severity of symptoms compared (study entry and completion) and the degree of improvement (study completion)which may or not be attributable to the study intervention. Other symptom profile measurements will be used to assist the clinician in the rating of this measure.

Children's Global Assessment Scale (CGAS) will be used at study entry and completion to provide a global measure on a scale of 0-100 (100 being superior) of the subject's level of functioning.

Urine drug screen: Urine drug screen to rule out presence of substances of abuse will be completed at screening.

Urine pregnancy testing: Urine test for pregnancy will be done for female participants prior

to initial neuroimaging procedures.

Neuroimaging:

The clinical MRI scanning of brain will occur at the MRI visit 1, to rule out any anatomical abnormality of the participants brain, such as brain tumor, hemorrhage, or other structural abnormality. This will occur at the Boys Town National Research Hospital. During the MRI visit 1, participants will receive their first fMRI session immediately before initiation of oxytocin or placebo treatment. The fMRI visit 1 can happen on the same day of the initial research assessment after the initial research assessment is completed.
Participants will be scanned on the 3.0 Tesla Philips scanner at Boys Town National Research Hospitals Radiology Department. If the child or parent prefers, the parent is welcome to stay with the child during the MRI scan. Pregnancy test will be done on all female participants, using urine sample collected no more than 24 hours before the scan. The participant will be escorted to the MRI scanner room. They will be given the instruction of the fMRI scanning procedure and neuropsychological tasks they will be performing in the scanner, by an MRI technician. Practice runs of neuropsychological tasks will be done, so the participant will become familiar with the tasks. After checking once more that the participant doesn't have any contra-indication to the MRI scanning, including metal objects, they will be escorted in to the MRI scanning room. Ear plugs will be placed by the MRI technician to mitigate the noise from the MRI machine. The MRI technician will guide the participant lying down on the bed of the scanner, and make sure they can see the mirror for the neuropsychological tasks, and also feel comfortable with the scanner. Instruction will be given that the participant needs to stay still. Once the participant is ready, the bed the participant is lying on will be guided into the magnetic coil field. The microphone will be checked once the participant is in the magnetic coil field, to make sure the participant ca hear the MRI technician, and also the MRI technician can hear the participant. Two fMRI tasks will be used: the affective Stroop, and the fearful expression. If the participant has never received MRI scanning of brain before, a clinical scanning of brain will be included to detect any potential anatomical abnormality. After they finish the neuropsychological tasks and anatomical scanning (~ 1 hour), they will be guided to the outside of the scanner. Post-scanning questionnaire will be filled to check if the participant performed the neuropsychological tasks well without difficulty, or had any event to report (such as feeling uncomfortable inside of the scanner). Total scan time is under 1 hour and total time for the visit will be under 2 hours. All these steps will be conducted at Boys Town National Research Hospital, the department of radiology.

The Fearful Expression Processing task

This is a shortened version of the paradigm previously utilized by our group (Marsh & Blair,

2008). During each trial the participant is asked to decide the gender of the face displayed. The face either demonstrates neutral affect or a morphed intensity of fear (50%, 100% or 150%). A trial involves: the presentation of a face (1500 ms) and then a fixation point (1000 ms). There is one run of this task, with 120 face trials (30 neutral, 30 50% fear, 30 100% fear and 30 150% fear) and 60 fixation point trials. In addition, there are 15 seconds of fixation point trials at the beginning and end of the run. Task duration is 8 minutes.

The Affective Stroop task

The affective task used here was an adapted version of the paradigm described in previous work (K. S. Blair et al., 2012; K. S. Blair et al., 2007). During each trail the participant is asked to decide how many numbers are displayed on the screen, instead of the value of the number. For congruent trials, the numbers were displayed with the same numerosity and number value (e.g., three 3s). For incongruent trials, the numbers were displayed with different numerosities and number values (e.g., four 3s). The individual numerical stimuli consisted of three, four, five, or six 3s, 4s, 5s, or 6s randomly presented within a 9-point grid. There are an equal number of congruent trials and incongruent trials (48 each for a run). These number pictures were preceded and followed by emotional stimuli pictures consisting of 48 positive, 48 negative, and 48 neutral pictures selected from the International Affective Picture System. A trial involves: the presentation of an emotional stimuli (400ms), a numerical display (400ms), the same emotional stimuli (400ms), and a blank (1300ms). Subject completed two runs, generating 288 picture-trial events (32 in each 9 categories) and 96 fixation points to generate a baseline.

The first MEG scan (MEG visit 1) will take place at the Center for MEG (South Doctors Tower, Ste. 222) on the day of their scheduled study. The MEG visit 1 can happen on the same day of the initial research assessment.
The participant will be escorted to the prep station inside the MEG suite by the MEG technician for MEG coil placement and further prepping prior to the study. The coils are simply small discs that are attached to the skin surface. After coils are placed, they will be lead into the magnetically shielded room, which houses the MEG system, and positioned by the MEG technician. Once positioned, the MEG technician will go over the instructions a second time to make sure the subject understands and has not forgotten items discussed during the consent process (e.g., to remain physically still). The MEG technician will then close the door to the magnetically-shielded room, walk to the acquisition workstation and test the intercom system by asking the participant a question (e.g., Can you hear me?) The MEG technician will then tell the participant we are ready to begin and remind them to stay very still. MEG data will then be acquired by the technician as the subject completes the behavioral task. The recording will last less than 10 minutes. The participant will then be informed via intercom that the scan is over and they can relax. After 3-5 minutes break, the

participant will be told we are ready to start again and the process of recording will be repeated as the participant performs another set of behavioral task. Once all of the tasks have been completed (~1 hour), the MEG technician will inform the subject they are finished and he/she will enter the room to lead them out into the MEG suite. Once outside the magnetically-shielded room, the MEG technician will remove the MEG coils from the participant and allow them to use the private bathroom with cleansing station to touch up their make-up and/or fix their hair (i.e., the MEG helmet typically flattens ones hair). He/she will then be able to pick up any of their belongings (e.g., purse) that was stored in the MEG participant lockers.

The Emotional Stroop task

For the emotional Stroop task (EST), three word lists are prepared, a threat list, a negative list, and a neutral list. Each list contains 30 monosyllabic words. The threat words include things encountered in dangerous situation (e.g. gun), the negative words are negative in valence, but not related to threat (e.g., bad). The neutral words are not threatening nor negative (e.g., tune). The three words lists are equated across lexical features including: length, frequency, orthographic, and phonological neighborhood size. Using the ELP database, the words are also equated on average naming latency, naming accuracy, lexical decision time, and lexical decision accuracy (Balota et al., 2007). The task contains 9 experimental blocks, each consisting of 30 color word naming trials from one of our EST lists. The order of the words within each list is randomized across presentation blocks. Within each trial, participants first view a fixation cross for 1 second, which is replaced by a list item that remains on the screen for 2 seconds. An experimenter codes the participants response as correct (i.e., correct color identification), incorrect (i.e., did not name a color, named the wrong color, or named the word), or as a noise trial (e.g., the participant coughs, etc.). The items are centered horizontally/vertically on a 43.5 by 35cm screen and positioned at eye-level approximately 110cm from the head. Items are presented in red, blue, or green font, and item color is randomly assigned. Reaction times are measured using a dual-plane accelerometer attached to the lower lip and digitized at 1kHz using a Grass amplifier. Voice onset is determined by a sharp increase in the amplitude of the accelerometer signal, which produces response time accuracy near 1ms.

In addition to the emotional Stroop task, subjects will also view simple images (no more disturbing or violent than subjects can be exposed to in their everyday life) and respond to the images by pressing button. Movements in the MEG scanner will be also measured.

Buccal Cheek Brush for genetic sampling:

During the initial research assessment session, the buccal cheek brush will be performed

collecting DNA samples for genotyping of the OTR. Cheek cells will be collected using a commercially-available kit (Qiagen) and will require participants to gently brush the buccal cavity 10 20 times with the pliable brush. DNA will be extracted and amplified via conventional PCR. Participants will be genotyped for a minimum of 11 single nucleotide polymorphisms (SNPs) in *OXTR* that have been implicated in social and psychiatric disorders (Aspé Sánchez et al., 2015), as well as several polymorphisms in CD38, a gene that codes for a glycoprotein that regulates oxytocin signaling and social function (Feldman et al., 2012). PCR products with blinded codes will be sequenced at the UNMC Sequencing Core Facilities.

Collection of the genetic sample is OPTIONAL and not mandatory for study participation.

Oxytocin/placebo administration

If the participants are assigned to the oxytocin treatment arm by randomization, they will be initiated on oxytocin administration after the MRI visit 1 and MEG visit 1. Following previous studies using intranasal oxytocin administration (Dadds et al., 2014; Guastella & MacLeod, 2012; MacDonald et al., 2011), subjects weighing >40kg will receive a total of 24 IU of oxytocin delivered as 2- 6 IU puffs to each nostril once daily. Subjects weighing < 40kg will receive a total of 12 IU of oxytocin delivered as 1- 6 IU puff to each nostril daily. Participants will receive 14 to 21 days of daily oxytocin/placebo administration. After 14 days of oxytocin/placebo administration, participants will be scheduled to have MRI visit 2 and MEG visit 2. After those two visits are completed, participants will stop oxytocin/placebo administration. Participants who are assigned to placebo treatment branch will receive identical bottles and instructions for delivery of all the other ingredients of nasal spray except oxytocin. The instruction and demonstration will be given to the parents or parent/legal guardian as the first administration of the nasal spray done at the clinic by either child and adolescent psychiatrist or advanced practice registered nurse. The daily administration will be done by dispatching either oxytocin or placebo nasal spray to the parents of the participants. The oxytocin and placebo nasal spray will be prepared by the University of Nebraska Medical Center research pharmacist who will be un-blinded to each subjects treatment assignment. The randomization will be done by the department of pharmacology by a computer-programmed randomization procedure.

The participants will have one or two weekly visits to the clinic, depending on the duration of the trial (one if it is 14 days 2 if it is more than 14 days and less than 21 days). If the participant is having two weekly visits, the first will be conducted by phone.They will be assessed for symptom level, nasal spray tolerance, and assessment of adverse effects. Participants will be initiated on psychiatric treatment if it is indicated by change of their psychiatric condition (such as worsening of psychiatric symptoms). In this case, they will be

withdrawn from the study.

The second fMRI and MEG scans will be completed after 14-21 days of oxytocin/placebo treatment. The final research assessment will be completed at that time. The duration of oxytocin treatment (14 to 21 days) will be decided by the scheduling and completion of MRI visit 2 and MEG visit 2.

Compliance with medication and adverse effects will be assessed at each visit.
If during the course of the study it is discovered that the participant has a disorder or condition that would disqualify him/her (e.g., unexpected side effect of oxytocin that will necessitate cessation of the treatment or medical compromise that will make it impossible to continue oxytocin treatment), but needs further evaluation, the participant will be immediately referred for further clinical assessment and intervention to their primary care provider or, if requested, an appropriate department at the University of Nebraska Medical Center.

C. Identify all procedures, interventions, evaluations and tests that are
1) Performed solely for research purposes.
1. WASI-II for IQ measurement
2. Diagnostic and symptom profile measurements (KSADS-PL, ARI, ICU, BASC-3, RPAQ)
3. fMRI and MEG scans
4. Buccal musoca sampling for oxytocin receptor analysis
5. Oxytocin or placebo treatment
6. Assessments of medication compliance and adverse effects
7. Urine drug screen
8. Urine pregnancy testing
9. CGI-Severity and CGI-Improvement ratings (CGI-S and CGI-I)
10. Children's Global Assessment Scale (CGAS)

2) Performed more frequently than they would be if the subject was not participating in the research.
Urine drug screen and pregnancy test may not be done in regular outpatient care. Neuroimaging may or may not be done as part of clinical practice. Assessment of symptoms and treatment compliance and related effects are standard practice.

3) Performed on the subjects in the course of their normal clinical care (i.e. for diagnostic or treatment purposes) where the data are used for research.
Clinical assessment for psychiatric symptoms.

D. Does this research involve genetic testing?

Yes

1) Is the genetic testing a portion of a more comprehensive therapeutic or non-therapeutic study?
Yes

a) Is the genetic testing portion of this research directly relevant to the subject's disease or condition?
Yes.

2) Will identifiers (e.g., name, initials, patient identification number, or code) be maintained which allow anyone to link the results of the genetic tests either directly or indirectly to the subject or will potentially identifying information be obtained from, or about, family members?
Yes

E. Will any un-used human biological material (HBM) be used to create a tissue bank for future research?
No

F. Describe briefly the statistical methods used to analyze the data.
Analysis of data/study outcomes

The purpose of the current study is to determine the impact, as indexed by Blood Oxygen Level Dependent (BOLD) response as well as improvement in symptom profiles, of the administration of oxytocin on pathophysiology of irritability and emotional dysregulation across various diagnoses of disruptive behavior and mood disorders. Using the two biomarker tasks, fear expression processing and affective Stroop, we will be able to determine the extent to which administration of oxytocin reduces the increased BOLD responses in neural areas (i.e., amygdala) to negative emotional stimuli. We will also determine the improvement of symptom profiles by evaluations including ARI, BASC-2, ICU and RPAQ.

The relationship between symptom measurement and neural response changes will be analyzed using both regression and categorical modes. *Hypothesis A, that oxytocin will improve irritability and emotional dysregulation, as well as reduce BOLD responses in amygdala to negative emotional stimuli, compared to placebo* will be tested by (1) a two sample t-test between placebo and oxytocin-treated groups on the symptom profile changes of the ARI, BASC-2, ICU, RPAQ; CGI-S and CGI-I; (2) a two sample t-test between placebo

and oxytocin-treated groups on the change of BOLD responses; (3) ANCOVAs with the treatment groups and the change of symptom profiles as the covariates on the change of BOLD responses.

To account for potential non-linear relationships polynomial fits will be explored, and categorical comparisons will also be made, of responders versus non-responders (with responders defined as those with 0.4 standard deviation of positive change on the symptom measurement scales, including the ARI, CBCL, ICU, and RPAQ).

Statistical methods for the internal pilot study

The first 20 patients will be enrolled and randomly assigned into placebo and oxytocin group. The primary outcome ARI will be measured at the baseline and last visit for each patient. The change of ARI will be calculated as the measure at the last visit minus the measure at the bassline for each patient. The treatment status of each patient will be labeled as A and B by the third party, and all persons associated with the internal pilot study will be kept blinded for group assignment. The SD of the change of ARI will be estimated for each intervention group, and will be used to compute the pooled SD for the internal pilot study. Recalculation of the sample size will be performed using a two sample independent t-test and the pooled SD. The retention rate will be assessed as well.

The data on genetic polymorphisms and OT-treatment outcomes on the neural and psychological measures will be used primarily as pilot data to advise future larger-scale studies. OXTR SNPs vary in frequency in western populations, but there should be sufficient exemplars of varying genotypes to allow preliminary analyses. For example, a commonly-identified OXTR SNP associated with variation in social behavior (rs53576) occurs in frequencies of 53.5% and 46.5% for the risky genotype (A/A and A/G) relative to resilient genotype (G/G) in a Caucasian sample (Jacob et al., 2007).

Finally, we will simultaneously test all measures (e.g., at baseline) in a multivariate analysis to determine the most important measures for predicting outcome in terms of behavioral change (Ecker et al., 2010). It is hoped that this will show which ones of the variables are the best predictors of treatment response, and which aspects are best influenced by treatment.

G. Indicate the study design/phase by checking the appropriate box(s).

Phase I
Phase I/II
Phase II
Phase II/III

Phase III
Phase IV
Other:
Case-Control
Cohort
Cross-sectional
♦ Randomized, parallel group
Randomized, cross-over
♦ Placebo-Controlled
Single Blind
♦ Double Blind
Triple Blind

DRUGS, BIOLOGIC DRUGS AND DEVICES

13. Drugs and Biologic Drugs
A. Does this study involve an investigational drug or biologic drug?
No

B. Does this research involve an FDA-approved and marketed drug or biologic drug?
Yes

14. Devices
A. Does this research involve an investigational device?
No

B. Does this research involve an FDA-approved and marketed device?
No

CONFIDENTIALITY AND PRIVACY

15. Confidentiality and Privacy
A. Will research data be stored:
1) On a secure server at UNMC/TNMC/CH&MC/UNO?
Yes

2) On a local hard drive?
Yes

a) Describe the location of the hard drive.
The office of the PI in the department of psychiatry at UNMC.

b) Describe how the local device will be secured (e.g. in a locked room).
It will be stored in a locked cabinet, in a locked room (PI's office).

c) Is the hard drive encrypted?
Yes

3) On a portable computer?
No

4) On a flash drive?
No

5) In a database accessible through the internet?
No

6) In hard copy?
Yes

a) Will the hard copies be stored at UNMC/TNMC/CH&MC/UNO during the conduct of the study (i.e. not the long term storage location)?
Yes

b) Will the hard copies be stored off campus during the conduct of the study (i.e. not the long term storage location)?
No

c) Describe the physical methods to protect the hard copies (e.g. locked file cabinet or locked briefcase).
The hard copies will be locked in a cabinet in the PI's locked office in the outpatient clinic of the department of psychiatry, UNMC.

d) Will hard copies ever be transported from one site to another site (on or off campus)?
No

7) Other?

Yes

a) Describe where data will be stored.
The MRI data will be stored at the Boys Town National Research Hospital.
The MEG data will be stored at the MEG center of UNMC.

b) Describe how data will be secured.
Both Boys Town National Research Hospital and MEG center of UNMC will have secured server where the fMRI and MEG data are stored. This is a standard procedure of neuroimaging facilities.

The primary investigator will have access to those servers of the Boys Town National Research Hospital and the MEG center of UNMC remotely via internet, to download the neuroimaging data (fMRI and MEG) to the computer at the department of psychiatry secured in a safe place. This access will be granted by the passwords provided to the primary investigator from those facilities. The primary investigator will conduct neuroimaging data analysis. The computer for storing neuroimaging data and analysis will be accessed only by using password, and the door of the room where the computer is located is to be locked.

B. Will any of the following subject identifiers be recorded (at any time) in association with the research data?
Yes

1) Indicate the subject identifiers that will be recorded:
- Name
- Postal address information: street address, city, county, precinct, ZIP code
- All elements of dates (except year) related to an individual (e.g. birth, admission, discharge)
- Telephone numbers

Fax numbers
- Electronic mail addresses
- Social Security numbers
- Medical Record numbers

Health plan beneficiary numbers
Account numbers
Certificate/license numbers
Vehicle identifiers and serial numbers, including license plate numbers
Device identifiers and serial numbers
Web Universal Resource Locators (URLs)

Internet Protocol (IP) address numbers
Biometric identifiers, including finger and voice prints
Full face photographic images [and any comparable images]
No identifiers will be maintained

2) Will a unique subject identifying number, characteristic or code be used to protect the confidentiality of the data? This includes codes assigned by the investigator to link data to other identifiers like the subject s name or medical record number.
Yes

a) Where will the key, that links the unique subject identification code to the subject s name or other identifier, be stored?
The subject identifying number will be created by consecutive number series designated to each subject.

The key that links the unique subject identification code will be maintained by the study coordinator in a cabinet secured in the locked office (separate from the office where the data are stored) of the outpatient clinic of the department of psychiatry, UNMC. This is accessible to the PI and the coordinator.

3) What is the justification for recording the specific identifiers listed above?
♦ Schedule appointments
Collect continuous clinical information from the medical records
♦ Follow-up with subjects
Link stored tissue with subject identification for it to be withdrawn in the future if requested
♦ Other. Explain. ssn needed for payment of study stipend

4) How long will the subject identifiers be maintained in association with the research data?
Subject identifiers will be maintained until research aims are achieved and completed.

5) How will the research data be archived or destroyed when the data is no longer required?
All hard copies will be confidentially shredded.

The fMRI, MEG and anatomical data will be stored in a secured server (COINS) that was developed specifically for the neuroimaging data for two weeks before being transferred to the UNMC computer at the department of psychiatry for further analysis of BOLD responses. The server is automatically set up that the data will be destroyed permanently by

cryptographic erase after this two weeks of period.

Once the study is completed, the data stored in the computer will be destroyed by the standard sanitization process by UNMC IT team. This will involve the cryptographic erase. This will be executed in accordance with UNMC policy No. 6016, destruction/disposal of private and confidential information

6) Will research data that contain subject identifiers be disclosed to any other investigators at UNMC, TNMC, UNO or CH&MC who are not listed in Section I of this application?
No

7) Will research data that contain subject identifiers be disclosed to any investigators outside of UNMC, TNMC, UNO or CH&MC?
No

8) Will research data that contain subject identifiers be disclosed to any commercial sponsor, contract research organization (CRO) or Data and Safety Monitoring Board (DSMB)?
No

9) Will research data that contain subject identifiers be disclosed to any other external organization or entity (e.g., NCI cooperative groups)?
No

10) Will research data be shared with third party payers?
No

C. What provisions will be in place to protect the subject's privacy? Check all that apply.
♦ Obtaining consent in a private conference room or area
♦ Ensuring that only personnel listed on the IRB application Section I.3(A-E) are present during the consent process
♦ Ensuring that the fewest number of individuals possible are aware of the subject's participation in the research.
♦ Ensuring that the research activities are performed in as private of a place as possible
Other. Explain.

D. Does this research involve data banking at UNMC, TNMC, UNO or CH&MC for future

research that is not related to this study?
No

E. Does this research involve data banking by an outside organization (e.g. NCI Cooperative Group, pharmaceutical company) for future, unspecified research that are not integral to the current research?
No

RISK/BENEFIT ASSESSMENT

16. Potential Risks
What are the potential risks associated with each research procedure, intervention, evaluation and/or test? If data are available, estimate the probability that a given harm may occur and its potential reversibility.
Risks and discomfort can be expected from the interviews and examinations, the fMRI, the MEG, the pregnancy testing and drug screening, the administration of nasal spray oxytocin and placebo. Risks and discomforts with each study procedure will now be described.

Interview and examinations

Psychiatric interview and mental status examination can evoke emotional discomfort and anxiety when it is regarding personal information or past/present psychiatric history taking. The participants and their parents will be instructed to inform the investigators of this immediately so the interview and examination can be re-directed or ceased should this happen. Also participants and their parents will be instructed that they don't have an obligation to answer all the questions, and they can withdraw from the protocol any time. The interviews and examinations will be done by either a board certified child and adolescent psychiatrist, or an advanced practice registered nurse. All investigators who will conduct the interviews and examinations are trained mental health providers with extensive research experience in child and adolescent psychiatry.

Functional MRI

Functional MRI scans are widely regarded as a safe, noninvasive procedure for visualization of brain tissue in both adults and children. This study will be performed on an FDA approved scanner at Boys Town National Research Hospital. FDA standards for minimal risk MRI require that four criteria be met: 1) a static magnetic field no greater than 4T, 2) specific absorption rates a) no greater than 4W/kg for the entire body for 15 minutes, b) no greater than 3W/kg over the head for 10 minutes, and c) no greater than 8W/kg in any gram of tissue in the head or torso or 12W/kg in any gram of tissue in the extremities for five

minutes, 3) a time rate of change in the field that does not produce physical discomfort or painful nerve stimulation, and 4) a peak sound pressure level that does not exceed 140 dB or A-weighted R.M.S. pressure level that does not exceed 99dBA with hearing protection. Each of the guidelines will be monitored throughout the study to ensure that none are exceeded.
Participants are at risk for injury from an MRI study if they have metal objects in their bodies such as pacemakers, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses, cochlear implants, or shrapnel fragments. Parents will be asked about the presence of such objects using the standard pre-MRI safety checklist from the department of radiology of the Boys Town National Research Hospital. In addition, at MRI visits 1 and 2, parents will fill out a form to identify any new medical events since the child was screened/last scanned. Individuals with these contraindications will not receive an MRI study scan. During a scan, a loud rhythmic tapping or banging sound is heard. This noise is caused by the switching of the gradient coils that is necessary to produce the image. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Protective earplugs are inserted by trained staff, and a head support is used to minimize movement. If the hearing protection comes loose during the scan, the investigators will fix it right away. There are no known long-term risks of MRI scans. Participants will be closely observed at all times by staff who will terminate the scan if a child appears distressed by the experience.
Through the MRI scans a neurological disorder can be discovered. Should this occur, the child will be referred for clinical assessment to an appropriate health care provider.

One of the risks of an anatomical MRI which will be conducted with functional MRI is discovery of incidental findings. This may include benign anatomical variation (e.g. Chiari I malformation) or more serious findings (e.g. brain tumor). The radiology clinicians at the Boys Town National Research Hospital will review the anatomical MRI no later than 7 days after the image is obtained. If there is an incidental finding, this will be reported to Dr. Hwang who will then report it to the parent/guardian of the child. Dr. Hwang will discuss referral for additional evaluation or treatment with the parent/guardian as appropriate, including referral to the primary care provider or if requested, to an appropriate department of University of Nebraska Medical Center for appropriate further assessment and treatment.

MEG

In regard to MEG, subjects may experience discomfort from the paste and tape that is used to attach electrodes and head coils to the skin surface. Such discomfort may include skin irritation or accidental hair removal.
Participants will be closely observed at all times by staff who will terminate MEG scan if a child appears distressed by the experience.

Pregnancy testing and urine drug screening

The risk associated with performing a pregnancy test is finding out that one of our participants is indeed pregnant.It will be notified to the participants and the parents accordingly.

Administration of nasal spray oxytocin and placebo

The risk associated with oxytocin nasal spray administration are common side effects of oxytocin, including light headedness/vertigo, drowsiness/sleepiness, dry throat/mouth, nasal irritation, runny nose, abdominal discomfort, anxiety, elevation of mood, and headache. Also there are risks related to nasal spray, including irritation of nasal membrane, nosebleed, post-nasal drip, and irritation by bad taste/smell (MacDonald et al., 2011).
Although those side effects of oxytocin are possible to occur with administration of oxytocin nasal spray, it is not any more common than placebo in 45 randomized double-blind placebo trials including population of children and adolescents (MacDonald et al., 2011; Oya, Matsuda, Matsunaga, Kishi, & Iwata, 2015). Also short period time frame (2 weeks) of the trial will significantly lower the risk of side effects. We expect the potential risk of nasal spray itself such as irritation of nasal membrane, post-nasal drip, and irritation by bad taste/smell to be minor and transient, even when it occurs.

Participants will be examined as part of screening for their physical health and previous history of and response to oxytocin administration, and also will be monitored by either child and adolescent psychiatrist or nurse practitioner during the treatment time frame of oxytocin nasal spray or placebo. Should any side effect occur, we will monitor the course of side effects while the participant is in the time frame of treatment, providing visit to the outpatient clinic of the department of psychiatry at University of Nebraska Medical Center for check-up of sign/symptom and physical/neurological examination. If any significant side effect occurs, the participant will be referred for further clinical care as necessary.

Buccal Cheek Brush for genetic sampling

The Potential risk of buccal cheek brush for genetic sampling includes irritation of buccal cheek, minor bleeding of mucosa, and uncomfortable sense/taste of the brush. We expect the potential risk of buccal cheek brush to be minor and transient. If any of these events happen during the procedure, we will provide close monitoring while the participant is in the outpatient clinic of the department of psychiatry at University of Nebraska Medical Center. If any significant adverse event happens, the participant will be referred for further clinical care as necessary.

Genetic testing of oxytocin receptor

The potential risk of genetic testing of the oxytocin receptor is minimal. This will not contain any information regarding personal identification of the participants. Thus, the result of genetic testing will not be given to the participants or their parent/guardian. It will not be stored or banked for future study either.

17. Risk Classification
What is the overall risk classification of the research?
Minimal risk
♦ Greater than minimal risk
Significant risk

18. Minimization of Risk
A. Will the research utilize procedures already being performed on the subjects for diagnostic or treatment purposes?
No

B. Describe how the subjects of the research will be monitored by the investigators and other research personnel to ensure their safety.
Participants will be closely monitored at all times by UNMC and Boys Town National Research Hospital research staff who will terminate the scanning of MRI and/or MEG if a participant appears distressed by the experience. The participants will be observed via monitor screens while they are performing neuropsychological tasks in the scanner of MRI and MEG. Vital signs including blood pressure and pulse rate may be obtained if any participant showed distress.
Participants will be monitored for any side effect from oxytocin or placebo nasal spray during their visit to the outpatient clinic of the department of psychiatry at University of Nebraska Medical Center, during their treatment period (14 to 21 days). Participants and their parents will be given of the contact number to the outpatient clinic for any clinical concern or occurring of side effect. The research team will provide extra clinical visit if it is clinically necessary during the course of treatment.

C. Describe the process by which the PI will be informed and how the PI, in turn, will inform other research staff about events concerning subject safety (including (a) interim results; (b) adverse events; (c) unanticipated problems involving risks to subjects or others; (d) noncompliance; (e) complaints).
1) At UNMC/TNMC/CH&MC and/or UNO (check all that apply).

Not applicable. The PI is the only person listed in Section I of the IRB Application.
♦ By email or campus mail (for events which do not constitute immediate subject safety hazards)
♦ By phone
♦ By in-person meeting
♦ By scheduled submission of case report forms
Other. Explain.

2) At external study sites under the oversight of the Joint Pediatric IRB as applicable (check all that apply).
By email or mail (for events which do not constitute immediate subject safety hazards)
By phone
By in-person meeting or teleconference
By scheduled submission of case report forms
♦ Other. Explain. n/a

D. Describe the auditing plan for research conducted:
1) Within the Organization (UNMC, TNMC, UNO or CH&MC), identify who will conduct the audits and specify the audit frequency.
The audit will be conducted by the PI, the secondary investigators, and participating personnel at the end of every month throughout the duration of the study.

2) At external study sites under the oversight of the Joint Pediatric IRB, identify who will conduct the audits and specify the audit frequency.
N/A.

E. Is there is an independent DSMB for this study?
Yes

Will you be submitting the DSMB charter?
Yes

F. Describe the specific criteria by which the investigator would withdraw individual subjects from the research (for example, medical criteria, such as specific toxicity or lack of efficacy or non-medical criteria, such as non-compliance).
Withdrawal Criteria
1. Initiation of any medication that may have psychotropic effects (newly introduced antidepressants, antipsychotics, anxiolytics, stimulants, and non-stimulant ADHD medications).

2. Discovery of neurologic disorder (including seizures) or anatomical abnormality of brain (including brain neoplasm, hydrocephalus) during participation.
3. Discovery of substance abuse or dependence.
4. Inability of the participant to complete fMRI or MEG due to claustrophobia despite previous questioning.
5. Participants who do not want to continue with the study.
6. Participants who cannot or will not cooperate with study procedures.
7. Participants who experience strong discomfort or develop side effect following the administration of oxytocin or placebo nasal spray.
8. Participants who experience significant worsening of psychiatric symptoms that warrant change of treatment (such as inpatient psychiatric hospitalization).

G. Describe the specific criteria for halting or early termination of the study (for example statistical evidence of unacceptable toxicity or early demonstration of efficacy or lack of efficacy).

The study would be halted in followings;

1. Early evidence showing lack of efficacy on irritability or worsening of irritability by oxytocin treatment: After the preliminary phase of the study (10 patients on each arms of oxytocin and placebo trial), if it turns out that children and adolescents experience significant worsening of their psychiatric/behavioral symptoms, or have no change in their psychiatric/behavioral symptoms, we then will consider terminating the study.
2. MEG and/or fMRI become inoperable
3. Serious injury related to procedure (MEG, fMRI, or oxytocin administration) occurs

H. Describe plans and resources available to promptly address any subject injury.

Investigators will be closely monitoring the outcomes of the study and the tolerability of the procedures throughout the conduct of the trial. Additionally, the investigators have expertise in conducting clinical trial in the pediatric behavioral health population, and in the use of fMRI, and MEG.

19. Potential Benefits to the Subject

Are there potential benefits to the subjects that may reasonably be expected from participation in the research?

Yes

Describe.

The diagnostic assessment (K-SAIDS) and symptoms assessment by multiple measurements may provide more comprehensive information about the mental health status of the subject, since they are more thorough and comprehensive than routine clinical

assessment. For example, they may find undiagnosed mood or anxiety issues (major depressive disorder, or social anxiety disorder) that could be informed to the subjects and their parents/guardians for further appropriate treatment and intervention. The subject may experience temporary improvement in irritability and emotional dysregulation with oxytocin treatment for the period of clinical trial.

20. Potential Benefits to Society

What are the anticipated benefits (i.e., value) to society that may reasonably be expected to result from this research?

By completion of the study, we aim to obtain better knowledge of treatment and change of pathophysiology in children and adolescents with irritability and emotional dysregulation. This will provide opportunity of improved care for this population by clinicians. It will also hold significant promise in areas such as early and accurate detection of illness, treatment monitoring, and basic understanding of irritability and emotional dysregulation in pediatric population.

21. Alternatives to Participation

A. How do the study procedures or courses of treatment differ from the care that the subject might receive were he/she not to participate in the research?

Participants in this study will receive experimental treatment of oxytocin for their irritability and emotional dysregulation. Oxytocin is not approved for the treatment of irritability and emotional dysregulation in pediatric patients and is not commercially available for this. . Diagnostic and treatment of irritability and emotional dysregulation is available in the UNMC department of psychiatry, psychology and other providers throughout the community.

B. Are there any reasonably available alternatives in the non-research context which would have the potential for providing the same benefits (treatment or other) to subjects?

Not applicable. There are no direct benefits to subjects; the alternative is to not participate in the research.

♦ Yes. Describe: Regular psychiatric assessment and follow-up with behavioral and/or psychopharmacological intervention can be potentially beneficial for the children and adolescents with irritability and emotional dysregulation. Functional MRI and MEG scanning are not currently used in treatment of disruptive behavior and mood disorders.

No. Explain:

C. Would any of the study procedures or courses of treatment in the protocol be available to the prospective subject if they elected not to participate?

No

Explain.
Oxytocin is an experimental drug for irritability in pediatric population, and is not part of routine psychiatric treatment.

Functional MRI, MEG, and oxytocin receptor genetic testing are not part of routine psychiatric care for this population. fMRI and MEG are available clinically if indicated and ordered by a medical provider. Oxytocin receptor genetic testing is not likely indicated for any reason at this point beyond the purpose of its use in this study, and would not likely be part of care outside the study.

D. How do the risks of the research compare with the risks of alternative procedures or courses of treatment described above?
Participating in the research may involve risk of procedures (oxytocin administration, MRI, and MEG), and loss of confidentiality. The risk of participating in the study is greater than the alternative procedures of treatment.

E. How do the anticipated benefits of the research compare with the benefit of alternative procedures or courses of treatment described above?
Oxytocin may not have more benefit that currently available pharmacotherapies or behavioral interventions.

FINANCIAL OBLIGATIONS AND COMPENSATION

22. Financial Obligations of the Parent(s)/Guardian(s) of the Subject
A. Who will pay for procedures and treatments performed solely for research purposes?
Sponsor
♦ Grant
CRC, CCTR
Costs or fees waived by TNMC, UNMC- P, CH&MC or CSP
Subject's health insurance
Medicare/Medicaid
Department/Section funds
Other. Explain.
Parent(s)/guardian(s).

B. Are there any other financial obligations that the parent(s)/guardians of the subject will incur as a result of participating in the study (e.g. travel expenses, meals, supplies)?

No

23. Compensation to the Subject for Participation
Will the subject and/or their parent(s)/guardian(s) receive any compensation for participation?
Yes

Describe the form of compensation, dollar amount (if applicable) and the prorated compensation plan (if applicable).
$20.00 per visit for child
$20.00 per visit for parent
Since the protocol will have total of 3-5 visits in total, depending on the scheduling of assessment and scan sessions, the total possible compensation for both the child and parent would be $200.00 ($20.00 x 5 + $20.00 x5).

A stipend check will be issued at the time of completion of the subject's participation in the study. The check will be issued to the parent/guardian unless otherwise specified.

PRIOR REVIEW

24. Prior IRB Review
A. Has this study (or one substantially similar) been previously submitted to the Joint Pediatric IRB (or the UNMC IRB) and then withdrawn by the investigator for any reason?
No

B. To the best of your knowledge, has this study (or one substantially similar) been considered by another IRB and not granted approval?
No

SUBJECT IDENTIFICATION & RECRUITMENT

25. Method of Subject Identification and Recruitment
A. Will prospective subjects be identified through initial contact by the investigator?
Yes

1) Identified through (check all that apply):
♦ Clinic
Hospital inpatient units

Previous research participants
♦ Investigator, clinic or hospital-maintained databases or registries
♦ Other. Explain. Electronic health record

2) Describe how the research staff has ethical access to the potential subjects.
Participants will be recruited from the outpatient clinic of the department of psychiatry at UNMC. Dr. Hwang is faculty in the department of psychiatry. Ms. Vaughan sees patients clinical at the Munroe Meyer Institute, Developmental and Behavioral Pediatrics. Participants will also be recruited from local providers and other community clinics by letter, fliers, and newspaper ads.

Patient's at the outpatient clinic of the department of psychiatry, UNMC will be identified via Epic chart review by the P.I., and designated members of the study team who are also employees of the department of psychiatry and have appropriate access to patient records. The department chair provided permission for the P.I. and study team to access all clinical patient records at the outpatient clinic of UNMC, the department of psychiatry. The P.I. and designated study team members will identify patients potentially eligible for study participation, by reviewing clinical encounters in the Epic chart. The P.I. will then discuss with the treating physicians that their patients may qualify and ask the treating physicians to ask the patient if it would be fine to be contacted for participation in the study. Designated study team members will then coordinate scheduling of study related visits including screening visits and post-enrollment visits and procedures.

B. Will prospective subjects make the initial contact with the research personnel to inquire about the study?
Yes

1) Identified through (check all that apply):
♦ Referral by clinician or other parties specifically for the research
♦ Flier
Newspaper advertisement
Television spot
Radio announcement
♦ Word of mouth
Public UNMC study database
♦ Other. Explain. Electronic health record; social media (facebook, twitter) using approved flier

C. Will this study be listed in the clinical trial registry at www.clinicaltrials.gov?
Yes

Provide the NCT number.
NCT 02824627

OBTAINMENT OF INFORMED CONSENT

26. Waiver or Alteration of Informed Consent
Is a waiver or alteration of consent requested for either 1) all of the subjects or 2) a subset of subjects?
No

27. Waiver of a Signed Consent Form
Is a waiver of the requirement to obtain a signed consent form requested?
No

28. Process of Permission (Informed Consent) for Parent(s)/Guardian(s)
A. When will the parent(s)/guardian(s) of the prospective subject be approached relative to their child's actual participation in the study?
Participants and their parent/guardian will be approached for participation at the time of a clinic visit at the UNMC Department of Psychiatry, or during a scheduled initial research assessment.

B. Where will informed consent be obtained, and how will the environment be conducive to discussion and thoughtful consideration by the parent(s)/guardian(s)?
Informed consent will be obtained in person in a private area of the outpatient clinic of the department of psychiatry, at UNMC, or by video call or telephone. The participant and his/her parent/guardian will be give time to read the consent form, including the rights of research subjects, and will be allowed to ask questions regarding the study. If consent takes place in person, they may take the forms home for consideration, and are free to discuss them with other significant people (primary care provider, other relatives, etc) prior to agreeing to participate. If consent is obtained via telephone or video call with the participant and parent/guardian, the consent document will be emailed to the parent/guardian or shared during the video call for the parent/guardian to review. After verbal consent is obtained from parent/guardian and assent is obtained from participant, a copy of the consent document signed by research personnel will be copied and mailed to participant and parent/guardian to be signed and returned. Once this signed copy is received, it will be signed by research staff and dated again, noting receipt of the signed consent form. This form will be kept in the study record and a copy will be made for the participant and parent/guardian to keep.

If the participant and parent/guardian are in the outpatient clinic, consent may be obtained by video call in separate rooms to minimize contact if social distance cannot be reasonably maintained.

C. Who will be involved in the process of consenting the parent(s)/guardian(s) about their child's participation in the study and what are their responsibilities?
The P.I. and the lead coordinator. Either Dr. Hwang or Ms. Vaughan will review the informed consent with the participant and his/her parent/guardian. Dr. Hwang will ultimately answer any questions the participant and parent/guardian have, and he will also ask questions to determine their level of understanding. Dr. Hwang will obtain informed consent.

D. How much time will be allotted to the process of consent?
The participants and their parents will be allowed sufficient time to consider participation in the study. The consent process will take as long as necessary for the participants and their parents to make an informed decision. We estimate 30-60 minutes. If it appears that the participant or his/her parent will have inadequate time to fully consider enrollment the participant will not be enrolled in the study. The P.I. or the lead coordinator will go over the consent form in detail outlining the proposed research and will answer any questions the participant or the parent may have.

E. How will the process of consent be structured for parent(s)/guardian(s) who are likely to be more vulnerable to coercion or undue influence?
The participant and his/her parent will be in a private area at the outpatient clinic of the department of psychiatry at UNMC and will be allowed sufficient time to read and process the consent form before signing it. If sufficient time is not reserved in the clinic the participant and his/her parent will take the consent form home to read, consult with others if they want to. If consent is obtained remotely by telephone or video call, the consent document will be emailed in advance to review or shared during the video call. The subject and his/her parent/guardian may wish to utilize the research subject advocate, other family members or friends in making a decision regarding participation in the study. At the time of consent the P.I. or the lead coordinator will question the participant and his/her parent on the nature of the research and responsibility of the P.I., and the participant/parent. If at any time during the final process of the consenting there is a lack of comprehension the potential participation of the participant will be withdrawn.

F. Will non-English speaking subjects be enrolled in this research and/or will non-English speaking parent(s)/guardians be consenting for the prospective subject?
No

Provide justification for why non-English speaking subjects will be excluded.

The measurements we will use, including BASC-2, the ARI, the ICU, the RPAQ, the K-SADS, and WASI are all in English. Translation is not available for all measures.

G. How will it be determined that the parent(s)/guardian(s) understood the information presented?
The participant and his/her parent will be asked to give an overview of the study in their own words. Incomplete understanding or misunderstanding of the study will lead to further discussion and explanation by the consenting personnel.

H. Will there be a formal process of on-going re-consent (over and above re-consent associated with changes in protocol)?
No

29. Process of Obtaining Assent From the Child
A. Will the investigator ask children and adolescents to assent to participate in the research?
Yes

B. How will it be determined that the child understood the information presented?
The child will be asked to give an overview of the study in their own words. Incomplete understanding or misunderstanding of the study will lead to further discussion and explanation by the consenting personnel.

C. Will children reach the age of majority (i.e., 19 years old) during the course of the study?
No

30. Consent Forms and study information sheets
Indicate the type of consent forms and study information sheets to be used in this research:
♦ Parental/Guardian consent form
Youth Study Information Sheet
Child Study Information Sheet
Screening consent form
Addendum consent form
Adult consent form
Other:

31. Documentation of Consent and Assent
List who will sign the consent form as the "Person Obtaining Consent".
Hwang, Soonjo

Soltis-Vaughan, Brigette Suzanne

32. Information Purposely Withheld
Will any information be purposely withheld from the parent(s)/guardian(s) of the subject or the subject during the research or after completion of the research?
Yes

A. What specific information will be withheld?
During one of the fMRI tasks (fearful expression processing task), the child will be told to determine the gender of the face on the screen. In fact this task is designed to assess the amygdala activity to the negative emotional expression of the face with different degree of intensity.

B. What is the justification for this non-disclosure?
This task is designed to provoke subliminal response of amygdala to the intensity of fearful expression of faces the subjects will view.

C. Will information that has been withheld eventually be shared with the subject and/or their parent(s)/guardian(s)?
No

Provide justification.
After the first scan, they won't be informed for they will be scheduled for the second scan. Although disclosing the withheld information after the second scan will not impact the study, there are no plans for disclosure.

RESOURCES

33. Describe the resources available to safely conduct this study at <u>each</u> study site specified in Section I.7.
Funding is being provided through an intramural grant from the department of psychiatry. Space for clinical assessments and storage of study records is available in the department of psychiatry. Neuroimaging facilities are located at UNMC and Boys Town National Research Hospital.

Investigators are trained in working with children and adolescents with disruptive mood and behavior disorders. Imaging lab staff are appropriately trained and supervised. On-call access to the UNMC department of psychiatry is available 24/7.

Immediate medical assessment/treatment will be available at the University of Nebraska Medical Center, and Boys Town National Research Hospital. If the participant seeks emergency care or hospitalization is required other than at the University of Nebraska Medical Center, the participant should alert the treating physician that they are participating in a research study being conducted by the investigator listed on the consent form.

If the participant becomes ill physically, or becomes worse in his/her psychiatric symptoms, as a direct result of a study-related procedure or because the participant took the study drug, appropriate medical care for the immediate treatment of the illness or injury will be provided to the participant.

If the participant is injured during the study, the investigator will discuss with the participant and his/her parent the available medical treatment options.

LITERATURE REVIEW

34. References

Provide a full listing of the key references cited in the background (Section II.3). The references should clearly support the stated purpose of the study.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual 5*. Washington D.C.: American Psychiatric Association.

Avenevoli, S., Blader, J. C., & Leibenluft, E. (2015). Irritability in Youth: An Update. *J Am Acad Child Adolesc Psychiatry, 54*(11), 881-883. doi:10.1016/j.jaac.2015.08.012

Balota, D. A., Yap, M. J., Cortese, M. J., Hutchison, K. A., Kessler, B., Loftis, B., . . . Treiman, R. (2007). The English Lexicon Project. *Behav Res Methods, 39*(3), 445-459.

Berg, J. M., Lilienfeld, S. O., Reddy, S. D., Latzman, R. D., Roose, A., Craighead, L. W., . . . Raison, C. L. (2013). The Inventory of Callous and Unemotional Traits: A Construct-Validational Analysis in an At-Risk Sample. *Assessment*. doi:1073191112474338 [pii]
10.1177/1073191112474338 [doi]

Blair, K., Shaywitz, J., Smith, B. W., Rhodes, R., Geraci, M., Jones, M., . . . Pine, D. S. (2008). Response to emotional expressions in generalized social phobia and generalized anxiety disorder: evidence for separate disorders. *Am J Psychiatry, 165*(9), 1193-1202. doi:10.1176/appi.ajp.2008.07071060

Blair, K. S., Geraci, M., Smith, B. W., Hollon, N., DeVido, J., Otero, M., . . . Pine, D. S.

(2012). Reduced dorsal anterior cingulate cortical activity during emotional regulation and top-down attentional control in generalized social phobia, generalized anxiety disorder, and comorbid generalized social phobia/generalized anxiety disorder. *Biol Psychiatry, 72*(6), 476-482. doi:S0006-3223(12)00364-2 [pii]
10.1016/j.biopsych.2012.04.013 [doi]
Blair, K. S., Smith, B. W., Mitchell, D. G., Morton, J., Vythilingam, M., Pessoa, L., . . . Blair, R. J. (2007). Modulation of emotion by cognition and cognition by emotion. *Neuroimage, 35*(1), 430-440. doi:S1053-8119(06)01117-7 [pii]
10.1016/j.neuroimage.2006.11.048 [doi]
Brotman, M. A., Rich, B. A., Guyer, A. E., Lunsford, J. R., Horsey, S. E., Reising, M. M., . . . Leibenluft, E. (2010). Amygdala activation during emotion processing of neutral faces in children with severe mood dysregulation versus ADHD or bipolar disorder. *Am J Psychiatry, 167*(1), 61-69. doi:10.1176/appi.ajp.2009.09010043
Chen, F. S., Kumsta, R., von Dawans, B., Monakhov, M., Ebstein, R. P., & Heinrichs, M. (2011). Common oxytocin receptor gene (OXTR) polymorphism and social support interact to reduce stress in humans. *Proc Natl Acad Sci U S A, 108*(50), 19937-19942. doi:10.1073/pnas.1113079108
Dadds, M. R., MacDonald, E., Cauchi, A., Williams, K., Levy, F., & Brennan, J. (2014). Nasal oxytocin for social deficits in childhood autism: a randomized controlled trial. *J Autism Dev Disord, 44*(3), 521-531. doi:10.1007/s10803-013-1899-3
Deveney, C. M., Connolly, M. E., Haring, C. T., Bones, B. L., Reynolds, R. C., Kim, P., . . . Leibenluft, E. (2013). Neural mechanisms of frustration in chronically irritable children. *Am J Psychiatry, 170*(10), 1186-1194. doi:10.1176/appi.ajp.2013.12070917
Diseth, T. H. (2005). Dissociation in children and adolescents as reaction to trauma--an overview of conceptual issues and neurobiological factors. *Nord J Psychiatry, 59*(2), 79-91. doi:10.1080/08039480510022963
Dougherty, L. R., Smith, V. C., Bufferd, S. J., Carlson, G. A., Stringaris, A., Leibenluft, E., & Klein, D. N. (2014). DSM-5 disruptive mood dysregulation disorder: correlates and predictors in young children. *Psychol Med, 44*(11), 2339-2350. doi:10.1017/s0033291713003115
Ecker, C., Marquand, A., Mourao-Miranda, J., Johnston, P., Daly, E. M., Brammer, M. J., . . . Murphy, D. G. (2010). Describing the brain in autism in five dimensions--magnetic resonance imaging-assisted diagnosis of autism spectrum disorder using a multiparameter classification approach. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 30*(32), 10612-10623. doi:10.1523/JNEUROSCI.5413-09.2010
Euler, F., Jenkel, N., Stadler, C., Schmeck, K., Fegert, J. M., Kolch, M., & Schmid, M. (2015). Variants of girls and boys with conduct disorder: anxiety symptoms and callous-unemotional traits. *J Abnorm Child Psychol, 43*(4), 773-785. doi:10.1007/s10802-014-9946-x
Forbes, E. E., Olino, T. M., Ryan, N. D., Birmaher, B., Axelson, D., Moyles, D. L., & Dahl, R.

E. (2010). Reward-related brain function as a predictor of treatment response in adolescents with major depressive disorder. *Cogn Affect Behav Neurosci, 10*(1), 107-118. doi:10/1/107 [pii]
10.3758/CABN.10.1.107 [doi]
Frick. (2004). *The Inventory of Callous-Unemotional Traits*. Unpublished Ratings Scale. Department of Psychology. University of New Orleans. New Orleans.
Guastella, A. J., & MacLeod, C. (2012). A critical review of the influence of oxytocin nasal spray on social cognition in humans: evidence and future directions. *Horm Behav, 61*(3), 410-418. doi:10.1016/j.yhbeh.2012.01.002
Guy, W. (1976). ECDEU Assessment Manual for Psychopharmacology.
Herzhoff, K., & Tackett, J. L. (2015). Subfactors of oppositional defiant disorder: converging evidence from structural and latent class analyses. *J Child Psychol Psychiatry*. doi:10.1111/jcpp.12423
Hillebrand, A., Singh, K. D., Holliday, I. E., Furlong, P. L., & Barnes, G. R. (2005). A new approach to neuroimaging with magnetoencephalography. *Hum Brain Mapp, 25*(2), 199-211. doi:10.1002/hbm.20102
Hironaga, N., & Ioannides, A. A. (2007). Localization of individual area neuronal activity. *Neuroimage, 34*(4), 1519-1534. doi:10.1016/j.neuroimage.2006.10.030
Hulvershorn, L. A., Mennes, M., Castellanos, F. X., Di Martino, A., Milham, M. P., Hummer, T. A., & Roy, A. K. (2014). Abnormal amygdala functional connectivity associated with emotional lability in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry, 53*(3), 351-361.e351. doi:10.1016/j.jaac.2013.11.012
Hwang, S., White, S. F., Nolan, Z. T., Sinclair, S., & Blair, R. J. (2014). Neurodevelopmental changes in the responsiveness of systems involved in top down attention and emotional responding. *Neuropsychologia, 62*, 277-285. doi:10.1016/j.neuropsychologia.2014.08.003
Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., . . . Wang, P. (2010). Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry, 167*(7), 748-751. doi:10.1176/appi.ajp.2010.09091379
Karalunas, S. L., Fair, D., Musser, E. D., Aykes, K., Iyer, S. P., & Nigg, J. T. (2014). Subtyping attention-deficit/hyperactivity disorder using temperament dimensions: toward biologically based nosologic criteria. *JAMA Psychiatry, 71*(9), 1015-1024. doi:10.1001/jamapsychiatry.2014.763
Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., . . . Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child & Adolescent Psychiatry, 36*(7), 980-988. doi:10.1097/00004583-199707000-00021
Khanna, M. M., Badura-Brack, A. S., McDermott, T. J., Shepherd, A., Heinrichs-Graham, E., Pine, D. S., . . . Wilson, T. W. (2015). Attention training normalises combat-related

post-traumatic stress disorder effects on emotional Stroop performance using lexically matched word lists. *Cogn Emot*, 1-8. doi:10.1080/02699931.2015.1076769

Koch, S. B., van Zuiden, M., Nawijn, L., Frijling, J. L., Veltman, D. J., & Olff, M. (2015). Intranasal Oxytocin Administration Dampens Amygdala Reactivity Towards Emotional Faces in Male and Female PTSD Patients. *Neuropsychopharmacology*. doi:10.1038/npp.2015.299

Krieger, F. V., Leibenluft, E., Stringaris, A., & Polanczyk, G. V. (2013). Irritability in children and adolescents: past concepts, current debates, and future opportunities. *Rev Bras Psiquiatr, 35 Suppl 1*, S32-39. doi:10.1590/1516-4446-2013-s107

Labuschagne, I., Phan, K. L., Wood, A., Angstadt, M., Chua, P., Heinrichs, M., . . . Nathan, P. J. (2010). Oxytocin attenuates amygdala reactivity to fear in generalized social anxiety disorder. *Neuropsychopharmacology, 35*(12), 2403-2413. doi:10.1038/npp.2010.123

Lagges, A. M., & Dunn, D. W. (2003). Depression in children and adolescents. *Neurol Clin, 21*(4), 953-960.

Lecavalier, L. (2006). Behavioral and emotional problems in young people with pervasive developmental disorders: relative prevalence, effects of subject characteristics, and empirical classification. *J Autism Dev Disord, 36*(8), 1101-1114. doi:10.1007/s10803-006-0147-5

Leibenluft, E., Charney, D. S., Towbin, K. E., Bhangoo, R. K., & Pine, D. S. (2003). Defining clinical phenotypes of juvenile mania. *Am J Psychiatry, 160*(3), 430-437.

Leibenluft, E., & Stoddard, J. (2013). The developmental psychopathology of irritability. *Dev Psychopathol, 25*(4 Pt 2), 1473-1487. doi:10.1017/s0954579413000722

Lozier, L. M., Cardinale, E. M., VanMeter, J. W., & Marsh, A. A. (2014). Mediation of the relationship between callous-unemotional traits and proactive aggression by amygdala response to fear among children with conduct problems. *JAMA Psychiatry, 71*(6), 627-636. doi:1847577 [pii]
10.1001/jamapsychiatry.2013.4540 [doi]

MacDonald, E., Dadds, M. R., Brennan, J. L., Williams, K., Levy, F., & Cauchi, A. J. (2011). A review of safety, side-effects and subjective reactions to intranasal oxytocin in human research. *Psychoneuroendocrinology, 36*(8), 1114-1126. doi:10.1016/j.psyneuen.2011.02.015

Marsh, A. A., & Blair, R. J. (2008). Deficits in facial affect recognition among antisocial populations: a meta-analysis. *Neurosci Biobehav Rev, 32*(3), 454-465. doi:S0149-7634(07)00107-8 [pii]
10.1016/j.neubiorev.2007.08.003 [doi]

Marsh, A. A., Finger, E. C., Mitchell, D. G., Reid, M. E., Sims, C., Kosson, D. S., . . . Blair, R. J. (2008). Reduced amygdala response to fearful expressions in children and adolescents with callous-unemotional traits and disruptive behavior disorders. *Am J Psychiatry, 165*(6), 712-720. doi:appi.ajp.2007.07071145 [pii]
10.1176/appi.ajp.2007.07071145 [doi]

Oya, K., Matsuda, Y., Matsunaga, S., Kishi, T., & Iwata, N. (2015). Efficacy and safety of oxytocin augmentation therapy for schizophrenia: an updated systematic review and meta-analysis of randomized, placebo-controlled trials. *Eur Arch Psychiatry Clin Neurosci.* doi:10.1007/s00406-015-0634-9

Perlman, S. B., Jones, B. M., Wakschlag, L. S., Axelson, D., Birmaher, B., & Phillips, M. L. (2015). Neural substrates of child irritability in typically developing and psychiatric populations. *Dev Cogn Neurosci, 14*, 71-80. doi:10.1016/j.dcn.2015.07.003

Raine, A., Dodge, K., Loeber, R., Gatzke-Kopp, L., Lynam, D., Reynolds, C., . . . Liu, J. (2006). The Reactive-Proactive Aggression Questionnaire: Differential Correlates of Reactive and Proactive Aggression in Adolescent Boys. *Aggress Behav, 32*(2), 159-171. doi:10.1002/ab.20115

Reynolds, C. R., Kamphaus, R.W. (2015). *Behavior Assessment System for Children, 3rd ed.* Bloomington, MN.: Pearson.

Schaffer D, Gould MS, Brasic J, et al (1983). A children's global assessment scale (CGAS). Archives of General Psychiatry, 40, 1228-1231.

Sebastian, C. L., McCrory, E. J., Dadds, M. R., Cecil, C. A., Lockwood, P. L., Hyde, Z. H., . . . Viding, E. (2014). Neural responses to fearful eyes in children with conduct problems and varying levels of callous-unemotional traits. *Psychol Med, 44*(1), 99-109. doi:10.1017/s0033291713000482

Skuse, D. H., Lori, A., Cubells, J. F., Lee, I., Conneely, K. N., Puura, K., . . . Young, L. J. (2014). Common polymorphism in the oxytocin receptor gene (OXTR) is associated with human social recognition skills. *Proc Natl Acad Sci U S A, 111*(5), 1987-1992. doi:10.1073/pnas.1302985111

Stoddard, J., Hsu, D., Reynolds, R. C., Brotman, M. A., Ernst, M., Pine, D. S., . . . Dickstein, D. P. (2015). Aberrant amygdala intrinsic functional connectivity distinguishes youths with bipolar disorder from those with severe mood dysregulation. *Psychiatry Res, 231*(2), 120-125. doi:10.1016/j.pscychresns.2014.11.006

Stringaris, A., Goodman, R., Ferdinando, S., Razdan, V., Muhrer, E., Leibenluft, E., & Brotman, M. A. (2012). The Affective Reactivity Index: a concise irritability scale for clinical and research settings. *J Child Psychol Psychiatry, 53*(11), 1109-1117. doi:10.1111/j.1469-7610.2012.02561.x

Stringaris, A., Maughan, B., Copeland, W. S., Costello, E. J., & Angold, A. (2013). Irritable mood as a symptom of depression in youth: prevalence, developmental, and clinical correlates in the Great Smoky Mountains Study. *J Am Acad Child Adolesc Psychiatry, 52*(8), 831-840. doi:10.1016/j.jaac.2013.05.017

Tao, R., Calley, C. S., Hart, J., Mayes, T. L., Nakonezny, P. A., Lu, H., . . . Emslie, G. J. (2012). Brain activity in adolescent major depressive disorder before and after fluoxetine treatment. *Am J Psychiatry, 169*(4), 381-388. doi:10.1176/appi.ajp.2011.11040615 [doi]

Thomas, L. A., Kim, P., Bones, B. L., Hinton, K. E., Milch, H. S., Reynolds, R. C., . . . Leibenluft, E. (2013). Elevated amygdala responses to emotional faces in youths with

chronic irritability or bipolar disorder. *Neuroimage Clin, 2*, 637-645. doi:10.1016/j.nicl.2013.04.007
Tourian, L., LeBoeuf, A., Breton, J. J., Cohen, D., Gignac, M., Labelle, R., . . . Renaud, J. (2015). Treatment Options for the Cardinal Symptoms of Disruptive Mood Dysregulation Disorder. *J Can Acad Child Adolesc Psychiatry, 24*(1), 41-54.
Viding, E., Sebastian, C. L., Dadds, M. R., Lockwood, P. L., Cecil, C. A., De Brito, S. A., & McCrory, E. J. (2012). Amygdala response to preattentive masked fear in children with conduct problems: the role of callous-unemotional traits. *Am J Psychiatry, 169*(10), 1109-1116. doi:1367818 [pii]
10.1176/appi.ajp.2012.12020191 [doi]
Wakschlag, L. S., Estabrook, R., Petitclerc, A., Henry, D., Burns, J. L., Perlman, S. B., . . . Briggs-Gowan, M. L. (2015). Clinical Implications of a Dimensional Approach: The Normal:Abnormal Spectrum of Early Irritability. *J Am Acad Child Adolesc Psychiatry, 54*(8), 626-634. doi:10.1016/j.jaac.2015.05.016
Wechsler, D. (1991). *Manual for the Wechsler Intelligence Scale for Children- Third Edition (WISC-III)*. San Antonio, TX: Psychological Corporation.
Wechsler, D. (1997). *WAIS-III ad WMS-III Technical Manual*. San Antonio, TX: Psychological Corporation.
Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: Psychological Corporation.
Wechsler, D. (2011). *Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II)*. San Antonio, TX: NCS Pearson.
Wiggins, J. L., Brotman, M. A., Adleman, N. E., Kim, P., Oakes, A. H., Reynolds, R. C., . . . Leibenluft, E. (2016). Neural Correlates of Irritability in Disruptive Mood Dysregulation and Bipolar Disorders. *Am J Psychiatry*, appiajp201515060833. doi:10.1176/appi.ajp.2015.15060833
Yatawara, C. J., Einfeld, S. L., Hickie, I. B., Davenport, T. A., & Guastella, A. J. (2015). The effect of oxytocin nasal spray on social interaction deficits observed in young children with autism: a randomized clinical crossover trial. *Mol Psychiatry*. doi:10.1038/mp.2015.162

Aspé Sánchez, M., Moreno, M., Rivera, M.-I., Rossi, A., & Ewer, J. (2015). Oxytocin and vasopressin receptor gene polymorphisms: role in social and psychiatric traits. *Frontiers in Neuroscience*, *9*, 510.
Feldman, R., Zagoory-Sharon, O., Weisman, O., Schneiderman, I., Gordon, I., Maoz, R., Ebstein, R. P. (2012). Sensitive parenting is associated with plasma oxytocin and polymorphisms in the OXTR and CD38 genes. *Biological Psychiatry*, *72*(3), 175181.
Hofmann, S. G., Fang, A., & Brager, D. N. (2015). Effect of intranasal oxytocin administration on psychiatric symptoms: A meta-analysis of placebo-controlled studies. *Psychiatry Research*, *228*(3), 708714.
Jacob, S., Brune, C. W., Carter, C. S., Leventhal, B. L., Lord, C., & Cook, E. H. (2007).

Association of the oxytocin receptor gene (OXTR) in Caucasian children and adolescents with autism. *Neuroscience Letters*, *417*(1), 69.
MacDonald, K. S. (2015). Sex, receptors, and attachment: a review of individual factors influencing response to oxytocin. *Social Hormones and Human Behavior: What Do We Know and Where Do We Go from Here*, 34.

SECTION III

SUBMISSION DEADLINE

A. Full Board Review:
The IRB meets monthly, on the fourth Tuesday of the month. No more than 15 applications (i.e., initial review of a new study, re-review of a tabled study) will be reviewed at each meeting. All reviews are performed on a first-come first-served basis. The IRB meeting schedule and deadline dates can be found on the IRB website at www.unmc.edu/irb.

B. Expedited Review
Applications that qualify for expedited review have no submission deadline and can be reviewed independent of the IRB meeting schedule. Please call the Office of Regulatory Affairs for assistance in determining if your study meets the requirements for expedited review.

SUBMISSION CHECKLIST

Check all that apply.
Subject recruitment material
♦ Pharmacy and Therapeutics (P&T) Committee Investigational Drug Study Registry and/or Marketed Drug Form
Investigational Device Review Committee (IDRC):): Review by the IDRC is required for all protocols involving the use of investigational or marketed devices.
For studies conducted at CH&MC: Performance site approval for all non-UNMC, TNMC, UNO and CH&MC sites
♦ For studies conducted at CH&MC: Copy of all questionnaires, surveys, assessment tools, and other relevant materials
For studies conducted at CH&MC: Clinical Trial Master Matrix as required by UNMC and TNMC.
For studies conducted at CH&MC: Detailed protocol
For studies conducted at CH&MC: Investigator's brochure
For studies conducted at CH&MC: Grant Application
For studies conducted at CH&MC: IRB Review Fee Form for all commercially sponsored research projects.
For studies conducted at CH&MC: UNMC Disclosure of Potential Conflict of Interest Form for the Principal Investigator if a financial interest has been declared in Section I.10.
For studies conducted at CH&MC: UNMC Disclosure of Potential Conflict of Interest Form for any responsible personnel with a financial interest declared in Section I.10.
Other

No attachments

ADDITIONAL REVIEW REQUIREMENTS

Final IRB approval and release of studies is contingent upon approval by the following UNMC committees or departments. Check the appropriate boxes:

♦ **Pharmacy and Therapeutics (P&T) Committee:** Review by the P&T Committee is required for all protocols involving the use of investigational or marketed drugs.

UNMC Eppley Cancer Center Scientific Review Committee (SRC): Review by the SRC is required for all protocols involving cancer patients.

Institutional Biosafety Committee (IBC): Review by the IBC is required for all protocols involving the use of gene transfer and vaccines.

Radioactive Drug Research Committee (RDRC): Review by the RDRC is required for all protocols involving the use of a radio-labeled drug for which the investigator or the institution holds the IND.

Sponsored Programs Administration (SPA)/Office of Regulatory Affairs: For commercial sponsored studies, the consent form and contract will be compared for consistency by the ORA. Final IRB approval and release is contingent upon completion of a signed contract, verified by SPA, for all commercially sponsored research.

Conflict of Interest Committee (COIC): All responsible personnel listed in I.3A-E of the IRB application (i.e., PI, Secondary Investigator, Participating Personnel, and Coordinator(s)) must disclose **any** financial interest in the research (see Section I.10 of this application). Data and Administrative Personnel are exempt. The COIC will review any financial interest which is classified as significant.

Investigational Device Review Committee (IDRC): Review by the IDRC is required for all protocols involving the use of investigational or marketed devices.

Other Review

No Additional Reviews Required

ADDENDUM G
Research Involving Genetic Testing

Title of Protocol

Investigating the impact of oxytocin on irritability/emotional dysregulation in children and adolescents with disruptive behavior and mood disorders, and the possible mediating role of amygdala activity

Principal Investigator

Hwang, Soonjo - Dept Of Psychiatry Home - 402-552-6351 -
soonjo.hwang@unmc.edu

Characteristics of the Research

1. Will the following identifiers be maintained or identifying information be obtained? Check all that apply.

♦ Identifiers (e.g., name, initials, patient identification number, or code) will be maintained which will allow anyone to link the results of the genetic tests either directly or indirectly to the subject.

Potentially identifying information will be obtained from, or about, family members.

Characteristics of the Subject Population

2. Will children (i.e., 18 years of age or younger) be included in the genetic testing portion of the research?

Yes

Provide justification.

Childhood and adolescence is a vitally important period for the prevention of and early-intervention for disruptive behavior and mood disorders (Leibenluft & Stoddard, 2013). All of the disorders included in this protocol demonstrate an onset of symptoms in childhood and adolescence (American Psychiatric Association, 2013). In addition, working with children and adolescents provides more immediate access to the underlying pathophysiology of irritability and emotional dysregulation. In contrast, the pathophysiology seen in adults with chronic irritability and emotional dysregulation reflects not only the primary condition but also consequences of irritability and emotional dysregulation (e.g. anxiety disorder, borderline personality disorder, and especially, substance abuse/dependence). Children and adolescents have a lower risk of substance dependence, which is exclusionary.

3. Will cognitively or decisionally impaired persons be included in the genetic testing

portion of the research?
No

Methods and Procedures
4. Describe the genetic tests to be performed.
During the initial research assessment session, the buccal cheek brush will be performed collecting DNA samples for genotyping of the OTR. Cheek cells will be collected using a commercially-available kit (Qiagen) and will require participants to gently brush the buccal cavity 10 20 times with the pliable brush. DNA will be extracted and amplified via conventional PCR. Participants will be genotyped for a minimum of 11 single nucleotide polymorphisms (SNPs) in OXTR that have been implicated in social and psychiatric disorders (Aspé Sánchez et al., 2015), as well as several polymorphisms in CD38, a gene that codes for a glycoprotein that regulates oxytocin signaling and social function (Feldman et al., 2012). PCR products with blinded codes will be sequenced at the UNMC Sequencing Core Facilities.

5. Is there a reasonable likelihood that these tests, now or in the foreseeable future, could lead to diagnosis of a medical or behavioral condition, prediction of risks for these conditions, or identification of carriers?
No

6. Will pedigrees be obtained?
No

Disclosure of Results
7. Criteria for Disclosure of Study Results to Subjects.
Will study results or incidental findings be disclosed or made available to subjects, or, in the case of children or incompetent subjects, to their parents, guardians or legally authorized representatives (LARs)?
No

C. If there are no plans to disclose results to subjects, provide justification.
The genetic test result of oxytocin receptor at the individual level will not have any statistical or clinical meaning. Thus, it will not provide any meaningful information to the parent or the child.

Disclosure of Results to Children
9. If there are plans to disclose results to subjects, then will results of the study or of incidental findings obtained in the course of the study be disclosed to children?

No

10. Will parental consent be required prior to disclosure of study results to children?
No

Potential Risks
11. What are the risks associated with data obtained in the course of the genetic testing (either as a direct result of the test, or as a result of incidental finding)?
The potential risk of genetic testing of the oxytocin receptor is minimal. This will not contain any information regarding personal identification of the participants. Thus, the result of genetic testing will not be given to the participants or their parent/guardian. It will not be stored or banked for future study either.

Minimization of Risks
12. Protection Against Risks Associated With Results of Genetic Testing
What procedure(s) will be used to prevent/minimize any potential risks associated with data obtained in the course of the genetic testing (either as a direct result of the test, or as a result of incidental finding)?
We will only use and analyze oxytocin receptor-related genes pertaining to the clinical trial (oxytocin or placebo trial). Thus, it will not contain any individually identifiable or clinically pertaining information.

13. Confidentiality
A. What methods will be employed to assure confidentiality of results obtained?
We will only use research ID generated by the protocol without any identifiable personal information.

B. Will other investigators at UNMC or at other locations have access to biological material or data generated or obtained in the course of this study?
No

14. Counseling
What provisions have been made for the counseling of subjects prior to involvement in this study, and at the time that study results are to be disclosed to subjects?
During the consenting process, the P.I. and consenting person will make sure that the genetic study is only related to analysis of oxytocin receptor. We will make sure that parents and their children understand that this will not contain any individually identifiable information, or clinically pertaining information.

In addition to this, Dr. Jeffrey French will be an associate investigator of this study, and will be consulted in case of any issues related to the genetic test. Dr. French has an extensive experience of conducting genetic test and analysis on oxytocin receptor.

ADDENDUM Q
Investigational New Drugs or Biologic Drugs

Title of Protocol
Investigating the impact of oxytocin on irritability/emotional dysregulation in children and adolescents with disruptive behavior and mood disorders, and the possible mediating role of amygdala activity

Principal Investigator
Hwang, Soonjo - Dept Of Psychiatry Home - 402-552-6351 -
soonjo.hwang@unmc.edu

A. Investigational New Drugs and Biologic Drugs
1. Does this research involve an investigational drug or biologic drug?
No

B. Investigations Using FDA-Approved and Marketed Drugs or Biologic Drugs
1. Does this research involve an investigational use of an FDA-approved and marketed drug or biologic drug?
Yes

2. Do any of the FDA-approved and marketed drug(s) or biologic drug(s) have an IND number?
No

1) Exemption I
1a) Are all of the drug products(s) lawfully marketed in the United States?
Yes

1b) For any of the FDA-approved and marketed drug(s) or biologic drug(s), will the results of this study be used by the manufacturer to support (a) a new indication, (b) a significant change in the labeling, or (c) a significant change in the advertising?
No

1c) With the use of any of the FDA-approved and marketed drug(s) or biologic drug(s), does the study involve a route of administration or dosage level, or use in a subject population or other factor that significantly increases the risks (or decreases the acceptability of the risks)?

No

1d) Confirm, for the record, that the investigation will be conducted in compliance with 21 CFR 50 and 21 CFR 56.
Yes

1e) Will the investigation be conducted without invoking 21 CFR 50.24 (exception from informed consent requirements for emergency research)?
No

3. Provide an FDA Use-in-Pregnancy category (A, B, C, D or X) for each drug or biologic drug used in this research.
C