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Intranasal oxytocin impedes the ability to ignore task-irrelevant facial expressions of sadness in students with depressive symptoms

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Summary The administration of oxytocin promotes prosocial behavior in humans. The mechanism by which this occurs is unknown, but it likely involves changes in social information processing. In a randomized placebo-controlled study, we examined the influence of intranasal oxytocin and placebo on the interference control component of inhibition (i.e. ability to ignore task-irrelevant information) in 102 participants using a negative affective priming task with sad, angry, and happy faces. In this task, participants are instructed to respond to a facial expression of emotion while simultaneously ignoring another emotional face. On the subsequent trial, the previously-ignored emotional valence may become the emotional valence of the target face. Inhibition is operationalized as the differential delay between responding to a previously-ignored emotional valence and responding to an emotional valence unrelated to the previous one. Although no main effect of drug administration on inhibition was observed, a drug $\times$ depressive symptom interaction ($\beta = -0.25$; $t = -2.6$, $p < 0.05$) predicted the inhibition of sad faces. Relative to placebo, participants with high depression scores who were administered oxytocin were unable to inhibit the processing of sad faces. There was no relationship between drug administration and inhibition among those with low depression scores. These findings are consistent with increasing evidence that oxytocin alters social information processing in ways that have both positive and negative social outcomes. Because elevated depression scores are associated with an increased risk for major depressive disorder, difficulties inhibiting mood-congruent stimuli following oxytocin administration may be associated with risk for depression.

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Oxytocin is well known for its functions in periphery which include eliciting uterine contractions during labor and milk ejection during lactation. However, it also acts on receptors distributed widely in the brain, including the limbic-hypothalamic system, midbrain regions, and brainstem (Gimpl and Fahrenholz, 2001; Landgraf and Neumann, 2004). Oxytocin is involved in promoting social affiliation across a variety of different species through its actions in the central nervous system (Insel, 1997; Carter et al., 2007; Campbell, 2008; Donaldson and Young, 2008; Neumann, 2008; Ross and Young, 2009). It has well-established effects on maternal care (Pedersen, 1997; Kendrick, 2000; Bosch, 2011) and pair bonding (Young et al., 2001; Insel, 2010) through its actions at midbrain, hypothalamic and other limbic sites. It was recently reported that oxytocin also facilitates naturally-occurring prosocial behavior (i.e. preference for a social stimulus versus a non-social stimulus) in rat and mice (Lukas et al., 2011). A number of studies in humans report that oxytocin facilitates positive interactions and trust in a variety of contexts (Kosfeld et al., 2005; Baumgartner et al., 2008; Ditzen et al., 2009; Mikolajczak et al., 2010; Naber et al., 2010). In these studies, the mechanism by which oxytocin facilitates prosocial behavior is not known.

One hypothesis is that oxytocin influences prosocial behavior by altering the processing of social information, perhaps by increasing the salience of social stimuli and attenuating early automatic threat processing that impedes approach behavior. There is some empirical support of this proposal. Animal studies indicate that oxytocin is important for social learning and recognition of conspecific mates and offspring (Neumann, 2008; Higashida et al., 2010). In humans, although oxytocin increased the perceived familiarity of previously seen faces (Rimmele et al., 2009), other studies have found that oxytocin has no effect on memory for faces (Di Simplicio et al., 2009), or that it differentially affects memory depending on the facial expression of emotion (Guastella et al., 2008b; Savaskan et al., 2008; Campbell, 2010). Although its effects on memory are equivocal, oxytocin enhanced the identification of happy faces (Marsh et al., 2010) and words associated with sexuality, bonding, and social relationships (Unkelbach et al., 2008), and increased ratings of trustworthiness and attractiveness when viewing pictures of strangers (Theodoridou et al., 2009). These effects on the detection and appraisal of emotional information may be due to the fact that oxytocin, relative to placebo, elicited longer gaze duration around the eyes than other parts of the face (Guastella et al., 2008a; Gamer et al., 2010). Most of the research in this area has focused on stimulus identification or evaluation tasks, requiring complex elaborative cognitive processing.

Changes in how social signals are processed may occur through changes in the efficiency at which attentional systems select information in a complex environment, and filter or inhibit incoming emotional information. Only a few studies have examined the effects of oxytocin on selective attention (Di Simplicio et al., 2009; Schulze et al., 2011; Ellenbogen et al., 2012), and there are no studies on inhibition. Inhibitory functions, according to recent theory and research (Nigg, 2000; Friedman and Miyake, 2004), are comprised of a number of distinct and heterogeneous components including the ability to withhold a prepotent or dominant behavioral response, to resist or decrease access of intrusive thoughts or images to working memory, and to decrease or suppress interference from distracting information in the current environment. Of particular interest to the present study is the latter component, termed ''interference control''. Inhibitory interference control is central to regulating the content of working memory, particularly for limiting the access of irrelevant information into consciousness and maintaining a coherent stream of thought. This aspect of inhibition is an essential component of selective attention because it enables attention to be allocated to particular foci by suppressing the processing of task-irrelevant information (Posner et al., 1978; Tipper and Cranston, 1985). If interference control is weakened, irrelevant information is believed to enter information processing pathways and working memory, using up limited cognitive resources and triggering ancillary processes (i.e. rumination, fear response, distracting thoughts, etc.) that could impede goal-directed behavior. For example, depressive ruminations or brooding in depressed individuals may represent one such consequence of faulty interference control with respect to sad or dysphoric information (Joormann and Gotlib, 2010; Zetsche and Joormann, 2011).

Individual differences in the interference control aspect of inhibition can be estimated with a negative priming paradigm (Tipper, 1985; Tipper and Cranston, 1985; Joormann, 2004). Negative priming refers to a cognitive phenomenon whereby the response to a stimulus attribute (i.e. emotional valence) that was previously ignored is apparently disrupted or delayed, which has been described as evidence of an inhibitory mechanism of attention. In the modified version of the task, which assesses the inhibition of *emotional* stimuli (Goeleven et al., 2006; Joormann, 2006), participants are instructed to respond to a target stimulus while ignoring a simultaneously presented emotional stimulus that is clearly identified as irrelevant to the task and to be ignored. On the subsequent trial, the emotional valence of the previously-ignored stimulus may become the emotional valence of the target. Inhibition is operationalized as the differential delay between trials requiring participants to respond to a previously ignored emotional valence and trials requiring participants to respond to an emotional valence not presented in the previous trial. These procedures have been used with negative emotional words (Joormann, 2004, 2006) and pictures displaying sad facial expressions (Goeleven et al., 2006; Taylor et al., 2011). Interestingly, difficulties inhibiting irrelevant sad stimuli have been found in dysphoric students (Joormann, 2006; Frings et al., 2007), individuals with a history of depression (Joormann, 2004), and clinically depressed participants (Goeleven et al., 2006; Joormann and Gotlib, 2010). These reports suggest that the inhibition of emotional information may be an important determinant of the regulation of negative emotion, particularly among clinically depressed participants and dysphoric persons who are at increased risk for major depressive disorder.

The present study aimed to address two important issues. First, this is the first study to examine the effects of intranasal oxytocin on the interference control aspect of inhibition. This component of inhibition was assessed with a negative priming task using pictorial facial expressions of negative (sad and angry) and positive affect (happy), known as ''negative affective priming'' (Joormann, 2004). The study complements a previous investigation of attentional shifting