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The Role of Oxytocin in Modulating Neural Oscillations in Nulliparous Women

A Thesis Submitted to the

Yale University School of Medicine

in Partial Fulfillment of the Requirements for the

Degree of Doctor of Medicine

by

Xiaoyue Mona Guo

2016

ABSTRACT

THE ROLE OF OXYTOCIN IN MODULATING NEURAL OSCILLATIONS IN NULLIPAROUS WOMEN. Xiaoyue Mona Guo, Helena J.V. Rutherford, Linda C. Mayes. Child Study Center, Yale University, School of Medicine, New Haven, CT.

The hormone oxytocin (OT) has been implicated in social cognition and behavior as well as in modulating important affiliative relationships such as parenting; meanwhile, intranasal OT administration is gaining popularity as a means to modulate neural activity in brain regions during experimental tasks. However, the neural mechanisms underscoring the changes associated with OT administration have yet to be fully elucidated. Using electroencephalography (EEG), this thesis project aims to further our understanding of how OT affects brain activity and response to infant cues. In a double-blind placebo controlled design, OT's effect on resting-state neural oscillations and event-related potentials (ERPs) to face stimuli were examined in a cohort of nulliparous women of childbearing age. Specifically, we examined the effects of intranasal OT on delta, beta, and delta-beta coupling during the resting state, and the amplitudes of the ERP components N170, P300, and the Late Positive Potential (LPP) to infant and adult faces. Prior work has suggested that cross-frequency coupling may be a useful way to study cognitive processing, whereas the N170, P300 and LPP are all components involved in the processing of facial and emotional stimuli. We found that OT, relative to placebo, decreased delta-beta coupling across multiple brain regions; ERP data showed that OT administration led to an increased amplitude of the P300 component to infant faces compared with adult faces. Taken together, these findings demonstrate that OT administration may lead nulliparous women to allocate greater attentional resources to infant faces than adult faces via a neural mechanism captured by delta-beta coupling.

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Note:

The delta-beta correlation data associated with my thesis has been submitted for publication in the journal *NeuroImage.* I was also fortunate enough to present the work at a poster session during the Society for Social Neuroscience's 2015 Annual Meeting in Chicago.

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INTRODUCTION

Over the past decade, oxytocin (OT) has made news headlines from "OT makes people more trusting" to "Hormone OT jump-starts maternal behavior" [Data Source: Google Trends (www.google.com/trends)]. This so-called "love hormone" has gained attention in the research field for both its seeming influence on an increasing myriad of human behaviors and its potential for use in clinical populations. However, despite the four-fold increase in the number of publications over the past decade on OT and social cognition or behavior [1], there continue to be an absence of knowledge about OT's basic neurophysiological effects. What's more, notably lacking are studies on female participants due to the difficulties of controlling for hormonal interactions.

This thesis will provide a brief overview of the roles OT may play in social contexts and of how electroencephalography (EEG) can help inform this body of research, particularly for women. The studies described will investigate how OT administration affects brain responses in a cohort of healthy nulliparous women as measured by EEG both at rest and in response to social and nonsocial cues.

Physiologic Roles of Oxytocin

Derived from the Greek word *oxutokia* (*oxus* or 'sharp' + *tokos* or 'childbirth' = 'sudden delivery'), OT is a neuropeptide produced by the hypothalamus that acts as both a peripheral hormone and a central neurotransmitter. OT belongs to an ancient class of molecules known as nonapeptides, which are found in virtually every vertebrate phylum, with a lineage that can be traced through invertebrates. Despite the different types of nonapeptides within diverse species, they all are usually expressed selectively

in the brain and gonads (with OT shown to be synthesized further in somatic organs such as the heart, thymus and gastrointestinal tract [2]), are influenced by gonadal steroids, and are important for social behavior [3]. Much of what we understand of oxytocin's physiologic activity are from animal models, and very early studies suggested the importance of OT and the OT receptor in triggering critical aspects of pair bond formation and maternal behavior in rodents [3]–[5] which have since been replicated in higher-order mammals and primates [5], [6].

In humans, OT has a few well-described natural effects: in women, OT induces uterine contractions during parturition and is involved in milk release during breastfeeding. For both men and women, OT is released during sexual stimulation and orgasm, may reduce urine volume and induce natiuresis through co-activation of vasopressin receptors, and is involved in the modulation and regulation of the hypothalamic-pituitary-adrenal (HPA) axis [3]. On a cellular level, oxytocinergic neurons project to limbic, mid-, and hindbrain structures including the hippocampus and amygdala; they also have indirect effects on the activity of higher cortical functioning and the synaptic transmission of other neurotransmitters, including serotonin [7]–[9].

Importantly, there is a greater understanding of how the OT system is endogenously mediated by changes in OT receptors, whether via dynamic regulation in density and location by hormones like estrogen, or genetic and epigenetic differences between individuals. Pregnancy is a leading example, when elevated estrogen levels prime the maternal brain for increased synthesis of both OT and OT receptors, and lead to marked increases in OT receptor density in the uterus, mammary myoepithelium, and hypothalamus [10]. More recently, single nucleotide polymorphisms in the OT receptor

gene have been suggested to affect the efficiency of OT signaling in individuals [11], particularly with regards to caregiving behaviors such as parental touch [12] or response to infant faces [13]. However, a meta-analysis found that the direct social/behavioral impact of these genetic variances are inconsistent and small in magnitude [14], with increasing research now focusing on epigenetic modifications of the receptor gene via early childhood experiences [15], [16].

Influence of Intranasal Oxytocin on Social Behavior

Given these traditional associations of OT with affiliative behaviors, it is not surprising that OT has been broadly mapped onto human neurobiology with its actions translated towards affecting important human relationships (see reviews [10], [17]). To assess experimentally the central actions of OT in humans, intranasal administration has gained wide support and popularity of use. While minimal pharmacokinetic information exists on intranasal OT, a number of studies evidenced elevated levels of salivary OT for up to seven hours post administration [18]–[20]. More importantly, the nasal route circumvents the blood-brain barrier and leads to replicable behavioral and functional changes [15], [21]. However, it is worth noting that this methodology is not without its criticisms; taking into account the prevalence of somatic OT receptors and that a modest percentage of intranasal OT reaches the cerebral spinal fluid compared to the peripheral circulation, care needs to be taken in interpreting behavioral results as centrally versus peripherally driven [22].

Increasingly, OT has been associated with various aspects of positive human sociability including supporting partner communication and interactions [23], [24], improving emotion recognition in faces [25], [26], and increasing trustworthiness and trust

building [27]–[29]. In healthy populations, these results translate to a promise of stress reduction and anxiolysis [30], [31] as well as enhanced prosocial behavior [11]. Coupled with clinical research showing that plasma levels of OT are inversely related to depressive [32] and psychotic [33] symptomology, therapeutic considerations have risen for OT use in a host of patient intervention protocols from autism and schizophrenia to post-traumatic stress disorder and depression [34]–[37]. The crux of these treatment effects may lie in OT's anxiolytic properties, as it decreases an individual's aversion to negative internal or external stimuli [15].

However, despite excitement about OT's potential pharmacologic role, little is known about the neural basis underlying these effects, and inconsistencies abound between various studies in dosages used (from 2 IU to 320 IU) and the durations to wait after spray administration before measuring changes in the dependent variables [10], [15], [38]. Moreover, there is burgeoning evidence that OT also has negative influences such as increasing feelings of exclusion [39], and that the behavioral presentation depends on the individual. The end-effect of OT appears to be moderated by environmental contexts, personal characteristics, and early childhood experiences. Specifically, OT plays a stronger role when considering in-group situations, and in participants with lower attachment anxiety and supportive parenting backgrounds [15], [40].

Differential Oxytocin Effects on Women

Oxytocin and the Mother

Encompassing all the above described affiliative behaviors of trust and empathy is the act of parenting. Unsurprisingly, the earliest evidence suggesting OT's influence beyond

that of reproduction and parturition physiology was the stimulation of a nurturing, maternal phenotype in virgin rats that were centrally administered with OT [41]. Multiple human and animal studies since have supported this observation and implicated OT in having a key role in the formation and development of the infant-parent bond [6], [42]. For example, affectionate and stimulatory parenting behaviors are correlated with OT levels in new mothers and fathers, respectively [10], and securely attached mothers have a stronger OT response following a play interaction with their child as compared to insecurely attached mothers [43]. Moreover, a steady rise in OT levels from the first through third trimester in a pregnant woman is correlated with higher self-reported bonding scores to her unborn infant [44]. There also appears to be a genetic basis underlying the parental OT pathway, with low-risk OT receptor alleles corresponding with more sensitive parental care [12], and stronger preference for infant faces [13], [45].

One way to experimentally study parenting is through examining and comparing the response to infant versus non-infant cues. This predilection for infant cues (faces and cries) that seems to instinctively trigger feelings of protection and caretaking may arise from an innate positive affect towards the "baby schema," a collection of infantile characteristics like big eyes and round features [46]. Multiple studies show individuals having greater responses in brain regions associated with face processing, attention, and reward when viewing infant versus adult faces; the use of images or sounds from a parent's own infant further enhances these responses (see review [47]). With its association with affiliative behavior, intranasal OT administration also unsurprisingly increases sensitivity to infant cues [45], [48].

More recent work suggests that a number of individual differences, including substance use [49] and depression [50] may also affect the neural response to infant cues. As stress and addiction both impact prefrontal cortical function [51], [52] these states may have detrimental effects on executive function as it relates to parenting behavior [53]. Evidence further shows OT to have a bidirectional relationship with HPA activity [54] and drug exposure [55]. In rodents, chronic OT administration leads to a reduction of the acute stress response [56]; OT has also been shown to be released by the heart and vasculature, suggesting a role in the modulation of cardiac activity and vascular tone [57], [58]. Accordingly, in mothers 2 – 6 months postpartum, the amount of plasma OT following stress induction was related to lower cardiac and vascular reactivity and increased levels of norepinephrine [59]. This attenuation of the HPA axis by OT is further observed with lactating mothers, where a rise in OT following breastfeeding is inversely related to ACTH and cortisol levels, and the act of breastfeeding can decrease HPA responses to a stress exposure [44]. These studies suggest potential benefits of OT in modulating the physiological stress responses that are critical factors in parenting; they further suggest that OT may have a wider regulatory function than previously thought.

More broadly, global gray matter volume has been shown to significantly increase in mothers from 2 – 4 weeks to 3 – 4 months postpartum [60], supporting a notion that cortical reorganization over the postpartum period serves to facilitate parenting behavior and the orientation of attention and perception towards the infant. The exact neurological basis of parenting, however, is still unknown. An area of accumulating evidence is the idea that that reward neural circuits in mothers are recruited when they are engaged with infant cues, particularly of their own infants [61]. Several

studies have shown the importance of increasing orbitofrontal cortex activity in various aspects of parenting, including when listening to infant cries versus white noise [62], [63], viewing pictures of own infant faces versus unknown infant faces [64], perceiving infant faces as compared to adult faces [65], and distinguishing maternal from romantic attachment [66]. OT administration has been shown to directly affect neural activation of similar regions, with a recent meta-analysis of fMRI studies on mother-infant interactions finding greater activation of the left insula but decreased activation of the dorsomedial frontal cortex in the maternal brain [67].

Oxytocin in Nulliparous Women

Despite rich research on the maternal-infant relationship, it is difficult to understand the changes that occur in a woman's affiliative processing abilities throughout the course of pregnancy and into early and late-postpartum periods. This is made even more complicated by further differences in the neural response to infant cues while comparing parents to non-parents [68], suggesting a unique parental neurologic state that could be in part modulated by OT. Multiple studies describe how intranasal OT administration modifies a nulliparous woman's neural and behavioral responses to infant cues to being more similar to those of a postpartum woman. For instance, nulliparous participants given OT have increased empathy and decreased negative affect towards a crying infant, and report higher arousal by photos of infants [69]–[71].

The OT literature has burgeoning data supporting the existence of underlying sexual dimorphism modifying OT's physiologic effects and the importance of appreciating these sex-dependent effects particularly for translational research [72]. Indeed, a recent rodent study suggested a direct link between sexual dimorphism in OT-

producing areas of the brain and sex-specific behaviors. By optogenetically turning on a group of hypothalamic neurons, the researchers were able to increase a virgin female rats' pup retrieval behavior and circulating OT levels in rats of both sexes, providing new causative data on gender differences in social or reproductive behaviors [73]. In human women compared to men, OT is associated with almost opposite neural imaging findings particularly in the temporal lobes and subcortical areas such the amygdala [38], [74]. The neuropeptide has also been shown to reduce self-reported anxiety measures in women who use emotion-oriented coping mechanisms but not men [75], and generally leads to more "tend and befriend" traits instead of the "fight and flight" responses of the male participants [76], [77]. Similarly, there is some indication that OT makes a male's neural responses, especially older men's, more similar to that of females [78], [79].

Despite gender being a well-explored moderator of OT effects on social cognition, a significant limitation to our understanding of maternal-infant relationships is a scarcity of data using non-maternal female populations. This bias is evident in the 44 publications using intranasal OT prior to 2010, where 32 used an all-male participant pool and only one used an all-female group [17]. In order to avoid potential interactions and confounding by hormonal variances, researchers often do not recruit female participants, and thus our foundation of OT-related knowledge has predominantly been anchored on male-oriented studies. For the studies that do use females and males, some show a lack of gender differences (i.e., [80]–[82]), possibly due to differences in study design and inclusion/exclusion criteria of the participants (including but not limited to OT dosage, oral contraceptive use, menstrual cycle, and parity).

A well-controlled, mechanistic understanding of OT's effects on the nulliparous female brain thus still requires study. This thesis employs a female-only sample given the limited knowledge of OT effects on neural activity in this group, to help augment our sex-specific appreciation of OT modulation.

Assessing Neural Responses to Oxytocin Using Electrophysiology

Given the sometimes conflicting and inconsistent results of intranasal OT research, there is growing interest towards exploring its effects using behavioral and functional neuroimaging [83]. The majority of these intranasal OT studies have employed functional magnetic resonance imaging (fMRI), a methodology relying on changes in blood oxygenation to determine brain activity [38]. However, electroencephalography (EEG) provides a valuable alternative to imaging data by enabling a *direct* index of neuronal activity through measuring post-synaptic potentials of cortical pyramidal neurons [84]. The few studies using EEG have mostly shown that OT administration mainly alters cortical activity during social tasks, specifically, and that these neural effects correspond with performance on these tasks [38]. Through complementing the spatial resolution of fMRI findings with the temporal resolution of EEG studies, a more comprehensive picture of the neurophysiology behind OT administration on human cognitive and social behavior can be formed.

Delta-Beta Coupling

In EEG, tightly coupled neural correlates can be measured as oscillations of varying frequency: slow waves (i.e., delta, theta) are thought to reflect subcortical emotion and motivational processes, whereas fast waves (i.e., alpha, beta, gamma) are thought to

reflect more cortical cognitive control processes [85]. Prior research has found no changes in the neural activity of individual frequency bands with OT administration when EEG was recorded at rest without social stimuli or tasks [38], [86]. As such, interest has increasingly veered away from the study of individual frequency bands to focus on cross-frequency coupling, measured as correlations between the amplitudes of slow- and fast-wave oscillations, to understand complex brain interactions more fully. Indeed, this method may be more sensitive to the complexities of OT effects [87].

In particular, amplitude-amplitude coupling between delta and beta activity may represent a synchronization or interface between emotional or motivational systems and higher-order cognition, given the likely subcortical and cortical generators of these oscillations, respectively [85]. Support for this approach can be garnered from studies examining delta-beta correlations when the interplay of affect and cognition may be compromised, particularly in relation to increased levels of stress and anxiety. For example, there is a positive association between the strength of delta-beta coupling and basal cortisol levels [88]; intranasal administration of cortisol also increases this correlation, an effect that was amplified in participants with higher levels of behavioral inhibition [89]. Furthermore, delta-beta coupling is increased in more anxious individuals and decreased after the treatment of anxiety [90]. Consequently, given the previously described properties of OT in decreasing stress and anxiety, OT administration may modulate cross-frequency coupling on EEG despite not affecting the activity of individual frequency bands.

In the first portion of the current study, EEG served as a viable tool for evaluating and understanding the underlying neural mechanisms of OT in healthy nulliparous women

in the absence of any social or behavioral task. Through observing OT effect on the amplitudes of delta, beta, and delta-beta coupling at rest, we can directly examine the role of OT at the neural interface of emotional or motivational systems and cognition [85]. Given the aforementioned relationship of delta-beta coupling with anxiety, it was hypothesized that administration of intranasal OT, relative to placebo, would decrease delta-beta coupling, consistent with OT's association with decreasing stress and anxiety. As previous research has not shown changes in delta and beta oscillations following hormonal manipulations, it was anticipated that these individual frequency bands would similarly be unaffected by OT administration.

Event-Related Potentials to Infant Faces: N170, P300, LPP

Evoked or event-related potentials (ERPs) are another way of observing the brain's electrical potentials as elicited by specific sensory events. Whereas the rhythmic oscillations of EEG show a more general state of activity, ERPs enable the analysis of the synchronized processes of a population of neurons underlying perceptual, attentional, and cognitive responses in a time-locked manner.

Characteristic ERP waveforms are associated with different visual stimuli; faces are particularly prominent in the literature as eliciting a stereotypical response. The N170, a negative ERP component 170ms after the presentation of the stimulus, is an early marker of the structural encoding of human faces [91], [92]. Correlating with fMRI, the N170 is most prominent over brain areas implicated in face processing (e.g.,the fusiform gyrus) [34]. Infant faces have been shown to differentially affect this component compared to adult faces in parents and non-parents alike, while being modulated by bond formation between a parent and their infant [93]. Indeed, the N170

response is affected by individual differences in sensitivity to infant cues such as parental status and mood [50], [94]. It has also been shown to be modulated by the infant's emotional expression (particularly of distress), although the literature is mixed regarding how the amplitude of the N170 changes in response to the cue versus other parental characteristics like depressive symptomology [95].

The P300 or P3 positivity component is another well-described ERP configuration triggered by detection of or attention to an improbable, 'oddball' stimulus [92]. Compared with the immediacy of components like that N170 that correspond with the initial perception of a stimulus, the P300 is associated with a later stage of cognitive processing that requires more long-term memory and recognition [96]. Overall, it appears to reflect attention allocation towards motivationally salient and task-relevant stimuli, as the P300 amplitude is directly related to subjective perceptions of the probability of and attentional engagement to the stimulus [96], [97]. Crucially, P300 activity has been evidenced to be sensitive to prosocial behavior [98], and emotional stimuli in particular leads to a sustained P300 dubbed the late positive potential (LPP). More specifically, the LPP reflects a conscious allocation of attention to, and presumed continuous processing of, motivationally significant emotional stimuli [97].

Both the P300 and LPP have been explored in the context of the presumed relative importance of processing infant cues [95]. The P300 is greater in amplitude when mothers are tested with cues of their own versus an unknown infant [93], [99] and greater with distressed infant faces [68]. For the LPP, mothers who were more accurate in face recognition tasks to negative infant expressions had larger amplitudes [13] while neglectful mothers in a separate study had attenuated LPP amplitudes to all

emotional infant faces [94]. Similar to the N170, characteristics of the P300 and LPP also appear to be modulated by individual differences, such as the desirability or preference for the stimuli, parental status, anxiety, and early childhood experiences [93], [97], [100], [101].

Taken together, the N170, P300, and LPP embody different processing modalities of infant cues, with the former representing earlier, more automatic perception and the latter representing higher-order cognition. Newer evidence suggests that face processing may be influenced by the affective significance of the stimuli and therefore interact with emotion or reward systems [102]; a few imaging studies show an interaction between the fusiform gyrus and the amygdala or orbitofrontal cortex during face viewing [65], [102]. Although dopamine and norepinephrine have been implicated in the manifestation of the P300 and LPP [97], there are a few studies exploring neurohormonal involvement with other ERP responses. Oxytocin, with its reported roles in attention allocation for faces and emotional events, may be an integral molecular modulator of these neural responses particularly with regard to affiliative stimuli.

In the second part of this thesis, we performed an ERP analysis on the N170, P300, and LPP components, employing neutral and distressed infant and adult faces with non-social stimuli (houses) as a control. Given OT's aforementioned properties in social behavior, it was expected that OT administration would increase sensitivity to faces compared with houses, and emotional compared with neutral faces. A prior study showed that mothers with certain alleles of the OT receptor gene have earlier latencies for the N100 (a negativity differentiating emotional facial expressions) only in

response to infant faces [13]. Other studies showed that elevated P300 amplitudes were directly associated with OT levels in foster parents viewing photos of their child [103], while OT administration led to larger LPP amplitudes with emotional faces [100]. As such, it was hypothesized that OT administration would increase both the early N170 component and the later P300 and LPP amplitudes in our cohort of nulliparous women. Specifically, we hypothesize that OT will further increase the amplitudes of the N170 and P300 for infant compared with adult faces, and LPP for distressed faces compared with neutral faces.

STATEMENT OF PURPOSE

Aim:

The specific aim of this thesis is to determine how OT affects (1) resting-state neural oscillations and (2) event-related potentials in response to social stimuli in healthy, nulliparous women.

Hypotheses:

Intranasal OT administration will:

(1) Decrease delta-beta coupling in participants at rest without affecting the activity of the individual delta and beta frequency bands

(2) Increase sensitivity of the participants to social stimuli as compared to placebo, measured as increased amplitudes of the:

   a. N170 to infant faces compared with adult faces

   b. P300 to infant faces compared with adult faces

   c. LPP to emotional (distressed) faces compared with neutral faces

METHODS

Note: Helena Rutherford (HR) and Linda Mayes (LM) designed the experiments and trained me (XMG), Nathan Hayes (NH), and Kelsey Graber (KG) on all protocols. NH and KG performed the telephone eligibility screening. XMG, NH, and KG conducted the visits and ran the participants through the face-viewing tasks. XMG and HJVR analyzed the data and HJVR performed the statistical analyses.

Participants

Twenty-six healthy, nulliparous women from the Yale University and New Haven community were recruited using flyers for two study visits scheduled four weeks apart to facilitate continuity in menstrual cycle phase. Eligibility was assessed by telephone screening and exclusion criteria included pregnancy, use of any hormonal birth control, clinically significant medical or psychiatric illnesses, and use of psychotropic medications. A full list of inclusion/exclusion criteria are listed in Table 1.

All participants gave informed consent during the first visit and were compensated $80 for each visit ($160 total). Two participants did not return for a second visit and the data from one participant could not be analyzed due to excessive artifacts. Therefore, the final sample consisted of 23 nulliparous women (22 single, 1 married), aged 18 – 31 years (M=23.3; SD=3.3). Using self-reported menstrual data, half of the participants were in the luteal phase of their menstrual cycle. All were high school graduates (M=16.7 years of education; SD=2.0). Self-identified ethnicity was: Caucasian/White (n=14), Asian-American/Asian (n=5), African-American/Black (n=1), Hispanic/Latina (n=1) and Other (n=2). One participant reported current cigarette use, and two

reported current marijuana use; no participants had present or past alcohol or substance abuse as gauged by the Addiction Severity Index Lite CF [104] interview.

Table 1. Inclusion and exclusion criteria used for telephone screening of participants

Inclusion Criteria	**Exclusion Criteria**
• Adults ages 18-64 • Good medical health • Ability to understand and speak English • Nulliparity	• *Medical Illnesses*: o Moderate or severe acute or chronic medical illnesses (e.g. cardiac disease, diabetes, epilepsy, influenza). • *Cardiovascular risk factors*: o History of hypertension with baseline blood pressure above 140 mm Hg (systolic) over 90 mm Hg (diastolic) o Any history of syncope and/or baseline blood pressure below 100 mm Hg (systolic) • *CNS disease*: o Known history of brain abnormalities (e.g., neoplasms, subarachnoid cysts), cerebrovascular disease, infectious disease (e.g., abscess), or other central nervous system disease o History of head trauma that resulted in a persistent neurologic deficit, or loss of consciousness > 3 minutes • *Medication status*: o The use of contraceptive hormones o The use of any psychotropic medications **excluding** those individuals on stable doses of a neuroleptic and/or an antidepressant medication for at least the past 6 weeks

Procedure

All procedures were approved by Yale School of Medicine Human Investigation Committee (HIC: 1309012677) and registered under clinicaltrials.gov (Identifier: NCT02238379). Both visits occurred between 1200h and 1500h in order to minimize diurnal variations in hormone levels, with attempts to schedule the participant at the same time on both days [105]–[107]. Participants refrained from exercising and alcohol use for 24 hours, caffeine intake for 12 hours, and smoking and eating for two hours before each visit. Upon arrival, participants had their blood pressures measured and completed pregnancy, urine drug, and breath alcohol and carbon monoxide testing. No

participants were pregnant or evidenced recent substance use in their urine toxicology or breathalyzer tests.

Given the intranasal route of the spray administration, participants filled out a nasal questionnaire (www.nwentallergy.com) to document the presence and severity of symptoms such as nasal congestion and itching. All participants had minimal symptoms, with total scores of less than four (out of 15) during their first visit and with one participant scoring six during the second visit due to a recovering upper respiratory illness. Moreover, participants completed various personality questionnaires including the State-Trait Anxiety Inventory (STAI) [108], the Beck Depression Inventory-II (BDI) [109], the Perceived Stress Scale (PSS) [110], and the Parental Bonding Instrument (PBI) [111] during each visit (Table 2). The only statistical difference found was for State Anxiety, with participants scoring lower on the visits where they received OT compared to placebo sprays (M=30.8, SD=7.2 versus M=34.7, SD=10.9; p=0.03). However, both scores lay well below the cutoff for clinically significant anxiety symptoms, and Trait Anxiety was not statistically different between conditions. Finally, routine safety monitoring with blood pressure, heart rate, and temperature measurements was conducted throughout the visit.

In this double-blind, within-subject crossover design, participants received, at random and counterbalanced, either OT (United States Pharmacopeia) or a placebo delivered by nasal spray. Both substances were in identical bottles and prepared by the Investigational Pharmacy at Yale-New Haven Hospital. After priming the bottle, participants administered four puffs of spray, alternating nostrils with 15 seconds between puffs, of 4 IU/puff resulting in a total dose of 24 IU. This OT dosage was chosen

because of there being no adverse behavioral and neurobiological effects in previously reported intranasal administrations [112]. The placebo spray contained all ingredients except the active OT. In post-experiment interviews, participants were unable to identify better than chance whether they received the OT (n=4 guessed correctly) or placebo (n=5 guessed correctly) spray. After a 45 minute rest period, participants first completed the ERP Experiment lasting 25 minutes, followed by the EEG Experiment (described below). Each visit lasted approximately two hours, with both visits having the same procedural flow.

Table 2. Mean scores and standard deviation (SD) for questionnaires completed by participants on separate visits prior to nasal spray delivery. Paired two-tailed t-tests were used to calculate p-value for comparison between conditions if appropriate.

Questionnaire	Placebo	Oxytocin	p-value
Beck Depression Inventory [a]	4.3 (SD=5.9)	4.1 (SD=6.2)	0.93
Perceived Stress Scale [b]	17.7 (SD=7.3)‡	17.0 (SD=8.0)	0.31
State-Trait Anxiety Inventory [c]			
State Anxiety	34.7 (SD=10.9)	30.8 (SD=7.2)	0.03
Trait Anxiety	30.3 (SD=7.6)	29.9 (SD=7.9)	0.79
Parental Bonding Instrument [d]			
Maternal Care	29.6 (SD=6.8)		
Paternal Care†	27.7 (SD=8.8)		
Maternal Protection	13.2 (SD=7.9)		
Paternal Protection†	11.1 (SD=8.8)		

†1 participant did not report paternal care or protection scores
‡1 participant had incomplete questionnaire

[a] Scores <13 indicate minimal depression
[b] Scores of 16-20 indicate slightly higher than average stress
[c] Scores >40 suggest clinically significant anxiety symptoms
[d] Optimal parenting is defined as high care (maternal>27, paternal>24) and low protection (maternal<13.5, paternal<12.5). Reported data are averaged from both visits.

EEG Acquisition

All data were collected in a sound-attenuated room under low ambient light conditions. A 128 Hydrocel Ag/AgCl electrode sensor net (Electrical Geodesics, Inc.; Tucker, 1993) was soaked in a warm potassium chloride solution and fitted according to manufacturer specifications evenly and symmetrically across the participant's scalp from nasion to inion and from the left to right ear. Continuous EEG was recorded using Net Station 4.2.1 with a sampling rate of 250 Hz and high impedance amplifiers (Net Amps 200, 0.1Hz high pass, 100Hz low pass). Electrodes were referenced to the vertex (Cz) during EEG recording and impedances were kept below 40 kΩ.

EEG Experiment

After the ERP Experiment and approximately 70 minutes after intranasal administration of OT or placebo sprays, participants completed a resting state eyes-open eyes-closed EEG task. This task consisted of a continuous series of six one-minute recording periods as participants sat quietly in alternating eyes-open (EO) and eyes-closed (EC) conditions (i.e. OCOCOC).

ERP Experiment

Participants were asked to sit quietly for 45 minutes after administration of either the OT or placebo spray with blood pressure and heart rate monitored throughout. The experimental task began with nine practice trials containing stimuli not included in the experiment (photographs of farmyard animals) following the same protocol as the experimental trials. The trial sequence consisted of a central fixation cross (jittered

between 400 – 600ms), stimulus presentation (1000ms), and a blank screen (1000ms). All stimuli were randomly selected and presented on a uniform black background.

Experimental stimuli were grayscale photographs of 12 unique infant faces, 12 unique adult faces, and 24 unique houses. With identity held constant, half (6) of the faces in each group for both infants and adults showed distressed expressions while the other half (6) showed neutral expressions. Pre-tests were conducted using all the face stimuli to confirm their emotional content.

Each participant completed four blocks of 108 experimental trials. Within each block, 48 face stimuli (50% of the faces were infants; 50% of the expressions were distressed) and 48 house stimuli were presented. In order to assure participant attention, an additional 12 catch trials requiring a key press response were included in each experimental block, but were not included in the final analysis. In total there were 192 house trials and 192 face trials (48 Adult Distress, 48 Adult Neutral, 48 Infant Distress, and 48 Infant Neutral). The face-viewing experiment took approximately 25 minutes to complete.

Data Analysis

All analyses were performed blind the spray condition of each participant. Net Station 4.5 was used to pre-process all raw EEG data and prepare the data for statistical analysis. Secondary analyses of any interactions between the self-report questionnaires (i.e. STAI, PSS, BDI, PBI) and EEG data will be conducted in a follow-up study and are not reported below.

EEG Experiment

To analyze EEG data during the resting conditions, the data was segmented into two-second epochs, yielding 90 possible epochs for each of the EO and EC conditions. Artifact detection was 200μV for bad channels and Ocular Artifact Removal (OAR; [113]) using a blink slope threshold of 14μV/ms was applied to the EEG data. Eye blink and movement threshold was set to 150μV. Spline interpolation was used to replace channels with artifacts in more than 40% of trials. EEG data were then re-referenced to the average reference of all electrodes and baseline-corrected. Following pre-processing, there were on average 73 (range: 34-90) EO epochs and 78 (range: 36-90) EC epochs ($t(48)=-2.03$, $p=.048$).

Data were exported to Matlab 7.9.0 (R2009b MathWorks, Natick, MA) where Fast Fourier Transform analyses were performed. The average spectral power for delta (0.5–4Hz) and beta (13–25Hz) frequencies were extracted and natural log transformed (ln) given their non-normal distributions. Subsequent statistical analyses were performed on the correlation between the ln power of delta and beta frequencies and averaged across electrodes sites in: central (C3, C4, Cz), prefrontal (Fp1, Fp2), frontal (F3, F4, F7, F8, Fz), parietal (P3, P4, Pz), temporal (T3, T4, T5, T6), and occipital (O1, O2) regions (consistent with the 10-20 electrode system; Jasper, 1958; Figure 3D). Ln delta and beta power were also compared when averaging across all electrode sites. Although spectral data from EO and EC conditions are often averaged together to represent a single resting state condition, we compared the ln delta and beta power within and between EO and EC conditions given differences that have been reported previously between these two resting EEG conditions [114], [115].

Next, Steiger's [116] modification of Dunn and Clark's [117] z score was used to test for differences between two non-overlapping dependent correlations [118], and 95% confidence intervals were calculated [119]. Given the directional hypothesis of decreased delta-beta correlations associated with OT, one-tailed tests were employed. Effect size is presented as partial eta-squared (η2partial), where .01 represents a small effect size, .06 represents a medium effect size, and .14 represents a large effect size [120]. Greenhouse-Geisser corrections were used when sphericity assumptions were violated.

ERP Experiment

For data processing to analyze the ERPs, each EEG file was first digitally filtered with a 30 Hz low-pass filter for reduction of environmental noise artifacts. The EEG signal was subsequently segmented into one-second epochs, beginning 100 ms before and ending 900 ms after the onset of the stimulus. Spline interpolation was used to replace electrode channels with artifacts in more than 50% of the trials and OAR using a blink slope threshold of 14 μV/ms was also applied to all data.

Electrode clusters as they cover the scalp are presented in Figure 1. Electrodes of interest were selected for the N170 using scalp regions characteristically eliciting the N170 [121], and conforming to electrode sites used in published dense-array EEG face perception studies [50], [122]. These electrode sites consisted of two clusters of six electrodes over the left lateral posterior scalp (58 59, 64, 65, 68, and 69) and the right lateral posterior scalp (89, 90, 91, 94, 95, and 96). Data for ERP analysis were averaged across the six sites in each hemisphere. The N170 time window was derived and customized for each participant using the Net Station user-defined event function; this

enabled statistical extraction of each component and ensured they were representative of waveform variability. Specifically, the N170 that was extracted for statistical analysis was identified and marked as an event at each electrode site per participant. The time window ranged across participants from 150 ms to 225 ms, with the N170 peak defined as the minimum amplitude falling in that window.

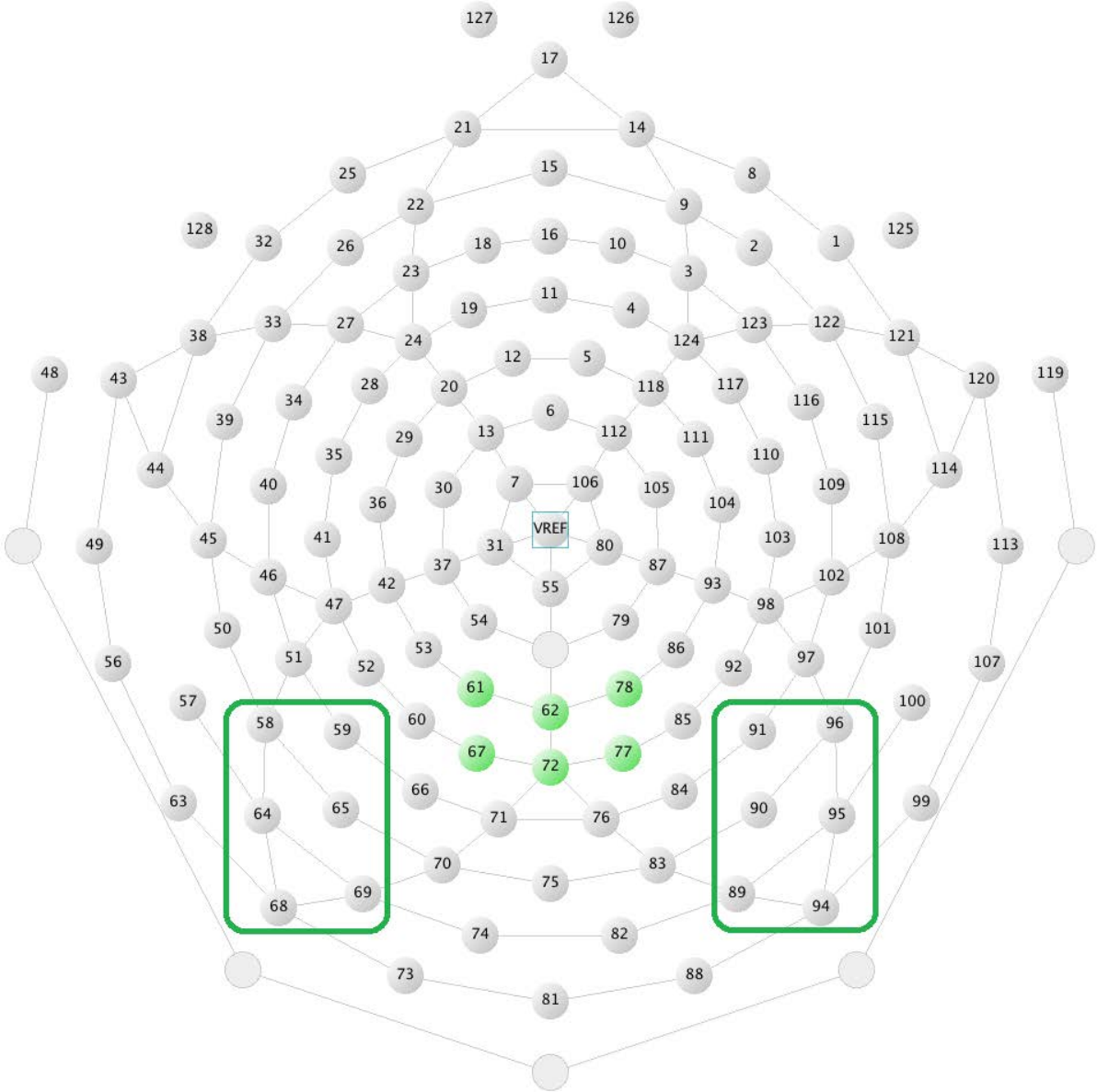

Figure 1. Electrode array layout with clusters of interest highlighted (top of figure is nasion). N170 (Circled) = Left hemisphere: 58 59, 64, 65, 68, 69; Right hemisphere: 89, 90, 91, 94, 95, 96. P300/LPP (Shaded) = 61, 62, 67, 72, 77, 78.

For the P300 and the LPP, ERP data were averaged over six electrode sites typically used in P300 research (61 62, 67, 72, 77, and 78; [99], [123]) that also overlap with published dense-array LPP research [100], [101]. Using time windows of 200 to 400 ms and 500 to 800 ms after stimulus onset, we measured the mean amplitudes of the P300 and the LPP, respectively. Next, the P300 and LPP were both examined in the averaged data of each participant to confirm that the component of interest was captured at each electrode site. Finally, the mean amplitudes were statistically extracted for each participant.

Statistical analysis was performed using repeated measures of analysis of variance (ANOVA). All data were also assessed for their appropriateness for parametric analyses and house stimuli were separately analyzed from face stimuli for all components. Similar to the EEG Experiment, effect size is presented as η2partial.

The N170 data for houses were analyzed with a two (spray: OT, placebo) by two (hemisphere: left, right) within-subject ANOVA while faces were analyzed using a two (spray: OT, placebo) by two (face: infant, adult) by two (emotion: distressed, neutral) by two (hemisphere: left, right) within-subject ANOVA. For both the P300 and LPP, a two-tailed paired t-test was conducted to assess the effect of OT versus placebo administration on house stimuli; a two (spray: OT, placebo) by two (face: infant, adult) by two (emotion: distressed, neutral) within-subject ANOVA was conducted for face stimuli. Of note, one participant was excluded as an outlier for LPP analyses following boxplot assessments.

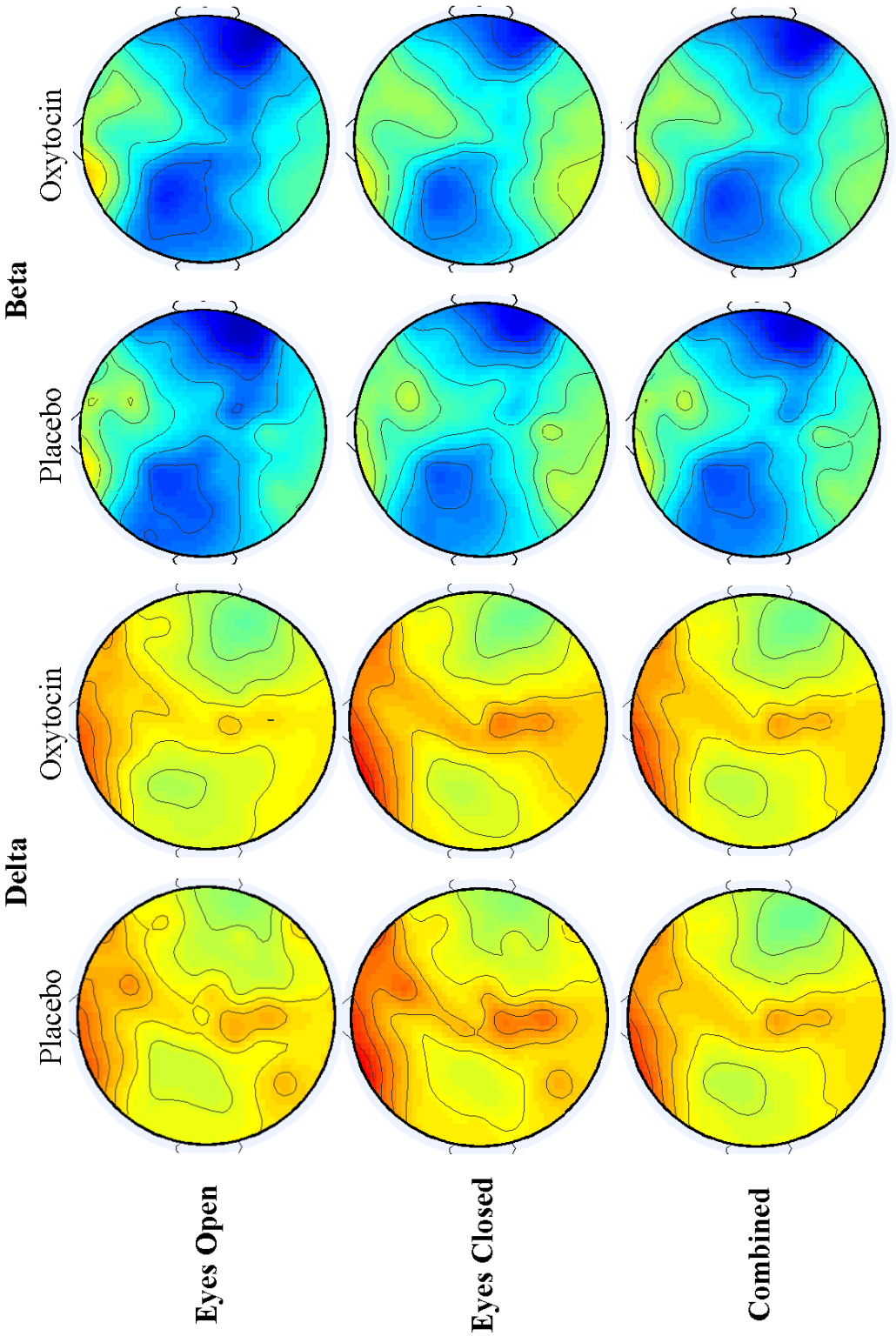

Figure 2. Delta and beta power for each resting condition (eyes open, eyes closed, and averaged eyes open and closed) and spray type (OT, placebo). Note: Separate power scales are used for delta and beta maps.

RESULTS

EEG Experiment

Delta and beta powers

Scalp topographies for the raw delta and beta powers across each of the experimental conditions (EO, EC, EOEC) are presented in Figure 2. The ln power for each electrode, resting condition, and spray condition were first separately examined (Table 3) and found to have no main effect of spray for either delta [$F(1,22)=1.48$, $p=.24$, $\eta 2partial=.06$] or beta [$F<1$] frequencies. This confirmed that resting delta and beta were unaffected by OT administration relative to placebo.

Table 3. Natural log transformed delta and beta power for each electrode site (including a total power averaged across sites) as a function of resting EEG condition (eyes open, eyes closed) and spray type (OT, placebo).

	Electrode Site						
	Prefrontal	Frontal	Central	Parietal	Temporal	Occipital	Total
Eyes Closed							
Delta-Oxytocin	1.97	1.06	0.50	0.95	0.67	1.01	0.96
Delta-Placebo	1.88	0.86	0.48	0.81	0.41	0.80	0.80
Beta-Oxytocin	-1.95	-2.64	-2.90	-2.56	-2.74	-1.99	-2.55
Beta-Placebo	-2.07	-2.72	-2.84	-2.54	-2.86	-2.19	-2.61
Eyes Open							
Delta-Oxytocin	1.57	0.88	0.36	0.71	0.62	0.83	0.78
Delta-Placebo	1.50	0.65	0.36	0.48	0.37	0.65	0.61
Beta-Oxytocin	-1.68	-2.70	-3.09	-2.92	-2.95	-2.38	-2.71
Beta-Placebo	-1.77	-2.76	-3.08	-2.95	-3.06	-2.56	-2.78

There was a main effect of resting EEG condition for both delta [$F(1,22)=10.80$, $p=.003$, $\eta 2partial=.34$] and beta [$F(1,22)=13.29$, $p=.001$, $\eta 2partial=.38$], with greater power during EC relative to EO. For delta, there was a main effect of electrode site [$F(3,76)=40.06$, $p<.001$, $\eta 2partial=.65$], with greater delta in prefrontal and parietal regions and lower delta in central regions. These main effects were qualified by resting condition and electrode site interaction [$F(3,62)=7.52$, $p<.001$, $\eta 2partial=.26$], showing variability in the magnitude of delta during EO and EC conditions (with this difference being smallest in temporal electrode sites). There was also a main effect of electrode site for beta [$F(5,110)=30.85$, $p<.001$, $\eta 2partial=.58$], with greater power in prefrontal, parietal and temporal regions. Similarly, these main effects were qualified by a resting condition and electrode site interaction [$F(2,40)=36.19$, $p<.001$, $\eta 2partial=.62$] where beta was greater in EO and EC conditions in prefrontal regions but greater in EC than EO conditions in other regions.

There were no other interactions between these variables [F's<1] for either delta or beta. Taken together, these data illustrate how delta and beta vary as a function of the resting EEG condition as well as the electrode site where these frequency bands are recorded. Critically, delta and beta powers did not differ as a function of OT or placebo administration.

Cross-frequency coupling

Delta-beta correlations were next examined between OT and placebo conditions. Figure 3 depicts delta-beta correlations for EC (Panel A), EO (Panel B), and EOEC averaged together (Panel C).

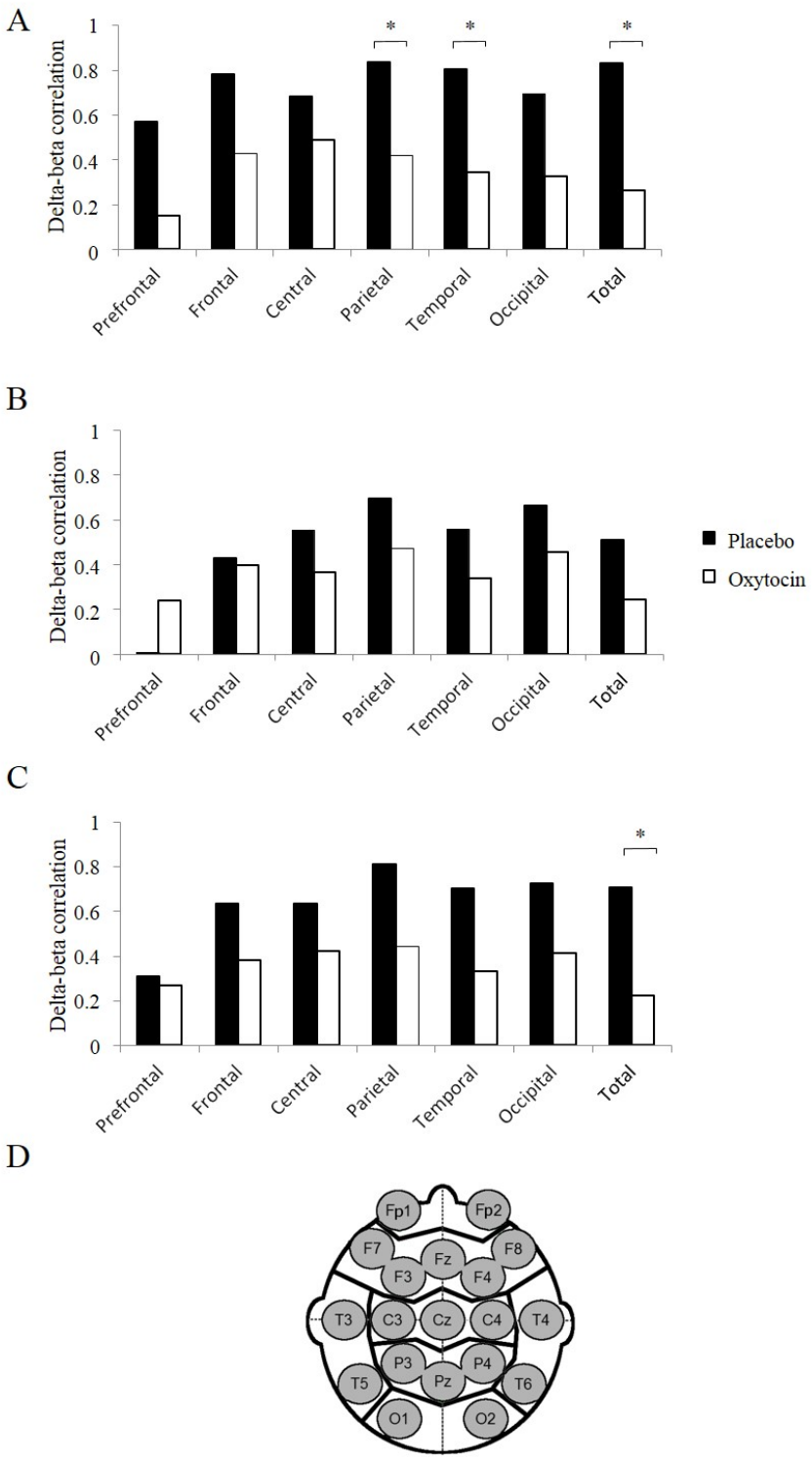

Figure 3. Delta-beta correlations for placebo and OT conditions at each electrode region (listed on the horizontal axis) for the Eyes Closed condition (Panel A), Eyes Open condition (Panel B), and Averaged Eyes Open and Closed conditions (Panel C). Schematic of position and naming of electrodes using the 10-20 EEG system (Panel D). *Statistical reduction in delta-beta correlation between OT and placebo conditions ($p<.008$; corrected for multiple comparisons); Fp=Prefrontal; F=Frontal; C=Central; T=Temporal; P=Parietal; O=Occipital

In the EC condition, OT administration resulted in decreased delta-beta correlation across all electrode sites relative to placebo [z=3.25; p < .01; 95% CI: 0.21–0.99]. Examining individual electrode locations separately, delta-beta correlations were differentiated by spray condition at prefrontal [z=1.69; p<.05; 95% CI: -0.66–0.88], frontal [z=2.14; p<.05; 95% CI: 0.03–0.75], parietal [z=2.80; p<.01; 95% CI: 0.12-0.81], temporal [z=2.58; p<.01; 95% CI: 0.10–0.88], and occipital [z=1.71; p<.05; 95% CI: -0.06–0.80] sites. Central electrode sites did not show a condition difference [z=0.99; p=.16; 95% CI: -0.19–0.60]. Notably, after Bonferonni correction for multiple comparisons across each site (p<.008), only comparisons between parietal and temporal sites remained statistically significant.

The EO condition had a similar trend for decreased delta-beta correlation after OT administration, although no individual electrode site reached statistical significance [z's<1.15; p's>.12]. After averaging EOEC together as done in prior research, OT administration significantly decreased the global delta-beta coupling across all electrode sites [z=2.15; p .02; 95% CI: 0.04–0.92]. However, there was no condition difference at individual electrode sites or after correcting for multiple conditions (NB: parietal [z=2.28; p<.05; 95% CI: 0.05–0.77] and temporal [z=1.69; p<.05; 95% CI: -0.06–0.82] sites approached statistical significance).

In summary, intranasal OT administration decreased the resting state EEG delta-beta correlation in the averaged EOEC condition, but predominantly affected the EC condition.

ERP Experiment

N170

The N170 amplitude for houses showed no main effect of spray (F<1), hemisphere [(F(1,23)=2.36, p=.14, η2partial=.04], or their interaction (F<1). For faces, there was a main effect of emotion [F(1,23)=11.38, p=.003, η2partial =.33] and face type [F(1,23)=5.11, p=.034, η2partial=.18], but no main effect of spray [F(1,23)=1.06, p=.31, η2partial =.04], hemisphere (F<1), or any interactions (p's >.14). Of note, the mean N170 amplitude was attenuated for houses (M=-1.15 mV; SD=1.34) compared with all face types, regardless of expression (Infant M=-3.46 mV, SD 2.40; Adult M=-3.27 mV, SD 2.13).

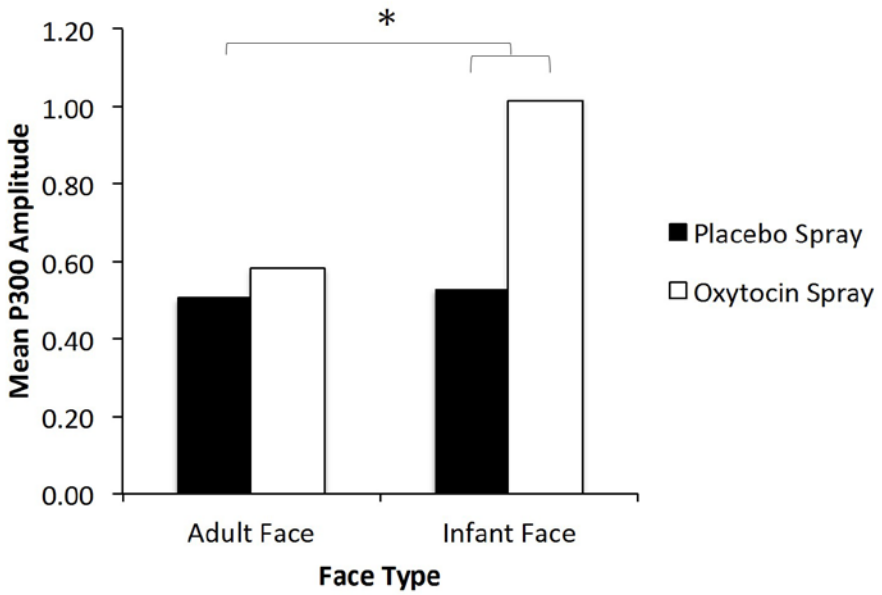

Figure 4. Mean P300 amplitudes for adult and infant face stimuli after placebo and OT administration. * Mixed effects within subject ANOVA showed main effect of face (p=.03) and Face x Spray interaction (p=.03).

P300

A paired t-test comparing mean P300 amplitude for houses after placebo or OT showed no significant difference [t(23)=-1.41, p=.17]. For face stimuli, the P300 amplitude was modulated by face type [F(1,23)=5.21, p=.03, η2partial=.19], which was qualified by a face x spray interaction, [F(1,23)=5.20, p=.03, η2partial=.18]. There was no main effect of spray [F(1,23)=1.75, p=.20, η2partial =.07] or emotion (F<1). Figure 4 shows the mean P300 amplitude for each face type and spray condition, depicting how OT administration selectively led to an increased P300 for infant faces compared with adult faces.

LPP

A paired t-test comparing mean LPP amplitudes for houses showed no significant difference between the placebo and OT conditions [t(22)=1.12, p=.27]. There were also no main effects of spray, face type, emotion or their interactions for the face stimuli (p's>.05).

DISCUSSION

Despite the large number of social cognition and behavioral studies that have employed intranasal OT administration, the neural mechanisms modulated by this neuropeptide remains elusive and not well understood. In this present study, the influence of intranasal OT was assessed using electroencephalography in a group of healthy, nulliparous women. We examined how OT compared with placebo influenced the resting state EEG correlations between delta and beta frequency bands, and affected ERP responses to social and nonsocial stimuli.

During resting state EEG recording, while OT did not modulate the amplitudes of delta and beta oscillations individually, it did decrease the cross-frequency coupling of delta and beta across EEG scalp sites. Exploring ERP data, OT administration led to increased P300 amplitude in response to infant faces as compared to adult faces, without affecting N170 or LPP amplitudes. Taken together, these findings suggest that a potential mechanism through which to understand how OT administration modulates attention allocation for infant cues may be by studying the interrelationships between neural oscillations; delta-beta represents one such relationship but other oscillations should be examined as well.

Neural Responses to Oxytocin

To our knowledge, this is the first study to explore how OT administration affects the correlation between spectral powers. Accumulating research is focusing on understanding neural network functions through the interactions between fast and slow wave EEG activity, which are thought to represent cortical and subcortical

generators, respectively [87]. Indeed, previous research on cross-frequency coupling have been conducted using cortisol [89] and testosterone [124]; those researchers similarly observed hormone modulation of cross-frequency coupling without any effect on individual resting delta and beta frequencies. These findings suggest that the observed changes in delta-beta correlation may not be due to general neural activity or arousal changes from the hormone administration, but rather reflect spectral coherence changes in the underlying neurobiological systems.

As low-frequency oscillations like delta waves are physiologically thought to arise from subcortical regions while high-frequency oscillations like beta waves are hypothesized to originate in cortical circuits, the apparent changes in delta-beta correlation may represent shifts in subcortical-cortical interactions [85]. To date, a majority of research describes increased delta-beta coupling as associated with anxiogenic contexts and emotional dysregulation [87], which converges well with OT's anxiogenic properties [125]. Interestingly, a few studies suggest that alterations in this coupling are driven by and are more sensitive to changes in delta activity than beta [87], [88], implying greater subcortical influences on this relationship. Since slow waves are thought to be involved in the discrimination of emotional stimuli [126], perhaps changes in delta-beta coupling reflect changes in emotional salience. One subcortical brain structure that is strongly involved with emotion—and anxiety—is the amygdala. Converging with this, OT administration has been shown to alter the functional connectivity between the amygdala and the bilateral insula and medial and dorsal anterior cingulate cortices in patients with social anxiety viewing fearful faces [127].

An advantage of using dense-array EEG methodology is the scalp coverage it provides despite poor spatial resolution beyond the cortical surface. We found that decreased delta-beta coupling was more pronounced in the temporal and parietal regions, which corresponds with fMRI data suggesting that OT effects are the most strongly influenced and produced the largest effect sizes across research studies in the temporal lobes [38]. These findings correspond with research implicating the temporal regions in the processing of emotional cues [128]–[131] and the parietal regions in attentional processing [132], [133]. Furthermore, delta-beta coupling has been suggested to be a neural correlate of attentional avoidance of threat [134]. Thus, one interpretation of decreased coupling in temporal and parietal lobes with OT administration may be that the anxiolytic effects of OT dampen attentional processing of affective stimuli through modulation of these neural networks.

A strength of the current study is the examination of neural oscillations at multiple electrode sites, separately and together, for the different resting conditions. We notably found that although modulation of delta-beta coupling by OT was present when data from the eyes-closed and eyes-opened recording periods were averaged together as is typically done in EEG research, it was most prominent in the eyes-closed resting condition. The physiology behind this phenomenon is not clearly understood, although studies have shown that there is increased spontaneous activity [115] and generalized low frequency power increase [114] during EC conditions which may render the oscillation changes to be more easily visualized. Regardless, it may be valuable to consider these conditions separately as well as together in future research. Indeed, except for at the prefrontal electrodes, OT administration led to decreased delta-beta

coupling at trend-level significance during the eyes-open condition across the scalp, which may reflect a need for a larger sample size to better elicit this phenomenon.

Oxytocin and Infant Cues

Through capitalizing on the temporal strength of ERPs, we learned how OT may affect different stages of stimulus processing—from perception and the N170 to attention and cognition with the P300 and LPP. In our cohort of healthy nulliparous women, the N170 was expectedly attenuated for house compared to face stimuli, and enhanced for infant faces and distressed expressions compared to adult faces and neutral expressions, respectively. This is consistent with prior studies showing increased N170 amplitude with infant faces, particularly those that are distressed [68], [93], [94]. Modulation of the N170 by face type and emotion is in line with the component's association with low-level categorization of visual stimuli, and suggests the importance of efficient processing of infant faces and the discrimination of distress.

On the other hand, neither the P300 nor the LPP were modulated by emotional expression. OT administration increased the amplitude of only the P300 component after participants viewed infant faces compared with adult faces, and did not affect the amplitudes of the N170 or LPP as was originally hypothesized. Such an outcome implies that OT mainly affects the temporally later stages of stimulus processing without changing the initial perceptual processing of the faces themselves. The increased amplitude of the P300 demonstrates that OT administration was associated with participants allocating greater attentional resources to infant faces than adult faces. OT consequently selectively rendered infant faces more salient and relevant, which is congruent with prior research implicating OT in increasing participants' sensitivity to

infant cues [45] and in the enhancement of the P300 when participants evaluate stimuli of greater motivational importance [97].

Whereas our results of OT's effect on resting delta-beta coupling suggested anxiolysis through a dampening of baseline attentional processes, its effect on the P300 conversely suggested increased attentional allocation to infant stimuli. These seemingly inconsistent results may be due to resting-state EEG oscillations inherently measuring different aspects of neuronal processing than ERPs, or can be resolved through the perspective that OT renders infant cues to be both more salient and less anxiety-provoking. Further taking into consideration that OT had the greatest impact on delta-beta correlation in the parietal and temporal lobes, multiple ERP and fMRI studies have inferred the generation of the P300 to be from an interaction between the frontal and the temporal-parietal lobes [96], [135]. New research has also shown OT's ability in altering the balance of inhibitory and excitatory neurons projecting from the hypothalamus to the cortex; these connections appear to directly control the development in virgin mice of a behavioral response to crying pups and subsequent memory formation for the socially relevant sounds [136]. Altogether, our data supports a role for OT in modulating neuronal circuitry from subcortical to neocortical regions, and selectively strengthening resource and attentional allocation to neural processes that are involved in handling infant cues, while potentially making these cues less aversive.

The lack of either face, emotion, or OT effect on the LPP was surprising, given its intimate relationship functionally and electrophysiologically with the P300. Our results were in contrast to prior research finding greater LPP positivity after OT administration

in female undergraduates to emotional faces [100]. However, this published study was predominantly driven by participants reporting lower maternal love withdrawal, and was affected by oral contraceptive use. The authors suggested that participants with higher love withdrawal may have maximum facial or emotional processing even under placebo administration and would not gain the benefit of additional OT [100]. This is consistent with other research connecting early childhood experiences with OT sensitivity [15], and may explain why we did not observe an effect without elucidating and analyzing our participants based on these personal characteristics. Since the LPP represents a *conscious* allocation of attention compared to the P300 [97], individual traits may play a greater role in impacting this component and would be a direction of future research. Consistent with this idea is a recently published study showing enhanced LPP in a cohort of mothers shown distressed compared to neutral infant faces [101], which together with our lack of LPP effect by infant faces in a nulliparous group, further provides support for a uniquely maternal brain.

Along the same vein, although infant faces elicited stronger N170 amplitudes than adult faces in our cohort of nulliparous women, OT did not modulate this difference. The N170 has been shown to be greater in response to infant cues in parents and individuals in romantic relationships than in individuals who are single or have no children [93], [137]. Although all our participants have never been pregnant, we did not ask for relationship status or caregiving experiences which may both play modulating roles. However, it may be that low-level perceptual or visual processing (represented by the N170) are simply not affected by OT [138]. In fact, there is some data showing that the N170 to infant faces is not modulated by parental status [50] or by familiarity of the

infant to the mother [99]. As such, OT administration may not change early neural responses to an already salient infant cue.

Limitations and Future Directions

An important limitation to many intranasal OT studies is small sample sizes leading to underpowered results and low positive predictive values [139]. We strived to offset this limitation through stringent inclusion and exclusion criteria and a within-participant experimental design. However, the generalizability of these results to male participants needs to be established, and future studies using mixed male and female samples could directly enable between-gender comparisons as well as a replication of our findings among other female subjects. Moreover, the importance of individual differences on OT's influence requires the need for establishing how varying socio-emotional and personality traits, as well as physiological or pathological states such as pregnancy or depression, may contribute to its effects (e.g. [140]). Further analysis is ongoing to examine any interactions between the self-report questionnaires (regarding anxiety, depression, stress, and early bonding experiences) completed by our participants and the neuro-electrophysiological data; these results will be explored in a separate manuscript.

While we found that OT administration did not affect resting delta or beta oscillatory power, exploring other frequency bands may be worthwhile. Furthermore, although the difference between relative and absolute power measures is beyond the scope of this thesis, it is important to note that these measured oscillations of individual frequency bands represent proportions of multiple frequencies in a recorded EEG, all of which may be differentially affected (or not) by substance administration. We focused solely

on delta-beta correlations due to prior research identifying their role in modulating stress- and anxiety-associated contexts, as well as in interfacing with emotion and cognition [85], [89], [90], [124]. Indeed, some studies have shown intranasal OT leading to greater low alpha / mu (8-10Hz) and beta suppression during the viewing of biological motion [141]. Thus, exploration of OT effects within, as well as across, other frequency bands and experimental paradigms may be warranted. It is also worth noting that the analyses we report assumed a linear correlation between the amplitudes of these oscillations, while other studies have suggested distal brain regions may have non-linear relationships representing different sets of brain dynamics and functions [142]. We also only examined amplitude-amplitude synchrony between delta and beta, in contrast to phase-phase or phase-amplitude measures [143] which can elucidate other important mechanistic associations of cognitive function (reviewed in [142]).

In regards to the event-related potentials, our results could be further informed by including faces with positive expressions to compare neural responses to negative and neutral faces. Since identity and emotional processing of faces are intimately interlocked [102], we may expect similar results irrespective of emotional valence. However, multiple studies suggest that infant happiness or distress as represented by facial expression and cries may activate very different brain regions in parents and non-parents [61], [68], [70]. There is also is a dearth of studies assessing the span of basic emotions since studies have primarily focused on happy and angry as representation for positive and negative expressions [25]. For the P300 in particular, we focused on its amplitude as a whole, instead of separately analyzing its individual temporal components or its latency. The P3a and P3b subcomponents of the P300 represent

mechanisms arising from different brain loci [96] and may be differentially affected by both facial or emotional category and OT administration.

Finally, although EEG arises from neurotransmission and neural activity, it is ultimately a correlational technique; the precise anatomic origins of our results are not known and require additional neuroimaging studies aimed towards determining neuroanatomical and neurophysiological correlates. It is also possible that the commonly used dosage of 24IU intranasal OT is insufficient for delivering an effective cerebral concentration. This can either, or both, mask any true neurological effects or lead to inaccurate apportionment of peripherally driven OT effects to central OT activity [22], [139]. The latter situation is less likely for this thesis given our direct neural measurements using EEG, but it would be beneficial to conduct dose-response studies and examine whether these neural relationships are functions of OT levels. Through using varying OT dosages and measuring saliva OT levels at different experimental time points, we can more effectively link dynamic hormonal changes with social or electrophysiological behavior.

Conclusion

In summary, the present study explored how intranasal OT administration affected the neural oscillations and responses to infant faces in a cohort of healthy, nulliparous women. We demonstrated that OT decreased delta-beta coupling in the resting brain and increased the amplitude of the P300 as elicited by infant faces compared with adult faces. This provides a potential mechanism through which intranasal OT may modulate brain and social behavior on a neural level, and supports the value of EEG in examining the integration of dynamically changing cortical and subcortical neural networks. By measuring cross-frequency correlations, we were able to explore the complex

interactions that OT modulates between subcortical and cortical brain regions, while the use of ERP further provided us the ability to identify the processing stage at which OT influences the handling of affiliative stimuli. Overall, this thesis adds to the intranasal OT literature a potential tool for measuring OT action with delta-beta coupling, and provides new data on how OT acts upon the female brain.

REFERENCES

[1] L. J. Young and L. M. Flanagan-Cato, "Editorial comment: oxytocin, vasopressin and social behavior.," *Horm. Behav.*, vol. 61, no. 3, pp. 227–9, Mar. 2012.

[2] I. Gordon, C. Martin, R. Feldman, and J. F. Leckman, "Oxytocin and social motivation.," *Dev. Cogn. Neurosci.*, vol. 1, no. 4, pp. 471–93, Oct. 2011.

[3] T. R. Insel, "The challenge of translation in social neuroscience: a review of oxytocin, vasopressin, and affiliative behavior.," *Neuron*, vol. 65, no. 6, pp. 768–79, Mar. 2010.

[4] C. A. Pedersen, J. A. Ascher, Y. L. Monroe, and A. J. Prange, "Oxytocin induces maternal behavior in virgin female rats.," *Science*, vol. 216, no. 4546, pp. 648–50, May 1982.

[5] C. Sue Carter, "Neuroendocrine perspectives on social attachment and love," *Psychoneuroendocrinology*, vol. 23, no. 8, pp. 779–818, Nov. 1998.

[6] C. Lieberwirth and Z. Wang, "Social bonding: regulation by neuropeptides.," *Front. Neurosci.*, vol. 8, p. 171, Jan. 2014.

[7] R. Landgraf and I. D. Neumann, "Vasopressin and oxytocin release within the brain: a dynamic concept of multiple and variable modes of neuropeptide communication.," *Front. Neuroendocrinol.*, vol. 25, no. 3–4, pp. 150–76, Jan. 2004.

[8] R. Stoop, "Neuromodulation by oxytocin and vasopressin in the central nervous system as a basis for their rapid behavioral effects.," *Curr. Opin. Neurobiol.*, vol. 29, pp. 187–93, Dec. 2014.

[9] A. Meyer-Lindenberg, "Impact of prosocial neuropeptides on human brain function.," *Prog. Brain Res.*, vol. 170, pp. 463–70, Jan. 2008.

[10] K. Macdonald and T. M. Macdonald, "The peptide that binds: a systematic review of oxytocin and its prosocial effects in humans.," *Harv. Rev. Psychiatry*, vol. 18, no. 1, pp. 1–21, Jan. 2010.

[11] H. Yamasue, J. R. Yee, R. Hurlemann, J. K. Rilling, F. S. Chen, A. Meyer-Lindenberg, and H. Tost, "Integrative approaches utilizing oxytocin to enhance prosocial behavior: from animal and human social behavior to autistic social dysfunction.," *J. Neurosci.*, vol. 32, no. 41, pp. 14109–17, Oct. 2012.

[12] R. Feldman, O. Zagoory-Sharon, O. Weisman, I. Schneiderman, I. Gordon, R. Maoz, I. Shalev, and R. P. Ebstein, "Sensitive Parenting Is Associated with Plasma Oxytocin and Polymorphisms in the OXTR and CD38 Genes," *Biol. Psychiatry*, vol. 72, no. 3, pp. 175–181, Aug. 2012.

[13] M. J. Peltola, S. Yrttiaho, K. Puura, A. M. Proverbio, N. Mononen, T. Lehtimäki, and J. M. Leppänen, "Motherhood and oxytocin receptor genetic variation are associated with selective changes in electrocortical responses to infant facial expressions.," *Emotion*, vol. 14, no. 3, pp. 469–77, 2014.

[14] M. J. Bakermans-Kranenburg and M. H. van Ijzendoorn, "A sociability gene? Meta-analysis of oxytocin receptor genotype effects in humans.," *Psychiatr. Genet.*, vol. 24, no. 2, pp. 45–51, Apr. 2014.

[15] M. J. Bakermans-Kranenburg, M. H. van IJzendoorn, M. H. Puglia, T. S. Lillard, J. P. Morris, and J. J. Connelly, "Sniffing around oxytocin: review and meta-analyses of trials in healthy

and clinical groups with implications for pharmacotherapy," *Transl. Psychiatry*, vol. 3, no. 5, p. e258, May 2013.

[16] M. H. Puglia, T. S. Lillard, J. P. Morris, and J. J. Connelly, "Epigenetic modification of the oxytocin receptor gene influences the perception of anger and fear in the human brain," *Proc. Natl. Acad. Sci.*, vol. 112, no. 11, pp. 3308–3313, Mar. 2015.

[17] P. A. Bos, J. Panksepp, R.-M. Bluthé, and J. van Honk, "Acute effects of steroid hormones and neuropeptides on human social-emotional behavior: a review of single administration studies.," *Front. Neuroendocrinol.*, vol. 33, no. 1, pp. 17–35, Jan. 2012.

[18] A. Gossen, A. Hahn, L. Westphal, S. Prinz, R. T. Schultz, G. Gründer, and K. Spreckelmeyer, "Oxytocin plasma concentrations after single intranasal oxytocin administration - A study in healthy men," *Neuropeptides*, vol. 46, no. 5, pp. 211–215, 2012.

[19] N. Striepens, K. M. Kendrick, V. Hanking, R. Landgraf, U. Wüllner, W. Maier, and R. Hurlemann, "Elevated cerebrospinal fluid and blood concentrations of oxytocin following its intranasal administration in humans.," *Sci. Rep.*, vol. 3, p. 3440, 2013.

[20] M. H. van Ijzendoorn, R. Bhandari, R. van der Veen, K. M. Grewen, and M. J. Bakermans-Kranenburg, "Elevated salivary levels of oxytocin persist more than 7 h after intranasal administration," *Front. Neurosci.*, vol. 6, no. December, p. 174, 2012.

[21] J. Born, T. Lange, W. Kern, G. P. McGregor, U. Bickel, and H. L. Fehm, "Sniffing neuropeptides: a transnasal approach to the human brain," *Nat. Neurosci.*, vol. 5, no. 6, pp. 514–516, May 2002.

[22] G. Leng and M. Ludwig, "Intranasal Oxytocin: Myths and Delusions.," *Biol. Psychiatry*, vol. 79, no. 3, pp. 243–250, May 2015.

[23] B. Ditzen, M. Schaer, B. Gabriel, G. Bodenmann, U. Ehlert, and M. Heinrichs, "Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict.," *Biol. Psychiatry*, vol. 65, no. 9, pp. 728–31, May 2009.

[24] D. Scheele, N. Striepens, O. Güntürkün, S. Deutschländer, W. Maier, K. M. Kendrick, and R. Hurlemann, "Oxytocin modulates social distance between males and females.," *J. Neurosci.*, vol. 32, no. 46, pp. 16074–9, Nov. 2012.

[25] S. Shahrestani, A. H. Kemp, and A. J. Guastella, "The impact of a single administration of intranasal oxytocin on the recognition of basic emotions in humans: a meta-analysis.," *Neuropsychopharmacology*, vol. 38, no. 10, pp. 1929–36, 2013.

[26] G. Domes, M. Heinrichs, A. Michel, C. Berger, and S. C. Herpertz, "Oxytocin improves 'mind-reading' in humans.," *Biol. Psychiatry*, vol. 61, no. 6, pp. 731–3, Mar. 2007.

[27] M. Kosfeld, M. Heinrichs, P. J. Zak, U. Fischbacher, and E. Fehr, "Oxytocin increases trust in humans.," *Nature*, vol. 435, no. 7042, pp. 673–6, Jun. 2005.

[28] P. J. Zak, R. Kurzban, and W. T. Matzner, "Oxytocin is associated with human trustworthiness.," *Horm. Behav.*, vol. 48, no. 5, pp. 522–7, Dec. 2005.

[29] T. Baumgartner, M. Heinrichs, A. Vonlanthen, U. Fischbacher, and E. Fehr, "Oxytocin shapes the neural circuitry of trust and trust adaptation in humans.," *Neuron*, vol. 58, no. 4, pp. 639–50, May 2008.

[30] O. Weisman, O. Zagoory-Sharon, I. Schneiderman, I. Gordon, and R. Feldman, "Plasma oxytocin distributions in a large cohort of women and men and their gender-specific

associations with anxiety.," *Psychoneuroendocrinology*, vol. 38, no. 5, pp. 694–701, May 2013.

[31] M. Tops, J. M. van Peer, J. Korf, A. A. Wijers, and D. M. Tucker, "Anxiety, cortisol, and attachment predict plasma oxytocin.," *Psychophysiology*, vol. 44, no. 3, pp. 444–9, May 2007.

[32] A. Frasch, T. Zetzsche, A. Steiger, and G. F. Jirikowski, "Reduction of plasma oxytocin levels in patients suffering from major depression.," *Adv. Exp. Med. Biol.*, vol. 395, pp. 257–8, Jan. 1995.

[33] L. H. Rubin, C. S. Carter, L. Drogos, H. Pournajafi-Nazarloo, J. A. Sweeney, and P. M. Maki, "Peripheral oxytocin is associated with reduced symptom severity in schizophrenia.," *Schizophr. Res.*, vol. 124, no. 1–3, pp. 13–21, Dec. 2010.

[34] N. M. Corrigan, T. Richards, S. J. Webb, M. Murias, K. Merkle, N. M. Kleinhans, L. C. Johnson, A. Poliakov, E. Aylward, and G. Dawson, "An investigation of the relationship between fMRI and ERP source localized measurements of brain activity during face processing.," *Brain Topogr.*, vol. 22, no. 2, pp. 83–96, Sep. 2009.

[35] M. E. Rich and H. K. Caldwell, "A Role for Oxytocin in the Etiology and Treatment of Schizophrenia.," *Front. Endocrinol. (Lausanne).*, vol. 6, p. 90, Jan. 2015.

[36] M. Olff, S. B. J. Koch, L. Nawijn, J. L. Frijling, M. Van Zuiden, and D. J. Veltman, "Social support, oxytocin, and PTSD.," *Eur. J. Psychotraumatol.*, vol. 5, p. 26513, Jan. 2014.

[37] A. Clarici, S. Pellizzoni, S. Guaschino, S. Alberico, S. Bembich, R. Giuliani, A. Short, G. Guarino, and J. Panksepp, "Intranasal adminsitration of oxytocin in postnatal depression: implications for psychodynamic psychotherapy from a randomized double-blind pilot study," *Front. Psychol.*, vol. 6, no. April, p. 426, Apr. 2015.

[38] R. Wigton, J. Radua, P. Allen, B. Averbeck, A. Meyer-lindenberg, P. Mcguire, S. S. Shergill, and P. Fusar-poli, "Neurophysiological effects of acute oxytocin administration : systematic review and meta-analysis of placebo-controlled imaging studies," *J Psychiatry Neurosci*, vol. 40, no. 1, pp. 1–23, 2015.

[39] C. K. W. De Dreu, L. L. Greer, M. J. J. Handgraaf, S. Shalvi, G. A. Van Kleef, M. Baas, F. S. Ten Velden, E. Van Dijk, and S. W. W. Feith, "The neuropeptide oxytocin regulates parochial altruism in intergroup conflict among humans.," *Science*, vol. 328, no. 5984, pp. 1408–11, Jun. 2010.

[40] M. Olff, J. L. Frijling, L. D. Kubzansky, B. Bradley, M. A. Ellenbogen, C. Cardoso, J. A. Bartz, J. R. Yee, and M. van Zuiden, "The role of oxytocin in social bonding, stress regulation and mental health: an update on the moderating effects of context and interindividual differences.," *Psychoneuroendocrinology*, vol. 38, no. 9, pp. 1883–94, Sep. 2013.

[41] C. A. Pedersen and A. J. Prange, "Induction of maternal behavior in virgin rats after intracerebroventricular administration of oxytocin," *Proc. Natl. Acad. Sci.*, vol. 76, no. 12, pp. 6661–6665, Dec. 1979.

[42] H. E. Ross and L. J. Young, "Oxytocin and the neural mechanisms regulating social cognition and affiliative behavior.," *Front. Neuroendocrinol.*, vol. 30, no. 4, pp. 534–47, Oct. 2009.

[43] L. Strathearn, P. Fonagy, J. Amico, and P. R. Montague, "Adult attachment predicts maternal brain and oxytocin response to infant cues.," *Neuropsychopharmacology*, vol. 34, no. 13, pp. 2655–66, Dec. 2009.

[44] M. Heinrichs, B. von Dawans, and G. Domes, “Oxytocin, vasopressin, and human social behavior,” *Frontiers in Neuroendocrinology*, vol. 30, no. 4. pp. 548–557, 2009.

[45] A. A. Marsh, H. H. Yu, D. S. Pine, E. K. Gorodetsky, D. Goldman, and R. J. R. Blair, “The influence of oxytocin administration on responses to infant faces and potential moderation by OXTR genotype.,” *Psychopharmacology (Berl).*, vol. 224, no. 4, pp. 469–76, Dec. 2012.

[46] M. L. Glocker, D. D. Langleben, K. Ruparel, J. W. Loughead, R. C. Gur, and N. Sachser, “Baby Schema in Infant Faces Induces Cuteness Perception and Motivation for Caretaking in Adults.,” *Ethology*, vol. 115, no. 3, pp. 257–263, Mar. 2009.

[47] L. Luo, X. Ma, X. Zheng, W. Zhao, L. Xu, B. Becker, and K. M. Kendrick, “Neural systems and hormones mediating attraction to infant and child faces.,” *Front. Psychol.*, vol. 6, p. 970, Jan. 2015.

[48] M. M. E. Riem, M. J. Bakermans-Kranenburg, S. Pieper, M. Tops, M. A. S. Boksem, R. R. J. M. Vermeiren, M. H. van Ijzendoorn, and S. A. R. B. Rombouts, “Oxytocin modulates amygdala, insula, and inferior frontal gyrus responses to infant crying: a randomized controlled trial.,” *Biol. Psychiatry*, vol. 70, no. 3, pp. 291–7, Aug. 2011.

[49] N. Landi, J. Montoya, H. Kober, H. J. V Rutherford, W. E. Mencl, P. D. Worhunsky, M. N. Potenza, and L. C. Mayes, “Maternal neural responses to infant cries and faces: relationships with substance use.,” *Front. psychiatry*, vol. 2, p. 32, Jan. 2011.

[50] L. K. Noll, L. C. Mayes, and H. J. V Rutherford, “Investigating the impact of parental status and depression symptoms on the early perceptual coding of infant faces: an event-related potential study.,” *Soc. Neurosci.*, vol. 7, no. 5, pp. 525–36, Jan. 2012.

[51] L. C. Mayes, “Arousal regulation, emotional flexibility, medial amygdala function, and the impact of early experience: comments on the paper of Lewis et al.,” *Ann. N. Y. Acad. Sci.*, vol. 1094, pp. 178–92, Dec. 2006.

[52] N. D. Volkow, J. S. Fowler, G. J. Wang, R. Hitzemann, J. Logan, D. J. Schlyer, S. L. Dewey, and A. P. Wolf, “Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers.,” *Synapse*, vol. 14, no. 2, pp. 169–77, Jun. 1993.

[53] K. Deater-Deckard, M. D. Sewell, S. A. Petrill, and L. A. Thompson, “Maternal working memory and reactive negativity in parenting.,” *Psychol. Sci.*, vol. 21, no. 1, pp. 75–9, Jan. 2010.

[54] C. A. Stratakis and G. P. Chrousos, “Neuroendocrinology and pathophysiology of the stress system.,” *Ann. N. Y. Acad. Sci.*, vol. 771, pp. 1–18, Dec. 1995.

[55] W. R. Lovallo, “Cortisol secretion patterns in addiction and addiction risk.,” *Int. J. Psychophysiol.*, vol. 59, no. 3, pp. 195–202, Mar. 2006.

[56] K. Uvänas-Moberg, I. Arn, and D. Magnusson, “The psychobiology of emotion: the role of the oxytocinergic system.,” *Int. J. Behav. Med.*, vol. 12, no. 2, pp. 59–65, Jan. 2005.

[57] M. Jankowski, F. Hajjar, S. A. Kawas, S. Mukaddam-Daher, G. Hoffman, S. M. McCann, and J. Gutkowska, “Rat heart: a site of oxytocin production and action.,” *Proc. Natl. Acad. Sci. U. S. A.*, vol. 95, no. 24, pp. 14558–63, Nov. 1998.

[58] M. Jankowski, D. Wang, F. Hajjar, S. Mukaddam-Daher, S. M. McCann, and J. Gutkowska, “Oxytocin and its receptors are synthesized in the rat vasculature.,” *Proc. Natl. Acad. Sci. U. S. A.*, vol. 97, no. 11, pp. 6207–11, May 2000.

[59] K. M. Grewen and K. C. Light, “Plasma oxytocin is related to lower cardiovascular and sympathetic reactivity to stress.,” *Biol. Psychol.*, vol. 87, no. 3, pp. 340–9, Jul. 2011.

[60] P. Kim, J. F. Leckman, L. C. Mayes, R. Feldman, X. Wang, and J. E. Swain, “The plasticity of human maternal brain: Longitudinal changes in brain anatomy during the early postpartum period.,” *Behav. Neurosci.*, vol. 124, no. 5, pp. 695–700, Oct. 2010.

[61] L. Strathearn, J. Li, P. Fonagy, and P. R. Montague, “What’s in a smile? Maternal brain responses to infant facial cues.,” *Pediatrics*, vol. 122, no. 1, pp. 40–51, Jul. 2008.

[62] J. P. Lorberbaum, J. D. Newman, J. R. Dubno, A. R. Horwitz, Z. Nahas, C. C. Teneback, C. W. Bloomer, D. E. Bohning, D. Vincent, M. R. Johnson, N. Emmanuel, O. Brawman-Mintzer, S. W. Book, R. B. Lydiard, J. C. Ballenger, and M. S. George, “Feasibility of using fMRI to study mothers responding to infant cries.,” *Depress. Anxiety*, vol. 10, no. 3, pp. 99–104, Jan. 1999.

[63] J. P. Lorberbaum, J. D. Newman, A. R. Horwitz, J. R. Dubno, R. B. Lydiard, M. B. Hamner, D. E. Bohning, and M. S. George, “A potential role for thalamocingulate circuitry in human maternal behavior.,” *Biol. Psychiatry*, vol. 51, no. 6, pp. 431–45, Mar. 2002.

[64] J. B. Nitschke, E. E. Nelson, B. D. Rusch, A. S. Fox, T. R. Oakes, and R. J. Davidson, “Orbitofrontal cortex tracks positive mood in mothers viewing pictures of their newborn infants.,” *Neuroimage*, vol. 21, no. 2, pp. 583–92, Feb. 2004.

[65] M. L. Kringelbach, A. Lehtonen, S. Squire, A. G. Harvey, M. G. Craske, I. E. Holliday, A. L. Green, T. Z. Aziz, P. C. Hansen, P. L. Cornelissen, and A. Stein, “A specific and rapid neural signature for parental instinct.,” *PLoS One*, vol. 3, no. 2, p. e1664, Jan. 2008.

[66] A. Bartels and S. Zeki, “The neural correlates of maternal and romantic love.,” *Neuroimage*, vol. 21, no. 3, pp. 1155–66, Mar. 2004.

[67] M. Rocchetti, J. Radua, Y. Paloyelis, L.-A. Xenaki, M. Frascarelli, E. Caverzasi, P. Politi, and P. Fusar-Poli, “Neurofunctional maps of the ‘maternal brain’ and the effects of oxytocin: a multimodal voxel-based meta-analysis.,” *Psychiatry Clin. Neurosci.*, vol. 68, no. 10, pp. 733–51, Oct. 2014.

[68] A. M. Proverbio, V. Brignone, S. Matarazzo, M. Del Zotto, and A. Zani, “Gender and parental status affect the visual cortical response to infant facial expression.,” *Neuropsychologia*, vol. 44, no. 14, pp. 2987–99, Jan. 2006.

[69] H. A. Rupp, T. W. James, E. D. Ketterson, D. R. Sengelaub, B. Ditzen, and J. R. Heiman, “Amygdala response to negative images in postpartum vs nulliparous women and intranasal oxytocin.,” *Soc. Cogn. Affect. Neurosci.*, vol. 9, no. 1, pp. 48–54, Jan. 2014.

[70] M. M. E. Riem, A. Voorthuis, M. J. Bakermans-Kranenburg, and M. H. van Ijzendoorn, “Pity or peanuts? Oxytocin induces different neural responses to the same infant crying labeled as sick or bored,” *Dev. Sci.*, vol. 17, no. 2, pp. 248–256, Mar. 2014.

[71] H. A. Rupp, T. W. James, E. D. Ketterson, D. R. Sengelaub, B. Ditzen, and J. R. Heiman, “Lower sexual interest in postpartum women: relationship to amygdala activation and intranasal oxytocin.,” *Horm. Behav.*, vol. 63, no. 1, pp. 114–21, Jan. 2013.

[72] T. R. Insel, “Translating Oxytocin Neuroscience to the Clinic: A National Institute of Mental Health Perspective,” *Biol. Psychiatry*, vol. 79, no. 3, pp. 153–154, Nov. 2015.

[73] N. Scott, M. Prigge, O. Yizhar, and T. Kimchi, “A sexually dimorphic hypothalamic circuit controls maternal care and oxytocin secretion,” *Nature*, vol. 525, no. 7570, pp. 519–522,

Sep. 2015.

[74] G. Domes, A. Lischke, C. Berger, A. Grossmann, K. Hauenstein, M. Heinrichs, and S. C. Herpertz, "Effects of intranasal oxytocin on emotional face processing in women.," *Psychoneuroendocrinology*, vol. 35, no. 1, pp. 83–93, Jan. 2010.

[75] C. Cardoso, A.-M. Linnen, R. Joober, and M. A. Ellenbogen, "Coping style moderates the effect of intranasal oxytocin on the mood response to interpersonal stress."

[76] B. Ditzen, U. M. Nater, M. Schaer, R. La Marca, G. Bodenmann, U. Ehlert, and M. Heinrichs, "Sex-specific effects of intranasal oxytocin on autonomic nervous system and emotional responses to couple conflict.," *Soc. Cogn. Affect. Neurosci.*, vol. 8, no. 8, pp. 897–902, Dec. 2013.

[77] D. Scheele, N. Striepens, K. M. Kendrick, C. Schwering, J. Noelle, A. Wille, T. E. Schläpfer, W. Maier, and R. Hurlemann, "Opposing effects of oxytocin on moral judgment in males and females.," *Hum. Brain Mapp.*, vol. 35, no. 12, pp. 6067–76, Dec. 2014.

[78] J. K. Rilling, A. C. Demarco, P. D. Hackett, X. Chen, P. Gautam, S. Stair, E. Haroon, R. Thompson, B. Ditzen, R. Patel, and G. Pagnoni, "Sex differences in the neural and behavioral response to intranasal oxytocin and vasopressin during human social interaction.," *Psychoneuroendocrinology*, vol. 39, pp. 237–48, Jan. 2014.

[79] A. Campbell, T. Ruffman, J. E. Murray, and P. Glue, "Oxytocin improves emotion recognition for older males.," *Neurobiol. Aging*, vol. 35, no. 10, pp. 2246–8, Oct. 2014.

[80] C. Cardoso, M. A. Ellenbogen, and A.-M. Linnen, "The effect of intranasal oxytocin on perceiving and understanding emotion on the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT).," *Emotion*, vol. 14, no. 1, pp. 43–50, Feb. 2014.

[81] M. A. Ellenbogen, A.-M. Linnen, R. Grumet, C. Cardoso, and R. Joober, "The acute effects of intranasal oxytocin on automatic and effortful attentional shifting to emotional faces.," *Psychophysiology*, vol. 49, no. 1, pp. 128–37, Jan. 2012.

[82] S. Leknes, J. Wessberg, D.-M. Ellingsen, O. Chelnokova, H. Olausson, and B. Laeng, "Oxytocin enhances pupil dilation and sensitivity to 'hidden' emotional expressions.," *Soc. Cogn. Affect. Neurosci.*, vol. 8, no. 7, pp. 741–9, Oct. 2013.

[83] S. L. Evans, O. D. Monte, P. Noble, and B. B. Averbeck, "Intranasal oxytocin effects on social cognition: A critique," *Brain Res.*, vol. 1580, pp. 69–77, 2013.

[84] S. J. Luck, *An introduction to the event-related potential technique.* Cambridge: MIT Press, 2005.

[85] G. G. Knyazev, "Motivation, emotion, and their inhibitory control mirrored in brain oscillations," *Neurosci. Biobehav. Rev.*, vol. 31, no. 3, pp. 377–395, 2007.

[86] R. Huffmeijer, L. R. A. Alink, M. Tops, M. J. Bakermans-Kranenburg, and M. H. van IJzendoorn, "Asymmetric frontal brain activity and parental rejection predict altruistic behavior: moderation of oxytocin effects.," *Cogn. Affect. Behav. Neurosci.*, vol. 12, no. 2, pp. 382–92, Jun. 2012.

[87] D. J. L. G. Schutter and G. G. Knyazev, "Cross-frequency coupling of brain oscillations in studying motivation and emotion," *Motiv. Emot.*, vol. 36, no. 1, pp. 46–54, 2012.

[88] D. J. L. G. Schutter and J. Van Honk, "Salivary cortisol levels and the coupling of midfrontal delta-beta oscillations," *Int. J. Psychophysiol.*, vol. 55, no. 1, pp. 127–129, 2005.

[89] J. M. van Peer, K. Roelofs, and P. Spinhoven, “Cortisol administration enhances the coupling of midfrontal delta and beta oscillations,” *Int. J. Psychophysiol.*, vol. 67, no. 2, pp. 144–150, 2008.

[90] V. Miskovic, D. A. Moscovitch, D. L. Santesso, R. E. McCabe, M. M. Antony, and L. A. Schmidt, “Changes in EEG cross-frequency coupling during cognitive behavioral therapy for social anxiety disorder.,” *Psychol. Sci.*, vol. 22, no. 4, pp. 507–516, 2011.

[91] M. Eimer, “The face-specific N170 component reflects late stages in the structural encoding of faces.,” *Neuroreport*, vol. 11, no. 10, pp. 2319–24, Jul. 2000.

[92] S. A. Hillyard, “Event-Related Potentials (ERPs) and Cognitive Processing,” in *Encyclopedia of Neuroscience*, L. R. Squire, Ed. San Diego: Elsevier, 2009, pp. 13–18.

[93] O. Weisman, R. Feldman, and A. Goldstein, “Parental and romantic attachment shape brain processing of infant cues,” *Biol. Psychol.*, vol. 89, no. 3, pp. 533–538, Mar. 2012.

[94] M. J. Rodrigo, I. León, I. Quiñones, A. Lage, S. Byrne, and M. A. Bobes, “Brain and personality bases of insensitivity to infant cues in neglectful mothers: An event-related potential study,” *Dev. Psychopathol.*, vol. 23, no. 01, pp. 163–176, Feb. 2011.

[95] A. N. Maupin, N. J. Hayes, L. C. Mayes, and H. J. V Rutherford, “The Application of Electroencephalography to Investigate the Neural Bases of Parenting: A Review.,” *Parent. Sci. Pract.*, vol. 15, no. 1, pp. 9–23, Jan. 2015.

[96] J. Polich, “Updating P300: an integrative theory of P3a and P3b.,” *Clin. Neurophysiol.*, vol. 118, no. 10, pp. 2128–48, Oct. 2007.

[97] G. Hajcak, A. MacNamara, and D. M. Olvet, “Event-Related Potentials, Emotion, and Emotion Regulation: An Integrative Review,” *Dev. Neuropsychol.*, vol. 35, no. 2, pp. 129–155, Jan. 2010.

[98] R. W. Carlson, L. B. Aknin, and M. Liotti, “When is giving an impulse? An ERP investigation of intuitive prosocial behavior.,” *Soc. Cogn. Affect. Neurosci.*, p. nsv077, Jun. 2015.

[99] H. Doi and K. Shinohara, “Event-related potentials elicited in mothers by their own and unfamiliar infants’ faces with crying and smiling expression.,” *Neuropsychologia*, vol. 50, no. 7, pp. 1297–307, Jun. 2012.

[100] R. Huffmeijer, L. R. A. Alink, M. Tops, K. M. Grewen, K. C. Light, M. J. Bakermans-Kranenburg, and M. H. van IJzendoorn, “The impact of oxytocin administration and maternal love withdrawal on event-related potential (ERP) responses to emotional faces with performance feedback,” *Horm. Behav.*, vol. 63, no. 3, pp. 399–410, Mar. 2013.

[101] S. M. Malak, M. J. Crowley, L. C. Mayes, and H. J. V Rutherford, “Maternal anxiety and neural responses to infant faces.,” *J. Affect. Disord.*, vol. 172C, pp. 324–330, Oct. 2014.

[102] P. Vuilleumier and G. Pourtois, “Distributed and interactive brain mechanisms during emotion face perception: evidence from functional neuroimaging.,” *Neuropsychologia*, vol. 45, no. 1, pp. 174–94, Jan. 2007.

[103] J. Bick, M. Dozier, K. Bernard, D. Grasso, and R. Simons, “Foster Mother-Infant Bonding: Associations Between Foster Mothers’ Oxytocin Production, Electrophysiological Brain Activity, Feelings of Commitment, and Caregiving Quality,” *Child Dev.*, vol. 84, no. 3, pp. 826–840, May 2013.

[104] A. T. McLellan, J. S. Cacciola, D. Carise, and T. H. Coyne, “The Addiction Severity Index-

Lite-Clinical Factors Version (ASI-Lite-CF).” The Treatment Research Institute, Philadelphia, 1999.

[105] J. A. Amico, R. Tenicela, J. Johnston, and A. G. Robinson, “A time-dependent peak of oxytocin exists in cerebrospinal fluid but not in plasma of humans,” *J. Clin. Endocrinol. Metab.*, vol. 57, no. 5, pp. 947–951, 1983.

[106] H. Artman, S. Reppert, M. Perlow, S. Swaminathan, T. Oddie, and D. Fisher, “Characterization of the daily oxytocin rhythm in primate cerebrospinal fluid.,” *J. Neurosci.*, vol. 2, no. 5, pp. 598–603, 1982.

[107] M. L. Forsling, H. Montgomery, D. Halpin, R. J. Windle, and D. F. Treacher, “Daily patterns of secretion of neurohypophysial hormones in man: Effect of age.,” *Exp. Physiol.*, vol. 83, no. 3, pp. 409–418, 1998.

[108] C. D. Spielberger, R. L. Gorsuch, R. Lushene, P. R. Vagg, and G. A. Jacobs, *Manual for the State-Trait Anxiety Inventory*. Palo Alto: Consulting Psychologists Press, 1983.

[109] A. T. Beck, R. A. Steer, and G. K. Brown, *Manual for the Beck Depression Inventory–II*. San Antonio: Psychological Corporation, 1996.

[110] S. Cohen, T. Kamarck, and R. Mermelstein, “A global measure of perceived stress.,” *J. Health Soc. Behav.*, vol. 24, no. 4, pp. 385–96, Dec. 1983.

[111] G. Parker, H. Tupling, and L. B. Brown, “A Parental Bonding Instrument,” *Br. J. Med. Psychol.*, vol. 52, no. 1, pp. 1–10, Mar. 1979.

[112] E. MacDonald, M. R. Dadds, J. L. Brennan, K. Williams, F. Levy, and A. J. Cauchi, “A review of safety, side-effects and subjective reactions to intranasal oxytocin in human research.,” *Psychoneuroendocrinology*, vol. 36, no. 8, pp. 1114–26, Sep. 2011.

[113] G. Gratton, M. G. H. Coles, and E. Donchin, “A new method for off-line removal of ocular artifact,” *Electroencephalogr. Clin. Neurophysiol.*, vol. 55, no. 4, pp. 468–484, 1983.

[114] A. S. Geller, J. F. Burke, M. R. Sperling, A. D. Sharan, B. Litt, G. H. Baltuch, T. H. Lucas, and M. J. Kahana, “Eye closure causes widespread low-frequency power increase and focal gamma attenuation in the human electrocorticogram,” *Clin. Neurophysiol.*, vol. 125, no. 9, pp. 1764–1773, 2014.

[115] C. Yan, D. Liu, Y. He, Q. Zou, C. Zhu, X. Zuo, X. Long, and Y. Zang, “Spontaneous brain activity in the default mode network is sensitive to different resting-state conditions with limited cognitive load,” *PLoS One*, vol. 4, no. 5, p. e5743, 2009.

[116] J. H. Steiger, “Tests for comparing elements of a correlation matrix.,” *Psychological Bulletin*, vol. 87, no. 2. pp. 245–251, 1980.

[117] O. Dunn and V. Clark, “Comparison of tests of the equality of dependent correlation coefficients,” *J. Am. Stat. Assoc.*, vol. 66, no. 336, pp. 904–908, 1971.

[118] B. Diedenhofen and J. Musch, “cocor: A comprehensive solution for the statistical comparison of correlations,” *PLoS One*, vol. 10, no. 4, p. e0121945, 2015.

[119] G. Y. Zou, “Toward using confidence intervals to compare correlations.,” *Psychol. Methods*, vol. 12, no. 4, pp. 399–413, 2007.

[120] J. Cohen, “Statistical power analysis for the behavioral sciences,” *Statistical Power Analysis for the Behavioral Sciences*, vol. 2nd. p. 567, 1988.

[121] S. Bentin, T. Allison, A. Puce, E. Perez, and G. McCarthy, "Electrophysiological Studies of Face Perception in Humans," *J. Cogn. Neurosci.*, vol. 8, no. 6, pp. 551–565, Nov. 1996.

[122] C. H. M. Cheung, H. J. V Rutherford, L. C. Mayes, and J. C. McPartland, "Neural responses to faces reflect social personality traits.," *Soc. Neurosci.*, vol. 5, no. 4, pp. 351–9, Jan. 2010.

[123] J. Polich, J. E. Alexander, L. O. Bauer, S. Kuperman, S. Morzorati, S. J. O'Connor, B. Porjesz, J. Rohrbaugh, and H. Begleiter, "P300 topography of amplitude/latency correlations.," *Brain Topogr.*, vol. 9, no. 4, pp. 275–82, Jan. 1997.

[124] D. J. L. G. Schutter and J. Van Honk, "Decoupling of midfrontal delta-beta oscillations after testosterone administration," *Int. J. Psychophysiol.*, vol. 53, no. 1, pp. 71–73, 2004.

[125] R. J. Windle, N. Shanks, S. L. Lightman, and C. D. Ingram, "Central oxytocin administration reduces stress-induced corticosterone release and anxiety behavior in rats," *Endocrinology*, vol. 138, no. 7, pp. 2829–2834, 1997.

[126] G. G. Knyazev, J. Y. Slobodskoj-Plusnin, and a. V. Bocharov, "Event-related delta and theta synchronization during explicit and implicit emotion processing," *Neuroscience*, vol. 164, no. 4, pp. 1588–1600, 2009.

[127] S. M. Gorka, D. A. Fitzgerald, I. Labuschagne, A. Hosanagar, A. G. Wood, P. J. Nathan, and K. L. Phan, "Oxytocin modulation of amygdala functional connectivity to fearful faces in generalized social anxiety disorder," *Neuropsychopharmacology*, vol. 40, no. April, pp. 1–31, 2014.

[128] R. H. Bennett, D. Z. Bolling, L. C. Anderson, K. a. Pelphrey, and M. D. Kaiser, "fNIRS detects temporal lobe response to affective touch," *Soc. Cogn. Affect. Neurosci.*, vol. 9, no. 4, pp. 470–476, 2014.

[129] J. V Haxby, E. A. Hoffman, and M. I. Gobbini, "The distributed human neural system for face perception," *Trends Cogn. Sci.*, vol. 4, no. 6, pp. 223–233, 2000.

[130] B. J. Liddell, K. J. Brown, A. H. Kemp, M. J. Barton, P. Das, A. Peduto, E. Gordon, and L. M. Williams, "A direct brainstem-amygdala-cortical 'alarm' system for subliminal signals of fear," *Neuroimage*, vol. 24, no. 1, pp. 235–243, 2005.

[131] C. Wong and J. Gallate, "The function of the anterior temporal lobe: A review of the empirical evidence," *Brain Res.*, vol. 1449, pp. 94–116, 2012.

[132] M. Corbetta and G. L. Shulman, "Control of goal-directed and stimulus-driven attention in the brain.," *Nat. Rev. Neurosci.*, vol. 3, no. 3, pp. 201–215, 2002.

[133] M. I. Posner, J. A. Walker, F. A. Friedrich, and R. D. Rafal, "How do the parietal lobes direct covert attention?," *Neuropsychologia*, vol. 25, no. 1A, pp. 135–145, 1987.

[134] P. Putman, "Resting state EEG delta-beta coherence in relation to anxiety, behavioral inhibition, and selective attentional processing of threatening stimuli," *Int. J. Psychophysiol.*, vol. 80, no. 1, pp. 63–68, 2011.

[135] W.-J. Huang, W.-W. Chen, and X. Zhang, "The neurophysiology of P 300--an integrated review.," *Eur. Rev. Med. Pharmacol. Sci.*, vol. 19, no. 8, pp. 1480–8, Apr. 2015.

[136] B. J. Marlin, M. Mitre, J. A. D'amour, M. V. Chao, and R. C. Froemke, "Oxytocin enables maternal behaviour by balancing cortical inhibition," *Nature*, vol. 520, no. 7548, pp. 499–504, Apr. 2015.

[137] M. Purhonen, R. Kilpeläinen-Lees, a Pääkkönen, H. Yppärilä, J. Lehtonen, and J. Karhu,

"Effects of maternity on auditory event-related potentials to human sound.," *Neuroreport*, vol. 12, no. 13, pp. 2975–2979, Sep. 2001.

[138] G. Herzmann, C. W. Bird, M. Freeman, and T. Curran, "Effects of oxytocin on behavioral and ERP measures of recognition memory for own-race and other-race faces in women and men," *Psychoneuroendocrinology*, vol. 38, no. 10, pp. 2140–2151, Oct. 2013.

[139] H. Walum, I. D. Waldman, and L. J. Young, "Statistical and Methodological Considerations for the Interpretation of Intranasal Oxytocin Studies.," *Biol. Psychiatry*, vol. 79, no. 3, pp. 251–257, Jun. 2015.

[140] M. H. Van Ijzendoorn, R. Huffmeijer, L. R. A. Alink, M. J. Bakermans-Kranenburg, and M. Tops, "The impact of oxytocin administration on charitable donating is moderated by experiences of parental love-withdrawal," *Front. Psychol.*, vol. 2, no. OCT, pp. 1–8, 2011.

[141] A. Perry, S. Bentin, I. Shalev, S. Israel, F. Uzefovsky, D. Bar-On, and R. P. Ebstein, "Intranasal oxytocin modulates EEG mu/alpha and beta rhythms during perception of biological motion," *Psychoneuroendocrinology*, vol. 35, no. 10, pp. 1446–1453, Nov. 2010.

[142] F. Darvas, K. J. Miller, R. P. N. Rao, and J. G. Ojemann, "Nonlinear phase-phase cross-frequency coupling mediates communication between distant sites in human neocortex.," *J. Neurosci.*, vol. 29, no. 2, pp. 426–435, 2009.

[143] R. T. Canolty and R. T. Knight, "The functional role of cross-frequency coupling.," *Trends Cogn. Sci.*, vol. 14, no. 11, pp. 506–15, Nov. 2010.