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**UACCESS EDOC NUMBER (FOR PROJECTS REQUIRING AN IRB FEE)**

**PROJECT TITLE:** A Non-Pharmacologic Method For Enhancing Sleep in PTSD

## INVESTIGATOR

| | |
|---|---|
| Principal Investigator Name, Degree(s): | William D. "Scott" Killgore, Ph.D. |
| Principal Investigator UA netID | killgore |
| Status/Rank: | Professor |
| Center: | |
| Section: | |
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## ADVISOR CONTACT INFORMATION (REQUIRED FOR ALL STUDENTS AND RESIDENTS)

| | |
|---|---|
| Name, Degree(s), UA NetID: | N/A |
| Contact phone: | |
| Official University Email: | |

## ALTERNATE/COORDINATOR CONTACT INFORMATION

| | |
|---|---|
| Name, **UA NetID**: | Bryan Clines, **bclines** |
| Contact phone: | (520) 621-3454 |
| Official University Email: | bclines@psychiatry.arizona.edu |

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## SECTION 1: REQUIRED SIGNATURES

### 1. PRINCIPAL INVESTIGATOR

I will conduct my research according to the University of Arizona HSPP Investigator Manual.

| Signature | Date | Print Name |
|---|---|---|
| | 06/30/14 | William D. "Scott" Killgore, Ph.D. |

### 2. ADVISOR (FOR ALL STUDENTS AND RESIDENTS ACTING AS THE PI)

I will oversee the student researcher according to the University of Arizona HSPP Investigator Manual.

N/A

| Signature | Date | Department |
|---|---|---|
| | | |

### 3. SCIENTIFIC/SCHOLARLY REVIEW (CANNOT BE ASSOCIATED WITH THE PROJECT)

I have examined the proposal cited above, and find that the information contained therein is complete and that the scientific or scholarly validity of the project appears appropriate.

| Signature | Date | Print Name |
|---|---|---|
| | 06/17/14 | Nicholas Breitborde, Ph.D. |

| Official University Email | Phone number |
|---|---|
| breitbor@email.arizona.edu | (520)626-7534 |

### 4. DEPARTMENT/CENTER/SECTION REVIEW

I have reviewed this application and determined that all departmental requirements are met and that the investigator has adequate resources to conduct the Human Research.

| Signature | Date | Print Name |
|---|---|---|
| | 06/10/14 | Karen Weihs, M.D. |

| Official University Email | Phone number |
|---|---|
| weihs@email.arizona.edu | (520)626-8940 |

### 5. RESPONSIBLE PHYSICIAN (PROJECTS INVOLVING MEDICAL PROCEDURES WHICH THE PI IS NOT AUTHORIZED TO CONDUCT)

I am a physician licensed by the State of Arizona (or US license for the SAVAHCS). I will be responsible for ensuring that all procedures that are part of this project and that require the attendance of a licensed physician will have a suitable physician present during the procedures. If at any time this is not possible, I will inform the IRB before any procedures are conducted.

N/A

| Signature | Date | Print Name |
|---|---|---|
| | | |

## 6. Native American or International Indigenous Populations Review

Signature needed only if research takes place in Indian Country or among international Indigenous populations, actively recruits Native Americans or international Indigenous populations for enrollment, and/or requires stratification of Native Americans or international Indigenous populations as one of the statistical analyses or study aims.

☐ **Social and Behavioral Projects: American Indian Studies,** (520)621-7108
☐ **Biomedical Procedures: Office of Outreach and Multicultural Affairs,** (602)827-2327

I have examined the proposal cited above and advise that further appropriate tribal/Indigenous approval [ ]is [ ]is not necessary.

N/A

| Signature | Date | Print Name |
|---|---|---|

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## SECTION 2: GENERAL INFORMATION

| | |
|---|---|
| **1.** Not including this project submission, how many: | |
| a. Human Research studies is the PI involved in as key personnel? | 4 to be IRB approved for opening, key personnel on 6 studies |
| b. Active subjects are there in the PI's open Human Research study/ies? | 15 active subjects at Harvard of 155 enrolled or completed; studies to be transferred to a site PI upon Dr. Killgore's transfer |
| c. Investigators are involved on the PI's open Human Research studies? | 3 |
| d. Research coordinators are involved on the PI's open Human Research studies? | 5 |
| **2.** What is the expected length of this project? | 4 years |
| **3.** Retention of study materials before, during, and after completion of the project: | |
| a. Where will the original signed consent and PHI Authorization documents be stored (building name and room)? | UAHS 7309 or 7310A |
| b. How long will the data/consents be kept after conclusion of the project? | ☒ 6 years<br>☐ Other: |
| **4.** If the Human Research project is funded, identify all sponsoring entity/ies): | Department of Defense |
| **5.** If funding support is from a federal agency (such as a training grant, infrastructure grant, salary support, project grant, etc.), list federal agency and grant number | Department of Defense PT130770 |
| **6.** Total funding amount **OR** per subject amount: | $3,823,700 |

7. The Principal Investigator hereby affirms that ALL individuals who meet the definition of "investigator" for this project in the current "Policy on Investigator Conflict of Interest in Research" have completed the mandatory Conflict of Interest training (http://orcr.arizona.edu/coi/training) and Disclosure of Significant Financial Interests (https://uavpr.arizona.edu/COI/). ☒ Yes
8. Will this project be registered on ClinicalTrials.gov because …? ☒ Yes ☐ No
   a. the local PI is the sponsor of the clinical trial (including NIH-funded clinical trials where the local PI is the funding recipient OR IND holder);
   **OR**
   b. The PI has been designated by a sponsor, contractor, grantee, or awardee to register the clinical trial to ClinicalTrials.gov, as the Responsible Party (responsible for conducting the trial, and has sufficient data rights)

   **If yes,** please check the appropriate box:
   ☒ ClincialTrials.gov "NCT" number for this trial (define): NCT02370173
   ☐ Registration pending
   ☐ Clinical trial does not require registration (click above to see what studies qualify)

## SECTION 3. PROJECT NARRATIVE

### 1) Background

During the past decade, over 2 million U.S. military personnel have deployed on potentially dangerous missions in support of the wars in Iraq and Afghanistan [1]. Combat duty is inherently hazardous and many deployed Soldiers have experienced intense and personally life-threatening situations or witnessed horrific and traumatic events. The neuroendocrine stress response that is associated with these types of potentially life-threatening experiences prepares the brain and body for survival. As part of this survival response, several brain systems become hyper-responsive and sensitized to potential threat. In particular, exaggerated amygdala responses during stressful experiences enhance the encoding of vivid and indelible emotional memories [2, 3]. For some combat veterans, the intensity and horrific nature of these experiences is perceived as so overwhelming that they continue to have sustained physiological arousal, heightened startle reflexes, and uncontrollable intrusive memories and nightmares that persist for years or even decades after the traumatic experience. If these symptoms are sustained and lead to impairments in daily functioning, the service member may be diagnosed with post-traumatic stress disorder (PTSD). Initial rates of PTSD in Soldiers returning from combat duty in Iraq and Afghanistan were reported to be as high as 17% [4], and subsequent reports have confirmed rates as high as 20% [5], depending on the method of assessment. Furthermore, PTSD often presents as a comorbid disorder with a range of other

psychiatric and/or somatic problems [6-8]. Treatment for PTSD usually involves some combination of cognitive therapy, exposure therapy, and pharmacotherapy. Unfortunately, current therapeutic interventions show variable efficacy and frequent treatment failures [9, 10]. Consequently, alternative approaches or augmentations to existing treatments are needed.

**Sleep disruption in PTSD**

Sleep disruption has been labeled the "hallmark of PTSD." In fact, sleep problems appear to be the most prevalent complaint of individuals with PTSD [11], and may contribute significantly to the persistence and severity of the disorder [12-14]. A recent meta-analysis confirmed the presence of sleep abnormalities in patients with PTSD, including excessive stage 1 sleep, reduced slow wave sleep, and elevated rapid-eye-movement density, when compared to unaffected individuals [15]. Over two-thirds of combat veterans with PTSD endorse problems with sleep, particularly insomnia and nightmares [13, 16, 17], with rates of self-reported sleep complaints exceeding 90% in some studies [18]. Neylan and colleagues (1998) found that initial insomnia (difficulty falling asleep) occurred in 44% of combat veterans with PTSD, 6% of veterans without PTSD and 5% of healthy comparison subjects. Moreover, 91% of veterans with PTSD reported difficulties maintaining sleep (i.e., staying asleep after initial sleep onset) [19]. In another study, early morning awakening was reported by 43% of individuals with PTSD compared to 13% of individuals without PTSD [20]. Nightmares leading to awakening have been reported to occur frequently in about 50% of combat veterans with PTSD, compared to only 5% of veterans without PTSD and 3% of healthy controls [19]. Moreover, the severity of sleep disturbance correlates with overall PTSD symptom severity [21, 22], even when accounting for the effects of potentially confounding variables such as alcohol use and psychiatric comorbidity [23]. Recent findings suggest that insomnia and sleep problems may actually play a mediating role between combat stressors and the eventual development of psychological symptoms among veterans of the war in Iraq [24]. Soldiers who develop insomnia in the months following a combat deployment are more likely to show symptoms of PTSD and depression when re-assessed at one year post-deployment [25], and sleep problems are better predictors of suicide among military personnel than measures of either depression or hopelessness [26]. Thus, sleep may be a leverage point for affecting recovery from PTSD.

Research on conditioned fear points to a critical role for sleep in the treatment of PTSD. Indeed, PTSD has been conceptualized as a disorder of fear conditioning, involving hyper-responsive fear reactions via sustained and exaggerated amygdala activation [27]. There is a large animal literature showing that quality sleep facilitates the extinction of conditioned fear [28-31]. Moreover, Pace-Schott and colleagues, recently demonstrated the same effect in humans [32], showing that after a person has been conditioned to fear a particular stimulus and then provided with multiple extinction trials, the extinction response only generalizes to other similar stimuli following a night of undisturbed sleep, but fails to generalize to other similar stimuli if post-learning sleep is prevented. These results suggest that extinction of conditioned fear is facilitated by sleep. Other research shows that sleep disruption amplifies the effects of anxiety on anticipatory brain functioning in the amygdala [33]. By extension, the potential for rapid recovery from PTSD may be hampered by the inability to obtain normal restorative sleep. In other words, the PTSD patient may be locked in a vicious circle whereby one of the major symptoms of the disorder may itself be preventing full recovery and leading to continuation or even exacerbation of symptoms. Therefore, effective treatment and recovery from PTSD may be crucially dependent upon, or

at the very least facilitated by, direct interventions aimed at improving the quality and duration of the individual's sleep.

**Light Therapy for Sleep Disruption & Implications for PTSD**

The most common approaches to sleep disturbance involve short-term prescription hypnotic medications, but these can have negative or even dangerous side effects [34]. Therefore, alternative, non-pharmacologic approaches are needed. While psychological or behavioral treatments may be helpful, many service members perceive stigma associated with traditional talk-therapy approaches. An alternative non-pharmacologic approach that shows promise for treating sleep disruption is bright light therapy (BLT), particularly within the short-wavelength (i.e., blue) spectrum [35-40]. Exposure to bright light at certain times of the day has been shown to reset the timing of the sleep and wake cycle [41], enhance subjective and objective measures of alertness [42, 43], increase prefrontal brain activation [44], and to improve overall sleep quality [43]. The effectiveness of BLT is potentially mediated by the entrainment of circadian cycles that regulate sleep and other homeostatic bodily functions [45-48]. Light exposure during the early morning phase-advances the timing of the circadian clock, while exposure during the late evening delays it [49].

Sleep-wake cycles and other endogenous circadian rhythms are regulated predominantly by the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN generates an endogenous rhythm of slightly over 24 hours [50]. This rhythm is entrained or synchronized by environmental cues, most prominently by light exposure cycles that correspond to transitions from night to day. This process is mediated by photoreceptive ganglion cells in the retina (i.e., melanopsin receptors), which appear to be specialized for relaying light/dark information, particularly within the blue wavelengths, to the SCN via the optic nerve [51]. This information is then sent from the SCN to the pineal gland, resulting in the synthesis and release of the hormone melatonin which signals the biological night and prepares the organism to sleep [40, 52, 53].

Initial studies on circadian effects of light showed that bright white light effectively suppresses melatonin and shifts both melatonin secretion and circadian rhythms [40, 54-56], resulting in shifts in sleep and wakefulness periods [57, 58]. More recently, it has been found that shorter wavelength light in the blue spectrum (446-477nm) is particularly effective at suppressing melatonin [59], and outperforms longer wavelength red light in terms of melatonin-suppression, circadian phase shifting, antidepressant effects, and increasing alertness [38, 39, 60-65]. Given that the melanopsin receptors appear to be primarily responsive to blue wavelength light [40], and that similar melatonin suppressing effects can be produced with significantly lower light intensities in the blue-wave spectrum, numerous studies have now begun to focus on using this wavelength for improving daytime alertness, subjective sleep quality [43], and phase advancing individuals with delayed sleep phase disorders [39, 48]. BLT is particularly effective for circadian rhythm sleep disorders [66-68], which involve a shift between the individual's sleep pattern and the pattern desired by social norms [69]. BLT also appears to improve the irregular sleep-wake patterns seen in Alzheimers' dementia, which involve periodic sleep disruption and nightly restlessness [69].

Bright light therapy has long been recognized as an extremely effective treatment for Seasonal Affective Disorder (SAD)[70]. Evidence for the efficacy BLT in SAD has accumulated over nearly three decades of research investigations, including a number of placebo-controlled trials. Some studies have

shown that either morning or evening BLT is superior to placebo, while others find greater evidence of morning light superiority [41]. More recently, BLT has also shown efficacy in nonseasonal Major Depression, producing net reductions in depression and anxiety symptoms in the range of 12-35% compared with dim light placebo conditions [71-73], and having potent synergistic effects when used as an adjunct to medication. BLT also appears to have a mild anxiolytic effect [74], and has recently been shown to be effective in reducing anxiety and depression in patients with seizure disorders [75]. In several studies, significant effects on mood were found within 1 week or less of BLT treatment initiation [73], with increasing benefits seen over several weeks. Recent evidence also suggests blue light wavelengths may be particularly effective for reducing depressive symptoms and features [61, 76, 77]. Importantly, the effectiveness of BLT in SAD and nonseasonal depression appears comparable to that of antidepressant medication [78], with the additional advantages of a low side effect profile [79] and quicker onset of action [73, 80]. Moreover, BLT provides a viable option for patients who resist, refuse, or do not respond to pharmacological treatment.

In summary, there is convincing evidence that BLT has therapeutic effects on anxiety and depression, and has strong effects on the normal circadian rhythm of alertness and sleep-wake cycles. These features are all central to the symptomatology of PTSD, yet no published studies have examined the effects of BLT on PTSD outcome. One unpublished pilot study at the University of South Carolina and Dorn VA Medical Center using 10000 Lux BLT (broad spectrum white light) for 45 minutes per day for two weeks in 9 PTSD patients. Compared with placebo, BLT was associated with greater percent improvement in scores on the Clinical Global Impression Scale and the Clinician Administered PTSD Scale (CAPS-5), with more than 20% improvement found for BLT, while less than 4% of placebo participants showed improvement (Youngstedt, Ginsberg, Kline, & Zielinski, unpublished data). These pilot results suggest that BLT may be an effective treatment for PTSD, though larger controlled studies are needed to provide confirmation and to examine the effects of BLT on particular PTSD symptoms. Based on the evidence summarized above, we propose that BLT in the blue wavelength spectrum will lead to significantly improved sleep, less depression, and less anxiety among combat veterans and other individuals with PTSD, and that these improvements will lead to a global improvement in overall PTSD severity relative to control groups with and without combat exposure. Based on recent evidence suggesting that the effect of light therapy on melatonin, sleep, and mood is mediated primarily via short wavelength blue light melanopsin receptors in the eye, we propose to compare an active treatment device with wavelengths peaking at 469 nm (blue) versus an identical placebo device fitted with amber colored diodes (see Figure 1). Thus, this study will be the first, large placebo controlled study examining the effectiveness and neuroimaging correlates of BLT in PTSD.

Figure 1. Blue Light (BL) and amber placebo light (PL) devices

## A. 3. Preliminary Data

Our group has a long history of using functional neuroimaging techniques to study PTSD. Using a paradigm known as the Masked Affect Task (MAT), our lab reported that combat exposed veterans with PTSD showed exaggerated amygdala responses to fear-related facial stimuli perceived below the threshold of conscious awareness when compared to combat exposed veterans without PTSD [27]. We have now collected pilot data on 65 participants, including 14 individuals with PTSD, 14 individuals with panic disorder, and 15 participants with simple phobias using this same paradigm. As evident in the figure, compared to healthy controls or other anxiety groups viewing masked fearful faces, patients with PTSD showed greater activation within the amygdala, one of the primary brain structures involved in the assessment of threat. PTSD subjects also showed reduced activation within the ventromedial prefrontal cortex relative to healthy controls. This suggests that the hyperarousal and exaggerated startle reflexes associated with PTSD may be partly the result of abnormal responses in the amygdala. At present, no neuroimaging studies have yet examined the role of sleep in this process. However, recent data from Yoo and colleagues suggests that loss of normal sleep is associated with reduced functional connectivity between the VMPFC and the amygdala, suggesting that sleep loss may reduce the ability of the prefrontal cortex to regulate the emotional responses of the amygdala [81]. We have also conducted an fMRI study showing that reduced sleep is associated with altered functional connectivity between the VMPFC and amygdala, and the strength of such connectivity is directly related to the severity of symptoms of anxiety, depression, and reduced emotional functioning [82]. Our preliminary studies of cognitive functioning during sleep deprivation support the prefrontal-emotional dysregulation model [83-92]. Notably, the anterior cingulate cortex (ACC) and hippocampus demonstrate abnormalities in neurometabolites such as n-acetylaspartate (NAA), a putative marker of neuronal integrity, in patients with PTSD (Karl and Werner, 2010).[83-92] Because sleep disruption is one of the most common symptoms of PTSD, the associated reduction in sleep quantity and quality may serve to exacerbate the difficulties these patients have regulating emotions, serving to develop a vicious circle of hyperarousal, decreased sleep, and emotional dysregulation.

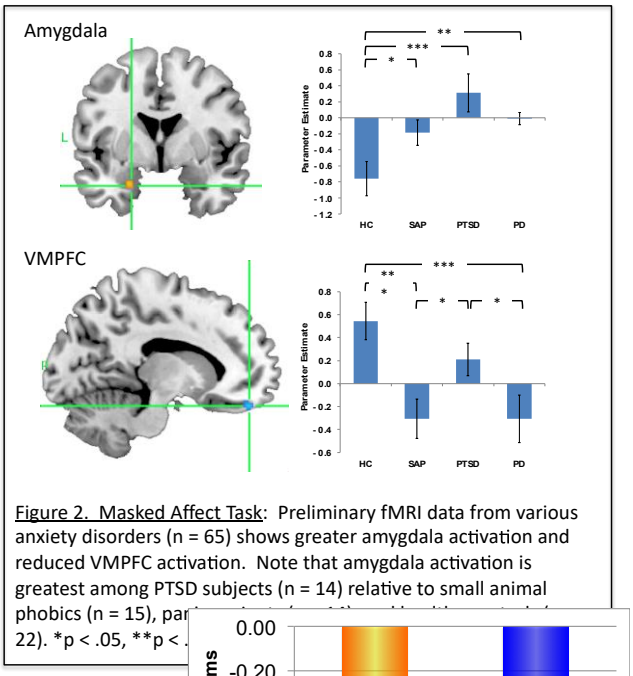



Figure 2. Masked Affect Task: Preliminary fMRI data from various anxiety disorders (n = 65) shows greater amygdala activation and reduced VMPFC activation. Note that amygdala activation is greatest among PTSD subjects (n = 14) relative to small animal phobics (n = 15), par… 22). *p < .05, **p < .

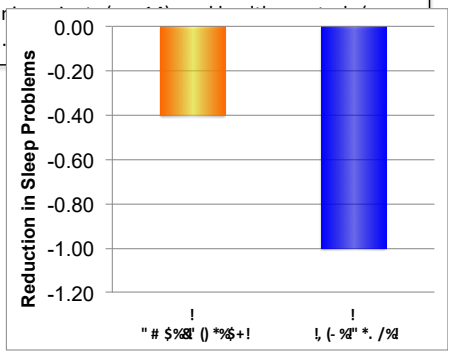



Figure 3. Scores on the Pittsburgh Sleep Quality Index (PSQI) showed greater reduction in sleep problems following 6-weeks of treatment with the active blue light (n = 7) treatment versus amber light (n = 5) placebo.

The proposed investigation will examine changes in sleepiness, neuropsychological functioning, symptom severity, as well as brain functioning and neurochemistry before and after a 6-week treatment period with BLT. To this end, we have collected pilot data showing that 6-weeks of daily morning exposure to BL improves sleep, cognitive performance, brain functioning, and underlying axonal integrity in concussion patients compared to equivalent exposure to amber placebo light (PL). Our preliminary findings in a small pilot sample of 12 participants (BL $n = 7$; PL $n = 5$) suggest that BL treatment may be effective at improving sleep and accelerating recovery. While fully cognizant of the fact that these data are preliminary, we present the following findings to provide support for the feasibility of the study design and demonstrate our capacity to collect, process, and analyze relevant data.

Subjective Symptom Improvement. Figure 3 depicts subjective sleep quality, as measured with the Pittsburgh Sleep Quality Index (PSQI) pre- and post-intervention by group. While there was no change in the Amber Light Placebo group between pre- and post-treatment assessment, by trend, PSQI scores were reduced in the Blue Light group ($p = .07$), suggesting improvement. Of note, in contrast to the Amber Light group, for which sleep quality remained clinically abnormal (i.e., PSQI $\geq 5$), the post-treatment PSQI mean reflected good sleep quality for the Blue Light group (i.e., PSQI $< 5$). These findings suggest that BL was more effective in improving subjective sleep quality than the PL treatment.

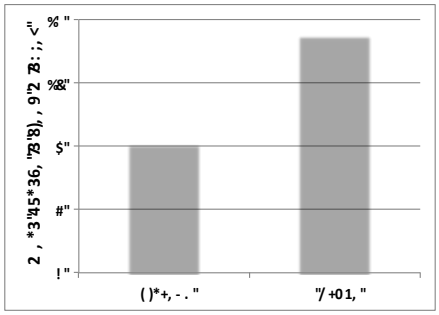


Figure 4. Compared to the placebo light (n = 5), the active blue light (n = 7) treatment resulted in a greater improvement in the number of minutes of sleep (via actigraphy) after 6-weeks.

Actigraphic Sleep: Participants were monitored using wrist actigraphy for the duration of the study (1-week before treatment and throughout the treatment period). We compared actigraphic sleep between the baseline week and the final week of the study. After removal of one outlier ($z > 2.5$), participants in the BL group (n = 6) showed an increase in the minutes of sleep objectively measured by wrist actigraphy compared to the PL group (n = 5) (see Figure 4). On the whole, those in the amber placebo group improved by only 8.1 minutes of additional sleep per night, whereas those in the active BL group gained nearly twice as many minutes of sleep per night on average (i.e., 15.0 minutes). Findings suggest that BL was associated with greater improvement in objective sleep quantity than PL.

Objective Sleepiness/Alertness. On an objective measure of sleepiness, participants were monitored with electroencephalography (EEG) while attempting to sleep for 20 minutes in a quiet, darkened room. Figure 5 shows daytime sleepiness, as measured with the Multiple Sleep Latency Test (MSLT) at 11:50am, 1:50pm and 3:50pm pre- and post-intervention by group. There was a significant change in sleep onset latency between pre- and post-treatment by group (p=.02), with the BL group taking longer to fall asleep in sleep-conducive

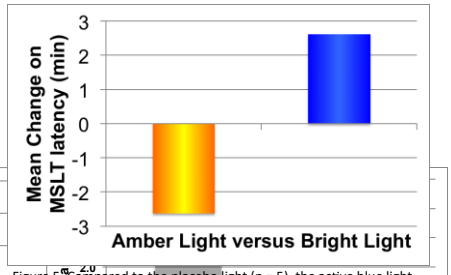



Figure 5. Compared to the placebo light (n = 5), the active blue light (n = 7) treatment resulted in a greater latency to fall asleep during the daytime MSLT after 6-weeks.

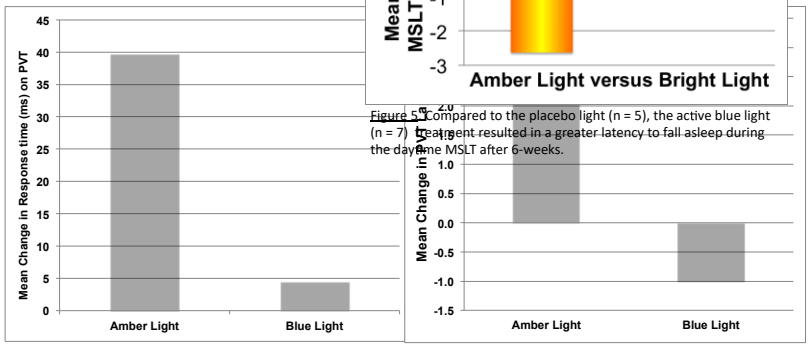



Figure 6. Compared to the placebo light (n = 5), 6-weeks of active blue light (n = 7) treatment was associated with significantly faster response time and fewer attentional lapses on the psychomotor vigilance test (PVT) .

conditions than the PL group. This indicates greater enhancement of alertness in the BL group following treatment compared to the PL condition.

Psychomotor Vigilance Test (PVT): The PVT is a 10-minute computerized measure of sustained attention and psychomotor vigilance that has been shown to be exquisitely sensitive to sleep deprivation. The PVT currently serves as the "gold standard" for assessing degradation in alertness and vigilance following sleep loss. Figure 6 depicts mean change in response time for correct trials for one of three PVT administrations. There was a significant group difference, with the PL group showing slower mean response times between pre- and post-treatment assessment. In addition, there was a significant group difference on PVT attentional lapses (i.e., response time > 500ms) between pre- and post-treatment assessment, with more attentional lapses in the PL than the BL group. This preliminary finding is presented in Figure 6. Together, these findings suggest that BL was associated with greater post-treatment alertness and vigilance compared to PL treatment.

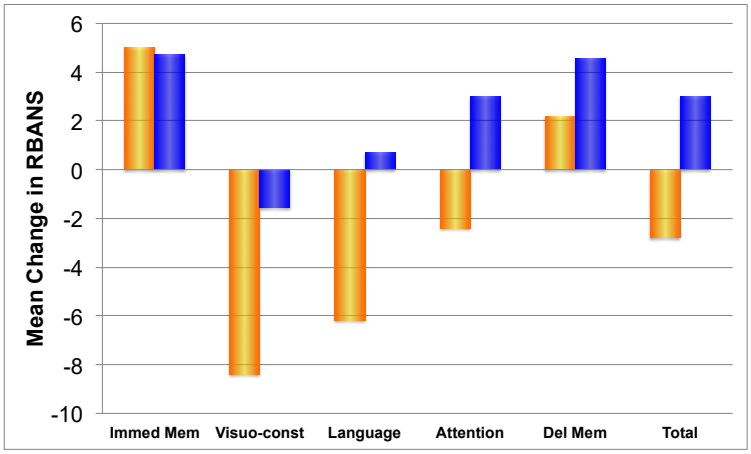



Figure 7. Six-weeks of active blue light (n = 7) treatment resulted in improvements across a number of neurocognitive domains on the Repeatable Battery for Neuropsychological Status relative to the amber light placebo group (n = 5).

d) Neuropsychological Performance Changes: Figure 7 depicts the change in cognitive functioning, as measured with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) between pre- and post-intervention assessment by group. Of note, the BL group showed not only a marked increase in Total test performance, but also a significant improvement on the Attention and Delayed Memory subscales. In contrast, in the PL group, cognitive performance declined in three of five subscales (i.e., Visuo-constructional, Language, and Attention) and Total test performance, but not for the BL group. Importantly, the difference in change between pre- and post-treatment group proved significant or marginally significant for the Visuo-constructional subscale ($p = .06$), Language subscale ($p = .03$) and Total test performance ($p = .04$) between PL and BL groups. This suggests that sleep improvement in the BL group was paralleled by improvements in cognitive functioning, while such findings were not observed for the PL group.

e) Task-Related Functional MRI: Figure 8 shows functional brain activation for 14 subjects (7 BL, 7 PL) during the n-back working memory task and the multi-source interference task (MSIT) that subjects performed in the MRI scanner pre-and post-treatment (blue = BL > PL; amber = PL > BL). Specifically, the figure shows increases in medial prefrontal cortex activation between pre- and post-assessment for the most difficult task condition (i.e., 2-back) in the blue light condition. Blue light also resulted in increased activation within the thalamus and dorsolateral prefrontal cortex (DLPFC) on the MSIT following six weeks of BL compared to PL treatment.

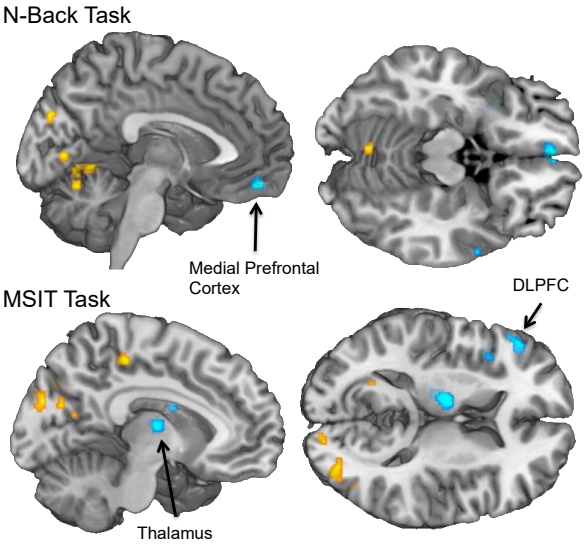



Figure 8. Functional MRI Findings: The blue light (n =7) condition showed significantly greater increases in functional activation during the N-Back task and MSIT task compared to the amber light placebo group (n = 7) within the medial prefrontal cortex, dorsolateral prefrontal cortex (DLPFC) and thalamus. $P < .005$, $k \geq 10$.

f) Resting State Functional Connectivity: Participants also completed a 6-minute resting state functional connectivity (rsFC) MRI scan which allows the identification of intrinsic patterns of temporal correlation among various regions within the brain. Based on our prior published work in healthy controls showing that minor fluctuations in nocturnal sleep, even as little as an hour or two, can have significant effects on rsFC [93], we hypothesized that improvement in sleep in subjects with mTBI would also be associated with improved functional connectivity within behavioral control and memory regions of the brain. As shown in Figure 9, we found that six weeks of BL treatment was associated with significantly ($p < .05$) greater inter-regional functional connectivity for the prefrontal cortex and hippocampus with other cortical regions in this very preliminary sample (7 BL, 5 PL). In contrast, those receiving PL showed greater functional connectivity of the insula with other posterior cortical regions, suggesting greater emotional/visceral sensory processing in the PL group. Overall, BL treatment was associated with increased functional connectivity between memory and attention processing regions.

g) Diffusion Tensor Imaging: Participants also completed a diffusion tensor imaging (DTI) scan. These data were preprocessed in FSL (i.e., eddy current correction, reconstruction of diffusion tensors, estimation of diffusion parameters, registration to anatomical image and standard space). For demonstration of feasibility, preliminary data (8 BL, 8 PL) have been analyzed in FSL, although the sample is currently too small to conduct statistical parametric analyses. Pre- to post-treatment increases in fractional anisotropy (FA) were seen in key regions implicated in PTSD, including the rostral and subgenual anterior cingulate regions for those receiving BL but not for the amber PL group. Greater FA is generally considered to signify better white matter health. These preliminary data raise the intriguing possibility that improvement in sleep during the six-week treatment period with BL may lead to an accelerated re-myelination process relative to those in the PL group. We believe further research into this intriguing and potentially important possibility and its relation to PTSD symptom change is warranted.

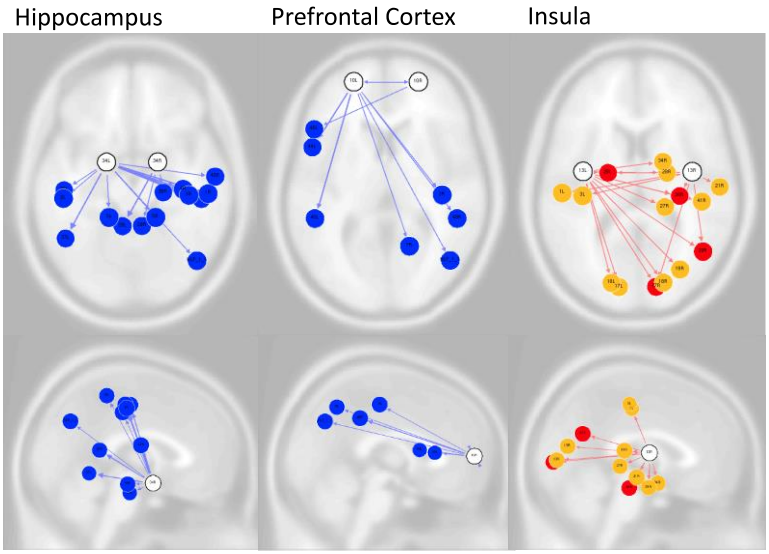



Figure 9. The blue light (n = 7) condition showed significantly greater increases in resting state functional connectivity between the hippocampus and other posterior sensory regions, and increased functional connectivity between the prefrontal cortex and a number of other higher order association regions compared to the amber light placebo group (n = 5), which showed greater post-treatment functional connectivity of the visceral and bodily awareness regions.

Summary. Our preliminary findings clearly demonstrate that the methods proposed herein are feasible and that our team can effectively collect, process, and analyze the data, thereby accomplishing the aims of the study. We have now implemented this paradigm with over 30 brain injured participants, and all were able to complete the study procedures without difficulty. Furthermore, the case findings we highlight also provide limited but compelling evidence that the BLT program was associated with improvement in symptoms, neuropsychological status, and neurocircuitry changes in the hypothesized direction. Thus, the preliminary data suggest that the protocol we propose is feasible and shows significant promise for improving sleep and brain functioning.

## B. SPECIFIC AIMS/HYPOTHESES

Project Overview. Combat veterans and other individuals with PTSD will complete two comprehensive sessions including neurobehavioral assessments, repeated polysomnographic sleep studies, and neuroimaging sessions (functional MRI, structural MRI, and proton spectroscopy) separated by 6 weeks of actigraphically monitored at-home treatment. During the intervening 6 weeks, participants will be randomly assigned to receive 30 minutes of daily morning blue light therapy (BL) or an amber light placebo treatment (PL). Sleep quality and quantity will be measured using subjective reports, objective actigraph readings, and polysomnography. Globally, we hypothesize BL will improve sleep quality and quantity relative to PL, and these improvements will be associated with improvements in neurocognitive

function, alterations in proton metabolites in the limbic system and medial prefrontal cortex, and reduced PTSD symptom severity at follow-up assessment. The following are the Specific Aims and Hypotheses:

**AIM 1**: Evidence suggests that morning bright light therapy suppresses daytime melatonin and leads to an entrainment of the circadian rhythm that modulates daytime alertness and nighttime sleep. The first objective will be to assess the validity of this effect in PTSD patients.

**Hypothesis 1: Six weeks of BLT will improve sleep relative to PL among PTSD subjects.**

**1a**: Six weeks of morning blue light therapy (BLT) will improve objective and subjective measures of sleep duration and quality as measured by actigraphy, sleep logs, sleep scales, and polysomnography relative to an amber light placebo therapy (PL) condition.

**AIM 2**: If light therapy is successful in entraining the circadian rhythm and improving nighttime sleep in patients with PTSD, this should be associated with improvement in symptoms and cognitive functioning, as sleep has been shown to be critical in the process of extinguishing conditioned fears. Therefore, the second Aim is to evaluate the association between changes in sleep patterns and improvement in symptom expression, emotional wellbeing, and cognitive functioning in patients with PTSD. However, even if Aim 1 is not successful, the present study will provide important cross-sectional data regarding the relationship between measured sleep, cognitive functioning, and fear extinction in individuals with PTSD.

**Hypothesis 2: BL will improve cognitive functioning, symptoms of PTSD, and generalization of fear extinction relative to PL.**

**2a**: Six weeks of BL will improve measures of neurocognitive (i.e., memory and executive functions) and mood functioning relative to PL.

**2b**: The PTSD group receiving six weeks of BL will show significant reduction in self-reported symptom scores on the PTSD symptom checklist and CAPS, lower emotional distress on clinical measures, and greater *generalization of conditioned fear extinction* relative to the PTSD group receiving PL.

**AIM 3**: At present, there are no known studies that have examined the neurobiological correlates of symptom improvement in patients with PTSD following light exposure therapy. The present study aims to provide clear evidence of functional and neurochemical changes that are associated with changes in sleep, cognition, and PTSD symptoms from pre- to post-treatment. Even if Aim 1 is not supported, the obtained cross sectional data will provide critical insights regarding the association between sleep, neurometabolites, and brain function within patients with PTSD. This correlational information is currently lacking for PTSD and will fill an important knowledge gap regardless of whether the light therapy is successful.

**Hypothesis 3: Six weeks of BL will produce reliable changes in brain activation and neurochemistry relative to PL, particularly for PTSD subjects.**

**3a**: Relative to PL, six weeks of BL will lead to significantly increased ventromedial prefrontal activation and reduced amygdala activation during the backward masked affect fMRI task.

**3b**: Relative to PL, six weeks of BL will lead to significantly greater negative functional connectivity between the ventromedial prefrontal cortex and amygdala during resting state fMRI.

**3c**: Relative to PL, six weeks of BL will be associated with increased activation of the VMPFC, and reduced activation within the amygdala and dorso-medial prefrontal cortex during the extinction recall scan.

**3d**: Relative to PL, six weeks of BL will be associated with increased levels of GABA and reduced glutamate in the amygdala-hippocampal complex and anterior cingulate gyrus as measured by proton magnetic resonance spectroscopy (1H MRS).

**3e**: Relative to PL, six weeks of BL will produce increased levels of N-acetyl-aspartate (NAA), choline (Cho), and reduced phosphocreatine (Cr) within the amygdala-hippocampal complex and anterior cingulate gyrus.

**AIM 4**: The fourth Aim is to demonstrate whether changes in subjective and objective measures of sleep are associated with changes in symptom severity, cognitive functioning, brain activation, and neurochemistry. Regardless of the success of the light therapy approach outcome in Aim 1, the available data will provide some of the first longitudinal data examining changes in sleep patterns over time in individuals with PTSD and their correlation with these other metrics. Thus, useful data will be acquired even if the primary hypothesis of Aim 1 is not supported.

**Hypothesis 4: Improvements in sleep noted in Hypothesis 1, will be linearly correlated with improvements in cognitive and symptom functioning in Hypothesis 2 and structural and functional brain changes in Hypothesis 3.**

**4a**: Changes in sleep parameters identified in Hypothesis 1 will correlate with improvements in memory, executive functioning, and neuropsychological performance on neurocognitive measures described in Hypothesis 2.

**4b**: Changes in sleep parameters identified in Hypothesis 1 will correlate with changes in neurochemistry as outlined in Hypothesis 3d and 3e above.

## 2) Lay Summary (approximately 400 words)

Sleep disturbance is nearly ubiquitous among individuals suffering from PTSD and is a major problem among service members returning from combat deployments. Recent evidence suggests that adequate restorative sleep may a crucial component in the ability to generalize fear extinction learning, and ultimately may be a key feature in the process of recovery from PTSD. The proposed study aims to test a novel, inexpensive, and easy to use non-pharmacologic approach to improving sleep among service members and other individuals with PTSD. Our approach is based on recent scientific discoveries regarding the role of the photosensitive retinal ganglion cell system in regulating sleep-wake patterns. Moreover, our protocol employs a novel, non-pharmacologic intervention for influencing this system to regulate sleep and cognition. Primary outcome measures will include not only PTSD symptom improvement but also include cutting-edge neuroimaging of brain structure, function, connectivity, and neurochemistry changes. The proposal is firmly **grounded in the emerging scientific literature** regarding sleep, light exposure, brain function, anxiety, and resilience. Prior evidence suggests that blue light therapy is effective for improving mood and fatigue, and our pilot data further suggest that this treatment may be effective for improving daytime sleepiness and brain functioning in brain injured individuals. Thus, this intervention, in our own research and in the work of others, has been shown to affect critical sleep regulatory systems. Improving sleep may be a vital component of recovery in these service members. Our approach would directly address this issue. Our preliminary data have shown that this approach is extremely well tolerated and is effective for improving sleep, mood, cognitive performance, and brain function among individuals with brain injuries. The protocol is actually less

burdensome than it appears, as over 30 participants have already successfully completed this same protocol in our pilot study of mild traumatic brain injury without any complaints or discontinuations due to excessive burden. Finally, the **potential impact** of this study is high because of the capability of transitioning the research to direct clinical application almost immediately. If the BL treatment is demonstrated as effective, this approach would be readily available for nearly immediate large-scale implementation, as the devices have been widely used for years in other contexts, are already safety tested, and commercially available from several manufacturers for a very low cost. Thus, the impact of this research on treating PTSD would be high and immediate.

## 3) Setting of the Human Research

This study requires three visits including an initial assessment and two testing/scanning sessions separated by six-weeks of daily light exposure treatment at home.

For the initial assessment and the baseline testing session, subjects will be seen at the Lab of Dr. Killgore in the University of Arizona Department of Psychiatry. There, subjects will complete personality assessments, a comprehensive cognitive assessment battery, and several tests of motor functioning.

Magnetic Resonance Imaging (MRI) Procedures: The data collection will occur at the research-dedicated University of Arizona scanner facility that houses a new 3 Tesla magnet (see Equipment for description). For functional neuroimaging, audio and visual stimulus presentation equipment is available through the Resonance Technologies headphone/goggle system or high-definition MRI-compatible LCD-display (viewed through a mirror in the head cage). An fMRI compatible EEG system including caps, cabling, and pre-amplifier is integrated with this space (see Equipment for description). Scanner data are transferred securely to a RAID storage system for subsequent transfer to PI laboratories. Offline analysis will take place in the Laboratory of PI Dr. Killgore.

In January 2013, the University of Arizona purchased a Siemens Magnetom TIM Skyra 3T that is capable of high-resolution imaging capabilities. This whole-body 3.0T device will be configured with 48 receiver channels and up to 204 integrated coil elements. It is capable of integrated parallel acquisition techniques and provides higher signal to noise in the parallel imaging mode than its predecessor, the Trio. The maximum acceleration factor using parallel imaging is 16 using either mSENSE or GRAPPA, and 3D scanning can be accelerated in two directions (maximum acceleration factor of 4 in second direction). The gradients of the Skyra have a maximum amplitude of 45 mT/m and a maximum slew rate of 200 T $Tm^{-1}s^{-1}$, yielding a minimum rise time of 225µs. The vector gradient performance (vector summation of all three gradient axes) results in a maximum effective amplitude of 78 mT/m and a maximal effective slew rate of 346 $Tm^{-1}s^{-1}$. All three gradient coils are force-compensated to reduce vibration and deliver superior eddy current performance. The water cooled gradient amplifier has a maximum amplitude potential of 2,250 volts and a maximum current output of 750 amps. The instrument has a minimum slice thickness (in two dimensions) of 0.1 mm and a minimum partition thickness (in three dimensions) of 0.05 mm. The instrument produces high sensitivity, with main field, or B0, homogeneity of 1.4 ppm VRMS for a 40 cm diameter spherical volume. Single shot EPI sequences for measuring diffusion-weighted data sets with up to 256 directions of diffusion weighting are also a part of this instrument's capability. It provides

diffusion tensor imaging and parametric maps derived from fractional anisotropy calculated in real time, automatically. Additional sequence options include Arterial Spin Labeling, and susceptibility weighted imaging (SWI) with both fully supported with parametric and phase map reconstructions.

All structural and functional MRI studies will be conducted in concert with the University of Arizona Translational Bioimaing Resource. Subjects in this study will be studied in a scanner that has a field strength of 3 Tesla. This field strength has been approved by the FDA for routine clinical use. The three instruments are maintained by GE service engineers and currently meet or exceed manufacturer's specifications on performance. For functional neuroimaging, audio and visual stimulus presentation equipment is available through the Resonance Technologies headphone/goggle system.

A research area, Room 1564 (400 square feet), located immediately adjacent to the 3.0 Tesla scanner, is equipped with 3 PC/Linux workstations and sgi O2 for data transfer and storage, image processing, and data manipulation. All workstations are networked through a central hub and are protected against external tampering using firewalls within the UAMC computer network.

Functional MRI is mostly done in MR3, a General Electric 3.0T HD Signa Excite scanner. It is equipped with Optimized ACGD Gradients (40mT/m, 150 mT/m/ms slew rate running 12x software). It is a 55cm diameter long bore magnet. This instrument is equipped with a head coil, 8 channel HR brain array, a phased array neurovascular coil, 8 channel phased array spine coil, extremity coils (knee and wrist) and a torso coil. MR3 has multinuclear spectroscopy capability and high order shims.

## 4) Resources available to conduct the Human Research

Dr. Killgore's effort is 100% devoted to research; he does not have clinical or teaching time mandated as part of his FTE. He funds several Research Technicians and Research Assistants and one lab manager.

The Department of Psychiatry has staff devoted to research administration, including an upper level administrator and a regulatory coordinator. All have experience with IRB/regulatory matters and grants administration. Business office staff is knowledgeable in grants finance and accounting, and federal work-study students devoted to research are available for data entry and other administrative support.

Dr. Killgore's Lab includes computing equipment such as backup drives and external hard drives, backup surge protectors, intercom system, neuroimaging workstations with 6 TB minimum storage each; Actiwatch sleep monitors watches, docks, and software analysis programs; Coulbourne Fear Conditioning Suite, FaceRead + Observer XT System, sleep profiler ambulatory EEG monitoring systems, and other software including EPrime, MatLab, SPSS, and Adobe Captivate.

The Department of Psychiatry provides personal computer resources for word processing, email transmission, internet access, and simple statistical analysis for staff, in addition to laser printers, fax machines, scanners and photocopy machines. In addition to these resources, the University of Arizona maintains full computer and data analytic processing components available to all university faculty on a fiber-optic network system, with automatic daily backup available on a secure server. There is full time computer support in the Department of Psychiatry for these resources.

This project may use non-FDA-approved devices that are approved for use on the Translational Bioimaging Resource (TBIR) MRI scanner through IRB protocol 1911166043, "Translational

Bioimaging Resource Umbrella MRI Protocol." TBIR, a UA Core Facility (https://ua.ilab.agilent.com/landing/3645#/about), is housed within the UA Biosciences Research Laboratory (BSRL) building.

All study personnel will have up to date CITI training and study protocol training from the PI or PI designee.

## 5) Study Population

The target population is combat-exposed military personnel and other non-military individuals who meet diagnostic criteria for PTSD. Participants in the study will include active duty or recently discharged combat-exposed military personnel from Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) meeting DSM-V diagnostic criteria for PTSD, in addition to some individuals from the general population who meet DSM-V diagnostic criteria for PTSD to achieve a total sample size of 90 participants, which we anticipate will require enrolling up to 108 individuals to account for attrition. An age range of 18-50 years has been selected to minimize possible developmental and degenerative effects that could be expected in younger and older subjects and to encompass the age range of the majority of military personnel. Participants will be recruited from several sources. Active duty participants will be recruited according to the guidelines specified by the CDMRP upon award receipt. The PI, a U.S. Army Reserve Research Psychologist (Lieutenant Colonel), already has a number of established relationships and collaborations with leaders in the Army Medical Department (AMEDD), the Pentagon, several major medical treatment facilities (MTFs), and all three of the Army's primary research laboratories, including the Walter Reed Army Institute of Research (WRAIR), the U.S. Army Institute of Environmental Medicine (USARIEM), and the U.S. Army Aeromedical Research Laboratory (USAARL). It is anticipated that potential recruitment of active duty, Reserve, and National Guard participants will be effectively facilitated according to the guidelines specified by the CDMRP. Participants will be recruited primarily from the Tucson area via IRB approved internet, newspaper, and radio advertisements, and contact with individual units. Facebook advertisements and flyers will also be utilized to recruit subjects, as described in greater detail below.

**Inclusion Criteria:**

1) age 18-50 years;
2) right handedness or right-hand dominance as assessed by the Edinburgh Handedness Inventory (EHS) (necessary to avoid mixed lateralization on brain imaging);
3) SCID diagnosis consistent with PTSD

**Exclusion Criteria:**

1) History of head injury with loss of consciousness for greater than 30 minutes, or post-traumatic amnesia for >24 hours, or major neurological illness (e.g. epilepsy, multiple sclerosis/MS);
2) Chronic medical (e.g. heart conditions, cystic fibrosis, diabetes, cancer, HIV/AIDS, HEP C, thyroid problems, high blood sugar) or psychiatric (e.g. bipolar disorder/manic or hypomanic episodes, personality disorders, schizophrenia/other psychotic disorders, severe OCD or ADHD) conditions that would confound interpretation of results;

3) Left-handedness or left-hand dominance if ambidextrous (could affect brain lateralization and add error variance to scanning);
4) Abnormal visual acuity that cannot be corrected by contact lenses (necessary to see stimuli in the magnetic environment of the scanner);
5) IQ estimate less than 70;
6) Metal within the body, pregnancy, or other contraindication for MRI procedures;
7) Ongoing trauma (e.g. currently being in an abusive relationship) or non-qualifying trauma (e.g. index trauma emotional/verbal abuse, children being taken away by the CPS, divorce, natural deaths by age or illness);
8) Previous formal treatment with light therapy;
9) History of light-induced migraine or epilepsy; medical complications that could elevate the risk of discomfort associated with light-therapy;
10) Use of medications that could affect functional neuroimaging results (e.g., beta-blockers, mood stabilizers, atypical antipsychotics, benzodiazepines, hypertension medication, chemotherapy, photosensitive medications etc.). Patients currently taking other psychotropic medications (i.e., "treatment as usual") must be stabilized for at least 4-weeks prior to participation. Although participants will not be excluded from participation, detailed history and dosages will be documented and examined as appropriate in statistical analyses.
11) Current suicidal intent based on an assessment conducted by a licensed clinical psychologist;
12) Currently taking or anticipating the need to take sleep-inducing medications (e.g., zolpidem) or supplements that have known effects on sleep (e.g., melatonin) during the course of the study.
    a. Patients currently taking other psychotropic medications (i.e., "treatment as usual") must be stabilized for at least 4-weeks prior to participation. Although participants will not be excluded from participation, detailed history and dosages will be documented and examined as appropriate in statistical analyses. Due to the broad range of sleeping disturbances that are observed with PTSD and the likely difficulty in recruiting sufficient numbers of participants, we will not be excluding any particular sleep disorder, but will collect data regarding these sleep related problems so that it may be possible to statistically control for the effect of the BLT treatment on different forms of sleep problems;
13) Index trauma occurring before the participant is 18 years of age;
14) Index trauma occurring 10 years or longer prior to participation in the study;
15) WRAT4 reading test score indicative of less than a 6$^{th}$ grade level of reading comprehension;
16) Drug use: Marijuana use not exclusionary. Past drug dependence (other than marijuana) not exclusionary if individuals have sustained remission (no drug use in the past 12 months).

## 6) Recruitment Methods and Consenting Process

Please note: *The Human Research Protection Office (HRPO) with US Army Medical Research and Materiel Command must approve any major amendment to this study prior to its implementation. Therefore, implementation of any amendment which requires HRPO approval, including use of revised consents, will not begin until HRPO approval is received.*

Participants will be recruited from several sources. Active duty participants will be recruited according to the guidelines specified by the Department of Defense's (DoD's) Congressionally Directed Medical Research Programs (CDMRP) upon award receipt. The PI, a U.S. Army Reserve Research Psychologist (Lieutenant Colonel), already has a number of established relationships and collaborations with leaders in the Army Medical Department (AMEDD), the Pentagon, several major medical treatment facilities (MTFs), and all three of the Army's primary research laboratories, including the Walter Reed Army Institute of Research (WRAIR), the U.S. Army Institute of Environmental Medicine (USARIEM), and the U.S. Army Aeromedical Research Laboratory (USAARL). It is anticipated that recruitment of active duty, Reserve, and National Guard participants will be effectively facilitated and will proceed according to the guidelines specified by the CDMRP. Civilian veterans, Reserve Soldiers, National Guard Soldiers, and nonmilitary combat-exposed civilians will also be recruited primarily from the local Tucson and surrounding area, from clinical programs within the Department of Psychiatry, and local events and advertisements on the web (including our own websites, appropriate sections of community websites and forums [e.g. Craigslist], Facebook or other social media, and reputable clinical trial referral websites [e.g. StudyKik], and similar websites). Our lab will post IRB approved advertising text on similarly themed Facebook groups, which allow for outside posts of this nature. We will adhere to any page specific posting requirements as well as Facebook Terms of Service for appropriate behavior. We may also utilize print, radio advertisements, TV, and UAHS and College of Medicine hallway and lobby monitors and flyers on campus, as well as UA list serves such as 3D memos etc. (ad text will be IRB approved), Residence Halls, and other UA buildings (with the appropriate recruitment site authorization obtained prior).

We will make approved screening surveys (e.g., *Recruitment Survey.pdf*) available on UA departmental (e.g., Department of Psychiatry, Department of Psychology) or other UA-affiliated websites (e.g., UAHS Clinical Research Studies website), as well as other online media appropriate for research advertising such as clinical trial referral websites, survey websites (e.g., Qualtrics, Survey Monkey), research data management (e.g., REDCap), and crowdsourcing websites (e.g., Amazon Mechanical Turk [MTurk]). Crowd-sourcing platforms facilitate recruitment of and payment to individuals for their participation in online surveys. When disseminated via this method, our surveys will be restricted to participants who live in Arizona and will be securely hosted in Qualtrics, REDCap, or other such reputable survey-host.

In addition, UA Clinics (i.e. CAPS, Campus Health, etc.), and outside clinics/businesses in the greater Tucson area will be utilized to refer patients to the study. Treating physicians at clinics may be informed of the study and the inclusion/exclusion criteria, if they feel they have a patient who qualifies they will provide the patient with a study recruitment flyer and the patient will contact our office if they are interested. Recruitment site authorization will be obtained prior to recruitment occurring at any site; this documentation will be kept within our research files. A trained research assistant will initially screen individuals who respond to these advertisements via telephone interview. Individuals meeting basic eligibility requirements will be scheduled for an intake visit. Participants whose intake visits are scheduled more than six weeks after the date of the initial phone screen will be given a shortened follow-up phone screen prior to the intake visit, in order to ensure that no changes have taken place which may affect their eligibility. Recruitment and advertisement materials will include brief descriptions of the

purpose of the study, the general procedures of the study, important inclusion and exclusion criteria, the amount of compensation, and the phone number or email address to contact if interested.

To encourage full participation and minimal subject discontinuation, subject compensation will follow the prorated schedule as seen in Section 12.

Subjects will be made aware via the Informed Consent Form that if they are active duty military personnel, they are not eligible to receive compensation for time spent completing assessments unless they are on official military leave status in accordance with Title 24 United States Code 30. Therefore, any active duty military personnel not on leave status will not receive compensation for time spent completing assessments as attested to by all subjects as part of the informed consent process. We will request that subjects attest to their understanding of this by initialing the following:

*Participants who are active duty cannot be compensated for any of the research activities while they are "on-duty". It will be the volunteer's responsibility to ensure they have taken leave and obtained the right permissions, if required, in order to receive compensation for this study.*

_____ ***Please initial to indicate you acknowledge this requirement.***

**If you are active duty military personnel**, you are not eligible to receive compensation for time spent completing assessments while you are "on duty." In accordance with Title 24 United States Code 30, active duty military personnel must be on leave status during each of the three assessment sessions in order to be compensated. If you are on active duty, **it is your responsibility** to ensure that you have completed the appropriate paperwork for leave and obtained the necessary permissions to allow you to participate in this study. If you are on leave status, you will be compensated for the 3 assessment sessions according to the schedule listed above.

**Screening Procedures:**

Potential subjects will be screened over the phone by a clinically trained research assistant to verify that subjects meet all inclusion criteria and do not meet any of the exclusionary criteria. Information collected during screening will not be used as a part of the research data. Subjects who meet basic eligibility requirements will be scheduled for an intake visit. Informed consent will be obtained prior to initiating any further screening procedures. After informed consent has been determined, a supervised Research Technician who has been trained and meets predetermined qualifications to administer a Structured Clinical Interview by doctoral level clinical psychologists with training and experience administering these instruments will conduct a structured clinical interview to screen for any psychiatric diagnoses. Once eligibility for the study has been confirmed or rejected, the subject will be placed into the appropriate experimental group, or excluded from the study if any information yielded from this visit is consistent with the exclusionary criteria.

**Informed Consent Process:**

- Either the PI or a trained research assistant will be responsible for explaining the study, answering questions, and obtaining written informed consent from participants.

- Initial description of the study will be provided during the telephone screening process. The actual consent process will occur during the in-person intake visit. The consent process is the first part of the visit, and will take place in a private office. The participant will have the opportunity to read the consent form, and each section will be explained in detail by the research assistant. The participant will have a chance to ask questions and have them answered fully before making a decision to participate. All volunteers will receive a copy of the signed consent form once they and the study staff member obtaining consent have signed the form.
- Only adult participants with normal intellectual capacity (IQ≥70) will be included in the study. Any evidence of altered mental status or capacity, due to substances, medications, cognitive status, or injury will result in discontinuation of the consent process.
- Participants will be consented in a private office, but may be accompanied by anyone of their choosing. There will be no time pressure and potential volunteers may discuss possible participation with anyone and may choose to suspend the consent process and return on another occasion, as long as they have not been disqualified or the study has terminated.
- Participants will be monitored closely by study staff and queried about continued participation after completion of each major component of the study (i.e., neurocognitive testing, functional imaging, sleep study, etc.) and if there are visible signs that the participant may be having difficulty tolerating the procedures.
- We will not enroll subjects who cannot provide written informed consent; therefore plans to consent the subject's Legally Authorized Representative are not applicable.
- Because the study requires the ability to read many self-report instruments and complete several written tasks, we will not be enrolling anyone that cannot read with at least 6th grade proficiency, as indicated by the WRAT 4 Reading test. Because the study requires the ability to comprehend a variety of self-report instruments that are only available in English, we will not be enrolling participants whose primary language is not English. No waiver of consent is being sought for this study.
- All participants will be adults (age 18 to 50), thus issues regarding assent from minors are not relevant.

## 7) Procedures involved in the Human Research

**General Procedure:** Over a 4-year period, 108 participants between the ages of 18 and 50 will be recruited to participate (to reach a final n of 90 subjects, assuming 20% attrition). Participants will comprise active duty, Reserve, National Guard, or recently discharged combat-exposed military personnel or DoD contractors from Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) meeting DSM-V diagnostic criteria for PTSD, in addition to some non-military individuals who meet the DSM-V diagnostic criteria for PTSD. Combat-exposed individuals within 10 years of return from OIF/OEF will be eligible. An age range of 18-50 years has been selected to minimize possible developmental and degenerative effects that could be expected in younger and older subjects and to encompass the age range of the majority of military personnel.

Prior to data analysis, subjects who consent will have a follow-up phone call where they will be administered the PCL-5, PHQ-9, and be asked about general sleep problems using the ESS and ISI.

The procedures will essentially be identical to those used successfully in our pilot study of patients with mTBI. Participants will attend three laboratory sessions (see Figure 10 below). Visit 1 involves informed consent, demographic data collection, and basic psychiatric assessment. Participants will be provided with a wrist actigraph sleep monitor. After a week of at home monitoring, each participant will return for Visit 2, which is involves comprehensive neurocognitive assessment, neuroimaging, fear conditioning testing, objective sleepiness monitoring and heart rate monitoring. Then participants will be randomly assigned to one of two light therapy conditions (n = 45 per group) differing only in the wavelength emitted by each light therapy device. Participants will be randomly assigned to either the BL condition or the PL condition, using computerized permuted block randomization to match groups by gender. Participants assigned to the active treatment condition will undergo 6-weeks of at-home treatment with a light device fitted with blue light (BL) diodes, while those assigned to the Placebo (PL) condition will undergo 6-weeks of identical treatment with a device fitted with amber light diodes. To objectively monitor sleep, participants will wear a wrist actigraph for the duration of the study. During the 6 weeks of treatment, participants will use the light device for 30-minutes each morning, within 2-hours of awakening (verified via light sensor built into the wrist actigraph, daily time stamped electronic sleep diary, and compliance as measured by wattage usage/time meter). After 6-weeks, participants return for Visit 3 and undergo a follow-up neurocognitive assessment, neuroimaging, fear conditioning, objective sleepiness monitoring, and heart rate monitoring. These procedures have been extremely successful and well tolerated in our pilot study.

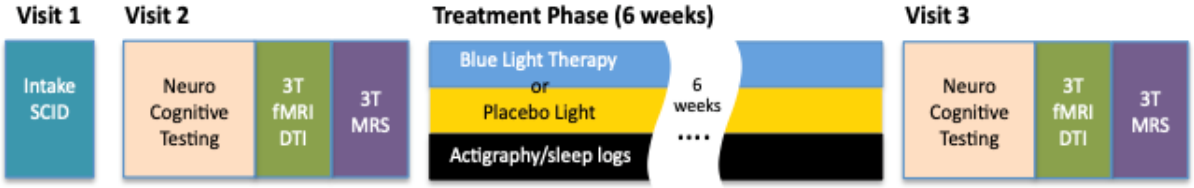



Figure 10. Study Design: Participants attend 3 separate sessions. Visit 1 is simply an intake session that includes consent forms and SCID assessment. Visit 2 and 3 are identical, and include a comprehensive neurocognitive test battery, and neuroimaging. Visit 2 and 3 are separated by a 6-week treatment period with either Blue Light Therapy or Amber Placebo Light Treatment.

**Subject Screening:** Participants whose intake visits are scheduled more than six weeks after the date of the initial phone screen will be given a shortened follow-up phone screen prior to the intake visit, in order to ensure that no changes have taken place which may affect their eligibility.

**Intake Visit (Visit 1)**: Participants will be given a full description of the study, have the opportunity to ask questions, and will provide written informed consent, and will be evaluated for PTSD severity using the Structured Clinical Interview for DSM-V (SCID). The Morningness Eveningness Questionnaire (MEQ) will be administered to assess circadian rhythm disturbances prior to light treatment. The combat exposure scale (CES) will also be administered to participants with combat-related PTSD to inform us of the extent and nature of combat exposure in military participants. The Weschler Abbreviated Scale of Intelligence (WASI-II) will be administered to control for variation in intelligence levels amongst participants. The AUDIT and MUSE questionnaires will also be given to determine the degree and extent of alcohol and marijuana use, though neither of these scales will be utilized as a means to determine

exclusion from the study. The Rivermead Post-Concussive Symptoms Questionnaire (RPCSQ) will be administered to confirm that any participants who may have experienced concussion during their traumatic event did not lose consciousness or experience post-traumatic amnesia. Research Technicians who have been trained and meet predetermined qualifications to administer a Structured Clinical Interview by doctoral level clinical psychologists with training and experience with these instruments will administer the SCID. All SCID administrations will be reviewed via supervision by a qualified doctoral level clinical psychologist immediately following the participant's interview. Female participants will also provide information about their menstrual cycle (length of cycle and time since last menses) because this is critical in the interpretation of brain metabolite levels during magnetic resonance spectroscopic imaging. We do not know if MRI scanning presents a risk to unborn fetuses, so we will ask all female participants of childbearing potential to complete a urine pregnancy test immediately prior to the scan. Female participants must have a negative pregnancy test before the MRI scan can be initiated. This pregnancy test will be performed in the Department of Psychiatry. All subjects will wear a heart rate monitor for the duration of this visit. Selection criteria for all subjects are as follows:

During Visit 1, participants will be fitted with a wrist-worn actigraph to monitor sleep/wake patterns. This device will also log exposure to light in three wavelengths (red, green, blue) to measure compliance with the protocol. Participants will also be introduced to the online sleep diary collection system and will be given an automated email each morning reminding them to log in and complete the sleep diary.

**Visits 2 and 3: Assessment/Scanning Visits:** One week after Visit 1, participants will return for Visit 2. Participants will complete a detailed demographic (Day of Scan Questionnaire (DSIQ)) and health questionnaire and will be fitted for a heart rate monitor to be worn for the duration of the visit, save for the MRI scan where heart rate will be measured by MRI safe leads as part of the MRI scanner. Subjects will complete a comprehensive baseline assessment of neurocognitive and emotional functioning, coping capacity, and resilience. Participants will also undergo a validated *de novo* fear conditioning and extinction procedure [98-101], and a series of functional neuroimaging and neurochemistry scans. Additionally, participants will complete subjective and objective measures of sleepiness and alertness throughout the day. The following specific tasks and procedures will be administered during the assessment session:

**Emotional Functioning/Coping/Symptom Severity:** PTSD severity will be assessed using the 20-item National Center for PTSD Checklist, Military Version (PCL-5), Patient Health Questionnaire (PHQ-9), and Clinician Administered PTSD Scale-5 (CAPS-5). Further assessment of psychopathology will be made via administration of the Beck Depression Inventory (BDI-II); Beck Anxiety Inventory (BAI); and Spielberger State-Trait Anxiety Inventory (STAI). Participants will also complete measures resilience (Connor-Davidson Resilience Scale (CD-RISC)), Evaluation of Risks (EVAR), the Satisfaction with Life Scale (SWLS) and the Gratitude Questionnaire (GQ6). The Balloon Analogue Risk Test (BART) will be done to measure risk taking.

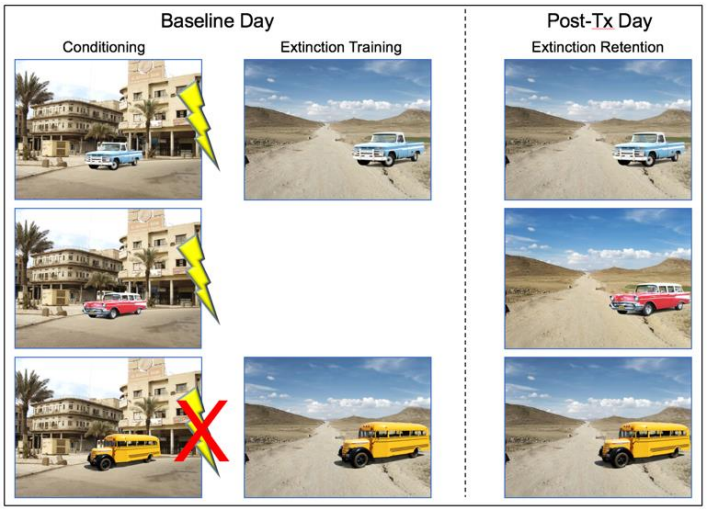
**Subjective Sleep Measures:** To assess general sleep quality, daytime sleepiness, and parasomnias, participants will complete the Pittsburgh Sleep Quality Index (PSQI)[102], the Epworth Sleepiness Scale (ESS) [103], the Insomnia Severity Index (ISI)[104], and the Disturbing Dream and Nightmare Severity Index (DDNSI) [22]. The Stanford Sleepiness Scale (SSS) [105] will be completed at

three times during the assessment day. The Functional Outcome of Sleep Questionnaire (FOSQ) and Sleep Diaries A & B will also be done.

**Neurocognitive Assessment:** All participants will complete a comprehensive neurocognitive assessment battery to include:

1. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The RBANS is a brief battery of well-normed neuropsychological tests with two alternate forms (RBANS A and RBANS B) to permit repeated testing. The test provides several index scores, including: Total Score, Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory. This brief battery will be administered to assess change in cognitive performance in each group following treatment. Subject responses will be recorded via recording device for the Semantic Fluency portion of the RBANS assessment in order to ensure that their complete responses are captured given that they may respond faster than the study team may otherwise be able to record. No identifiers will be used and these recording will be assigned to the subject ID number only. Recordings will be listened to the same day they are created and compared to the initial response collection to ensure the study team captured the subject's complete response, anything missed will be transcribed onto the RBANS form. The recording will then be deleted.

2. Fear Conditioning Paradigm. Our group has developed a fear-conditioning/fear extinction paradigm that is highly effective at discriminating individuals with PTSD from healthy controls [98-101]. The protocol consists of 4 experimental phases: Habituation, Conditioning, Extinction and Extinction Recall. Subjects first choose a level of mild electric shock that is "highly annoying but not painful" while being administered shocks of increasing intensities through electrodes connected to two fingers. For this paradigm, the conditioned stimuli (CSs) consist of digital photographs of three differently colored vehicles (blue, red or yellow) displayed on a computer screen within the image of two different photographic environments (contexts), a "conditioning context" in which the unconditioned (shock) stimulus (US) accompanies certain CSs (CS+s) during Conditioning and an "extinction context" in which CS+s occur without USs during the Extinction and Extinction Recall phases. Before each experimental phase except Habituation, subjects are told they "may or may not be shocked." During Conditioning, 16 CS+'s (8 each of 2 different colors) are presented in the conditioning context and a 0.5-sec US (shock) immediately follows the offset of 10 of 16 CS+ presentations (5 of the 8 of each CS+ color). Sixteen randomly interspersed presentations of the third vehicle color (CS-s) are never paired with the US. During the Extinction phase, one CS+ color (CS+E) appears 16 times in the extinction context, along with 16 interspersed CS-s and no USs. The other CS+ color (CS+U) does not appear and therefore remains un-extinguished. During the Extinction Recall phase, the 8 CS+Es and 8 CS+Us are presented in the extinction context with 16 interspersed CS-s and no USs. The measurement of conditioned fear is



palm-recorded skin conductance response (SCR), a reliable index of sympathetic activation. Participants will be conditioned and undergo extinction prior to entry into the scanner. During scanning, participants will again be confronted with the previously extinguished stimuli to evaluate extinction recall, a hallmark deficit of PTSD. It is expected that improved sleep due to the BL condition will lead to improved generalization of the extinction response and extinction recall.

**Modified Sleep Latency Test (MSLT):** Participants will undergo 3 MSLT procedures with polysomnographic (PSG) recording over the course of the assessment day. A trained technician will fit each participant with a standard electrode montage for PSG recording. Standard PSG will be recorded using the Polysmith 11.0 system that is installed in our sleep laboratory facilities. During each MSLT, the participant will be given up to 20 minutes to fall asleep in a private, darkened, sound-attenuated bedroom. PSG recordings will be scored by a trained technician to determine the latency to fall sleep. The mean latency to sleep is taken as an indication of objective sleepiness.

**Psychomotor Vigilance Test (PVT):** The PVT is a 10-minute computerized measure of sustained attention and psychomotor vigilance that has been shown to be exquisitely sensitive to sleep deprivation. The PVT currently serves as the "gold standard" for assessing degradation in alertness and vigilance following sleep loss.

**Functional Neuroimaging**: Subjects will be screened for any contraindications to MRI and magnetic materials. The investigator or MRI Technologist will explain the MRI system and the scan that they are about to take part in. The subject will be asked to lie down on the scanner bed. Some part of the subject's body may be covered or enclosed within an FDA or UA HSPP approved MRI coil. The subject may be asked to interact with a peripheral system such as a button, joystick, or TV system before, during, or after the scan.

Blood Oxygen Level Dependent (BOLD) functional magnetic resonance imaging (fMRI) will be collected at the University of Arizona Translational Bioimaing Resource. The MRI hardware and procedures immediately to follow are approved by the FDA. A Siemens Skyra 3T whole body high-speed imaging device equipped for echo planar imaging (EPI) (Siemens Medical Systems, Iselin, NJ) will be used. Head movement will be restricted using expandable foam cushions. After an automated scout image is acquired and shimming procedures performed to optimize field homogeneity, high-resolution 3D MPRAGE sequences (TR/TE/flip angle=7.25ms/3ms/7°) with an in-plane resolution of 1.3 mm, and 1 mm slice thickness, will be collected for spatial normalization, positioning the slice prescription, and for subsequent morphometric analysis. Then a T1-weighted (TR/TE/flip angle=8sec/39msec/90°) and a T2-weighted (TR/TE/flip angle=10sec/48ms/120°) sequence will be used to gather sets of images to assist in registration of the functional data to the high-resolution anatomical scan. Functional MRI images (blood oxygenation level dependent or BOLD; Kwong et al 1992) will be acquired using a gradient echo T2*-weighted sequence (TR/TE/flip angle=2 sec/40msec/90°). Prior to each scan, four images are acquired and discarded to allow longitudinal magnetization to reach equilibrium. The T1, T2, and gradient-echo functional images will be collected in the same plane (whole brain acquisition; axonal slices angled perpendicular to the AC-PC line) with the same slice thickness (3.125 mm, skip 1mm; voxel size 3.125 x 3.125 x 3.125 mm), excitation order (descending) and phase encoding (head-to-foot). During fMRI, participants will complete four functional tasks:

**1.** Masked Affect Task (MAT): This task, first developed by our group back in the mid-1990's [110], presents a series of facial expressions displaying happiness or fear, each for only 16 msec and masked immediately by a neutral image from a different poser for 184 msec (Figure 14). At this rate of presentation, the "masked" affective expression is not consciously perceived, yet is still processed via an extrastriate pathway to the amygdala that bypasses normal cortical processing. This task has been shown to selectively activate the amygdala in healthy participants. Moreover, in our laboratory, exaggerated amygdala response has been found on this task in patients with PTSD [27]. Our laboratory has extensive experience using this task with patients with PTSD and anxiety disorders [27, 111-115], and healthy adults and children [116-118].

**2.** Extinction Recall (ER): This task measures the retention of the extinction memory established during the previous fear conditioning session. While undergoing fMRI, participants will view the previously conditioned images from the Fear Conditioning and Extinction Task. Here, 8 CS+E, 8 CS+U, and 16 CS- trials will be presented (without any shocks). Skin conductance responses will also be collected while participants are undergoing the scan. During this task, the contrast of interest will be CS+E vs. CS+U, permitting the isolation of psychophysiological and brain responses that are specific to extinction recall.

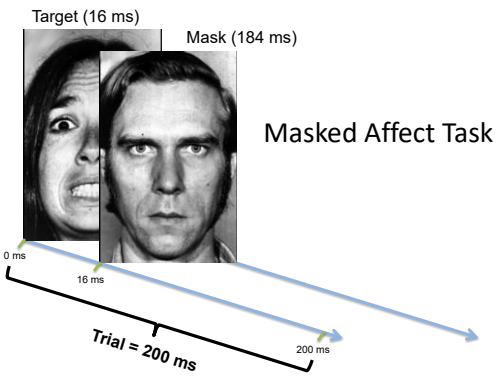



Figure 14. Masked Affect Task: A target emotional facial expression is presented for 16 ms and masked immediately by a neutral face for a longer duration (184 ms). This effectively prevents awareness of the target emotional expression, although it is perceived at a non-conscious level.

**3.** Resting State Scan (RS): Emerging evidence suggests that the brain shows stable patterns of functional connectivity during the resting state and that these patterns may be particularly useful in elucidating specific networks [119-122]. Therefore, in addition to the probe tasks described above subjects will also be scanned for 10 minutes with eyes closed and instructed to let their "mind wander." Functional connectivity will be evaluated from pre- to post-treatment for the two conditions.

**4.** Anticipation Task: The Emotional Anticipation Task was adapted on the basis of Aupperle et al.'s (2013) study design and lasts a total of 7 min and 8 seconds. Two version of the anticipation tasks will be used, in order to have two different versions of the tasks for the baseline and follow up visit. Participants are presented with a grey background with a black arrow alternating randomly in its direction from left to right (Baseline). Participants are instructed to indicate via button press which direction the arrow was pointing in. Participants are told that when the screen turns yellow, a negative picture will soon appear (Negative Anticipation (NA)). If the screen turns blue, a positive picture will soon appear (Positive Anticipation (PA)), and if the screen turns green a positive *or* a negative picture will soon appear (Uncertain Anticipation (UA)). The picture stimuli consist of positive and negative pictures from the International Affective Picture System (IAPS). The most unpleasant (e.g., mutilated bodies) as well as the most pleasant (e.g., animals) pictures were chosen from the picture set. The aim of this task is to investigate whether the intervention changes neural responses during anticipation of negative stimuli.

**Spectroscopic Neuroimaging**: While all MRI hardware used during this study is FDA-approved, as part of the MRI session, one MRI sequence will be conducted that uses investigational software that enables collection of unique spectroscopic data. This scan, referred to as the MEGA-PRESS sequence, uses Proton Magnetic Resonance Spectroscopy (MRS) to measure chemicals in the brain, specifically, cerebral metabolites and neurotransmitter concentrations. It is very similar to other FDA-approved MRS sequences, but it does a better job at quantifying certain metabolites, namely, GABA. Per the Master Research Agreement (MRA) between Siemens and the University of Arizona, as a Works in Progress (WIP), the MEGA-PRESS sequence complies with all FDA guidelines for magnetic resonance imaging (*https://www.fda.gov/regulatory-information/search-fda-guidance-documents/criteria-significant-risk-investigations-magnetic-resonance-diagnostic-devices-guidance-industry-and*) and is suitable for testing in a clinical environment. Because of this, the MEGA-PRESS sequences does not increase the risk to subjects.

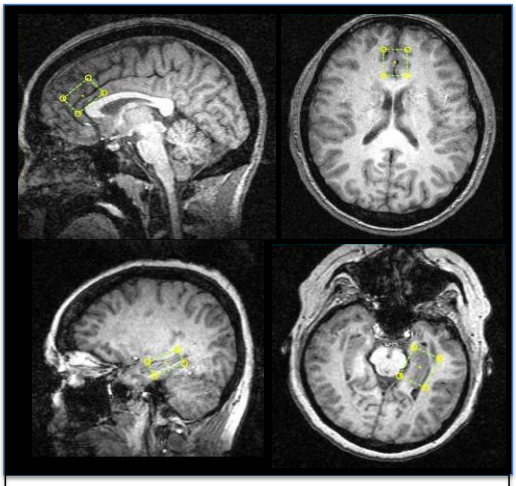


Figure 15. MRS Spectroscopy: Placement of voxels within the dorsal ACC and left hippocampus.

A key element of the proposed project involves assessment of changes in brain neurochemistry as a function of 6-weeks of light therapy treatment and associated changes in sleep quality. Growing evidence suggests that some of the deficits in memory and emotional regulation that occur for patients with PTSD are related to alterations in neurochemistry within key regions of the hippocampus and ACC (Karl & Werner, 2010). In particular, patients with PTSD show decreased NAA in the hippocampus and ACC, as well as reduced concentrations of choline in the hippocampus and increased levels in the ACC. These are often compared directly as ratios relative to creatine (Cr). Assuming that improved sleep leads to improvement in emotional functioning, this will permit us to identify a potential mechanism for this improvement. Presently, for 1H MRS imaging, two voxels will be placed, one encompassing the dorsal anterior cingulate cortex just anterior to the genu of the corpus collosum and another placed at the amygdala-hippocampal complex within the mesial temporal lobe (see figure 15). All $^{1}$H MRS measurements will be performed using a Siemens TIM Trio 3T whole body high-speed imaging device (Siemens Medical Systems, Iselin, NJ) and a 32-channel single-tuned (170.3 MHz) “birdcage” coil for radiofrequency (RF) transmission and signal reception, both of which are approved by the FDA. The following brain metabolites will be collected and analyzed: alanine (Ala), aspartate (Asp), choline (Cho), Gamma Amino Butyric Acid (GABA), Glutamate (Glu), Glutamine (Gln), glutathione (GSH), glycine (Gly), myo-I, N-acetylaspartate (NAA), N-acetylaspatylglutamate (NAAG), creatine (Cr), phosphocreatine (PCr), scyllo-inositol (Scy), taurine (Tau) and lactate (Lac).

**At Home Six-Week Light Exposure Treatment**: At the conclusion of Visit 2, participants will be randomly assigned to either the BL condition or the PL condition, using computerized permuted block randomization to match groups by gender. All participants will be given a goLITE® unit to take home and provided with detailed training and instruction on its use. Depending on the light condition assigned, the goLITE will include either blue or amber LEDs. The goLITE BLU is commercially available and has a narrow bandwidth, peaking at $\lambda = 469$ nm, at 214 Lux, and panel irradiance mW/cm$^2$) = 1.23 at 20 cm. A similar appearing amber LED system (goLITE AMBER) will be employed for the PL devices, but will peak at $\lambda = 578$ nm, at 188 Lux, and total irradiance (mW/cm$^2$) = 0.35. Both of these devices have undergone extensive ocular safety testing (Sliney, 2009) and have been used successfully without incident in our prior study. Each participant will be instructed to use the unit each morning (within 2 hours of awakening and prior to 10:30 am) for 30 minutes per day over the next 6 weeks. Participants are permitted to engage in sedentary activities (e.g., read, watch TV, surf the internet, eat, engage in daily hygiene) while the unit is activated, as long as the light is within arm's reach and projecting to the eyes from within a 45-degree angle to either side (see Figure 14). A wattage use meter will be connected to the goLITE device to measure participant compliance in terms of duration, timing, and intensity of light exposure. They will be asked to record this via the Sleep Diaries A & B. This same procedure has been used in our prior work and has been well tolerated by participants, allowing them considerable flexibility to choose whether to use the light immediately upon arising, or after morning hygiene, meals, drive, etc., but while still ensuring that all treatment occur in the morning hours.

Figure 16. Participants will maintain the device at arms length within the peripheral vision for 30 minutes each morning.

Safety and efficacy of the device itself is not being tested, rather, the effects of specific wavelengths of light on human performance; the device is simply used as a convenient method to deliver the light in a controlled and reliable way in order to assure the scientific validity of the results.

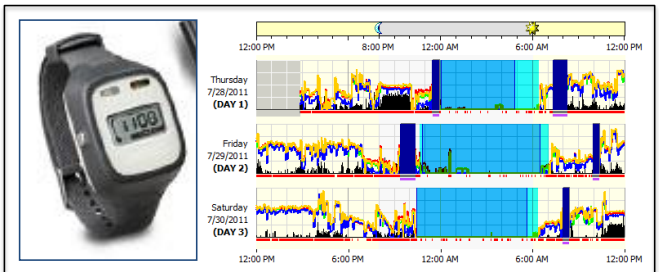



Figure 17. Actiwatch Spectrum and Actigram: The device collects wrist activity data (black bars)that are translated into sleep/wake periods (white/red bars at bottom of graph), as well as minute by minute light exposure (yellow = total light; blue = blue light; green = green light; red = red light).

**Actigraphic Sleep Measurement**: Daily sleep, activity, and light exposure will be collected via the Respironics Actiwatch Spectrum®. This actigraphic wrist-watch device uses a built-in accelerometer to unobtrusively measure and record ambulatory activity levels and sleep 24 hours a day. This data can then be analyzed via sleep analysis software (Actiware 5®) that includes algorithms that transform activity data into probable sleep periods. The Actiwatch Spectrum also includes three-color light sensors that provide irradiance and luminous lux recordings in three-color bands of the visible spectrum, including red, green, and blue (Figure 17). The light sensor will be used to verify that subjects are in fact undergoing the daily light treatment and will permit covariation of other daily light sources in the statistical analyses. The device also records periods of off-wrist time to determine compliance. Data

will be scored by the Actiware 5® program, checked for validity, and summary indices of total sleep time, sleep efficiency, sleep onset latency, wake after sleep onset (WASO), and fragmentation index will be calculated for each day and averaged across the study period.

**Compliance Monitoring:** Compliance with the study requirements will be monitored in several ways. First, participants are required to log into the internet each day to complete the sleep diary and report timing of light usage. This is an effective means for monitoring general compliance. On-line compliance will be monitored, and participants will be contacted by phone and/or email if they have not logged in for more than 48 hours. Second, use of the lights will be monitored by a recording device built into the light device that records a time stamp each time the light is engaged. Third, participants are required to wear the wrist acticgraph at all times. This device includes a light monitor that is sensitive to various wavelengths of light. This light data will be evaluated at the conclusion of the study to identify whether there is a detectible change in blue/red light during the period of reported light exposure.

**Post-Treatment Assessment and Scan**: At the completion of 6-weeks of BL or PL, participants will return to the imaging center for Visit 3 to complete an identical series of assessment and neuroimaging tasks as in Visit 2, as well as a repeated administration of the CAPS. Participants will return wrist actigraphs and the goLITE device.

Please note that subjects will be offered and required to wear earplugs and/or earphones to minimize the scanner noise. Subjects will be able to converse with a staff member via a microphone and speaker system at all times during the scanning session. Subjects will be provided with an emergency button to indicate an immediate concern. Subjects may ask to have a scan stopped and discontinue participation in the study at any time.

**Follow-Up**. After subjects complete the study, prior to data analysis, subjects will be sent an email (*Follow-up Script.doc*) with a link to an online ICF Addendum (*PTSD_ICF_addendum.doc*) and, if they agree, subjects will complete a 10- to 15-minute follow-up online survey, where they will be administered the PCL-5, PHQ-9, and be asked about general sleep problems using the ESS and ISI. If subjects cannot complete this follow-up online, follow-up assessments will be administered over the phone.

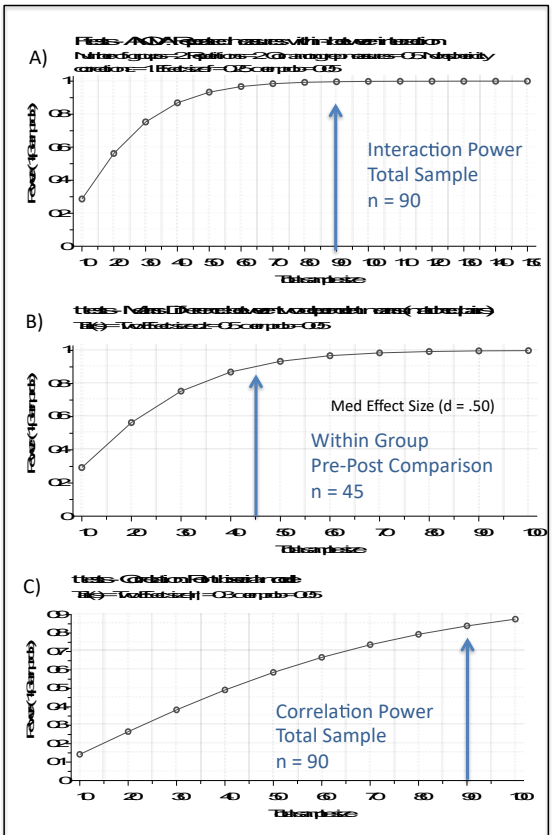



Figure 18. Power analyses show that the proposed sample size should be adequate to address the primary hypotheses.

## D. DATA ANALYSIS

**Global Statistical Analysis Approach**: Behavioral data from the neurocognitive, sleep, and symptom measures will be evaluated for clinical severity and transformed into change metrics from baseline to post-treatment sessions. Baseline characteristics between subject groups will be examined using analysis of variance (ANOVA) and chi-square tests, as appropriate, and randomization will be stratified by severity of PTSD

and gender. Randomization will consist of permuted blocks to achieve balance over time. Repeated measures analysis of variance (ANOVA) and linear mixed-model approaches will be used for the primary analyses examining the efficacy of light treatment condition on measures of mood and sleep. Between group factors will correspond to the two light conditions (BL vs PL) and will control for any baseline differences in demographic variables and severity scores as appropriate. Based on specific hypotheses, separate ANOVAs will be performed for each type of dependent variable (e.g., subjective sleep scores, CAPS-2 symptom scores, mood scores, MRS metabolites). The relationship between these change indices and sleep variables will be analyzed using correlation and linear regression models in SPSS. Tests for normality will be conducted for all variables. In the case on non-normality, appropriate data transformation or non-parametric techniques will be employed (e.g., Kruskal-Wallis or Friedman tests for ANOVA; Mann-Whitney U or Wilcoxon for 2-group comparisons). Inflation of Type I error will be controlled first through the use of planned comparisons based on the hypotheses and the use of protected omnibus F-tests. Post-hoc analyses will be undertaken with protected comparisons (e.g., Tukey) or Bonferroni adjustment. Functional MRI data will be analyzed using statistical parametric mapping (SPM8) software, implementing the general linear model to compare pre- to post-therapy changes in functional responses between the active and placebo groups and across diagnostic groups, and sleep variables will be tested as covariates in the models. Finally, proton spectroscopy data for each of the metabolites will be quantified and compared for pre- to post-therapy changes in metabolite concentrations between the active and placebo treatment groups and across diagnostic groups. Type I error during neuroimaging will be controlled via whole brain False Discovery Rate (FDR) correction or small volume corrections using Family Wise Error (FWE) rate within *a priori* specified regions of interest. To handle missing data, we will first determine the potential cause of the data loss. Statistically, missing data can be considered as falling into three types: 1) missing completely at random, 2) missing at random, or 3) missing not at random. The type of missing data will dictate the approach. Assuming type 1, and that the number of missing values is low, we will use a standard listwise deletion procedure. However, assuming that a larger number of values is missing, and data are not missing completely at random, we will be able to apply missing data imputation methods.

**Power Analysis**: A power analysis based on a proposed sample size of 90 subjects suggested that with an omnibus 2 between-groups (BL vs. PL) x 2 within-subjects (pre- vs post-treatment) mixed design, assuming a moderate effect size ($f = .25$), and $\alpha = .05$, there should provide be adequate power to detect most effects. First, the primary hypotheses of the study focus on interaction effects across groups (i.e., treatment x session interactions), which will have exceptional power $(1-\beta) = 0.99$ to detect a moderate effect size at $\alpha = .05$ (see Figure 18A). Paired comparisons within each group of will also have excellent power of .91 to detect moderate effect size changes ($d = .50$), with 2-tailed tests (see Figure 18B). Without regard to group differences, a sample size of 90 would yield power = 0.84 to detect a moderate linear association (i.e., $r \geq .30$) between a predictor variable (e.g., average sleep; change in sleep parameters, PTSD symptom severity; neurocognitive performance; etc.) and an outcome variable (e.g., fMRI signal intensity changes; spectroscopic metabolite changes; etc.), with a two-tailed test at $\alpha = .05$ (see Figure 16). Thus, the proposed sample size of $n = 45$ per group appears to provide adequate power for testing the major hypotheses of the proposed study.

**Functional Image Pre-Processing:** Functional neuroimaging data will be preprocessed in SPM8 [123]. Following standard algorithms, functional images will be slice-time corrected, co-registered to their anatomical T1-weighted images, realigned, unwarped to correct for field inhomogeneity, normalized to the standard three-dimensional space of the Montreal Neurological Institute (MNI), spatially smoothed using an isotropic Gaussian kernel (full width half maximum [FWHM] = 6 mm), and resliced to 2x2x2 mm isotropic voxels using sinc interpolation. Depending on the specific task, functional data will be convolved to an event-related or boxcar waveform based on the experimental design and the canonical hemodynamic response function. Artifact detection will be conducted with the Artifact Detection Tool (ART) program. Images with global intensities exceeding 3 standard deviations or scan-to-scan movement exceeding 1mm will be statistically regressed out of the design matrix. For event related analyses, individual subject motion parameters will also be included as nuisance regressors in the design matrix.

**FMRI Statistical Analysis:** At the first stage, activation during the conditions of interest will be fitted using the general linear model in SPM8 for each subject individually. This procedure yields a statistical parametric map that isolates the activity unique to the condition of interest (e.g., masked affect) relative to the activity associated with the control condition (e.g., simple perception of neutral facial expressions). Thus, for each subject, a "contrast image" will be produced that reflects the pattern of BOLD signal change due to the independent variable for each task. At the second stage, subject specific contrast images will be entered as the dependent variables in a series of random effects analyses in SPM8 [124]. Functional data will be analyzed from two approaches, including region of interest (ROI) analyses and whole brain exploratory analyses.

1. ROI Analyses. First, a series of region of interest (ROI) analyses will be performed. The primary hypotheses for the MAT involve changes in the amygdala, anterior cingulate gyrus, and ventromedial prefrontal cortex for the MAT, whereas the ACC and dorsolateral prefrontal cortex are hypothesized to differ across groups for the MSIT. Consequently, ROIs will be placed in these regions, defined according to the boundaries of the published anatomical atlas of Tzourio-Mazoyer and colleagues [125] and PickAtlas Utility [126]. These ROI analyses will be carried out at an FDR small volume corrected threshold of $p = .05$, $k$ (extent) = 10. Each of the probe tasks has been selected because of its prior involvement in the neurocircuitry of PTSD.
2. Whole Brain Exploratory Analyses. Furthermore, whole brain analyses will be undertaken to examine global patterns of activation for each of the previously described analyses. Because these analyses will be exploratory in nature, they will be evaluated at a stringent correction for multiple comparisons using a whole brain family-wise error (FWE) correction of $p < .05$, $k = 10$.
3. Resting State Functional Connectivity Analysis: Preprocessed resting state data will be analyzed using the fMRI Functional Connectivity Toolbox (CONN). Physiological and other noise sources are reduced through the implementation of a CompCor strategy implemented within the toolbox. For each subject, gray and white matter masks will be created from the previously segmented images in SPM8 and entered as nuisance covariates in the analyses, as will subject specific motion parameters. Regions of Interest (ROIs) will be created from the Automated Anatomical Labeling Atlas [125]. ROI to ROI and seed-to-voxel analyses will be run individually at the first level and then imported into a second level random effects group analysis. Primary seed regions for connectivity analyses will include the

subgenual and rostral ACC, VMPFC, and amygdala. Data will be analyzed at an FDR corrected significance level of $p < 05$.

**MRS Analyses**: The goal will be to determine whether BL treatment is more effective than PL at altering bran metabolites that are associated with alertness, cognitive processing, and inhibitory capacity. All MRS processing will be carried-out in a fully automated fashion using methods previously published by our group [127]. Metabolite ratios will be derived as a ratio of each raw metabolite integral to the total sum of the creatine and phosphocreatine integrals, and will be T1-corrected using values previously reported in the literature. Our primary endpoints of interest are Glu (excitatory neurotransmitter), GABA (inhibitory neurotransmitter), and NAA (marker of neuronal energy production). Standard linear and mixed model approached will be employed for comparing metabolite ratios between the active BL and placebo light conditions within the dorsal ACC and amygdala-hippocampal complex. As described above, all analyses will be undertaken with $\alpha = .05$, employing corrections for multiple comparisons (e.g., Tukey post-hoc corrections; Bonferroni corrections) as appropriate. We expect that the active BL condition will lead to increased levels of GABA, N-acetyl-aspartate (NAA), and choline (Cho), and reduced glutamate and phosphocreatine (Cr) in the amygdala-hippocampal complex and anterior cingulate gyrus compared to the PL condition. Furthermore, it is expected that these changes will be linearly related to changes in sleep parameters and cognitive/symptom score changes from pre- to post-assessment.

## 8) Risks to subjects

Participation in this study may involve some risks or discomforts, which are described below.

During the study visits, subjects may be asked some questions during the brief clinical interview and on the questionnaires that deal with personal or emotional matters. These questions might cause psychological discomfort. Subjects may refuse to answer any questions that make them uncomfortable. If they reveal during these sessions that they are currently or have recently had thoughts of self-harm or suicide, appropriate follow-up evaluation and referral for care will be ensured. Results of the clinical evaluation will be kept in a locked cabinet and identified using only subject unique study identification number.

Subjects may find the sensation of the electric shock used in the picture-viewing task to be uncomfortable. However, they will be able to choose their own level of shock, which should be strong enough to annoying or uncomfortable, but not painful. The apparatus that provides the shock is powered by a 9-volt electric battery, identical to those used in toy electronics. These mild shocks are not dangerous or harmful, but may be annoying.

Unlike X-rays or CAT scans, magnetic resonance (MR) technology does not use ionizing radiation. Instead, it uses strong magnetic fields and radio waves to collect the images and data. With the exception of one sequence (MEGA-PRESS spectroscopy work-in-progress (WIP) pulse sequence), all MRI procedures involved are standard. The radio frequency exposure, magnetic fields and gradients, and noise levels produced by the MRI sequences used in this study are no greater than or fall below the FDA's limits, so subjects are exposed to no greater risk than those of routine MRI scans (see *MEGA-PRESS Sequence Manual.pdf* and *Request allowance for running MEGA-PRESS WIP* (Rouse, Trouard, et al,

2019). During the scan, subjects will wear a birdcage coil around their heads; this is an FDA-cleared device and its use in this study will be as approved by FDA.

The four risks the FDA associates with MRI scanning are: 1) tissue heating due to RF fields, 2) peripheral nerve stimulation due to quick changes in magnetic field, 3) hearing damage due to acoustic noise, and 4) force and torque on magnetic materials in or on a participant. That said, the FDA lists "MRI Devices within FDA specified parameters" as non-significant risk devices. The research scanner in the TBIR fits within this description. With regard to tissue heating and peripheral nerve stimulation, the Siemens scanner is not capable of running a sequence that is outside the FDA safety guidelines. With regard to hearing damage, volunteers wear ear protection when in the scanner. In addition, any non-FDA approved sequence conducted is within FDA parameters for tissue heating, peripheral nerve stimulation, and hearing damage.

With regard to force and torque on magnetic materials, anyone entering the magnet room must remove all metal objects from their body. In addition, significant risks may exist for people with:

- Cardiac pacemakers
- Metal clips on blood vessels (also called stents)
- Artificial heart valves
- Artificial arms, hands, legs, etc.
- Brain stimulator devices
- Implanted drug pumps
- Ear implants
- Eye implants or known metal fragments in eyes
- Exposure to shrapnel or metal filings (wounded in military combat, sheet metal workers, welders, and others)
- Other metallic surgical hardware in vital areas
- Certain tattoos with metallic ink
- Certain transdermal (skin) patches such as NicoDerm (nicotine for tobacco dependence), Transderm Scop (scopolamine for motion sickness), or Ortho Evra (birth control)

Volunteers are screened before entering the magnet to be sure they do not have any of these items. If subjects are unsure whether they have any of these items in their body, they will be informed that most would have been implanted as part of a surgical procedure, and that trying to remember past operations may help them remember if they have any implanted devices or history of exposure to shrapnel or metal filings, and, if so, they will not be able to participate in this study.

Significant risks also can arise if certain materials (many types of metal objects) are brought into the scanning area, as they can be pulled into the magnet at great speed, which might cause serious injury. Therefore, these types of items are not permitted in the scanning area. Subjects will not be allowed to bring anything with them into the scanning room.

The MR exams are painless, and except for pulsating sounds or vibrations, subjects will not be aware that scanning is taking place.

The scans will take place on a 3T scanner, which are approved by the FDA for routine clinical studies in children and adults. However, as part of the MRI session, subjects will receive an MRI scan that measures chemicals in the brain, the MEGA-PRESS sequence, that is not FDA approved, though it does comply with the same FDA guidelines used for routine FDA approved MRI scans. Therefore, all MRI scans used in this study do not expose subjects to any more risk that a routine MRI exam.

Although there are no known risks from these scans, there could be adverse effects that are delayed or very mild, such that they have not yet been recognized. Most people experience no ill effects from these scans, but some people do report claustrophobia (fear of being in enclosed small spaces), dizziness, mild nausea, headaches, and a metallic taste in their mouth, double vision, or the sensation of flashing lights. Some subjects also experience feelings of panic and/or anxiety. These symptoms are rare, and if present, disappear shortly after leaving the scanner. In addition to these physical risks, the MRI system can be psychologically unsettling to some volunteers that are bothered by loud noises or small spaces.

Volunteers can ask to be removed from the scanner at any point during the procedure without any repercussions.

Steps taken to minimize risk:

For the first three MRI risks described above, all sequences operate within the FDA limits of non-significant risk. For the fourth risk, force/torque on magnetic materials, all volunteers are checked multiple times for these materials before entering the magnetic field. In addition, volunteers can ask to be removed from the scanner at any point during the procedure without any repercussions.
Subjects will be screened for any contraindications to MRI and magnetic materials. The investigator or MRI Technologist will explain the MRI system and the scan that they are about to take part in. The volunteer will be asked to lie down on the scanner bed. Some part of the volunteer's body may be covered or enclosed within an FDA or UofA HSPP approved MRI coil. The volunteer may be asked to interact with a peripheral system such as a button, joystick, or TV system before, during, or after the scan.

Although both light devices (placebo [PL] and blue light [BLT]) are safe to use (Sliney, 2009, 2006; Apollo Health, 2009), we will minimize unnecessary direct exposure to the bright lights to reduce the possibility of discomfort or persistent visual symptoms. Although looking directly at the LEDs for brief periods is not known to be harmful, it is unnecessary and may lead to glare, eyestrain, or other irritating visual sensations that can be easily avoided by keeping the panel at an angle in the peripheral vision. It is sufficient that the light reaches the eyes indirectly from the side. Looking directly at the LEDs does not provide any additional benefit. Prolonged staring at the LEDs could lead to significant eye irritation, lingering afterimages, or other symptoms such as headaches. Although the light emissions of the device are well within safe limits and no problems have ever been reported, we want to minimize any risks or discomforts. While extremely unlikely, it is possible that prolonged continuous staring at the

LEDs could lead to more severe changes in vision such as photoretinitis, a condition that is most commonly associated with looking for too long at very bright light sources such as snow on a bright sunny day or looking at the sun during an eclipse. Such a condition could lead to temporary or long-term vision problems. As individuals may differ in sensitivity to light, some subjects may experience eye fatigue or irritation during the use of the light exposure device. If subjects notice any unusual sensations or discomforts, they are advised to discontinue use and to contact the Principal Investigator immediately.

Thus, to minimize risk, subjects will be instructed via the following for the goLITE Blu:

**NOTE: DO NOT STARE DIRECTLY AT THE LIGHTS ON THE LED PANEL. IT IS SUFFICIENT THAT THE LIGHT REACHES YOUR EYES DIRECTLY FROM THE SIDE.**

There is the potential for skin irritation due to the heart rate monitor leads or wearing the actiwatch. This can be alleviated with use of lotions and/or creams.

## 9) Potential benefits to subjects and/or society

It is not anticipated that subjects will derive direct benefit from participation in the proposed study. However, it is anticipated that findings from this study will help to advance scientific and medical understanding of treatment of PTSD and sleep disorders. The study will provide basic scientific information about the effects of short wavelength light on sleep patterns and potential treatment of PTSD. Such information may improve the ability to treat sleep disorders and cognitive performance among patients with PTSD.

Incidental MRI findings:
Study assessments (labs, MRI scans, psychological assessments, etc.) are not intended to provide medical benefit. Personnel involved conducting this study may not be trained or licensed to clinically review lab findings, MRI images, etc. If study personnel notice something irregular in subjects' study information, the investigator may provide de-identified reports or images to a licensed physician, radiologists, or other qualified practitioner for further review. In the unlikely case that such a qualified clinician determines a finding to be an irregularity, subjects will be advised to consult their primary care physician. Subjects may be provided copies of their study information or MRI images for this purpose, but this medical consultation will be on subjects' own time and at their cost. If subjects are provided a copy of their study information, we make no promises as to the clinical value of the data. The University of Arizona and its employees have no funds set aside for the payment of treatment expenses that may arise from subjects volunteering for an MRI scan.

There may be instances in which an abnormality exists but is not identified in our analyses. Our team is not trained in clinically diagnosing issues pertaining to abnormalities found in the collected data. Further, our data analyses are not intended to treat, diagnose, or replace the expertise of a medical doctor or a medical diagnosis. As such, the University of Arizona and its employees are not responsible for

abnormalities that go undetected through participation in these research activities and subjects will be told that they should not rely on our data or analyses to reveal abnormalities.

## 10) Provisions to protect the privacy of subjects and the confidentiality of data

Collected data are computerized. A unique study-specific ID number is assigned to each subject and used for identification purposes. A separate password-protected data file, stored on a stand-alone PC, maintains the ID number and identifying information for each participant. Only the PI and Project Coordinator have access to that file.

Data collected will be entered into REDCap in de-identified format. Subjects' identities will be linked via a coded/subject ID. REDCap requires authorized users to enter a username and password unique to each study staff member.

Study data will be maintained on secure servers maintained by University of Arizona College of Medicine IT, accessible only through secure UA networks by UA-affiliated computers. Only authorized researchers associated with this project will be given access via a unique medadmin username and password.

All information regarding experimental subjects are kept in a locked file cabinet in the University of Arizona Department of Psychiatry. The signed consent forms are stored separately from the research data in a locked file cabinet in the Department of Psychiatry. Any study forms that contain personally identifying information for our participants (e.g., signed consent forms, payment information) are kept separately from research records and data in separate locked filing cabinets in the Department of Psychiatry. All subject voice recordings will be used to verify that the study team collected complete responses and will be verified and deleted the same day they are collected. These recordings will only be linked to subject IDs during that period.

The Imaging Center will be provided with Subject ID numbers only. MRI Records are kept in a locked office. Subject identifiable information is not used for research data. HIPAA requirements will be followed to protect subject confidentiality.

For subjects who agree, their information will be saved for future use to allow possible contact for other studies conducted by the PI.

A final study report will be made available to the sponsor, the Department of Defense (DoD). Only non-identifiable data will be shared. DoD maintains a secure file transfer system, "DoD SAFE," which can be used to securely transfer study information to the sponsor.

Research data will be stored in a secure area for a period of 6 years following the conclusion of the study. All data and links will be destroyed as soon as possible.

## 11) Cost to subjects

There are no costs to subjects, except for their time.

## 12) Subject compensation

Potential subjects who complete pre-screening surveys (*Recruitment Survey.pdf*) through crowdsourcing websites will be compensated in line with the specific site's payment policy (e.g., Amazon

Mechanical Turk will pay $0.60 after the survey is completed, a rate of $0.12 per min in compliance with research guidelines for fair wages within the MTurk community, with a predetermined 5-minute effort allotted).

Subjects will receive $1200 for completion of all three study sessions, successful adherence to daily light exposure treatment, and compliance with all study procedures and proper use of all study equipment. This payment is also intended to cover all transportation expenses to and from the study site.

If subjects choose to withdraw from the study prematurely or are disqualified for any reason, subjects will be compensated according to the following schedule for the time subjects were undergoing scanning and testing:

- Discontinuation during or following the initial intake visit: $75 ($25/hour, 3 hours max for day), following return and adherence of all study-related tasks and equipment.
- Discontinuation before the end of second visit: $17.05/hour, up to a maximum of 8.5 hours and $145 for the day (i.e., max = $220 total for both days), following return and adherence of all study-related tasks and equipment.
- Discontinuation any time during the 6-week light exposure period: $220 maximum total payment, following return and adherence to all study-related tasks and equipment.
- Fully compliant participants will receive $980 for completion of all light exposure sessions, proper use of light meter, and completion of all research activities during the final visit. Payment to participants who discontinue their participation between the second visit and the final visit is variable depending on days of light exposure missed:
  - 1 day missed: Maximum total payment $1200
  - 2 days missed: Maximum total payment of $1195
  - 3 days missed: Maximum total payment of $1190
  - 4 days missed: Maximum total payment of $1180
  - 5 days missed: Maximum total payment of $1160
  - 6 days missed: Maximum total payment of $1120
  - 7 days missed: Maximum total payment of $1040
  - 8 days missed: Maximum total payment of $880
  - 9 days missed: Maximum total payment of $560
  - More than 9 days missed: $220 maximum from completion of first 2 visits

Payment cannot be rendered until all study-related equipment has been returned. In order to be compensated for participation in this study, subjects must be a U.S. citizen or other person legally entitled to earn money in the U.S. By law, payments to subjects may be considered taxable income.

**If the participant is an active duty military personnel**, the participant is not eligible to receive compensation for time spent completing assessments while they are "on duty". In accordance with Title 24 United States Code 30, active duty military personnel must be on leave status during each of the three assessment sessions in order to be compensated. If the participant is on active duty, **it is their responsibility** to ensure that they have completed the appropriate paperwork for leave and obtained the

necessary permissions to allow them to participate in this study. If the participant is on leave status, they will be compensated for the 3 assessment sessions according to the schedule listed above.

The necessary information to capture receipt of subject payment will be collected via the Subject Payment Form.

Method of payment: Participants will be paid in cash or check. Patients may need to complete a W-9 (IRS Request for Taxpayer Identification Number and Certification) in the Psychiatry business office depending on the amount of compensation being provided for this study and their extent of involvement.

## 13) Medical care and compensation for injury

Subjects will be offered the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill their insurance company or other third parties, if appropriate, for the care they get for the injury. We will try to have these costs paid for, but subjects may be responsible for some of them.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay subjects or give them other compensation for an injury, should one occur. However, they are not giving up any of their legal rights by signing this form.

If subjects think they have been injured or have experienced a medical problem as a result of taking part in this research study, they are to tell the person in charge of this study as soon as possible.

Siemens will pay for the actual cost of reasonable and necessary medical treatment if a study subject is injured during the Trial, to the extent the injury is a direct result of the proper performance of study procedures that:

- are pursuant to the study plan,
- are not standard of care, unless included in the study plan,
- would not otherwise have been performed but for a subject's participation in the study,
- are not a result of the negligence or willful misconduct of UA personnel, and
- are not the result of normal progression of a study subject's underlying disease.

## 14) Monitoring the data for subject safety

The principal investigator will oversee the collection, maintenance, and analysis of all data. The UA HSPP will be contacted immediately in the case of unexpected adverse events. This is not a treatment trial. Sai Parthasarathy, MD, is director of the sleep laboratory and oversees collection of sleep PSG and actigraphy data. Patricia Haynes, PhD, is an expert in PTSD and contributes to the design, development, analysis and interpretation of data. In addition to Dr. Haynes, in the event a subject should report suicidal ideation and she is not available for consultation/assessment, Michael Grandner PhD, or another qualified clinician, will provide assessment to promote the well-being of the subject. Ted Trouard, PhD, is an expert in the development and application of novel MRI technologies and will assist with collection of

magnetic resonance spectroscopy imaging, analysis strategies, and statistical analysis of MRS and DTI data.

Subjects may refuse to answer any questions that make them uncomfortable. In addition, subjects may terminate their participation in the study at any time. If significant psychopathology (e.g., threat of harm to self or others) is discovered at any time during or after a subject's visit, we will contact one of the psychiatrists on staff to determine the level of risk and establish a contract for safety. If the subject does not already have an established relationship with a psychiatrist, we will provide the appropriate referrals for psychiatric evaluation.

Assessment of MRI scanning-related safety issues will occur at every scanning session by the study staff. Risks to subjects will be minimized by following standard MRI procedures. Individual scans will be aborted if any safety parameters are breached. If the safety issue involves the patient that cannot be eliminated within the time course of the study, their involvement in the study will be terminated. If the safety issue involves the scanner or the scanning environment, no further scans will be conducted from that point, until assurances are made that all safety parameters have returned to allowable limits.

Female participants must have a negative pregnancy test before the MRI scan can be initiated. If the results of the pregnancy test are positive, one of the clinically trained study investigators will explain why the scan cannot be completed.

No long-lasting physical or economic harm is anticipated during scanning. Every effort will be made to reassure the patient and minimize any such discomforts while scanning. Subjects will be offered and required to wear earplugs and/or earphones to minimize the scanner noise. Subjects will be able to converse with a staff member via a microphone and speaker system at all times during the scanning session. Subjects will be provided with an emergency button to indicate an immediate concern. Subjects may ask to have a scan stopped and discontinue participation in the study at any time.

In case of an adverse event, the principal investigator will evaluate and report such events to the UA HSPP per UA HSPP guidelines as well as report to HRPO per federal guidelines.

The diagnostic assessment, MRI, and heart rate measures may reveal previously unidentified psychiatric disorders and/or brain or heart abnormalities the subject didn't know they had. If any abnormalities are identified, they will be provided with information about the finding and encouraged to follow up with their primary care physician. Subjects will be made aware that we are not providing psychiatric, neuroradiological, or other clinical services; only that we will let them know in the event that anything abnormal is noticed by the study team. We are unable to assume responsibility or offer compensation for related medical costs that they make as a result of being informed of an abnormal finding.

There may be instances in which an abnormality exists but is not identified in our analyses. Our team is not trained in clinically diagnosing issues pertaining to abnormalities found in the collected data. Further, our data analyses are not intended to treat, diagnose, or replace the expertise of a medical doctor or a medical diagnosis. Thus, subjects will be aware that they should not rely on our analyses to reveal abnormalities in their data, and our lab claims no responsibility for abnormalities that go undetected during participation in any research related activities.

## 15) Withdrawal of subjects

If any disqualifying condition is discovered during the study or if it becomes evident that the participant is unable or unwilling to comply with study procedures, research study staff may withdraw that individual from the study.

Subjects can voluntarily withdraw from the study at any time by speaking with the PI or study team. The study will then ensure the subject withdraws from the study safely and will provide any necessary follow-up care.

In order to protect subjects, study resources and the integrity of study data, the Principal Investigator reserves the right to remove any subject at his discretion from the study. This will be communicated to prospective subjects during the consent process.

If a subject chooses to withdraw from the study or his/her participation is ended prematurely, any information collected up to that point will be kept.

## 16) Sharing of results with subjects

Subjects will be informed of any new information that pertains to their rights or safety immediately.

Subjects have the right to see and get a copy of their health information that is used or shared for treatment or for payment. To ask for this information, subjects will contact the person in charge of this research study. Subjects may only get such information after the research is finished.

| SECTION 4: LIST OF ATTACHMENTS FOR THIS SUBMISSION | |
|---|---|
| **Document Name** | **Version Date** |
| **1.** F107 | **1.** 06/10/14 |
| **2.** Informed Consent Form | **2.** 07/14/14 |
| **3.** UAMC SRA Approval Letter | **3.** 06/05/14 |
| **4.** Grant Award/Notice of Funding | **4.** 04/25/14 |
| **5.** PI CV | **5.** N/A |
| **6.** goLITE Blu Pamphlet | **6.** 2013 |
| **7.** Edinburgh Handedness Inventory | **7.** N/A |
| **8.** PHQ-9 | **8.** 1999 |
| **9.** CAPS-5 | **9.** N/A |
| **10.** BDI -II | **10.** N/A |
| **11.** BAI | **11.** N/A |
| **12.** STAI | **12.** N/A |
| **13.** CD-RISC | **13.** 09/21/11 |
| **14.** PSQI | **14.** 1989 |
| **15.** ESS | **15.** N/A |
| **16.** DDNSI | **16.** Unk |
| **17.** SSS | **17.** N/A |

| | |
|---|---|
| **18.** RBANS | **18.** 1998 |
| **19.** Polysmith 11.0 | **19.** N/A |
| **20.** Watch & Light Subject Guide, v.2 | **20.** N/A |
| **21.** Subject Payment Form (BL PTSD) | **21.** 07/14/14 |
| **22.** Training Face Image Pairs Set A | **22.** N/A |
| **23.** Training Face Image Pairs Set A | **23.** N/A |
| **24.** ISI | **24.** N/A |
| **25.** Light Device/Watts up Pro instructions | **25.** N/A |
| **26.** Note to File | **26.** N/A |
| **27.** Shock Expectation Questionnaire | **27.** N/A |
| **28.** DSIQ-Baseline visit | **28.** N/A |
| **29.** DSIQ-Post treatment visit | **29.** N/A |
| **30.** PCL 5-Criterion A | **30.** N/A |
| **31.** SCID-V | **31.** Unk |
| **32.** Watt's up PRO/Light Device agreement | **32.** Unk |
| **33.** Compensation schedule handout | **33.** N/A |
| **34.** Actiwatch Spectrum Pro instruction guide | **34.** N/A |
| **35.** Sleep Diary A | **35.** N/A |
| **36.** Sleep Diary B | **36.** N/A |
| **37.** Phone Screen—BL PTSD | **37.** N/A |
| **38.** Phone Script | **38.** 06.15.15 |
| **39.** Combat Exposure Scale (CES) | **39.** 06.15.15 |
| **40.** WRAT4 Reading Comprehension Test | **40.** N/A |
| **41.** Rivermead Post Concussion Symptoms Questionnaire (RPCSQ) | **41.** N/A |
| **42.** Alcohol Use Disorders Identification Test (AUDIT) | **42.** N/A |
| **43.** Marijuana Use Questionnaire (MUSE) | **43.** N/A |
| **44.** BL PTSD Recruitment flyer | **44.** 06.02.15 |
| **45.** BL PTSD Recruitment flyer version B (for non-military) | **45.** 06.02.15 |
| **46.** BL PTSD recruitment handout | **46.** 06.02.15 |
| **47.** Satisfaction With Life Scale (SWLS) | **47.** |

## Submission List for F200: Application for Human Research

**<u>Required</u> items for all F200 submissions:**

- F107: Verification of Training Form
- Current PI/Co-PI CVs or biosketch, if not included with copy of grant application

**Other Items as applicable:**

- **Biosafety Review letter** (for UA - Institutional Biosafety Committee)
- **Certificate of Confidentiality**
- **Compressed Gases Review letter** (for UA – Research Instrumentation)
- **Contract** – complete or draft copy of contract including budget
- **Data Collection Tools** – surveys, questionnaires, diaries not included in the protocol, data abstraction form for records review
- **Data Monitoring Charter and Plan**
- **Drug/Device information** – Investigator's Brochure, drug product sheet, device manual, user's manual, instructions for use, package insert, IND/IDE documentation, FDA 1572 form, 510k indication, FDA exemption, sponsor determination of device risk, etc.
- **Export Control Review**
- **Grant Application(s)** – complete copy of grant, regardless of home institution or funding agency, and a copy of the Notice of Grant Award
- **Informed Consent/Permission/Assent Form(s)** – including study specific release of information documents, DHHS approved sample consent forms. If consent will not be documented in writing, a script of information to be provided orally to subjects
- Other Approval letters (e.g., school districts, Tribal, other IRB approvals)
- **Participant Materials** – All written materials to be provided to or meant to be seen or heard by subjects (e.g. study newsletter, physician to participant letter, wallet cards, incentive items, holiday/birthday cards, certificates, instructional videos/written guides, calendars, certification of achievement, etc.)
- **PHI Authorization Form(s)**
- **Protocol** – including all amendments/revisions, sub- or extension-studies
- **Radiation Safety Review** letter
- **Recruitment Materials** – telephone scripts, flyers, brochures, websites, email texts, radio/television spots, newspaper advertisements, press releases, etc.
- **Scientific Review Committee** letter (for cancer related projects – AZCC SRC; other units as applicable if the unit has a scientific review committee)
- **Site Authorizations** for research purposes and/or access to administrative records/samples
  - External sites (such as schools, other hospitals or campuses, etc.)
  - UAHN University Campus, South Campus and clinics Site Review Authority (SRA) approval
- **Supplemental site information** (for sites engaged in research where the UA is the IRB of record)
  - Copy of any approvals granted from that site (including determinations if this site has an IRB of its own)
  - Site-specific F107
  - Copy of the site's human subjects training policy
  - CV and medical license (if applicable) of site PI
- **Travel Authorization documentation** (for UA – Office of Global Initiatives)
- **Use of retrospective research samples and/or data** – IRB approval letter, original consent under which samples/data were collected, letter allowing access to samples

## Submitting documents to the IRB

All materials must be typed and submitted electronically. Maintain electronic copies of all information submitted to the HSPP office in case revisions are required. It is recommended that version dates be used while naming documents.

1. Documents must be submitted to the VPR-IRB@email.arizona.edu account and not to individual staff email accounts. After contact by a staff member future correspondence may be communicated directly to the staff member concerning the submission.

2. **If acknowledgement of receipt is needed, please request a "Read Receipt" through your email server.** If you use Microsoft Outlook 2007, this is accomplished by clicking "Options" and choosing the "Request a Read Receipt" checkbox in a new email.

3. One submission request per email (e.g. one new project submission, one continuing review plus attachments, or one modification request).

4. All submissions must have signatures. An email acknowledgement in place of a signature will not be acceptable. If electronic signatures are not available for use, the signature pages may be signed and scanned as a separate Adobe PDF document and attached to the submission email.

5. **Microsoft Word documents are REQUIRED** for (applications, consents, recruitment materials, and data collection instruments (if available). PDFs may be submitted for documents that typically are not revised by the IRB (e.g. Investigator Brochures, sponsor protocols).

6. The email subject line must include: IRB # (if assigned one), PI Last Name, and type of submission (Modification, New Project, Continuing Review, Reportable Item, etc.).

7. The email must provide a list of the documents submitted for review. While the documents attached do not have to adhere to a specific naming scheme, it is requested that each document be named to clearly reflect what is inside.

**Submissions not following these guidelines will be returned without review**