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Intranasal oxytocin reduces social perception in women: Neural activation and individual variation

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ABSTRACT

Most intranasal oxytocin research to date has been carried out in men, but recent studies indicate that females' responses can differ substantially from males'. This randomized, double-blind, placebo-controlled study involved an all-female sample of 28 women not using hormonal contraception. Participants viewed animations of geometric shapes depicting either random movement or social interactions such as playing, chasing, or fighting. Probe questions asked whether any shapes were "friends" or "not friends." Social videos were preceded by cues to attend to either social relationships or physical size changes. All subjects received intranasal placebo spray at scan 1. While the experimenter was not blinded to nasal spray contents at Scan 1, the participants were. Scan 2 followed a randomized, double-blind design. At scan 2, half received a second placebo dose while the other half received 24 IU of intranasal oxytocin. We measured neural responses to these animations at baseline, as well as the change in neural activity induced by oxytocin. Oxytocin reduced activation in early visual cortex and dorsal-stream motion processing regions for the social > size contrast, indicating reduced activity related to social attention. Oxytocin also reduced endorsements that shapes were "friends" or "not friends," and this significantly correlated with reduction in neural activation. Furthermore, participants who perceived fewer social relationships at baseline were more likely to show oxytocin-induced increases in a broad network of regions involved in social perception and social cognition, suggesting that lower social processing at baseline may predict more positive neural responses to oxytocin.

Introduction

Oxytocin is a neuropeptide that plays a role in social behavior across vertebrate species (Insel, 2010). In humans, exogenous oxytocin administered via nasal spray modulates social information processing and social behavior, including face perception, eye gaze, cooperation, and trust (reviewed in (Guastella and MacLeod, 2012; Kanat et al., 2014; Meyer-Lindenberg et al., 2011; Van and Bakermans-Kranenburg, 2012)). These results have stimulated interest in oxytocin's potential as a pharmacological intervention for social cognitive disorders like autism and social anxiety. However, researchers are increasingly recognizing that intranasal oxytocin's impact on social behavior may not be so simple and straightforward. In a 2011 meta-analysis, 43% of surveyed studies showed no significant main effect of intranasal oxytocin (Bartz et al., 2011). This high rate of negative findings when results are averaged across an entire group suggests significant modulation by factors that vary across individuals or contexts. Furthermore, Bartz and colleagues' meta-analysis found that 21% of surveyed studies reported effects that run counter to oxytocin's generally accepted "prosocial" role, including envy, mistrust, and social amnesia (e.g., Shamay-Tsoory et al., 2009; Declerck et al., 2010; Bartz et al., 2011; De Dreu et al., 2011).

Substantial recent effort has been devoted to disentangling the mechanisms underlying variation in oxytocin response. Modulatory factors identified to date include genetic and physiological traits, including allelic variation in the oxytocin receptor, methylation of the oxytocin receptor gene, and baseline plasma oxytocin levels (Feng et al., 2015; Montag et al., 2013; Jack et al., 2012); life history factors, including childhood experiences and parental separation (Meinlschmidt and Heim, 2007; Flanagan et al., 2015); and psycholo-

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gical and behavioral traits, including personality, attachment style, emotional sensitivity, and sociability (Alcorn et al., 2015; Bartz et al., 2015; De Dreu, 2012; Leknes et al., 2013; Groppe et al., 2013); reviewed in (Guastella and MacLeod, 2012; Bartz et al., 2011). Another variable that clearly modulates response to oxytocin is sex. To date, the majority of intranasal oxytocin research has been carried out in males. However, evidence suggests that intranasal oxytocin may affect the brains of males and females differently (reviewed in (Kanat et al., 2014)). In some cases, sex differences appear to be quite pronounced. For example, Chen et al. (2015) found that whereas oxytocin blocked the amygdala and insula response to unreciprocated cooperation (a socially aversive interaction) in men, it failed to do so in women. Feng et al. (2015) found that whereas oxytocin increased striatal activation in response to reciprocated cooperation (a rewarding social interaction) in men, it reduced this activation in women. These studies suggest that at least in some contexts, oxytocin could have different effects in females compared to males, highlighting the need for a fuller understanding of the effects of intranasal oxytocin in the brains of women.

To date, evidence that intranasal oxytocin blocks or reverses social processing in women comes mainly from studies on negative-valence emotional stimuli (Domes et al., 2010; Lischke et al., 2012; Frijling et al., 2016) and social economic games (Feng et al., 2015; Chen et al., 2015). An important question is whether this same pattern would hold true for tasks that probe other aspects of social processing, such as the detection of animacy and attribution of intentionality. One experimental paradigm that is well-suited to address this question involves animations of simple moving geometric shapes. The first study of this type, carried out by Heider and Simmel (1944), established that despite the absence of any overt social information like faces or body parts, people perceive these cartoons as involving animate "characters" who engage in behaviors like playing, chasing, or hiding, and are motivated by goals, feelings, and beliefs (Heider and Simmel, 1944). Since that seminal study, a long line of additional studies have established that the perception of animacy in these cartoons can be linked to causal dependencies in the shapes' movement (Scholl and Tremoulet, 2000); that individuals with autism spectrum disorders show reduced social attribution in this task (Castelli et al., 2002; Klin and Jones, 2006; Klin, 2000); that within healthy controls, responses to these stimuli are influenced by individual differences in plasma oxytocin levels and patterns of brain activation (Jack and Pelphrey, 2015; Lancaster et al., 2015); and that the perception of animacy in these cartoons is linked to activation in a distributed network involved in social perception and social cognition (Blakemore et al., 2003; Gobbini et al., 2011; Lee et al., 2014; Santos et al., 2010; Tavares et al., 2008; Osaka et al., 2012). Recently, one study (Scheele et al., 2015a, 2015b) reported that intranasal oxytocin increased anthropomorphizing during a moving shapes task within a female sample, but neural changes were not investigated. Furthermore, all participants in this study were using hormonal contraceptives, which affect endogenous oxytocin levels (Silber et al., 1987; Stock et al., 1989) as well as neural and behavioral response to intranasal oxytocin (Scheele et al., 2016). In the current study, we investigated the effect of intranasal oxytocin on the perception of social relationships and brain activation in a naturally-cycling female sample. Women using hormonal contraception were excluded in order to study responses to intranasal oxytocin separately from the potential modulating effects of oral birth control. In order to establish baseline neural responses to intranasal oxytocin, all participants received intranasal placebo spray at scan 1. At scan 2, in a randomized, double-blind, repeated-measures, placebo-controlled design, half of the participants received a second placebo dose, while the other half received intranasal oxytocin. The fMRI task involved animations of simple moving geometric shapes based on Heider and Simmel's (1944) original stimuli. These animations, termed the Dynamic Interactive Shapes Clips, or DISC, depict either random movement or social interaction, and involve attentional cues to either social relationships or size changes.

Methods

Participants

Participants were recruited from the community of students and staff at Emory University and Georgia State University and were compensated a total of $240 for participation in two scanning sessions. All participants gave written informed consent, and the study was approved by the Emory University and Georgia State University Institutional Review Boards and the U.S. Food and Drug Administration. The current study focused on an entirely female sample of 28 women. 6 participants self-identified as Caucasian, 8 as Asian, 13 as African-American, and 1 as Other. We included only women who were normally cycling by self-report and who were not using hormonal contraception. Additional exclusion criteria included current or recent pregnancy, a history of seizures or other neurological disorders, alcoholism, substance abuse, hypertension, cardiovascular disease, diabetes, other endocrine diseases or malignancy, head trauma, use of psychoactive medication, and persistent or disabling asthma or migraines. While we did not have the resources to confirm cycle phase via blood sample, we attempted to schedule all scans during the luteal phase of the menstrual cycle (the last 14 days of the cycle) using participant self-report. Scan 2 occurred approximately 30 days after scan 1 in 21 participants (mean interval 30.86 days, standard deviation +/−4.82 days). In 7 participants, scheduling conflicts prevented us from re-scanning close to the same cycle point 1 month later, so in these situations we opted to re-scan 2 months later (mean interval 61.00 days, standard deviation +/− 4.00 days). Verification of cycle phase via blood sample would have been preferable and this is a limitation of the current study. This study included 14 participants in each of the oxytocin and placebo groups. The age difference between groups was marginally significant ($t(26)=1.948$, $p=.062$; oxytocin group mean (SD)=22.08 (.71); placebo group mean (SD)=24.08 (.75)). In order to ensure that this difference did not contribute to experimental results, neuroimaging analyses controlled for age.

Oxytocin and placebo administration

At scan 1, all participants self-administered a 24 IU of intranasal placebo spray. Although the experimenter became inadvertently aware that all participants would receive placebo at scan 1, participants were blind to all aspects of study design. At both scans, Participants were told they would receive either placebo or oxytocin. At scan 2, approximately 30 days later, in a double-blind design, placebo participants self-administered a second placebo dose, whereas oxytocin participants self-administered 24 IU of intranasal oxytocin (Syntocinon-Spray, Novartis). This study design had 3 important features for data interpretation. First, including nasal spray administration (either placebo or oxytocin) in every scan controlled for potential effects of self-administration unrelated to oxytocin, including any possible effects of the non-oxytocin components of the spray or of the physical act of self-administration. Second, including a control group which received placebo at both scan 1 and scan 2 allowed us to definitively attribute any changes observed in the oxytocin group to the drug, rather than to simple task-repetition effects. Third, including a baseline placebo condition in the oxytocin group allowed us to investigate how individual variation in baseline social processing relates to individual variation in response to intranasal oxytocin, since the same individuals were scanned both with and without oxytocin. The Emory Investigational Drug Service randomly assigned participants to the placebo or oxytocin group, prepared oxytocin or placebo doses for each participant, and maintained records of group assignment; both participants and experimenters were blind to the contents of the nasal spray. The placebo spray was specifically designed to mimic the scent of the oxytocin spray and in pilot studies, no subjects reported a difference in odor. Each 5 ml of syntocinon spray contained the