Nonconventional Interventions for Chronic Post—Traumatic Stress Disorder (PTSD): Ketamine, Repetitive Trans-Cranial...

Article *in* Journal of Trauma & Dissociation · July 2015

DOI: 10.1080/15299732.2015.1046101 · Source: PubMed

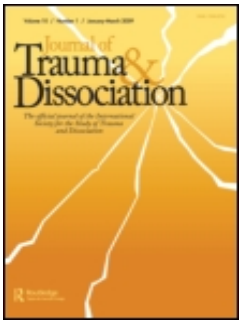
CITATIONS
4

READS
380

4 authors, including:

Basant K Pradhan
Cooper University Hospital & Cooper Med Scho...
42 PUBLICATIONS **179** CITATIONS
SEE PROFILE

Tapan Parikh
Cooper University Hospital
10 PUBLICATIONS **18** CITATIONS
SEE PROFILE



Journal of Trauma & Dissociation

ISSN: 1529-9732 (Print) 1529-9740 (Online) Journal homepage: http://www.tandfonline.com/loi/wjtd20

Nonconventional interventions for chronic post-traumatic stress disorder: Ketamine, repetitive trans-cranial magnetic stimulation (rTMS), and alternative approaches

Basant Pradhan MD, Jessica Kluewer D'Amico MA, Ramkrishna Makani MD, MPH & Tapan Parikh MD, MPH

To cite this article: Basant Pradhan MD, Jessica Kluewer D'Amico MA, Ramkrishna Makani MD, MPH & Tapan Parikh MD, MPH (2016) Nonconventional interventions for chronic post-traumatic stress disorder: Ketamine, repetitive trans-cranial magnetic stimulation (rTMS), and alternative approaches, Journal of Trauma & Dissociation, 17:1, 35-54, DOI: 10.1080/15299732.2015.1046101

To link to this article: http://dx.doi.org/10.1080/15299732.2015.1046101

JOURNAL OF TRAUMA & DISSOCIATION
2016, VOL. 17, NO. 1, 35–54
http://dx.doi.org/10.1080/15299732.2015.1046101

Routledge
Taylor & Francis Group

ARTICLE

Nonconventional interventions for chronic post-traumatic stress disorder: Ketamine, repetitive trans-cranial magnetic stimulation (rTMS), and alternative approaches

Basant Pradhan, MD [a], Jessica Kluewer D'Amico, MA[b], Ramkrishna Makani, MD, MPH [a] and Tapan Parikh, MD, MPH [a]

[a]Department of Psychiatry, Cooper University Hospital and Cooper Medical School of Rowan University, Camden, New Jersey, USA; [b]Cooper Medical School of Rowan University, Camden, New Jersey, USA

ABSTRACT

It is alarming that only 59% of those who have post-traumatic stress disorder (PTSD) respond to selective serotonin reuptake inhibitors. Many existing treatments, both pharmacological and nonpharmacological, do not directly target trauma memories that lay at the core of the PTSD pathogenesis. Notable exceptions are medications like ketamine and propranolol and trauma-focused psychotherapies like eye-movement desensitization and reprocessing therapy (developed by Shapiro) and Trauma Interventions using Mindfulness Based Extinction and Reconsolidation (TIMBER) for trauma memories (developed by Pradhan). Although the antidepressant effects of ketamine are no longer news, ketamine's effects on treatment refractory PTSD (TR-PTSD) is a recent concept. As TR-PTSD has a marked public health burden and significant limitations in terms of treatment interventions, a thorough assessment of current strategies is required. Research to bring clarity to the underlying pathophysiology and neurobiology of TR-PTSD delineating the chemical, structural, and circuitry abnormalities will take time. In the interim, in the absence of a 1-size-fits-all therapeutic approach, pragmatically parallel lines of research can be pursued using the pharmacological and nonpharmacological treatments that have a strong theoretical rationale for efficacy. This article aims to review the current literature on interventions for PTSD, most notably ketamine, trans-cranial magnetic stimulation treatment, yoga and mindfulness interventions, and TIMBER. We present an outline for their future use, alone as well as in combination, with a hope of providing additional insights as well as advocating for developing more effective therapeutic intervention for this treatment-resistant and debilitating condition.

ARTICLE HISTORY
Received 8 November 2014
Accepted 23 April 2015

KEYWORDS
Alternative medicine; complementary medicine; innovative treatments; psychopharmacology; psychotherapeutic; severe mental illness; trauma memory; traumatic stress

Psychopharmacology, despite its great clinical use, has its limitations, particularly when it is used to treat complex, debilitating disorders, such as post-traumatic stress disorder (PTSD). It is quite alarming that 50% to 60% of people in the United States are exposed to trauma during their lifetime,

CONTACT Basant Pradhan, MD Pradhan-Basant@Cooperhealth.edu Cooper University Hospital, 401 Haddon Avenue, Suite 354, E&R Building, Camden, NJ 08103.

and about 8% of Americans may have PTSD at any given time (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). About 42% of these receive only minimally adequate treatment (Hoge et al., 2014). PTSD is also often comorbid with depression, drug abuse, and suicide and more often than not responds poorly to conventional treatments. Although certain forms of psychotherapy and pharmacological treatments have some proven efficacy in the treatment of PTSD, a Cochrane review found that only 59% of patients with PTSD responded to selective serotonin reuptake inhibitors (Stein, Ipser, & Seedat, 2006), the current first-line psychotropics for this condition. In the context of trauma memories and their expression in PTSD, it is important to note that the effects of extinction of trauma memories are not permanent, because extinction, unlike reconsolidation, does not directly modify the existing memory. Instead, it leads to the formation of a new memory trace (called *extinction memory*) that suppresses activation of the initial trace and results in extinction learning (Westbrook, Iordanova, McNally, Richardson, & Harris, 2002). The efficacy of this inhibition, however, is strongly *context dependent* and contingent on the *spatial, sensory, and temporal contexts* in which these trauma memories were acquired and subsequently reinforced and perpetuated through various conditioned learning. Specifically, the reemergence of a previously extinguished fear is known to occur, in rodents and humans alike, under three general conditions (Monfils, Cowansage, Klann, & LeDoux, 2009): (a) renewal, when the conditioned stimulus is presented outside of the extinction context; (b) reinstatement, when the original unconditioned stimulus is presented unexpectedly; or (c) spontaneous recovery, when a substantial amount of time has passed. This could explain the less than optimal efficacy of extinction-only-based treatments, including prolonged exposure therapy (Foa, Hembree, & Rothbaum, 2007).

Also, extinction-only-based treatments can be anxiety provoking and may pose tolerability issues because in these treatments patients are encouraged to approach the trauma memories directly and repeatedly (Becker, Zayfert, & Anderson, 2004; Pitman et al., 2002; Zayfert & Becker, 2000). Some researchers (Kilpatrick & Best, 1984) have voiced concerns about potentially retraumatizing patients with these approaches. Another important limiting factor is that extinction-only approaches do not update the existing trauma memories; rather, they just suppress them (Schiller et al., 2010). Even more concerning is that only a very limited number of therapies target the trauma memories and their expression via clinical symptoms, which are believed to be the root causes of perpetuation of clinical symptoms and dysfunctions seen in patients with PTSD. One particular therapy that targets trauma memories is eye-movement desensitization and reprocessing therapy (EMDR; Shapiro, 1999, 2001). It has been suggested that EMDR reduces the strength of hippocampally mediated episodic trauma memories and the negative effects of trauma, which are generally perceived to be dependent on

the amygdala (Stickgold, 2002). A recent study reported that EMDR can foster the neurophysiological integration of dissociated aspects of traumatic memories and, consequently, allows for a decrease in hyperarousal symptoms (Farina et al., 2014). However, further details of the mechanisms involved have yet to be identified. Although EMDR has been found to be beneficial in some studies, some authors opine that considerable variability exists in the findings of controlled studies, making definitive conclusions difficult to achieve (Mac Cluskie, 1998). As a translational mindfulness-based cognitive therapy module, *Trauma Interventions using Mindfulness Based Extinction and Reconsolidation* (TIMBER) for trauma memories (Pradhan, 2014, pp. 209–212) is a novel, integrated, and trauma-specific psychotherapy. As the name suggests, it uses combined extinction and reconsolidation mechanisms on trauma memories and their expression. TIMBER attempts to modify expression of the memory using a standardized protocol that causes cognitive-emotive restructuring through the use of cognitive–behavioral and standardized meditation interventions (both therapist-assisted sessions and home practice). This results in reappraisal of the symptoms, new learning, and eventually amelioration of symptoms of PTSD.

From a pharmacological standpoint, most of the medications currently used in the treatment of PTSD primarily target the brain monoamine systems (serotonin, norepinephrine, or in some cases dopamine). However, none of these medications target the glutamate system, a neurotransmitter that is increasingly being implicated in PTSD (Feder et al., 2014) and also in treatment-resistant depression (Aan Het Rot, Zarate, Charney, & Mathew, 2012; DiazGranados et al., 2010; Murrough et al., 2013). Notable exceptions are glutamate modulators like ketamine and D-cycloserine (Cukor, Spitalnick, Difede, Rizzo, & Rothbaum, 2009). The glutamate (N-methyl-D-aspartate [NMDA]) receptor is implicated in fear extinction mechanisms. Indeed, preliminary studies have shown that as a glutamate modulator, ketamine might rapidly and effectively relieve the symptoms of PTSD; however, the effects of a single dose typically last only for 4–7 days and up to 2 weeks maximum, and multiple doses are not without side effects (Feder et al., 2014; Murrough et al., 2013). These constitute the major limitations of its therapeutic use and necessitate a strong rationale for its use in a modified way or in combination with other treatment approaches (e.g., TIMBER as described later).

As evidenced from the research, repetitive trans-cranial magnetic stimulation (rTMS) seems to have important therapeutic effects in PTSD, but often these are short term, and information is lacking about maintenance treatment (Pallanti & Bernardi, 2009). To overcome these limitations, some researchers (Osuch et al., 2009) have used combined approaches using a placebo (sham rTMS) controlled crossover design that used a combination of exposure therapy with rTMS (20 sessions at 100% motor threshold for 30 min over the right prefrontal cortex [PFC]). Their results showed

significant improvement in symptoms of hyperarousal in the combination group compared to the group with exposure therapy and sham rTMS. As PTSD is a huge public health burden and also has significant limitations in terms of poor prognosis, significant comorbidity, and a relative lack of effective treatments, revisiting current strategies and attempts at the development of innovative therapeutic interventions that might address the existing therapeutic gaps is long overdue. In this article, we review the current literature on the role of ketamine, rTMS, yoga and mindfulness-based interventions, and psychotherapies like TIMBER as the emerging treatment options for PTSD.

The glutamate-modulating effects of ketamine are complex, and knowledge of them is still evolving

The literature investigating the use of ketamine in PTSD has been not only sparse but also controversial, although more recently there has been more clarity on ketamine's utility in PTSD. In a recent randomized double-blind controlled trial (n = 41; Feder et al., 2014) investigating the effect of ketamine infusion on moderate to severe PTSD, PTSD symptoms as measured by Impact of Event Scale–Revised scores improved significantly in the ketamine group compared to the controls at the 24-hr mark. All three PTSD symptom clusters (intrusion, avoidance, and hyperarousal) remained significantly improved at 48 hr, 72 hr, and 7 days postinfusion, and these effects remained even after comorbid depressive symptoms were controlled for.

Although ketamine is traditionally known to act as a noncompetitive antagonist of the glutamate (NMDA) receptors, the relationship between ketamine and glutamate seems rather complex. Ketamine may facilitate or inhibit glutamatergic transmission depending on many factors, including its dosage, the location of the receptor (presynaptic vs. postsynaptic), and so on (Huntley, Vickers, & Morrison, 1994; Miwa, Robinson, & Kawai, 1993; Moghaddam, Adams, Verma, & Daly, 1997). The commonly administered dosage for the treatment of PTSD or depression (0.5 mg/kg body weight) may actually increase the release of two endogenous excitatory amino acids: glutamate and aspartate (Bustos et al., 1992; Liu & Moghaddam, 1995). By blocking the NMDA (postsynaptic) receptors, ketamine makes the glutamate available for the postsynaptic non-NMDA glutamate receptors (AMPA and kainate), which in turn affect the memory mechanisms by influencing the transmission of other neurotransmitters, such as dopamine, acetylcholine, and gamma-aminobutyric acid (GABA) in the PFC and the frontoparietal regions (Moghaddam et al., 1997). Also, ketamine inhibits the GABAergic (inhibitory) inputs to the glutamate-containing neurons in the PFC, which ultimately results in enhancement of their firing rate.

Putative mechanisms that may explain the therapeutic effects of ketamine in PTSD

Many levels of evidence, most notably from the mechanisms involved in modulation of the stress response and trauma memories (Ravindran & Stein, 2009), implicate the role of glutamate in the pathophysiology of PTSD. However, the relationship between PTSD and glutamate appears complex and full of many contradictory findings. The various manifestations of PTSD are hypothesized to result from both hyper- and hypoglutamatergic states in the various brain areas; research data clarifying these are still evolving (Chambers et al., 1999; Nair & Singh Ajit, 2008). Changes in glutamate levels play a key role in the initiation and maintenance of the hypothalamic–pituitary–adrenal (HPA) axis response (Jezová, Tokarev, & Rusnák, 1995; Tokarev & Jezová, 1997). Other evidence from animal studies as well suggests that glutamate influences the HPA axis by modulating the release of Corticotrophin Releasing Hormone (CRH) in response to stress (Gabr, Birkle, & Azzaro, 1995; Zelena, Mergl, & Makara, 2005). Glutamate plays a key role in trauma memory formation that lies at the core of PTSD (Shin & Liberzon, 2010). Specifically, long-term potentiation and synaptic plasticity, the key cellular processes thought to mediate the consolidation of memory and learning, are dependent on glutamate (more specifically NMDA) activity (Kandel, 2001; Siegelbaum & Kandel, 2013). Following traumatic events, elevated glutamate levels may serve to encode and consolidate traumatic memories (Joca, Ferreira, & Guimarães, 2007).

As learning and memory are both glutamate-dependent processes, ketamine may cause a disruption of the trauma memories (Jeffrey, 2009). It has been argued that both flashbacks and intrusive memories, the two major symptoms of PTSD, may be due to failure of the extinction mechanism associated with fear conditioning, which is a glutamate-dependent process (Falls, Miserendino, & Davis, 1992; Kvavilashvili, 2014). This provides a strong theoretical rationale for the use of ketamine to decrease the fear conditioning and to ameliorate the recall/re-expression of traumatic memories, the core psychopathology seen in PTSD. This has been proven in studies of laboratory animals and also of human subjects with PTSD (Feder et al., 2014). The administration of NMDA antagonists has been shown to block the acquisition of fear conditioning in the amygdala and hippocampus (Cammarota et al., 2004; Joca et al., 2007) and promote new learning and memory that could suppress prior conditioned responses (Bouton & Bolles, 1979). Preclinical studies of rats have shown that after the acquisition of conditioned fear, intra-amygdalar administration of NMDA antagonists prior to extinction training impaired retention of the extinction behavior (Baker & Azorlosa, 1996; Falls et al., 1992). In addition, clinical trials have shown that D-cycloserine, a partial agonist at the NMDA receptor, blocks the fear learning and facilitates the extinction of conditioned fear learning in

animal models as well as in some human trials (Davis, Ressler, Rothbaum, & Richardson, 2006; Ledgerwood, Richardson, & Cranney, 2005). However, ketamine has an added advantage over D-cycloserine in the form of its very rapid clinical effects (within 4–6 hr of infusion).

Studies of ketamine in traumatized rats found that ketamine normalized decreased brain-derived neurotrophic factor levels in the hippocampus, suggesting that the effect of ketamine in PTSD may be partially mediated by changes in hippocampal brain-derived neurotrophic factor levels (Zhang et al., 2014). Another study using an animal model found that *mammalian target of rapamycin* (mTOR) plays an important role in the molecular effects of the ketamine pathway: If the mTOR protein synthesis pathway was blocked, the behavioral as well as biochemical effects of ketamine were found to be abolished (Li et al., 2010). However, despite these amazing advancements in knowledge, at this time the exact mechanisms of action of ketamine in PTSD are not known precisely. Ketamine possibly blocks prefrontal cortical access to the memory traces stored in the cortical, hippocampal, and amygdalar system (Pradhan, 2014), which may explain its therapeutic effects, including its long-known dissociative amnesia.

The utility of TMS in PTSD

As described below, clinical trials performed over the past two decades have demonstrated the effectiveness of rTMS in PTSD. The first pilot study (Grisaru, Amir, Cohen, & Kaplan, 1998) demonstrated significant improvements in PTSD symptoms after the 24-hr mark. In an open trial involving six patients with treatment-resistant PTSD, significant improvement was observed in hostility, insomnia, anxiety, and depression, and a small but significant improvement was seen in core PTSD symptoms (Rosenberg et al., 2002). Another study (Cohen et al., 2004), a double-blind, randomized controlled trial in 24 patients, supported these findings. Its results demonstrated that patients who received high-frequency (>1 Hz) rTMS experienced greater improvement in core PTSD symptoms compared to patients who received low-frequency (<1 Hz) or sham stimulation, suggesting that neuronal circuitry in the right PFC may be implicated in PTSD. Another study (Boggio et al., 2010) supported these findings. In that study, a significant decrease in PTSD symptoms was observed in the high-frequency and right PFC group compared to the left PFC and low-frequency group, which led the authors to propose that the right PFC, after rTMS treatment, possibly inhibits the episodic memory of the left PFC via transcallosal inhibition. Another randomized control trial using low-frequency rTMS to the right PFC at 90% motor threshold for 10 sessions demonstrated significant improvement in core symptoms of PTSD and depression in 20 veterans compared to controls (Watts, Landon, Groft, & Young-Xu, 2012). These

improvements were maintained for 2 months after completion of the TMS course, with a decrease in clinical improvement over time. The efficacy of the low-frequency, right PFC rTMS protocols in the treatment of non-PTSD-type anxiety disorders supports the use of this type of rTMS for PTSD (Watts et al., 2012).

Another randomized study (n = 30) involved three groups: two groups with active deep TMS and the other with sham TMS, three sessions weekly for 4 weeks (Isserles et al., 2013). Significant improvement in the intrusive component of the Clinician-Administered PTSD Scale was observed (M scores = 88 pretreatment vs. 61 posttreatment, $p < .05$). This not only indicates the potential of TMS to treat PTSD symptoms but also suggests the role of medial prefrontal cortex (mPFC) hypoactivity in the manifestation of the disorder.

Putative mechanisms that may explain the therapeutic effects of rTMS in PTSD

Neuroimaging data in patients with PTSD suggest that these patients have functional abnormalities in the right hemisphere of the brain, which includes the amygdala, orbitofrontal cortex, dorsolateral PFC, ventromedial PFC, and HPA axis (Isserles et al., 2013; Pallanti & Bernardi, 2009). Note that earlier evidence of the involvement of the right hemisphere of the brain in PTSD was mainly based on clinical parameters rather than neuroimaging. One study that utilized functional magnetic resonance imaging has suggested the involvement of the right insular cortex and striatum in PTSD (Cisler et al., 2014). Decreased GABAergic functions in bilateral brain areas are found in patients with PTSD; rTMS treatment reversed these, but only in the right hemispheric regions, and improved PTSD symptoms (Rossi et al., 2009). The involvement of the right hemisphere in PTSD has been further demonstrated in clinical studies, which have found that right-sided rTMS is more effective than left-sided treatment (Karsen, Watts, & Holtzheimer, 2014). These authors did not find any difference in terms of clinical outcome with respect to the efficacy of high-frequency versus low-frequency stimulations. Another study (Tillman et al., 2011) showed that rTMS applied to the right frontal lobe of patients suffering from PTSD significantly reduced the event-related potential (P300; claimed to be a biomarker of trauma response) in response to combat-related trauma triggers.

It is noteworthy that currently the only indication of rTMS approved by the U.S. Food and Drug Administration is for unipolar depression, in which its therapeutic effects are known to be exerted through stimulation of the left prefrontal cortex. However, despite these recent advancements, TMS research has a long way to go with respect to elucidating its precise mechanisms of action, which hopefully could explain many questions, including the differential effects with respect to the laterality of stimulations in different neuropsychiatric

disorders. As far as PTSD is concerned, it is possible that rTMS may work by stimulating the PFC, most likely its ventromedial aspects, thereby inhibiting the hyperactive amygdala and the overactive sympathetic system, which might explain its effects in reducing hyperarousal symptoms (Cristancho, Cristancho, & O'Reardon, 2013; Morris, Öhman, & Dolan, 1998). As evidenced by animal models of the stress response (Ipser, Pillay, Stein, & Van Honk, 2007), it is also possible that changes within the HPA axis as well as dopaminergic and serotonergic systems of the brain may also be involved. Apart from the putative hypotheses already mentioned, one possible explanation for these differential effects of left- or right-sided stimulation in rTMS could be due to the differential distribution of the excitatory (glutamatergic) or inhibitory (GABAergic) fibers in the cortex in various psychiatric disorders, including in PTSD (Kim, Inan, Berman, & Pessah, 2009; Malsert et al., 2013). It is also possible that both low- and high-frequency rTMS could have different neurophysiological effects. Given these putative neurobiological mechanisms as well as the clinical and empirical rationale, rTMS can be considered a viable therapeutic option for PTSD.

Some possible issues with the therapeutic use of ketamine and rTMS

In spite of the potential utility of ketamine as a viable and effective treatment for PTSD, its major limitations so far have been short-lasting effects after a single dose and concerns about side effects (hypertensive, addictive, psychotomimetic, and dissociative effects) of frequent or multiple doses (Feder et al., 2014; Murrough et al., 2013). Two retrospective studies (Schönenberg, Reichwald, Domes, Badke, & Hautzinger, 2008; Strayer & Nelson, 2008) claimed that ketamine may possibly exacerbate symptoms of PTSD. However, the retrospective design of both of these studies is an important methodological limitation. Findings from some other studies (for a detailed review, please see Cukor et al., 2009) refuted the findings of these two studies and, it is interesting to note, demonstrated a lower prevalence of PTSD in patients in the ketamine group compared to the nonketamine control. This has led some to propose that ketamine might be used to decrease the prevalence of PTSD symptoms and thus might lead to early prevention of PTSD (Jeffrey, 2009).

Given that the recreational use of ketamine (i.e., Special K) has increased in recent years, there are valid concerns about ketamine's abuse potential (Morgan, Riccelli, Maitland, & Curran, 2004). Many researchers (Pal, Berry, Kumar, & Ray, 2002; Zigman & Blier, 2013) have argued that ketamine abuse has been seen mostly in the context of polysubstance abuse, which does not fit the profile of the typical patient suffering from PTSD. It is noteworthy that the side effects mentioned previously are generally seen with the use of ketamine at anesthetic doses (>1.5–2 mg/kg body weight). More recent

research on the use of ketamine in subanesthetic doses (0.5 mg/kg body weight) in depression (DiazGranados et al., 2010) and in PTSD with comorbid depression (Pradhan et al., 2013–15; unpublished data involving a more than 1-year follow-up of 15 adult patients with chronic PTSD) did not show any of these side effects. The majority of the literature suggests that ketamine at the subanesthetic dose is safe and well tolerated in most patients (Aan Het Rot et al., 2012; Murrough et al., 2013). However, additional studies are definitely required to shed further light on this.

Although the research evidence for the therapeutic use of ketamine or rTMS is promising, the studies reviewed in this article are not without limitations. The most notable limitations of both rTMS and ketamine have been short-lasting effects and concerns about potential side effects. Additionally, the studies from which information is derived, have smaller sample sizes (e.g., many studies on rTMS individually have only 10–12 patients) and some studies (particularly on rTMS) are open label trials by design. Despite these important limitations, many studies have been methodologically sound and do suggest the therapeutic potential of rTMS and ketamine for treating PTSD alone or PTSD with comorbid depression. Nonetheless, there is a clear need for replication of these findings in additional randomized controlled trials with a sound methodology.

Complementary and alternative medicine interventions in PTSD: yoga, mindfulness, and TIMBER

Complementary and alternative medicine interventions like yoga and meditation in PTSD offer some promise in research studies, as outlined below. In addition to their utility as self-management techniques that empower the person, other benefits are their low cost, lack of side effects, lack of concerns about drug interactions, and so on. As outlined in recent literature on trauma therapy (Ford, Courtois, Steele, Hart, & Nijenhuis, 2005; Lang et al., 2012), the essential elements of mindfulness are focused attention, compassion, empathy, and a nonjudgmental attitude. Depersonalization and dissociation, two common symptoms of PTSD, reflect a relative lack of integration between the mind (*psyche*) and body (*soma*), and thus conceptually speaking they are opposite to the state of mindfulness in which one is fully in touch with oneself in a coherent manner in the present moment with a full and integrated awareness of one's existence, one's sensations, and the various mental functions. In contrast to *dissociation*, which is so pervasive in patients with PTSD, mindfulness practice promotes *dis-association* (detachment) from the experience, which ensures calm observation in an attentive manner (Pradhan, 2014).

In addition to their empirical use, some research studies have provided clinical and neurobiological rationale for the use of yoga and mindfulness interventions in psychiatric disorders, including PTSD (for detailed reviews,

please see Balasubramaniam, Telles, & Doraiswamy, 2013; Brown & Gerbarg, 2005). The autonomic nervous system plays an important role in complex stress responses: Activity of the sympathetic system increases and that of the parasympathetic system decreases during the normal stress response, and this pattern becomes pathologically exaggerated in PTSD (Heim & Nemeroff, 2002). Increased central nervous system adrenergic activity, resulting in greater release of norepinephrine and increased sensitivity to norepinephrine at receptor sites, has been implicated in PTSD (Taylor, Freeman, & Cates, 2008). This is more pronounced at night and has been associated with poor sleep and nightmares (Cukor et al., 2009). Also, studies have shown that prolonged adrenergic activation in the immediate aftermath of a trauma increases risk for PTSD (Vaiva et al., 2003), possibly through increased fear conditioning (Orr et al., 2000) and as a consequence of the release of an excessive amount of epinephrine during the trauma (Pitman et al., 1991). Studies done over the past 20 years reflecting numerous types of traumas, including combat trauma (Keane et al., 1998), motor vehicle collisions (Blanchard et al., 1996), and sexual abuse in female subjects (Orr et al., 1998), have shown that increased heart rate in response to the trauma triggers is one of the most robust autonomic findings. This provides further evidence that PTSD could be a hyperadrenergic and relatively low parasympathetic state. In studies of PTSD, the efficacy of sympatholytic agents like prazosin or clonidine in the treatment of nightmares (Raskind et al., 2007; Taylor et al., 2008; Thompson, Taylor, McFall, Barnes, & Raskind, 2008) and propranolol, both for treatment of trauma reactivity (Brunet et al., 2008) and as a preventive measure (Pitman et al., 2002; Vaiva et al., 2003), further supports this hypothesis. In contrast, yoga and mindfulness-based treatments have been shown to produce the exact opposite effects (i.e., they lower sympathetic output and enhance parasympathetic activity; Brown & Gerbarg, 2005; Vedamurthachar, 2002). In addition to the autonomic nervous system, the other brain structures playing crucial roles in the arousal response and memory mechanisms in PTSD are the PFC (both dorsolateral and ventromedial areas), amygdala, thalamus, hippocampus, and global attention network of the frontoparietal cortex (Portas et al., 1998). The thalamus governs the flow of sensory information to cortical processing areas and, through the inhibitory GABAergic neurons, blocks the distribution of this information to the various areas. As an inhibitory neurotransmitter, GABA plays a key role in the prevention of arousal response, both in normal stress response and in PTSD as well. It is interesting that, compared to physical exercises, yoga and mindfulness interventions are associated with increased thalamic release of GABA, as evidenced by the magnetic resonance spectroscopy scans of patients (Streeter et al., 2007, 2010). Another positron emission tomography study utilizing 11 C-Raclopride demonstrated a significant increase in dopamine levels during meditation practice (Kjaer et al., 2002). It

should be noted that the dopamine system, via the basal ganglia, is believed to participate in regulating the glutamate system, which plays an important role in trauma memories and their expression. The major neurotransmitters (GABA, dopamine, and glutamate) are implicated in both PTSD and interventions involving yoga and mindfulness. Thus, the use of yoga and mindfulness-based treatments in PTSD is based not only on an empirical rationale but also the emerging biological rationale as well. Yoga and mindfulness interventions in PTSD can be broadly categorized into two types: (a) nontargeted approaches, which use yoga and meditation in a general or nonspecific way; and (b) targeted approaches, which specifically target the trauma memories and their expression (e.g., TIMBER).

The efficacy of yoga and meditation interventions was studied in a series of four open pilot studies of the treatment of PTSD in Vietnam veterans (Brown & Gerbarg, 2005; Carter & Byrne, 2004). In Study 1, eight participants showed marked improvement in depression on various scales but not insomnia or anger expression during a 6-week program of Iyengar yoga postures (Iyengar, 2007). Long-term improvement (21 weeks) was maintained with home practice and 1-hr group sessions, once a week (Radloff, 1977). In Study 2, Iyengar poses for anxiety produced no additional benefit in eight veterans with PTSD and were therefore discontinued. In Study 3, eight PTSD veterans added *Ham Su* meditation and pranayama breathing to the Iyengar yoga postures for depression. In addition to drops in depression scores, participants showed marked improvements in sleep initiation, disturbed sleep, flashbacks, and anger outbursts. Several subjects used the pranayama to calm themselves when they awoke at night or when they felt road rage. The fourth study found that patients with PTSD benefited from Sudarsan Kriya yoga training (Sageman, 2002). One interesting finding emerging from these studies is that although practice of the yogic postures (Sanskrit *asana*, physical aspects of yoga) reduced depression, it had no impact on symptoms of intrusion or hyperarousal or anger outbursts of PTSD until other interventions like yogic breathing (Sanskrit *pranayama*) were added. Also, treatment of depression with yogic breathing resulted in decreased levels of cortisol following treatment, which provides further evidence of the utility of combined physical (posture) and meditative aspects of yoga in PTSD (Gangadhar, Janakiramaiah, Sudarshan, & Shety, 1999). Of note is that traditionally yoga *in its entirety* consists of eight limbs (Sanskrit *Ahtanga Yoga*), which includes yogic (balanced) lifestyle, postures, pranayama and meditation, its sixth and seventh limbs (Satchidananda, 1990). Thus, combined, synergistic, and targeted use of many elements of yoga rather than isolated or piecemeal use has been found to be more effective. Thus, there is now emerging evidence to consider yoga and mindfulness-based interventions as potentially beneficial, low-risk adjuncts for the treatment of PTSD as well as depression, stress-related medical illnesses, and substance abuse (Bormann, Thorp, Wetherell, & Golshan, 2008; Brown & Gerbarg, 2005;

Wolfsdorf & Zlotnick, 2001). Although they are preliminary and have to be proven in larger studies as well as with respect to their precise mechanisms of action, the results of these studies as well as the emerging biological rationale strongly suggest their use in PTSD. However, because yoga and meditation interventions are quite complex and more often than not are used in a nonspecific way, these studies have yet to evaluate their independent contributions or what exact role the individual components play in these. One main issue in research is that the nonspecific and unstandardized use of yoga and mindfulness interventions can be difficult to evaluate. Thus, more standardized and targeted approaches are necessary not only to ensure the use of these interventions in a more objective and targeted fashion but also to compare their efficacy across studies or with other treatment modalities. Recognizing these issues as well as the limitations in the utility of only the physical aspects of yoga, Pradhan has developed several disorder-specific psychotherapy models that use yoga *in its entirety in targeted and broader ways* (that include all eight limbs) rather than piecemeal and that are broadly categorized under *yoga and mindfulness-based cognitive therapy* (detailed in Pradhan, 2014). TIMBER is the PTSD-specific yoga and mindfulness-based cognitive therapy protocol.

TIMBER: a translational mindfulness protocol using a targeted approach

As mentioned before, TIMBER (Pradhan, 2014; Pradhan et al., 2015) is a translational type of mindfulness-based cognitive therapy that targets in a personalized way trauma memories and their expression in patients with chronic PTSD. The methodology of TIMBER integrates principles of mindfulness-based exposure therapy (Pradhan, 2014, pp. 211–212) with a neurobiological understanding of trauma memories (Monfils et al., 2009; Schiller et al., 2010; Shin & Liberzon, 2010; Siegelbaum, Kandel, & Yuste, 2013), including the interplay between the memory extinction and memory reconsolidation mechanisms in constructing the trauma memories. As a treatment modality for PTSD, its efficacy has been tested in preliminary studies of patients ages 14 to 60 years, either alone (Pradhan et al., 2013–2015) or in combination with medications (Pradhan et al., 2013–2015, unpublished data: This is a double-blind placebo controlled crossover study that examined the efficacy of a single infusion of a 0.5 mg/kg body weight dose of ketamine combined with TIMBER in 15 patients with chronic and refractory PTSD and comorbid depression). Although neural circuitry that TIMBER may influence has not been tested in neuroimaging protocols, based on the already existing research on pathways involved in PTSD, we speculate that the putative brain areas that might be involved could be the fronto-thalamic tri-circuits and the working connections between the amygdala and the prefrontal cortex, the two major hubs involved in the complex communications network that not only process the fear

memories but also regulate their expression in context dependent manner. Perhaps manipulation of these fear circuits in combination with controlled exposures to the fear-inducing stimuli and reappraising them using mindfulness based detachment and monitoring (MBDM), as done in TIMBER, work together to ease the symptoms of PTSD and other anxiety disorders. The various components of TIMBER and the putative mechanisms are discussed in Pradhan (2014, pp. 209–212, 114–115; Pradhan et al., 2015).

Conclusions and future directions

In spite of some limitations and concerns, the field of therapeutics in PTSD is currently progressing toward the use of innovative treatment approaches. Interventions like ketamine, rTMS, and TIMBER are examples of such approaches. The long-term effects of ketamine and rTMS still remain to be investigated, and information on the maintenance phase is sparse. Yet their therapeutic potential as evidenced from the studies is robust and side effects have in general been mild and transient, at least in acute phase protocols (Cristancho et al., 2013; Jeffrey, 2009). Although the data are preliminary and not yet published, the combined use of TIMBER and ketamine (a single infusion of subanesthetic dose) elicited a more effective and more sustained response in our study mentioned earlier (Pradhan et al., 2013–2015, unpublished data). Thus, overall the potential benefits of ketamine or rTMS outweigh the potential risks, and these interventions can be important therapeutic bridges that can be utilized either alone or in combination with other treatment methods. Considering the disabling nature of PTSD; its poor prognosis; the lack of optimal treatments; its notorious comorbidity with treatment-resistant depression, panic disorder, and drug abuse; and the clinical rationale as well as the preliminary evidence suggesting their potential effectiveness, these novel interventions are too promising to ignore. Nonetheless, replicating these findings in future studies, as well as investigating the utility of other potentially effective therapeutic interventions, is long overdue for these patients.

ORCID

Basant Pradhan http://orcid.org/0000-0003-4788-3819
Ramkrishna Makani http://orcid.org/0000-0002-0297-0719
Tapan Parikh http://orcid.org/0000-0002-6313-2372

References

Aan Het Rot, M., Zarate, C. A., Charney, D. S., & Mathew, S. J. (2012). Ketamine for depression: Where do we go from here? *Biological Psychiatry*, *72*(7), 537–547. doi:10.1016/j.biopsych.2012.05.003

Baker, J. D., & Azorlosa, J. L. (1996). The NMDA antagonist MK-801 blocks the extinction of Pavlovian fear conditioning. *Behavioral Neuroscience*, *110*(3), 618–620. doi:10.1037/0735-7044.110.3.618

Balasubramaniam, M., Telles, S., & Doraiswamy, P. M. (2013). Yoga on our minds: A systematic review of yoga for neuropsychiatric disorders. *Frontiers in Psychiatry*, *3*(117), 1–16. doi:10.3389/fpsyt.2012.00117

Becker, C. B., Zayfert, C., & Anderson, E. (2004). A survey of psychologists' attitudes towards and utilization of exposure therapy for PTSD. *Behaviour Research and Therapy*, 42(3), 277–292.

Blanchard, E. B., Hickling, E. J., Buckley, T. C., Taylor, A. E., Vollmer, A., & Loos, W. R. (1996). Psychophysiology of posttraumatic stress disorder related to motor vehicle accidents: Replication and extension. *Journal of Consulting and Clinical Psychology*, *64*(4), 742–751.

Boggio, P. S., Rocha, M., Oliveira, M. O., Fecteau, S., Cohen, R. B., Campanha, C., & Fregni, F. (2010). Noninvasive brain stimulation with high-frequency and low-intensity repetitive transcranial magnetic stimulation treatment for posttraumatic stress disorder. *Journal of Clinical Psychiatry*, *71*(8), 992–999. doi:10.4088/JCP.08m04638blu

Bormann, J. E., Thorp, S., Wetherell, J. L., & Golshan, S. (2008). A spiritually based group intervention for combat veterans with posttraumatic stress disorder: Feasibility study. *Journal of Holistic Nursing*, *26*(2), 109–116. doi:10.1177/0898010107311276

Bouton, M. E., & Bolles, R. C. (1979). Role of conditioned contextual stimuli in reinstatement of extinguished fear. *Journal of Experimental Psychology: Animal Behavior Processes*, *5*(4), 368–378. doi:10.1037/0097-7403.5.4.368

Brown, R. P., & Gerbarg, P. L. (2005). Sudarshan Kriya yogic breathing in the treatment of stress, anxiety, and depression: Part II—Clinical applications and guidelines. *Journal of Alternative and Complementary Medicine*, *11*(4), 711–717. doi:10.1089/acm.2005.11.711

Brunet, A., Orr, S. P., Tremblay, J., Robertson, K., Nader, K., & Pitman, R. K. (2008). Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. *Journal of Psychiatric Research*, *42*(6), 503–506. doi:10.1016/j.jpsychires.2007.05.006

Bustos, G., Abarca, J., Forray, M. I., Gysling, K., Bradberry, C. W., & Roth, R. H. (1992). Regulation of excitatory amino acid release by N-methyl-D-aspartate receptors in rat striatum: In vivo microdialysis studies. *Brain Research*, *585*(1–2), 105–115. doi:10.1016/0006-8993(92)91195-K

Cammarota, M., Bevilaqua, L. R., Bonini, J. S., Rossatto, J. I., Medina, J. H., & Izquierdo, N. (2004). Hippocampal glutamate receptors in fear memory consolidation. *Neurotoxicity Research*, *6*(3), 205–212. doi:10.1007/BF03033222

Carter, J., & Byrne, G. (2004). *A two year study of the use of yoga in a series of pilot studies as an adjunct to ordinary psychiatric treatment in a group of Vietnam war veterans suffering from post traumatic stress disorder*. Retrieved from http://www.therapywithyoga.com/Vivekananda.pdf

Chambers, R. A., Bremner, J. D., Moghaddam, B., Southwick, S. M., Charney, D. S., & Krystal, J. H. (1999). Glutamate and post-traumatic stress disorder: Toward a psychobiology of dissociation. *Seminars in Clinical Neuropsychiatry*, *4*(4), 274–281.

Cisler, J. M., Steele, J. S., Lenow, J. K., Smitherman, S., Everett, B., Messias, E., & Kilts, C. D. (2014). Functional reorganization of neural networks during repeated exposure to the traumatic memory in posttraumatic stress disorder: An exploratory fMRI study. *Journal of Psychiatric Research*, *48*(1), 47–55. doi:10.1016/j.jpsychires.2013.09.013

Cohen, H., Kaplan, Z., Kotler, M., Kouperman, I., Moisa, R., & Grisaru, N. (2004). Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in posttraumatic stress disorder: A double-blind, placebo-controlled study. *American Journal of Psychiatry*, *161*(3), 515–524. doi:10.1176/appi.ajp.161.3.515

Cristancho, M. A., Cristancho, P., & O'Reardon, J. P. (2013). Other therapeutic psychiat-ric uses of superficial brain stimulation. *Handbook of Clinical Neurology*, *116*, 415–422.

Cukor, J., Spitalnick, J., Difede, J., Rizzo, A., & Rothbaum, B. O. (2009). Emerging treatments for PTSD. *Clinical Psychology Review*, *29*(8), 715–726. doi:10.1016/j.cpr.2009.09.001

Davis, M., Ressler, K., Rothbaum, B. O., & Richardson, R. (2006). Effects of D-cycloserine on extinction: Translation from preclinical to clinical work. *Biological Psychiatry*, *60*(4), 369–375. doi:10.1016/j.biopsych.2006.03.084

DiazGranados, N., Ibrahim, L. A., Brutsche, N. E., Ameli, R., Henter, I. D., Luckenbaugh, D. A., & Zarate, C. A. (2010). Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *Journal of Clinical Psychiatry*, *71*(12), 1605–1611. doi:10.4088/JCP.09m05327blu

Falls, W. A., Miserendino, M. J., & Davis, M. (1992). Extinction of fear-potentiated startle: Blockade by infusion of an NMDA antagonist into the amygdala. *Journal of Neuroscience*, *12*(3), 854–863.

Farina, B., Imperatori, C., Quintiliani, M. I., Castelli Gattinara, P., Onofri, A., Lepore, M., & Della Marca, G. (2014). Neurophysiological correlates of eye movement desensitization and reprocessing sessions: Preliminary evidence for traumatic memories integration. *Clinical Physiology and Functional Imaging*. Advance online publication. doi:10.1111/cpf.12184

Feder, A., Parides, M. K., Murrough, J. W., Perez, A. M., Morgan, J. E., Saxena, S., & Charney, D. S. (2014). Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: A randomized clinical trial. *JAMA Psychiatry*, *71*(6), 681–688.

Foa, E. B., Hembree, E. A., & Rothbaum, B. O. (2007). *Prolonged exposure therapy for PTSD: Emotional processing of traumatic experiences: Therapist guide*. New York, NY: Oxford University Press.

Ford, J. D., Courtois, C. A., Steele, K., Hart, O., & Nijenhuis, E. R. (2005). Treatment of complex posttraumatic self-dysregulation. *Journal of Traumatic Stress*, *18*(5), 437–447.

Gabr, R. W., Birkle, D. L., & Azzaro, A. J. (1995). Stimulation of the amygdala by glutamate facilitates corticotropin-releasing factor release from the median eminence and activation of the hypothalamic-pituitary-adrenal axis in stressed rats. *Neuroendocrinology*, *62*(4), 333–339. doi:10.1159/000127022

Gangadhar, B. N., Janakiramaiah, N., Sudarshan, B., and Shety, K.T. (1999). Stress-Related Biochemical Effects of Sudarshan Kriya Yoga in Depressed Patients Studyconducted by the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India and published in reports of the Art of Living Foundation International Research Committee.

Grisaru, N., Amir, M., Cohen, H., & Kaplan, Z. (1998). Effect of transcranial magnetic stimulation in posttraumatic stress disorder: A preliminary study. *Biological Psychiatry*, *44*(1), 52–55. doi:10.1016/S0006-3223(98)00016-X

Heim, C., & Nemeroff, C. B. (2002). Neurobiology of early life stress: Clinical studies. *Seminars in Clinical Neuropsychiatry*, *7*(2), 147–159. doi:10.1053/scnp.2002.33127

Hoge, C. W., Grossman, S. H., Auchterlonie, J. L., Riviere, L. A., Milliken, C. S., & Wilk, J. E. (2014). PTSD treatment for soldiers after combat deployment: Low utilization of mental

health care and reasons for dropout. *Psychiatric Services, 65, 997–1004*. doi:10.1176/appi.ps.201300307

Huntley, G. W., Vickers, J. C., & Morrison, J. H. (1994). Cellular and synaptic localization of NMDA and non-NMDA receptor subunits in neocortex: Organizational features related to cortical circuitry, function and disease. *Trends in Neurosciences*, *17*(12), 536–543. doi:10.1016/0166-2236(94)90158-9

Ipser, J. C., Pillay, N. S., Stein, D. J., & Van Honk, J. (2007). Transcranial magnetic stimulation for post-traumatic stress disorder. *The Cochrane Library*. USA: John Wiley & Sons, Ltd.

Isserles, M., Shalev, A. Y., Roth, Y., Peri, T., Kutz, I., Zlotnick, E., & Zangen, A. (2013). Effectiveness of deep transcranial magnetic stimulation combined with a brief exposure procedure in post-traumatic stress disorder: A pilot study. *Brain Stimulation*, *6*(3), 377–383. doi:10.1016/j.brs.2012.07.008

Iyengar, B. K. S. (2007). *BKS iyengar yoga: The path to holistic health Penguin*. UK: Penguin Books.

Jeffrey, R. (2009). A brief report of research: Evaluating the effects of ketamine on memory in posttraumatic stress disorder. *Dimensions of Critical Care Nursing*, *28*(2), 83. doi:10.1097/DCC.0b013e31819af560

Jezová, D., Tokarev, D., & Rusnák, M. (1995). Endogenous excitatory amino acids are involved in stress-induced adrenocorticotropin and catecholamine release. *Neuroendocrinology*, *62*(4), 326–332. doi:10.1159/000127021

Joca, S. R., Ferreira, F. R., & Guimarães, F. S. (2007). Modulation of stress consequences by hippocampal monoaminergic, glutamatergic and nitrergic neurotransmitter systems. *Stress*, *10*(3), 227–249. doi:10.1080/10253890701223130

Kandel, E. R. (2001). The molecular biology of memory storage: A dialogue between genes and synapses (Nobel lecture). *Bioscience Reports*, *21*, 565–611. doi:10.1023/A:1014775008533

Karsen, E. F., Watts, B. V., & Holtzheimer, P. E. (2014). Review of the effectiveness of transcranial magnetic stimulation for post-traumatic stress disorder. *Brain Stimulation*, *7*(2), 151–157. doi:10.1016/j.brs.2013.10.006

Keane, T. M., Kolb, L. C., Kaloupek, D. G., Orr, S. P., Blanchard, E. B., Thomas, R. G., … Lavori, P. W. (1998). Utility of psychophysiology measurement in the diagnosis of post-traumatic stress disorder: Results from a department of Veteran's Affairs cooperative study. *Journal of Consulting and Clinical Psychology*, *66*(6), 914–923. doi:10.1037/0022-006X.66.6.914

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month *DSM–IV* disorders in the National Comorbidity Survey replication. *Archives of General Psychiatry*, *62*(6), 617–627. doi:10.1001/archpsyc.62.6.617

Kilpatrick, D. G., & Best, C. L. (1984). Some cautionary remarks on treating sexual assault victims with implosion. *Behavior Therapy*, *15*(4), 421–423.

Kim, K. H., Inan, S. Y., Berman, R. F., & Pessah, I. N. (2009). Excitatory and inhibitory synaptic transmission is differentially influenced by two ortho-substituted polychlorinat-ed biphenyls in the hippocampal slice preparation. *Toxicology and Applied Pharmacolo-gy*, *237*(2), 168–177.

Kjaer, T. W., Bertelsen, C., Piccini, P., Brooks, D., Alving, J., & Lou, H. C. (2002). Increased dopamine tone during meditation-induced change of consciousness. *Cognitive Brain Research*, *13*(2), 255–259. doi:10.1016/S0926-6410(01)00106-9

Kvavilashvili, L. (2014). Solving the mystery of intrusive flashbacks in posttraumatic stress disorder: Comment on Brewin (2014). *Psychological Bulletin*, *140*(1), 98–104. doi:10.1037/a0034677

Lang, A. J., Strauss, J. L., Bomyea, J., Bormann, J. E., Hickman, S. D., Good, R. C., & Essex, M. (2012). The theoretical and empirical basis for meditation as an intervention for PTSD. *Behavior Modification*, *36*, 759–786. doi:10.1177/0145445512441200

Ledgerwood, L., Richardson, R., & Cranney, J. (2005). D-cycloserine facilitates extinction of learned fear: Effects on reacquisition and generalized extinction. *Biological Psychiatry*, *57*(8), 841–847. doi:10.1016/j.biopsych.2005.01.023

Li, N., Lee, B., Liu, R.-J., Banasr, M., Dwyer, J. M., Iwata, M., … Duman, R. S. (2010, August 20). mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*, *329*, 959–964. doi:10.1126/science.1190287

Liu, J., & Moghaddam, B. (1995). Regulation of glutamate efflux by excitatory amino acid receptors: Evidence for tonic inhibitory and phasic excitatory regulation. *Journal of Pharmacology and Experimental Therapeutics*, *274*(3), 1209–1215.

Mac Cluskie, K. C. (1998). A review of eye movement desensitization and reprocessing (EMDR): Research findings and implications for counsellors. *Canadian Journal of Counselling*, *32*(*2*), 116–137.

Malsert, J., Guyader, N., Chauvin, A., Polosan, M., Szekely, D., Bougerol, T., & Marendaz, C. (2013). Saccadic performance and cortical excitability as trait-markers and state-markers in rapid cycling bipolar disorder: A two case follow up study. *Frontiers in Psychiatry*, *3*, 112. doi:10.3389/fpsyt.2012.00112

Miwa, A., Robinson, H. P., & Kawai, N. (1993). Presynaptic glutamate receptors depress inhibitory postsynaptic transmission in lobster neuromuscular synapse. *Journal of Neurophysiology*, *70*(3), 1159–1167.

Moghaddam, B., Adams, B., Verma, A., & Daly, D. (1997). Activation of glutamatergic neurotransmission by ketamine: A novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *Journal of Neuroscience*, *17*(8), 2921–2927.

Monfils, M., Cowansage, K. K., Klann, E., & LeDoux, J. E. (2009, May 15). Extinction-reconsolidation boundaries: Key to persistent attenuation of fear memories. *Science*, *324*, 951–955. doi:10.1126/science.1167975

Morgan, C. J., Riccelli, M., Maitland, C. H., & Curran, H. V. (2004). Long-term effects of ketamine: Evidence for a persisting impairment of source memory in recreational users. *Drug and Alcohol Dependence*, *75*(3), 301–308. doi:10.1016/j.drugalcdep.2004.03.006

Morris, J. S., Öhman, A., & Dolan, R. J. (1998, June 4). Conscious and unconscious emotional learning in the human amygdala. *Nature*, *393*, 467–470. doi:10.1038/30976

Murrough, J. W., Iosifescu, D. V., Chang, L. C., Al Jurdi, R. K., Green, C. E., Perez, A. M., & Mathew, S. J. (2013). Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site randomized controlled trial. *American Journal of Psychiatry*, *170*(10), 1134–1142.

Nair, J., & Singh Ajit, S. (2008). The role of the glutamatergic system in posttraumatic stress disorder. *CNS Spectrums*, *13*(7), 585–591.

Orr, S. P., Lasko, N. B., Metzger, L. J., Berry, N. J., Ahern, C. E., & Pitman, R. K. (1998). Psychophysiologic assessment of women with posttraumatic stress disorder resulting from childhood sexual abuse. *Journal of Consulting and Clinical Psychology*, *66*(6), 906–913. doi:10.1037/0022-006X.66.6.906

Orr, S. P., Metzger, L. J., Lasko, N. B., Macklin, M. L., Peri, T., & Pitman, R. K. (2000). De novo conditioning in trauma-exposed individuals with and without posttraumatic stress

disorder. *Journal of Abnormal Psychology*, *109*(2), 290–298. doi:10.1037/0021-843X.109.2.290

Osuch, E. A., Benson, B. E., Luckenbaugh, D. A., Geraci, M., Post, R. M., & McCann, U. (2009). Repetitive TMS combined with exposure therapy for PTSD: A preliminary study. *Journal of Anxiety Disorders*, *23*(1), 54–59. doi:10.1016/j.janxdis.2008.03.015

Pal, H. R., Berry, N., Kumar, R., & Ray, R. (2002). Ketamine dependence. *Anaesthesia and Intensive Care*, *30*(3), 382–384.

Pallanti, S., & Bernardi, S. (2009). Neurobiology of repeated transcranial magnetic stimulation in the treatment of anxiety: A critical review. *International Clinical Psychopharmacology*, *24*(4), 163–173. doi:10.1097/YIC.0b013e32832c2639

Pitman, R. K., Altman, B., Greenwald, E., Re, L., Macklin, M. L., Poiré, R. E., & Steketee, G. S. (1991). Psychiatric complications during flooding therapy for posttraumatic stress disorder. *Journal of Clinical Psychiatry*, *52*(1), 17–20.

Pitman, R. K., Sanders, K. M., Zusman, R. M., Healy, A. R., Cheema, F., Lasko, N. B., & Orr, S. P. (2002). Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. *Biological Psychiatry*, *51*(2), 189–192. doi:10.1016/S0006-3223(01)01279-3

Portas, C. M., Rees, G., Howseman, A. M., Josephs, O., Turner, R., & Frith, C. D. (1998). A specific role for the thalamus in mediating the interaction of attention and arousal in humans. *Journal of Neuroscience*, *18*(21), 8979–8989.

Pradhan, B. K. (2014). *Yoga and mindfulness based cognitive therapy—A clinical guide*. Switzerland: Springer International.

Pradhan, B. K., Gray, R. M., Parikh, T., Akkireddi, P., & Pumariega, A. (2015). Trauma interventions using Mindfulness Based Extinction and Reconsolidation (TIMBER©) as monotherapy for chronic PTSD: A pilot study. *Adolescent Psychiatry*, *5*(2), 125–131. doi:10.2174/2210676605020150430155038

Pradhan, B.K., Pumariega A.J., Goldberg M., Torjman M., Wainer I. (ongoing study from 8/2013-Present): Combined ketamine and mindfulness based cognitive therapy for patients with refractory post-traumatic stress disorder (PTSD): Comparison of treatment efficacy and pharmaco-genomic and metabolomic profiles. Collaborative study between Departments of Psy-chiatry and Anesthesia at the Cooper University Hospital, Camden, NJ and the Bio-analytical Chemistry and Drug Discovery Section of the National Institute on Aging (NIA/NIH).

Radloff, L. S. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*, *1*(3), 385–401. doi:10.1177/014662167700100306

Raskind, M. A., Peskind, E. R., Hoff, D. J., Hart, K. L., Holmes, H. A., Warren, D., & McFall, M. E. (2007). A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biological Psychiatry*, *61*(8), 928–934. doi:10.1016/j.biopsych.2006.06.032

Ravindran, L. N., & Stein, M. B. (2009). Pharmacotherapy of PTSD: Premises, principles, and priorities. *Brain Research*, *1293*, 24–39. doi:10.1016/j.brainres.2009.03.037

Rosenberg, P. B., Mehndiratta, R. B., Mehndiratta, Y. P., Wamer, A., Rosse, R. B., & Balish, M. (2002). Repetitive transcranial magnetic stimulation treatment of comorbid posttraumatic stress disorder and major depression. *Journal of Neuropsychiatry and Clinical Neurosciences*, *14*(3), 270–276. doi:10.1176/jnp.14.3.270

Rossi, S., De Capua, A., Tavanti, M., Calossi, S., Polizzotto, N. R., Mantovani, A., & Ulivelli, M. (2009). Dysfunctions of cortical excitability in drug-naive posttraumatic stress disorder patients. *Biological Psychiatry*, *66*(1), 54–61. doi:10.1016/j.biopsych.2009.03.008

Sageman, S. (2002). How SK can treat the cognitive, psychodynamic, and neuropsychiatric problems of post traumatic stress disorder. In *Proceedings: Science of Breath. International*

Symposium on Sudarshan Kriya, Pranayam and Consciousness, March 2–3, 2002, New Delhi, New Delhi: All India Institute of Medical Sciences, 2002; 29–32.

Satchidananda, S. (1990). *The yoga sutras of patanjali*. Yogaville, WV: Integral Yoga Dist.

Schiller, D., Monfils, M.-H., Raio, C. M., Johnson, D. C., Ledoux, J. E., & Phelps, E. A. (2010, January 7). Preventing the return of fear in humans using reconsolidation update mechanisms. *Nature*, *463*, 49–53. doi:10.1038/nature08637

Schönenberg, M., Reichwald, U., Domes, G., Badke, A., & Hautzinger, M. (2008). Ketamine aggravates symptoms of acute stress disorder in a naturalistic sample of accident victims. *Journal of Psychopharmacology*, *22*(5), 493–497. doi:10.1177/0269881107082481

Shapiro, F. (1999). Eye movement desensitization and reprocessing (EMDR) and the anxiety disorders: Clinical and research implications of an integrated psychotherapy treatment. *Journal of Anxiety Disorders*, *13*(1–2), 35–67. doi:10.1016/S0887-6185(98)00038-3

Shapiro, F. (2001). *Eye movement desensitization and reprocessing: Basic principles, protocols, and procedures* (2nd ed.). New York, NY: Guilford Press.

Shin, L. M., & Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology*, *35*, 169–191. doi:10.1038/npp.2009.83

Siegelbaum, S., Kandel, E., & Yuste, R. (2013). Synaptic integration in the central nerv-ous system. *Principles of Neural Science, 5th Edn.* McGraw-Hill, *New York*, 210–235.

Stein, D. J., Ipser, J. C., & Seedat, S. (2006). Pharmacotherapy for post traumatic stress disorder (PTSD). *Cochrane Database of Systematic Reviews*, *1*(1). doi:10.1002/14651858.CD002795.pub2

Stickgold, R. (2002). EMDR: A putative neurobiological mechanism of action. *Journal of Clinical Psychology*, *58*(1), 61–75. doi:10.1002/jclp.1129

Strayer, R. J., & Nelson, L. S. (2008). Adverse events associated with ketamine for procedural sedation in adults. *American Journal of Emergency Medicine*, *26*(9), 985–1028. doi:10.1016/j.ajem.2007.12.005

Streeter, C. C., Jensen, J. E., Perlmutter, R. M., Cabral, H. J., Tian, H., Terhune, D. B., … Renshaw, P. F. (2007). Yoga asana sessions increase brain GABA levels: A pilot study. *Journal of Alternative and Complementary Medicine*, *13*(4), 419–426. doi:10.1089/acm.2007.6338

Streeter, C. C., Whitfield, T. H., Owen, L., Rein, T., Karri, S. K., Yakhkind, A., … Jensen, J. E. (2010). Effects of yoga versus walking on mood, anxiety, and brain GABA levels: A randomized controlled MRS study. *Journal of Alternative and Complementary Medicine*, *16*(11), 1145–1152. doi:10.1089/acm.2010.0007

Taylor, H. R., Freeman, M. K., & Cates, M. E. (2008). Prazosin for treatment of nightmares related to posttraumatic stress disorder. *American Journal of Health-System Pharmacy*, *65*(8), 716–722. doi:10.2146/ajhp070124

Thompson, C. E., Taylor, F. B., McFall, M. E., Barnes, R. F., & Raskind, M. A. (2008). Nonnightmare distressed awakenings in veterans with posttraumatic stress disorder: Response to prazosin. *Journal of Traumatic Stress*, *21*(4), 417–420. doi:10.1002/jts.v21:4

Tillman, G. D., Kimbrell, T. A., Calley, C. S., Kraut, M. A., Freeman, T. W., & Hart, J. (2011). Repetitive transcranial magnetic stimulation and threat memory: Selective reduction of combat threat memory P300 response after right frontal lobe stimulation. *Journal of Neuropsychiatry Clinical Neuroscience*, *23*, 40–47. doi:10.1176/appi.neuropsych.23.1.40

Tokarev, D., & Jezová, D. (1997). Effect of central administration of the non-NMDA receptor antagonist DNQX on ACTH and corticosterone release before and during immobilization stress. *Methods and Findings in Experimental and Clinical Pharmacology*, *19*(5), 323–328.

Vaiva, G., Ducrocq, F., Jezequel, K., Averland, B., Lestavel, P., Brunet, A., & Marmar, C. R. (2003). Immediate treatment with propranolol decreases posttraumatic stress disorder two

months after trauma. *Biological Psychiatry*, *54*(9), 947–949. doi:10.1016/S0006-3223(03)00412-8

Vedamurthachar, A. (2002). Biological effects of sudarshan kriya on alcoholics. *National Institute of Mental Health and Neurosciences*, Bangalore, India.

Watts, B. V., Landon, B., Groft, A., & Young-Xu, Y. (2012). A sham controlled study of repetitive transcranial magnetic stimulation for posttraumatic stress disorder. *Brain Stimulation*, *5*(1), 38–43. doi:10.1016/j.brs.2011.02.002

Westbrook, R. F., Iordanova, M., McNally, G., Richardson, R., & Harris, J. A. (2002). Reinstatement of fear to an extinguished conditioned stimulus: Two roles for context. *Journal of Experimental Psychology: Animal Behavior Processes*, *28*(1), 97–110. doi:10.1037/0097-7403.28.1.97

Wolfsdorf, B. A., & Zlotnick, C. (2001). Affect management in group therapy for women with posttraumatic stress disorder and histories of childhood sexual abuse. *Journal of Clinical Psychology*, *57*(2), 169–181. doi:10.1002/(ISSN)1097-4679

Zayfert, C., & Becker, C. B. (2000). Implementation of empirically supported treatments for PTSD: Obstacles and innovations. *The Behavior Therapist*, *23*, 161–168.

Zelena, D., Mergl, Z., & Makara, G. B. (2005). Glutamate agonists activate the hypothalamic-pituitary-adrenal axis through hypothalamic paraventricular nucleus but not through vasopressinerg neurons. *Brain Research*, *1031*(2), 185–193. doi:10.1016/j.brainres.2004.10.034

Zhang, L. M., Zhou, W. W., Ji, Y. J., Li, Y., Zhao, N., Chen, H. X., & Li, Y. F. (2014). Anxiolytic effects of ketamine in animal models of posttraumatic stress disorder. *Psychopharmacology, 232*, 663–672. doi:10.1007/s00213-014-3697-9

Zigman, D., & Blier, P. (2013). Urgent ketamine infusion rapidly eliminated suicidal ideation for a patient with major depressive disorder: A case report. *Journal of Clinical Psychopharmacology*, *33*(2), 270–272. doi:10.1097/JCP.0b013e3182856865