Imaging in posttraumatic stress disorder

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Purpose of review

Posttraumatic stress disorder (PTSD) is an unusual diagnosis in requiring an external environmental stressor to be present, in addition to the conventional signs and symptoms. Early controversies surrounded the validity of its criteria and whether there was a common neural basis for this disorder. This review summarizes recent neuroimaging studies, which have begun to clarify the basis of PTSD by combining imaging data with investigations of the stress response, and by employing fear and extinction learning paradigms to probe the underlying neural changes in those with the disorder.

Recent findings

We examine the recent literature with three main aims. First, to assess whether structural changes in PTSD are causal of or secondary to the condition. Second, to summarize current understanding of the relationship between neural activation and the stress responses within the autonomic nervous system in PTSD patients and controls. Finally, we examine neural mechanisms underlying the response to fear and reward, demonstrating how these are altered in PTSD.

Summary

A greater understanding of the brain mechanisms underlying healthy responses to fear and stress, and their alterations in PTSD, has opened up a new spectrum of possible pharmacological agents by which to approach to PTSD therapy and has begun to reveal the neural processes underlying the common failure of response to current treatments.

Keywords

fear, functional, imaging, PTSD, reward, structural

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Introduction

For those who suffer posttraumatic stress disorder (PTSD), a world which once seemed full of appetitive potential has become fraught with perceived aversive threat [1]. This alteration in the mind has been shown through neuroimaging to be associated with equally striking changes in the brain. Not only do PTSD sufferers exhibit functional changes in brain centres involved in memory, fear processing, and emotion, but they also demonstrate structural abnormalities in these areas, which include hippocampus, amygdala, and medial prefrontal cortex [2]. However the direction of structural and functional causality, the overlap between normal stress responses and PTSD, and the role of neural processing of fear in PTSD remain contentious.

Can brain changes predispose to the development of posttraumatic stress disorder?

Several studies have demonstrated structural changes in PTSD, particularly in hippocampus, amygdala, and anterior cingulate cortex (ACC) [3]. Is it possible to disentangle brain changes that predispose to the disorder from those which arise as a consequence of PTSD? Employing structural MRI, Gilbertson *et al.* [4] found that the twins of combat-exposed severe PTSD sufferers, as well as the sufferers themselves, had significantly smaller hippocampal volumes than non-PTSD twin pairs. This suggests that smaller hippocampal volume predisposes to the development of PTSD following trauma. However, recently these findings were not replicated by the same group [5]. Instead, Kasai *et al.* found that, compared both with noncombat-exposed twins and with combat-exposed twins without PTSD, combat-exposed twins with PTSD had significantly lower grey matter density of the pregenual ACC. This suggests that ACC changes follow the development of PTSD. Taken together, results from these studies imply that certain brain changes follow development of PTSD, whereas others predispose to it. However, smaller hippocampal volume, if found in future studies to be a robust precursor to PTSD, cannot be viewed as a specific predisposing factor, since similar changes have been highlighted in schizophrenia [6].

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It is possible that within-area changes in PTSD may be both a predisposing factor and a consequence of the disorder. A recent study suggests that hippocampal loss is significantly negatively correlated with duration of PTSD [7]. Taken together with the findings of Gilbertson *et al.*, this implies that a primary hippocampal volume decrease predisposes to PTSD, and that PTSD in turn causes a secondary loss of volume. Such duality of cause and effect may also apply in the ACC. Using a Vietnam veteran twin-study design, Shin *et al.* [8•] employed positron emission tomography (PET) to investigate functional changes in PTSD patients. The authors reported increased resting regional cerebral activity within the ACC in healthy twins whose combat-exposed twin had developed PTSD, compared with healthy probands whose combat-exposed twin did not develop PTSD. This suggests that increased metabolic activity in ACC may be a familial risk factor for the development of PTSD. Taken together with the finding of an acquired structural deficit in ACC in PTSD by Kasai *et al.* [5], these results suggest that subtle alterations in this region are evident prior to the onset of any disorder, observed initially as functional metabolic change but which become more prominent after developing the disorder, sufficient to be observable as a structural deficit.

These studies suggest that abnormalities in brain structure and function may predispose to the development of PTSD, as well as developing in PTSD sufferers. Prospective studies examining the longitudinal development of brain changes in the years following onset of PTSD will provide more accurate views of the balance of these effects in different brain regions.

Neuroimaging the stress response

Considerable data from animal and human studies suggests that heightened stress responses induce neural toxicity and diminution in volume of certain brain areas. Animal studies in support of this hypothesis show a link between chronic stress and damage to the hippocampal region, via corticosteroid neurotoxicity and other mechanisms [9]. Early PTSD research focused on evidence in humans for dysregulated stress responses, examining plasma corticosteroid and adrenocorticotropic hormone (ACTH) levels. Although some studies found dysregulation in the limbic hypothalamic pituitary axis (LHPA) [10], others did not [11]. Thus, although PTSD is in name a disorder of stress, the extent to which this moniker reflects its pathophysiology remains unclear.

Recently, this question has been addressed by studies combining imaging with hormonal measurements of the LHPA axis. King *et al.* [12•] combined PET imaging with measurements of plasma ACTH levels in Vietnam veterans with and without PTSD. In response to personal traumatic scripts, around half the patients (in both patient and control groups) mounted an ACTH stress response. ACTH response was associated with a large deactivation of rostral Medial prefrontal cortex (mPFC), rostral ACC, and orbitofrontal cortex. However, no difference in ACTH response, or in regional cerebral blood flow (rCBF), was apparent when comparing PTSD sufferers who were ACTH responders with control ACTH responders. This suggests that there is no systematic relationship between PTSD and dysregulation of the LHPA axis.

More recently, Carrion *et al.* [13] examined the relationship between structural brain changes in PTSD and levels of the corticosteroid cortisol. In a sample of patients aged 10–16 years, the authors found significantly decreased left prefrontal cortical volume compared with controls, as well as a negative relationship between cortisol levels and prefrontal cortex (PFC) volume across the entire sample. This relationship was not significant, however, in either group alone, suggesting that combining groups provided enough statistical power for the finding of a negative relationship between cortisol levels and PFC volume to be robust, but that the groups themselves were similar in this regard. Thus, both functional and structural data demonstrate a relationship between corticosteroid activity and PFC function, but do not show any systematic differences in this relationship in PTSD patients compared with controls.

However, recent work using functional magnetic resonance imaging (fMRI) suggests that brain responses associated with autonomic activation, measured using skin conductance response (SCR), do appear different in patients with PTSD. Felmingham *et al.* [14•] found that, during an auditory odd-ball task, both PTSD patients and controls had SCRs of similar magnitude and number. Controls responded with increased ventral ACC (vACC) activation to oddball stimuli when they also showed an altered SCR response. In contrast, when PTSD patients mounted a SCR, this was associated with an increased response in dorsal ACC (dACC) compared with controls. These results highlight differential activation of closely related cortical regions in PTSD despite behavioural responses of similar magnitude and probability.

Future work incorporating an assessment of the time course of hormonal responses may tease out subtle changes in LHPA activation associated with PTSD. A recent study found greater daily variations in cortisol levels in traumatized versus nontraumatized youths, the authors suggesting that these extremes of variation might contribute to neurotoxicity [15]. Further studies are needed to elucidate the complex relationship between PTSD and stress.

Fear, reward, memory: posttraumatic stress disorder re-evaluated

Following recognition of the limitations of traditional comparisons of patients and control subjects in paradigms narrowly focused on inducing PTSD symptoms, there has been increasing interest in basic neuropsychological processes which are likely to be activated in a wide range of daily settings [16]. Of particular interest are studies of the processing of fearful stimuli, associated with activation in a network of areas including the amygdala, mPFC, and hippocampus in healthy participants [17]. Naturally, the process by which fearful stimuli are subsequently made neutral or else extinguished holds intuitive appeal as being highly relevant to PTSD, in which extinction of learned fear responses is considered a core difficulty [16,18]. Successful fear extinction learning refers to the elimination of a learned fear response. Milad *et al.* [17] employed an operant conditioning process to induce fear extinction learning in patients with PTSD, and trauma-exposed controls, during fMRI scanning. During fear conditioning, ventromedial prefrontal cortex (vmPFC) blood-oxygen level dependent (BOLD) responses increased in controls, but decreased in patients; by contrast, amygdala responses increased in patients, but decreased in controls. However, SCR responses were similar in controls and patients, suggesting equivalent learning. During extinction recall, which occurred 1 day after patients learnt that one of two conditioned stimuli had become innocuous, SCR responses in controls to the stimulus that had been extinguished were significantly smaller compared with the stimulus that had not been extinguished. The PTSD group, however, showed no such diminution in SCR response between stimuli, suggesting diminished recall of extinction memory. BOLD responses in the extinction stage were significantly greater in vmPFC and hippocampus in controls compared with PTSD patients, and significantly greater in dACC in patients compared with controls.

These data suggest that failure to activate vmPFC and hippocampus during recall, and overactivation of dACC during recall, contribute to deficient expression of extinction memory in PTSD patients. A more recent study has extended these results, showing that not only do patients maintain fear responses to conditioned stimuli themselves, but they generalize these responses to the contexts in which fearful cues are presented [19•].

It seems clear, then, that PTSD can in part be understood as a dysregulation in unlearning of fear responses. But does this offer a complete framework to understand the disorder? According to the wider clinical criteria, clearly not: anhedonia and emotional numbing are elements of PTSD which do not have direct fear-related correlates. A promising recent study has instead focused on these motivation-related symptoms by examining the question of reward processing in PTSD.

Elman *et al.* [20•] used fMRI to image participants during a 'wheel-of-fortune' paradigm designed to induce both expectancy of reward (corresponding to the 'spinning' phase of one of three wheels) and outcome (the gain or loss of money when the wheel stops). Based on the termination patterns of dopaminergic neurons, the authors expected alterations in reward-signalling in the striatum. As predicted, the authors found less activation to monetary gains versus losses in both dorsal and ventral striatum in PTSD patients when compared with controls. This decrement was correlated with self-reported motivational and social deficits. Interestingly, recent evidence suggests that, in healthy participants, if the threat of pain is associated with potential reward, ventral striatal activation diminishes, as does activation in vACC [21••]. Although Elman *et al.* interpret their results as reflecting a primary decrease in the capacity to experience pleasure, it is also possible that the decreases in striatal activation in PTSD may be linked to an overvalued anticipation of pain, involving neural structures associated with fear processing. This latter possibility has led to the suggestion that the loss of appreciation of pleasure consequent on an overvalued expectation of pain may underlie many symptoms of PTSD [22•].

Therapeutic implications

Several pharmacological and psychotherapeutic approaches to PTSD exist. Selective serotonin reuptake inhibitors (SSRIs) are approved for use in PTSD, and, of the psychotherapies, cognitive behavioural therapy and eye-movement desensitization (EMDR) are most commonly employed [23]. These approaches are ineffective in 25–50% of all patients who enrol in clinical trials [23,24]. Why do certain patients fail to respond to interventions which are so effective in others? Imaging studies have begun to investigate structural and functional differences between these groups. In addition, studies described above are beginning to be used to guide trials of novel therapeutic agents.

In line with meta-analyses [24], Bryant *et al.* [25] found that half of patients responded to cognitive behavioural therapy (CBT) with improved Clinician Administered PTSD Scale (CAPS) scores ($n = 7$), whereas half did not ($n = 6$). Based on pretherapy structural MRI scans, the authors showed that nonresponders had significantly smaller rostral anterior cingulate cortex (rACC) volumes compared with responders. Given the role of cingulate cortex in extinction of fear learning, described above, and the similarity of CBT exposure therapy and extinction of fear learning, this finding is consistent with the notion of PTSD as a disorder of extinction. The authors suggest

that patients with larger rACC volumes are better able to control fear responses to exposure therapy, and therefore avoid the overwhelming stress response which can reduce the efficacy of CBT in many PTSD patients. Consistent with this notion, the rACC has previously been implicated in cognitive control over emotional processes [26].

More recently, Nardo *et al.* [27•] administered EMDR and examined MRI grey matter density in Stockholm train-drivers who had developed PTSD following either assaults or 'person under a train' accidents. Nonresponders ($n = 5$) to EMDR displayed decreased grey-matter density in a variety of brain areas, including posterior cingulate and right amygdala, compared with responders ($n = 10$). In addition to structural changes, functional brain changes in PTSD sufferers may predict treatment response to therapy [28]. CBT nonresponders showed excessive bilateral amygdala and vACC BOLD activation when rapidly presented with backward-masked (unconsciously perceived) fearful faces during fMRI scanning.

Imaging studies are also being used to guide novel therapies. A recent investigation combined repetitive frontal trans-cranial magnetic stimulation (rTMS) with imaginal exposure therapy [29•]. Although only eight PTSD treatment-refractory patients were recruited, and no control group was used, the small decrease in hyperarousal symptoms which the authors found with rTMS plus exposure therapy suggests the need for larger studies in this area.

Driven in part by imaging studies, the new conception of PTSD as reflecting dysregulated approach-avoidance behaviour has led to novel pharmacological agents being proposed. Recently, methylenedioxymethamphetamine (MDMA), a Class A substance in the United Kingdom, has been tested in a small group of PTSD treatment-resistant patients ($n = 12$) in combination with psychotherapy, compared with psychotherapy plus placebo ($n = 8$) [30•]. The authors postulated that MDMA's prosocial and euphoric effects would counteract fear responses during therapy and permit patients to re-experience traumatic memories without a stress response, thereby facilitating extinction of fear learning. Indeed, a significant decrease in CAPS scores was found in 10/12 in the MDMA treatment group patients compared with 2/8 in the placebo group. Though this study must be interpreted with caution due to small sample size and a choice of psychotherapy which is not well validated for PTSD, further work in this area may prove fruitful. MDMA exerts its effects largely through serotonin release, suggesting a mechanism of action in treatment similar to SSRIs. However, in addition, MDMA leads to release of neurohormones, including oxytocin. Oxytocin has been shown to decrease amygdala activity to fear-inducing breaches in trust, and to increase trust-related behaviour [31]. For these reasons, and several others, oxytocin has very recently been proposed as a putative pharmacological tool in the treatment of PTSD [32•].

In summary, imaging studies are revealing structural and functional causes for differential patient response to standard treatments, and, by enlarging the framework in which we understand PTSD, they are beginning to suggest novel therapeutic interventions.

Conclusion

This review has presented data elucidating the complex and possibly two-way relationship between structural changes and PTSD. One possible mechanism for such structural changes and PTSD is activation of the LHPA axis, by memories or other stimuli perceived as threatening, which may lead to corticosteroid-related neurotoxicity. However, although the LHPA axis may be activated more frequently in PTSD, the relationship between activation and neural activity appears similar in patients and controls. Sophisticated behavioural/imaging experiments in fear extinction have shown that formerly fear-inducing, but currently innocuous, stimuli are still perceived as fearful by PTSD sufferers, who show persistently enhanced autonomic activation and changes in activity in hippocampus, ACC, and mPFC to such stimuli. By contrast, brain responses to reward-related stimuli appear to be attenuated in those with PTSD. A novel view of the condition is emerging as a result of these studies, which suggests that the condition may best be understood as a dysregulation in approach-reward and fear-avoidance processing. Frequent activations of the LHPA axis, and neurotoxicity, may be sequelae of, or maintain, this imbalance. This new conception is generating novel proposals for therapies targeted at neural systems of fear and reward. At the same time, imaging studies have revealed systematic neural biases underlying the failure of current treatments in some patients, and such data may help to guide future therapeutic regimes.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 81–82).

1 Janoff-Bulman R. Shattered assumptions: towards a new psychology of trauma. Maxwell Macmillan Canada, Maxwell Macmillan International: Free Press; 1992.

2 Shin LM, Rauch SL, Pitman RK. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. Ann N Y Acad Sci 2006; 1071:67–79.

3 Francati V, Vermetten E, Bremner JD. Functional neuroimaging studies in posttraumatic stress disorder: review of current methods and findings. Depress Anxiety 2007; 24:202–218.

4 Gilbertson MW, Shenton ME, Ciszewski A, *et al.* Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci 2002; 5:1242–1247.

5 Kasai K, Yamasue H, Gilbertson MW, *et al.* Evidence for acquired pregenual anterior cingulate gray matter loss from a twin study of combat-related posttraumatic stress disorder. Biol Psychiatry 2008; 63:550–556.

6 Syvälahti EK. Biological factors in schizophrenia. Structural and functional aspects. Br J Psychiatry Suppl 1994; 23:9–14.

7 Felmingham K, Williams LM, Whitford TJ, *et al.* Duration of posttraumatic stress disorder predicts hippocampal grey matter loss. Neuroreport 2009; 20:1402–1406.

8 • Shin LM, Lasko NB, Macklin ML, *et al.* Resting metabolic activity in the cingulate cortex and vulnerability to posttraumatic stress disorder. Arch Gen Psychiatry 2009; 66:1099–1107.
One of the few studies that attempt to distinguish functional brain changes which result from PTSD from those which may predispose to acquiring the condition. The finding of increased dACC activation in PTSD patients and their twins suggests a familial, predisposing component to the disorder, challenging the notion of the traumatic event as the sole causative factor in PTSD.

9 Sapolsky RM, Armanini MP, Packan DR, *et al.* Glucocorticoid feedback inhibition of adrenocorticotropic hormone secretagogue release. Relationship to corticosteroid receptor occupancy in various limbic sites. Neuroendocrinology 1990; 51:328–336.

10 Yehuda R, Southwick SM, Nussbaum G, *et al.* Low urinary cortisol excretion in patients with posttraumatic stress disorder. J Nerv Ment Dis 1990; 178:366–369.

11 Metzger LJ, Carson MA, Lasko NB, *et al.* Basal and suppressed salivary cortisol in female Vietnam nurse veterans with and without PTSD. Psychiatry Res 2008; 161:330–335.

12 • King AP, Abelson JL, Britton JC, *et al.* Medial prefrontal cortex and right insula activity predict plasma ACTH response to trauma recall. Neuroimage 2009; 47:872–880.
This study gains credence by presenting an interesting negative result: PTSD patients did not display greater activation of LHPA axis or systematic changes in brain activation compared with controls. Rather, large variability in stress-response and neural activity was found across all participants, calling into question the relationship between PTSD and stress.

13 Carrion VG, Weems CF, Reiss AL. Stress predicts brain changes in children: a pilot longitudinal study on youth stress, posttraumatic stress disorder, and the hippocampus. Pediatrics 2007; 119:509–516.

14 • Felmingham KL, Williams LM, Kemp AH, *et al.* Anterior cingulate activity to salient stimuli is modulated by autonomic arousal in posttraumatic stress disorder. Psychiatry Res 2009; 173:59–62.
A methodologically ambitious study which is the first to link changes in neural imaging with autonomic arousal in PTSD patients compared with controls. By using a standard oddball auditory stimulus design, rather than attempting to induce specific trauma-related activation, this study is also part of a growing number which seek to understand how PTSD patients respond to stimuli more akin to those in daily life than direct reminders of trauma, such as combat sounds.

15 Weems CF, Carrión VG. Brief report: diurnal salivary cortisol in youth – clarifying the nature of posttraumatic stress dysregulation. J Pediatr Psychol 2009; 34:389–395.

16 Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research – past, present, and future. Biol Psychiatry 2006; 60:376–382.

17 Milad MR, Wright CI, Orr SP, *et al.* Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. Biol Psychiatry 2007; 62:446–454.

18 Shin LM, Handwerger K. Is posttraumatic stress disorder a stress-induced fear circuitry disorder? J Trauma Stress 2009; 5:409–415; doi: 10.1002/jts.20442.

19 • Rougemont-Bücking A, Linnman C, Zeffiro TA, *et al.* Altered processing of contextual information during fear extinction in PTSD: an fMRI Study [Internet]. CNS Neurosci Ther 2010. doi: 10.1111/j.1755-5949.2010.00152.x. [Epub ahead of print]
An interesting extension to previous work, which shows that altered recall of fear extinction in PTSD patients extends to the context in which the stimuli are experienced. Although this is unsurprising given the nature of conditioning paradigms, it nonetheless begins to provide a scientific basis for the tendency of PTSD sufferers to re-experience events given environmental reminders.

20 • Elman I, Lowen S, Frederick BB, *et al.* Functional neuroimaging of reward circuitry responsivity to monetary gains and losses in posttraumatic stress disorder. Biol Psychiatry 2009; 66:1083–1090.
A study whose methodology should be both emulated and improved: emulated, because it provides interesting initial data on alterations in reward-related processing in PTSD patients, and improved, because it employed a low-threshold measure of attention (a screen press) which might not control fully for attentional effects between groups.

21 •• Talmi D, Dayan P, Kiebel SJ, *et al.* How humans integrate the prospects of pain and reward during choice. J Neurosci 2009; 29:14617–14626.
Data in healthy subjects from a group pioneering understanding of the neural basis of reward shows for the first time that the possibility of pain reduces neural activity subserving reward expectation in ventral striatum. It would be of great interest to repeat this study in PTSD patients, who might have a greater baseline expectation of pain and display an altered balance of pain/pleasure integration.

22 • Stein MB, Paulus MP. Imbalance of approach and avoidance: the yin and yang of anxiety disorders. Biol Psychiatry 2009; 66:1072–1074.
The authors propose a view of PTSD which encompasses both excessive fear and diminished reward responses. The main value of this article is its staunch encouragement of further research into reward-related deficits in PTSD.

23 Foa E, International Society for Traumatic Stress Studies. Effective treatments for PTSD: practice guidelines. New York: the Guilford Press; 2000.

24 Bradley R, Greene J, Russ E, *et al.* A multidimensional meta-analysis of psychotherapy for PTSD. Am J Psychiatry 2005; 162:214–227.

25 Bryant RA, Felmingham K, Whitford TJ, *et al.* Rostral anterior cingulate volume predicts treatment response to cognitive-behavioural therapy for posttraumatic stress disorder. J Psychiatry Neurosci 2008; 33:142–146.

26 Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci (Regul Ed) 2000; 4:215–222.

27 • Nardo D, Högberg G, Looi JCL, *et al.* Gray matter density in limbic and paralimbic cortices is associated with trauma load and EMDR outcome in PTSD patients. J Psychiatr Res 2010; 44:477–485.
The first study attempting to understand the neural basis of different responses to EMDR therapy in PTSD patients. Part of a growing body of work finding distinct structural differences in the brains of PTSD patients who do not respond to current treatments.

28 Bryant RA, Felmingham K, Kemp A, *et al.* Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for posttraumatic stress disorder. Psychol Med 2008; 38:555–561.

29 • Osuch EA, Benson BE, Luckenbaugh DA, *et al.* Repetitive TMS combined with exposure therapy for PTSD: a preliminary study. J Anxiety Disord 2009; 23:54–59.
This study acknowledges its preliminary nature, and its results are not particularly promising for rTMS. Also, the authors' rationale for attempting to deactivate frontal structures is not entirely clear. However, it is striking that, even in this small sample of patients refractory to other treatments, some additional benefit may be associated with rTMS. There is enough here to prompt larger-scale investigations, possibly directing stimulation at different brain regions.

30 • Mithoefer MC, Wagner MT, Mithoefer AT, *et al.* The safety and efficacy of {+/-}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study [Internet]. J Psychopharmacol 2010. doi: 10.1177/0269881110378371. [Epub ahead of print]
Controversial though the therapeutic use of the class A substance MDMA must be, results from this study suggest that further trials are warranted on a larger scale, and with a form of adjunct psychotherapy, such as CBT or EMDR, which is known to be effective in PTSD.

31 Baumgartner T, Heinrichs M, Vonlanthen A, *et al.* Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. Neuron 2008; 58:639–650.

32 • Olff M, Langeland W, Witteveen A, Denys D. A psychobiological rationale for oxytocin in the treatment of posttraumatic stress disorder. CNS Spectr 2010; 15:522–530.
The authors draw together a wide cross-section of studies from within and beyond the PTSD literature in their persuasive attempts to prompt further investigation into the role of oxytocin as a novel therapeutic agent in PTSD.