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A Psychobiological Rationale for Oxytocin in the Treatment of Posttraumatic Stress Disorder

Miranda Olff, PhD, Willie Langeland, PhD, Anke Witteveen, PhD, and Damiaan Denys, MD, PhD

ABSTRACT

Although cognitive-behavioral therapy (CBT) is an effective treatment for posttraumatic stress disorder (PTSD), many patients fail to attain remission with CBT. The authors propose augmentation of CBT with oxytocin in the treatment of PTSD. Oxytocin has a combination of pharmacologic effects that result in a "sense of safety" for the patient, which is a prerequisite to successful treatment of PTSD. We suggest a dual explanatory mechanism as to why oxytocin may be effective: through a reduction of fear response (decreasing amygdala activation, inhibiting fear response, and enhancing extinction learning) and through an increase of social interaction (activating social reward-related brain regions increasing engagement in the therapeutic alliance). Given that PTSD is marked by deficits in anxiety/stress regulation and in social functioning, and that oxytocin is implicated in both of these areas, oxytocin seems a likely candidate for treatment of patients with PTSD. Further clinical studies of the therapeutic value of oxytocin are indicated.

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FOCUS POINTS

- There is preclinical and clinical support for implication of oxytocin in the pathophysiology of psychiatric disorders involving disturbed stress regulation as well as disrupted attachment and/or social deficits.
- Oxytocin may exert an effect on posttraumatic stress disorder (PTSD) through a dual mechanism, including a reduction of fear response and increase of social functioning.
- Oxytocin has a combination of pharmacologic effects that result in a "sense of safety" for the patient, which is a prerequisite to successful treatment of PTSD.

INTRODUCTION

Posttraumatic stress disorder (PTSD) involves a disturbed fear response as well as disrupted social interaction and emotional reward, particularly from social experiences.

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PTSD is a significant health problem with an overall estimated lifetime prevalence of ~8% in the general population, with 2–3 times higher rates of PTSD in women than in men.[1-3] If untreated, the disorder typically follows a chronic, unremitting course leading to substantial impairments in social and relational functioning.

Regarding therapeutic strategies, trauma-focused cognitive-behavioral therapy (CBT) with exposure as its prominent element, is the treatment of choice for PTSD. Numerous randomized controlled trials (RCTs) and meta-analyses have demonstrated its efficacy in reducing symptoms of both acute and chronic PTSD when compared to other therapeutic strategies.[4-8] However, not all patients seem to benefit fully from CBT, because a substantial percentage of patients drop out of treatment, remain symptomatic, or relapse after initially having responded to exposure therapy.[7,9,10] Promising results in enhancing the effectiveness of treatments for PTSD come from studies that add a pharmacologic agent to exposure, eg, D-cycloserine (DCS).[11] These novel strategies emerged from studies that have mapped some of the core pathways and neurotransmitters involved in fear extinction.[12-14] All avenues to boost treatment response by adding a pharmacologic agent to CBT, however, have yet not been fully explored.[15] A potential candidate for new augmenting treatments is the central hormone oxytocin. In the present paper a dual psychobiological mechanism by which oxytocin may exert an effect on PTSD is described.

OXYTOCIN

It has been demonstrated that oxytocin may be implicated in the pathophysiology of psychiatric disorders involving disturbed stress regulation as well as disrupted attachment and/or social deficits (eg, social withdrawal) such as autism, obsessive-compulsive disorder, social phobia, mood disorders, borderline personality disorder, and PTSD.[16-18] Given that PTSD is marked by deficits in social functioning and anxiety/stress regulation, and that oxytocin is implicated in both these areas, oxytocin seems a likely candidate for treatment of patients with PTSD.

Oxytocin administration has been found to reduce amygdala activation and decreased coupling to the brain regions involved in autonomic and behavioral responses to fear.[19] This finding is of importance for PTSD research, since the amygdala, which is central in the biological response to danger signals, is highly responsive in patients with PTSD. In addition, PTSD has been associated with increased activity of the sympathetic nervous system and with a dysregulated hypothalamic-pituitary-adrenal (HPA) system, such as low basal cortisol levels and enhanced cortisol response to challenge. By dampening stress reactivity, oxytocin might help ameliorate (intensity and frequency of) stress symptoms associated with PTSD. Beyond the reduction of fear and anxiety, oxytocin positively influences social reward circuits,[20] making it a promising candidate for treatment of PTSD. Initial promise for oxytocin as an augment to psychotherapy for PTSD comes from clinical trials already testing 3,4-methylenedioxymethamphetamine (MDMA) (the pharmaceutical version of "ecstasy")-assisted psychotherapy in people with PTSD.[21] Recent findings in humans[22] show that MDMA robustly induces oxytocin release and that oxytocin may be involved in the characteristic prosocial effects of MDMA that could help patients with PTSD.

PSYCHOBIOLOGICAL MECHANISMS FOR OXYTOCIN AS A NOVEL TREATMENT APPROACH

The authors suggest a dual explanatory mechanism as to why and how oxytocin may be effective in PTSD: through a reduction of fear response (decreasing amygdala activation, increasing extinction learning, and affecting the neuroendocrine stress response); and through an increase of social functioning (activating social reward-related brain regions increasing engagement in social support and therapeutic alliance).

Reduction of Fear Response

Oxytocin and Amygdala: *Medial Prefrontal Cortex Interactions*

The first biological mechanism through which oxytocin may be effective in PTSD concerns extinction of conditioned fear by strengthening (ventro)medial prefrontal cortex (vmPFC) inhibition of the amygdala-mediated fear response. PTSD may develop from impaired extinction of conditioned fear responses, and the exposure-based treatments of PTSD are thought to be effective through extinction learning. With this essential form of emotional learning, the patient is to re-learn the appropriate response to the trigger situation through repeated expo-

sure to the safe but fear evoking conditioned stimulus (eg, through imaginary exposure to the traumatic experience) in the absence of the harmful unconditioned stimulus (eg, the real consequences of the trauma) with which it was paired previously.[23] Inhibition of fear responses and improved emotional regulation is demonstrated in a range of anxiety disorders following extinction-based exposure therapy.[13]

Although strictly speaking, little is known about the exact mechanism through which oxytocin exerts its effects, both animal and human studies have shown that higher levels of oxytocin are associated with facilitation of fear extinction.[24-28] Fear extinction is mediated by inhibitory control of the vmPFC over amygdala-based fear processes.[29] Major trauma may disrupt the normal patterns of medial prefrontal and amygdala regulation.[30] Dysfunctional activity in both these brain areas has been reported in PTSD.[31,32] A recent meta-analysis showed that the prefrontal areas, corresponding to the same areas implicated in extinction learning, are deficient in PTSD.[33] Hyperresponsivity of the amygdala in particular, may be relevant for treatment response to CBT for PTSD.[31,34] Moreover, it has been shown that reduction of PTSD symptoms in exposure therapy is associated with reduced amygdala activation during fear processing.[35]

Higher levels of oxytocin are associated with decreases in stress and anxiety and facilitation of extinction of conditioned avoidance behavior.[25,26] Both animal and human studies indicate that oxytocin affects amygdala activation. More particularly, oxytocin increases vmPFC activity and decreases amygdala activity which may improve emotion regulation and decrease avoidance behavior.[36,37]

In rodents, it has been shown that oxytocin acts on the amygdala to reduce fear[38,39] and to modulate aggression.[40] Huber and colleagues[27] recently demonstrated that receptors for oxytocin and arginine vasopressin (AVP) are located within the central nucleus of the amygdala. These findings are consistent with those of Bale and colleagues,[41] indicating central nervous system region-specific oxytocin receptor expression, with anxiolytic effects following infusion of oxytocin through activation of protein kinase A in the central nucleus of the amygdala. The central nucleus appears to be a place where the expression of fear is modulated,[42] suggesting that these neuropeptides may be related to distinct aspects of the fear response. Studies in rodents show that oxytocin and vasopressin have opposing effects on the emotional expression of the fear response.[43] It has been hypothesized that stimulation of oxytocin receptors leads to inhibition within the amygdala, suggesting an oxytocin-mediated downregulation of fear responses.[27,44,45]

In humans, several studies have provided evidence that oxytocin reduces fear-related amygdala activity.[28,46-49] The action of oxytocin on the amygdala during the perception of threatening social cues has been outlined by research indicating that oxytocin attenuates negative affective evaluations associated with aversively conditioned stimuli through modulation of the amygdala and fusiform gyrus.[48] For example, intranasal oxytocin administration markedly reduces amygdala responsiveness.[28,46] A placebo-controlled study by Kirsch and colleagues[28] indicated that oxytocin potently reduces activation of the amygdala and decreases coupling of the amygdala to brainstem regions implicated in autonomic and behavioral manifestations of fear. In line with this, oxytocin was shown to attenuate amygdala responses to positive facial expressions,[46] aversively conditioned emotional response to social stimuli,[48] to painful stimulation,[49] and during prosocial behavior.[47] These results indicate a role for oxytocin in social emotional processing, and provide a rationale for exploring therapeutic strategies in disorders in which abnormal amygdala function is implicated such as in PTSD.

As yet, there are few novel strategies that have been trying to increase extinction learning by augmenting the efficacy of CBT by adding DCS, which binds to neurotransmitter receptors *N*-methyl-D-aspartate receptors in the amygdala.[50,51] It appears that DCS strengthens extinction memories, so they may be more easily retrieved during subsequent exposures to fear-relevant cues. Considering the focus of the current paper, one of the more exiting developments of recent years has been the augmentation of psychotherapy for anxiety disorders with MDMA. The first preliminary studies in PTSD show promising results.[52,53] In addition, open-label trials of MDMA augmented psychotherapy[54] and controlled human studies[55,56] suggest that MDMA strengthens the therapeutic alliance, decreases avoidance behavior and improves tolerance for recall and processing of painful

memories.[21] MDMA has a combination of pharmacologic effects that could provide a balance of activating emotions while feeling safe and in control. What is particularly interesting about the reviewed findings on MDMA augmentation of CBT is the major possible biological explanation for why MDMA could help individuals with PTSD, namely that it is known to increase the release of oxytocin.[57,58] We argue that a much more direct and possibly more powerful route would be to administer oxytocin itself. Overall, this research supports a new approach to the treatment of psychological disorders that enhances the adaptive learning via medication.

Oxytocin has been implicated in learning and memory processes,[59,60] but whereas the effects of oxytocin on memory have been investigated very actively in animals, research in humans remains relatively limited.[61-66] The small number of studies that were carried out showed inconsistent findings, possibly due to the variety of the experimental methods, including memory testing, stimulus material, and dose, route, and timing of oxytocin administration.[67] It is interesting to note that Heinrichs and colleagues[61] argue that there are gender-specific differences in the effect of oxytocin in reproduction-related memory. Future research on the role of oxytocin in learning and memory in humans taking into account possible gender differences is needed.

Oxytocin and Neuroendocrine Stress Responses

A large body of evidence links oxytocin with neuroendocrine and psychosocial stress reduction in non-human mammals.[68-70] In line with this research, initial studies suggest similar stress-reducing effects of oxytocin in humans.[71,72] Because increased levels of oxytocin serve to suppress both sympathetic arousal and HPA) axis responses to stress, it may be important in PTSD where both these systems are dysregulated.

Several studies in humans found support for a negative relationship between basal plasma oxytocin levels and norepinephrine, blood pressure, and heart rate.[73-75] Oxytocin also inhibits stress-induced activity of the HPA axis.[76-78] Higher oxytocin levels have also been associated with faster HPA recovery in women after an acute stress laboratory challenge.[71] Heinrichs and colleagues[72] explored the relationship between oxytocin and stress response by administering oxytocin during the Trier Social Stress Test. They found that oxytocin interacts with received social support by suppressing both the subjective and cortisol response to the stressor. The stress response was most affected by the combination of oxytocin and social support. The effect of receiving oxytocin alone appeared to be about equivalent to the effect of receiving social support alone with regard to measures of endocrine and subjective measures of anxiety. Comparisons of pre and poststress anxiety levels revealed an anxiolytic effect of oxytocin.

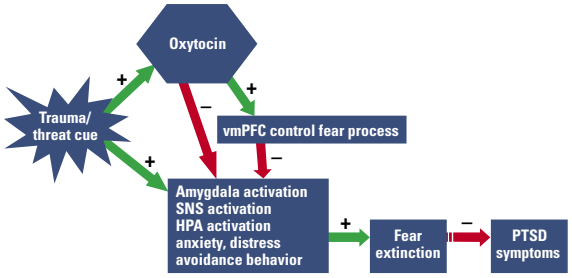
Figure 1 integrates the reviewed findings regarding the modulation of the fear response by oxytocin in a heuristic model.

Increase of Social Functioning

Oxytocin Activates Reward-Related Brain Regions

Oxytocin appears to interact with the brain's reward system, with higher oxytocin levels being associated with increases in the experience of reward. The nucleus accumbens plays a central role in reward function,[79,80] while the subgenual prefrontal cortex modulates reward processes[81] and is implicated in the pathophysiology of PTSD.[82,83] Preclinical findings that indicate a relationship between chronic stress exposure and striatal dopaminergic hypoactivity argue for a link between PTSD and reward deficits.[84,85] PTSD is not only associated with a higher prevalence of substance abuse,[86] but it bears diagnostic features that suggest a reward system dysfunction. The most notable of these are the emotional numbing symptoms, including loss of interest and pleasure (ie, anhedonia), which has been linked with reward function deficits in PTSD.[87-89] This implies that the failure of individuals with PTSD to profit from offered social support as

FIGURE 1.
Modulation of the fear response by oxytocin ("fear system")



vmPFC=ventromedial prefrontal cortex; SNS=sympathetic nervous system; HPA=hypothalamic-pituitary-adrenal system; PTSD=posttraumatic stress disorder; +=stimulating; –=inhibiting,

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in emotional numbing, may reflect not only a desire to avoid fear reactions, but also the failure to appreciate social reward.

Oxytocin, Social Support, and the Therapeutic Relationship

On top of the well-documented "fear" system, there is evidence for a "safety" system on grounds of brain circuits responsible for social affiliation. Oxytocin may have a role in the stress response, social affiliation, and the readiness for experiencing attachment security.[90] Oxytocin levels are increased by close relationships and social support and reduced by sad emotions or social isolation.[91] There is a clear association between oxytocin and the experience of social support.[92] Although little is known as of yet about oxytocin-mediated responses to trauma, the lack of social support after a trauma is one of the most significant predictors of PTSD.[93,94]

Intranasal oxytocin administration has been shown to increase the ratio of positive to negative behaviors during a marital conflict discussion.[95] Among studies in which participants were engaged in an experimental task in the presence of a loved one, individuals who reported greater social support had higher oxytocin levels.[74,75] An interesting recent study by Gouin and colleagues[96] on marital behavior, oxytocin, and wound healing showed that individuals with higher oxytocin levels not only displayed more social bonding with the spouse (ie, positive communication behaviors during a structured social support task), but also healed experimental wounds faster than the remainder of the sample. It remains to be examined whether effects during psychotherapy are comparable to those of spousal support and whether effects of oxytocin administration during treatment may increase receptivity to positive social interactions on a long-term basis.

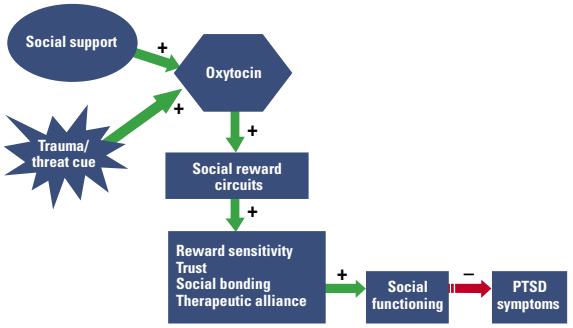
It has been shown that administration of oxytocin increases trust in humans.[97] As such, oxytocin administration in psychotherapy may strengthen engagement in the therapeutic alliance. A substantial empirical literature has identified that the therapeutic alliance, defined broadly as the collaborative bond between therapist and patient, is the most consistent predictor of psychotherapy outcome. The strengths of the patient-therapist relationship appears to be a critical common factor across treatment modalities[98,99] and may be of particular importance in PTSD, especially PTSD related to interpersonal trauma.[100-102] The effect of therapeutic alliance (a warm and understanding bond) on PTSD symptom reduction (effect size=.46)[101] was about twice the size typically reported in other studies on psychotherapy outcome.[98,99] In addition, the therapeutic alliance may play an important role in the outcome of pharmacotherapy, possible by helping creating a "holding" environment where the patient feels taken care of, protected, understood, and accepted.[103,104]

Given the link between oxytocin and trust, prosocial behavior,[22,47,97,105-106] and the subjective perception of attachment security,[107] oxytocin may be a good candidate to target as an add-on treatment in the course of the psychotherapeutic process.[108] Clients' more secure attachments relationships may be related to more positive alliances with therapists and to outcome.[109,110]

In addition, oxytocin and attachment seem to interact in suppressing subjective anxiety and physiological stress responses.[111] Early stress and abuse experiences (particularly childhood emotional abuse and neglect[112,113] and early parental separation[114]) seem to disrupt the normal development of the oxytocin system in children, a mechanism critical to the regulation of emotional behaviors increasing the risk of developing PTSD.[112,115,116] This may lead to long-term disruptions in the ability to be calmed and comforted by social bonding interactions. Providing a sense of safety and emphasizing the therapeutic relationship as a place of support may be enhanced by oxytocin.

Figure 2 integrates the reviewed findings regarding the modulation of social functioning by oxytocin in a heuristic model.

FIGURE 2.
Modulation of social functioning by oxytocin ("safety system")



PTSD=posttraumatic stress disorder; +=stimulating; –=inhibiting.

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SEX DIFFERENCES IN THE OXYTOCIN SYSTEM AND PTSD

Given that PTSD is two to three times more frequent in women than men and that oxytocin may play a role in this sex differences,[3] there may be consequences for the efficacy of treatment with oxytocin across genders. However, human studies of oxytocin are rare and mostly done in males only. Studies comparing findings in males and females mostly derive from animal research. Oxytocin levels tend to be higher in females compared to males.[117-120] Based on animal research, one may argue that the oxytocin system responds differently in males and females. The effects of oxytocin on brain and behavior are sexually dimorphic, especially during the course of development and rely on different neural substrates in males and females.[120] One possible reason for the differences between the sexes may be because in males the developmental effects of oxytocin are mediated, at least in part, through differential effects on vasopressin (receptors).[121,122] However, findings on sex differences in the oxytocin system do not directly mean that females would respond more to exogenous oxytocin administration.

Estrogen, with the well-documented capacity to increase the synthesis and possibly release of oxytocin, may help create the sex differences.[123] Among the features of the oxytocin system that are at least partially estrogen-dependent are the synthesis of oxytocin and the oxytocin receptor.[120-123] Estrogen appears to increase oxytocin receptor gene expression and receptor binding, and animal studies have found that greater oxytocin release occurs in females versus males in response to threat.[123-125] In addition, the effect of oxytocin on neuroendocrine and autonomic reactions to threat or danger may be components of adaptive and sexually dimorphic responses to stressors. Estrogens activate the HPA axis,[126] while androgens tend to inhibit the HPA axis,[127] which may also have consequences for sex-specific pathogenesis of stress-related disorders.

Sexually dimorphic differences also exist in coping mechanisms, including the willingness to use social interactions to downregulate anxiety.[91] Men typically use more active coping and overt defensive behaviors which may rely on AVP, while oxytocin is important to behaviors that are characterized by immobility and passive and social coping strategies[123] typically used more by women. Actually, a meta-analysis on gender differences in coping showed that the largest differences were found for emotion-focused coping /seeking social support.[128] A tendency to respond to threat by befriending behaviors or by seeking social support from others, as opposed using more active, instrumental coping styles may help explain gender differences in the prevalence of anxiety disorders, including PTSD.[3,129] In addition, even if both genders lack social support, this lack is more strongly related to the development of posttraumatic stress symptoms in women than in men.[130-132] Women also seem to be more sensitive to the effects of social reward than men.[133]

Overall, since women may be more vulnerable to not mounting an adequate oxytocin-response due to reduced social support in the (acute) aftermath of trauma, examining the oxytocin-mediated response to trauma may be of specific benefit to women. Whether women also may benefit more from oxytocin administration under circumstances where their stress system is being challenged needs to be tested. Much of the work investigating oxytocin in humans has been conducted in samples of all men.[28,71,72,97,114,134] Further studies will tell us whether the results seen in male samples generalize to females as well.

FUTURE RESEARCH

It is notable that PTSD involves a disturbed fear response, a disruption of social behavior and emotional reward (particularly from social experiences), and that oxytocin may exert an effect on PTSD through several psychobiological mechanisms. Future clinical trials in PTSD should be developed to assess whether the effectiveness of CBT or exposure therapy may be increased by augmentation with oxytocin. A missing part of research in this area is the consideration of possible synergies between biochemical and behavioral interventions. Clearly, a key direction of further research is addressing optimal timing and dosing, for both acute trauma and chronic PTSD depending on the acute goal of treatment (eg, enhancing adaptive learning and therapeutic alliance). The peak central effects of oxytocin are expected 30–50 minutes after administration. For example, Born and colleagues[135] showed that the levels of insulin and vasopressin already begin to rise within 10 minutes of administration, with peak levels

attained in cerebrospinal fluid at least after 30 minutes following intranasal administration. Further studies will tell us whether oxytocin should be administered only once; for example, shortly after acute traumatization in combination with psychological first aid or social support, or more frequently during prescribed sessions in the case of PTSD or chronic traumatization, to increase building of the therapeutic alliance and reduce fear responses. In line with results reported for the use of DCS in fear learning, we expect that chronic administration of oxytocin to patients during weeks or months will not show effects on symptoms of anxiety.[136] However, when administered in short bursts during (prescribed) psychological experiences, it may enhance treatment outcome. This may include emotionally significant learning experiences such as extinction-based learning or emotionally significant social interactions (promoting social bonding). More synergistic biobehavioral interventions in the sense of the aforementioned targeted biological-behavioral interactions in the treatment of trauma-related disorders need to be developed in the future.

In addition, neuroimaging studies of the oxytocin-targeted brain regions should further our understanding of the underlying neural mechanisms of the addition of oxytocin. Furthermore, since little is known about the effects of oxytocin administration on psychophysiological stress responses (sympathetic or autonomic nervous system) in PTSD,[134] researchers should assess psychophysiological outcomes such as heart rate variability as well.

CONCLUSION

There is a clear need for RCTs investigating whether intranasal oxytocin, given in the context of CBT for PTSD, modulates therapeutic alliance and treatment outcome. Exploring new avenues for treatment is particular important for this debilitating disorder because current approaches fail to provide optimal efficacy. Treatment effects may be improved by exogenous oxytocin administration but also by increasing endogenous levels of oxytocin; for example, through optimalization of social support, and most likely through the combination of both. The literature is still largely based on animal studies, and it is hoped that this article will inspire more research in humans in this area of interest. Considering the preliminary nature of the literature we do present an innovative line of research with a potential to provide a substantial shift in the efficacy of treatment for PTSD. Further studies will tell us whether the findings reported here live up to their initial promise. ***CNS***

REFERENCES

1. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry.* 1995;52(12):1048-1060.
2. de Vries GJ, Olff M. The lifetime prevalence of traumatic events and posttraumatic stress disorder in the Netherlands. *J Trauma Stress.* 2009;22(4):259-267.
3. Olff M, Langeland W, Draijer N, Gersons BP. Gender differences in posttraumatic stress disorder. *Psychol Bull.* 2007;133(2):183-204.
4. Bradley R, Greene J, Russ E, Dutra L, Westen D. A multidimensional meta-analysis of psychotherapy for PTSD. *Am J Psychiatry.* 2005;162(2):214-227.
5. Bisson JI, Ehlers A, Matthews R, Pilling S, Richards D, Turner S. Psychological treatments for chronic post-traumatic stress disorder. Systematic review and meta-analysis. *Br J Psychiatry.* 2007;190:97-104.
6. Mendes DD, Mello MF, Ventura P, Passarela CM, Mari JJ. A systematic review on the effectiveness of cognitive behavioral therapy for posttraumatic stress disorder. *Int J Psychiatry Med.* 2008;38(3):241-259.
7. Cloitre M. Effective psychotherapies for posttraumatic stress disorder: a review and critique. *CNS Spectr.* 2009;14(1 Suppl 1):32-43.
8. Roberts NP, Kitchiner NJ, Kenardy J, Bisson JI. Systematic review and meta-analysis of multiple-session early interventions following traumatic events. *Am J Psychiatry.* 2009;166(3):293-301.
9. Foa EB, Zoellner LA, Feeny NC, Hembree EA, varez-Conrad J. Does imaginal exposure exacerbate PTSD symptoms? *J Consult Clin Psychol.* 2002;70(4):1022-1028.
10. Devilly GJ, Huther A. Perceived distress and endorsement for cognitive- or exposure-based treatments following trauma. *Aust Psychologist.* 2008;43(1):7-14.
11. Davis M, Ressler K, Rothbaum BO, Richardson R. Effects of D-cycloserine on extinction: translation from preclinical to clinical work. *Biol Psychiatry.* 2006;60(4):369-375.
12. Richardson R, Ledgerwood L, Cranney J. Facilitation of fear extinction by D-cycloserine: theoretical and clinical implications. *Learn Mem.* 2004;11(5):510-516.
13. McNally RJ. Mechanisms of exposure therapy: how neuroscience can improve psychological treatments for anxiety disorders. *Clin Psychol Rev.* 2007;27(6):750-759.
14. Norberg MM, Krystal JH, Tolin DF. A meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy. *Biol Psychiatry.* 2008;63(12):1118-1126.
15. Stein DJ, Ipser J, McAnda N. Pharmacotherapy of posttraumatic stress disorder: a review of meta-analyses and treatment guidelines. *CNS Spectr.* 2009;14(1 Suppl 1):25-31.
16. Bartz JA, Hollander E. The neuroscience of affiliation: forging links between basic and clinical research on neuropeptides and social behavior. *Horm Behav.* 2006;50(4):518-528.
17. Marazziti D, Dell'osso MC. The role of oxytocin in neuropsychiatric disorders. *Curr Med Chem.* 2008;15(7):698-704.
18. Heinrichs M, von Dawans B, Domes G. Oxytocin, vasopressin, and human social behavior. *Front Neuroendocrinol.* 2009;30:548-557.
19. Meyer-Lindenberg A. Impact of prosocial neuropeptides on human brain function. *Prog Brain Res.* 2008;170:463-470.
20. Norris FH, Kaniasty K. Received and perceived social support in times of stress: a test of the social support deterioration deterrence model. *J Pers Soc Psychol.* 1996;71(3):498-511.
21. Johansen P, Krebs T. How could MDMA (ecstasy) help anxiety disorders? A neurobiological rationale. *J Psychopharmacol.* 2009;23:389-391.
22. Dumont GJ, Sweep FC, van der SR, et al. Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration. *Soc Neurosci.* 2009;4(4):359-366.
23. Myers KM, Davis M. Mechanisms of fear extinction. *Mol Psychiatry.* 2007;12:120-150.
24. Ibragimov R. Influence of neurohypophyseal peptideson the formation of active avoidance conditioned reflex behavior. *Neurosci Behav Physiol.* 1990;20:189-193.
25. Uvnäs-Moberg K. Oxytocin linked antistress effects: the relaxation and growth response. *Acta Physiol Scand Suppl.* 1997;640:38-42.
26. Uvnäs-Moberg K. Oxytocin may mediate the benefits of positive social interaction and emotions. *Psychoneuroendocrinol.* 1998;23(8):819-835.
27. Huber D, Veinante P, Stoop R. Vasopressin and oxytocin excite distinct neuronal populations in the central amygdala. *Science.* 2005;308(5719):245-248.
28. Kirsch P, Esslinger C, Chen Q et al. Oxytocin modulates neural circuitry for social cognition and fear in humans. *J Neurosci.* 2005;25(49):11489-11493.
29. Phelps EA, Delgado MR, Nearing KI, LeDoux JE. Extinction learning in humans: role of the amygdala and vmPFC. *Neuron.* 2004;43(6):897-905.
30. Williams LM, Kemp AH, Felmingham K, et al. Trauma modulates amygdala and medial prefrontal responses to consciously attended fear. *Neuroimage.* 2006;29(2):347-357.
31. Shin LM, Rauch SL, Pitman RK. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Ann N Y Acad Sci.* 2006;1071:67-79.
32. Liberzon I, Sripada CS. The functional neuroanatomy of PTSD: a critical review. *Prog Brain Res.* 2008;167:151-169.
33. Milad MR, Rauch SL, Pitman RK, Quirk GJ. Fear extinction in rats: implications for

human brain imaging and anxiety disorders. *Biol Psychol.* 2006;73(1):61-71.
34. Bryant RA, Felmingham K, Kemp A et al. Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for post-traumatic stress disorder. *Psychol Med.* 2008;38(4):555-561.
35. Felmingham K, Kemp A, Williams L et al. Changes in anterior cingulate and amygdala after cognitive behavior therapy of posttraumatic stress disorder. *Psychol Sci.* 2007;18(2):127-129.
36. Bohus B, Kovacs GL, de Wied D. Oxytocin, vasopressin and memory: opposite effects on consolidation and retrieval processes. *Brain Res.* 1978;157(2):414-417.
37. Amico JA, Robinson AG. *Oxytocin: Clinical and Laboratory Studies.* New York, NY: Elsevier; 1985.
38. Amico JA, Mantella RC, Vollmer RR, Li X. Anxiety and stress responses in female oxytocin deficient mice. *J Neuroendocrinol.* 2004;16(4):319-324.
39. Gulpinar MA, Yegen BC. The physiology of learning and memory: role of peptides and stress. *Curr Protein Pept Sci.* 2004;5(6):457-473.
40. Bosch OJ, Meddle SL, Beiderbeck DI, Douglas AJ, Neumann ID. Brain oxytocin correlates with maternal aggression: link to anxiety. *J Neurosci.* 2005;25(29):6807-6815.
41. Bale TL, Davis AM, Auger AP, Dorsa DM, McCarthy MM. CNS region-specific oxytocin receptor expression: importance in regulation of anxiety and sex behavior. *J Neurosci.* 2001;21(7):2546-2552.
42. Pare D, Quirk GJ, LeDoux JE. New vistas on amygdala networks in conditioned fear. *J Neurophysiol.* 2004;92(1):1-9.
43. Viviani D, Stoop R. Opposite effects of oxytocin and vasopressin on the emotional expression of the fear response. *Prog Brain Res.* 2008;170:207-218.
44. Debiec J. Peptides of love and fear: vasopressin and oxytocin modulate the integration of information in the amygdala. *Bioessays.* 2005;27(9):869-873.
45. LeDoux JE. Emotion circuits in the brain. *Annu Rev Neurosci.* 2000;23:155-184.
46. Domes G, Heinrichs M, Glascher J, Buchel C, Braus DF, Herpertz SC. Oxytocin attenuates amygdala responses to emotional faces regardless of valence. *Biol Psychiatry.* 2007;62(10):1187-1190.
47. Baumgartner T, Heinrichs M, Vonlanthen A, Fischbacher U, Fehr E. Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. *Neuron.* 2008;58(4):639-650.
48. Petrovic P, Kalisch R, Singer T, Dolan RJ. Oxytocin attenuates affective evaluations of conditioned faces and amygdala activity. *J Neurosci.* 2008;28(26):6607-6615.
49. Singer T, Snozzi R, Bird G, et al. Effects of oxytocin and prosocial behavior on brain responses to direct and vicariously experienced pain. *Emotion.* 2008;8(6):781-791.
50. Ressler KJ, Rothbaum BO, Tannenbaum L, et al. Cognitive enhancers as adjuncts to psychotherapy: Use of D-cycloserine in phobic individuals to facilitate extinction of fear. *Arch Gen Psychiatry.* 2004;61:1136-1144.
51. Hofmann SG, Meuret AE, Smits JA, et al. Augmentation of exposure therapy for social anxiety disorder with D-Cycloserine. *Arch Gen Psychiatry.* 2006;63:298-304.
52. Bouso JC, Doblin R, Farré M, Alcázar MA, Gómez-Jarabo G. MDMA-assisted psychotherapy using low doses in a small sample of women with chronic posttraumatic stress disorder. *J Psychoactive Drugs.* 2008;40:225-236.
53. Mithoefer M, Mithoefer A, Wagner M. Methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in subjects with chronic posttraumatic stress disorder: A Phase II clinical trial completed 19 September, 2008. Poster presented at: 24th Annual Meeting of the International Society of Traumatic Stress Studies; Chicago, IL.
54. Greer G, Tolbert R. Subjective reports of the effects of MDMA in a clinical setting. *J Psychoactive Drugs.* 1986;18:319-327.
55. Dumont GJH, Verkes RJ. A review of acute effects of 3,4-methylenedioxymethamphetamine in healthy volunteers. *J Psychopharmacol.* 2006;20:176-187.
56. Kolbrich EA, Goodwin RS, Gorelick DA, Hayes RJ, Stein EA, Huestis MA. Physiological and subjective responses to controlled oral 3,4-methylenedioxymethamphetamine administration. *J Clin Psychopharmacol.* 2008;28:432-440.
57. Thompson MR, Callaghan PD, Hunt GE, Cornish JL, McGregor IS. A role for oxytocin and 5-HT(1A) receptors in the prosocial effects of 3,4 methylenedioxymethamphetamine ("ecstasy"). *Neurosci.* 2007;146:509-514.
58. Thompson MR, Callaghan PD, Hunt GE, McGregor IS. Reduced sensitivity to MDMA-influenced facilitation of social behaviour in MDMA-pre-exposed rats. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32:1013-1021.
59. van Ree JM, Bohus B, Versteeg DH, de Wied D. Neurohypophyseal principles and memory processes. *Biochem Pharamcol.* 1978;27(14):1793-1800.
60. de Wied D. Behavioural actions of neurohypophysial peptides. *Proc R Soc Lond B Biol Sci.* 1980;210(1178):183-195.
61. Heinrichs M, Meinlschmidt G, Wippich W, Ehlert U, Hellhammer DH. Selective amnesic effects of oxytocin on human memory. *Physiol Behav.* 2004;83:31-38.
62. Ferrier BM, Kennett DJ, Devlin MC. Influence of oxytocin on human memory process. *Life Sci.* 1980;27(58):2311-2317.
63. Bruins J, Hijman R, van Ree JM. Effect of a single dose of desglycinamide-[Arg8]vasopressin or oxytocin on cognitive process in young healthy subjects. *Peptides.* 1992;13:461-468.
64. Fehm-Wolfsdorf G, Born J, Voigt KH, Fehm HL. Human memory and neurohypophyseal hormones: opposite effects of vasopressin and oxytocin. *Psychoneuroendocrinol.* 1984;9:285-292.
65. Fehm-Wolfsdorf G, Bachholz G,Born J,Voigt K, Fehm HL. Vasopressin but not oxytocin enhances cortical arousal: an integrative hypothesis on behavioural effects of neurohypophyseal hormones. *Psychopharmacol.* 1988;94:496-500.
66. Geenen V, Adam F, Baro V, et al. Inhibitory influence of oxytocin infusion on contingent negative variation and some memory tasks in normal men. *Psychoneuroendocrinol.* 1988;13:367-375.
67. Fehm-Wolfsdorf G, Born J. Behavioral effects of neurohypophyseal peptides in healthy volunteers: 10 years of research. *Peptides.* 1991;12:1399-1406.
68. Carter CS, DeVries AC, Getz LL. Physiological substrates of mammalian monogamy: the prairie vole model. *Neurosci Biobehav Rev.* 1995;19(2):303-314.
69. Petersson M. Cardiovascular effects of oxytocin. *Prog Brain Res.* 2002;139:281-288.
70. Young LJ, Wang Z. The neurobiology of pair bonding. *Nat Neurosci.* 2004;7(10):1048-1054.
71. Taylor SE, Gonzaga GC, Klein LC, Hu P, Greendale GA, Seeman TE. Relation of oxytocin to psychological stress responses and hypothalamic-pituitary-adrenocortical axis activity in older women. *Psychosom Med.* 2006;68(2):238-245.
72. Heinrichs M, Baumgartner T, Kirschbaum C, Ehlert U. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biol Psychiatry.* 2003;54(12):1389-1398.
73. Turner RA, Altemus M, Enos T, Cooper B, McGuinness T. Preliminary research on plasma oxytocin in normal cycling women: investigating emotion and interpersonal distress. *Psychiatry.* 1999;62(2):97-113.
74. Grewen KM, Girdler SS, Amico J, Light KC. Effects of partner support on resting oxytocin, cortisol, norepinephrine, and blood pressure before and after warm partner contact. *Psychosom Med.* 2005;67(4):531-538.
75. Light KC, Grewen KM, Amico JA. More frequent partner hugs and higher oxytocin levels are linked to lower blood pressure and heart rate in premenopausal women. *Biol Psychol.* 2005;69(1):5-21.
76. Neumann ID, Torner L, Wigger A. Brain oxytocin: differential inhibition of neuroendocrine stress responses and anxiety-related behaviour in virgin, pregnant and lactating rats. *Neuroscience.* 2000;95(2):567-575.
77. Windle RJ, Kershaw YM, Shanks N, Wood SA, Lightman SL, Ingram CD. Oxytocin attenuates stress-induced c-fos mRNA expression in specific forebrain regions associated with modulation of hypothalamo-pituitary-adrenal activity. *J Neurosci.* 2004;24(12):2974-2982.
78. Parker KJ, Buckmaster CL, Schatzberg AF, Lyons DM. Intranasal oxytocin administration attenuates the ACTH stress response in monkeys. *Psychoneuroendocrinol.* 2005;30(9):924-929.
79. Wise RA, Bauco P, Carlezon WA, Jr., Trojniar W. Self-stimulation and drug reward mechanisms. *Ann N Y Acad Sci.* 1992;654:192-198.
80. Di Chiara G. Nucleus accumbens shell and core dopamine: differential role in behavior and addiction. *Behav Brain Res.* 2002 ;137(1-2):75-114.
81. Drevets WC, Ongur D, Price JL. Neuroimaging abnormalities in the subgenual prefrontal cortex: implications for the pathophysiology of familial mood disorders. *Mol Psychiatry.* 1998;3(3):220-221.
82. Rauch SL, Shin LM, Segal E, et al. Selectively reduced regional cortical volumes in post-traumatic stress disorder. *Neuroreport.* 2003;14(7):913-16.
83. Sailer U, Robinson S, Fischmeister FP et al. Altered reward processing in the nucleus accumbens and mesial prefrontal cortex of patients with posttraumatic stress disorder. *Neuropsychologia.* 2008;46(11):2836-2844.
84. Puglisi-Allegra S, Imperato A, Angelucci L, Cabib S. Acute stress induces time-dependent responses in dopamine mesolimbic system. *Brain Res.* 1991;554(1-2):217-222.
85. Cabib S, Puglisi-Allegra S. Stress, depression and the mesolimbic dopamine system. *Psychopharmacol (Berl).* 1996;128(4):331-342.
86. Jacobsen LK, Southwick SM, Kosten TR. Substance use disorders in patients with posttraumatic stress disorder: a review of the literature. *Am J Psychiatry.* 2001;158(8):1184-1190.
87. Elman I, Ariely D, Mazar N et al. Probing reward function in post-traumatic stress disorder with beautiful facial images. *Psychiatry Res.* 2005;135(3):179-183.
88. Elman I, Lowen S, Frederick BB, Chi W, Becerra L, Pitman RK. Functional neuroimaging of reward circuitry responsivity to monetary gains and losses in posttraumatic stress disorder. *Biol Psychiatry.* 2009;66:1083-1090.
89. Hopper JW, Pitman RK, Su Z et al. Probing reward function in posttraumatic stress disorder: expectancy and satisfaction with monetary gains and losses. *J Psychiatr Res.* 2008;42(10):802-807.
90. Stein DJ. Oxytocin and vasopressin: social neuropeptides. *CNS Spectr.* 2009;14(11):602-606.
91. Taylor SE, Klein LC, Lewis BP, Gruenewald TL, Gurung RA, Updegraff JA. Biobehavioral responses to stress in females: tend-and-befriend, not fight-or-flight. *Psychol Rev.* 2000;107(3):411-429.
92. Neumann ID. Involvement of the brain oxytocin system in stress coping: interactions with the hypothalamo-pituitary-adrenal axis. *Prog Brain Res.* 2002;139:147-162.
93. Brewin CR, Andrews B, Valentine JD. Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. *J Consult Clin Psychol.* 2000;68(5):748-766.
94. Ozer EJ, Best SR, Lipsey TL, Weiss DS. Predictors of posttraumatic stress disorder and symptoms in adults: a meta-analysis. *Psychol Bull.* 2003;129(1):52-73.
95. Ditzen B, Schaer M, Gabriel B, Bodenmann G, Ehlert U, Heinrichs M. Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. *Biol Psychiatry.* 2009;65(9):728-731.
96. Gouin JP, Carter CS, Pournajafi-Nazarloo H, et al. Marital behavior, oxytocin, vasopressin, and wound healing. *Psychoneuroendocrinol.* 2010. In press.
97. Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E. Oxytocin increases trust in humans. *Nature.* 2005;435(7042):673-676.
98. Horvath AO, Symonds BD. Relation between working alliance and outcome in psychotherapy: A meta-analysis. *J Counseling Psychol.* 1991;38(2):139-149.
99. Martin DJ, Garske JP, Davis MK. Relation of the therapeutic alliance with outcome and

other variables: a meta-analytic review. *J Consult Clin Psychol.* 2000;68(3):438-450.
100. Cloitre M, Koenen KC, Cohen LR, Han H. Skills training in affective and interpersonal regulation followed by exposure: a phase-based treatment for PTSD related to childhood abuse. *J Consult Clin Psychol.* 2002;70(5):1067-1074.
101. Cloitre M, Stovall-McClough KC, Miranda R, Chemtob CM. Therapeutic alliance, negative mood regulation, and treatment outcome in child abuse-related posttraumatic stress disorder. *J Consult Clin Psychol.* 2004;72(3):411-416.
102. Charuvastra A, Cloitre M. Social bonds and posttraumatic stress disorder. *Annu Rev Psychol.* 2008;59:301-328.
103. Morris JB, Beck AT. The efficacy of antidepressant drugs. A review of research (1958-1972). *Arch Gen Psychiatry.* 1974;30(5):667-674.
104. Krupnick JL, Sotsky SM, Simmens S et al. The role of the therapeutic alliance in psychotherapy and pharmacotherapy outcome: Findings in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *J Consult Clin Psychol.* 1996;64(3):532-539.
105. Insel TR, Fernald RD. How the brain processes social information: searching for the social brain. *Annu Rev Neurosci.* 2004;27:697-722.
106. Zak PJ, Kurzban R, Matzner WT. Oxytocin is associated with human trustworthiness. *Horm Behav.* 2005;48:522-527.
107. Buchheim A, Heinrichs M, George C et al. Oxytocin enhances the experience of attachment security. *Psychoneuroendocrinol.* 2009;34(9):1417-1422.
108. Heinrichs M, Domes G. Neuropeptides and social behaviour: effects of oxytocin and vasopressin in humans. *Prog Brain Res.* 2008;170:337-350.
109. Mallinckrodt B. Clients' representations of childhood emotional bonds with parents, social support, and formation of the working alliance. *J Counseling Psychol.* 1991;38(4):401-409.
110. Horvath AO, Greenberg LS. *The Working Alliance: Theory, Research and Practice.* New York, NY: Wiley; 1994.
111. Tops M, van Peer JM, Korf J, Wijers AA, Tucker DM. Anxiety, cortisol, and attachment predict plasma oxytocin. *Psychophysiol.* 2007;44(3):444-449.
112. Fries AB, Ziegler TE, Kurian JR, Jacoris S, Pollak SD. Early experience in humans is associated with changes in neuropeptides critical for regulating social behavior. *Proc Natl Acad Sci U S A.* 2005;102(47):17237-17240.
113. Heim C, Young DJ, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. Lower CSF oxytocin concentrations in women with a history of childhood abuse. *Mol Psychiatry.* 2009;14:954-958.
114. Meinlschmidt G, Heim C. Sensitivity to intranasal oxytocin in adult men with early parental separation. *Biol Psychiatry.* 2007;61:1109-1111.
115. Benoit M, Bouthillier D, Moss E, Rousseau C, Brunet A. Emotion regulation strategies as mediators of the association between level of attachment security and PTSD symptoms following trauma in adulthood. *Anxiety Stress Coping.* 2009;26:1-18.
116. Carter S. The chemistry of child neglect: Do oxytocin and vasopressin mediate the effects of early experience? *PNAS.* 2005;102(51):18247-18248.
117. Kramer KM, Cushing BS, Carter CS, Wu J, OttingerMA. Sex and species differences in plasma oxytocin using an enzymeimmunoassay. *Can J Zool.* 2004;82:1194-1200.
118. Zingg HH. Oxytocin (p. 779-802). In: D Pfaff et al, eds. *Hormones, Brain and Behavior.* Vol. III. San Diego, CA: Academic Press; 2002.
119. Zingg HH, Laporte SA. The oxytocin receptor. *Trends Endocrinol Metab.* 2003;14:222-227.
120. Carter CS. Sex differences in oxytocin and vasopressin: Implications for autism spectrum disorders? *Behavioural Brain Res.* 2007;176:170-186.
121. Yamamoto Y, Cushing BS, Kramer KM, Epperson PD, Hoffman GE, Carter CS. Neonatal manipulations of oxytocin alter expression of oxytocin and vasopressin immunoreactive cells in the paraventricular nucleus of the hypothalamus in a gender-specific manner. *Neurosci.* 2004;125(4):947-955.
122. Bales KL, Plotsky PM, Young LJ, et al. Neonatal oxytocin manipulations have long-lasting, sexually dimorphic effects on vasopressin receptors. *Neurosci.* 2007;144:38-45.
123. Carter CS, Boone EM, Pournajafi-Nazarloo H, Bales KL. The consequences of early experiences and exposure to oxytocin and vasopressin are sexually-dimorphic. *Developmental Neurosci.* 2009;31:332-341.
124. de Kloet ER, Voorhuis DA, Boschma Y, Elands J. Estradiol modulates density of putative 'oxytocin receptors' in discrete rat brain regions. *Neuroendocrinol.* 1986;44(4):415-421.
125. McCarthy MM. Estrogen modulation of oxytocin and its relation to behavior. *Adv Exp Med Biol.* 1995;395:235-245.
126. Bao A-M, Hestiantoro A, Van Someren EJW, Swaab DF, Zhou J-N. Colocalization of corticotropin-releasing hormone and oestrogen receptor in the paraventricular nucleus of the hypothalamus in mood disorders. *Brain.* 2005;128:1301-1313.
127. BaoA-M, Fischer DF, Wu Y-H et al. A direct androgenic involvement in the expression of human corticotropin-releasing hormone. *Mol Psychiatry.* 2006;11:567-576.
128. Luckow A, Reifman A, McIntosh DN. Gender differences in coping: A meta-analysis. Poster presented at: the 106th Annual Convention of the American Psychological Association; San Francisco, CA; 1988.
129. Craske MG. *The Origins of Phobias and Anxiety Disorders: Why More Women than Men.* Oxford, England: Elsevier Science; 2003.
130. Andrews B, Brewin CR, Rose S. Gender, social support, and PTSD in victims of violent crime. *J Trauma Stress.* 2003;16(4):421-427.
131. Ahern J, Galea S, Fernandez WG, Koci B, Waldman R, Vlahov D. Gender, social support, and posttraumatic stress in postwar Kosovo. *J Nerv Ment Dis.* 2004;192(11):762-770.
132. Weismann MM, Nerai Y, Das A, et al. Gender differences in posttraumatic stress disorder among primary care patients after the World Trade Center attack of September 11, 2001. *Gender Med.* 2005;2:76-87.
133. Spreckelmeyer KN, Krach S, Kohls G, et al. Anticipation of monetary and social reward differently activates mesolimbic brain structures in men and women. *Soc Cogn Affect Neurosci.* 2009;4(2):158-165.
134. Pitman RK, Orr SP, Lasko NB. Effects of intranasal vasopressin and oxytocin on physiologic responding during personal combat imagery in Vietnam veterans with posttraumatic stress disorder. *Psychiatry Res.* 1993;48(2):107-117.
135. Born J, Lange T, Kern W, McGregor GP, Bickel U, Fehm HL. Sniffing neuropeptides: a transnasal approach to the human brain. *Nat Neurosci.* 2002;5:514-516.
136. Heresco-Levy U, Kremer I, Javit DC, et al. Pilot-controlled trial of D-cycloserine for the treatment of post-traumatic stress disorder. *Int J Neurospychopharmacol.* 2002;5:301-307.