

## The effect of intranasal administration of oxytocin on fear recognition

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### ABSTRACT

The oxytocinergic system has recently been placed amongst the most promising targets for various psychiatric treatments due to its role in prosocial behavior and anxiety reduction. Although recent studies have demonstrated a general effect of administration of oxytocin on emotion recognition, no study to date has examined the effect of oxytocin on each emotion separately. In the present study, a double-blind placebo-controlled crossover design was used in a dynamic facial expression task, in order to assess the effects of administration of oxytocin on emotion recognition. A single dose of oxytocin or a placebo was administered intranasally to 27 healthy male subjects 45 min prior to task performance. The results showed that a single intranasal administration of oxytocin, as opposed to the placebo, improved the subjects' ability to recognize fear, but not other emotions. These results suggest a specific role for oxytocin in fear recognition, which could be relevant for clinical disorders that manifest deficits in processing emotional facial expressions, particularly fear.

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### 1. Introduction

The ability to perceive and understand the mental state of others constitutes the foundation of interpersonal communication, which relies on important verbal, as well as non-verbal, information. One important means for conveying non-verbal information is through facial expressions, which reflect the dynamically changing emotional state of others in response to their internal and external experiences. Therefore, an accurate recognition of emotional facial expressions is necessary for adaptive social functioning in interpersonal situations (Carr & Lutjemeier, 2005; Karow & Connors, 2003).

Given that peptide hormones such as oxytocin have been implicated in the regulation of mammalian social behavior in general and emotion recognition in particular (Domes et al., 2007a; Guastella, Carson, Dadds, Mitchell, & Cox, 2009; Guastella, Mitchell, & Dadds, 2008), it could be reasoned that oxytocin would have a modulating effect on our ability to accurately recognize emotions from facial expressions.

Oxytocin is a nonapeptide, which in addition to its known peripheral hormonal function in uterine contractions and lactating in nursing females (Insel, Young, & Wang, 1997), it also serves as a neuromodulator in the central nervous system. Oxytocin has an anxiolytic effect and plays a role in various complex prosocial behaviors, such as maternal behavior and trust (Bartz & Hollander,

2006; Insel & Fernald, 2004; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005; Windle, Shanks, Lightman, & Ingram, 1997), as well as mediating the beneficial effect of social support in stressful social situations (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003).

A recent study, conducted by Guastella et al. (2008), examined the role of the hormone oxytocin on sensitivity to eye gaze. They administered a single dose of oxytocin intranasally to the subjects, who were then monitored via an eye-tracker while viewing neutral black-and-white facial expressions. The authors reported that the subjects who received oxytocin spent more time gazing at the eye region of the faces and returned more frequently to this area, as compared to the subjects who received a placebo. Although the study was conducted on neutral expressions, the authors suggested that oxytocin has a direct influence on the ability to perceive and understand the emotional state of others, which contributes profoundly to interpersonal communication. In accordance with this study, Domes et al. (2007a) have reported that a single dose of oxytocin, administered intranasally, had a general effect on enhancing subjects' ability to recognize emotions.

While these studies demonstrate the general effect of oxytocin administration on emotion recognition, as far as we know no study to date have examined the selective effect of oxytocin on the recognition of separate basic emotions.

An abundance of studies argue in favor of a particular high survival value for fear, and its rapid detection (Green & Phillips, 2004; Liddell et al., 2005; Reinders et al., 2006; Williams et al., 2007; Williams et al., 2006). In an ERP study, Williams et al. (2006) found evidence to support the hypothesis that signals of fear (e.g. fearful facial expression) are favored in neural processing, so that other

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kinds of signals will be suppressed until detection of danger will be completed.

Recent findings suggest a specific role for fear recognition in prosocial behavior. Marsh, Kozak, and Ambady (2007) found that accurate recognition and identification of a fearful facial expression predicted prosocial behavior, better than gender, mood or empathic tendencies. Moreover, impaired recognition of a fearful expression is a consistent characteristic of children and adolescents with callous-unemotional traits and aggressive behavior disorders, and adult individuals with anti-social tendencies (Blair, Colledge, Murray, & Mitchell, 2001; Carr & Lutjemeier, 2005; Marsh and Blair, 2008; Marsh et al., 2008). Carr and Lutjemeier (2005) have found that youth offenders' ability to recognize fearful expression had a moderate inverse relationship with self-reports of violent aggressive actions and a moderate positive relationship with their ability to empathize with the emotional experience of others, thus, further reinforcing the link between fear recognition, empathy and behavior.

Given the importance of fear detection for survival and its role in prosocial behavior it was hypothesized that administration of oxytocin may have a selective effect on recognition of fear.

Furthermore, numerous studies have examined the neuroanatomical basis of the perception of physical manifestations of emotions, suggesting that distinctive neurological regions are involved in the processing of emotions (Adolphs, Damasio, Tranel, & Damasio, 1996; Murphy, Nimmo-Smith, & Lawrence, 2003; Phan, Wager, Taylor, & Liberzon, 2002). One finding repeatedly demonstrated in the literature is the robust relationship between fear recognition and the amygdala (Adolphs, 2008; Adolphs, Tranel, Damasio, & Damasio, 1994; Asghar et al., 2008; LeDoux, 1998; Morris et al., 1996; Whalen et al., 1998, 2001). Imaging studies show a differential response of the human amygdala following the presentation of a facial expression reflecting fear, as opposed to happiness (Morris et al., 1996; Whalen et al., 1998; Wright et al., 2001); anger (Clark, Nearing, & Cronin-Golomb, 2008; Whalen et al., 2001); or disgust (Phillips et al., 1998, 2004).

Adolphs et al. (1994) reported a remarkable case study in which the patient suffered from an almost complete bilateral amygdala destruction, and demonstrated a specific impairment in the recognition of fearful facial expressions.

Interestingly, recent findings have reported an inhibitory effect of oxytocin on activation of the amygdala (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Domes, Heinrichs, Michel, Berger, & Herpertz, 2007; Kirsch et al., 2005; Petrovic, Kalisch, Singer, & Dolan, 2008; Singer et al., 2008). Using fMRI, Kirsch et al. (2005) found that intranasal administration of a single dose of oxytocin reduced activation of the amygdala in response to a fear-inducing stimulus (fearful and angry facial expressions), as compared to the effect of placebo. Importantly, the reduced activation of the amygdala was found to be more pronounced for socially relevant stimuli (faces), than for less socially relevant stimuli (scenes), supporting a social-specific role for oxytocin. Similar findings were evident in another fMRI study (Domes et al., 2007b), which found that oxytocin attenuated amygdala activation in response to facial expressions of different valence.

Given the role of the amygdala in emotion recognition, these findings appear to be in contrast with reports regarding improvement in emotion recognition following administration of oxytocin (Domes et al., 2007b; Guastella et al., 2008).

In this regard it is important to mention that Bosch, Meddle, Beiderbeck, Douglas, and Neumann (2005) have reported that when anxious female rats are presented with an intruder, oxytocin release is higher within the central nucleus of the amygdala (CeA), as compared to non-anxious female rats. Furthermore, Huber, Veinante, and Stoop (2005) reported an opposite modulation effect for oxytocin and vasopressin on the excitatory input into the CeA.

Accordingly, oxytocin excites neurons in the lateral and capsular division of the CeA, which inhibits neurons in the medial part of the CeA, which ultimately stimulates fear response.

Thus, although it is evident that oxytocin inhibit the activation of the amygdala (Baumgartner et al., 2008; Domes et al., 2007a; Kirsch et al., 2005; Petrovic et al., 2008; Singer et al., 2008), it seems plausible that oxytocin has an initial excitatory effect on the amygdala (Huber et al., 2005).

An equally reasonable possibility is that the effects of oxytocin on emotion recognition are mediated by other frontal or temporal regions. For example it is possible that the oxytocinergic system is related to a core area in the mirror neuron system, namely the inferior frontal gyrus (IFG). Indeed, recently, Domes et al. (2009) have demonstrated increased blood-oxygen-level-dependent (BOLD) signal in the IFG in response to angry and happy faces following oxytocin treatment, While Loup et al. (1991) have not detected oxytocin receptors in human amygdala (Loup et al., 1991; Loup et al., 1989).

Given the social significance of fear recognition and the relationship between fear recognition and the amygdala and other frontal regions, we hypothesized that a single intranasal administration of oxytocin would have a differential and selective effect on the recognition of fear, as compared to other emotions.

In contrast to previous studies (Domes et al., 2007b), our study used a dynamic emotional facial expression recognition task, which we believe has stronger ecological validity insofar as it reflects a more realistic interpersonal situation that requires emotion recognition (Karow & Connors, 2003). It has been shown that movies showing faces changing dynamically are excellent method for measuring emotion recognition (Mayer, DiPaolo, & Salovey, 1990). Indeed, in social and emotional situations in real-life, static facial expressions of emotion are seen only in photographs, while most of the time we face expressions that changes over time (Niedenthal, Brauer, Halberstadt, & Inner-Ker, 2001). While studies to date have examined the general role of oxytocin in emotion recognition using static images, no study has examined each of the six basic emotions (happy, sad, fearful, disgust, angry, and surprised) separately in a task that involves dynamic changes in emotional expression.

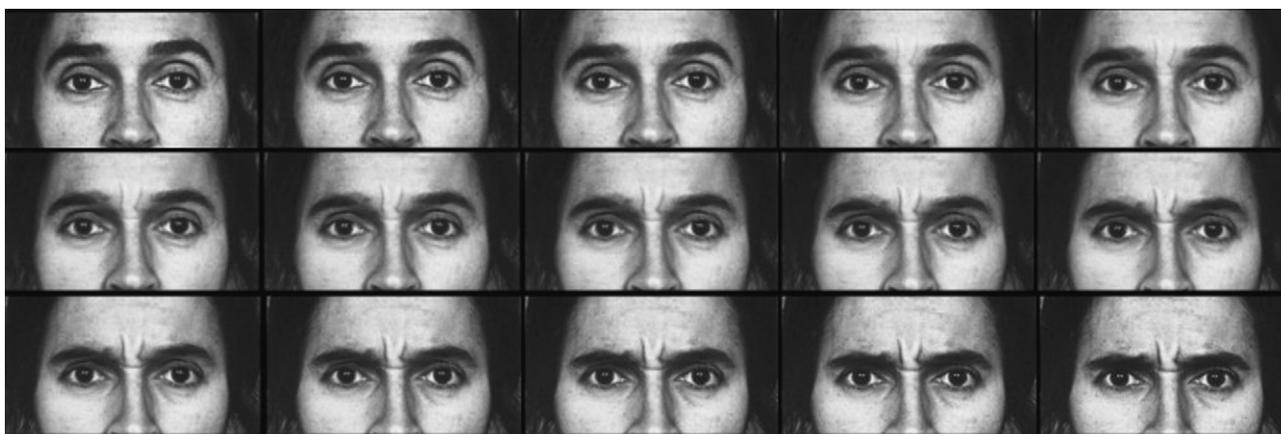
## 2. Methods

### 2.1. Participants

Twenty-seven healthy male subjects participated in the study. The participants were students who were recruited through advertisements and received a financial reward for their participation (mean age = 26.93, SD = 3.51). All participants were interviewed by a senior psychiatrist. Exclusion criteria were an acute, unstable, significant, or untreated medical illness (including arrhythmia, psychiatric conditions, and head injury); a history of alcohol or drug abuse; mental retardation (IQ less than 75); and disturbances in visuo-motor coordination. All participants were instructed to avoid using psychotropic substances (such as caffeine and nicotine) at least 12 h prior to the experiment. Two subjects were excluded from the original sample because of smoking or drinking coffee on the day of the trial. Two additional subjects were excluded following a debriefing procedure in which they claimed to have strongly felt which substance they were given at each trial. Examination of the substances administration list at the end of the experiment revealed they were indeed correct. Though they had no true knowledge of the substance they were actually receiving, to ensure that the study was indeed blind, they were removed from statistical analysis. All subjects gave their oral and written consent before participation. The study protocol was approved by the Helsinki committee of Shalvata Mental Health Center, as well as by the Israeli Ministry of Health.

### 2.2. Substance administration

A double-blind placebo-controlled crossover design was used, with subjects randomly assigned into groups for the first administration of either oxytocin or placebo. One week later, each subject underwent a second administration switching to the other substance. Thus, every subject received both the oxytocin and the placebo. A single dose of 24 IU oxytocin or placebo containing saline solution (Syntocinon-Spray, Novartis) was administered intranasally to the subjects 45 min prior to task performance. Subjects were given three puffs per nostril, with each puff containing 4 IU. This dosage and waiting time correspond to those previously used



**Fig. 1.** Frames sample out of 100 frames composing one video clip, in which a neutral face is gradually morphed into an angry face.

in experiments designed to investigate the human behavioral effects of intranasally administered oxytocin (Domes et al., 2007b; Kirsch et al., 2005; Kosfeld et al., 2005). On an informally debriefing at the end of the experiment, subjects were unable to discriminate between oxytocin and placebo (except of the two participants who were excluded from the study).

### 2.3. Behavioral task

Forty-five minutes following substance administration, participants completed a computerized version of the Depression Adjective Check Lists (DACL; S2) in order to track mood changes following treatment. The DACL is a self-report instrument for the measurement of affect and is comprised of a 32-item adjective checklist describing mood states. It is useful in the measurement of transient mood and the immediate effects of environmental (internal and external) influences, as well as in the daily monitoring of mood.

Following completion of the DACL questionnaire, subjects underwent an emotional facial expression recognition task. The task involved the use of computer-generated images in which facial expressions changed gradually and continuously from a neutral expression to an emotional expression. The face stimuli were grey-scale standardized photographs of six different individuals whose facial expressions varied to reflect the six basic emotions (happy, sad, fearful, disgust, angry, and surprised). The subject's task was to detect the onset of each emotional facial expression.

Each face stimulus was enclosed within a rectangular frame measuring 6.1 cm × 8.9 cm, subtending 5.0 × 7.3° of visual angle at a 70-cm viewing distance (173 × 251 pixels on a 256 grey-level scale). Three male and three female images were selected from the Ekman series (Ekman and Friesen, 1975, 1976). All stimuli were presented on a 17-in. computer screen against a black background. Using graphic image morph software (Face Morph Lite 2.0), the facial expressions were gradually alternated from neutral to one of the six basic emotions. The emotion recognition test was designed with e-prime 2.0 software. Six stimuli were displayed for each individual character, making for a total of 36 stimuli. Starting with the same neutral emotion, each face was gradually morphed into a different emotion (see Fig. 1). To mimic the average course and rapidity of natural facial change, as suggested by Niedenthal et al. (2001), each frame was presented for 100 ms, resulting in

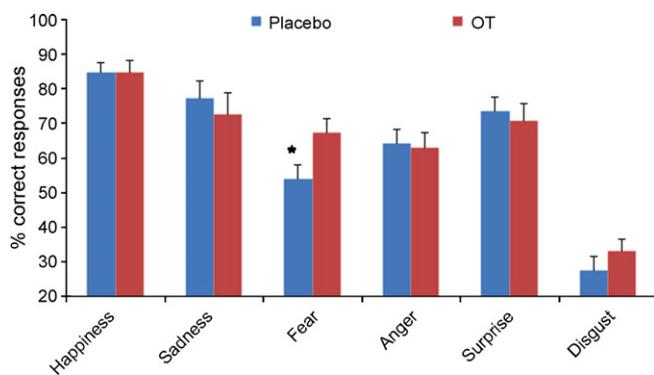
a frame ratio of 10 fps. Each clip included 100 frames, lasting for 10 s. The advantage of the morphing technique is that the emotional facial expression appears gradually in a controlled fixed and timed manner. As in real emotional expression, at some point, there is initial evidence of a possible emotional expression. Thus, while having ecological validity of dynamic emotional changes, the task also enables control across all stimuli over the change rate, which would not be possible in true emotional movies.

For the emotion recognition test, the subjects were asked to press the spacebar key once they recognized an emotion emerging from the neutral face. Reaction time and frame onset were recorded as dependent variables. Immediately after pressing the spacebar key, subjects were asked to report which emotion they recognized by choosing from the six emotions in a forced-choice paradigm. This paradigm was chosen in light of LaBar, Crupain, Voyvodic, and McCarthy (2003) findings, which strongly suggest that dynamic facial affect expressions, as opposed to static affect expressions, are preferred by many neural regions involved in emotion perception. According to the authors, dynamic facial expressions more closely represent real-life experiences of the social communication of emotions.

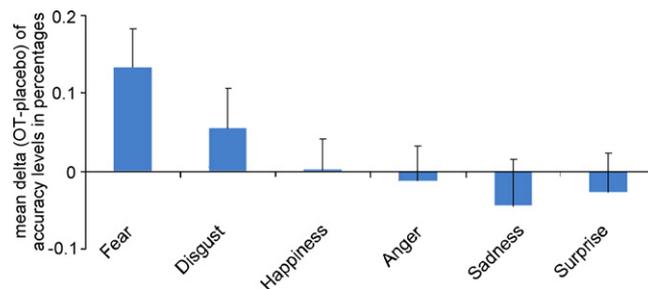
## 3. Results

### 3.1. Accuracy scores

To examine the effect of oxytocin on the ability to recognize accurately emotions, two-way repeated measures ANOVA was performed between type of drug and type of emotion. This analysis revealed a significant interaction of Substance × Emotion for the accuracy level of emotional facial expression recognition ( $F(5,20)=2.722$ ,  $p<0.05$ ), indicating a differential effect of the administered substance on accurate recognition of the different emotions (see Fig. 2). An additional significant effect for emotion type was found ( $F(5,20)=21.87$ ,  $p<0.001$ ), indicating that recognition of happiness was the most accurate [84.8 (17.35)], followed by that of sadness [72.76 (29.670)], surprise [70.68 (17.82)], fear [67.16 (21.43)] and anger [62.88 (22.18)]. The least accurate was the recognition of disgust [33 (25.87)]. There was no significant substance effect ( $F(1,24)=0.63$ , ns).



**Fig. 2.** Repeated measures analysis shows a significant treatment effect. Separate repeated ANOVA (with Bonferroni corrections) indicated significant treatment effect only for fear recognition (\*), but not for the recognition of happiness, sadness, anger, disgust, or surprise.



**Fig. 3.** Repeated measure analysis reveals a significant difference between accuracy delta (mean accuracy level during oxytocin condition minus mean accuracy level during placebo condition) of fear and that of happiness, sadness, surprise and anger.

Separate repeated ANOVA (with Bonferonni corrections) revealed a significant difference between the oxytocin and placebo conditions only for the recognition of fear ( $F(1,24) = 7.16, p < 0.05$ ), but not for the recognition of happiness ( $F(1,24) = 0.003, ns$ ); sadness ( $F(1,24) = 0.479, ns$ ); anger ( $F(1,24) = 0.077, ns$ ); surprise ( $F(1,24) = 0.288, ns$ ); or disgust ( $F(1,24) = 1.14, ns$ ). These results indicate that the subjects were better in recognizing fear after administration of oxytocin, as compared to the placebo.

To further confirm the selective drug effect on fear recognition, for each subject, we calculated an average delta between the drug and the placebo conditions in each of the emotions. Repeated measures ANOVA revealed a significant difference between the delta scores of the six emotions ( $F(5,20) = 2.72, p < 0.05$ ).

Simple contrasts analysis revealed a significant difference between delta accuracy of fear and that of happiness ( $F(1,24) = 7.53, p = 0.011$ ), sadness ( $F(1,24) = 5.55, p = 0.027$ ), surprise ( $F(1,24) = 4.55, p = 0.043$ ) and anger ( $F(1,24) = 4.3, p = 0.05$ ). No significant differences were observed between the fear delta and the and disgust delta ( $F(1,24) = 1.3, ns$ ) (Fig. 3).

### 3.2. Reaction time

To examine the effect of oxytocin administration on processing speed, a two-way repeated measures ANOVA was conducted. This analysis revealed no significant interaction of Substance  $\times$  Emotion for the reaction time of emotional facial expression recognition ( $F(5,9) = 0.21, ns$ ). There was an emotion effect ( $F(5,9) = 2.34, p < 0.05$ ), indicating lower reaction time in the recognition of disgust as opposed to fear ( $F(1,22) = 4.41, p < 0.05$ ) in the oxytocin condition, as well as in the placebo condition ( $F(1,20) = 6.15, p < 0.05$ ). In addition, reaction time in the placebo condition was significantly lower for the recognition of disgust as opposed to anger ( $F(1,20) = 5.23, p < 0.05$ ), and that of disgust as opposed to surprise ( $F(1,20) = 5.24, p < 0.05$ ), and of reaction time for the recognition of happiness as opposed to that of surprise ( $F(1,15) = 4.76, p < 0.05$ ). These effects correspond to a well known phenomenon of automatic speed processing of the different emotions, which finds a faster recognition of happiness, and slower recognition of fear (Leppanen & Hietanen, 2004; Tracy & Robins, 2008). There was no overall substance effect ( $F(1,13) = 0.186, ns$ ), indicating that administration of oxytocin did not have a general effect on the rapidity of the subjects.

### 3.3. Oxytocin and mood

In order to rule out the possibility that oxytocin had a general effect on mood, we examined participants' ratings of the Depression Adjective Check Lists, a self-report instrument for the measurement of affect, which participants completed 45 min following substance administration (with either oxytocin or placebo) and immediately before undergoing the emotional facial expression recognition task. As can be seen in Fig. 4, the results show no drug effect ( $F[1,24] = 3.34, ns$ ) nor any interaction with valence (positive, negative) ( $F[1,24] = 0.44, ns$ ). These findings are in line with previous reports (Domes et al., 2007b; Kosfeld et al., 2005). There was a general valence effect ( $F[1,24] = 36.65, p < 0.05$ ) found, indicating that participants were generally in a positive mood. However, their mood was not affected by the administration of oxytocin.

## 4. Discussion

The results of the present study demonstrate that a single dose of oxytocin has a selective effect on the ability of healthy male subjects to accurately recognize emotional facial expressions, namely fearful expressions, as opposed to other emotional expressions.

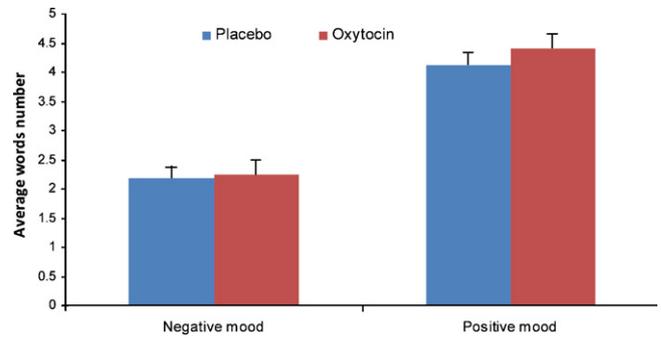


Fig. 4. Repeated measures analysis did not reveal any treatment effect on general mood ratings.

The present study's results do not coincide with those of Domes et al. (2007b), who reported that a single dose of oxytocin, administered intranasally, had a general enhancing effect on subjects' ability to recognize emotions. One explanation for this discrepancy is the different focus of the two studies. While Domes et al. examined the general ability to accurately perceive emotional facial expressions, with an emphasis on easy versus difficult emotional expressions, our study examined the effect of oxytocin on each of the six basic emotions separately.

Another explanation for the disparity between this study and that of Domes et al., relates to the differences between the tasks. In Domes et al.'s study, still photos of different emotional expressions were displayed at their maximal affective state. In contrast, our study used a dynamic emotional facial expression recognition task, which we believe to be of greater ecological validity insofar as it reflects a more realistic interpersonal situation that requires emotion recognition. As Karow and Connors (2003) suggest, examining emotional facial expression recognition via a dynamic real-life method, such as video clips, provides a more accurate picture of the human ability to recognize emotions conveyed by facial expressions.

An additional strength of this study is the crossover design of the protocol, which enabled us to compare changes in performance within subjects, following oxytocin administration and following placebo administration. The current protocol has the advantage of overcoming individual differences.

As noted above, recent neuroimaging evidences suggest that administration of oxytocin inhibits amygdala activation (Baumgartner et al., 2008; Domes et al., 2007a; Kirsch et al., 2005; Petrovic et al., 2008; Singer et al., 2008), which appears to be in contradiction with the improvement in fear recognition observed in the present study. Based on Huber et al. (2005), it appears that oxytocin has an initial excitatory effect on the amygdala, which results in the second phase in inhibition of the amygdala. Although highly speculative, it is possible that this initial excitatory effect is associated with rapid fear detection. This possible interpretation should be treated with caution as no imaging techniques were used in the present study.

Nonetheless, an alternative explanation is that other brain regions were involved in the effects of improved fear recognition following administration of oxytocin. Frontal regions, for example, are associated with emotional facial expression recognition, and there is evidence for the involvement of a number of regions in the frontal lobes with recognition of fear (Kilts, Egan, Gideon, Ely, & Hoffman, 2003; Phillips et al., 2004; Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998; Vuilleumier & Pourtois, 2007; Williams et al., 2006).

van der Gaag, Minderaa, and Keysers (2007) have suggested that the inferior frontal gyrus and the superior temporal sulcus compose a mirror neuron system for the motor components of

facial expressions, while the amygdala and insula may represent an additional system for emotional states such as fear. Interestingly, different studies exhibited evidences for the presence of oxytocin binding sites in different areas in the rat's frontal lobe that are involved in emotional processing (Febo, Numan, & Ferris, 2005; Ferris, 2008; Smeltzer, Curtis, Aragona, & Wang, 2006). Moreover, Loup et al. (1991) have demonstrated intense regions of oxytocin binding sites in the human frontal lobe, such as the inferior frontal gyrus (Broca's area). Given this neuropeptide's prosocial role, it is possible that administration of oxytocin modulated different cortical regions that are imperative for a higher-level processing of consciously threatening stimuli, and by thus improving emotional recognition of fear.

Fear recognition is closely related to adaptive interpersonal functioning, as it enables the understanding of others' distressed affective state of mind and possibly facilitates a response (Marsh et al., 2007). Given the pivotal role of fear recognition in social context, the present study results could have important implications for future research and possible treatment of psychiatric disorders in which emotion recognition in general, and fear recognition specifically, is one of the clinical manifestations. For example, schizophrenic patients are known to have specific deficits in reading others' affective state of mind (Edwards, Jackson, & Pattison, 2002; Kohler et al., 2003; Michalopoulou et al., 2008; Shamay-Tsoory et al., 2007). Interestingly, Goldman, Marlow-O'Connor, Torres, and Carter (2008) report in their study that oxytocin levels in the plasma of schizophrenic patients predict their ability to accurately recognize the intensity of emotional facial expressions, thus providing additional support for oxytocin's role in perceiving others' affective state of mind. Given the previous evidence of schizophrenic patients' deficits in emotional facial expression recognition, especially for negative emotions, future studies should examine the effect of oxytocinergic treatments on the ability of these patients to accurately recognize emotional facial expressions.

Furthermore, a recent study examined the neural activation of schizophrenic patients during an emotional facial expression recognition task (Gur et al., 2007). The results indicate a specific impairment in their ability to recognize fearful facial expressions, corresponding to an increased activation of their amygdala. In contrast, healthy subjects showed a normal level of accuracy for fearful facial expression recognition, along with a reduced activation of the amygdala. These results are in accordance with the present study results in regard to the supposedly paradoxical combination of increased fear recognition and reduced amygdala activation, which appears to be inverted in people suffering from schizophrenia.

Nonetheless, the psychiatric conclusions and speculations regarding the brain systems involved in this effect should be considered with caution, considering the study's small sample size. Future studies on a larger scale could validate our results and deepen our understanding of oxytocin's modulatory role on amygdala activation during the recognition of fearful facial expressions, as well as its particular effect on the cortical circuit that involves in fear recognition. From a clinical perspective, further research might have important implications for the treatment of psychiatric disorders that manifest deficits in this critical ability.

Another important limitation of this study is the use of saline as placebo. Other widely used forms of placebo contain all inactive ingredients except for the neuropeptide. Nonetheless, in the present study a placebo of saline was used as done in other medical experiments using intranasal administration of biological substances (for example, Eccles, Eriksson, Garreffa, & Chen, 2008; Granier et al., 2009; Kaya, Sahin, Koken, Kose, & Cevrioglu, 2008; Mackle et al., 2008; Parker, Buckmaster, Schatzberg, & Lyons, 2005; Rosenwasser, Mahr, Abelson, Gomes, & Kennedy, 2008). Future studies should replicate our results using impeccable placebo.

In conclusion, our results demonstrate the pronounced effect of a single intranasal administration of oxytocin on the ability to recognize fearful facial expressions. The ability to detect and understand fearful affective states in others is essential to adaptive social functioning, as it promotes the creation of empathy and prosocial behavior.

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## References

- Adolphs, R. (2008). Fear, faces, and the human amygdala. *Current Opinion in Neurobiology*, 18(2), 166–172.
- Adolphs, R., Damasio, H., Tranel, D., & Damasio, A. R. (1996). Cortical systems for the recognition of emotion in facial expressions. *The Journal of Neuroscience*, 16(23), 7678–7687.
- Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature*, 372(6507), 669–672.
- Asghar, A. U., Chiu, Y. C., Hallam, G., Liu, S., Mole, H., Wright, H., et al. (2008). An amygdala response to fearful faces with covered eyes. *Neuropsychologia*, 46(9), 2364–2370.
- Bartz, J. A., & Hollander, E. (2006). The neuroscience of affiliation: Forging links between basic and clinical research on neuropeptides and social behavior. *Hormones and Behavior*, 50(4), 518–528.
- Baumgartner, T., Heinrichs, M., Vonlanthen, A., Fischbacher, U., & Fehr, E. (2008). Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. *Neuron*, 58(4), 639–650.
- Blair, R. J., Colledge, E., Murray, L., & Mitchell, D. G. (2001). A selective impairment in the processing of sad and fearful expressions in children with psychopathic tendencies. *Journal of Abnormal Child Psychology*, 29(6), 491–498.
- Bosch, O. J., Meddle, S. L., Beiderbeck, D. I., Douglas, A. J., & Neumann, I. D. (2005). Brain oxytocin correlates with maternal aggression: Link to anxiety. *The Journal of Neuroscience*, 25(29), 6807–6815.
- Carr, M. B., & Lutjemeier, J. A. (2005). The relation of facial affect recognition and empathy to delinquency in youth offenders. *Adolescence*, 40(159), 601–619.
- Clark, U. S., Nearing, S., & Cronin-Golomb, A. (2008). Specific impairments in the recognition of emotional facial expressions in Parkinson's disease. *Neuropsychologia*, 46(9), 2300–2309.
- Domes, G., Heinrichs, M., Glascher, J., Buchel, C., Braus, D. F., & Herpertz, S. C. (2007). Oxytocin attenuates amygdala responses to emotional faces regardless of valence. *Biological Psychiatry*, 62(10), 1187–1190.
- Domes, G., Heinrichs, M., Michel, A., Berger, C., & Herpertz, S. C. (2007). Oxytocin improves "mind-reading" in humans. *Biological Psychiatry*, 61(6), 731–733.
- Domes, G., Lischke, A., Berger, C., Grossmann, A., Hauenstein, K., & Heinrichs, M. et al. (2009). Effects of intranasal oxytocin on emotional face processing in women. *Psychoneuroendocrinology*, in press.
- Eccles, R., Eriksson, M., Garreffa, S., & Chen, S. C. (2008). The nasal decongestant effect of xylometazoline in the common cold. *American Journal of Rhinology*, 22(5), 491–496.
- Edwards, J., Jackson, H. J., & Pattison, P. E. (2002). Emotion recognition via facial expression and affective prosody in schizophrenia: A methodological review. *Clinical Psychology Review*, 22(6), 789–832.
- Ekman, P., & Friesen, W. V. (1976). *Pictures of facial affect*. Palo Alto, CA: Consulting Psychologists Press.
- Ekman, P., & Friesen, W. V. (1975). *Unmasking the face: A guide to recognizing emotions from facial clues*. Prentice Hall.
- Febo, M., Numan, M., & Ferris, C. F. (2005). Functional magnetic resonance imaging shows oxytocin activates brain regions associated with mother-pup bonding during suckling. *Journal of Neuroscience*, 25(50), 11637–11644.
- Ferris, C. F. (2008). Functional magnetic resonance imaging and the neurobiology of vasopressin and oxytocin. *Progress in Brain Research*, 170, 305–320.
- Goldman, M., Marlow-O'Connor, M., Torres, I., & Carter, C. S. (2008). Diminished plasma oxytocin in schizophrenic patients with neuroendocrine dysfunction and emotional deficits. *Schizophrenia Research*, 98(1–3), 247–255.
- Granier, M., Dadure, C., Bringuier, S., Bonnet-Boyer, M. C., Ryckwaert, Y., Loriaux, E., et al. (2009). Intranasal lidocaine plus naphazoline nitrate improves surgical conditions and perioperative analgesia in septorhinoplasty surgery. *Canadian Journal of Anaesthesia*, 56(2), 102–108.
- Green, M. J., & Phillips, M. L. (2004). Social threat perception and the evolution of paranoia. *Neuroscience and Biobehavioral Reviews*, 28(3), 333–342.
- Guastella, A. J., Carson, D. S., Dadds, M. R., Mitchell, P. B., & Cox, R. E. (2009). Does oxytocin influence the early detection of angry and happy faces? *Psychoneuroendocrinology*, 34(2), 220–225.
- Guastella, A. J., Mitchell, P. B., & Dadds, M. R. (2008). Oxytocin increases gaze to the eye region of human faces. *Biological Psychiatry*, 63(1), 3–5.

- Gur, R. E., Loughhead, J., Kohler, C. G., Elliott, M. A., Lesko, K., & Ruparel, K. (2007). Limbic activation associated with misidentification of fearful faces and flat affect in schizophrenia. *Archives of General Psychiatry*, *64*(12), 1356–1366.
- Heinrichs, M., Baumgartner, T., Kirschbaum, C., & Ehlert, U. (2003). Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biological Psychiatry*, *54*(12), 1389–1398.
- Huber, D., Veinante, P., & Stoop, R. (2005). Vasopressin and oxytocin excite distinct neuronal populations in the central amygdala. *Science*, *308*(5719), 245–248.
- Insel, T. R., & Fernald, R. D. (2004). How the brain processes social information: Searching for the social brain. *Annual Review of Neuroscience*, *27*, 697–722.
- Insel, T. R., Young, L., & Wang, Z. (1997). Central oxytocin and reproductive behaviours. *Reviews of Reproduction*, *2*(1), 28–37.
- Karow, C. M., & Connors, E. C. (2003). Affective communication in normal and brain-damaged adults: An overview. *Seminars in Speech and Language*, *24*(2), 69–91.
- Kaya, E., Sahin, F. K., Koken, G., Kose, M., & Cevrioglu, A. S. (2008). Acute effect of intranasal estrogen on cerebral and cerebellar perfusion in postmenopausal women. *Maturitas*, *59*(1), 72–82.
- Kilts, C. D., Egan, G., Gideon, D. A., Ely, T. D., & Hoffman, J. M. (2003). Dissociable neural pathways are involved in the recognition of emotion in static and dynamic facial expressions. *Neuroimage*, *18*(1), 156–168.
- Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., et al. (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. *The Journal of Neuroscience*, *25*(49), 11489–11493.
- Kohler, C. G., Turner, T. H., Bilker, W. B., Brensinger, C. M., Siegel, S. J., Kanas, S. J., et al. (2003). Facial emotion recognition in schizophrenia: Intensity effects and error pattern. *The American Journal of Psychiatry*, *160*(10), 1768–1774.
- Kosfeld, M., Heinrichs, M., Zak, P. J., Fischbacher, U., & Fehr, E. (2005). Oxytocin increases trust in humans. *Nature*, *435*(7042), 673–676.
- LaBar, K. S., Crupain, M. J., Voyvodic, J. T., & McCarthy, G. (2003). Dynamic perception of facial affect and identity in the human brain. *Cerebral Cortex*, *13*(10), 1023–1033.
- LeDoux, J. (1998). Fear and the brain: Where have we been, and where are we going? *Biological Psychiatry*, *44*(12), 1229–1238.
- Leppanen, J. M., & Hietanen, J. K. (2004). Positive facial expressions are recognized faster than negative facial expressions, but why? *Psychological Research*, *69*(1–2), 22–29.
- Liddell, B. J., Brown, K. J., Kemp, A. H., Barton, M. J., Das, P., Peduto, A., et al. (2005). A direct brainstem-amygdala-cortical 'alarm' system for subliminal signals of fear. *Neuroimage*, *24*(1), 235–243.
- Loup, F., Tribollet, E., Dubois-Dauphin, M., & Dreifuss, J. J. (1991). Localization of high-affinity binding sites for oxytocin and vasopressin in the human brain. An autoradiographic study. *Brain Research*, *555*(2), 220–232.
- Loup, F., Tribollet, E., Dubois-Dauphin, M., Pizzolato, G., & Dreifuss, J. J. (1989). Localization of oxytocin binding sites in the human brainstem and upper spinal cord: An autoradiographic study. *Brain Research*, *500*(1–2), 223–230.
- Mackle, T., Gendy, S. S., Walsh, M., McConn-Walsh, R., Costello, R. W., & Walsh, M. T. (2008). Role of sphingosine 1-phosphate receptor expression in eosinophils of patients with allergic rhinitis, and effect of topical nasal steroid treatment on this receptor expression. *The Journal of Laryngology and Otology*, *122*(12), 1309–1317.
- Marsh, A. A., Finger, E. C., Mitchell, D. G., Reid, M. E., Sims, C., Kosson, D. S., et al. (2008). Reduced amygdala response to fearful expressions in children and adolescents with callous-unemotional traits and disruptive behavior disorders. *The American Journal of Psychiatry*, *165*(6), 712–720.
- Marsh, A. A., Kozak, M. N., & Ambady, N. (2007). Accurate identification of fear facial expressions predicts prosocial behavior. *Emotion*, *7*(2), 239–251.
- Mayer, J. D., DiPaolo, M., & Salovey, P. (1990). Perceiving affective content in ambiguous visual stimuli: A component of emotional intelligence. *Journal of Personality Assessment*, *54*(3–4), 772–781.
- Michalopoulou, P. G., Surguladze, S., Morley, L. A., Giampietro, V. P., Murray, R. M., & Shergill, S. S. (2008). Facial fear processing and psychotic symptoms in schizophrenia: Functional magnetic resonance imaging study. *The British Journal of Psychiatry*, *192*(3), 191–196.
- Morris, J. S., Frith, C. D., Perrett, D. I., Rowland, D., Young, A. W., Calder, A. J., et al. (1996). A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature*, *383*(6603), 812–815.
- Murphy, F. C., Nimmo-Smith, I., & Lawrence, A. D. (2003). Functional neuroanatomy of emotions: A meta-analysis. *Cognitive, Affective & Behavioral Neuroscience*, *3*(3), 207–233.
- Niedenthal, P. M., Brauer, M., Halberstadt, J. B., & Inner-Ker, A. H. (2001). When did her smile drop? Facial mimicry and the influences of emotional state on the detection of change in emotional expression. *Cognition and Emotion*, *15*(6), 853–864.
- Parker, K. J., Buckmaster, C. L., Schatzberg, A. F., & Lyons, D. M. (2005). Intranasal oxytocin administration attenuates the ACTH stress response in monkeys. *Psychoneuroendocrinology*, *30*(9), 924–929.
- Petrovic, P., Kalisch, R., Singer, T., & Dolan, R. J. (2008). Oxytocin attenuates affective evaluations of conditioned faces and amygdala activity. *Journal of Neuroscience*, *28*(26), 6607–6615.
- Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage*, *16*(2), 331–348.
- Phillips, M. L., Williams, L. M., Heining, M., Herba, C. M., Russell, T., Andrew, C., et al. (2004). Differential neural responses to overt and covert presentations of facial expressions of fear and disgust. *Neuroimage*, *21*(4), 1484–1496.
- Phillips, M. L., Young, A. W., Scott, S. K., Calder, A. J., Andrew, C., Giampietro, V., et al. (1998). Neural responses to facial and vocal expressions of fear and disgust. *Proceedings of the Biological Sciences*, *265*(1408), 1809–1817.
- Reinders, A. A., Glascher, J., de Jong, J. R., Willemsen, A. T., den Boer, J. A., & Buchel, C. (2006). Detecting fearful and neutral faces: BOLD latency differences in amygdala-hippocampal junction. *Neuroimage*, *33*(2), 805–814.
- Rosenwasser, L. J., Mahr, T., Abelson, M. B., Gomes, P. J., & Kennedy, K. (2008). A comparison of olopatadine 0.2% ophthalmic solution versus fluticasone furoate nasal spray for the treatment of allergic conjunctivitis. *Allergy and Asthma Proceedings*, *29*(6), 644–653.
- Shamay-Tsoory, S. G., Shur, S., Barcai-Goodman, L., Medlovich, S., Harari, H., & Levkovitz, Y. (2007). Dissociation of cognitive from affective components of theory of mind in schizophrenia. *Psychiatry Research*, *149*(1–3), 11–23.
- Singer, T., Snozzi, R., Bird, G., Petrovic, P., Silani, G., Heinrichs, M., et al. (2008). Effects of oxytocin and prosocial behavior on brain responses to direct and vicariously experienced pain. *Emotion*, *8*(6), 781–791.
- Smeltzer, M. D., Curtis, J. T., Aragona, B. J., & Wang, Z. (2006). Dopamine, oxytocin, and vasopressin receptor binding in the medial prefrontal cortex of monogamous and promiscuous voles. *Neuroscience Letters*, *394*(2), 146–151.
- Sprengelmeyer, R., Rausch, M., Eysel, U. T., & Przuntek, H. (1998). Neural structures associated with recognition of facial expressions of basic emotions. *Proceedings of the Biological Sciences*, *265*(1409), 1927–1931.
- Tracy, J. L., & Robins, R. W. (2008). The automaticity of emotion recognition. *Emotion*, *8*(1), 81–95.
- van der Gaag, C., Minderaa, R. B., & Keysers, C. (2007). Facial expressions: What the mirror neuron system can and cannot tell us. *Society for Neuroscience*, *2*(3–4), 179–222.
- Vuilleumier, P., & Pourtois, G. (2007). Distributed and interactive brain mechanisms during emotion face perception: Evidence from functional neuroimaging. *Neuropsychologia*, *45*(1), 174–194.
- Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., & Jenike, M. A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *The Journal of Neuroscience*, *18*(1), 411–418.
- Whalen, P. J., Shin, L. M., McInerney, S. C., Fischer, H., Wright, C. I., & Rauch, S. L. (2001). A functional MRI study of human amygdala responses to facial expressions of fear versus anger. *Emotion*, *1*, 170–183.
- Williams, L. M., Liddell, B. J., Kemp, A. H., Bryant, R. A., Meares, R. A., & Peduto, A. S. (2006). Amygdala-prefrontal dissociation of subliminal and supraliminal fear. *Human Brain Mapping*, *27*(8), 652–661.
- Williams, L. M., Kemp, A. H., Felmingham, K., Liddell, B. J., Palmer, D. M., & Bryant, R. A. (2007). Neural Biases to covert and overt signals of fear: Dissociation by trait anxiety and depression. *The Journal of Neuroscience*, *19*(10), 1595–1608.
- Windle, R. J., Shanks, N., Lightman, S. L., & Ingram, C. D. (1997). Central oxytocin administration reduces stress-induced corticosterone release and anxiety behavior in rats. *Endocrinology*, *138*(7), 2829–2834.
- Wright, C. I., Fischer, H., Whalen, P. J., McInerney, S. C., Shin, L. M., & Rauch, S. L. (2001). Differential prefrontal cortex and amygdala habituation to repeatedly presented emotional stimuli. *Neuroreport*, *12*(2), 379–383.