

Mindfulness Treatment for Anger in Veterans with PTSD

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Study Protocol

Background

High Rates of Anger and Aggression in Veterans with PTSD. Posttraumatic stress disorder (PTSD) is frequently diagnosed in military veterans and is characterized by increases in anger and aggressive behavior. Vietnam veterans with PTSD have been found to exhibit higher rates of violent outbursts, hostility, and poorer anger control (McFall et al., 1999), while OEF/OIF veterans with PTSD symptoms have been found to exhibit aggressive urges, difficulties managing anger and difficulties controlling violent behavior (Elbogen et al., 2010).

Anger and Aggression can have a significant detrimental impact on veterans and their families, and can cause serious impairments in social, occupational and other important areas of functioning. Dysregulated anger can create fear and distress in significant others, family members, and friends resulting in deteriorated relationships and feelings of isolation on the part of the aggressor (Reilly & Shopshire, 2002). Angry outbursts can affect veterans' ability to maintain employment and can affect traffic safety to the extent that it results in "road rage". Finally, more severe forms of aggression and violent behavior (i.e., homicide) in the community have been observed among veterans with PTSD, as recently reported in several news media outlets.

Researchers believe that as a result of PTSD, veterans are more likely to enter into "survival mode", which is characterized by heightened arousal, increased vigilance in recognizing potential threats, and a lower threshold for responding to perceived threats (Chemtob et al., 1997). These processes make it difficult for veterans to be able to regulate their anger and engage in self-monitoring behaviors or other inhibitory processes, resulting in an increased propensity to engage in aggressive behavior. Consistent with this model, studies of veterans with PTSD have shown that the hyperarousal symptom cluster, characterized by increased hypervigilance and an exaggerated startle response is more strongly associated with aggressive behavior compared to the re-experiencing and avoidance/numbing clusters (Taft et al., 2007).

Limitations of Existing Approaches to Treating PTSD-related Anger and Aggression. Problems associated with anger and aggression in veterans with PTSD emphasizes the need for developing and evaluating effective treatments to assist these individuals in regulating their anger and decreasing aggression. Unfortunately, there is a dearth of research examining the effectiveness of anger and aggression treatments in the military (Moreland et al., 2012). The few studies that have been conducted have typically focused on cognitive-behavioral therapy (CBT)-based interventions, which are only moderately effective (Moreland et al., 2012). Anger and aggression interventions based on CBT may be limited in several respects:

(1) Although CBT-based interventions may be somewhat effective in decreasing anger, they may not be effective in decreasing aggressive behavior due in part to the lack of techniques that effectively decrease the specific PTSD-symptoms that are most strongly associated with aggression, namely increased hyperarousal and physiological reactivity. (2) The techniques included in CBT-based interventions may not be helpful in assisting veterans with PTSD achieve awareness and insight into their anger states, which is believed to be important for effective

management of anger and aggression (Howells, 2004). (3) Standard anger and aggression interventions tend to be long, involving a big time commitment from veterans.

Mindfulness-based Interventions as an Alternative to Treating PTSD-related Anger and Aggression. Mindfulness-based interventions might be better able to address the aforementioned limitations of CBT-based interventions and therefore be more successful in decreasing anger and aggression among veterans with PTSD. Rooted in Eastern meditation practices, mindfulness is believed to involve 1) the self-regulation of attention on one's immediate experience, and 2) adopting an orientation of curiosity, openness, and acceptance toward one's experiences in the present (Baer et al., 2006; Bishop et al., 2004). The application of mindfulness to mental health problems has increased over the past several decades and the empirical literature suggests that mindfulness (or mindfulness-based interventions) may be effective in reducing such problematic conditions as stress, pain, anxiety, and depression (Baer, 2003) in addition to symptoms of PTSD (Niles et al., 2012; Polusney et al., 2015).

Research with civilian samples also has shown that mindfulness is effective in decreasing anger and aggression. For example, Robbins et al. (2012) examined the effectiveness of a multi-session mindfulness treatment using a community sample and found that participation resulted in significant decreases in aggressive anger expression and difficulties regulating emotions, in addition to increases in trait mindfulness and self-compassion. Using a sample of court-referred women with alcohol abuse/dependence and aggression problems, Wupperman et al. (2012) found that a mindfulness intervention was effective in not only decreasing aggression, but also alcohol and drug use.

One of the most popular and well-researched interventions is Mindfulness Based Stress Reduction (MBSR) developed by Jon Kabat-Zinn (1990). MBSR is a group-based program designed for use with individuals experiencing a wide range of physical and mental health problems and focuses on teaching mindfulness meditation as well as mindfulness of everyday activities and emotional states. Studies examining the effectiveness of MBSR have found it to be effective in ameliorating a wide range of medical and mental health diagnoses (Baer, 2003). However, to our knowledge, only one study has examined the effectiveness of MBSR in decreasing anger and aggression (Robbins et al., 2012). To date, no researchers have examined the effectiveness of MBSR in decreasing anger and aggression among veterans with PTSD.

Mechanisms of Action of Mindfulness Treatment. One of the ways in which mindfulness is believed to exert its effects is by increasing one's ability to tolerate and regulate difficult emotions (Holzel et al., 2011). This is relevant to PTSD and aggression, given evidence linking emotion regulation difficulties to PTSD (Tull et al., 2007) as well as to the perpetration of aggression (Shorey et al., 2011). In addition, mindfulness has been shown to decrease physiological arousal and stress reactivity as indicated by reductions in heart rate and skin conductance levels (e.g., Campbell-Sills et al., 2006; Delizonna, Williams, & Langer, 2009; Goleman & Schwartz, 1976). Taken together, mindfulness may decrease the potential for an individual with PTSD to become angry and to engage in aggressive behavior by decreasing associated physiological reactivity and helping one regulate difficult emotions in response to stress.

Use of Experimental Procedures to Elicit Physiological Reactivity and Assess Aggression.

Studies examining the effectiveness of anger and aggression interventions for veterans with PTSD have a number of methodological limitations, including a heavy reliance on self-report data to determine their effectiveness and a lack of understanding of the mechanisms in which such interventions bring about change. Inclusion of laboratory-based paradigms, for example those designed to assess aggression may be more powerful as they would provide a more objective means to assess aggression and would allow one to examine in real time, the extent to which certain techniques, such as mindfulness meditation, decrease aggression. The external validity of aggression paradigms (e.g., the Taylor Reaction Time task; Taylor, 1967) has been demonstrated through their associations with self-report measures of aggression (Giancola & Parrott, 2008), as well as their ability to differentiate violent from non-violent individuals (Cherek et al., 1997). Furthermore, one of the ways in which aggression paradigms are currently used is to examine the effectiveness of different pharmacotherapies in the treatment of aggressive behavior, for example Paroxetine (Berman et al., 2009) and Topiramate (Lane et al., 2009). Furthermore, use of procedures to elicit physiological reactivity in response to trauma cues in individuals with PTSD prior to assessing aggression would allow researchers to determine how techniques such as mindfulness meditation may decrease such reactivity when they encounter traumatic reminders in the environment, and how it may prevent aggressive behavior in the “heat of the moment”. This would be important given that research with civilians has shown that excessive autonomic arousal interferes with self-regulatory processes (Patterson & Newman, 1993) resulting in impulsive aggression, and in veterans increases in physiological reactivity triggered by exposure to combat-related cues are associated with self-report measures of aggression (Taft et al., 2007). In sum, use of experimental paradigms to assess aggressive behavior in combination with challenge procedures to elicit physiological reactivity among veterans with PTSD would provide an excellent way to test the effectiveness of novel psychotherapeutic techniques for PTSD-related anger and aggression that has been triggered as a result of such exposure, including mindfulness meditation.

Significance:

Although anger and aggression are commonly observed in military veterans with PTSD, there are few interventions that have been developed and tested to treat anger and aggression in this population. Mindfulness may be one such treatment that would be particularly useful in decreasing anger and aggression as it could (1) more effectively target the PTSD-specific symptoms most strongly associated with aggression, (2) assist veterans with PTSD in achieving awareness and insight into their anger states, which is important for the regulation of anger and aggressive reactions, and (3) be easily implemented and would not require a large time commitment from individuals. Findings showing that MBSR is effective in reducing anger and aggressive behavior in veterans with PTSD would be important as it could be an additional treatment that could be offered to veterans with PTSD who are struggling with these problems. Such an intervention could help decrease anger and prevent the perpetration of aggression among veterans with PTSD, thus preventing the detrimental consequences that anger and aggression can have on the lives of veterans, their families, and society at large.

Research Plan:

Overview: The proposed project will examine whether Mindfulness Based Stress Reduction (MBSR) decreases anger and aggression in veterans with PTSD. This project also will examine two potential mechanisms of action of MBSR: physiological reactivity and emotion regulation. This project will examine the initial efficacy of MBSR in a pilot randomized controlled study with 60 veterans with PTSD experiencing problems with anger and aggression. Participants will attend a baseline laboratory session to assess initial levels of self-reported anger and aggression and will then be randomly assigned to participate in a group PTSD psychoeducational course (the Trauma Recovery Education Course (TREC)) or group MBSR. After completing TREC or MBSR, all participants will participate in a post-treatment laboratory session in which self-reported anger and aggression will be assessed. In addition, during the laboratory session, participants will complete an experimental portion where they will be exposed to trauma-related stimuli, followed by participation in an experimental paradigm designed to assess aggressive behavior. After completing the post-treatment session, all participants will attend a 3-month follow-up session to assess long-term gains in the management of anger and aggression.

Participants:

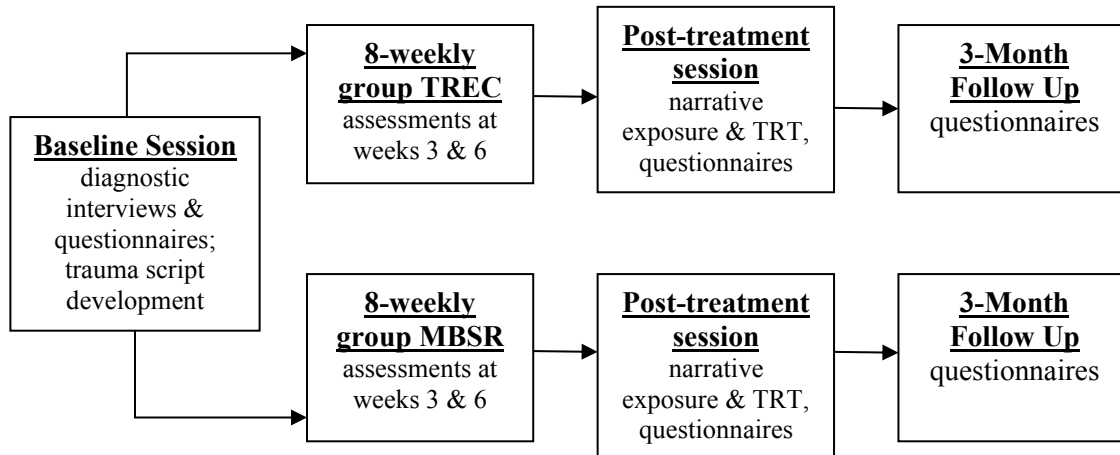
Inclusion Criteria: We will enroll 60 veterans with PTSD. To be eligible for the study, participants must meet current DSM-V diagnostic criteria for PTSD (American Psychiatric Association, 2013). PTSD will be established by interview using the Clinician Administered Posttraumatic Stress Disorder Scale for the DSM-V (CAPS-5; Weathers et al., 2013a). Participants must also indicate current difficulties with anger and aggression as indicated by a score of 20 or higher on the trait anger scale of the State Trait Anger Expression Inventory-2 (STAXI-2, Spielberger, 1999), indicating moderate to severe anger problems. Veterans from all eras will be eligible to participate.

Exclusion Criteria: Participants with a current diagnosis of bipolar disorder, psychotic disorder, or current substance use disorder with severe symptoms. Participants also must not have a seizure disorder and must not be taking any medications that would affect cognition or behavior on the aggression task, including pain medication, benzodiazepines, or antipsychotics. Participants also must not have a positive drug (e.g., amphetamine, opiates, and cocaine) or alcohol urine screen at the post-treatment session (see below), as these substances could affect performance on the study tasks implemented at that session. Finally, participants must not currently be receiving concurrent individual therapy or group therapy focused on anger and aggression and must not currently be participating in the modified TREC group offered at the West Haven VA (WHVA).

Research Design and Methods

For an overview of the time line for study procedures, see Figure 2.

Figure 2. Timeline of Study Procedures



Recruitment: Potential participants will be recruited through the Mental Health and Primary Care Clinics at the West Haven VA and the Newington VA Medical Centers. Providers will be informed of the project and will be asked to inform patients who might be interested about a study evaluating the effectiveness of an intervention “designed to help veterans who have been exposed to traumatic life events manage difficult emotions”. Flyers also will be posted throughout both campuses and the broader VA community advertising the study. In addition, participants also will be recruited through the National Center for PTSD (NCPTSD) Recruitment Screening Protocol. This protocol is a program coordinated through the NCPTSD that is designed to recruit participants for studies that are being conducted at the National Center that focus on traumatic stress. Through the protocol, potential participants will be recruited not only through flyers, but also through public advertisements (newspaper, radio, internet posting) by word of mouth, contact with community service groups and clinics (in addition to the West Haven and Newington VA mental health clinics, the Connecticut Mental Health Center, Yale Depression Research Program and the Yale Psychiatric Research Hospital), and the National Center for PTSD newsletter.

Procedure: Potential participants not recruited through the Recruitment Screening Protocol will be screened over the telephone for initial eligibility. This will include no diagnosis of bipolar disorder, a psychotic disorder, or substance use disorder with severe symptoms, no history of seizures, and not currently taking any prescription medications for pain, antipsychotics, or benzodiazepines. Potential participants also will be asked if they have been exposed to PTSD Criterion A stressors: exposure to actual or threatened death, serious injury, or sexual violence by directly experiencing the event, witnessing in person the event(s) as they occurred to others, or learning that the event(s) occurred to a close family member or close friend. If so, they will be asked if they thought about these experiences when they didn't want to, experienced a lot of anxiety about them or had been bothered by repeated disturbing memories, feelings, or dreams. Potential participants also will be asked if they are currently experiencing any difficulties with anger or aggression (e.g., irritable behavior, angry outbursts, acting aggressively). During this screening procedure, no personally identifiable information will be collected during the phone screen unless the person appears to be eligible for the study and is interested in scheduling a study appointment. Those who meet these criteria will be scheduled for a final eligibility and baseline assessment session that will take place at the West Haven VA.

Participants recruited through the Recruitment Screening Protocol will be contacted and provided with information about the study and if interested will also be scheduled for a final eligibility and baseline session. (Information on their initial eligibility will have been assessed previously).

Eligibility and Baseline Assessment Session: Participants will be provided with details of the study and written informed consent will be obtained. At the start of the baseline session, participants will be given an informed consent document to read and sign. The informed consent will review the purpose of the study as well as all of the procedures to be conducted during the study. The informed consent also will include a description of the Taylor Aggression Paradigm that will be completed at the post-treatment session. Specifically, this will include 1) a description of the experimental task (including exchanging shocks with the “other participant”); 2) a description of the tolerance threshold procedure; 3) a description of the “20” shock (described as double the participant’s tolerance threshold); and 4) a description of the physiological measurements. The purpose of the task will be described as looking at whether mindfulness is associated with motor performance. Aspects of the task which will be omitted in the initial consent are: 1) that the purpose is the study response to provocation; 2) that there is no opponent; and 3) that the participant will not actually receive a shock above their tolerance threshold. These consent procedures are consistent with what have been used previously in studies using this task and represent the minimal possible deception necessary for the task to be valid. There are no risks that subjects will be unaware of when providing informed consent. In fact the actual risks of participating are less than what are described to participants (e.g., they will not receive a shock above their threshold). All aspects of deception will be revealed to participants during the debriefing procedure.

Potential participants will then undergo a formal diagnostic interview (i.e., the CAPS-5, see below) to ensure PTSD status, as well as a brief assessment (State Trait Anger Expression Inventory-2, STAXI-2, see below) to determine whether they are currently experiencing difficulties with anger and aggression. They also will undergo an additional diagnostic interview (Structured Clinical Interview for the DSM-5 Disorders-Research Version (SCID-5-RV), see below) to determine whether they meet criteria for any other psychological disorders.

Trauma Scripting Procedure. After completing the diagnostic interviews (CAPS-5/SCID-5-RV), eligible participants will participate in a trauma-script development procedure as part of a well-validated, script-driven trauma imagery task (Pitman et al., 1987). For this procedure, participants will be asked to identify their most traumatic experience. If they identify more than one event, they will be asked to choose the one that they consider the most distressing. They will first be asked to describe the experience in writing using a script preparation form and then will be asked to indicate which of several different subjective visceral and muscular reactions (e.g., heart beating slower/faster, feeling sweaty, stomach in knots, feeling warm, hands trembling, tension in arms, nausea) may have accompanied the experience. Participants’ written responses will then be reviewed and they will be asked to clarify or expand on the details if necessary. After the session, a script lasting approximately 60 seconds in duration will be composed that portrays the traumatic experience in the second person, present tense, and incorporates the different visceral or muscular reactions. The script will then be audio recorded for playback

during the experimental portion of the post-treatment session. A research assistant (who will be named later upon being hired) will read the narrative scripts to be audio-recorded.

During this baseline session, participants will also complete a battery of self-report questionnaires (see below for full details) to assess baseline levels of anger and aggression.

Randomization Procedures. After participants have completed the Baseline Screening and Evaluation Session they will be randomized to either the TREC group or the MBSR group. To decrease the amount of time participants have to wait before starting group treatment, randomization will be implemented at the group level. That is, after 6 participants are recruited, they will be randomly assigned using urn randomization procedures, to either the TREC group or the MBSR group.

Post-treatment Session: After all participants have completed their assigned interventions (TREC or MBSR) they will be scheduled for the post-treatment session to be held in the biological studies laboratory at the WHVA. At this session, all participants will complete a battery of self-report questionnaires to assess post-treatment levels of anger and aggression (see below).

Participants will also engage in the trauma-imagery procedure, followed by participation in the Taylor Reaction Time Task (TRT; Taylor, 1967). For this part of the post-treatment session, participants will be seated in one of two humidity and temperature controlled sound-proof booths located in the biological studies laboratory at the WHVA. Participants will be seated in front of a monitor and keyboard connected to a computer located outside of the booths. An intercom will be placed next to the keyboard for participants to use to communicate with the experimenter during the tasks. After orientation to the subject room, electrodes will be attached and the subject will be instructed to sit quietly for 5 minutes to assess baseline recordings. Next, participants will listen to the 60-second audio recording of the script depicting their traumatic event. They will be instructed to listen carefully during the playing of the script and to attempt to imagine as vividly as possible the experience as it is presented. After the script terminates, participants will be instructed to continue to imagine the experience from beginning to end (for 60 seconds) until they hear a tone. Participants will then be instructed to rest (for 5 minutes) until a second tone is heard and then they will then make several ratings of their subjective experiences while they were recalling the traumatic event. Next, they will complete the Taylor Reaction Time Task (TRT; Taylor, 1967) to assess provoked aggression.

Debriefing

At the end of the post-treatment session, once all of the procedures have been completed, the experimenter will conduct a verbal debriefing with participants during which they will clarify all aspects of the deception that occurred during the TRT so that there is no misinformation, assess any distress that the participants may have experienced, and make every effort to minimize this distress through the debriefing discussion.

Debriefing participants following completion of a research study is a standard component of research with human subjects and serves several especially important functions in studies involving deception. These include: 1) allowing the participant to provide fully informed consent for the use of their data in the study; 2) providing the participant the opportunity to express any

negative feelings about their participation in the study and in turn giving the experimenter the opportunity to ameliorate any harm; and 3) educating the participant about the purpose and nature of the study, which may be beneficial for the participant. Smith and Richardson (1983) identified several aspects of research that have the potential to impact subjects' perceptions of harm following research that involves deception. These include: 1) informed consent (providing adequate expectations for the procedures that will take place); 2) the considerateness of the experimenter; 3) the quality of the debriefing explanation; 4) the perceived trustworthiness of psychologists; 5) enjoyment of participation; and 6) educational benefit of the debriefing. We will make an effort through our consent and debriefing procedures to address each of these issues in order to reduce the potential for harm that may be associated with the use of deception.

At the end of the study appointment once all of the procedures and questionnaires have been completed, the experimenter will conduct a verbal debriefing with the subject during which he or she will clarify all aspects of the deception so that there is no remaining misinformation, assess any harm that the participant may have experienced, and make every effort to minimize this harm through the debriefing discussion. Subjects will be asked to complete a post-task consent which will present this information in writing (again describing in detail the actual purpose of the task and clarify all aspects of the deception, similar to the debriefing script). Participants will be asked to indicate whether they would or would not like their data on the TRT to be used (analyzed) in the study. If the subject indicates that he or she would not like their data used, their research records will be stored in the completed file in a locked cabinet so that the records may be reviewed in case of an IRB audit. However, the data will not be entered into any database for statistical analysis.

To the extent that participants are experiencing any remaining distress as a result of their trauma exposure, the experimenter will work with the participant to assist them in returning to baseline levels of functioning. Finally, before ending the study appointment, participants will be informed that they will be contacted between 48-72 hours and then again one-week after their participation to follow-up about any negative reactions they may have had as a result of this portion of the session.

At the end of the post-treatment session, participants will be scheduled for a follow-up session to take place approximately 3 months after the post-treatment session to be held at the WHVA.

Follow-up Session. At this session, all participants will complete a similar assessment battery as was completed at the baseline and post-treatment sessions to assess any changes in levels of anger and aggression that may have occurred over the previous 3 months.

Drug and Alcohol Screening

At the beginning of the post-treatment session, participants will be asked to provide a urine sample to test for urine toxicology. If participants test positive on urine toxicology exams, we will encourage these individuals to maintain abstinence and they will be rescheduled. We will offer brochures for local substance use treatment facilities as appropriate. The extent to which participants are experiencing any symptoms of withdrawal will also be determined using the Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar; Sullivan et al., 1989). If participants indicate that they are experiencing any symptoms of withdrawal, they will be asked to reschedule their appointment at a later date. We will provide referrals to appropriate primary

care providers as appropriate.

Compensation

Participants will be compensated for their time and inconvenience while taking part in study procedures. Participants will be paid \$100 for the baseline and post-treatment sessions, and \$50 for the follow-up session. Participants also will be paid \$20 for completing questionnaires during week 3 and week 6 of treatment (for a total of \$40). Participants will not be paid for their participation in the TREC or MBSR intervention.

Assessments: See Table 1 for a listing of the primary assessments used in the current study.

Table 1. Schedule of Assessments

| | Baseline | 3-week | 6-week | Post-Treatment | 3-month Follow-up |
|--|----------|--------|--------|----------------|-------------------|
| Diagnostic Assessments | | | | | |
| Clinician Administered PTSD Scale for DSM-V: Past-Month Version (CAPS-5) | X | | | | |
| Structured Clinical Interview for DSM-5 Disorders-Research Version (SCID-5-RV) | X | | | | |
| Life Events Checklist-5 (LEC) | X | | | | |
| Primary Outcome Measures: Self-Report | | | | | |
| State Trait Anger Expression Inventory-2 (STAXI-2) | X | X | X | X | X |
| Buss-Perry Aggression Questionnaire (BPAQ) | X | X | X | X | X |
| Primary Outcome Measure: Experimental | | | | | |
| Taylor Reaction Time Task (TRT) | | | | X | |
| Secondary Outcome Measures | | | | | |
| Physiological Reactivity: Heart Rate, Skin Conductance | | | | X | |
| Emotion Regulation: State Difficulties in Emotion Regulation Scale (DERS-S) | | | | X | |
| Exploratory Outcome Measures | | | | | |
| Five Facet Mindfulness Questionnaire (FFMQ) | X | X | X | X | X |
| PTSD Checklist for the DSM-V (PCL-5) | X | X | X | X | X |
| Quantity-Frequency Variability Index (QFI) | X | X | X | X | X |
| Alcohol Dependency Scale (ADS) | X | X | X | X | X |

Baseline Session:

(a) PTSD, other psychiatric disorders, anger and aggression:

The DSM-V criteria for PTSD will be established using the Clinician Administered PTSD Scale: Past-Month Version (CAPS-5, Weathers et al., 2013a). The CAPS-5 will be used to confirm DSM-V PTSD diagnosis and to provide a continuous measure of PTSD severity (CAPS-5 total score). To facilitate the administration of the CAPS, participants will also complete the Life Events Checklist-5 (LEC; Weathers et al., 2013b), which is a self-report questionnaire used to assess the extent to which individuals experienced any of 17 different stressful or difficult life events (e.g., combat exposure, natural disaster, fire or explosion).

Participants will be assessed for psychiatric disorders at the baseline session using the Structured Clinical Interview for DSM-5 Disorders – Research Version (SCID-5-RV, First et al.,

2014). The information from the SCID will be used to exclude participants with severe psychiatric disorders (e.g., schizophrenia or bipolar disorder).

(b) Battery of Self-Report Questionnaires: Participants will also complete a battery of self-report questionnaires including assessments measuring anger and aggression, in addition to trait mindfulness, PTSD, and alcohol use:

- State Trait Anger Expression Inventory-2 (STAXI-2, Spielberger, 1999)
- Buss-Perry Aggression Questionnaire (BPAG; Buss and Perry, 1992)
- Five Facet Mindfulness Questionnaire (FFMQ; Baer et al., 2008)
- PTSD Checklist for the DSM-V (PCL-5; Weathers et al., 2013)
- Quantity-Frequency Variability Index (QFI; Cahalan, Cisin, & Crossley, 1969)
- Alcohol Dependency Scale (ADS; Skinner & Allen, 1982)

Interim Assessments: During the intervention period, at two time points (weeks 3 and 6 of therapy), participants will be asked to complete the STAXI-2, the BPAG, the FFMQ, the PCL-5, the QFI, and the ADS.

Post-treatment Session: Participants will complete the same battery of self-report questionnaires that was completed at the baseline session. In addition, participants also will complete the following assessments. (See Figure 3 below outlining the order of tasks during experimental portion of the post-treatment session.)

(c) Psychophysiological Assessments: During the experimental portion of the post-treatment session, physiological measurements will be recorded to assess reactivity during exposure to the trauma cue (script). Participants will sit quietly for 5 minutes to collect baseline (B) physiological assessments. This will be followed by the trauma-script reading (TR) and then the trauma-script imagery (TI) segments followed by a resting period (R) and assessment of subjective experiences.

Physiological measurements will include skin conductance levels (SC) and heart rate levels (HR). A BIOPAC MP150 system (BIOPAC, Santa Barbara, CA) that includes modules for HR and SC will be used to record physiologic analog signals. Physiologic analog signals will be digitized by an analog to digital converter. A notebook computer (IBM-compatible) with BIOPAC Acknowledge© software will be used to sample and store the digitized physiologic signals. Interbeat interval will be recorded in milliseconds via standard limb electrocardiogram leads connected to a High Gain Bioamplifier and converted to HR. Skin Conductance (SC) will be measured by an Isolated Skin Conductance coupler using a constant .5 V through 2, 9-mm (sensor diameter) Ag/AgCl electrodes filled with electroconductive gel placed on the hypothenar surface of the subject's non-dominant hand in accordance with published guidelines. The SC electrodes will be separated by 14 mm, as determined by the width of the adhesive collar.

The mean level of each physiologic variable (HR, SCL) will be computed for the last 30 seconds of the baseline (B) segment, for each of the two 30-second blocks during the 60-second trauma reading (TR), for each of the two 30-second blocks during the 60-second trauma imagery (TI) segments, and for the last 30-seconds of the resting (R) segment. Response (change scores) will be calculated by subtracting the baseline (B) value from the peak value of the four 30-

second blocks from the trauma imagery/trauma reading segments (TR/TI). Change scores also will be calculated by subtracting the peak trauma imagery/trauma reading value (TR/TI) from the resting period (R) value.

As a manipulation check, after the resting period (R), participants will complete a brief assessment to indicate how vivid the imagery was, their perceived arousal, the subjective pleasantness, and their sense of control. Participants also will be asked to rate the extent to which they experienced 6 discrete emotions (happiness, sadness, fear, surprise, anger, and disgust). Participants will be asked to rate their responses using a 12-point Likert-type scale ranging from 0 (not at all) to 12 (very much).

(d) State Emotion Regulation: State emotion regulation will be assessed using the State Difficulties in Emotion Regulation Scale (DERS-S, McLaughlin et al., 2007). This measure will be completed by participants following the trauma reading/trauma imagery (TR/TI; pre-task), and again following the resting period (R; post-task).

(e) Aggression: Aggression will be assessed using the Taylor Reaction Time task (TRT; Taylor, 1967). The TRT is a laboratory-based analogue paradigm for a provocative interpersonal encounter that is designed to study factors that may be causally related to provoked aggression. In the TRT, the research participant purportedly competes against another participant (the “opponent”; actually fictitious) in a series of 28 reaction time trials to see who has the faster reaction time. Prior to each trial, the participant and opponent select a shock level, ranging from 0, 1-10, or 20, for the other to receive if they should lose the reaction time trial (i.e., the loser on each trial receives the shock). Shocks are administered on losing trials to two fingertips on the non-dominant hand. Wins and losses are pre-programmed by the experimenter and equal 50% on the trials. Therefore the participant receives 14 shocks over the course of the task. However, the participant sees the level of shock selected by the opponent on all 28 trials and over the course of the task the “opponent” becomes more provocative by setting increasingly intense shocks. Three-quarters of the way through the task, the opponent attempts to administer a shock described as “extremely unpleasant” to the participant (the “20” shock). The participant wins this trial and therefore never receives this shock; however, they are provoked by the knowledge that the opponent would attempt to administer this shock. Actual shock levels used in the task are determined by a threshold procedure carried out prior to starting the task. Electrical stimulation will not exceed 100 V for 2 ms duration during the threshold procedure. All of the shocks the participant receives during the task are lower than their tolerance threshold.

During the task, the participant will be told that another research participant (called their “opponent”) is seated in the other booth in the biostudies laboratory. They will be told that they will interact with the opponent via computer to compete in a series of reaction time trials. Before the task, two electrodes will be placed on two of fingertips on the participant’s non-dominant hand. A threshold procedure will then be conducted to determine what is the lowest level of shock the participant can detect, and at what level the shock becomes uncomfortable and he or she does not want it to increase anymore. The shocks will be 2 ms in duration and will start at a very low level, so low that the participant will not feel the first one or even a few shocks. We will ask the participant to indicate at what point they first feel the shock. Then the shocks will continue to increase in intensity, and we will ask the participant to indicate when the shock is so unpleasant that they do not want it to increase anymore. At this point we will stop the threshold

procedure. An audio recording of the procedure being conducted with a (same-sex) research confederate will be played over the intercom to enhance the deception of the task. Before the task, instructions for doing the task will be read over the intercom. The instructions will explain that the “two” participants will be competing in a series of trials to see who has the faster reaction time. During the task, instructions will appear on the computer screen to press the spacebar and then to release it as quickly as possible when prompted by the computer. The person with the faster reaction time will win that trial, and the person with the slower reaction time will lose the trial and receive a shock. The instructions will explain that the “two participants” will set the shock levels for each other. This choice will be made before each of the 28 trials. The available shocks range from mild to strong and are labeled from 1-10, 0, or 20. The “10” shock will be equal to the participant’s respective tolerance threshold. The “9” shock will be 95% as intense as the “10”, the “8” will be 90% as intense, “7” will be 85% as intense, and so on down to the “1” shock. The “0” option will deliver no shock, and the “20” shock will deliver a shock that is twice the intensity of the respective tolerance thresholds. This shock will be described as “extremely unpleasant and potentially painful.” The participant will also be told that this level of shock “may cause tissue (skin) irritation (i.e., skin sensitivity and warmth, but not burning) that will resolve within a few hours.” Similar language has been used in previous studies (e.g., Berman et al., 2009) and is necessary to be consistent with the definition of aggression as a behavior that is “intended to harm another person” and not merely a behavior that is annoying or irritating. An attempt by the “opponent” or participant to administer this shock thus represents an unambiguous aggressive act. As described previously, the “opponent” attempts to administer this shock one time late in the task, but the participant never actually receives it because the task is programmed so that the participant always wins this trial. However, participants are provoked by the knowledge that the opponent intended to administer this shock. Note that the description of the shocks will be provided in the informed consent document. The experimenter will check in with the participant prior to starting the task to answer any questions and obtain the participant’s assent before continuing to the task. During the task, the participant will be monitored by video and audio (not recorded). Participants will be informed that the intercom to the experimenter will remain on during the task and they can stop the task at any time that they wish simply by asking to stop.

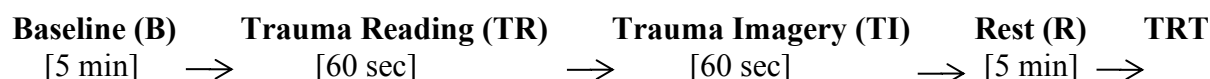
Electrical stimulation will be implemented using Biopac© equipment. Electrical stimulation will not exceed 100 V for 2 ms duration during the threshold procedure regardless of the participant’s ability to tolerate the shocks. The International Electrotechnical Commission has established recommendations for the amount of electrical stimulation that can be used with human participants (IEC 601-2-10), and the Biopac stimulator STMISOC was engineered so that the available maximum energy output is considerably less than the maximum set by the IEC. The behavior of interest on the TRT is (1) the mean shock level chosen by the participant across all trials, and (2) the number of “20” shocks chosen by the participant.

The validity of the TRT is supported by correlations between behavior on the TRT and self-reported life history of aggressive behavior and trait aggressiveness (Anderson & Bushman, 1997; Giancola & Chermack, 1998; McCloskey & Berman, 2003). The TRT has also been found to be most strongly associated with self-report measures of physical aggression, and to a lesser extent verbal aggression and trait hostility (Giancola & Parrott, 2008). Laboratory aggression paradigms have been the subject of several meta-analyses, including on the effects of various personality traits (Bettencourt et al., 2006) and of exposure to violent media (Anderson & Bushman, 2001) on aggression, and experiments using the TRT have been shown to yield

comparable effects (and effect sizes) to similar field-based studies of aggression (Anderson & Bushman, 1997). Naturally (given the subject matter and use of deception) laboratory aggression paradigms have been subject to close scrutiny (Bertelson, 1990), and the discussion surrounding this methodology has led to modifications of the Taylor task, such as the addition of the “0” shock option, which both enhances the validity of the task by providing a non-aggressive response option and reduces demand characteristics associated with the task (Berman et al., 2009).

(f) Post-TRT Manipulation Check Questionnaire. Participants will complete a post-task questionnaire after completing the TRT to determine the integrity of the experimental aggression manipulation. Participants will be asked to indicate what they thought the purpose of the task was and to indicate characteristics about their “opponent” (e.g., how old they thought their opponent was, whether they were male or female).

Figure 3. Order of tasks during the experimental portion of the post-treatment session



Follow-up Session. Participants will complete the same self-report questionnaires that were completed at the baseline and post-treatment sessions: STAXI-2, BPAQ, PCL-V, QFI, ADS, and the FFMQ.

Study Conditions:

Trauma Recovery Education Class (TREC). TREC is a group-based treatment that was developed by two staff clinicians at the WHVA. It is based in part on the first session of Cognitive Processing Therapy (Resick & Schnicke, 1993), which focuses on providing information on PTSD and traumatic reactions, and Motivational Enhancement Therapy (Miller & Rollnick, 2012). TREC provides psycho-education to veterans on PTSD, including common reactions to trauma and the role of avoidance, common problems associated with PTSD, as well as common barriers to care (e.g., stigma, maladaptive beliefs, fear). Additional content focuses on problem identification and goal setting, discussion of current problems and life issues, and treatment planning. The content of TREC is similar to other treatment control conditions used in RCTs with veterans with PTSD (e.g., Schnurr et al., 2001; Shea, Lambert, & Reddy, 2013). Such interventions emphasize therapist contact and support, as well as the provision of psychoeducation, instillation of hope and the expectation of improvement. The complete version of TREC will be implemented for the current project, which consists of 8, one-hour weekly sessions. TREC will be conducted by a doctoral level clinician (to be named) at the WHVA.

Mindfulness Based Stress Reduction (MBSR): MBSR, developed by Jon Kabat-Zinn (Kabat-Zinn, 1990) is a group-based intervention that was initially developed for individuals experiencing chronic pain and other stress-related disorders. Subsequent research has found it to be effective with individuals experiencing emotional distress including depression and anxiety (Baer, 2003). In MBSR, participants are taught different mindfulness meditation practices, including body scan (focusing attention to different areas of the body in sequence), sitting meditation (focusing attention to one’s breathing), and Hatha yoga postures (focusing attention

to different body sensations during gentle stretching). Participants also are taught how to practice mindfulness while engaging in ordinary activities including walking, standing, and eating. When practicing mindfulness, participants are instructed to focus their attention on the target of observation (e.g., breathing or walking). If any emotions, sensations, or thoughts arise, participants are instructed to note that they have occurred (i.e., to observe them) and to do so in a non-judgmental manner. They are then instructed to re-focus their attention to the present moment. Doing so helps participants to notice their thoughts and feelings, but not be overwhelmed or absorbed by their content (Kabat-Zinn, 1982). MBSR consists of 8, two-hour weekly sessions and will be delivered in group format. The MBSR groups will be conducted by Dr. Lorig Kachadourian.

Treatment Adherence: To enhance treatment adherence, manuals will be used for both the TREC and MBSR groups. Both TREC and the MBSR sessions will also be audio-recorded and reviewed. Checklists outlining the essential components of each condition will be used. After completion of the interventions, two raters will conduct tape ratings for fidelity analyses. Approximately 20% of the tapes from each intervention (TREC, MBSR) will be rated. Prior to tape rating, the two raters, who will be blind to study objectives, will receive training in fidelity analysis. Following training, inter-rater reliability will be established by having the two raters rate an initial sample of approximately 10 tapes. A second calibration sample of 5 tapes will then be conducted to focus additional training efforts on items where reliability is inadequate. A third calibration sample of 5 tapes will be conducted midway through the tape rating phase to ensure raters maintain high levels of reliability.

Strategies used to Minimize Study Attrition.

Several procedures will be used to enhance adherence and retention for the proposed study. (1) At the outset of the study, potential participants will be provided with a thorough description of the study procedures so that they fully understand the tasks that will be used and the time commitment involved. (2) Participants' contact information will be obtained at the baseline session in addition to at least 2 collateral informants. (3) Appointment cards and reminder calls will be made for all appointments. (4) Participants who miss sessions will be contacted immediately. (5) To the extent that participants develop any concerns about the treatment or their overall participation in the study, they will be addressed in a timely manner. (6) Participants will be reimbursed for their time and effort.

Data Monitoring Plan and Data Analyses

Data Safety and Monitoring Plan

All research staff on the proposed protocol will review and be familiar with the VA Connecticut Healthcare System Human Research Protection Program (HRPP) Standard Operating Procedures. Dr. Kachadourian is the individual responsible for data and safety monitoring in the proposed research study. She will perform quality control activities including regular data verification and protocol compliance checks on a weekly basis for this minimal risk study. Dr. Petrakis also will be informed of study progress in weekly laboratory meetings and day-to-day interactions with research staff.

Dr. Kachadourian will oversee procedures ensuring privacy of participants and confidentiality of data. All research staff will share responsibility for maintaining privacy and confidentiality. Private information accessed will only be visible to research staff.

Confidentiality of information will be maintained by protecting data using encrypted drives, VA firewalls, and fully de-identified datasets. All hardcopies of data and information will be secured in a locked room at the West Haven VA and maintained by Dr. Kachadourian and other research project staff. Electronic data that contain identifiers are only located on the VA server behind VA firewalls.

The research staff will also be using REDcap, a free, secure VA Web application that allows for the collection and entry of research data. In addition to enabling users to develop surveys and databases without additional software, REDcap helps researchers enter, store and manage project data. All data entries will have a study code number but no identifying information. Registration records including the signed consent form will be stored separately from these study records.

Dr. Kachadourian will be responsible for reporting adverse events and protocol deviations either personally observed, reported by research staff, or reported by research volunteers. Research staff will inform Dr. Kachadourian of adverse events or protocol deviations as soon as reasonably possible after occurrence. Dr. Kachadourian will be responsible for the documentation of adverse events and protocol deviations for both annual review and individual events or deviations with decision making guided by the HRPP Standard Operating Procedures for Reporting Research Events and Problems. Unanticipated problems involving risks to subjects or others will be reported to the ACOS for Research and the HSS as soon as possible and no later than three business days after knowledge of the problem. All research staff members will be informed of adverse events or protocol deviations. If protocol changes are required, the Dr. Kachadourian will submit modifications to the protocol and consent forms to the HSS as needed, and protocol changes will not be implemented prior to HSS approval unless necessary to avoid hazard to a participant, which is not expected in this minimal risk study.

If a research volunteer discloses suicidal or homicidal ideation or intent through study questionnaires or direct report to any research staff or investigators, the staff will immediately notify Dr. Kachadourian who will determine the appropriate course of response to minimize harm to the volunteer or others. Research staff will remain with the volunteer until Dr. Kachadourian takes necessary action. This protocol presents minimal risks to the subjects and adverse events or other problems are not anticipated. In the unlikely event that such events occur, serious and unanticipated and related adverse events or unanticipated problems involving risks to subjects or others will be reported in writing within 48 hours to any appropriate funding and regulatory agencies. VA HSS will be informed of adverse events as described above. The investigator will apprise fellow investigators and study personnel of all adverse events that occur during the conduct of this research project through weekly laboratory meetings and via email.

In Case of Acute Clinical Distress

None of the measures in the study specifically asks about current suicidal or homicidal ideation; however, it is possible that subjects may disclose such ideation either spontaneously or during the screening interview. If a volunteer reports suicidal or homicidal ideation or any intent to harm oneself or another person, we will complete the following procedures. Research staff will inform Dr. Kachadourian about the participant's statements. Dr. Kachadourian will conduct further questioning on the nature of the ideation or intent, consider the participant's statements, identify risk and protective factors for suicide or homicide, and possibly perform further clinical assessments (e.g., Beck Hopelessness Scale) to best inform clinical decision making. Dr. Kachadourian will determine if there is imminent risk to self or other based on these factors.

Should this be the case, she will explain the need to break confidentiality and encourage the subject to voluntarily go with her to the VACHS Psychiatric Emergency Room (PER). If the individual refuses to voluntarily go to the PER, Dr. Kachadourian will call x4900 VA Police to escort the subject to the PER. The veteran will be encouraged to seek psychiatric services and resources will be provided as appropriate. The procedures will be documented in a VA CPRS Research note. A follow-up phone call will be made with the research volunteer on the following day.

Rarely during the TRT do participants show dramatic displays of emotion verbally or through gestures. This is likely because the participant is seated alone in the experimental room and is not face-to-face with the person with whom they are interacting. Furthermore, participants have the means to respond to provocation simply by pressing a button (selecting the intensity of shock on the next trial). As described to participants in the *Task Instructions*, the experimenter will monitor the participant throughout the task via video and audio monitor (not recorded). The following plan will be used to respond to any apparent distress during the task. Some display of emotion (verbal responses to the task and gesturing) is not a concern as the task is a provocation task. Research studies often utilize symptom induction procedures that are specifically designed to induce an increase in certain emotions. While inducing anger is not a specific goal of the task, some anger or exasperation will not impel the experimenter to stop the task. If it appears, based on the clinical judgment of Dr. Kachadourian that the emotion displayed by the participant is a cause for concern, the experiment will be paused and the experimenter (Dr. Kachadourian) will check in with the participant (e.g., “You seem upset, how are you doing?”). The experimenter will offer to discontinue the task, or if, in their judgment, the participant is too upset to reasonably continue, the experimenter will make the decision to stop the task. In the latter circumstance the investigator would end the task and talk further with the participant (e.g., “What specifically made you upset?” etc). As long as the participant does not appear to be an imminent danger to others, the experimenter will ask the participant to fill out the post-task mood rating scale (to allow the participant an opportunity to “cool off”) and will then debrief the participant about the study (regardless of whether the participant has completed the other task procedures, such as questionnaires) and address the source of the participant’s distress. The experimenter will attempt to help the participant “return to baseline” using clinical skills or by having the participant fill out more questionnaires (if they are willing to) before ending the session and having the participant leave. If at any point during the study the participant appears to represent a danger to self or others, the PI will implement the risk assessment and response procedures described in the preceding paragraph.

Data Analyses

Data will first be subjected to data screening procedures. This will include examining the data through visual inspection to ensure there are no missing data or outliers and performing appropriate descriptive analyses to ensure that there are no violations to normality, homoscedasticity, multicollinearity, etc. To the extent that there are violations to assumptions of normality, transformations will be considered and utilized if necessary. Appropriate procedures also will be implemented to deal with any other potential violations of statistical assumptions using procedures outlined by Tabachnick & Fidell (2000).

Although random assignment will be utilized, follow-up statistical analyses will be conducted to ensure that there are no differences between the TREC and MBSR groups on demographic variables (e.g., age, ethnicity, education) in addition to differences between the two

groups on other variables that may include (but are not limited to) other psychiatric symptomatology and trait mindfulness. To the extent that there are differences on these variables, they will be included as co-variables in subsequent analyses. For all analyses, the extent to which participants are taking any medications, (categorized as ‘yes/no’) will be included as a statistical control.

Primary Aim 1 Hypothesis 1.1: Participants assigned to MBSR will report decreased levels of self-reported anger and aggression at post-treatment and at the 3-month follow up compared to those assigned to the TREC group. Scores on the State Trait Anger Expression Inventory-2 and the Buss-Perry Aggression Questionnaire will be used as the primary outcome variables for self-report anger and aggression. Intent-to-treat analyses will be conducted for these outcomes, which will be examined separately. Bonferroni adjustments will be implemented to control for Type 1 error. These data will be analyzed using mixed effects models with treatment, time, and treatment x time interaction as fixed effects. Subject will be the clustering factor and it will be nested within therapy group which will also be considered random. Different variance-covariance structures will be considered and the best one selected based on Schwartz’ Bayesian Information Criterion (BIC). Mixed effects models are the preferred method for analyses of such data as they use all available data on an individual, give unbiased results under general missing data assumptions and provide flexibility in modeling the correlation structure within subject. Significant interactions will be examined further using post-hoc tests.

Primary Aim 1, Hypothesis 1.2: Participants assigned to MBSR will exhibit lower levels of anger and aggression on the TRT compared to those assigned to the TREC group. Mixed effects models will be used to compare the TREC group to the MBSR group on responses on the TRT: (1) mean shock level across the TRT, and (2) total number of “20” shocks chosen on the TRT following the same strategy as for primary aim 1 hypothesis 1.1.

Secondary Aim 1, Hypothesis 1.1: Those assigned to MBSR will exhibit significant decreases in HR and SCL and increases in emotion regulation compared to those assigned to the TREC group. Mixed effects models will be used to compare the TREC group to the MBSR group on physiological variables (HR, SCL) and emotion regulation (DERS-S) following the same strategy as for primary aim 1, hypothesis 1.1.

Secondary Aim 1, Hypothesis 1.2: Within the MBSR group, decreases in physiological reactivity and increases in emotion regulation will be associated with decreases in aggression on the TRT. Pearson product moment correlations will be calculated to examine the association between changes in HR, SC, and emotion regulation and the TRT responses (i.e., mean shock level across the TRT and total number of “20” shocks chosen on the TRT).

Sample Size and Power Considerations

Although the proposed sample size may not be sufficient in establishing statistical significance but rather a pattern of results that suggest promising effects across anger outcomes, it is important to emphasize that the fundamental purpose of the pilot trial is to provide information for the planning of a future large scale clinical trial examining the efficacy of MBSR in decreasing anger and aggression in veterans with PTSD and examining additional mechanisms of action (i.e., behavioral, cognitive, social, biological) that lead to behavior change. To that end, the pilot RCT data will be used in power calculations to calculate the sample size for a later full-scale RCT examining MBSR for anger and aggression for veterans with PTSD.

Effect sizes for determining the sample size for the larger RCT will be calculated based on differences between the baseline and post-treatment scores on the self-report measures of

anger and aggression (STAXI-2, BPAQ), as well as the difference scores between the physiological measures (i.e., HR and SC) and emotion regulation obtained during the experimental portion of the post-treatment session. Comparisons will be made using a two-sample t-test. Due to the possibility that estimation of effect sizes based on pilot studies may be inaccurate (Kraemer et al., 2006), we will implement procedures recommended for improved characterization of effect sizes derived from pilot studies (Thabane et al., 2010). These include close consultation with clinicians who have used the treatment (i.e., Dr. Brewer), and accounting for the effect size uncertainty by constructing confidence intervals around the observed effect size.

Due to the nature of group treatment, additional considerations related to sample size will need to be considered given that a portion of the variance in treatment effects will be accounted for by clustering of effects within a particular group. Clustering group effects can be measured by an intra-class correlation ρ , which is defined as the ratio of variance due to the clustering variable relative to the total variance (cluster and error) (Schnurr et al., 2001). Once ρ has been determined, the adjusted sample size can be determined using the following formula: $m = n * N / (1 + (n - 1) \rho)$, where m is the effective number of independent observations after accounting for interclass correlation; n is the number of repeated measures per group; and N is the base sample size needed to detect the effect.

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