Oxytocin Dose-Dependent Effects on Brain Function During a Socially Dynamic Game in Autism Spectrum Disorders

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Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that is characterized by deficits in social interaction and communication, and by restricted and repetitive behavior. Oxytocin is a key modulator of social behavior and brain function (1). Acute administration of intranasal oxytocin (IN-OT) facilitates social learning (2). However, long-term trials with IN-OT have yielded inconsistent findings (3). Here, we conducted a dose-dependent study with IN-OT to examine its targeted action on the brain activity in adults with ASD.

Design & Hypothesis

- We conducted a randomized, double-blind, placebo-controlled, within-subject trial with intranasal oxytocin (IN-OT) (Syntocinon®, Novartis; 8IU, 24IU and 48IU) and placebo spray in 31 adults with ASD (men, ages between 18 and 45 years old).
- Neurotypical controls (men, matched for age and IQ, n=17) received intranasal placebo in a one-single blind fashion.
- Participants played **an interactive social ball-game** inside an MRI scanner approximately 60 minutes after receiving the nasal spray.
- ***We hypothesized that IN-OT would modulate the BOLD activity in emotional brain areas in a dose and context-dependent fashion.***

Methods

Subjects and Scanning: Subjects were recruited from the Emory Autism Center (ASD) or the community (controls) in Atlanta. ASD subjects underwent four fMRI scanning sessions in which they completed an interactive social ball game. The social ball game consisted of playing with groups of individuals who gave either positive or negative feedback during the game (in form of videos of approval and disapproval). Participants played the same game with computers with non-social feedback (non-social control game).

Whole Brain Analysis: General linear models were designed in FSL 6.0.3 for two human feedback runs and two computer feedback runs. Intermediate models for each subject session were constructed for human, computer, and human vs. computer runs. Higher level linear mixed effects models were constructed to model IN-OT dose with one explanatory variable and controlled for the subjects' repeated sessions. All results were reported for $Z > 2.3$ and cluster-$p < 0.05$.

ROI Analyses: A priori regions of interest were selected from the Harvard-Oxford Cortical and Sub-Cortical Atlases as well as the Juelich Atlas for analysis with repeated measures ANOVAs for IN-OT dose. Differences in activation were investigated for the human, computer, and human vs. computer feedback analyses. For significant ANOVAs, paired t-tests were conducted with LSD correction.

Results

1- Dose-dependent effect of oxytocin on anterior cingulate cortex

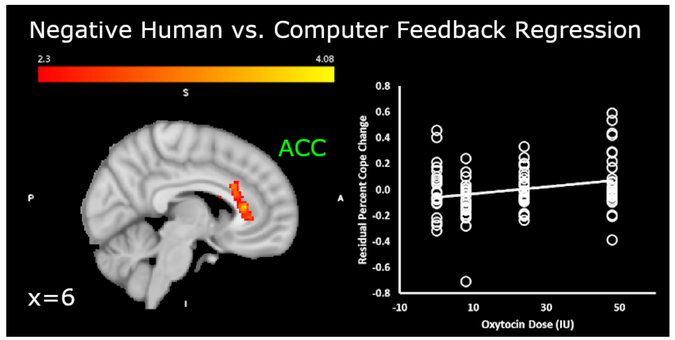

Figure 1: A region in the ACC (n=30, voxels=448; Z-max= 4.08; MNI peak coordinates (4,30,10)) showed a positive dose-related effect for negative human feedback compared to negative computer feedback. The plot shows the best fit line for the residual of the mean percent cope change with the different doses of IN-OT.

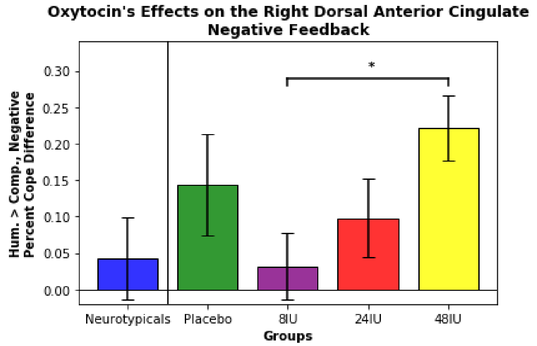

Figure 2: Mean±SEM percent change for a spherical right dorsal anterior cingulate ROI (MNI coordinates=(5,14,42), radius=5). The ANOVA was significant ($F(3,63)=2.93$, $p=0.040$, (n=22)), and the difference between 8IU and 48IU ($p=0.003$) was statistically significant.

2- Dose-dependent effect of oxytocin on amygdala and anterior Insula

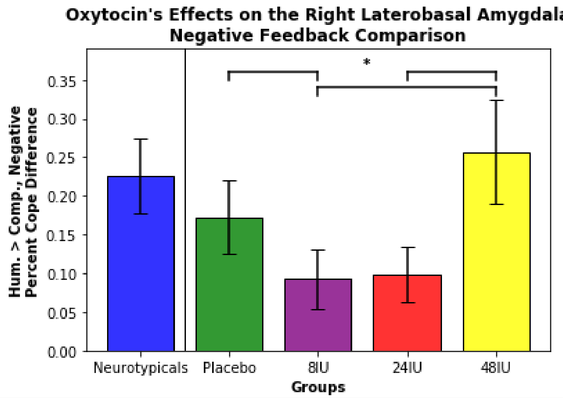

Figure 3: Mean±SEM values for the left laterobasal amygdala, as defined by the Juelich Atlas. The rmANOVA was significant ($F(2.06,43.33)= 3.40$, n=22). Significant differences in percent cope change were identified between placebo and 8IU ($p=0.004$), between 8IU and 48IU ($p=0.024$), and between 24IU and 48IU ($p=0.017$).

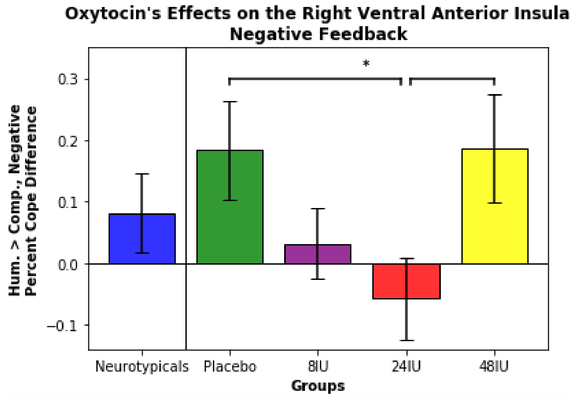

Figure 4: Mean±SEM percent change for the spherical ROI in the right ventral anterior insula ROI (MNI coordinates (44, 2, -8), radius=6). The ANOVA was significant ($F(2.04,42.88)=3.23$, $p=0.048$)). There were significant differences between placebo and 24IU ($p=0.038$) and between 24IU and 48IU ($p=0.006$).

Results

3- Dose-dependent effect of oxytocin on the nucleus accumbens

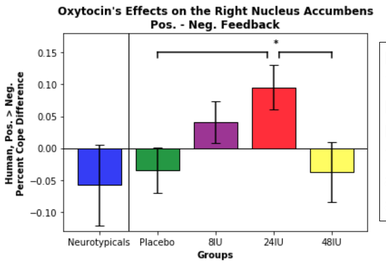

Figure 5:
The ANOVA was significant $F(3,72)=2.86$, $p=0.042$
Eta^2=0.106.
24IU enhanced the BOLD activity compared to 48IU and placebo.

Discussion

- As predicted, we found that acute intake of **IN-OT modulates the activity of key emotional brain areas, ACC, basolateral amygdala, anterior insula**, known to be involved in empathic responses, in response to negative social dynamic cues, in a dose-dependent fashion.
- More specifically, we found that lower doses of IN-OT (8IU and 24IU) reduce the BOLD activity of these brain areas in response to negative social feedback, as compared to placebo and to a higher dose of IN-OT (48IU).
- Interestingly, 24IU enhanced significantly the activity of reward brain areas (**nucleus accumbens**) in response to positive feedback during the social game, relative to other doses.
- Our findings suggest region-based, and probably function-based dose-response effects of oxytocin.

References and Acknowledgments

References.

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