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Intranasal oxytocin decreases cross-frequency coupling of neural oscillations at rest

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ABSTRACT

Recent research has suggested a role for the hormone oxytocin in social cognition and behavior. Administration of intranasal oxytocin modulates multiple brain regions during experimental tasks; however, the neural mechanisms that underscore the changes associated with oxytocin administration are yet to be fully elucidated. In a double-blind placebo controlled design using electroencephalography, the effects of intranasal oxytocin on neural oscillations (delta, theta, alpha, beta) and their coupling during the resting state were examined. Prior work suggested that coupling of slow and fast waves are indicative of the integration of motivational and cognitive processes. While neural oscillations were unaffected by oxytocin relative to placebo administration; oxytocin decreased delta-beta, delta-alpha, theta-alpha, and theta-beta coupling. These findings suggest that one mechanism through which intranasal oxytocin may modulate brain and behavior is through affecting the cross-frequency coupling of neural oscillations, a phenomenon that has been associated with specific cognitive and motivational states.

1. Introduction

Oxytocin is a neuropeptide hormone produced in the hypothalamus. While it has been well established that oxytocin plays a central role in parturition and lactation, more recent research has focused on the role of oxytocin in social behavior (Guastella and MacLeod, 2012). Indeed, an increasing number of studies have examined the consequences of intranasal administration of oxytocin on social cognition as measured by behavioral and functional neuroimaging methodologies (Evans et al., 2013). Critically, the neural basis of these oxytocin effects is not known. Animal studies have documented anxiolytic effects of oxytocin, decreasing corticosterone and behavioral responses to stress (Windle et al., 1997), and human studies have identified a host of brain regions, primarily in male participants, that may be modulated by intranasal oxytocin administration (Wigton et al., 2015). Modulation of these brain regions have been observed in the functional connectivity between subcortical and cortical structures (Gorka et al., 2014), as well as in those brain regions engaged with processing negatively-valenced stimuli (Heinrichs et al., 2009).

Notably, in human studies, both anxiolytic and anxiogenic effects of oxytocin have been reported (e.g., Eckstein et al., 2015; Grillon et al., 2013); however, these contradictory findings may reflect the type of affective response elicited by variations in experimental tasks. Contextual factors in human studies, including the task employed to elicit stress and the population under examination, may also differentially impact intranasal oxytocin modulation of the stress response (Cardoso et al., 2014). Despite the variability in these intranasal oxytocin effects, the experimental and clinical utility of administering oxytocin (Bakermans-Kranenburg and van IJzendoorn, 2013), potentially through decreasing stress, anxiety, and processing of negative affect, highlight that a more mechanistic and nuanced understanding of how this neuropeptide may be modulating brain functioning is required. Given the apparent complexities of oxytocin effects on brain and behavior, our understanding of oxytocin modulation on brain functioning would be greatly enhanced by measurement in non-social contexts (Grillon et al., 2013).

Most intranasal oxytocin studies have employed functional magnetic resonance imaging (fMRI), a technique that relies upon changes in blood oxygenation levels to index changes in brain functioning. While fMRI data may converge with neural activity (Logothetis et al., 2001), electroencephalography (EEG) represents a valuable tool in supplementing this existing imaging data. It affords the opportunity to more directly measure indices of neuronal activity, namely post-synaptic potentials of cortical pyramidal neurons (Luck, 2005). This tightly

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coupled neural correlate can be measured as oscillations of varying frequency: slow waves (e.g., delta, theta) are thought to reflect subcortical emotion and motivational processes, whereas fast waves (e.g., alpha, beta) are thought to reflect more cortical cognitive control processes (Knyazev, 2007). Few studies have examined how oxytocin, relative to placebo, administration affects neural oscillations as measured by EEG. One study reported that administration of oxytocin was associated with increased synchrony of alpha oscillations during a social coordination task (Mu et al., 2016). A second study reported that oxytocin, relative to placebo, administration resulted in enhanced alpha/mu and beta suppression measured during a biological motion paradigm (Perry et al., 2010). Therefore, oxytocin administration may modulate neural oscillations elicited during participation in socially-relevant tasks.

While it is possible to examine individual frequency bands and their associations with cognition and behavior, interest has increasingly focused on cross-frequency coupling (measured as band power correlations) between slow wave and fast wave oscillations. This cross-frequency approach is thought to be beneficial for more fully understanding complex brain functions (Schutter and Knyazev, 2012). Across the frequency spectrum, delta-beta coupling has been the most widely studied, and is thought to reflect an interface of emotional or motivational systems and cognition (Knyazev, 2007). Support for this notion can be drawn from studies examining delta-beta correlations when the interplay of affect and cognition may be compromised, primarily in relation to increased levels of stress and anxiety. For instance, increased delta-beta coupling is associated both with higher basal cortisol levels (Schutter and Van Honk, 2005) and the administration of cortisol – a coupling effect that was amplified in participants reporting higher levels of behavioral inhibition (van Peer et al., 2008), a characteristic which is associated with anxiety (Gray, 1982). Furthermore, greater delta-beta coupling has been associated with higher levels of state anxiety in anxiogenic contexts (Knyazev, 2011), while the treatment of anxiety has been associated with decreased delta-beta coupling (Miskovic et al., 2011a). In a preliminary report, children born to parents diagnosed with social phobia also had greater delta-beta coupling than children born to non-anxious parents (Miskovic et al., 2011b).

Although widely studied, cross-frequency coupling is not limited to the examination of delta-beta associations. For instance, delta-alpha coupling has also been assessed. Alpha activity is implicated in visual attention and is thought to mediate top-down control of processing visual stimuli through inhibition (Rihs et al., 2007). Greater delta-alpha coupling has also been associated with higher self-reported levels of behavioral inhibition in adults (Knyazev and Slobodskaya, 2003), with lower delta-alpha coupling being associated with increased levels of self-reported behavioral activation, extraversion, and conduct problems (Knyazev et al., 2003). Additionally, increased theta-gamma coupling during a reward-based task has been reported in participants high in behavioral activation (Knyazev and Slobodskoj-Plusnin, 2007). Theta is particularly relevant to the current study, given that increased theta is associated with higher levels of arousal (e.g., Del Percio et al., 2017) and experience of social distress (e.g., van Noordt et al., 2015). Given that oxytocin may modulate stress and anxiety (Cardoso et al., 2014; Eckstein et al., 2015; Grillon et al., 2013), theta, and theta coupling, may also be affected by the administration of oxytocin. Taken together, these studies indicate the importance of examining cross-frequency coupling between slow and fast wave oscillations beyond delta and beta to gain a more nuanced understanding of the potential spectral boundary conditions through which oxytocin, relative to placebo, may modulate neural oscillations.

In the current study, EEG data was recorded from healthy women at rest when their eyes were open and closed. A female only sample was employed given the limited knowledge of intranasal oxytocin effects on neural activity in this group, particularly when employing EEG (Mu et al., 2016; Perry et al., 2010; Wigton et al., 2015), and the importance of understanding oxytocin modulation across sexes. In one visit, women received oxytocin, and in a second visit they received placebo (randomized administration). Spectral powers (delta, theta, alpha, beta) were first examined within the two resting state conditions. Past research has not shown changes in delta and beta oscillations following hormonal manipulations; therefore, it was anticipated that these individual frequency bands would be unaffected by oxytocin administration. Given oxytocin modulation of alpha activity in prior task-based EEG studies, as well as decreases in theta being associated with less emotional arousal and distress, we hypothesized that alpha and theta would be modulated by oxytocin, relative to placebo.

Given the wealth of studies evidencing the malleability of delta-beta coupling to experimental conditions and individual difference measures, we first analyzed the impact of intranasal oxytocin on delta-beta coupling. We next examined cross-frequency coupling between neighboring spectral bands (theta, alpha) to determine the specificity of oxytocin modulation. It was hypothesized that administration of intranasal oxytocin, relative to placebo, would decrease delta-beta coupling, consistent with its association with decreased stress and anxiety. We also anticipated that oxytocin modulation would extend to other neighboring slow-fast wave associations, consistent with a broader role of cross-frequency coupling of neural oscillations engaged with cognitive and affective processes.

2. Materials and methods

2.1. Participants

The Human Investigations Committee at Yale School of Medicine approved all procedures. Twenty-six healthy nulliparous women were recruited through flyers posted in the community for two study visits. Employing a female-only sample provided the opportunity to gain greater insight into intranasal oxytocin effects on neural activity in women, an approach that is not typically explored given the methodological constraints of hormone-based studies in females. Telephone screening was conducted to determine eligibility. Exclusion criteria included pregnancy, use of any hormonal birth control, clinically significant medical or psychiatric illnesses, including blood pressure instability or central nervous system disease, as well as use of psychotropic medications. Two participants completed only one session and 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; mean weight 61 kg; SD = 11 kg), aged 18–31 years (M = 23.3; SD = 3.3), who were all high school graduates (M education 16.7 years; 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). All participants gave written informed consent and were compensated $80 for each visit ($160 total).

2.2. Procedure

Two study visits were scheduled four weeks apart to facilitate continuity in menstrual cycle phase (ascertained by participants reporting the last day of their menstrual cycle). During their study visits, approximately half of participants were in their luteal phase. Visits were conducted between 1200 h and 1500 h to minimize the influence of diurnal variations in oxytocin levels (Amico et al., 1983; Artman et al., 1982; Forsling et al., 1998). Participants were instructed not to exercise or drink alcohol during the 24 h prior to the visit, not to drink caffeinated beverages 12 h prior to the visit, and to refrain from smoking and eating 2 h prior to the visit. Upon arrival, blood pressure was assessed and participants completed a urine toxicology and pregnancy test. No participants were pregnant or evidenced recent substance use in their urine toxicology. Given the intranasal route of administration, all participants completed a nasal questionnaire (www.