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Sharon Palgi, Ehud Klein, and Simone Shamay-Tsoory

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BRIEF REPORT

The Role of Oxytocin in Empathy in PTSD

Sharon Palgi
University of Haifa and Rambam Health Care Campus, Haifa, Israel

Ehud Klein
Rambam Health Care Campus, Haifa, Israel

Simone Shamay-Tsoory
University of Haifa

Objective: Although impairments in social skills are common in posttraumatic stress disorder (PTSD), only a handful of studies have investigated the empathic abilities of patients with PTSD. The first aim of this study was to characterize emotional and cognitive empathy deficits among patients with PTSD. Furthermore, intranasal oxytocin (OT) has been reported as possibly improving emotional empathy, and it has recently been suggested that patients with PTSD may suffer from abnormal functioning of the oxytocinergic system. Therefore, the second aim of this study was to investigate whether intranasal OT may enhance empathic abilities in these patients. ***Method:*** Using a randomized, double-blind, placebo-controlled crossover design, we administered 24 International Units of oxytocin and placebo at a 1-week interval to 32 patients with PTSD and to 30 matched healthy controls and then measured participants' emotional and cognitive empathy. ***Results:*** Patients with PTSD exhibited deficits in both emotional and cognitive empathy, and these deficits were associated with the severity of their PTSD symptoms. The administration of OT did not improve empathic abilities in our sample, although it did tend to selectively enhance the ability of men with PTSD to recognize body motions of anger. ***Conclusions:*** These results indicate that patients with PTSD have deficits in both emotional and cognitive empathic abilities and that their empathic difficulties may underlie their impairments in social and interpersonal skills.

Keywords: oxytocin, PTSD, empathy, Theory of Mind, trauma

Posttraumatic stress disorder (PTSD) causes impairments in broad areas of functioning, including social and interpersonal skills (Charuvastra & Cloitre, 2008). Recent studies have suggested that these difficulties are caused, at least in part, by impairments in empathy (Plana, Lavoie, Battaglia, & Achim, 2014).

Empathy is a complex ability that helps individuals understand the thoughts, desires, and feelings of another (Shamay-Tsoory, 2011). Current theoretical frameworks of empathy suggest two possible separate subsystems for empathy that develop independently and are modulated by distinct neural systems: (a) emotional empathy, the ability to automatically experience affective reactions to the observed experiences of others and recognize the feelings of others, and (b) cognitive empathy, the ability to create theories about other people's mental states and cognitively adopt the perspective of others, also known as Theory of Mind (ToM). ToM can be divided into making inferences about the thoughts and feelings of others (first-order ToM) and about what others think about the thoughts and feelings of a third party (second-order ToM; Shamay-Tsoory, 2011).

A few recent studies have examined the empathic abilities of patients with PTSD. Although there is evidence for impaired emotional empathy and emotion recognition in PTSD, reports of difficulties in cognitive empathy among these patients are limited and conflicting (Mazza et al., 2012; Mazza et al., 2015; Nazarov et al., 2013). Therefore, the first aim of this study was to further explore empathic deficits in PTSD and to characterize the association between such deficits and the severity of PTSD symptoms.

One possibility is that oxytocin (OT), a neuropeptide that serves as a key mediator of complex social behaviors, including empathy (Kanat, Heinrichs, & Domes, 2014), may play a role in PTSD. OT is synthesized in the hypothalamic paraventricular and supraoptic nuclei, released into the brain and bloodstream from the posterior lobe of the pituitary gland. It functions as both a neurotransmitter and a hormone, by its effect of several brain areas, including the amygdala, the hippocampus, the paraventricular nucleus of the hypothalamus, and the brainstem, as well as peripheral sites, including the heart, the uterus, and regions of the spinal cord that regulate the autonomic nervous system. Moreover, OT functions as one of the hormones in the hypothalamic-pituitary-adrenal axis (HPA) that mediates, among others, the stress response (Ma,

Sharon Palgi, Department of Psychology, University of Haifa and Department of Psychiatry, Rambam Health Care Campus, Haifa, Israel; Ehud Klein, Department of Psychiatry, Rambam Health Care Campus; Simone Shamay-Tsoory, Department of Psychology, University of Haifa.

Correspondence concerning this article should be addressed to Sharon Palgi, Department of Psychology, Faculty of Social Welfare and Health Sciences, University of Haifa, Haifa 3498838, Israel. E-mail: sharonpalgi@gmail.com

Shamay-Tsoory, Han, & Zink, 2016). During the past decade, ample evidence has shown that OT mediates complex prosocial and affective behaviors (Kanat et al., 2014; Ma et al., 2016). In the context of empathy, OT has been shown to enhance emotional but not cognitive empathy (Hurlemann et al., 2010). This effect is particularly evident among less socially proficient individuals than among those who are socially skilled (Bartz et al., 2010). Moreover, it has recently been suggested, by the social salience hypothesis, that the effects of OT are more contextual and are affected by interindividual factors, including gender and personality traits (Shamay-Tsoory & Abu-Akel, 2016).

Several recent theoretical frameworks suggest that the oxytocinergic system functions abnormally among patients with PTSD and that intranasal OT may potentially be an effective pharmacological intervention for ameliorating symptoms of PTSD (e.g., Koch et al., 2014; Olff, Langeland, Draijer, & Gersons, 2007; Seng et al., 2013). These theoretical frameworks suggest that because OT appears to play an important role in the modulation of social bonding processes, stress regulation, and affect, it may be a promising potential preventive intervention for these patients. In practice, it has been suggested that OT may improve social bonding processes and stress regulation among these patients by reducing the activity of the amygdala–brainstem connectivity, enhancing the connectivity of the amygdala with the ventromedial prefrontal cortex (vmPFC) and hippocampus, and increasing the regulation of the HPA axis (Koch et al., 2014). Moreover, given that PTSD is more prevalent in females (Olff et al., 2007) and that the effects of OT are likely to be sex specific (Domes et al., 2010), gender differences have been suggested in the reactivity of the oxytocinergic system due to stress (Olff et al., 2007).

Very few studies, however, have examined the effects of OT administration on patients with PTSD. Pitman, Orr, and Lasko (1993) found that OT decreases physiological responses when individuals are confronted with combat imagery, whereas another study showed that OT may improve anxiety and irritability among these patients (Yatzkar & Klein, 2010). Recently, Munro et al. (2013) found elevation in plasma OT of women with PTSD during exposure to films associated with their traumatic event. Nevertheless, to our knowledge, the effects of OT on the empathic abilities of patients with PTSD have never been assessed. Therefore, the second aim of the current study was to investigate the effects of OT on empathy among patients with PTSD. As it is an initial study on the effect of OT among patients with PTSD, we used the most established single dose of the intranasal 24 International Units (IU) protocol (e.g., Domes et al., 2010; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005).

We hypothesized first that patients with PTSD would exhibit deficits in both cognitive and emotional empathy compared to healthy controls (HCs) and that OT would enhance emotional empathy but would not affect cognitive empathy in both groups. Given the proposed gender differences in the oxytocinergic system (Domes et al., 2010; Olff et al., 2007), we examined a possible interaction between the gender of the participants and the effects of OT on empathy.

Method

Participants

The participants included 32 patients with PTSD (male, $n = 23$, age 22–60 years) and 30 HC participants matched for age and sex (male, $n = 19$, age 21–59 years), without a history of psychiatric disorders, as confirmed by the Hebrew version of the Mini International Neuropsychiatric Interview (Sheehan et al., 2001). Participants with PTSD were outpatients with a certified *DSM-IV-TR* (American Psychiatric Association, 2000) diagnosis of PTSD; their diagnosis was made by two senior psychiatrists and was confirmed by the Clinician-Administered PTSD Scale (CAPS; Blake et al., 2000; for more details on the participants, see Palgi, Klein, & Shamay-Tsoory, 2016). All participants were instructed to avoid using caffeine and nicotine at least 12 hr prior to the experiment, gave their written consent before participation, and were compensated for their time. The study protocol was approved by the Helsinki committee of the Rambam Health Care Campus and by the Israel Ministry of Health.

Treatment Administration

A double-blind, placebo-controlled, within-subject design was used. Participants were randomly assigned to groups for the first administration of either OT or placebo. One week later, each participant underwent a second administration, switching to the other treatment. A single dose of 24 IU was administered intranasally 45 min prior to task performance in the form of three puffs per nostril, with each puff containing 4 IU OT (Syntocinon spray; Defiante) or placebo. This dosage and the waiting time correspond to those previously used in experiments designed to investigate human behavioral effects of intranasally administered OT (Kosfeld et al., 2005).

Assessment of Emotional Empathy: Biological Motion Task

The task involved 30 short films, each consisting of point-light biological motions expressing five basic emotions (anger, disgust, fear, happiness, sadness), with whole-body movements displayed on a black background. The actor in the film wore uniform dark gray clothes, and his facial features and expressions were not visible. Eleven 2-cm-wide strips of white reflective tape were placed on the actor's body. Thus, the film comprised only moving white reflective points of light that showed the biological motions expressed. After being shown each film, participants were asked to choose the most suitable emotional label from a list of five alternative emotions. Participants' scores consisted of the percentage of accurate answers from all answers, assigned separately to each emotion (for more details, see Atkinson, Heberlein, & Adolphs, 2007).

Assessment of Cognitive Empathy: First- and Second-Order ToM (Yoni Task)

The ToM task consisted of 64 trials, each showing a cartoon outline of a face (called Yoni) and four colored pictures of objects and/or face images, one in each corner of the computer screen. The participant was asked to point to the correct image to which Yoni is referring based on a sentence that appeared at the top of the screen and on available cues, such as Yoni's eye gaze or facial expression. In the first-order judgment, the four pictures included objects from a single category (e.g., fruit or faces); in the second-order judgment, the four stimuli comprised facial images and an object, and choosing the correct response required understanding

how each of these figures interacted with Yoni's mental state. Both judgment orders involved three main conditions: cognitive, affective, and physical. Participants' scores consisted of the percentage of accurate answers given separately for each condition (for more details, see Shamay-Tsoory & Aharon-Peretz, 2007).

Results

Independent sample t tests confirmed that the groups did not differ in age, $t(60) = 1.525$, *ns*; years of education, $t(60) = -.196$, *ns*; or estimated verbal IQ (the similarity subtest from the Wechsler Adult Intelligence Scale–III), $t(57) = -1.95$, *ns*. Chi-square testing indicated that the groups did not differ in participants' gender, $\chi^2(1) = .517$, *ns*.

The Effects of Intranasal Administration of OT on Emotional Empathy

A three-way repeated-measures analysis, with treatment (OT, placebo) and type of emotion (anger, disgust, fear, happiness, sadness) as within-participant factors and group (PTSD, HC) as between-participants factors, revealed a significant group effect, $F(1, 60) = 8.612$, $p = .005$, $\eta^2 = 1.26$, indicating that in general, PTSD patients were less accurate in performing the task compared to the HC group (see Figure 1). An additional significant effect was found for emotion type, $F(4, 240) = 48.897$, $p < .001$, $\eta^2 = .449$. Post hoc analysis (Bonferroni) indicated that recognition of happiness [$M = .900$ (0.019)] was more accurate than anger recognition [$M = .832$ (0.015), $p = .17$], anger was more accurately recognized than fear [$M = .742$ (0.23)] and sadness [$M = .706$ (0.03), $p = 0.001$], and these feelings were more accurately recognized than disgust [$M = .526$ (0.033), $p < .0001$]. No main effects of treatment, $F(1, 60) = 0.037$, $p = .849$, $\eta^2 = .001$, were found, nor were there any other significant interactions.

A secondary four-way repeated measures analysis of variance (ANOVA) was conducted, with participant gender (male, female) as additional between-participants factors, in order to examine the possible interaction between participant gender and the effects of OT on the biological-motion task. This analysis revealed a significant group effect, $F(1, 58) = 5.952$, $p = .018$, $\eta^2 = .093$, and a significant effect for emotion type, $F(4, 232) = 44.678$, $p < .001$, $\eta^2 = .435$. Moreover, a Significant treatment × Group × Participant gender interaction was found, $F(1, 28) = 5.686$, $p = .024$, $\eta^2 = .169$, indicating a differential effect of treatment between groups and genders. No main effects of treatment, $F(1, 58) = 0.455$, $p = .503$, $\eta^2 = .008$, or participant gender, $F(1, 58) = 0.037$, $p = .847$, $\eta^2 = .001$, were found, nor were there any other significant interactions.

Follow-up paired-samples t test comparisons were carried out to detect the source of the three-way interaction. Because a significant effect of emotion type was found, these comparisons were carried out for each emotion separately. These analyses revealed a marginally significant difference between the OT and the placebo treatments for recognition of anger among men with PTSD, $t(22) = 2.071$, $p = .050$, Cohen's $d = 0.537$, although these differences did not persist after Bonferroni correction for multiple comparisons. There were no differences between the OT and the

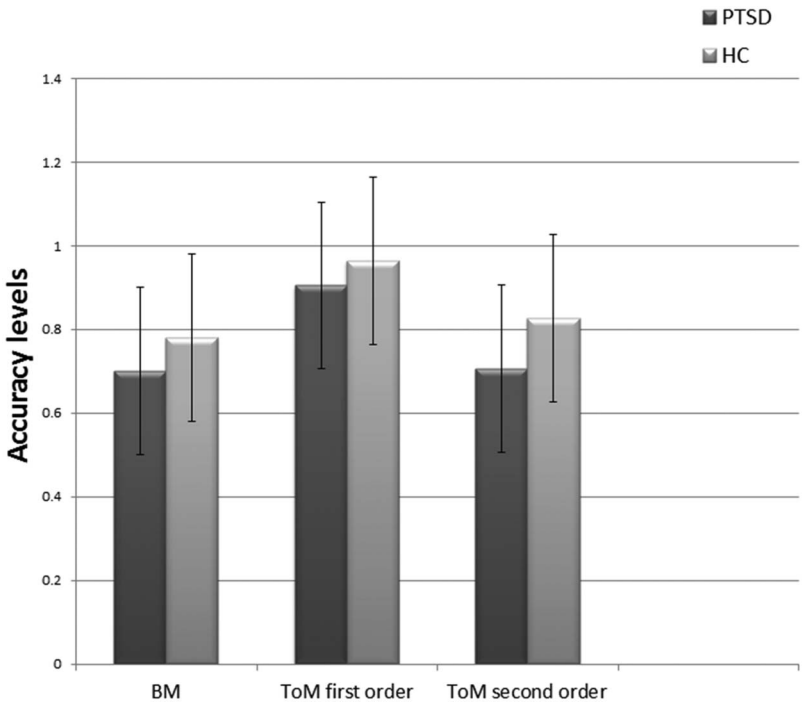

Figure 1. Patients with posttraumatic stress disorder (PTSD) were less accurate in recognizing emotions compared to the healthy control (HC) group in the biological-motion (BM) task, $F(1, 58) = 5.952$, $p = .018$, $\eta^2 = .093$; the Theory of Mind (ToM) first-order judgment, $F(1, 58) = 5.636$, $p = .021$, $\eta^2 = .089$; and in the ToM second-order judgment, $F(1, 58) = 8.209$, $p = .006$, $\eta^2 = .124$.

placebo treatments for recognition of any emotion among women with PTSD, $t(8) = -1.287$, $p = .234$, Cohen's $d = -0.6454$; HC men, $t(18) = -1.142$, $p = .268$, Cohen's $d = -0.349$; or HC women, $t(10) = 0.538$, $p = .608$, Cohen's $d = 0.247$. Furthermore, no significant differences were found between the OT and the placebo treatments in the recognition of any of the other four emotions for either of the groups or for participant gender.

The Effects of Intranasal Administration of OT on Cognitive Empathy: First-Order Judgment

A three-way repeated-measures analysis, with treatment (OT, placebo) and judgment type (cognitive, affective, physical) as within-participant factors and group (PTSD, HC) as between-participants factors, revealed a significant general group effect, $F(1, 60) = 6.919$, $p = .011$, $\eta^2 = .103$, indicating that PTSD patients were generally less accurate in first-order ToM judgments than were those in the HC group (see Figure 1). No main effects were found for treatment, $F(1, 60) = 0.289$, $p = .593$, $\eta^2 = .005$, or for types of judgment, $F(2, 60) = 0.235$, $p = .791$, $\eta^2 = .004$. Furthermore, no significant interactions were found between treatment and any of the other factors, indicating that, as hypothesized, intranasal OT did not affect the judgment of first-order ToM. A secondary four-way repeated-measures ANOVA was conducted, with participant gender (male, female) as additional between-participants factors, in order to examine the possible interaction between participant gender and the effects of OT, and this did not reveal any significant new effects.

Second-Order Judgment

A three-way repeated-measures analysis, with treatment (OT, placebo) and judgment type (cognitive, affective, physical) as within-participant factors and group (PTSD, HC) as between-participants factors, revealed a significant general group effect, $F(1, 60) = 9.946$, $p = .003$, $\eta^2 = .142$, indicating that PTSD patients were generally less accurate in second-order judgments of ToM than were those in the HC group (see Figure 1). Nevertheless, no main effects were found for treatment, $F(1, 60) = 0.065$, $p = .799$, $\eta^2 = .001$, and no significant interactions were found between treatment and any of the other factors, indicating that, as hypothesized, the administration of OT did not affect second-order ToM judgment. An additional significant effect was found for type of judgment, $F(2, 120) = 94.297$, $p < .001$, $\eta^2 = .611$. Post hoc analysis (Bonferroni) indicated that judgment of the physical condition [$M = .930$ (0.017)] was more accurate than of the affective condition [$M = .715$ (0.025), $p < 0.001$], and that judgment of the affective condition was more accurate than of the cognitive condition [$M = .664$ (0.025), $p < .0001$]. The rest of the effects were not significant. A secondary four-way repeated-measures ANOVA, with participant gender (male, female) as additional between-participants factors, did not reveal any new significant effects.

Emotional and Cognitive Empathy and PTSD Symptomatology

Bivariate correlations between PTSD symptomatology (as measured by the CAPS) and emotional empathy (as measured by the total biological-motion score, beyond the treatment conditions and the type of emotion) revealed significant correlations, $r = -0.368$, $p = .038$, and bivariate correlations between PTSD symptomatology and second-order ToM (as scores on second-order judgments on the Yoni task, beyond the treatment conditions and the judgment type) revealed marginally significant correlations, $r = -0.329$, $p = .066$. PTSD symptomatology did not correlate significantly with first-order ToM, $r = -0.51$, $p = .782$.

Discussion

In the present study, we sought to explore deficits in empathic abilities among patients with PTSD and to examine the effect of intranasally administered OT on empathic abilities in these patients. In line with our predictions, the current results suggest that patients with PTSD suffer from significant deficits in emotional and cognitive empathy. Zaki and Ochsner (2013) suggest that empathy includes three components: an affective component of experience sharing (i.e., emotional empathy), a cognitive mentalization component (i.e., cognitive empathy), and an empathic concern component. Here we examined affective and cognitive empathy in PTSD and report that we found impairment in both components of empathy. Our finding support previous evidence of impaired emotional empathy among patients with PTSD (Mazza et al., 2012, 2015; Nazarov et al., 2014). On the other hand, our findings on impaired cognitive empathy among these patients are somewhat different from that reported by Mazza et al. (2012, 2015). These differences may be explained by the different tasks used in our study and in the studies reported by Mazza et al.; whereas Mazza et al. (2012, 2015) used a simple cognitive empathy task (i.e., inferring the emotion of an individual in pictures), the present study used a more complex cognitive task, which includes making an inference about first- and second-order ToM judgment. Therefore, it is possible that differences in task difficulties may explain the discrepancies between the findings in those experiments.

Furthermore, our results suggest that deficits in emotional empathy were associated with the severity of PTSD symptoms. The deficits in emotional and cognitive empathy observed here may underlie patients' difficulties in understanding others, which may in turn account for the impairments in social and interpersonal skills and in social problem solving that characterize patients with PTSD (Charuvastra & Cloitre, 2008). Additionally, these deficits can coincide with neuroanatomical evidence pointing to abnormalities in the volume and functioning of brain regions in patients with PTSD that have, among other things, been associated with both cognitive and emotional empathy (Zoladz & Diamond, 2013). These results may indicate that patients with PTSD may benefit from psychotherapy interventions aimed at improving their empathic abilities (e.g., Palgi, Palgi, Ben-Ezra, & Shrira, 2014).

Nevertheless, our results failed to support our second hypothesis that a single dose of intranasal OT would enhance empathy among patients with PTSD. However, we did find that the effects of OT on emotional empathy interact with participant gender and group membership. Thus, intranasal OT tends to enhance the ability to recognize body motions of anger among men with PTSD, whereas it does not influence this ability among women with PTSD or among HC men and women, nor does it influence the ability to recognize other emotions in either group. This selective effect of OT can be understood by the social salience hypothesis (Shamay-Tsoory & Abu-Akel, 2016), which suggests that, among others, interindividual factors can selectively modulate the effects of OT.

Correspondingly, in this study, OT may tend to enhance the ability of men with PTSD to be alert to the salience of their emotional states, that is, to the feelings of anger that frequently characterize them (Olff et al., 2007), therefore increasing their ability to recognize this anger. This finding is consistent with current studies suggesting that OT enhances the salience of emotional states among other groups of psychiatric patients (Bartz et al., 2011; Mah, Van Ijzendoorn, Smith, & Bakermans-Kranenburg, 2013). Yet these results should be treated with caution as they are based on secondary analysis and on a study group with an unequal number of men and women participants.

Moreover, the current study has other limitations that need to be acknowledged. First, because this is a retrospective study, it cannot conclude whether the empathic deficits stem from the PTSD or whether they preceded it. Moreover, the patients in the study group were heterogeneous, with no control over the length and severity of their illness or additional drugs they were taking. In addition, this study examined single use of intranasal OT and therefore cannot draw any conclusions regarding sustained effects of the treatment on patients with PTSD; given the involvement of the HPA axis in PTSD (Zoladz & Diamond, 2013) and the effect of OT on that axis, it is important to further investigate sustained effects of intranasal OT among such patients.

In summary, our findings suggest that patients with PTSD suffer from significant and comprehensive deficits in emotional and cognitive empathic abilities and that these deficits are associated with severity of PTSD symptoms. Nevertheless, our results fail to support recent suggestions that intranasal OT may potentially be an effective pharmacological intervention for patients with PTSD. We did find that OT tends to enhance the ability to recognize body motions of anger among men with PTSD.

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