OXYASP STUDY PROTOCOL

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Study Design and Procedures

In a double-blind, placebo controlled, randomised crossover design, participants self-administered, under instruction from the researcher, 40 IU of IN-OT (Syntocinon; Novartis, Basel, Switzerland) or placebo (identical composition to Syntocinon except for the omission of oxytocin). Participants began the morphed faces task within 25-30 minutes of administration. The oxytocin dose employed was the highest clinically applicable safe dose administered to human volunteers, in keeping with a protocol which demonstrated significant neural activation over a period of 25–78 minutes with this dose (Paloyelis, Doyle et al. 2016). At a second session (occurring between three and twenty-eight days later), participants completed the fMRI task again under the alternative treatment condition. Participants were instructed to avoid food, drinks (except water), and nicotine two hours before starting the experiment. Participants completed the Morphed Faces task (see Figure 1). During the task, participants were asked to indicate the sex of each face with a left-right button press using the index and middle finger of their right hand during a single run, which lasted 9 minutes 56 seconds..

General linear model analysis of behavioural data

For the Morphed Faces task, means were first calculated across the whole sample for both accuracy and reaction time in rating the gender of the faces displayed. To investigate the effect of oxytocin and its interaction with other variables, for both accuracy and response latency data, a three group (NO, ASPD-P, ASPD+P) by two condition (oxytocin, placebo) by four intensity (40%, 60%, 80%, 100% of fearful facial expression) repeated-measures analysis of variance was conducted. Post-hoc

repeated-measures analysis of variance was performed for ASPD-P vs ASPD+P. SPSS version 25.0 was used. A threshold for significance of $p < 0.05$ (corrected) was set for all tests.

Primary outcome measure and MRI processing
Whole-brain blood oxygen level dependent (BOLD) fMRI data were acquired using a 3.0 Tesla General Electric Magnetic Resonance Scanner. The principle outcome measure was a regressor for modulation of neural activity (BOLD responsivity) by intensity of fearful expression. Specific MRI parameters, and full details of preprocessing and individual level analyses are available in supplementary materials.

MRI Data group analysis
Following preprocessing steps, modulated emotion data were entered into a 3 Group (NO, ASPD-P, ASPD+P) by 2 Condition (placebo, oxytocin) 3dMVM (ANOVA style computations) model. Within this framework, general linear tests were coded to assess differential effects of drug between the groups. Post hoc t-tests were conducted to decompose these interactions by examining between- and within- group effects. Correction for multiple comparisons was performed using a spatial clustering operation in AFNI's 3dClustSim, using the autocorrelation function (-acf) with 10,000 Monte Carlo simulations for the whole-brain analysis. Spatial autocorrelation was estimated from residuals from the individual-level GLMs. The initial threshold was set at $p = 0.005$. As outlined above, bilateral amygdala, anterior insula and midcingulate cortex, were selected a priori for ROI analysis. Small-volume corrections, calculated using an anatomically defined mask (TTN27, a Talaraich atlas from AFNI), yielded thresholds of $k = 13$ for anterior/mid-cingulate cortex, $k = 8$ for anterior insula, and $k = 2$ for amygdala at an initial significance threshold of 0.005 (multiple comparison corrected $p<0.05$).