The effects of intranasal oxytocin administration on resting state electroencephalography frontal asymmetry

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Abstract

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Research suggests that the nonapeptide oxytocin plays an important role in social functioning, and that the intranasal administration of exogenous oxytocin promotes prosocial behaviours. The mechanisms underlying oxytocin's effects on social cognition and behaviour are not yet well understood. One viable hypothesis is that oxytocin acts upon frontal asymmetry. Relative left frontal neural activation has been consistently associated with approach behaviours and shares a number of other similarities with intranasal oxytocin administration. For the first time, we examined the hypothesis that oxytocin increases relative left frontal neural activation using electroencephalography methodology. In a double-blind within-subject experiment, 48 participants self-administered a 24 I.U. dose of intranasal oxytocin and placebo approximately one week apart. Following drug administration, alpha band power was recorded at frontal and parietal sites during eight 60 second trials. Intranasal oxytocin administration did not produce any significant changes in frontal asymmetry ($F_{(1, 47)} = .273$, $p = .604$, partial $\eta^2 = .006$). This relation did not interact with sex nor measures of depression, which have been shown to moderate the effects of intranasal oxytocin in prior investigations. Oxytocin administration does not appear to increase relative left frontal neural activation. Additional considerations and interpretations are discussed.

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Introduction

Oxytocin (OT), a nonapeptide produced in magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus, is widely recognized for its role in reproduction and maternal behaviour in mammals (Carter, 1998; Gimpl & Farenholz, 2001). In the periphery, its effects on uterine contractions during parturition and milk let-down during breast feeding are well documented (Gimpl & Farenholz, 2001). OT has also been implicated in the subsequent development of maternal care behaviours and the formation of parent-child bonds, in both animals and humans (Atzil, Hendler, & Feldman, 2011; Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010; Feldman, Weller, Zagoory-Sharon, & Levine, 2007; Neumann, 2008). Conversely, the administration of OT antagonists following parturition has been shown to result in decreased maternal care in rodents (Pederson & Boccia, 2003).

More recently, researchers have found that OT plays a broader role in regulating social behaviours in animals and humans alike (Bartz & Hollander, 2006; Campbell, 2010; Ross & Young, 2009; Young & Zuoxin, 2004). In animals, OT administration leads to improved social recognition of conspecifics whereas OT antagonists have been associated with impaired recognition (Bielsky & Young, 2004; Ferguson, Aldag, Insel, & Young, 2001; Ferguson et al., 2000). In humans, the intranasal administration of OT facilitates emotion recognition (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007; Marsh, Yu, Pine, & Blair, 2010; Schulze et al., 2011), improves positive communication behaviours (Ditzen et al., 2009; Naber, van Ijzendoorn, Deschamps, van Engeland, & Bakermans-Kranenburg, 2010), and promotes trust and generosity in certain contexts (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Kosfeld,

Heinrichs, Zak, Fischbacher, & Fehr, 2005; Zak, Stanton, & Ahmadi, 2007; Mikolajczak et al., 2010; Mikolajczak, Pinon, Lane, de Timary, & Luminet, 2010). Further, individuals who are homozygous for the G allele of the rs53576 SNP – a gene related to the expression of OT receptors in humans – show increased empathy and lower stress-reactivity (Rodrigues, Saslow, Garcia, John, & Keltner, 2009), and are perceived by others as having a prosocial disposition towards strangers (Kogan, et al., 2011). It should be noted, however, that some research suggests that OT administration can promote negative behaviours (e.g., out-group aggression or bias) in competitive or conflictual contexts (De Dreu at al., 2010; De Dreu et al., 2011; De Dreu et al., 2012), perhaps as a deleterious consequence of increased in-group solidarity. In short, while the effects of OT on social behaviour are well documented, the mechanisms underlying its prosocial changes are still not well understood.

One potential hypothesis is that OT produces positive effects on social behaviour by altering motivational systems and promoting approach behaviours. Frontal asymmetry – the difference in neural activation between the left and right frontal lobes – has been consistently associated with such motivational systems (see Coan & Allen, 2003a for a review). More specifically, the behavioural activation system (BAS) – a model of appetitive motivation that reflects a tendency to be vigilant for and to approach appealing stimuli and reward cues in the environment (Gray, 1987) – has been associated with greater relative left frontal activity (Harmon–Jones & Allen, 1997; Sutton & Davidson, 1997; Coan & Allen, 2003b; De Pascalis, Cozzuto, Caprara, & Alessandri, 2013). In fact, one study in which researchers increased participant's approach motivation by manipulating their posture found parallel increases in relative left frontal activity, suggesting that both the BAS and its neural underpinnings are malleable to environmental influences (Price & Harmon-Jones, 2011). Conversely, the behavioural inhibition system (BIS) –

a model of avoidant motivation that reflects a tendency to be vigilant for and avoid unpleasant stimuli and punishment cues in the environment (Gray, 1987) – has been associated with greater relative right frontal activity (Harmon–Jones & Allen, 1997; Sutton & Davidson, 1997). Interestingly, research suggests that levels of endogenous plasma OT are positively correlated with reward dependence, at least in depressed populations (Bell et al., 2006). Reward dependence is a temperamental predisposition to be hyper-sensitive toward cues of approval and reward paired with a heightened likelihood to approach or pursue such cues (Cloninger, 1986). In terms of both behavioural and cognitive effects, this disposition that appears to overlap with the BAS, suggesting a possible link between OT and this system. Another finding that supports such a link is that both OT and frontal asymmetry have been associated with emotion recognition. While the right frontal lobes have been traditionally associated with emotion recognition regardless of valence (Davidson & Schwartz, 1976; Nakamura et al., 1999), there is evidence of a potential lateralization effect. For instance, greater relative right frontal activity has been related to the identification of negative affect while greater relative left frontal activity has been linked to the identification of positive affect (Balconi & Mazza, 2010). Similarly, images of faces displaying positive affect are identified more quickly when presented to the left hemisphere (right visual field; Reuter-Lorenz, Givis, & Moscovitch, 1983). Finally, injury to the right hemisphere results in greater deficits in the processing of negative rather than positive expression of emotions (Borod et al., 1998). This lateralization effect, referred to as the valence model (Balconi & Mazza, 2010), purports that the left hemisphere is specialized in processing positive emotions while the right hemisphere is specialized in negative emotions. Similarly, although OT administration has been associated with overall improved emotion recognition (Lischke et al., 2012), some research has found that this effect is more pronounced for images of positive affect

(Marsh et al., 2010; Schulze et al., 2011). Again, this pattern of findings suggest that OT may produce changes to social cognition and behaviour by increasing relative left frontal activity.

Lastly, frontal asymmetry has been linked to individual affective experiences. In short, individuals with greater relative left frontal activity experience more positive affect while individuals with greater relative right frontal activity experience more negative affect, both in terms of frequency and intensity (see Davidson, 1992 or Davidson, 2003 for a review). Additionally, greater relative right frontal activity has been associated with increased negative emotional reactivity in both adults (Davidson & Tomarken, 1989; Tomarken, Davidson, & Henriques, 1990) and children (Davidson & Fox, 1989). In fact, increased relative right frontal neural activation has been linked to current and past depressive episodes (Henriques & Davidson, 1991; Gotlib, 1998) and such a pattern of frontal activity is considered a risk factor for developing an affective disorder (Harmon-Jones & Allen, 1997; Stewart et al., 2010). Although there has been no direct link found between OT administration and state mood or emotional reactivity, endogenous OT has been associated with depressive symptomatology. The OT system appears to be dysregulated in individuals suffering from depression; however, the nature of this relation is still unclear. Most studies suggest that endogenous OT production is decreased in depressed participants (Frasch, Zetzsche, Steiger, & Jirikowski, 1995; Scantamburlo et al., 2007; Ozsoy, Esel, & Kula, 2009; Skrundz et al., 2011; Yuen et al., 2014), however some report opposite results (Parker et al., 2010). Despite these inconsistent findings, the potential link between OT and frontal asymmetry may be important in depression.

Taken together, these findings suggest that OT may promote prosocial behaviours and cognitions, in part, by altering frontal neural activity. Prior research has explored the effects of OT on the neural response to visual (Perry et al., 2010) and auditory (Fehm-Wolfsdorf et al.,

1988) stimuli, generally reporting a dampening effect. These effects appear to be most pronounced within the limbic region (see Bethlehem, van Honk, Auyeung, & Baron-Cohen, 2013 for a review), potentially a reflection of OT's receptor distribution. While some research using non-human animals has found that the highest density of such receptors is within the amygdala and hypothalamus, subsequent studies have reported tremendous amounts of variability both between (Insel & Shapiro, 1992) and within species (Ross et al., 2009). Interestingly, differences in receptor distribution between conspecifics have been associated with parallel differences in social behaviour (Ross et al., 2009), and changes in receptor density in response to hormonal manipulations have been observed in rodents (Patchev, Schlosser, Hassan, & Almeida, 1993). Although there is limited data regarding the distribution of OT receptors within the human brain, previous research has demonstrated effects of intranasal OT administration of frontal regions (Domes et al., 2007). To date, however, the effects of OT administration on frontal asymmetry as an outcome measure have not been investigated. The current study, for the first time, will directly investigate this relationship using electroencephalography (EEG). EEG is a non-invasive functional recording technique that use multiple electrodes placed at specific sites around the scalp to measure neural activity. While EEG technology lacks the high-spatial-resolution of other imaging techniques, it is a temporally-precise and cost-effective means of assessing changes in neural activation. Further, it has been successfully used to detect changes in frontal asymmetry in both healthy volunteer (Tomarken, Davidson, & Henriques, 1990; Coan & Allen, 2003b) and patient samples (Henriques & Davidson, 1991; Gotlib, 1998).

The present study will measure the effects of intranasal OT on frontal asymmetry with the hypothesis that OT administration will increase relative left frontal alpha band activity relative to

placebo. A focus on alpha band activation is most appropriate for this research question, as previous work has shown that this frequency provides the most consistent and reliable measure of individual differences in frontal asymmetry in both non-clinical (Tomarken, Davidson, Wheeler, & Kinney, 1992) and depressed samples (Allen, Urry, Hitt, & Coan, 2004). Additionally, most research investigating frontal asymmetry uses alpha frequency measurements (Towers & Allen, 2009), as do all of the aforementioned studies. Because peripheral levels of oxytocin appear to be dysregulated in persons with major depressive disorder, and depressive symptoms have moderated the effects of oxytocin on cognition in other studies (Ellenbogen, Linnen, Grumet, Cardoso, & Joober, 2012; Ellenbogen, Linnen, Cardoso, & Joober, 2013), the present study will consider depressive symptomatology as a potential moderator of the relationship between oxytocin and frontal asymmetry. It is predicted that changes in frontal asymmetry will be more pronounced in participants with high depressive symptoms than those with low depressive symptoms. Finally, given the possibility of sex differences underlying the effects of intranasal OT administration (e.g.: Bartz, Zaki, Bolger, & Ochsner, 2011; Kubzanskya et al., 2012), this study will also consider sex as a potential moderator. No hypothesis has been put forth as sex differences in studies of the intranasal administration of oxytocin have been equivocal, with some studies reporting null effects (Cardoso, Ellenbogen, & Linnen, 2012) and other studies finding greater drug effects in females (Domes et al., 2010) and in males (Theodoridou, Rowe, & Mohr, 2013).

Method

Participants

Forty-eight participants (24 female), aged 19 to 32 (Mean 23.7 ± 3.5), were recruited from the community using online advertisements. Potential participants were excluded if they

met any of the following criteria: current medical illness, current or past psychiatric disorder, current medication use (including psychotropic medication), current or past illicit drug use (with the exception of cannabis, which required at least one month of abstinence), and current tobacco use (with the exception of those consuming 5 or fewer cigarettes a week). Female participants who reported that they were or might become pregnant during the study were also excluded. Oversampling on the Beck Depression Inventory (Beck, Steer, & Brown, 1996) was employed, with 25% of participants reporting mild to severe depressive symptoms ($x \geq 14$). Informed written consent was obtained for all participants.

Electroencephalography data acquisition and signal processing

EEG recording and analysis was completed following recommended standard procedures (Pivik et al., 1993). Continuous EEG recordings were collected from the right and left mastoid sites, and 14 scalp sites (F7, F3, F4, F8, T7, C3, C4, T8, P7, P3, P4, P8, O1, O2) following the International 10–20 System (American Electroencephalographic Society, 1994). Recordings were collected using a lycra electrode cap (ElectroCap, Eaton, Ohio) with sewn-in tin electrodes. Four additional electrodes were used to monitor eye movement. Vertical eye movement was detected using electrodes placed above and below the right eye; horizontal eye movement was detected using electrodes placed on the lateral canthus of each eye. Recordings were made with AFz ground against a vertex (Cz) reference. The latter reference site was used for recording purpose only, as Cz-referenced data is not ideal for measuring alpha power at frontal sites (Hagemann, Naumann, & Thayer, 2001). Instead, offline averaged activity at the mastoid sites was used as reference. Only data from the mid-frontal (F3/F4) and mid-parietal (P3/P4, for comparison) sensors were used in the present report.

The EEG and electrooculogram signals were amplified by gains of 5000 and 2500 respectively and bandpass filtered (1 to 100 Hz) using a custom bioelectric amplifier from SA Instrumentation Company (San Diego, CA). Amplifier filter settings for all channels were 0.1 Hz (high-pass) and 100 Hz (low-pass). EEG data were digitized on-line at a sampling rate of 512 Hz. Signal quality was evaluated during a brief manual review. Subsequently, an automated routine from software developed by the James Long Company (EEG Analysis System, Caroga Lake, NY) was used to eliminate artifacts. The routine excluded periods that were above a 100μV threshold, eliminating artifacts resulting from movements, large scale muscle tension, and large eye movements. Automated artifact-scored data using this program is highly comparable to manually-scored artifact detection, with intraclass correlations of alpha power data using the two methods to be in the range of 0.94 - 1.00 (Vuga et al., 2008).

Artifact free EEG data were analyzed using a discrete Fourier transform (DFT), with a Hanning window of 1 s width and 50% overlap. EEG alpha band frequency (7.5 to 12.5 Hz) was computed (in μV^2) for the left and right midfrontal (F3/F4) and parietal (P3/P4) sites separately for the eyes-open (EO) and eyes-closed (EC) conditions. Analyses were conducted on the averaged EO and EC conditions, and separately in each condition. Computations for these asymmetry indexes is described below. Brain activity is an inverse measure of alpha power activity, meaning less alpha power represents more brain activity and vice versa.

Measures

Beck's Depression Inventory – II (BDI-II). The BDI-II (Beck et al., 1996) is a 21-item self-report inventory that measures depressive symptoms (e.g., I feel sad much of the time) experienced over the past two weeks. Responses are scored on a 4-point Likert Scale and scores on this inventory range from 0 to 63, with higher scores reflecting greater depressive symptoms.

The BDI demonstrates high internal reliability and discriminant validity (Storch, Roberti, & Roth, 2004). Further, the internal consistency within this sample was excellent (α = .923).

Beck's Anxiety Inventory (BAI). The BAI (Beck & Steer, 1993) is a 21-item self-report inventory that measures symptoms of anxiety (e.g., I am unable to relax) experienced over the past month. Responses are scored on a 4-point Likert Scale and scores on this inventory range from 0 to 63, with higher scores reflecting greater anxiety symptoms. The BAI demonstrates high internal reliability and discriminant validity (Creamer, Foran, & Bell, 1995). Further, the internal consistency within this sample was excellent (α = .979).

The Suicidal Behaviors Questionnaire-Revised (SBQ-R). The SBQ-R (Osman et al., 2001) is a 4-item self-report inventory that measures the presence and frequency of past suicidal thoughts and behaviours. Responses are scored on a 3- to 6-point Likert Scale, depending on the item, and scores on this inventory range from 0 to 18, with higher scores reflecting a greater risk of future suicidal behavior. The SBQ-R demonstrates high internal reliability and discriminant validity (Osman et al., 2001). Further, the internal consistency within this sample was adequate (α = .726).

The Ruminative Responses Scale Questionnaire (RRSQ). The RRSQ, a subscale of the Response Style Questionnaire (RSQ; Nolen-Hoeksema & Morrow, 1991), is a 22-item self-report inventory that measures the frequency of ruminative thoughts and behaviours (e.g., I think about a recent situation, wishing it had gone better) when experiencing negative mood. Responses are scored on a 4-point Likert Scale and scores on this inventory range from 0 to 88, with higher scores reflecting a greater tendency towards rumination. The RSQ demonstrates high longitudinal reliability and predictive validity for subsequent depressive episodes (Just & Alloy, 1997). Further, the internal consistency within this sample was excellent (α = .936).

Procedures

In this within-subject placebo-controlled study, participants came into the laboratory on two separate occasions, keeping time of day and day of the week were constant between testing sessions. Written informed consent was obtained from participants prior to the first laboratory session. Female participants were scheduled during the luteal phase of their menstrual cycle as to control for natural hormonal variations. Prior to their first session, participants completed an online battery of questionnaires. Upon arrival, the EEG cap was positioned according to standardized procedures (Pivik et al., 1993) and skin preparations included gently abrading the scalp at electrode sites and adding electrolyte gel. Participants were then given standardized instructions on the proper use of nasal spray bottles (Guastella et al., 2013) immediately prior to self-administering 24 I.U. of either OT or placebo. They were instructed to complete 6 sprays (4 I.U. each) in alternating nostrils. Each spray was separated by a 30 second interval, as timed by the experimenters. They were further instructed to keep the bottles upright and to avoid inhaling deeply during each spray. They were asked to not blow their noses for at least ten minutes following the administration procedure. Both the experimenters and the participants were blind to the contents of the bottles. Participants then relaxed for 30 minutes, during which time they were allowed to listen to music or read. During this period, they were prohibited from using their phones or contacting others via social media. Impedances for each electrode were then assessed using an electrode tester (*Checktrode*, UFI, Morro Bay, CA). Additional skin preparation and electrolyte gel was used as needed until impedances were below 10 kΩ.

During the EEG recording, participants were seated in front of a computer monitor (turned off), facing a one-way mirror. EEG recording took place during eight 60 second trials, four with eyes opened and four with eyes closed. During this procedure, the experimenter

entered the room to inform them when they needed to open or close their eyes. Both the ordering of asymmetry trials and drug conditions were counterbalanced between participants. Following EEG recording, participants completed an assessment of slow-wave event-related potentials during autobiographical memory retrieval (not reported here) as part of a larger data collection. 46 participants then returned seven days later (Mean 7 ± 1.2) for a second session which followed the same procedure; two female participants required longer delays (26 days and 32 days respectively) as to maintain menstrual phase constant. All participants were provided $80 as compensation for their time. Ethical approval of the project was obtained from the Human Research Ethics Committee at Concordia University (Montreal, Canada).

Statistical Analyses

Asymmetry scores were computed using mean amplitudes in the EO trials, EC trials, and across all trials for each participant. These means were used to obtain asymmetry scores following the left over right ratio method (Pivik et al., 1993). Frontal EEG asymmetry scores were computed as the ratio between alpha power at the left mid-frontal and right mid-frontal (F3/F4) recording sites. Parietal asymmetry scores were computed in a similar fashion (P3/P4) to determine if drug effects were specific to frontal sites. As such, larger asymmetry scores indicate greater relative left neural activation. Given that these scores were skewed, a natural logarithmic transformation was applied to the asymmetry data; this is the most reliable way to normalize absolute EEG data (Pivik et al., 1993). To assess for drug effects, asymmetry scores were compared using a series of repeated measures ANOVAs with drug condition as a within-subjects factor; sex was used as a between-subjects factor to explore possible moderating effects. Ordinary least squares regression was then used to determine if this relation was moderated by scores on the aforementioned self-report measures. For these analyses, potential moderators were

regressed on difference scores computed from the changes in asymmetry between drug conditions. All continuous moderators were centered. This is the recommended approach for estimating moderation in within-subject designs (Judd, Kenny, & McClelland, 2001). All analyses were run using SPSS version 22 (IBM Software, Armonk, NY).

Results

Data Integrity

Data for six sessions (6.5% of all data) was lost due to recording error. Missing data was imputed with multiple imputation using the *Amelia Package* in R (R Core Team, 2012). Scores for twenty-four outliers (2.1% of all data) were reduced to three standard deviation above or below the mean. Skewness and kurtosis were verified for all variables following the logarithmic transformation, and were found to be within the acceptable ranges (i.e., absolute values of less than 3.0 and less than 10.0, respectively) as outlined by Kline (2009).

Effects of Intranasal OT on EEG Asymmetry

The main effect of OT on frontal asymmetry scores was first analyzed using three separate repeated measures ANOVAs. Across all trials, OT administration resulted in an increase in relative left frontal neural activation compared to placebo (see Table 1 for descriptive statistics), but this difference was not statistically significant, $F_{(1, 47)} = .273$, $p = .604$, partial $\eta^2 = .006$. The drug X sex interaction was not found to be statistically significant, $F_{(1, 47)} = .073$, $p = .788$, partial $\eta^2 = .002$. Similarly, no significant drug effect was found for the EO, $F_{(1, 47)} = .279$, $p = .600$, partial $\eta^2 = .006$, and EC trials, $F_{(1, 47)} = .243$, $p = .624$, partial $\eta^2 = .005$. The drug X sex interaction was not statistically significant in both the EO, $F_{(1, 47)} = .468$, $p = .497$, partial $\eta^2 = .010$, and EC trials , $F_{(1, 47)} = .312$, $p = .579$, partial $\eta^2 = .007$.

The above analyses were repeated at the parietal sites. No significant differences were found across all trials, $F_{(1, 47)} = 1.040$, $p = .313$, partial $\eta^2 = .022$, nor for the EO, $F_{(1, 47)} = .229$, $p = .634$, partial $\eta^2 = .005$, and EC trials, $F_{(1, 47)} = 1.074$, $p = .305$, partial $\eta^2 = .023$. Similarly, the drug X sex interaction was not statistically significant across all trials, $F_{(1, 47,1)} = .024$, $p = .879$, partial $\eta^2 = .001$, nor for the EO, $F_{(1, 47)} = .010$, $p = .922$, partial $\eta^2 = .000$, and EC trials, $F_{(1, 47)} = .040$, $p = .842$, partial $\eta^2 = .001$. Of note, the direction of observed changes was opposite to the frontal sites, with OT administration resulting in decreased relative left neural activation across all trials and the EC trials, and increased relative left neural activation in the EO trials.

Exploration of Moderation Effects for Intranasal OT on Frontal EEG Asymmetry

A series of four regression analyses were used to investigate four potential moderating variables in the relation between OT administration and EEG asymmetry across all trials. BDI, BAI, SBQ, and RSSQ were used as predictors of the change in frontal asymmetry between drug conditions. All such analyses were non-significant, indicating that the effects of OT on frontal asymmetry were not dependent on these variables. See Tables 2 and 3 for correlational measures between the moderators and asymmetry scores. See Table 4 for a more detailed description of the moderation results. See Table 5 for descriptive statistics of all self-report measures.

Additional Analyses

It has been argued that log transformed data no longer accurately represents the associated raw data, and that this techniques should be used with caution (Changyong et al., 2014). As such, all aforementioned analyses were also run using non-transformed data as a precautionary measure. The obtained results were nearly identical to those reported above. The only noteworthy discrepancy was that OT administration increased relative left neural activation in frontal recording sites across all types of trials (OT: Non-transformed mean of .9806, standard

deviation of .1801; Placebo: Non-transformed mean of .9608, standard deviation of .1436). Similarly, OT administration decreased relative left neural activation in parietal recording sites across all types of trials (OT: Non-transformed mean of .7649, standard deviation of .2953; Placebo: Non-transformed mean of .8803, standard deviation of .5548). However, the magnitude and effect sizes of the changes remained small.

Discussion

The goal of the present study was to assess whether the administration of exogenous oxytocin, relative to placebo, alters frontal alpha EEG asymmetry. While it is well established that intranasal OT administration (e.g., Baumgartner et al., 2008; Kosfeld et al., 2005) and relative left frontal neural activation (e.g., Harmon–Jones & Allen, 1997; Coan & Allen, 2003b) are both associated with increases in prosocial and approach behaviours towards appetitive social stimuli, the potential direct relation between OT administration and relative left hyperfrontality had never been explored. To the best of our knowledge, this study is the first to examine the effects of intranasal OT administration on frontal asymmetry.

Three primary findings emerged. First, contrary to our hypothesis, OT administration did not result in a statistically significant change in frontal asymmetry. Relative to placebo, OT administration did produce an increase in relative left frontal neural activation as predicted; however, both the magnitude of this change and its effect size were small and did not achieve conventional statistical significance. Thus, cognitive and behavioural changes associated with exogenous OT administration may thus be linked to changes in brain regions other than the frontal cortex, but that also have an important role in mediating social behaviour. Alternative neurobiological pathways might encompass other areas that are affected by OT, including those involved in emotional processing and empathic understanding, such as the amygdala (Domes et

al., 2007), or in regulating physiological functions (e.g., heart rate, sex drive, body temperature) that relate to mood and motivation, such as the brain stem and hypothalamus (Kirsch et al., 2005). Similarly, the neural effects of OT administration may be more salient outside of the alpha bandwidth frequency range, in delta or theta waves perhaps, which were not investigated in the present study. Otherwise, it is possible that OT is acting largely in the peripheral nervous system. It has been argued elsewhere that OT's ability to cross the blood-brain barrier and directly stimulate CNS targets may be overstated (Leng & Ludwig, 2015), and that the source of its effect may occur outside of the central nervous system. One viable hypothesis is that OT acts on the sympathetic nervous system by dampening the autonomic stress response, which could promote social and approach behaviours (Quintana, Kemp, Alvares, & Guastella, 2013). In fact, it has been found that OT administration reduces the cortisol response to purely physiological stressors (exercise challenge: Cardoso, Ellenbogen, Orlando, Bacon, & Joober, 2013). Although moderation of cortisol levels by oxytocin may occur at any level of the hypothalamic-pituitary-adrenal axis, it is likely that this moderation by oxytocin is occurring at the level of the pituitary gland, outside of the CNS, based on studies of adrenocorticotropin hormone following peripheral oxytocin administration.

Second, contrary to our hypothesis, the effects of intranasal OT administration on frontal asymmetry were not moderated by any of our measures of depression and related constructs. Levels of suicidality, rumination, and overall depressive symptomatology did not account for any important differences in the effect of intranasal OT between participants, in contrast to previous studies of social cognition (Ellenbogen et al., 2012; Ellenbogen et al. 2013) and cardiovascular function (Norman et al., 2011). Given that the oxytocinergic system appears to be dysregulated in depressed individuals (Cyranowski et al., 2012; Scantamburlo et al., 2007) and that the

aforementioned studies have found moderation by depressive symptoms, the null finding was surprising. One possibility is that such moderation effects are limited to behavioural outcomes related to self-control and emotional information processing (see Ellenbogen et al., 2012 and Ellenbogen et al., 2013). Another possibility is that the present study lacked sufficient power to detect moderation. Although within-subject designs are particularly robust in detecting main effects of drug (Meyers, Gamst, & Guarino, 2013), they have limited power in detecting moderation. It is important to note that our previous studies showing moderation used between subject designs. Recent reviews of the oxytocin literature have highlighted the fact that OT effects on behaviour are characterized by small effect sizes (Wallum, Waldman, & Young, 2015).

Some important limitations should be mentioned. Firsts, although EEG is useful in assessing brain asymmetry, it provides no important information regarding areas of brain activation beyond the cortex. Clearly, subcortical regions are important in understanding OT's effects on social behavior (Adolphs, 2003; Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011). Second, while the BDI has adequate predictive validity, it is only designed to measure temporary changes in mood state over the previous week. As such, a single administration of this tool may not have been sensitive enough to detect moderation effects. Repeated assessments would have provided a more reliable measure of depressive symptomatology, which may have resulted in different findings. Lastly, and most importantly, our current sample may have been underpowered. Results from previous meta-analyses (Shahrestani, Kemp & Guastella, 2013; Van Ijzendoorn & Bakermans-Kranenburg, 2012) show that OT's broader influence on social cognition in humans is typically limited to a small effect size (Hedge's *g* of approximately 0.30). While this investigation was based on such previous reports, it is possible that the effect of

intranasal OT on neural activity are smaller than anticipated. Therefore, a much larger sample may have been required to detect statistically significant effects (see Wallum et al., 2015) of OT administration, as mentioned above. As a consequence, our probability of incorrectly retaining the null hypothesis could have been inflated. This is further evidenced by the fact that our results were in the expected direction, despite failing to reach statistical significance.

In summary, our results do not indicate that intranasal OT administration produces statistically significant changes in frontal EEG asymmetry. As OT's effect on frontal alpha asymmetry has never been directly examined, the present results provide important data when considering how, and if, oxytocin has effects in the brain (Leng & Ludwig, 2015). Existing biases in the publication of null results (Ferguson & Heene, 2012) might account for the aforementioned discrepancies within the OT literature. That is, a failure to publish null results may create the illusion of contention or corroboration when, in fact, the majority of investigations conclude that no effect is present (Walum et al., 2015). Nonetheless, future research may benefit from a more nuanced approach. For instance, a dose-response analysis may reveal discrepant findings, as previous research has shown that the effects of OT increase positively with dose (Cardoso et al., 2013). Further, investigating changes in frontal activation, and not exclusively frontal asymmetry, may prove to be a viable avenue of research. Similarly, future investigations could move beyond frontal alpha band asymmetry, examining changes in other EEG frequencies or even patterns of changes across multiple frequencies. Delta wave activity, for example, originates from deeper in the medial frontal cortex (with high connectivity to limbic brain regions), and has been hypothesized to be associated with reward processing and salience (Knyazev, 2007), both of which are believed to be important in understanding how OT alters social behavior (Bartz et al., 2011). Additionally, the use of a larger and more

representative sample could correct some of the limitations inherent to this current investigation. Given that OT may have more pronounced effects in social or otherwise challenging contexts, subsequent research might move beyond resting state asymmetry to investigate the interplay between OT and task-dependant asymmetry.

Table 1

Descriptive Statistics for Log Transformed EEG Asymmetry Ratio Scores (Left/Right) across Administration Trials

	Oxytocin				Placebo			
	Min	Max	Mean	SD	Min	Max	Mean	SD
Frontal (F3/F4)								
Total	-.490	.480	-.035	.176	-.620	.250	-.052	.165
EO	-.500	.560	-.059	.200	-.660	.210	-.053	.167
EC	-.490	.440	-.034	.172	-.610	.280	-.049	.166
Parietal (P3/P4)								
Total	-1.50	.620	-.350	.415	-1.59	1.29	-.264	.518
EO	-1.00	.620	-.182	.339	-1.52	.970	-.212	.444
EC	-1.56	.610	-.372	.443	-1.61	1.32	-.285	.561

Note. SD = Standard deviation; EO = Eyes open; EC = Eyes Closed; N = 48;

Table 2

Pearson Bivariate Correlations between Questionnaire Data and Log Transformed EEG Frontal Asymmetry Ratio Scores (Left/Right) across Administration Trials

	1	2	3	4	5	6	7
1. Total OT	1						
2. Total PLC	.107	1					
3. Sex	.148	.103	1				
4. BDI	-.252	-.016	.223	1			
5. BAI	-.126	-.009	-.013	.697 **	1		
6. SBQ	-.324 *	-.326*	.087	.561**	.524 **	1	
7. RRS	-.030	-.095	.166	.416 **	.393 **	.319 *	1

Note. Total OT = Oxytocin across all trials; Total PLC = Placebo across all trials; * $p < 0.05$; ** $p < 0.01$; N = 48.

Table 3

Pearson Bivariate Correlations between Questionnaire Data and Log Transformed EEG Parietal Asymmetry Ratio Scores (Left/Right) across Administration Trials

	1	2	3	4	5	6	7
1. Total OT	1						
2. Total PLC	.324 *	1					
3. Sex	-.240	-.168	1				
4. BDI	-.150	-.172	.223	1			
5. BAI	.022	.080	-.013	.697 **	1		
6. SBQ	-.249	.042	.087	.561**	.524 **	1	
7. RRS	-.020	-.079	.166	.416 **	.393 **	.319 *	1

Note. Total OT = Oxytocin across all trials; Total PLC = Placebo across all trials; * $p < 0.05$; ** $p < 0.01$; N = 48.

Table 4

Moderated Regression Analyses Predicting Change in Frontal Asymmetry from Drug Condition across Administration Trials

Moderator	*B*	*SE*	*t*	*p*
BDI	-.005	.004	-1.265	.212
BAI	-.002	.003	-.614	.542
SBQ	-.001	.016	-.095	.925
RRS	.016	.051	.310	.758

Note. SE = Standard Error; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; SBQ = Suicidal Behaviours Questionnaire; RRS = Ruminative Response Scale; N = 48.

Table 5

Descriptive Statistics for Self-Report Measures

	Min	Max	Mean	SD	Skew	Kurtosis
BDI	0	40	9.583	9.231	1.360	1.596
BAI	0	40	11.208	9.629	1.130	1.206
SBQ	3	11	4.812	2.169	1.034	.101
RRS	1	4	1.934	.614	.775	1.198

Note. SD = Standard deviation; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; SBQ = Suicidal Behaviours Questionnaire; RRS = Ruminative Response Scale; N = 48.

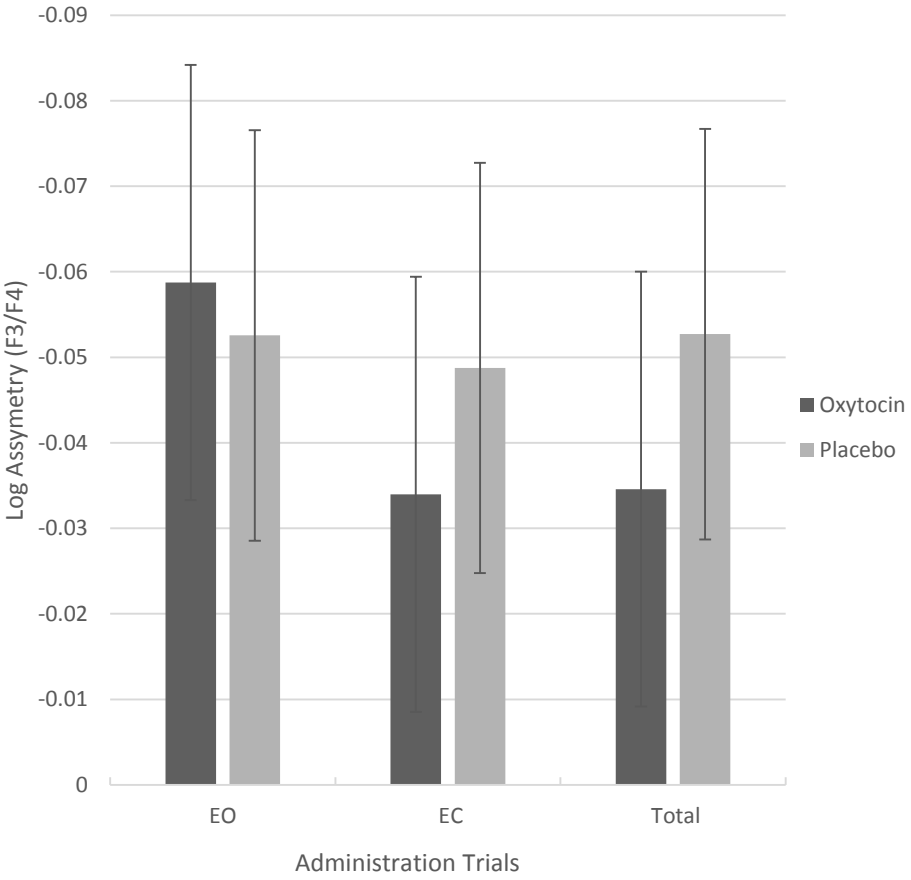

Figure 1. Mean frontal asymmetry ratios (F3/F4) between drug conditions, separated by trial type. EO = Eyes open; EC = Eyes closed. Error bars represent standard errors from the mean.

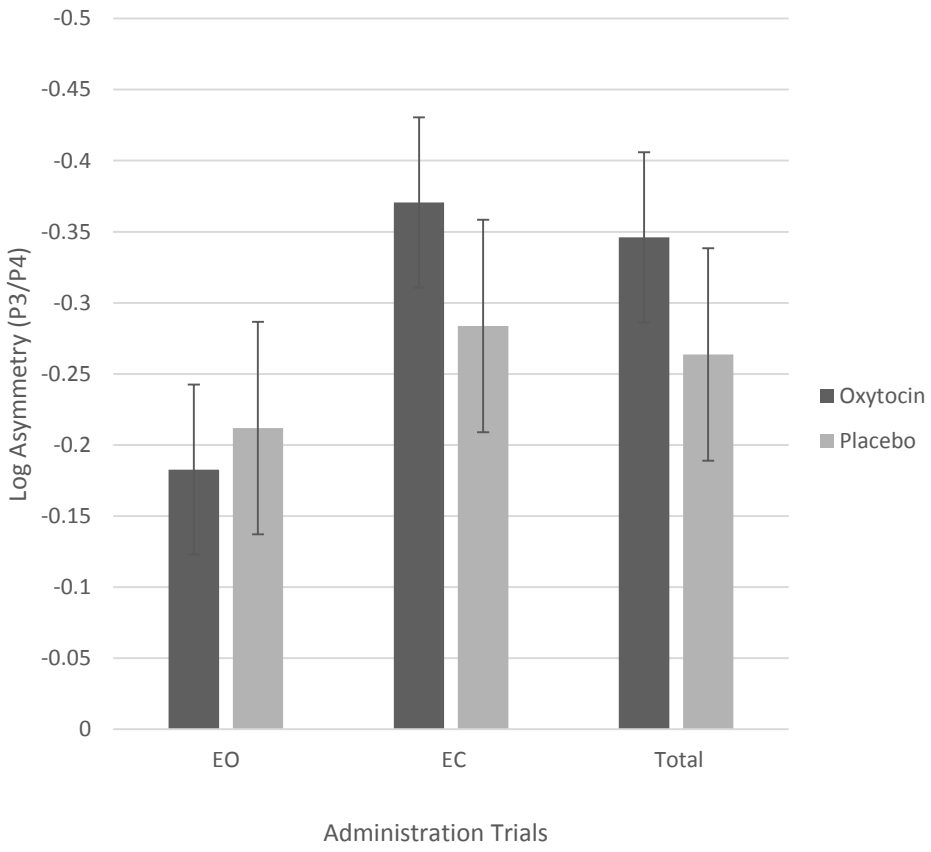

Figure 2. Mean parietal asymmetry ratios (P3/P4) between drug conditions, separated by trial type. EO = Eyes open; EC = Eyes closed. Error bars represent standard errors from the mean.

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