Investigating the impact of Oxytocin on irritability in children and adolescents with disruptive behavior and mood disorders

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Abstract

Background Irritability is a significant mental health issue in pediatric population with various psychiatric diagnoses. One of the established neurobiological mechanism of irritability is increased activation in the neural areas of acute threat response system. OXT, with its most commonly suggested mechanism as reduction of activation in the acute threat response system, can be potentially a mechanism-based treatment option for irritability, targeting the key neural areas.
Objectives To determine the efficacy of OXT intranasal administration for high levels of irritability in pediatric population with various psychiatric diagnoses.
Methods Randomized double-blind clinical trial of OXT intranasal administration (3 weeks) for children and adolescents (10-18 years old) with ADHD, CD, ODD, and DMDD. Neuroimaging modalities (fMRI and MEG) are applied to visualized the neural changes in the target areas of acute threat response system.
Results 26 participants were recruited. 24 of 26 completed the clinical trial. OXT intranasal administration demonstrated significant reduction of the key neural areas (mPFC and PAG) of acute threat response system, compared to placebo in youths with high levels of irritability. MEG captured effectively the key neural area (amygdala) activation to negative emotional stimuli.
Conclusion Not only the neuroimaging modalities successfully captured the increased activation in acute threat response system for youths with high levels of irritability, they also demonstrated reduction of the key neural areas of acute threat response system after OXT intervention, compared to placebo. OXT can be a promising mechanism-based treatment modality for high levels of irritability in youths with various psychiatric diagnoses.

Introduction

Irritability in pediatric population can be defined as an increased propensity to exhibit anger relative to one's peers. Children and adolescents with irritability demonstrate increased level of aggression/violent behavior, especially reactive aggression. An important translational neurobiological model of irritability implicates hyper-activation in acute threat processing (i.e. heightened response of the neural areas to emotional stimuli, especially negative emotional stimuli), and/or abnormal frustrative non-reward processing (Leibenluft, 2017).

Irritability manifests across various psychiatric diagnoses of pediatric population, including Attention-Deficit/Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), and Disruptive Mood Dysregulation Disorder (DMDD). For those diagnoses, dimensional approach to irritability (especially in regard to targeting of underlying neurobiological mechanism) merits better identification of neurobiology and development of common target-oriented treatment.

Chronic irritability is related to negative long-term outcomes (disruptive behavior, aggression/violence, delinquency, substance use, and depression/anxiety). Considering the high prevalence of irritability in pediatric population, it is a significant concern that there is remarkably little evidence-based treatment, and even less of treatment that is mechanism-based.

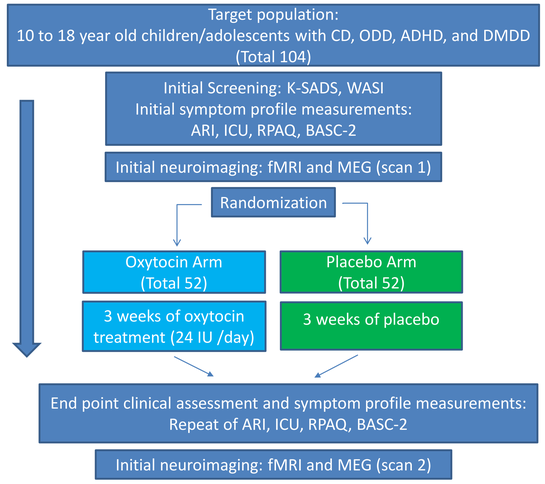
One potentially promising compound for treatment of irritability in pediatric population is intranasal oxytocin (OXT). Previous studies have shown that the most consistent neural impact of OXT administration implicates reduction of hyperactivity in the acute threat response system. These have been demonstrated in various psychiatric diagnoses (Borderline Personality Disorder, Generalized Anxiety Disorder, Post-Traumatic Stress Disorder). In addition to this, children and adolescents with Disruptive Behavior Disorder (DBD) show abnormal pattern of methylation on OXT receptor. However, OXT has not been investigated for this population.

Objective: To determine the efficacy of oxytocin on irritability in pediatric population and determine its relation to reduction of increased activation in the acute threat response system.

Hypothesis: Administration of OXT will be associated with improvement in levels of irritability as well as a decreased in the heightened response of acute threat response system to emotional stimuli. There will be a positive correlation between the level of reduction in response of acute threat response system to emotional stimuli following OXT intervention and the level of improvement in symptom profiles of irritability.

Methods

Study Design



Double-blind randomized clinical trial of OXT intranasal administration

Two neuroimaging modalities (fMRI and MEG) have been applied.

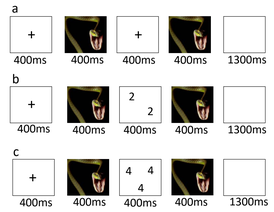


Figure 1: the Affective Stroop Task

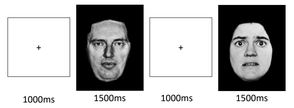


Figure 2: the Fearful Facial Expression Task

Statistical Analysis:

1. Individual level preprocessing (A):
   BOLD responses to emotional stimuli – BOLD responses to non-emotional stimuli
2. Group level preprocessing (B): (A) of post-intervention – (A) of pre-intervention
3. Group Analysis: T-test of (B) between placebo and OXT intervention groups.

- The preliminary statistical analyses were conduced by Dr. White at BTNRH and Dr. Faing Qiu at UNMC to keep the P.I. and other research personnel blinded to the randomization.

Results

Table 1. Demographics of the participants (n=26)

Age	**14.01 (SD=2.15)**
Female/Male	**7/19**
IQ	**95.25 (SD=16.71)**
Primary Diagnoses	**ADHD=13, DMDD=9, Mood Disorder=3, Withdrawal=1**
Secondary Diagnoses	**DMDD=6, ADHD=1, ODD=14, CD=2,**
Irritability Level (the initial ARI score)	**8.46 (SD=2.21)**
Reactive Aggression Level (the RPAQ-R score)	**16.69 (SD=2.80)**
Proactive Aggression Leve (the RPAQ-P score)	**6.92 (SD=2.64)**

Table 2. Completion Rate of the Affective-Cognitive Tasks

	Completion Rate
The Affective Stroop Task	**78.8%**
The Fearful Facial expression Task	**84.6%**
MEG	**78.8%**

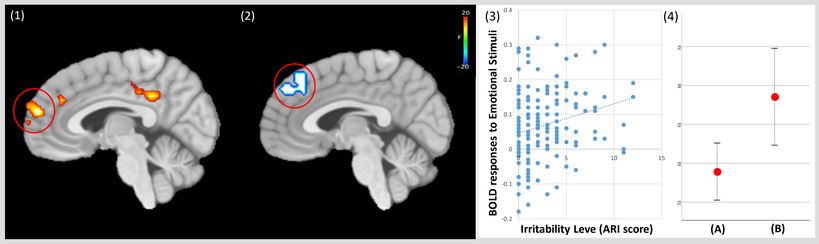


Figure 3. (1) Significantly increased BOLD responses in the rostro-medial prefrontal cortex (rmPFC) to emotional stimuli in youths with DBD and high levels of irritability on the Affective Stroop task from the previous study ; (2) Reduction in the rmPFC's activation to emotional stimuli (pre vs. post intervention changes) on the Affective Stroop task following OXT intranasal administration (5 youths) compared to the placebo (5 youths; 49 voxels at p=0.015); (3) There was significant correlation between the BOLD response in the rmPFC to emotional stimuli, and the level of irritability measured by the ARI; (4) Children and adolescents with high levels of irritability (the ARI score ≥ 4) demonstrated significantly increased activation of this area to emotional stimuli (A) compared to the youths without irritability (B; the ARI score <2).

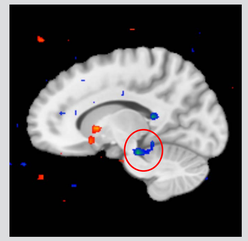
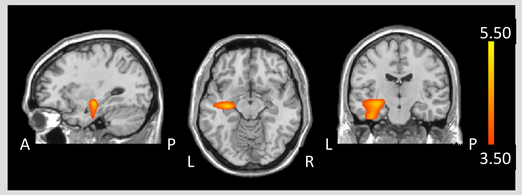


Figure 4. Significant reduction of BOLD responses to emotional stimuli in peri-aqueductal area (pre vs. post-intervention changes) on the Fearful Facial Expression Task following OXT intranasal administration (6 youths) compared to the placebo (6 youths; 26 voxels at p=0.05).



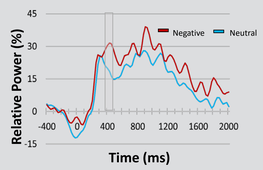


Figure 5. Significant activation of amygdala to negative valence words compared to neural valence words on MEG (11 participants, p<0.01).

Conclusion

1. Both fMRI affective-cognitive tasks and MEG effectively capture the hyperactivity in the neural areas of acute threat response system for youths with significant levels of irritability.
2. Both the Affective Stroop Task and the Fearful Facial Expression Task effectively capture and visualize the reduction of increased activation in the neural areas (mPFC and PAG) of acute threat response system for youths with significant levels of irritability, after OXT intranasal intervention compared to placebo.
3. OXT intranasal administration can be a clinically innovative and effective treatment modality for youths with significant levels of irritability, as a mechanism-based treatment modality.

Progress/Future Direction

1. Continue recruitment/conduction of current clinical trial of OXT intranasal administration, focusing on the neural as well as clinical changes.
2. Future NIMH grant application:

(1) U01

(2) First in Human and Early Stage Clinical Trials of Novel Investigational Drugs or Devices for Psychiatric Disorders (FOA: PAR-18-427)

(3) Proof of Concept Study

Acknowledgements

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