## A. SPECIFIC AIMS

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder associated with high rates of chronicity, poor quality of life, and severe impairments in interpersonal, occupational, and social functioning ( Taft, Watkins, Stafford, Street, & Monson, 2011; Kehle, S. M., Reddy, M. K., Ferrier-Auerbach, A. G., Erbes, C. R., Arbisi, P. A., & Polusny, M. A., 2011). While evidence-based psychotherapies for treatment of PTSD have been developed and disseminated within the Department of Veterans Affairs (VA), no treatment has shown universal effectiveness and there is great concern about attenuated treatment response and elevated treatment drop out in veteran populations (Schnurr, P. P., Friedman, M. J., Foy, D. W., Shea, M. T., et al., 2003a). The evaluation of alternative treatment modalities for veterans with PTSD is therefore an important priority. The Minneapolis VA Health Care System (MVAHCS) has offered Mindfulness-Based Stress Reduction (MBSR), a group-based intervention focused on mindfulness meditation, to veteran clinical populations since 2001, and our pilot data from veterans diagnosed with PTSD is promising. Despite support for the application of MBSR to other mental health and physical problems (Baer, 2003), MBSR has not been evaluated systematically as a treatment for PTSD. Moreover, the existing literature on MBSR is limited by methodological weaknesses (Baer, 2003; Ludwig & Kabat-Zinn, 2008). If shown to be efficacious through scientifically sound trials, MSBR may offer an effective, acceptable, and tolerable intervention for veterans suffering PTSD who are unable to engage in or complete traditional exposure-based therapies. The primary goal of this proposal is to *conduct a methodologically rigorous randomized controlled trial (RCT)* of MBSR in treating PTSD among veterans, examining both symptom outcomes and subsequent health services utilization. Given our compelling pilot data, we propose initial steps to *evaluate putative mechanisms of change* (self-report and neurobiological markers, i.e., EEG) through which MBSR may relate to PTSD symptom improvement. We also propose to *examine the acceptability of MBSR to the veteran population.*

The MVAHCS and the assembled team combines expertise in PTSD treatment and research, clinical trials, and neuroscience, with clinical expertise in MBSR and compelling pilot data to support the feasibility and scope of the current project. The efficacy of MBSR will be examined relative to present-centered group therapy (PCGT), a non-specific therapeutic comparison group. Veterans diagnosed with PTSD will be randomized to MBSR or PCGT for 9 weeks. Each intervention will be delivered in group format following manualization by trained clinicians receiving expert supervision. Treatment integrity will be independently monitored. Assessment of clinical outcomes post-treatment and at 2 months follow-up will be independently evaluated. Putative mechanisms of mindfulness meditation will be assessed using self-report and neurobiological markers. The proposed clinical trial is designed and powered to address the following primary objective.

**Primary Aim 1: To evaluate the efficacy of MBSR as a treatment for PTSD in veterans compared to PCGT over 9-weeks of treatment and at 2-month follow-up.**

H1: Veterans assigned to MBSR will show greater PTSD symptom improvement than veterans assigned to PCGT post-treatment and at 2-month follow-up. Symptom improvement will be measured by a clinically meaningful reduction in PTSD symptoms as measured by self report and independent clinical evaluation.

**Secondary Aim 1: To assess putative mechanisms of MBSR using mediation analysis.**

H2: Veterans assigned to MBSR will show greater self-reported mindfulness skills than veterans assigned to PCGT following the 9 weeks of treatment.

H3: Veterans' self-reported mindfulness skills over 9 weeks of treatment will predict PTSD symptom improvement.

H4: Veterans assigned to MBSR will show greater normalization of EEG than veterans assigned to PCGT.

H5: The degree of EEG change will predict improvement in PTSD symptoms.

**Secondary Aim 2: To identify differences in subsequent VA health services utilization among veterans across treatment conditions.**

H6: Veterans assigned to MBSR will demonstrate lower rates of health services utilization during the 2-month follow-up interval than veterans assigned to PCGT. Physical and mental health services utilization will be measured using VA administrative data.

**Exploratory Aims:**

1. To evaluate rates of drop-out, compliance, and consumer satisfaction with MBSR.
2. To evaluate outcomes and acceptability of treatment among veterans diagnosed with PTSD with a history of mild traumatic brain injuries.

## B. BACKGROUND AND SIGNIFICANCE

In this section, we will summarize published findings that have guided the design of the proposed study. First, we will illustrate the scope of the problem by reviewing the epidemiology and psychosocial impact of PTSD in veterans. Second, we will briefly review traditional evidence-based treatments for PTSD and present data supporting the importance of identifying alternative treatment approaches. Third, we will describe MBSR, a promising intervention for a broad range of clinical problems including PTSD, and will summarize the strengths and limitations of the evidence base for MBSR. Finally, we will review theory and research on potential mechanisms underlying mindfulness meditation and discuss how MBSR may lead to PTSD symptom improvements.

### Prevalence and impact of PTSD in veterans

PTSD is a debilitating psychiatric disorder characterized by intrusive and distressing recollections of a traumatic event, avoidance of reminders of the event, and symptoms of hyperarousal, such as impaired sleep, irritability, and decreased concentration. Estimates of the rate of lifetime PTSD in the US population have ranged from 7% to 12% ( Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E., 2005). The National Vietnam Veterans Readjustment Study (NVVRS) documented considerably higher rates with 19% to 30% of combat veterans suffering lifetime PTSD (Dohrenwend, B. P., Turner, J. B., Turse, N. A., Adams, B. G., Koenen, K. C., & Marshall, R., 2006). Data from the Departments of Defense (DOD) (Hoge, C. W., Castro, C. A., Messer, S. C., McGurk, D., Cotting, D. I., & Koffman, R. L. (2004), Veterans Affairs (VA) (Seal, Bertenthal, Miner, Sen, & Marmar, 2007), and our own studies (Polusny, M. A., Kehle, S. M., Nelson, N. W., Erbes, C. R., Arbisi, P. A., & Thuras, P., 2011) show rates of PTSD to be as high as 19% in soldiers returning from Iraq and Afghanistan. These rates are particularly alarming given that combat-related PTSD often has a high rate of delayed onset (Prigerson, Maciejewski, & Rosenheck, 2001; Wolfe, Erickson, Sharkansky, King, & King, 1999; Schnurr, Lunney, Sengupta, & Waelde, 2003b). In addition, many veterans report exposure to other trauma experiences, including sexual assault within and outside of the military, that frequently lead to PTSD (Frayne, Skinner, Sullivan, & Freund, 2003).

PTSD carries enormous costs to individuals as well as to society and to the VA system. Once PTSD develops, its course is frequently chronic with high rates of psychiatric co-morbidity (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). For example, we found over 85% of National Guard combat veterans diagnosed with PTSD had at least one additional diagnosis based on structured clinical interviews (Kehle et al., 2011). PTSD is associated with substantial impairment in occupational, interpersonal, and family functioning (Prigerson et al., 2001; Taft, C. T., Pless, A. P., Stalans, L. J., Koenen, K. C., King, L. A., & King, D. W., 2005; Taft et al., 2011) and poorer quality of life (Rapaport, Clary, Fayyad, & Endicott, 2005; Zatzick et al., 1997; Mendlowicz & Stein, 2000). PTSD is also associated with greater physical health complaints and medical disease burden (Hoge, Terhakopian, Castro, Messer, & Engel, 2007) and utilization of VA medical services (Seal, K. H., Maguen, S., Cohen, B., Gima, K. S., Metzler, T. J., Ren, L., 2010) even considering medical co-morbidities (Schnurr, Friedman, Sengupta, Jankowski, & Holmes, 2000). Finally, the societal costs associated with PTSD are vast. Estimates suggest approximately $3 billion of productivity is lost yearly due to PTSD  with the VA spending over $4.3 billion on disability compensation to veterans for PTSD in 2004 alone (VA Office of Inspector General, 2005). In 2010, more than 437,000 veterans received service-connected disability benefits for PTSD (Veterans Benefits Administration, 2010).

### Limitations of Existing Evidence Based Treatments for PTSD

The past two decades have witnessed encouraging advances in empirically-validated treatments for PTSD. Antidepressant medications, including some tricyclic antidepressants, monoamine oxidase inhibitors, and especially selective serotonin reuptake inhibitors have shown efficacy in RCTs.Anxiolytic medications have also shown some effect on the hyperarousal symptoms of PTSD in open-label trials (Van Etten & Taylor, 1998). Although pharmacotherapy appears to be helpful, the Institute of Medicine (IOM) concluded that the evidence from RCTs was currently inadequate to support the efficacy of pharmacotherapies in the treatment of PTSD (Institute of Medicine, 2007). Psychotherapy approaches have been associated with larger effect sizes(Van Etten et al., 1998), and among those approaches recently reviewed by the IOM (Institute of Medicine, 2007), exposure therapies, which include imaginal and in vivo exposure techniques as well as emotional processing to confront and work through feared trauma-related situations and memories, were found to have the most empirical evidence for successful treatment of PTSD. As a result, Prolonged Exposure (PE)

and Cognitive Processing Therapy (CPT) have been recommended by VA as first-line treatments for PTSD (Veterans Health Administration & Department of Defense, 2004) and an unprecedented dissemination effort is underway to train and support VA clinicians in providing PE and CPT (Karlin, B. E., Ruzek, J. I., Chard, K. M., Eftekhari, A., Monson, C. M., Hembree, E. A. et al., 2010).

Unfortunately, current data show that even the most empirically validated approaches for treating PTSD are not universally effective. Studies typically find substantial gains for only slightly more than half of treated patients, and those who respond often continue to show substantial residual difficulties (Bradley, Greene, Russ, Dutra, & Westen, 2005). Some evidence suggests that combat veterans show less pre- to post-treatment improvement in PTSD symptoms than individuals suffering PTSD related to traumatic events unrelated to combat (Bradley et al., 2005). Rates of premature dropout from exposure-based therapy approaches are high, especially among veterans with combat-related PTSD (Schnurr et al., 2003a). Data from clinical trials show that, on average, 1 in 5 patients drop out of PE (20.5%) (Institute of Medicine, 2007; Bradley et al., 2005), with rates as high as 50% reported in some studies (Schottenbauer, Glass, Arnkoff, Tendick, & Gray, 2008). Rates of premature drop-out appear even higher among patients not enrolled in RCTs who are treated in "real world" clinical practice. For example, Zayfert and colleagues reported drop-out rates as high as 72% (2005), and over two thirds (68%) of OEF/OIF veterans treated at one VA PTSD clinic prematurely dropped-out of PE. Although predictors of premature drop-out from traditional trauma-focused treatments remain unclear, aversive aspects of trauma-focused treatment procedures themselves (e.g., visualizing and repeatedly retelling one's most distressing trauma memory for a period of 45-60 minutes) may contribute to some veterans being unable to tolerate the cognitive-affective processing of trauma (Becker & Zayfert, 2001; Bradley et al., 2005). Indeed, there is some evidence that exposure-based therapy may cause a temporary increase in PTSD symptoms, and thus, may lead patients to leave treatment prematurely (Foa, Zoellner, Feeny, Hembree, & Alvarez-Conrad, 2002). Perhaps due to these and other clinical concerns about the safety and applicability of exposure based treatments, many clinicians are reluctant to recommend these traditional evidence-based treatments (Becker, Zayfert, & Anderson, 2004), resulting in relatively few veterans actually receiving them (Foy, D. W., Kagan, B., McDermott, C., Leskin, G. A., Sipprelle, R. C., & Paz, G., 1996). A survey of VA clinicians specializing in PTSD treatment found that fewer than 20% ever used exposure therapies, and fewer than 10% used them frequently (Rosen, C. S., Chow, H. C., Finney, J. F., Greenbaum, M. A., Moos, R. H., Sheikh, J. I., 2004) More recent data suggests very few OEF/OIF veterans with PTSD likely received these treatments (Seal et al., 2010). ***As such, there is an urgent need to consider and evaluate alternative approaches for the treatment of PTSD that may utilize more tolerable procedures, involve different mechanisms of change, and thus appeal to the sizeable number of veterans who are unwilling or unable to engage in and/or complete traditional trauma-focused treatments for PTSD.***

## Growing Interest in Meditation as an Alternative Intervention

Meditation can be conceptualized as a mental practice designed to achieve a variety of goals such as promoting relaxation, reducing stress or achieving a heighted sense of well-being (Lutz, Slagter, Dunne, & Davidson, 2008). While meditation has gained increasing acceptance in the United States as a method for promoting health (i.e., the 2007 Health Interview Survey found that 9.4 percent of adults had practiced meditation), a growing body of literature points to the potential value of meditation for the treatment of clinical disorders. However, meditation has not yet been evaluated as an intervention for PTSD in veterans. Meditation encompasses a broad range of practices with varying goals making it important to be specific about the type of meditation being studied (Lutz et al., 2008). Travis and Shear (Travis & Shear, 2010) proposed three broad categories of meditation that can be differentiated based on brain activity, attentional focus and control, subject-object relations, and information processing. The three categories include: automatic self-transcendent (e.g. Transcendental Meditation); focused attention (e.g. selective attention on a chosen object such as the breath); and open monitoring (e.g. dispassionate, non-evaluative awareness of ongoing experience; also described as mindfulness meditation). Of these, one of the most prominent and widespread examples of the open monitoring type of meditation is MBSR (Kabat-Zinn, Lipworth, & Burney, 1985).

## What is Mindfulness-Based Stress Reduction?

Originally developed by Dr. Jon Kabat-Zinn at the University of Massachusetts Medical Center in 1979, the MBSR program is an 8-week intensive training in mindfulness meditation. Mindfulness meditation such as that practiced in MBSR involves non-reactive monitoring of the moment-to-moment content of experience (Lutz et al., 2008). Mindfulness involves focusing on the present moment in a non-judgmental and accepting manner.

As a result of being fully present moment-to-moment, one may develop an awareness of what is occurring both within and outside oneself at each moment. Mindfulness implies a state of curious observation where there is no need to act on or label what is noticed. With the awareness that accompanies mindfulness, there is the potential to 1) develop the ability to recognize internal cues signifying the presence of stress, 2) notice the presence of judgments which arise and how they are expressed, 3) recognize the "chattering" mind which often dwells in the past or anticipates the future, and 4) identify thoughts associated with painful or distressing feelings or events and cultivate an ability to challenge the accuracy of these thoughts (Center for Spirituality & Health at the University of Minnesota, 2011). Mindfulness presents the opportunity to change one's relationship with one's thoughts to facilitate viewing thoughts as mere *mental events* and emotions as simply reactions to thoughts (Stahl & Goldstein, 2010). With the awareness that accompanies mindfulness, there comes an opportunity to learn how to consciously respond to stressful situations rather than to mindlessly react in habitual, and sometimes destructive, ways.

## Clinical Applications and Outcomes of MBSR

MBSR has been shown to be an effective intervention for a wide range of conditions involving both physical and psychological health (Bohlmeijer, Prenger, Taal, & Cuijpers, 2010). The MBSR program has been shown to be beneficial for individuals experiencing chronic pain (Kabat-Zinn, et al., 1985), mood disturbance (Rosenzweig, Reibel, Greeson, Brainard, & Hojat, 2003), and anxiety (Miller, Fletcher, & Kabat-Zinn, 1995). In a study of 22 patients diagnosed with generalized anxiety disorder or panic disorder, MBSR was associated with clinically and statistically significant reductions in anxiety and depression symptoms that were maintained three months after completion of the course (Kabat-Zinn et al., 1992), as well as three years later (Miller et al., 1995). In a study examining the effects of MBSR on social anxiety disorder, MBSR completers, when compared to baseline, exhibited both increased self-esteem and positive self-endorsement as well as decreased anxiety and negative self-endorsement (Goldin, Manber-Ball, Werner, Heimberg, & Gross, 2009). In a small RCT comparing MBSR to cognitive behavioral group therapy for the treatment of generalized social anxiety disorder, both treatment arms saw improvement; however, the CBGT group reported lower levels of anxiety and higher response and remission rates (Koszycki, Benger, Shlik, & Bradwejn, 2007). Mindfulness meditation training has also shown promise as a helpful treatment approach for substance abuse, which commonly co-occurs with PTSD. In a small RCT of patients diagnosed with a substance use disorder, subjects who completed mindfulness meditation training had lower levels of stress reactivity following treatment than those receiving cognitive behavioral therapy (Brewer et al., 2009).

## MBSR as an Alternative Treatment for PTSD

As we discussed above, traditional evidence-based, trauma-focused treatments for PTSD are effective for some individuals, but not all. It has been argued that current available treatments, PE and CPT in particular, may be too specifically and intensely trauma-focused for some individuals. Several authors suggest that mindfulness meditation may serve as a gentler form of exposure for individuals who find traditional trauma focused treatments intolerable (Baer, 2003; Follette & Vijay, 2009). Through focusing on the present moment in a non-judgmental and accepting manner, mindfulness meditation involves observing thoughts, feelings, and sensations. Vujanovic and colleagues describe this process as an indirect mechanism of cognitive-affective exposure, where one approaches rather than avoids one's uncomfortable state, takes on the role of an impartial witness or observer of experience, and thus, promotes distress tolerance (Vujanovic, Niles, Pietrefesa, Schmertz, & Potter, 2011). MBSR is one widely used standardized vehicle for progressively training individuals in the application of mindfulness skills. In MBSR, there is no requirement for the individual to directly confront the trauma. However, through regular mindfulness mediation practice focused on present-centered awareness and nonjudgmental acceptance of uncomfortable cognitive and emotional states, including trauma-related memories, MBSR, may serve well as a less intense form of exposure therapy for those individuals who do not respond well to PE/CPT (Follette et al., 2009).

An emerging literature on the relationship between mindfulness and PTSD supports MBSR as a potential alternative treatment for PTSD. Through cultivating awareness of the present moment in a non-judgmental and accepting manner, MBSR may decrease experiential avoidance which has been identified as a key factor in the development and maintenance of PTSD (Marx & Sloan, 2005; Plumb, Orsillo, & Luterek, 2004). Recent research has examined the relationship between mindfulness-based processes (e.g., observing, describing, nonreactivity to inner experience, nonjudging of inner experiences, acting with awareness) and severity of PTSD symptoms. Vujanovic and colleagues reported the mindfulness skills of non-judgmental acceptance and

acting with awareness were significantly, negatively associated with PTSD symptoms (Vujanovic, Youngwirth, Johnson, & Zvolensky, 2009). Similarly, in a sample of undergraduate students, nonjudgmental acceptance was significantly associated with PTSD symptoms, particularly avoidance (Thompson & Waltz, 2010). (Thompson et al., 2010) suggested that this nonjudgmental stance towards one's experience may be important in the treatment of PTSD and that it may be protective against the development of PTSD symptoms. Although based on non-clinical trauma-exposed samples, findings from these studies point to the potential utility of mindfulness mediation as a treatment for PTSD.

**To our knowledge, only one treatment outcome study has been published examining the efficacy of MBSR in treating PTSD.** In this study of 27 adult survivors of childhood sexual abuse, participants completed an 8-week MBSR intervention (Kimbrough, Magyari, Langenberg, Chesney, & Berman, 2010). Assessments of PTSD, anxiety, depressive symptoms, and mindfulness were conducted at baseline, 4, 8 and 24 weeks. **Although limited by the lack of a randomized controlled condition, results of this pilot study were promising and showed statistically significant improvements across all outcome measures.**

Taken together, findings from several small treatment outcome studies demonstrating the beneficial effects of MBSR for wide range of physical and psychological conditions including one study of trauma survivors, findings on the relationship between mindfulness and PTSD symptoms, as well as clinical and theoretical arguments, all suggest that MBSR may serve as a useful alternative treatment modality for PTSD. Our own MBSR pilot data, presented below in Preliminary Studies, also supports this claim. However, published studies to date have serious limitations including: small numbers of subjects, lack of active control groups, lack of objective endpoints, heterogeneous participant characteristics (limiting generalizability), lack of reproducible treatment methods, lack of monitoring of study staff protocol adherence, and lack of tracking of participant skill acquisition (Ludwig & Kabat-Zinn, 2008). Further, and most importantly, there are no data from RCTs demonstrating the efficacy of MBSR for PTSD in a veteran population.

**Thus, an RCT of the efficacy of MBSR in treating PTSD, with sufficient number of subjects, an active control treatment, standardized treatment methods with treatment fidelity monitoring, independent assessment of outcomes, and assessment of participant skill acquisition is a crucial step in the evaluation of this promising treatment for veterans suffering PTSD.**

## Mechanisms of Change in MBSR for PTSD

Potential psychological and neurophysiological mechanisms have been proposed as being important to understanding how MBSR might prove effective in the treatment of PTSD. From a psychological perspective, Vujanovic and colleagues outlined four clinical functions in which mindfulness practices may contribute to reducing PTSD symptoms: indirect exposure (discussed above); increased acceptance; increased psychological flexibility; and decreased arousal (Vujanovic et al., 2011). Through cultivating greater present-centered awareness and nonjudgmental acceptance of distressing internal experiences (e.g., trauma-related memories), mindfulness meditation may function as an indirect form of exposure. Furthermore, greater interoceptive awareness and acceptance of physical sensations might result in greater tolerance for uncomfortable physical sensations (e.g., physiological arousal in response to trauma-related external cues) through the mechanism of indirect exposure. Greater levels of nonjudgmental acceptance of internal experience can result in decreased shame, guilt, and difficulties with respect to self-acceptance (Thompson & Waltz, 2008). Regular mindfulness meditation practice may also lead to increased psychological flexibility, or the willingness to experience thoughts and feelings without attempting to control them, which can further enhance the process of indirect exposure to trauma-related memories. By decreasing physiological arousal and increasing emotion regulation (Baer, 2003), mindfulness meditation may lead to reduced hyperarousal symptoms such as anger, irritability, sleep disturbance, exaggerated startle response. Greater awareness of bodily cues may lead to a necessary awareness that allows for self-regulation in more adaptive way. Thus, an initial step to examining these psychological mechanisms would be to assess changes in mindfulness skills over the course of MBSR training and examine how mindfulness skills related to improvements in PTSD symptoms. This approach is supported by recent evidence showing mindfulness (nonjudgement as measured by the FFMQ) predicted additional variance in PTSD avoidance symptom severity (Thompson et al., 2010).

Neuroscience investigations of meditation have also highlighted potential physiological markers of change resulting from mindfulness practice. These investigations of the brain began in 1955 with the first EEG studies

and have subsequently grown to include other neuroimaging methods such as PET, MRI, spectroscopy and functional MRI. In a comprehensive review of the topic of meditation and brain measures Cahn and Polich (Cahn & Polich, 2006) identified several issues relevant to brain studies of meditation including the type of meditation (e.g. mindfulness vs. concentrative) and state vs. trait assessments. This points to the importance of obtaining independent neurophysiological measures of meditation. A potential advantage of such measures is that they can provide an independent, quantitative and individual measure over time. Such measures allow for the tracking of whether meditation is having an effect on brain indices, thereby complementing self-report measures. Few studies have examined the effect of MBSR on the brain. In a study of social anxiety disorder patients undergoing MBSR, subjects were examined with task based fMRI that found reduced amygdala activity and evidence of an enhanced attentional network (Goldin & Gross, 2010). EEG changes have been found with MBSR (Davidson et al., 2003) in as few as 8 weeks. In a study of healthy subjects participating in an 8-week MBSR course compared with a waitlist, eyes closed resting EEG was collected at baseline, immediately after the course, and 4 months after the course. A frontal alpha asymmetry index was computed based on the alpha band (8-13Hz) spectral density. No difference was found between groups at baseline, but greater left sided activation was observed at 8 weeks and at the 4 month time point. This supports the idea that persistent effects on brain EEG patterns can be measured and detected as soon as 8 weeks after the beginning of practice. This might provide a quantitative measure of participant skill acquisition.

Resting EEG findings on MBSR are complemented by a small but growing body of research on resting EEG in subject with PTSD. Findings for EEG resting abnormalities in PTSD have been mixed. Gordon and colleagues (Gordon, Palmer, & Cooper, 2010) found evidence of EEG alpha asymmetry in schizophrenia but not in PTSD. No resting EEG asymmetry was observed in another study of PTSD (Shankman, S. A., Silverstein, S. M., Williams, L. M., Hopkinson, P. J., Kemp, A. H., Felmingham, K. L., 2008). However, Kemp et al. found a positive correlation between PTSD severity and right-frontal lateralization (Kemp et al., 2010). In Preliminary Studies, we describe our preliminary findings with resting EEG that found significantly increased gamma band power (31-64Hz) in PTSD subjects compared with subjects without PTSD.

## Importance of Examining Mechanisms

The preceding section demonstrates that a potential benefit of the study of MBSR in the treatment of PTSD is that mechanisms of change have been proposed that can be measured by both self-report and neurobiological measures. MBSR is thought to address the maintaining processes of PTSD through teaching a nonjudgmental, accepting, and grounded approach to daily experience including trauma reminders, trauma-related symptoms, and trauma memories themselves (Walser & Hayes, 2006). As such, to the extent that one has mastered a practice and approach of mindfulness, the treatment should show an effect on improving PTSD symptoms. Self report measures have been developed that assess mindfulness and have been shown to predict relationships with MBSR treatments and outcomes (Thompson et al., 2010). Similarly, studies have shown that MBSR is associated with changes on a neurophysiological level that can be demonstrated via EEG, with increases in left sided alpha asymmetry observed after 8 weeks of MBSR training. Thus, technologies exist for evaluating not only outcomes of MBSR in the treatment of PTSD, but also the mechanisms by which MBSR is thought to provide its benefits. This provides an opportunity to evaluate the efficacy of the treatment as well as the potential proximal effects of the interventions.

A better understanding of mechanism can help identify what components of an intervention are important for specific disorder as well as support the comparison of different interventions (Kocovski, Segal, & Battista, 2009; Teasdale, Segal, & Williams, 2003). Both approaches are needed if refinement and more detailed comparisons of interventions are to occur.

Examination of treatment mechanisms is typically pursued following demonstration of effectiveness. However, *we believe that preliminary data (see Preliminary Studies below) from our VA clinical MBSR program showing improvement in PTSD and associated symptoms, mindfulness skills, and reduced health care utilization, provides sufficient justification to incorporate some measures in our proposed RCT. This will allow us to begin examining both psychological (mindfulness) and neurobiological (EEG) mechanisms to better inform our understanding of how MBSR works. These measures will also provide some initial information to facilitate treatment selection for individuals and potential avenues for refining interventions (Ludwig & Kabat-Zinn, 2008; Teasdale et al., 2003).* We would not expect patients receiving non-mindfulness based interventions, such as our control condition of PCGT, to show

changes in self-reports of mindfulness or changes in gamma EEG power. Thus, the examination of these markers of change in mindfulness and brain EEG patterns can further elucidate ways in which MBSR's effects occur beyond the supportive contact that is part of almost any clinical care.

## Summary, Conclusions, and Rationale for the Proposed Study

Many factors limit the effectiveness of traditional trauma-focused treatments for PTSD in veteran populations. Therefore, evaluation of alternative treatment approaches is essential to the provision of cutting-edge, evidence-based treatments for this pernicious disorder. MBSR is one promising alternative that is currently being utilized within VA for the treatment of PTSD and related psychopathology. MBSR may improve PTSD symptoms through "gentle exposure" to thoughts, feelings, and experiences without requiring intensive "flooding" or direct imaginal or in vivo exposure. Although promising, MBSR has not yet been systematically evaluated as a treatment for PTSD in an RCT. Preliminary findings, while promising, also demonstrate the need to rigorously test the efficacy of MBSR in treating PTSD among veterans. If efficacious, MBSR might offer a more tolerable, active treatment that improves PTSD outcomes for veterans unwilling or able to benefit from other first line trauma-focused treatments for PTSD. In the proposed research, we will examine whether MBSR will improve outcomes for veterans with PTSD compared to PCGT. We will also examine whether MBSR is associated with behavioral and neuroscience markers that are predictive of PTSD symptom improvements. Finally, we will examine whether MBSR leads to reductions in subsequent health services use, and whether this intervention is tolerable and acceptable to veterans as demonstrated by dropout rates and treatment satisfaction.

## C. PRELIMINARY STUDIES

### Research Team is Well Qualified to Undertake the Clinical Trial

The proposed clinical trial builds directly on the previous experience of this strong interdisciplinary team with complementary expertise in the clinical application of MBSR, PTSD, and neuroscience. It also further develops preliminary data from MVAHCS's strong MBSR program that has been treating veterans with mental health concerns including PTSD for over 10 years.

*Dr. Kelvin O. Lim,* Principal Investigator for this proposal, is a physician investigator with extensive experience in conducting clinical research imaging studies in a wide variety of populations including TBI, schizophrenia and substance abuse, funded by DOD and NIH. He serves as the Site Director of the Defense and Veterans Brain Injury Center in the MVAHCS. *Dr. Melissa Polusny*, Co-Investigator on the current proposal, is a clinician investigator with experience in conducting longitudinal studies of combat-related PTSD. She has served as PI on multiple funded (e.g., NIMH, DOD, VA) projects. As a national trainer and consultant for VA's Dissemination of Evidence-Based PTSD Treatment Initiative, Dr. Polusny has experience in training and supervising VA clinicians in the implementation of manualized PTSD treatments. *Dr. Christopher Erbes*, Co-Investigator, is an expert in the assessment and treatment of PTSD and is Program Manager for the MVAHCS Post-Traumatic Stress Recovery Clinic, a specialized outpatient PTSD program. He has served as PI on grants examining acceptability and preliminary effectiveness of alternative psychotherapies for PTSD, the influence of couple interactions on PTSD risk in recently returned OEF/OIF soldiers, and co-directs the DOD and HSR&D funded Readiness and Resilience in National Guard Soldiers (RINGS) Cohort Studies with Dr. Polusny. *Dr. Scott Sponheim,* Co-Investigator brings expertise in the research of brain disorders to this project. Dr. Sponheim is an expert on the electrophysiological and neuroimaging measurement of brain activity. His current work includes using multiple imaging modalities to better describe the spatial and temporal aspects of brain abnormalities underlying psychopathology and neurological conditions. Dr. Sponheim is PI on a large DOD funded grant on EEG and DTI to differentiate PTSD from mild TBI in OEF/OIF soldiers. *Dr. Paul Thuras*, study statistician, is an expert in study design, power and other statistical analysis, and data management. His primary focus is on the analysis of mental health data. He is currently the Research and Evaluation Program Director for the Mental Health patient service line in the MVAHCS. Dr. Thuras has extensive experience using multilevel and latent variable models examining change over time. He is currently working on several clinical trials and has extensive experience working with healthcare utilization data in the VA setting. *Drs. John Rodman and Nancy Koets* are clinical psychologists who have extensive clinical experience in facilitating MBSR sessions in the MVAHCS. Dr. Rodman has had a personal mindfulness practice since 2002 and received initial training in MBSR in 2003. He has taught MBSR in the community for three years. He is the Co-Coordinator of the Mindfulness-Based Interventions Program in the MVAHCS, overseeing the MBSR arm of the program. Last year he attended an advanced MBSR teacher training at the Center for Spirituality and Healing at the University of Minnesota. Dr. Koets has taught mindfulness skills to patient groups involved in Dialectical Behavior Therapy who were enrolled in a partial hospitalization program. In 2006, she completed training in Mindfulness-Based Cognitive Therapy (MBCT) from Zindal Segal. Last year she participated in the same advanced MBSR teacher-training as Dr. Rodman. *Dr. Greg Lamberty*, Co-Investigator, is a clinical neuropsychologist with interest in complementary and alternative approaches to treating veterans with complex psychological and medical presentations. Dr. Lamberty's expertise is in neuropsychological assessment with a wide range of patient populations, including somatization and somatoform disorders. He currently serves as the Program Coordinator/site PI for the Traumatic Brain Injury Model System program (jointly funded through the National Institute on Disability and Rehabilitation Research (NIDRR) and VA Central Office).

### Experience and Pilot Data from MBSR Groups Conducted with Veterans at MVAHCS

*Proposed study builds on established MBSR program in MVAHCS.* The MVAHCS has hosted an established clinical program of mindfulness based interventions since 2001. During the past 10 years, nearly 400 veterans have completed the full 8-week MBSR program. Our two MBSR group facilitators (Drs. Rodman and Koets) have over 10 years of experience in delivering MBSR and have facilitated the MBSR program at the VA since 2007. In addition to providing an excellent environment for more rigorous evaluation of MBSR as a treatment for PTSD, this program has also provided some promising preliminary data that strongly support the proposed project.

*Data from an initial pilot sample of 61 patients who received MBSR between 2001 and 2003 suggests a direct effect on PTSD symptoms.* For this cohort, there was significant improvement in PTSD symptoms $t(37)=2.82$, $p=.008$, $d=.46$, general psychological distress as measured by the Global Severity Index (GSI) of the Symptom Checklist-90, $t(37)=2.75$, $p=.009$, $d=.44$, experiential avoidance as measured by the Acceptance and Action Questionnaire (AAQ) $t(40)=2.32$, $p=.026$, $d=.35$, and thought suppression as measured by the White Bear Suppression Inventory (WBSI) $t(40)=2.13$, $p=.039$, $d=.34$. Overall, the dropout rate from the MBSR course was 25%, and overall adherence was 75%. For those who were adherent, changes in symptoms were comparable with significant decreases in PTSD symptoms, $t(30)=2.85$, $p=.008$, $d=.51$, GSI, $t(30)=2.14$, $p=.04$, $d=.39$, and WBSI, $t(32)=2.15$, $p=.039$, $d=.37$.

*Data from a subgroup of 15 patients with diagnosed PTSD who completed 8 weeks of MBSR shows significant improvement in PTSD symptoms* as measured by the Post-traumatic Stress Disorder Checklist (PCL), ($t(14)=2.33$, $p=.036$, $d=.6$. *Further, an analysis of VA administrative data shows mental health visits dropped significantly from 32.29 (one year period prior to MBSR) to 20.21 (one year after MBSR) ($p<.0009$), with an effect size $d=1.21$.*

*Pilot data suggests MBSR is an acceptable intervention among veterans.* Data from the initial pilot sample showed excellent satisfaction and utilization of MBSR practice: 96% reported lasting benefit from the program, 89% reported having made lifestyle changes as a result of participating in the program, 96% reported using some kind of formal meditation with two thirds reporting they meditated for over 30 minutes a session, 100% reported using some informal meditation technique, and 100% reported they would recommend the program to family or to a friend.

*Pilot data suggests MBSR is associated with changes in mindfulness skills and improvements in quality of life.* Data from a subsequent cohort of approximately 90 participants from the same MBSR program, collected from 2007 to 2010, continues to demonstrate the potential utility of MBSR in general, and with PTSD patients specifically. Among 24 patients who were diagnosed with PTSD, matched paired t-tests show significant improvement on measures of experiential avoidance (the AAQ ($t(23)=3.46$, $p=.002$, $d=.71$), quality of life (WHOQOL physical and psychological health domains [($t(22)=2.59$, $p=.017$, $d=.54$, ($t(22)=3.54$, $p=.002$, $d=.74$, respectively]), and acceptance without judgment and nonjudgmental description of experience (acceptance and describe subscales from the Kentucky Inventory of Mindfulness Skills (KIMS) instrument [($t(14)=4.39$, $p=.001$, $d=1.13$, ($t(14)=3.20$, $p=.006$, $d=.82$; respectively]). A subsample of 9 veterans given a new measure of mindfulness (the Five Facet Mindfulness Questionnaire; FFMQ) pre-post also showed significant improvement ($t(8)=3.24$, $p=.01$, $d=.93$.). A series of group by time interactions comparing the PTSD subgroup with other veterans without PTSD in MBSR showed that PTSD patients were able to benefit as well as other patients receiving MBSR, as no significant difference in rates of improvement between the two groups was found.

*In sum, pilot data gathered from two distinct cohorts of MBSR patients show that MBSR significantly reduces symptoms of distress and is equally effective in patients diagnosed with PTSD as in patients presenting with other mental health diagnoses. These pilot data also suggest MBSR leads to considerable improvement on specific measures of mindfulness (KIMS and FFMQ) and may lead to reductions in subsequent utilization of mental health services. While promising, these data are, of course, limited by the lack of a comparison group and require replication in an RCT.*

## Experience in Conducting Clinical Studies Involving PTSD

*RCT examining integrated versus sequential treatment of co-morbid PTSD/substance use disorder.* Currently, Dr. Polusny serves as site Co-PI for the CSR&D funded project, "Integrated vs. Sequential Treatments for Comorbid PTSD/Addiction among OEF/OIF Veterans." Focused exclusively on returning OEF/OIF veterans with comorbid SUD and PTSD, this RCT examines the efficacy and effectiveness of a sequential versus integrated treatment program of Prolonged Exposure and Motivational Enhancement therapy. As primary mentor for Dr. Shannon Kehle (Site PI), Dr. Polusny works in close collaboration with her in overseeing all aspects of the study, including the day-to-day administration of the grant, supervision of data collection, and scientific integrity of the project.

***Piloting the effectiveness of new therapies for PTSD.*** Dr. Erbes is PI of a foundation-funded pilot study (N = 20) that is underway examining the utility of narrative therapy as a treatment for PTSD. Narrative therapy is a post-modern, collaborative therapy that explicates trauma-related meanings and fosters creation of new meanings about the self, others, and the world. Narrative therapy is increasingly being used in the community and is conceptually well-suited for treatment of PTSD. However, this study is the first effort at a rigorous investigation of the treatment with this population and includes the development of treatment manuals, intensive training and supervision of clinicians, treatment fidelity ratings, and detailed structured clinical and self-report assessments of progress and symptoms throughout treatment.

## Expertise in Collecting and Analyzing EEG in Veteran Populations with PTSD

***PTSD is associated with abnormal resting state EEG power in a sample of OIF/OEF military personnel.***
We have completed initial processing of EEG data collected as part of a DOD-funded study of blast-related traumatic brain injury and PTSD (PI – Sponheim, Co-Investigators Polusny & Lim). Preliminary analyses of 84 subjects' eyes-closed & eyes-open resting EEG data included removal of artifact with ICA, segmentation into 4 second epochs with 50% overlap, and artifact tagging of amplitudes ±200 µV for all electrodes (see methods below). Frequency power (µV$^2$) was computed for all artifact-free epochs taking the square root of the power to yield a frequency amplitude measure (µV). Mean frequency spectral amplitudes were computed for 6 frequency bands (delta: 0~3 Hz; theta: 4~8 Hz; alpha: 8~12 Hz; beta-1: 13~20 Hz; beta-2: 21~30 Hz; gamma: 31~64 Hz). Effect sizes (Cohen's *d*) of the group comparisons were computed for 128 electrodes and non-parametric tests (Wilcoxon rank sum tests) were conducted to compare the frequency amplitudes between PTSD subjects and non-PTSD subjects. Individuals with PTSD demonstrated the most prominent abnormalities in gamma band power. Increased gamma activity was evident over central and left posterior brain regions in association with PTSD (see Figure 1). Because gamma activity is related to active cognition such an abnormality is suggestive of PTSD resulting in a less restful state in the eyes closed condition. Because mild traumatic brain injury (mTBI) due to blast is common in OEF/OIF soldiers and has been found to be associated with EEG abnormalities, we next excluded individuals with histories of blast mTBI. Figure 2 depicts increased gamma power that persists with PTSD after excluding blast mTBI. There is a shift in topography of abnormalities to more posterior brain regions. Consideration of blast history appears important in characterizing resting states in PTSD.
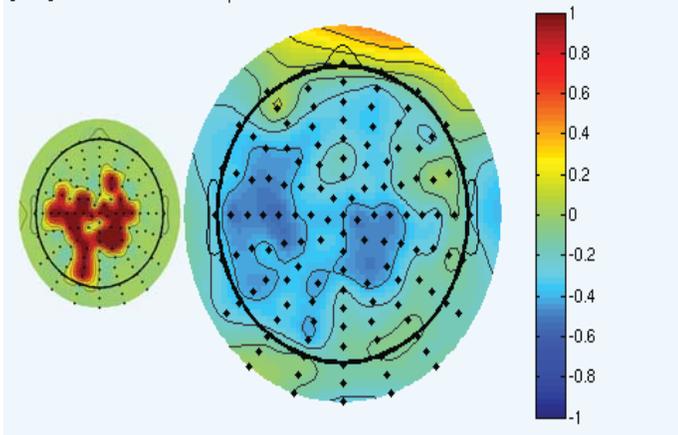


**Figure 1.** Effect size (large plot) of gamma frequency amplitude differences between OIF/OEF military personnel with PTSD (N=29) and without PTSD (N=55) during eyes closed rest. Increased gamma frequency activity was associated with PTSD (more blue [negative effect size]). These differences reached statistical significance (smaller plot) over central and left posterior regions. 22 of the PTSD individuals had reported symptoms of mild traumatic brain injury (mTBI) due to blast while 27 of the no PTSD
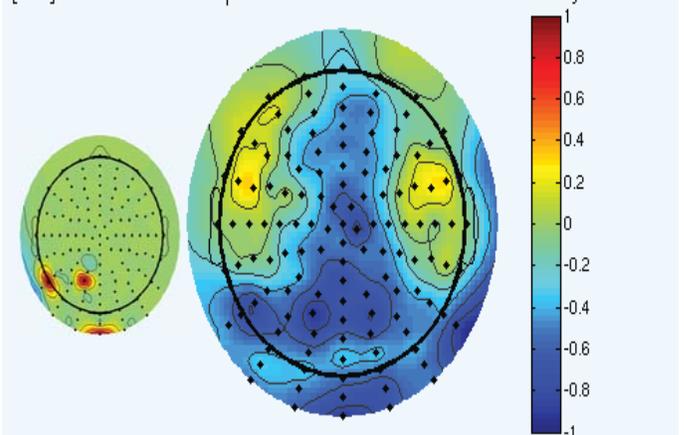
**Figure 2** Gamma frequency amplitude differences associated with PTSD in the absence of mTBI from blast. Effect size (large plot) between OIF/OEF military personnel with PTSD without blast mTBI (N=7) and without PTSD and without blast mTBI (N=28). Increased gamma frequency activity associated with PTSD was more posterior after individuals with mTBI were excluded with, and fewer points reached statistical difference (small plot) likely due to weaker statistical power.

A predicted effect of meditation in PTSD is that the intervention would lead to a more restful state and thus less gamma power and diminished gamma phase synchrony. Currently, we are pursuing more extensive analyses to follow-up on these preliminary findings of EEG power and phase synchrony abnormalities in PTSD. With the large existing data set we are well positioned to understand the baseline EEG characteristics of individuals with PTSD in order to more clearly map changes in brain function as a result of meditation.

## Expertise in Recruitment and Longitudinal Follow-up of Large Veteran Cohorts

***Readiness and Resilience in National Guard Soldiers (RINGS).*** Drs. Polusny and Erbes co-direct the Readiness and Resilience in National Guard Soldiers (RINGS) lab that has been funded through DOD, VA HSR&D, and foundation grants for the past 6 years. The RINGS project has conducted several large scale longitudinal studies of PTSD in National Guard soldiers before, during, and after combat deployments (Polusny et al., 2011). These studies have included structured clinical interviews (i.e., the Clinician Administered PTSD Scale (CAPS) and the Structured Clinical Interview for the DSM-IV (SCID)) in two cohorts of soldiers, including one containing 355 participants ( Kehle et al., 2011). In addition, the RINGS lab is currently conducting a new longitudinal study of soldiers and their spouse/partners prior to, during, and after a combat deployment. In this most recent, and ongoing, study we have enrolled 1,881 soldiers, 1,010 spouses or partners, and 628 family members in pre-deployment data collection, and are funded to follow-up with spouses/partners during the deployment and both soldiers and spouse/partners after the deployment. Notable for their longitudinal designs, depth of assessment, and success at retaining cohorts of soldiers over time spans of up to 4 years, RINGS projects have provided valuable information on predicting post-deployment distress (Polusny et al., 2011), during-deployment distress and PTSD symptoms (Ferrier-Auerbach et al., 2010), psychiatric diagnoses (Kehle et al., 2011), mental health service utilization (Kehle et al., 2010), and social, interpersonal and occupational impairment (Meis, Erbes, Polusny, & Compton, 2010; Meis, Barry, Kehle, Erbes, & Polusny, 2010) and have led to 16 peer reviewed publications studying PTSD and its correlates in combat veterans.

## Summary of Preliminary Work

In sum, the investigators have amassed promising initial data suggesting that MBSR may be a useful and efficacious treatment for PTSD. Pre- post- treatment analyses suggest improvement in PTSD symptoms, improvements in quality of life, and reduced use of mental health services following MBSR. Importantly, our team has also found markers of EEG abnormalities associated with PTSD which, in combination with other findings on EEG markers of mindfulness meditation, suggest that EEG may be a particularly useful means of studying change in mindfulness as a result of MBSR and possible mediator of treatment effects. Similarly, we have found changes in self reported mindfulness attitudes and practice that may be additional markers of treatment-associated change. The study team includes investigators with extensive background with MBSR, well-established histories of intensive study of PTSD among combat veterans, assessment of PTSD with both self-report and structured clinical measures, successful recruitment of large samples, retention of those samples over time, EEG investigations of individuals with PTSD, and investigation of psychotherapy with veteran PTSD populations.

## D. RESEARCH DESIGN AND METHODS

### Design Overview

The proposed study utilizes a 2 group randomized clinical trial design to test whether MBSR improves outcomes for veterans suffering from PTSD compared to PCGT, a non-specific, present-centered comparison group (see Figure 3). Given out pilot findings, we have proposed a study that hypothesizes MBSR will be superior to PCGT in improving PTSD symptoms. Participants will be male and female veterans (18 years and older) of any era or military background (i.e., Vietnam era, Gulf war era, or OEF/OIF, combat or non-combat) who suffer from PTSD. Participants will be recruited from the Posttraumatic Stress Recovery Program and Mental Health Clinics in the MVAHCS. Potential participants will be screened for eligibility using a two stage process (phone/chart review, followed by interview), and those meeting eligibility criteria will complete a baseline assessment 1-2 weeks prior to starting treatment. Participants will be randomly assigned to one of two treatment conditions, MBSR or PCGT. PCGT was chosen as a comparison because it is an established treatment approach that contains nonspecific, supportive elements of therapy that we wish to control for in our design (Schnurr et al., 2003a; Schnurr et al., 2007), but does not include elements of mindfulness meditation. Treatments are described in more detail below. Each intervention will be provided in group format for a total of 9 weeks. Independent evaluation of PTSD symptom severity will be completed at baseline and post-treatment. Self-report outcomes and markers of change in mindfulness practice will be assessed at two time interim points during therapy (weeks 3 and 6), at post-treatment, and at 2 months post-treatment.



Figure 3. Study Design
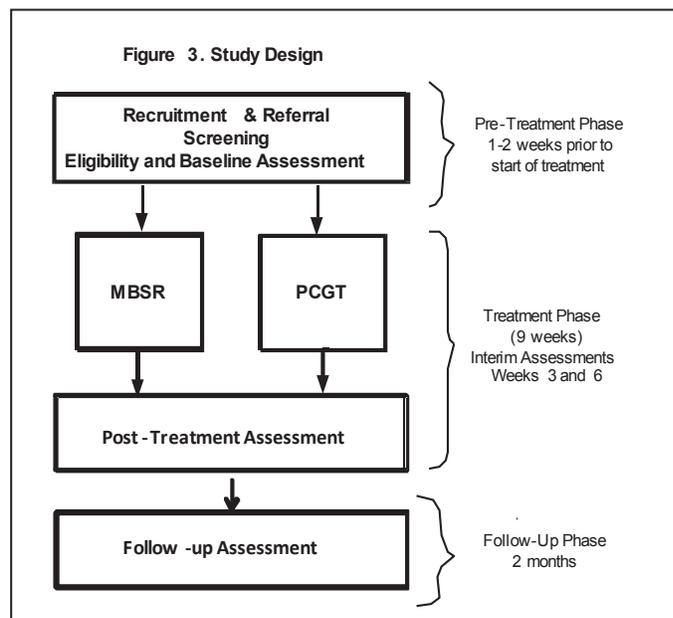
### Design Considerations

As with any clinical trial, a number of factors have been considered in the design of this proposal. The goal has been to provide a design that is feasible, efficient, and above all able to answer study aims and hypotheses. Some of the possible alternative designs, and reasons we did not select them, are listed in Table 1 below.

**Table 1. Design Considerations and Rationale for Choosing the Current Design**

| Consideration | Rationale |
|---|---|
| Allowing participants on psychotropic medications to be enrolled may dilute treatment effects | Requiring participants to not be taking psychiatric medications would 1) limit recruitment, 2) place pressure on potential participants to withdraw from medications that, while not eliminating PTSD symptoms, may be helpful to them, and 3) result in a sample that is not characteristic of many treatment seeking veterans who are already on (Kehle et al., 2010) |
| Using experienced MBSR therapists does not demonstrate the portability of the treatment manual (i.e., that novice therapists can be successfully trained to provide effective care) | MBSR is a treatment that requires therapists who are themselves practitioners of mindfulness meditation, which can require many months to develop. Given the 24 month duration of this project, training novice therapists in MBSR was beyond the scope of the project. Future studies will be required to address this issue. |
| The inclusion of a heterogenous group of participants from multiple eras and with multiple types of trauma can mask treatment effects if gender, era, or type of trauma moderates treatment effects. | Our clinical experience has not suggested a differential effect based on era, age, trauma type, or gender, and in fact it has been our practice to run heterogenous groups with promising results (as described above). Exploratory analyses will check for any such moderating factors which can be addressed statistically. |
| Comparison of MBSR to PE or CPT would allow a more direct comparison to other active treatments | Given that no RCT's have yet examined the efficacy of MBSR for PTSD, an equivalence trial of MBSR versus PE or CPT was seen as premature. Selection of a present-centered, supportive group comparison that controls for general therapeutic effects provides a more powerful test, and since many veterans do not receive PE or CPT, this comparison more closely matches "treatment as usual". |

## Subject Recruitment and Selection

Participants will be recruited primarily from veterans receiving mental health treatment in the MVAHCS. Referrals will occur from VA clinicians and clinics, and responses from posted fliers and study pamphlets. Potential participants will be provided with information about the study and screened through medical record chart review and by telephone to determine if they meet basic inclusion/exclusion criteria. Interested veterans who meet basic criteria will be scheduled for a more rigorous Eligibility and Baseline Assessment (see further details below).

*Eligibility Criteria.* We have selected the following eligibility criteria that identify a broad array of participants suffering from PTSD.

Inclusion Criteria:
1) Male or female veterans who are 18 years or older.
2) Must meet current DSM-IV criteria for PTSD based on the Clinician Administered PTSD Scale (CAPS).
3) If taking psychoactive medications, must be on a stable regime for 8 weeks or more.

Exclusion Criteria:
1) Current suicidal or homicidal ideation with intent and/or plan that, in the judgment of the investigator, should be the focus of treatment.
2) Meets current DSM-IV criteria for substance dependence (except nicotine or caffeine), bipolar affective disorder, schizophrenia or any psychotic disorder.
3) Has unstable or serious medical illness, including history of stroke, seizure disorder, or unstable cardiac disease, that would interfere with participation in treatment.
4) Severe cognitive impairment or moderate/severe traumatic brain injury.
5) Unable to comprehend or communicate in English.
6) Unwilling to accept random assignment or unwilling to refrain from participating in other active forms of psychotherapy during 8-week treatment.

Concurrent mental health treatment:  Current use of antidepressants or other psychotropics are not an exclusion criterion for participation in the trial. Given current treatment management of PTSD, it is expected that many patients will be on antidepressant medications. We will request the treating psychiatrist not change treatment during the trial unless absolutely necessary and we will track and record these modifications for sensitivity analyses. Care coordination or case management will not be discouraged or serve as basis for exclusion from the study unless it is approximating psychotherapy (i.e., involves meeting more than monthly). In order to evaluate MBSR as a primary treatment for PTSD, and not simply as an adjunctive approach, participants will be asked not to participate in concurrent group or individual psychotherapy.

*Feasibility of recruitment.* As outlined below, the MVAHCS system provides mental health care for a high volume of veterans diagnosed with PTSD and has an established clinical program of mindfulness-based interventions since 2001. Over the past 10 years, nearly 400 veterans have completed the full 8-week MBSR program. Therefore, we are confident that we will be able to recruit 180 participants over the 24 months of this study. As of Fiscal Year 2010, over 3,600 veterans enrolled at the MVAHCS were diagnosed with PTSD and receiving mental health treatment. Dr. Erbes (Co-Investigator) will take responsibility for the recruitment of participants. Dr. Erbes is the Program Manager for the Posttraumatic Stress Recovery (PTSR) team and is well situated to procure referrals from this and other mental health clinical teams in MVAHCS. The PTSR team has a strong track record of successfully recruiting veterans with PTSD for randomized clinical trials. PTSR has taken part in 2 large scale, VA-funded multi-site randomized trials including Cooperative Study 420, "Trauma-Focused Group Therapy for Posttraumatic Stress Disorder," and Cooperative Study 519, "Integrating Clinical Practice Guidelines for Smoking Cessation into Mental Health Care for Veterans with Posttraumatic Stress Disorder." In addition, Drs. Erbes and Polusny have successfully collected data from over 4,000 OEF/OIF military personnel and veterans who have given permission to be contacted to participate in future research. Currently, MVAHCS is a site for a VA CSR&D funded trial (Polusny, Site Co-PI) investigating an integrated versus sequential model of treatment for OEF/OIF veterans with comorbid PTSD and substance abuse. This ongoing trial has a recruitment target of 25 OEF/OIF veterans with co-morbid PTSD and substance abuse/dependence per year. Since the proposed trial is not limited to OEF/OIF veterans and specifically excludes veterans with co-morbid substance dependence, we do not anticipate recruitment efforts for this

ongoing trial will impact recruitment for the proposed study. Based on the volume of eligible veterans within the MVAHCS system and our track record of successful recruitment, we anticipate no difficulties in meeting targeted enrollment numbers for the proposed study.

## Pre-Screening

In order to reduce subject burden, we will obtain a waiver of HIPAA authorization and informed consent for recruitment and screening to allow potential subjects to be pre-screened by chart review and in person or by telephone prior to scheduling potential participants for an Eligibility and Baseline Assessment. Potential participants will be provided with information about the study and asked a series of questions to determine if they meet basic inclusion/exclusion criteria, such as veteran status, whether they are receiving active psychotherapy in the community, and whether they may be experiencing indicators of PTSD. They will be told that the treatment involves mixed gender groups and that group members may have experienced different types of trauma. Those interested in participating will be scheduled for an Eligibility and Baseline Assessment

## Informed Consent Procedures

Before participation in the Eligibility and Baselines Assessment, voluntary informed consent will be obtained in accordance with local IRB approvals. At the consent session, all assessments, EEG procedures, and information on treatment will be fully explained. Subject comprehension of information will be assessed by asking them to repeat back details of the procedures they have heard. Subjects' willingness to participate in assessments and random assignment to 1 of 2 treatments as part of the study will be confirmed and subjects will be given information about confidentiality and study payments.

## Assessment Procedures

All assessments will be conducted in person. Clinical interviews will be conducted by trained independent evaluators who are blind to participant treatment condition. Subject compensation will also be provided to increase participant retention and reduce missed assessments (see further details below).

***Eligibility and Baseline Assessment.*** The Eligibility and Baseline Assessment will be accomplished during 1-2 visits over a 7-14 day period prior to starting treatment. It will take a total of 5 hours. An Independent Evaluator will administer the CAPS and Structured Clinical Interview for DSM-IV (SCID) to confirm the diagnosis of PTSD and the absence of exclusionary diagnoses. In addition, other exclusion criteria will be assessed. Evaluation of exclusionary criteria involving severe cognitive impairment and moderate/severe TBI will be made based on medical record review in consultation with Dr. Lamberty (Co-Investigator). The research assistant will administer the self-report measures that assess PTSD symptoms, mindfulness skills, quality of life, somatic complaints, and expectancies regarding treatment and will collect EEG measures (see Electrophysiological Assessment). All interviews will be video recorded to allow for monitoring of assessment fidelity (see details below).

***Interim Assessments.*** During the intervention period, at two time points (Weeks 3 and 6 of therapy) participants will be asked to participate in interim assessments that will each take 1.5 hours. Participants will be asked complete a brief set of self-report questionnaires that assess PTSD symptom severity, mindfulness skills, expectancies regarding and satisfaction with treatment. They will also participate in an EEG recording session. To reduce subject burden, and decrease missing data, interim assessments will be conducted on the same day as treatment sessions whenever possible.

***Post-Treatment Assessment.*** Following completion of treatment (Week 9), participants will attend a Post-Treatment Assessment. The Post-treatment Assessment will take about 4.5 hours. Similar to the baseline assessment session, this assessment will involve self-report questionnaires of PTSD symptom severity, mindfulness skills, quality of life, and somatic complaints as well as measure of perceived effectiveness and satisfaction with services received; structured clinical interviews for PTSD; and EEG recordings. In addition, the veteran will be interviewed for 30 minutes about their perceptions of the therapy that they have received, their perceptions of what was helpful and what was not, and the changes they have noticed over the course of treatment. As before, all interviews will be video recorded.

***Follow-Up Assessment.*** The Follow-up Assessment will occur 2 months after the end of treatment (Week 16) and will involve the same procedures as the Post-Treatment assessment, with the exception of the interview about the treatment that will not be administered. The Follow-up Assessment will take about 4 hours.

## Independent Evaluation Integrity

The validity of results from the clinical trial is based upon the accurate and valid assessment of the target symptoms and related conditions. In order to ensure that assessments are reliable and valid, Independent Evaluators (IEs) will 1) undergo standardized training in all assessment instruments, 2) demonstrate reliability of assessment at the beginning of the protocol, 3) be closely supervised on site by Drs. Erbes and Lamberty (Co-Investigators) 4) attend weekly in person supervision sessions with Dr. Erbes and Dr. Lamberty, and 5) receive reliability checks on their evaluations throughout the protocol. Independent Evaluators will be master level clinicians and will complete 2 days of training in the CAPS and SCID by Dr. Erbes at the start of the study. Training will include the use of multimedia computer materials provided by the National Center for PTSD (NCPTSD) for the CAPS and instructional videos provided by the Biometrics Research Department/Columbia University for the SCID. In addition, Independent Evaluators will take part in supervised role plays and practice sessions. All assessments will be videotaped. The first assessments for each Independent Evaluator will be reviewed by Dr. Erbes or Dr. Lamberty, who will independently code the evaluation. Feedback will be given to each evaluator and each subsequent assessment will be reviewed until the evaluator has demonstrated reliability on 2 consecutive assessments. Drs. Erbes and Lamberty will be available for on-site consultation for all assessments. In addition, all independent evaluators will attend a weekly supervision session, conducted by Drs. Erbes and Lamberty, in which questions about evaluations are discussed and additional training is provided as necessary. A random selection of 10% of assessment session videos will be reviewed by Drs. Erbes and Lamberty to ensure consistency of assessment quality. Feedback will be provided for each session reviewed, to help prevent rater drift.

## Randomization Procedures

Our planned enrollment includes 90 veterans in each treatment condition, for a total sample size of 180 veterans (see **Sample Size Determination** below). Participants will be randomly assigned to MBSR or PCGT, using a minimization method of (Pocock & Simon, 1975). Randomization will be conducted using SAS PROC PLAN and will be blocked on CAPS severity to insure balance in symptom severity across treatment groups. Sealed and numbered envelopes will be provided to the study coordinator by the statistician (Dr. Thuras).

## Treatment Conditions

A total of 5 MBSR groups (each including 15-18 veterans which is standard practice for MBSR) and 10 PCGT groups (each including 8-9 veterans which is standard practice for PCGT) will be conducted over the course of the study. In all treatment conditions, sessions will be administered in a group format as detailed by treatment manuals and all sessions will be videotaped to monitor treatment fidelity.

***MBSR Intervention.*** The MBSR course will consist of nine weekly 2-hour experiential group sessions and a one-day silent retreat held between Sessions 7 and 8. MBSR will be administered following the protocol developed by Jon Kabat-Zinn (Kabat-Zinn, 1990), but will be modified to include an initial session on psychoeducation about PTSD and treatment rationale for how mindfulness training can lead to improvements in PTSD symptoms . The MBSR instructors will be two doctoral level psychologists (Drs. Rodman & Koets) who are each experienced in MBSR, maintain personal mindfulness meditation practices, and have experience in treating PTSD. The MBSR will teach participants to focus their attention through a variety of meditative techniques. Participants are trained to perceive the present moment (their immediate emotional and physical state, including discomfort) in a nonjudgemental and accepting way. Mindfulness mediation is posited to develop a capacity for perceiving negative emotional states with greater objectivity and reduce reactivity (Shapiro, Carlson, Astin, & Freedman, 2006). Through mindfulness training, participants learn to self-regulate, decrease physiological arousal, and increase their capacity for psychological flexibility (Vujanovic et al., 2011); (Walser & Westrup, 2007). Formal practice consists of sitting meditation, body scan, mindful walking, Qi Gong exercises, and standing and sitting yoga. Informal practice consists of engaging in routine daily activities in a mindful manner (e.g., brushing teeth, eating, doing the dishes). Since the benefits of MBSR are dependent upon adopting a regular, personal mediation practice, participants are encouraged to practice these skills at home 6 days per week and record daily practice time on a MBSR Tracking Log.

***PCGT Intervention.*** The PCGT intervention will consist of nine weekly 1.5 hour group sessions administered following an adaptation of the protocol used in VA Cooperative Study 420 (Shea, Wattenberg, & Dolan, 1997). PCGT provides a credible clinically relevant comparison intervention that controls for nonspecific therapeutic factors (Schnurr et al., 2007). PCGT is a group therapy model that provides support and addresses the participants' current problems, which are conceptualized as being related to PTSD, but does not directly focus on the person's trauma-related memories or facilitate participants' mindfulness (i.e., it does not invite an intense focus on the present moment, promote nonjudgmental awareness, etc.). Sessions 1 and 2 will focus on psychoeducation about PTSD, provide a credible treatment rationale, focus on building group cohesion and support, and goal setting. Sessions 3 through 8 will focus on the discussion of daily difficulties, with the final session 9 focusing on reviewing accomplishments and making plans for the future. Two doctoral-level clinicians with previous experience in treating PTSD will lead each group.

## Therapist Training, Supervision, and Treatment Fidelity

***Therapist training in MBSR*** will be provided by well-qualified and experienced instructors from the Center for Spirituality & Healing at the University of Minnesota **(see letter of support in the Appendix from Dr. Mary Jo Kreitzer, Founder & Director, Center for Spirituality & Healing)**. Over a period of one week the MBSR training will focus on a review of the MBSR manual (see brief outline of MBSR in the Appendix). Both therapists already have several years experience providing MBSR interventions, but a systematic review of the treatment manual will ensure standardization of procedures and increase adherence to the treatment manual. Therapists will also receive weekly in-person supervision from the MBSR trainers during the study. Supervision will include a review of videotaped sessions and focus on application of specific meditation techniques and adherence to the MBSR treatment manual. The combination of discussion, direction, and observation in supervision will help to ensure integrity and prevent therapist drift across time.

***Therapist training in PCGT*** will be provided by Dr. Melissa Wattenberg, consultant on this project with significant expertise in group treatment for PTSD (**see letter of support in the Appendix)**. As Clinical Supervisor for PCGT in CSP 420, Dr. Wattenberg provided training and supervision of 20 group therapists across 10 sites. Dr. Wattenberg will provide an intensive 2-day in-person training in the PCGT manual to Dr. Polusny (Co-Investigator) and two doctoral level clinicians with experience treating PTSD. Training will include providing a credible rationale, psychoeducation about PTSD, developing and maintaining group cohesion, staying focused on daily problems, as well as strategies to avoid non-treatment components (such as trauma disclosure or mindfulness based interventions). Dr. Polusny will serve as on-site clinical supervisor for PCGT and will consult monthly with Dr. Wattenberg regarding supervision issues. Dr. Polusny will provide weekly supervision for PCGT, which will involve review of taped sessions, discussions of individual (client) and group level problems, and conceptualization of issues from a present-centered focus.

***Treatment Fidelity.*** Treatment fidelity refers to the degree to which the therapist adheres to the techniques in the prescribed protocol and does not engage in therapeutic techniques that are inconsistent with the protocol. To assess adherence, therapy sessions will be videotaped and a random selection of sessions will be rated for adherence for each study therapist (i.e., therapists will be blind to which sessions are being rated). Adherence ratings and ongoing feedback will be provided to therapists. This procedure is likely to maximize adherence and competence across sessions and to reduce drift from the treatment protocol. A minimum of two sessions from each of the 10 groups (n=20, 22%) will be randomly selected and rated for adherence by a senior clinician independent of treatment delivery: MBSR sessions will be rated by experts in MBSR from the Center for Spirituality & Healing at the University of Minnesota; PCGT sessions will be rated by Drs. Wattenberg and Polusny. Specific elements of each treatment condition will be rated for protocol adherence. Ratings scales for adherence are included in Appendix 3.

## Assessment Schedules and Measures
Table 1 (see next page) illustrates the schedule of assessments to be gathered over the course of the study. The assessment battery includes instruments that will measure the primary outcome (PTSD symptom severity), DSM-IV PTSD and other diagnoses, putative mechanisms of change related to mindfulness meditation interventions (mindfulness skills and electrophysiology), as well as secondary outcomes.

**Table 1.  Assessment Schedule**

| Construct | Measure | Baseline & Eligibility Assessment | Interim Assessments | | Post-Treatment Assessment | Follow-Up Assessment |
|---|---|---|---|---|---|---|
| | | (1-2 weeks before start of treatment) | (Week 3) | (Week 6) | (Week 9) | (Week 16) |
| **Primary Outcome Measure** | | | | | | |
| PTSD Symptoms | PCL | X | X | X | X | X |
| **Interview Based and Laboratory Assessments** | | | | | | |
| PTSD Diagnosis | CAPS | X | | | X | X |
| Rule-out Diagnoses | SCID-CT | X | | | | |
| Electrophysiology | EEG Spectral Power | X | X | X | X | X |
| **Self-Report Outcome Measures** | | | | | | |
| Depression Symptoms | PHQ-9 | X | | | X | X |
| Somatization Symptoms | PHQ-15 | X | | | X | X |
| Quality of Life | WHOQOL-BREF | X | | | X | X |
| Mindfulness Skills | FFMQ | X | X | X | X | X |
| Post-Concussive Symptoms | NSI | X | | | | |
| **Perceptions of Psychotherapy Measures** | | | | | | |
| Perceptions of Therapy | CEQ | | X | X | X | X |
| Treatment Satisfaction | CPOSS | | X | X | X | X |

## Primary Outcome Measure

***PTSD Checklist (PCL).*** The PCL is a 17-item self-report scale intended to measure <u>PTSD symptom severity</u>. The respondent is asked to rate each item on a 5-point scale for how much the problem described by the statement has bothered him/her in the past month. The PCL has demonstrated excellent internal consistency (alpha = .94-.97), and test-retest reliability over 2 to 3 days was .96 for Vietnam veterans (Weathers, F. W., Litz, B. T., Keane, T. M., Herman, D. S., Steinberg, H. R., Huska, J. A., 1996). The PCL correlates highly with other measures of PTSD (Weathers, Litz, Herman, Huska, & Keane, 1993).

## Structured Clinical Interview Assessments

***Clinician Administered PTSD Scale (CAPS; (*** Blake, D. D., Weathers, F. W., Nagy, L. M., Kaloupek, D. G., Gusman, F. D., Charney, D. S., 1995)***.*** The CAPS is a semi-structured clinician rated interview scale for the <u>diagnosis of PTSD</u>. As the "gold standard" for PTSD diagnosis, the CAPS assesses exposure to potential traumatic events, affective responses to trauma (criterion A), and all other symptoms of the disorder. The CAPS has excellent reliability, yielding high internal consistency, inter-rater reliability and consistency across testing occasions. The CAPS has demonstrated excellent convergent and discriminant validity, diagnostic utility, and sensitivity to clinical change (Weathers, Keane, & Davidson, 2001).

***Structured Clinical Interview for DSM-IV (SCID).*** The SCID is a 60-minute, semi-structured interview with established reliability and validity (Lobbestael, Leurgans, & Arntz, 2011) that yields current and lifetime DSM-IV Axis I diagnoses for the major psychiatric disorders. The SCID will be used as an assessment of eligibility and of depressive disorders. The SCID Substance Abuse/Dependence, Psychosis, and Current Manic Episode modules will be given at baseline for eligibility assessment purposes only. The SCID Mood module, focusing on depression, will be given at post-treatment and follow-up sessions as well. To ease subject burden, the Clinical Trials (CT) version will be used.

## Electrophysiological Assessment

Each participant from each arm of the study will complete five 1 hour EEG sessions in order to document alterations in brain function over the course of study participation. The first session will assess baseline brain characteristics of resting state (eyes close, eyes open) and meditative states. Subsequent sessions for a

subject will consist of the same EEG protocol in order to assess changes in resting, and meditative states for those subjects assigned to the MBSR intervention, over the course of intervention and at follow-up.

***EEG Measurement Procedures.*** We will use electrodes embedded in an elastic cap to record from 64 scalp sites that conform to a standardized high-density EEG montage that provides an even distribution of recording sites across the scalp. The precise physical location of electrodes will be recorded in three dimensional space with respect to auricular and nasion landmarks using a commercially available digitizer. Individualized localization information will allow more accurate source derivations and provide a means by which to assess similarity of electrode placements for a subject across multiple recording sessions. To measure eye movements for the detection of bioelectrical artifacts vertical electro-oculograms (VEOG) will be recorded from above and below the right eye and horizontal electro-oculograms (HEOG) will be recorded from outer ocular canthi. Left and right forearm electromyographs (EMGs) and electrocardiograms (ECG) will be recorded in order to identify and reduce artifact and quantify aspects of muscle contraction associated with button presses. EEG will be recorded using a Biosemi Active Two EEG system (http://www.biosemi.com) that does not require abrasion of scalp sites and thereby facilitating the quick placement of many electrodes. EEG signals will be digitized at a rate of 512 Hz with 0.5 Hz low frequency cut-off and 200 Hz high frequency cut-off filters. Each participant will complete assessments of visual acuity and handedness as well as medication, alcohol, caffeine, and sleep in the last 24 hours. Self-report ratings of emotional state will be gathered using the Positive Affect Negative Affect Scale [PANAS] (Watson D, Clark LA, & Tellegen A., 1988). Prior to recording subjects will be given a few minutes to acclimate to the room.

**Resting State (Eyes Open and Eyes Closed Resting State).** The recording session will begin with eyes-closed and eyes-open resting state assessments of default mode brain function. Additionally, the resting states will include brief periods of cognitive demands ("begin at 100 and silently count backwards by 3" serially) in order to assess perturbations of the default mode function. Data will be gather during two blocks each composed of 6 one-minute conditions (Block A: eyes closed, eyes closed serial 3's, eyes closed, eyes open, eyes open serial 3's, eyes open; Block B: eyes open, eyes open serial 3's, eyes open, eyes closed, eyes closed serial 3's, eyes closed). Blocks A and B will be counterbalanced across subjects and a one minute break will be given between the two blocks.

**Meditative State (MBSR only, after baseline).** In order to assess brain state during meditation and any changes over the course of practice during the intervention, subjects receiving the MBSR intervention will be asked to engage in meditation while EEG data are recorded. Data will be gathered during 3 conditions (eyes closed-awake [3min], eyes closed- sitting meditation [10min], eyes closed-awake [3min]).

***EEG Preprocessing.*** Following data collection, recordings from scalp sites will be re-referenced to linked earlobes. Segments of EEG with obvious non-neurogenic signals will be deleted after visual inspection aided by amplitude threshold criterion applied to each electrode signal. Brief time periods of non-neurogenic noise in one or two electrodes will be interpolated from adjacent electrode signals using spherical spline interpolation (Perrin, F., Pernier, J., Bertrand D., & Echallier J.F., 1989). Independent component analysis (ICA) using a FastICA algorithm (Hyvarinen & Oja, 2000) will then be applied to eliminate artifacts from eye-movements, cardiac and muscle activity, and other non-neurogenic sources. However, prior to the completion of the ICA, principal component analysis (PCA) will be applied to the covariance matrix of EEG signals to reduce the number of independent components (ICs) and facilitate the visual review of ICs. Enough principal components will be retained to account for more than 99.5% of the variance in the original data. The selected principal components will be reconstituted into electrode signals. ICA will then be applied to the reconstituted signals and all resulting ICs will be inspected in terms of their topography, frequency power spectrum, and time course. ICs showing high temporal correlations with VEOG or HEOG signals and typical topography of high frontal polar activity will be identified as eye-movement artifacts. ICs characterized by a pattern of periodic deflections in the component time series, persistent activity throughout the recordings, low-frequency (<3 Hz) peak power spectrum, and a unilateral or bilateral posterior topography will be identified as cardiac artifacts. Muscle artifacts will be characterized by spectra with broad peak from 20 to greater than 60 Hz, topography showing prominent activity restricted to marginal electrodes close to facial muscles, and periods of high frequency activations (McMenamin, B.W., Shackman A.J., Maxwell, J.S., Greischar, L.L., Davidson, R.J., 2009). Brief periods of muscle artifact will be removed (i.e., less than 1/5 of the entire time-series), while longer periods of muscle artifact characterized by ICs will be addressed through elimination of the IC from the

reconstituted signal. After preprocessing with ICA and artifact removal, EEG recordings will be again reconstituted from the remaining ICs.

*EEG Frequency Spectrum Analysis.* We will apply a traditional approach to characterizing power in frequency bands of the resting state and meditation state. For resting state and meditative conditions, we will segment EEG data into 4 second epochs with 50% overlap of adjacent segments and apply Fast-Fourier Transforms to resolve frequency spectra for each subject. Power will be computed for delta (1~3 Hz), theta (4~8 Hz), alpha (8~12 Hz), beta-1 (13~20 Hz), beta-2 (21~30 Hz), and gamma (31~64 Hz) frequency bands. The primary EEG measure will be gamma band power measured over central regions; a region found to have increased gamma band power in our preliminary data (Figure 1), which we hypothesize will decrease with reduction in PTSD symptoms. An exploratory EEG measure we will examine is the frontal alpha asymmetry index described by (Davidson et al., 2003), which they found to increase following MBSR training in healthy subjects. This measure could provide a quantitative measure of participant skill acquisition.

## Self-Report Outcome Measures

*Patient Health Questionnaire (PHQ-9).* Two subscales of the PRIME-MD (Spitzer, Kroenke, & Williams, 1999) will be used. The first is the PHQ-9, which is a brief 9-item measure of depressive symptoms that has established reliability and validity in community and clinical populations (Spitzer et al., 1999). It will be used to assess change in symptoms that are related to PTSD symptoms.

*Patient Health Questionnaire – 15 (PHQ-15).* The PHQ-15 is a 15 item measure of somatization taken from the PRIME-MD that assesses common symptoms of somatization and also has established reliability and validity (Spitzer et al., 1999).

*World Health Organization Quality of Life – Brief (WHOQOL-BREF).* The WHOQOL-BREF is a 26-item brief assessment of quality of life in four factor-analytically confirmed dimensions: Physical, Psychological, Social, and Environmental. It has good to excellent internal consistency reliability and has shown predicted relationships with health status, single items assessing quality of life, and demographic variables.(Skevington, Lotfy, & O'Connell, 2004)

*Five Facet Mindfulness Questionnaire (FFMQ).* The FFMQ (Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006) is a 39 item measure of mindfulness derived from five factor-analytically confirmed dimensions; Observing, Describing, Acting with Awareness, Nonjudging, and Nonreactivity. The five facets have been shown to be internally consistent and correlated in expected directions with numerous other constructs in several samples. Regression, mediation, and confirmatory factor analyses support the validity of this measure.

*Neurobehavioral Symptom Inventory (NSI).* The Neurobehavioral Symptom Inventory (NSI) is a 22 item measure of symptoms commonly reported following concussion or mild traumatic brain injury (Cicerone & Kalmar, 1995). Severity for each symptom is rated on a 5 point scale from "none" (0) to "very severe (4) with subjects being asked to estimate how troubling symptoms have been over the course of the past two weeks. The total score is the sum of all ratings. Cluster scores for physical, cognitive, affective and sensory symptoms are also available (Cicerone et al., 1995). The NSI exhibits acceptable reliability and validity. The NSI will be administered at baseline to assess history of mTBI and quantify the presence of post-concussive symptoms, which will be included as an exploratory measure for assessing treatment effects among veterans with a history of mild TBI.

## Measures of Perception of Therapy

*The Credibility/Expectancy Questionnaire (CEQ).* The CEQ is a brief scale of belief in the rationale and logic of a treatment (credibility) and belief in a likely positive outcome from a treatment (expectancy). The CEQ has been shown to have acceptable internal consistency and test-retest reliability and to predict treatment reactions in expected ways (Devilly & Borkovec, 2000). The CEQ was modified slightly for this protocol to include questions about expectancy regarding changes in trauma symptoms. It has 8 items.

*Charleston Psychiatric Outpatient Satisfaction Scale – VA PTSD version (CPOSS; Frueh et al., 2002).* The CPOSS is a 16 item measure of patient satisfaction with services that was developed specifically for use

in VA PTSD outpatient clinics. It has shown excellent internal consistency reliability and acceptable convergent validity (Frueh et al., 2002).

***Post-Treatment Exit Interview.*** Exit interviews will be conducted by the project coordinator under the supervision of Dr. Erbes, who has experience with qualitative data collection. Participants will be asked questions using a semi-structured interview that enquires about perceived helpfulness of the intervention, aspects that are particularly useful or not useful, perceived changes in themselves over time, and how those changes relate to aspects of treatment. Exit interviews will be videotaped and transcribed for follow-up qualitative analysis.

## Health Services Utilization

We will assess veterans' utilization of mental health and physical health care services through administrative VA databases by accessing the following VA data warehouses: Patient Treatment File [PTF], Outpatient Care Files [OPC], Veterans Information System Technology Architecture [VISTA]. Dr. Thuras, who has extensive experience in retrieving and analyzing such administrative data, will tabulate the number of mental health stop coded visits and non-mental health coded visits used by participants in the 2 months prior to study enrollment and the 2 months following completion of treatment (i.e., until the Follow-up assessment). Further analyses for longer periods (e.g. 6 months pre and post treatment) will be carried out as the data become available.

## Compensation for assessment sessions

Participants will be compensated for completing the assessment sessions throughout the study. Assessment sessions involve individual clinical interviews, self-report questionnaires, and EEG recordings. Compensation for assessment sessions will be graduated according to the following schedule: $125 for Eligibility Screen and Baseline (1-2 weeks prior to starting treatment, approximately 5 hours), $40 for each Interim Assessment (Session 3 and Session 6, approximately 2 hours), $120 for Post-Treatment Assessment (at end of treatment, approximately 4.5 hours), and $120 for the Follow-up Assessment (2 months following end of treatment, approximately 4 hours). Participants who choose to withdraw from treatment during the study will still be eligible to complete assessment sessions and receive compensation for those sessions. Participants who withdraw from both treatment and study assessments prematurely will not be compensated for assessment sessions that have not yet taken place.

## Data Analysis Plan

***Sample Size Determination.*** We expected to enroll a total of 36 subjects per 4 month treatment period with a total of 5 treatment cohort periods (**see timeline below, next page**). We will accrue approximately 90 subjects per condition or 180 participants total. The power analysis was performed for PCL total symptoms using Nquery Advisor 4 (Statistical Solutions, 2000) under the following assumptions: (1) repeated measures ANOVA with the main effects of treatment (MBSR vs. PCGT) and time (0, 3, 6 ,9 and 16 weeks), and the treatment by time interaction; (2) compound symmetric covariance matrix, and; (3) 5% significance level. The estimates for the mean, standard deviation and intra-subject correlation were obtained from a pre-post measurements conducted by a Co- I among 24 veterans with PTSD receiving MBSR (see Preliminary Studies section).

Since subjects are randomly assigned to either MBSR or PCGT, and assignment is stratified by initial PTSD severity, we expect similar PTSD symptom levels at baseline between MBSR and PCGT conditions. The treatment effect is therefore captured by the treatment by time interaction, i.e., differential patterns of symptom change over time. The initial sample size of 180 patients (60-65 in each condition after attrition) will provide 80% power to detect an effect size of d=0.52. Based on our preliminary data and other publications (Kimbrough et al., 2010), we expect the effect size of the interaction to range from approximately d=.5 to .9 depending on the amount of intra-subject correlation. Preliminary data based on change in the AAQ found pre-post treatment changes of d=.71 and pre-post change on the FFMQ of d=.93. Data based on change in PTSD symptoms in patients diagnosed with PTSD showed a pre-post change of d=.6. Calculations based on preliminary data (PCL) show sample sizes of 45 per group would be sufficient to detect the effects observed in the pilot data. Hence, the study has sufficient power to detect the expected effect size of the primary objective even with a conservative attrition rate of 30%. For the secondary objectives, the sample size of 60 subjects per group will provide 80% power to detect a similar difference in measures of mindfulness (FFMQ) and EEG

changes. In the actual analysis, the power is likely to be higher as we will include all available data, specify an appropriate covariance structure, and adjust for potential confounders.

As illustrated in the timeline below, one MBSR group (consisting of 15-18 veterans) and two PCGT (each consisting of 8-9 veterans) groups will be conducted during each of five cohort treatment periods across the course of the study.

| | TASK | START | FINISH | 2011 Q3 | 2011 Q4 | 2012 Q1 | 2012 Q2 | 2012 Q3 | 2012 Q4 | 2013 Q1 | 2013 Q2 | 2013 Q3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Preparation, Hiring, & Training | 8/15/2011 | 10/14/2011 | ▬ | | | | | | | | |
| 2 | Cohort 1 | 10/15/2011 | 2/14/2012 | | ▬ | | | | | | | |
| 3 | Cohort 2 | 2/15/2012 | 6/14/2012 | | | ▬ | | | | | | |
| 4 | Cohort 3 | 6/15/2012 | 10/14/2012 | | | | | ▬ | | | | |
| 5 | Cohort 4 | 10/15/2012 | 2/14/2013 | | | | | | ▬ | | | |
| 6 | Cohort 5 | 2/15/2013 | 5/14/2013 | | | | | | | ▬ | | |
| 7 | Data Analysis and Writeup | 6/15/2013 | 8/14/2013 | | | | | | | | | ▬ |

**Analysis Plan.** The data analyses will be performed by Dr. Paul Thuras, Co-investigator on this project. Each subject will be assessed for the primary outcome variables (i.e. PCL) at baseline (1-2 weeks prior to starting intervention), 3, 6 and 9 weeks and 2 months post-treatment (16 weeks). We will initially examine a comparability of two treatment groups in terms of baseline characteristics such as age, symptom severity at baseline. If there is a significant imbalance in potentially important variables (e.g., history of mild traumatic brain injury, diagnosis of substance abuse), we will include them as covariates in the subsequent statistical analyses.

For the primary aim, (i.e., the analysis of the efficacy of MBSR compared to PCGT in reducing PTSD symptoms over 9 weeks of treatment and at 2-month follow-up), we will use mixed effects models (Gueorguieva & Krystal, 2004) if the data are normally distributed and generalized estimating equations (GEE) (Liang, Beaty, & Cohen, 1986) if the data are non-normally distributed. Both are flexible regression methods for incomplete repeated measures data and allow continuous and categorical covariates, fixed and time-dependent covariates, and a specification of unstructured as well as structured covariance matrix. They can be implemented using PROC MIXED (mixed effects models) and PROC GENMOD (GEE) available in SAS (Statistical Analysis System) or HLM (Scientific Software International). We will fit the model with the main effects of treatment, time, treatment by time interaction, and any important confounders and stratification variables (e.g., mTBI status, Substance use). As the subjects are being treated in groups (treatment cohorts), we will also include cohort as a Level 2 factor in the mixed model. Since the treatment groups are expected to be similar at baseline, the effects of the treatment will be captured by the treatment by time interaction (i.e., differential temporal patterns of alcohol use for two treatment groups). Both mixed effects models and GEE allow missing outcome variables (i.e., PCL at 16 weeks), but assume that data are missing at random given the covariates (e.g., treatment and time). We expect no missing covariate information (i.e., treatment assignment and assessment times).

As a secondary analysis, we will perform regression analyses examining change in mindfulness skills (as measured by the FFMQ) and appropriate EEG measures. Our primary EEG measure will be gamma band power from central brain regions. An exploratory measure of skill acquisition for MBSR will be the frontal alpha asymmetry index (Davidson et al., 2003). Mediation analyses will test for the role of change in FFMQ and EEG as mediators in the change in post-traumatic stress symptoms. These analyses will follow the causal steps proposed by Baron & Kenny (1986) and use the nonparametric bootstrapping procedure developed by (Preacher & Hayes, 2008) to test for significant mediation effects.

**Assessing Clinically Significant Change.** We will perform an analysis of clinically significant change in the CAP score, which provides a clinician-based indicator of PTSD symptom severity. Reductions in CAPS severity scores of 10 points and reductions in PCL total scores of 20 points will be considered clinically

significant changes. In our pilot data we observed 15% of the sample diagnosed with PTSD experiencing changes of that magnitude. If we expect a 15% difference between those patients receiving MBSR and those receiving PCGT in reaching this threshold of change (e.g. 20% vs. 5%), we would have 80% power ($p$=.05) to detect this degree of difference with 76 per group. At 60 per group this would yield 70% power to detect this difference.

***Missing Data.*** We will perform intent-to-treat analysis, meaning that all subjects randomized into the two treatment groups will be included in the analysis regardless of the extent of compliance with the treatment or withdrawals during the trial. This will create incomplete data because some subjects will withdraw from the study during the course of the treatment, thereby their responses will be considered missing after withdrawal. If dropout process is related to the outcome measure (i.e., symptom level), this will present a challenge in the analysis. The majority of the currently available statistical methods assume that data are missing at random. However, in this study, it is plausible that the likelihood of dropout is related to the level of or change in symptom level. For example, those with increase or no reduction in symptom level may be more likely to drop out of the study. When subjects drop out of the study, we will attempt to obtain data on reasons for dropout. We will analyze whether the dropout process is at random with respect to the outcome measures. If the dropout process is related to the outcome measures, we will utilize models that incorporate a nonrandom dropout mechanism (Little & Yau, 1996). These analyses will be carried out as the secondary analyses for hypothesis-generating purposes.

***Attrition.*** We conservatively anticipate an attrition rate of 30% and this has been considered when calculating the budget. Rationale for this estimate includes several factors**.** Our preliminary pilot data based on several years of running MBSR groups in a clinical practice setting show dropout rates of 25-30% over the past 10 years. This was for uncompensated treatment seeking patients. With the inclusion of participant compensation, this will provide additional incentive to complete the follow-up sessions.

## Summary

MBSR offers a potentially exciting alternative treatment for veterans suffering PTSD that may provide an important addition to the arsenal of existing and efficacious psychotherapies for PTSD. The importance of systematic and critical examination of the efficacy of this intervention, however, cannot be overstated. This proposal represents an important and innovative next step in evaluating mindfulness based treatments, specifically MBSR, as a treatment for PTSD. The multi-disciplinary study team will conduct a well controlled, well powered, carefully evaluated RCT to investigate the efficacy of MBSR in treating PTSD in veterans. The MVAHCS study site is ideal in that it has an active and accomplished MBSR clinical treatment program, an outstanding track record of subject recruitment and retention for clinical trials and other PTSD research studies, and a strong team of researchers and clinicians with complementary experience and expertise. The study team is also well situated to directly assess the putative mechanism of change for MBSR (including self reported mindfulness practice and EEG markers of change) among PTSD patients. This project will therefore provide a comprehensive and innovative evaluation of MBSR as a primary treatment for PTSD.

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