Oxytocin and Brain Responses in Maternal Addiction

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Study Protocol

The purpose of this study is to expand upon a previous study of maternal addiction, by conducting a randomized, double-blinded, placebo controlled, crossover study of intranasal oxytocin (OT) on maternal brain responses. 150 mothers from the University of Iowa and the Yale Child Study Center will be enrolled (75 with a history of drug addiction and 75 matched control mothers), along with their 2 to 12-month-old infants, to participate in four study visits over a two-month period.

Oxytocin administration and neuroimaging procedures. In this double-blinded placebo-controlled crossover challenge of intranasal OT, maternal brain responses to infant face cues and cries were assessed between participants on receiving either the active (OT) or the inactive (placebo) nasal spray prior to one of two fMRI scanning sessions. Participants, investigators and data analysts were blinded to the identity of the OT and placebo sprays. Infant face images were presented during each scanning session. Specifically, infant face images were presented from each of the four following face conditions: the mother's own infant's face (happy and sad) and an unknown infant's face (happy and sad).

Current smokers were allowed the opportunity to smoke 60 min prior to the scanning session, to avoid any confounding effects of acute nicotine intoxication or withdrawal. All participants will take a urinary pregnancy test prior to the start of the visit. If a mother tested positive, she was excluded from the study due to theoretical concerns about effects of OT and MRI exposure on the pregnancy. The urine samle was used to screen for recent drug use, using the RediCup 5 drug test (for amphetamines, cocaine, marijuana, opioids and benzodiazepines).

The mothers self-administered a dose of either OT (2 puffs per nostril [6 IU per puff] = 24 IU total) *or* the placebo spray on each of two fMRI scanning visits, with a randomized order of administration. A stopwatch was started at the moment the participants began intranasal administration, so that the fMRI session began around 50 minutes later. Just prior to drug administration, the mother completed the Positive and Negative Affect Scale (PANAS), to rate her current emotions compared to 40 min later. During the 50-minute delay until scanning, the mother had a breath alcohol and CO (for cigarette usage) test, and completed a series of questionnaires, and demographic information was updated. Fifty minutes after the administration of the nasal spray, the mother participated in the imaging session, passively viewing own and unknown infant faces, and listening to infant cries.

fMRI parameters. Using an event-related fMRI design, randomly presented images were viewed for 2 seconds, with a random inter-stimulus interval between 4 and 14 sec. The infant face images were equally divided into 2 affect groups – happy or sad (own-happy [OH], own-sad [OS], unknown-happy [UH], unknown-sad [US]). The intensity of happy and sad affect will be balanced between the "own" and "unknown" faces. Each participant was presented with 4 fMRI runs of 38 different stimulus-trials each (2 catch trials and 6 trials each of OH, OS, UH, US, OC, UC), or 152 trials in all. For the catch trials, participants were asked to press a button when seeing and hearing a bell. The following steps were taken to avoid order-effects. Each run contained all 38 stimulus-trials in a different pseudorandom order that is unique and fixed for that run throughout the study. The order of fMRI runs were randomized (e.g. 1-2-3-4, 2-4-3-1, etc.) in a different sequence for each participant, but consistent across both scanning visits.

All imaging was performed using a 3 Tesla MRI scanner. Visual images were generated using a computer controlled LCD projector, and presented to the mother via an overhead mirror display. Regional brain activation was assessed by measuring changes in blood-oxygen-level-dependent functional MRI signal (BOLD-fMRI). Participants participated in whole-brain functional runs of around 185 scans each (multiband imaging with a factor of 6; 52 slices; TR 1000 msec; TE 30 msec; flip angle, 65 degrees; 64 x 64 matrix [in plane resolution]; field of view [FOV] 220 mm; slice thickness 2.4 mm; gap thickness 2.4 mm). High-resolution T1-weighted structural images (166 slices, in plane resolution 256 x 256; FOV 245 mm; slice thickness 1 mm) were also acquired. After the scanning session, each mother rated each of the face images on how they thought the infant was feeling, as well as their own feelings of pleasure or arousal, using an adaptation of the Self-Assessment Manikin.

Statistical Analysis Plan

A mixed effects model with random intercepts was run in R (version 4.2.2) using the lme4 package. Given the repeated measures design and the fact that there were incomplete data (i.e., not all subjects were in the OT and placebo condition), the mixed effects model provides a way of examining the effect of condition, controlling for the fact within-subjects nature of the study. For Hypothesis 1, which focuses on the effect of OT vs. placebo, on the condition variable was included in the model. For Hypothesis 2, group (addiction and controls) as well as condition was included. The interaction between group and condition was initially explored. Since there were no significant interaction effects, they were not included in subsequent analyses. P-values from the mixed-effects models were obtained using the Kenward-Roger approximation. Estimated marginal means and their standard errors were obtained from the model results using the R package “modelbased” (https://cran.r-project.org/web/packages/modelbased/index.html).

Anatomically-defined regions of interest (ROIs) based on the Harvard-Oxford Atlas were used to extract fMRI BOLD data representing the contrast of Happy own faces vs. Happy unknown faces or Sad own faces vs. Sad unknown faces. The contrasts represent data across all four task runs.