Study Title: Bright Light Therapy for Treatment of Sleep Problems Following Mild Traumatic Brain Injury

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PROJECT TITLE: Bright Light Therapy for Treatment of Sleep Problems Following Mild TBI

INVESTIGATOR

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ADVISOR CONTACT INFORMATION (REQUIRED FOR ALL STUDENTS AND RESIDENTS)

Name, Degree(s), UA NetID:	N/A
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ALTERNATE/COORDINATOR CONTACT INFORMATION

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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.

	04/14/14	William D. "Scott" Killgore, Ph.D.
	Date	Print Name

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.

	04/10/14	Nicholas Breitborde, Ph.D.
Signature	Date	Print Name
breitbor@email.arizona.edu	(520)626-7534	
Official University Email	Phone number	

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.

	04/14/14	Karen Weihs, M.D.
Signature	Date	Print Name
weihs@email.arizona.edu	(520)626-8940	
Official University Email	Phone number	

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

SECTION 2: GENERAL INFORMATION

1. Not including this project submission, how many:

a. Human Research studies is the PI involved in as key personnel? — 3 to be IRB approved for opening, key personnel on 5 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? — 0

d. Research coordinators are involved on the PI's open Human Research studies? — 3

2. What is the expected length of this project? — 3 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)? — AHSC 7327A

b. How long will the data/consents be kept after conclusion of the project? — ☐ 6 years ☒ Other: Indefinitely

4. If the Human Research project is funded, identify all sponsoring entity/ies): — Department of Defense (DoD)

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 — Awaiting notice of award; Proposal ID PT130230

6. Total funding amount **OR** per subject amount: — To be determined; awaiting award

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): NCT02374918

☐ Registration pending

☐ Clinical trial does not require registration (click above to see what studies qualify)

SECTION 3. PROJECT NARRATIVE

1) Background

Mild traumatic brain injury (mTBI) has been described as the "signature injury" of the current conflicts in Iraq and Afghanistan (Fear et al., 2008). Improvised explosive devices (IEDs) are often the weapons of choice by insurgents in the current conflicts. With the advances in body armor, many casualties of an IED who would have been killed in earlier conflicts now have a high probability of surviving (Okie, 2005). The detonation of an IED produces a number of blast-related effects on the body, the severity of which is usually dependent on the proximity to the point of the explosion. Soldiers who are not directly killed by an IED explosion may still suffer blast related injuries from the overpressure wave, from flying debris, or from being propelled against the ground or a fixed object. Any of these can produce a head injury. Moderate and severe head injuries are typically obvious due to the level of external damage and debilitation, and usually result in rapid medical evacuation to a medical treatment facility. Less obvious injuries may also occur when a Soldier sustains a head injury but fails to lose consciousness and merely appears "stunned" or "dazed" to other unit members or may regain consciousness within a few seconds to minutes after the injury. In such cases, a mild traumatic brain injury (mTBI) or "concussion" is likely to have occurred, but may not be diagnosed until much later, if at all. Hoge and colleagues recently reported that 4.9% of a large sample of U.S. Army Soldiers returning from wartime deployment in Iraq endorsed having an injury with a loss of consciousness, while an additional 10.3% reported an injury with some form of altered mental status such as being "dazed, confused, or seeing stars" (Hoge et al., 2008). Typically, most mTBI patients show a resolution of their symptoms within a matter of days or weeks (McCrea et al., 2003), with nearly complete return to baseline functioning within 3 months of their injury. However, a small proportion of mTBI patients will continue to have chronic symptom complaints (Ryan & Warden, 2003), a condition which has been described as the post-concussive syndrome (PCS).

Patients with post-concussion syndrome have been shown to have deficits on tests of short term memory, divided attention, multi-tasking, information processing speed, and reaction time (Bigler, 2008; Pare, Rabin, Fogel, & Pepin, 2009), as well as alteration in mood and emotional functioning (Bigler, 2008). Many patients have other vague complaints including fatigue, dizziness, irritability, sleep disturbances, and chronic headaches (Bigler, 2008; Haboubi, Long, Koshy, & Ward, 2001; Packard, 2008). Furthermore, sleep disruption of one of the most common complaints in patients suffering from traumatic brain injuries (Baumann, Werth, Stocker, Ludwig, & Bassetti, 2007; Castriotta et al., 2007; Makley et al., 2008; Parcell, Ponsford, Redman, & Rajaratnam, 2008; Rao et al., 2008; Verma, Anand, & Verma, 2007; Williams, Lazic, & Ogilvie, 2008), with as many as 40 to

65% of patients with mTBI complaining of insomnia (Beetar, Guilmette, & Sparadeo, 1996; Dikmen, McLean, & Temkin, 1986). Sleep problems in these patients are associated with poorer outcome (Franckeviciute, Varzaityte, & Kimtys, 2008), while resolution of the sleep disturbance is associated with improvement in cognitive functioning (Makley et al., 2009). A recent study demonstrated that sleep disturbances, including reduced sleep efficiency, longer sleep onset latency and shorter REM onset latency, were more persistent in mTBI patients for nearly three years after the injury (Williams et al., 2008), and others have found similar long lasting sleep disruption in these patients (Schreiber et al., 2008). Additionally, sleep complaints have been correlated with increased likelihood of mood disturbance and headaches in post-concussive patients (Chaput, Giguere, Chauny, Denis, & Lavigne, 2009). It has been suggested that mTBI might produce alterations of the normal circadian rhythm, leading to delayed sleep phase syndrome and irregular sleep-wake patterns (Ayalon, Borodkin, Dishon, Kanety, & Dagan, 2007). Of mTBI patients with complaints of insomnia, 36% were recently found to have circadian rhythm sleep disorders that emerged following the brain injury (Ayalon et al., 2007). Moreover, the important relationship between sleep and recovery in patients with brain injuries was highlighted in a recent study that showed that sleep efficiency was correlated with the resolution of post-traumatic amnesia in patients with closed head injuries (Makley et al., 2009). Thus, there is little doubt that mTBI is associated with significant disruption of normal sleep patterns and that poorer sleep is associated with poorer recovery, while improvement in sleep problems is associated with improvement in cognitive functioning.

Despite recent evidence of the correlation between sleep quality and recovery from traumatic brain injury (Makley et al., 2009), and the well-established role of sleep in neural plasticity (Aton et al., 2009; Stickgold & Walker, 2007; Walker, 2009; Walker & Stickgold, 2006) and neurogenesis (Hairston et al., 2005; Meerlo, Mistlberger, Jacobs, Heller, & McGinty, 2009), there have been virtually no direct studies of the causal effects of sleep on recovery following mTBI. However, it is quite likely that sleep plays a critical role in recovery following brain injury. First, sleep facilitates learning of new skills and information and leads to functional reorganization of the brain (Orban et al., 2006). It has long been known that sleep following learning enhances subsequent retrieval and performance (Diekelmann, Wilhelm, & Born, 2009; Ellenbogen, Hulbert, Jiang, & Stickgold, 2009; Walker & Stickgold, 2006), and recent studies have shown that sleep is a critical factor in synaptic strengthening following learning (Aton et al., 2009) and that hippocampal-cortical reorganization occurs during sleep (Yordanova, Kolev, Wagner, & Verleger, 2009). New evidence also suggests that sleep quality before learning is also critical to hippocampal encoding, such that even a small disruption in sleep can affect declarative learning the subsequent day (Van Der Werf et al., 2009). Thus, sleep and new learning appear inextricably linked. Second, the quantity and quality of sleep affects a variety of hormonal systems that may influence brain function and repair, and sleep may also be important in reducing oxidative damage to neurons and provide an opportunity for neural resynchronization (Schulze, 2004). Sleep is also hypothesized to be critical to neural development (Marks, Shaffery, Oksenberg, Speciale, & Roffwarg, 1995), functioning, repair, and plasticity (Frank, 2006; Frank, Jha, & Coleman, 2006; Gally & Edelman, 2004). This plasticity is reflected in the growth of new synapses in response to learning (C. Smith, 1996). Moreover, some recent evidence suggests that sleep may be critical in the neurogenesis (Meerlo et al., 2009) and proliferation (Tung, Takase, Fornal, & Jacobs, 2005) of neurons in the hippocampus, a brain structure that is critical to the formation of new memories (Guzman-Marin, Bashir, Suntsova, Szymusiak, & McGinty, 2007;

Guzman-Marin et al., 2008; Hairston et al., 2005; Mueller et al., 2008). Prolonged sleep restriction or sleep deprivation appears to have cumulative effects that severely impair hippocampal cell neurogenesis, proliferation, and survival (Meerlo et al., 2009). Of relevance to the presently proposed study, a recent discovery suggests that melatonin, a hormone that is closely linked to light-dark cycles and circadian sleep patterns, is the only known exogenously applicable chemical associated with increased cell survival of newly formed neurons in the rat hippocampus (Ramirez-Rodriguez, Klempin, Babu, Benitez-King, & Kempermann, 2009). While no studies have directly examined the effects of sleep on recovery from mTBI, there is evidence that sleep is essential in restoring motor learning following a cerebrovascular accident (C. Siengsukon & L. A. Boyd, 2009). For example, patients recovering from stroke showed significant improvement in motor learning following sleep compared to those without sleep (C. F. Siengsukon & L. A. Boyd, 2009b). Moreover, this enhancement of learning was much stronger in the stroke rehabilitation group than in a healthy control group, suggesting that sleep may play an important role in recovery from brain injury. Other studies have shown that the quality and quantity of sleep following stroke is correlated with recovery of cognitive functions (Siccoli, Rolli-Baumeler, Achermann, & Bassetti, 2008). Emerging perspectives on rehabilitation are beginning to focus on the importance of sleep in rehabilitation of patients following brain injuries such as stroke (C. F. Siengsukon & L. A. Boyd, 2009a). Because mTBI disrupts normal neural functioning and may even lead to cell death, rehabilitative efforts may be most effective if they facilitate these processes, all of which are protected or enhanced by adequate sleep. Without adequate sleep, normal brain repair processes are likely to be hampered. Therefore, research efforts aimed at understanding the effects of sleep and circadian misalignment on the recovery process are necessary.

A particularly promising non-pharmacologic approach that shows potential in improving/modifying abnormalities of the circadian rhythm and sleep-wake schedule is bright light therapy, particularly within the blue-wavelength spectrum (Brainard et al., 2008; Phipps-Nelson, Redman, Schlangen, & Rajaratnam, 2009; Revell & Skene, 2007; M. R. Smith, Revell, & Eastman, 2008), which involves the selective application of bright light pulses at critical points in the circadian cycle (Brainard & Hanifin, 2005; Geuze et al., 2008; Skene, Lockley, Thapan, & Arendt, 1999). The crucial effect of light on the entrainment of the circadian rhythm of sleep and wakefulness is well documented (Czeisler & Gooley, 2007; Lockley, Brainard, & Czeisler, 2003; Roenneberg & Merrow, 2007; M. R. Smith, Cullnan, & Eastman, 2008), and bright light therapy has long been recognized as an extremely effective treatment for some types of neurobiolgically based mood disorders, such as Seasonal Affective Disorder (Anderson, Glod, Dai, Cao, & Lockley, 2009). Due to its mood altering effects, bright light therapy is also being explored for its effects on a variety of psychiatric conditions (Prasko, 2008; Terman, 2007).

A recent discovery has documented that there are photoreceptive ganglion cells in the retina (Dacey et al., 2005). These receptors do not appear to be involved in visual sensation, but instead have special pigmented cells that are responsive to the blue wavelengths of light, which are believed to be primarily involved in circadian regulation (Hanifin & Brainard, 2007). These melanopsin receptors are involved in light transduction and may have direct effects on several neurotransmitter and neuroendocrine systems, including serotonin (Ljubicic, Stipcevic, Pivac, Jakovljevic, & Muck-Seler, 2007) and melatonin (Brainard et al., 2001; Revell & Skene, 2007). The blue wavelengths of light, in particular, are believed to suppress melatonin (Brainard et al., 2008; Gammack, 2008;

Lockley & Gooley, 2006; Revell & Skene, 2007), a naturally produced hormone that is believed to be one of the primary regulators of daily rhythms, including sleep and wakefulness (Lewy, Emens, Jackman, & Yuhas, 2006; Revell & Eastman, 2005). For example, administration of a sustained pulse of blue-enriched bright light in the early morning hours before the circadian temperature nadir suppresses melatonin and reduces the circadian drive for sleep, leading to greater overnight alertness (Lockley et al., 2006; Santhi, Aeschbach, Horowitz, & Czeisler, 2008). Morning bright light also phase advances the normal circadian rhythm, thereby reducing sleep onset insomnia (Lack, Gradisar, Van Someren, Wright, & Lushington, 2008; Lack & Wright, 2007; Skene, 2003). Given that the melanopsin receptors appear to be primarily responsive to blue wavelength light (Revell & Skene, 2007), and that similar melatonin suppressing effects can be produced with significantly lower light intensities in the blue-wavelengths, numerous studies have now begun to focus on using this wavelength for improving daytime alertness, subjective sleep quality (Viola, James, Schlangen, & Dijk, 2008), and phase advancing individuals with delayed sleep phase disorders (Lockley et al., 2003; M. R. Smith, Revell et al., 2008).

Presently, no published studies have examined the effects of bright or blue-enriched light therapy on outcome in mTBI patients. For the proposed investigation, we hypothesize that blue-wavelength light therapy may be helpful in improving the sleep of patients with a recent history of mTBI and may also have other mood elevating effects (Anderson et al., 2009; Glickman, Byrne, Pineda, Hauck, & Brainard, 2006), both of which should promote positive treatment outcome in these individuals. Based on recent evidence that some wavelengths may provide greater suppression of melatonin than others (Glickman et al., 2006; Herljevic, Middleton, Thapan, & Skene, 2005; Skene, 2003; M. R. Smith, Revell et al., 2008; Thapan, Arendt, & Skene, 2001), we propose to use a commercially available device with wavelengths peaking within the blue spectrum (i.e., 467), which has shown documented success in treating seasonal affective disorder (Skene, 2003) and suppressing melatonin (Fucci et al., 2005).

Interestingly, preliminary data from our own laboratory examining the effects of a 10 minute pulse of blue-wavelength light (469 nm), using the goLITE BLU device proposed for the present study, demonstrates significant increases in brain regions involved in emotional control, alertness, and self-awareness, including the lateral prefrontal cortex, thalamus, and posterior cingulate gyrus during a conflict monitoring task (see figure).

This same cognitive task will be used as part of the proposed study during fMRI scanning. We propose that direct intervention to improve the sleep difficulties in mTBI via blue light therapy may lead to entrainment of the circadian rhythm, improved sleep, and enhancement of daytime alertness. These improvements are predicted to lead to improved emotional regulation, neurocognitive performance, and accelerated improvement in symptoms among patients with mTBI.

The primary aims of the proposed study are to examine the effectiveness of an six-week course of morning blue light therapy (MBLT) on objective and subjective measures of sleep, emotional functioning, mood, psychiatric symptom expression, and neuropsychological assessment using the most current version of the Automated Neuropsychological Assessment Metric (ANAM4) TBI battery. In addition, changes in behavioral functioning produced by MBLT will also be correlated with changes in Blood Oxygen Level Dependent (BOLD) functional magnetic resonance imaging (fMRI) during an executive control task, a virtual reality water-maze task that assesses hippocampal memory function, and a working memory n-back task. These tasks have been used extensively in our

laboratory and provide excellent resolution for evaluating functional changes within the target regions of the anterior cingulate gyrus, hippocampus, and prefrontal cortex. Furthermore, the proposed project will directly assess sleep functioning using actigraphy and correlate these changes in sleep with pre-to post-treatment changes in neurocognitive performance and symptom presentation, as well as functional activity changes.

Briefly, individuals who have experienced a mTBI, with or without loss of consciousness, as verified by a medical report, and who complain of sleep disturbance, will undergo an initial psychological assessment, and will be then fitted with an actigraph to wear for the duration of the study in order to measure baseline sleep as well as any changes in sleep patterns. Individuals will then return to complete two comprehensive neurobehavioral assessment and neuroimaging sessions (functional MRI, structural MRI/diffusion tensor imaging; DTI) separated by 6 weeks. During the intervening 6 weeks, participants will be randomly assigned to receive 30 minutes of morning blue light therapy (MBLT) or a sham placebo amber light treatment (SPLT) daily. Sleep quality and quantity will be measured via continuous wrist actigraphy monitors and self-report inventories.

For interested subjects participating in the last phase of recruitment, we will continue collecting wrist actigraphy and self-report data for an additional 6 weeks after completion of the baseline period and light therapy as an optional part of the study. It is hypothesized that MBLT will improve sleep quality and quantity relative to SPLT, and these improvements will be associated with changes in brain function, brain structure, and reduced post-concussion symptom severity at follow-up assessment.

Significance

Given the large number of military personnel returning from combat operations in Iraq or Afghanistan with reported or suspected head injuries (Hoge et al., 2008), the outcome of the present study could have significant impact on the delivery of health care to returning military veterans. Other than cognitive-behavioral therapies and avoidance of re-injury, there are few alternative treatments for patients suffering from post-concussive symptoms secondary to a mild traumatic brain injury. Alternative approaches to treatment, or adjunctive approaches that can be used to augment ongoing treatments, are clearly needed. Because sleep disruption is one of the primary complaints of individuals following mTBI, and sleep is critical to neurogenesis and neural plasticity, sleep enhancement seems to be an ideal candidate for direct intervention. If the sleep problems can be improved, it is more likely that emotional difficulties will be reduced, ongoing treatments will be enhanced, and brain functioning can be restored to the fullest extent possible. Furthermore, non-pharmacologic interventions are generally preferable and more cost effective than reliance upon prescription medications for sleep problems. Therefore, it is hypothesized that by using light therapy to entrain the circadian sleep-wake cycle, we may improve sleep in a sample of individuals with a recent history of concussion, and thereby increase the likelihood that they will recover more quickly, benefit more extensively from other forms of therapy, and build emotional and cognitive resilience. If effective, the proposed approach could be used in isolation or as an adjunct to ongoing therapy to reduce the impact of mTBI and post-concussive symptoms, thereby facilitating a more rapid recovery. Even if the proposed light therapy fails to prove effective at improving sleep or symptom profiles, the obtained cognitive and neuroimaging data, neurocognitive testing, and actigraphy data will prove

invaluable in developing further insights into the relationship between mTBI, sleep, and brain function.

2) Lay Summary (approximately 400 words)

Main Study Arm:

Dr. William Killgore and colleagues are conducting a research study funded by the Department of Defense to understand the effectiveness of a six-week course of light exposure on cognitive functioning, mood, activity, and sleep in people that have suffered a mild traumatic brain injury (mTBI) or "concussion." This study will consist of four visits to the University of Arizona.

During the course of the study, participants will complete two cognitive testing sessions and magnetic resonance imaging (MRI) scans (1 hour each), which will occur 6 weeks apart. During the intervening 6-week period, participants will use a commercially available light device to provide 30-minutes of light exposure each morning. During the two testing and MRI scan sessions, participants will undergo a series of tests of attention, concentration, memory, and other cognitive abilities, and will complete clinical measures to assess mood and post-concussion symptom severity. Daily activity and sleep patterns during the entire 13-week period will also be monitored using self-report diaries, questionnaires, and a wrist worn activity monitor. This monitoring will continue for an additional 6 weeks after termination of the light exposure for subjects who elect to participate in this optional research.

In this study, we will use functional and structural brain imaging techniques such as functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) to evaluate brain function and brain structure before and after the 6-week light exposure period. Identifying and mapping the brain systems before and after light exposure may help researchers develop further insights into the relationship between concussion, light exposure, sleep, and brain function.

Those deemed eligible to take part in this study will have experienced a mild traumatic brain injury (mTBI) or concussion during the past 18 months, but no sooner than four weeks prior to the screening. Approximately 40 individuals between the ages of 18 and 50 will participate in this study in order to obtain a final dataset of 30 due to attrition.

Healthy Control (HC)/Effect Localization Arm:

This study will also have a healthy control (HC)/effect localization arm. We will enroll 50 healthy individuals ages 18 to 50 for this arm of the study. A simple computer randomization will be performed that assigns slots before the study begins. This block randomization will ensure essentially equal numbers of males and females.

These subjects will perform very similar activities as subjects for the main arm of the study, albeit, pared down as it is a streamlined, basic form of the main study arm. Their participation is expected to last one day over two visits and no more than approximately 5.5 hours.

During their initial visit, subjects will be asked to complete a single cognitive testing session and magnetic resonance imaging (MRI) scan. Prior to the scan, subjects will wear an EKG (electrocardiogram) device for the duration of the visit, save for the MRI scan. Subjects will complete study assessments (DOSQ, MEQ, PANAS, BDI-II, WASI, CVLT, SWLS) and then will be asked to sit in a room for 60 minutes of either 30 minutes of amber placebo light exposure followed by exposure to a blue wavelength light device (goLITE BLU) or an amber placebo/sham light device in

the same room for the full 60 minutes. During the 30 minute wash out and 30 minute light exposure periods, subjects will be asked to sit quietly for 10 minutes and fixate on a large cross opposite them in order to help get clean EEG data. During this time, their EEG (electroencephalography) will be recorded via leads attached to the subject's scalp to help measure brain activity. It must be noted that because subjects will see the color of light they will be exposed to, it is impossible to blind subjects to the condition**.** Hopefully, subjects will not be to knowledgeable about the effects of various wavelengths of light. Following this, participants will get into the fMRI scanner and will undergo a series of tests of attention, concentration, memory, and other cognitive abilities (CVLT II, MSIT, N-Back, BMAT, Anticipation Task), and will complete clinical measures to assess mood. Subjects will have their heart rate monitored via EKG during baseline and post treatment visits only. Subjects will complete several post-scan tests and questionnaires including the PANAS to conclude their participation. Over the course of the initial visit, subjects will also have 3 saliva collections to measure their melatonin levels. Before concluding their initial visit, subjects will be given and instructed in the use of an Actiwatch device to wear until their follow-up visit the same day.

Subjects will be asked to return for a follow-up visit at approximately 8:30pm the same day to collect a fourth and final melatonin sample as well as return the Actiwatch.

In this study, we will use functional and structural brain imaging techniques such as functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) to evaluate brain function and brain structure. Identifying and mapping the brain systems before and after light exposure may help researchers develop further insights into the relationship between concussion, light exposure, sleep, and brain function and will provide brain targets for study in the analysis of the Main Study Arm.

Please note that all cognitive testing, questionnaires, and MRI/fMRI scanning for this healthy control arm are akin to the main arm of this study.

3) Setting of the Human Research

The main study arm requires three visits including an initial assessment and two testing/scanning sessions separated by six weeks of daily light exposure treatment at home. The healthy control or effect localization arm requires one day and two visits cumulatively lasting approximately 5.5 hours.

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. Dr. Killgore's lab in Suite 7304 consists of a lounge, two sleep lab rooms, and a testing room. 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 University of Arizona Medical Imaging.

MRI will be conducted at the Translational Bioimaging Resource (TBIR), housed in the basement of the Biosciences Research Labs (BSRL) building. The 12,000 sq. ft. TBIR serves as a university-wide resource for pre-clinical biomedical imaging. BSRL is equipped with waiting areas, dressing rooms, and storage lockers for participant comfort and convenience. The elevator down to the TBIR is limited access, operable only by staff with an authorized CatCard, who will escort subjects to the scanner area. Designated MRI participant parking is located directly across the street from the BSRL building. The TBIR houses a 3 Tesla Siemens Skyra VE11 capable of supporting a wide range of research, including arthritis, traumatic brain injury, PTSD, cancer treatment efficacy, depression, kidney transplant viability, CPR, Alzheimer's, complex grief, and healthy aging. 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, located immediately adjacent to the 3.0 Tesla scanner, is equipped with 3 PC/Linux workstations and an 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 at a minimum two full-time research technicians (Research Assistants) and one full-time postdoctoral research associate.

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 Sleep Deprivation 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.

University of Arizona Medical Center (UAMC) is a private, non-profit 487-bed acute-care hospital in Tucson, Arizona. UAMC has two units: University Campus and South Campus. The University of Arizona affiliated medical services include: University Medical Center, University Physicians Healthcare, and the College of Medicine. UAMC is part of Arizona Health Sciences Center (AHSC) campus, including the Colleges of Medicine, Nursing, Pharmacy and Public Health. Additionally, UAMC is an American Nurses Credentialing Center (ANCC) Magnet Hospital.

The Clinical and Translational Sciences Center (CaTS) storage area contains protected access freezers where all saliva samples will be stored and protected. The University of Arizona Cancer Center (UACC) lab room 4916 will serve as the site for melatonin sample analysis.

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

5) Study Population

Main Study Arm:

Forty (40) individuals between the ages of 18 and 50 with a documented history of a "concussion" or mTBI in the preceding 18 months but no sooner than 4 weeks prior to the screening will be recruited to participate in the main study arm. It is anticipated that approximately 6 participants (i.e., 17%) will withdraw early or fail to comply with procedures. Thus, a total of 40 participants will be run to achieve a total sample size of 30 complete datasets. The occurrence of a concussion or mTBI must be documented by a medical/objective professional (e.g., sports trainer, coach, physician, nurse, etc.) report. In addition, at least half of the participants recruited for each condition will be required to have complaints consistent with sleep onset insomnia (i.e., trouble falling asleep) as measured by Insomnia Severity Index (ISI) or delayed sleep phase disorder (i.e., not feeling sleepy at bedtime and/or not able to fall asleep until much later than bedtime). Participants with a lifetime history of head injury leading to loss of consciousness greater than 30 minutes will be excluded. Other exclusion criteria will include any current medical condition that would be contraindicated for scanning, other known neuropathology (e.g., tumor, neurodegenerative disease, normal pressure hydrocephalus, etc.), abnormal visual acuity that is not corrected by contact lenses, metal within the body, or time since injury exceeding 18 months.

Inclusion criteria:

- Age range between 18 and 50.
- The primary language of the subjects must be English.
- Subjects have experienced a "concussion" or mTBI within the preceding 18 months, but no sooner that 4 weeks prior to their screening. The occurrence of a concussion or mTBI must be documented by a medical report or other professional witness documentation.
- If documented, Glasgow Coma Scale in the range of 13-15 following the injury.
- At least half of subjects must have evidence of sleep onset insomnia or delayed sleep phase disorder.

Exclusion criteria:

- Any other history of neurological illness, current DSM-IV Axis I disorder, lifetime history of psychotic disorder, or head injury with loss of consciousness > 30 minutes
- Complicating medical conditions that may influence the outcome of neuropsychological assessment or functional imaging (e.g., HIV, brain tumor, etc.)
- Abnormal visual acuity that is not corrected by contact lenses
- Metal within the body (including those made of materials considered "MRI safe," such as permanent dental retainers or braces), claustrophobia, or other contraindications for neuroimaging (via MRI Metal Checklist)
- Less than 9th grade education
- Excess current alcohol use (more than 2 instances of intake of 5+ drinks (men) when or 4+ drinks (women) when drinking in the past two months, and/or on average drinking > 2 drinks per day (men); > 1 drinks per day (women) during the past two months (as verified via the Standard Drink handout for subjects)
- History of alcoholism or substance use disorder
- Significant use of illicit drugs

- History of marijuana use within the past 4 weeks, use of marijuana before the age of 16, and/or history of greater than moderate marijuana use throughout the participant's lifetime.
- Subjects who engage in shift-work, night work, or who have substantially desynchronized work-sleep schedules (i.e., sleeping later than 10:00 a.m. more than once a week) will be excluded.

Healthy Control/Effect Localization Arm:

Approximately Fifty (50) healthy individuals ages 18 to 50 will be recruited for enrollment into this study arm in order achieve a final collection of 30 useable datasets accounting for attrition. Healthy individuals for the purposes of this study are defined as being free of any history of concussion, or significant medical, neurological, or psychiatric illness that could affect brain function/structure (e.g., brain tumor; HIV; depression).

Inclusion criteria:

- Age range between 18 and 50.
- The primary language of the subjects must be English (started speaking at 2 years of age or younger, per self-report).

Exclusion criteria:

- Subjects have experienced a "concussion" or mTBI within the preceding 18 months. Any other history of neurological illness, current DSM-IV Axis I disorder, lifetime history of psychotic disorder, or head injury with loss of consciousness > 30 minutes
- Complicating medical conditions that may influence the outcome of neuropsychological assessment or functional imaging (e.g., HIV, brain tumor, etc.)
- Abnormal visual acuity that is not corrected by contact lenses
- Metal within the body, claustrophobia, or other contraindications for neuroimaging
- Less than 9th grade education
- Excess current alcohol use (more than 2 instances of intake of 5+ drinks (men) or 4+ drinks (women) when drinking in the past two months, and/or on average drinking > 2 drinks per day (men); > 1 drinks per day (women) during the past two months (as verified via the Standard Drink handout for subjects)
- History of alcoholism or substance use disorder
- Significant use of illicit drugs
- History of marijuana use within the past 4 weeks, use of marijuana before the age of 16, and/or history of greater than moderate marijuana use throughout the participant's lifetime.
- Subjects who engage in shift-work, night work, or who have substantially desynchronized work-sleep schedules (i.e., sleeping later than 10:00 a.m. more than once a week) will be excluded.

6) Recruitment Methods and Consenting Process

Potential subjects will be recruited 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 UAMC hospital screens and flyers in clinics and on UA and Pima Community College campuses, as well as UA list serves such as 3D memos etc (ad text will be IRB approved, and appropriate recruitment advertisement authorization obtained prior), UA-affiliated websites dedicated to research (e.g., the UAHS Clinical Research Studies website https://studies.medicine.arizona.edu/find-trial) residence Halls, and other UA buildings (with the appropriate recruitment site authorization obtained prior). We may recruit in private businesses (with prior permission for recruitment obtained prior) or in public spaces by handing out approved flyers or using other such recruitment material.

We will make approved screening surveys (e.g., *BL2_Pre-screen_survey.doc*) 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), 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. Web-based surveys will be securely hosted in Qualtrics, REDCap, or other such reputable survey-host.

Subjects will be recruited from the Introduction to Psychology (PSY101) course at U of A. Students enrolled in PSY 101 are required to participate in research as part of the course, and students are commonly recruited in class via mass survey; we will use only IRB-approved screening surveys for this purpose. This recruitment will take place online: PSY101 students will be given a link (https://arizona-psych.sona-systems.com/Default.aspx?ReturnUrl=/) on the Department of Psychology website and in the course syllabus and D2L page, which will lead to a survey (e.g., *BL2_Screen_survey.doc*) to determine eligibility. Once submitted, study staff will evaluate eligibility and contact those who are eligible.

In addition, UA Clinics (i.e. CAPS, Campus Health, etc..), Banner Health clinics (BUMCT Emergency Department, 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 which 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. Recruitment materials will be distributed according to applicable stipulations described above to neighboring cities such as Phoenix and Marana in addition to the greater Tucson area.

We will utilize a 3rd party company, Twilio (see https://www.twilio.com/learn/call-and-text-marketing), to initiate a mobile marketing campaign. The company provides a local telephone number to be associated with the study to which participants may call or text to reach us. The third party company allows access to automated texts wherein an interested subject may text a "keyword(s)" (as

decided by our laboratory) to instantly receive a reply with a link to the online screening form (*BL2_Screen_survey.docx)*.

Potential subjects will contact the number listed on the advertisement and will speak to a study representative who will explain the study requirements and eligibility criteria. Potential subjects will be pre-screened to ensure that they meet basic eligibility criteria. Screening data will be collected on the telephone screening form. Interested subjects who meet eligibility requirements will be scheduled to come to UA Psychiatry for the first visit.

Recruitment materials will be distributed according to applicable stipulations described above to neighboring cities such as Phoenix and Marana in addition to the greater Tucson area. We will also recruit retrospectively by accessing Banner Health Network's electronic medical record (EMR) for persons who have previously sought treatment for a head injury and who fit eligibility criteria for the study. Only information necessary to ascertain eligibility and contact these persons for recruitment will be abstracted. All data will be coded, and the data and master list will be kept separately and secured via encryption, password protection, and physical and electronic access limited only to necessary personnel. All links will be destroyed at the earliest opportunity. This pre-screening of the medical record for recruitment purposes will be conducted under a partial waiver of PHI Authorization. Treating physicians will send a recruitment letter (BL2_mTBI_EPIC_letter.doc), which contains a form by which subjects may provide permission to be contacted for this research, with possible follow-up by study staff via telephone if no response is received within 10 days of the treating physician mailing the letter. Patients who return the contact form accompanying the letter will be called by study staff, who will use the appropriate phone script (retrospective) to explain the study and ascertain interest. Patients who remain interested will then be asked if they are willing to answer additional questions to ascertain eligibility.

Staff from the UA Department of Emergency Medicine's Research Associates Program (RAP), or clinic staff may assist with recruitment in the clinic by obtaining contact information on a Permission to Contact Form (BL2_Permission_to_contact.doc) from interested individuals. This recruitment activity will not involve collection of PHI and RAP staff will not be involved in consenting for this study; rather, they will work with clinic staff to identify potential candidates for the study by reviewing patient eligibility with the medical team, including nurses, residents, attending physicians, etc., and serving as the liaison between the medical team and the research team. RAP volunteers/interns do not have medical record access for screening purposes, will not be involved in consenting nor answering study-specific questions, and not contributing to the development of the study in a significant way. They currently recruit by connecting with hospital staff and identifying patients who might qualify for a research study, then providing willing patients with information about the study in the way of fliers, consent documents, etc. Therefore, they are not included on the List of Research Personnel. All RAP volunteers have completed HIPAA and human subjects protection training.

Finally, we will recruit prospectively through healthcare providers at certain Banner Health clinics. Any healthcare providers enlisted to assist in recruitment will be added to the F107 as a member of the study team prior to involving their department in study recruitment procedures. Patients seeking treatment at BUMCT Emergency Department or other Banner Health facilities for a *new head injury* may be asked by their treating physician if they are interested in the study. Interested patients will be offered a Permission to Contact form (prospective) by the treating physician to

authorize contact by study staff to ascertain interest in the study. Patient contact information (phone number, mailing address, and/or email address) will be collected on the authorization form. Patients who sign the contact permission form will then be called by study staff, who will use the appropriate phone script (prospective) to explain the study and ascertain interest. Patients who remain interested will then be asked if they are willing to answer additional questions to ascertain eligibility. The contact permission form with the patient's contact information will be destroyed after the patient is contacted and the phone screening completed.

Written informed consent by the adult participant will be obtained by the principal investigator or his qualified designated representative prior to participation in the study. At the time of the first study visit, a qualified project staff member will carefully review the consent forms with the potential research participants. In addition to reviewing the study procedures, subjects will be informed of the voluntary nature of the study and that they can withdraw at any time. The potential risks and benefits of this study will be explained appropriate language. Subjects must be capable of understanding the nature of the study as well as the discomforts and potential benefits. Subjects will be given a copy of the signed Informed Consent Form. The study will not include subjects who do not have English as their primary language to ensure they are able to understand study procedures and activities.

Pertinent updates/changes to the research will be submitted to and approved by the IRB before being utilized. All recruitment materials for the Healthy Control Arm will be submitted for IRB approval prior to use. Subjects will read and sign updated consent forms reflecting these changes should they occur.

7) Procedures involved in the Human Research

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.*

This study will be conducted over a 3-year period. All main study arm participants will undergo an initial assessment and two testing/scanning sessions separated by 6-weeks of treatment with blue light or a sham placebo amber light treatment. Healthy control subjects will undergo an initial assessment and a single testing/scanning session only and their participation will be complete. Ten to 16 subjects will be run each year (i.e., 2 sessions per subject = 20-32 scan/assessment sessions per year). Data collection will continue for an additional 6 weeks after completion of light therapy for subjects who elect to participate in this optional research. Potential subjects will learn about the study through posted flyers, internet and radio advertisements, and physician referrals. Interested participants will call the pre-specified telephone number and will be given a brief introduction to the study and be informed about the exclusionary criteria and requirements of the study.

Before enrollment, interested participants will be required to contact their physician/medical provider/other professional witness (e.g., sports trainer, coach) to have documentation of head injury/concussion and severity provided. Participants meeting inclusion criteria will provide informed

consent during an initial assessment session and will then be scheduled for a baseline assessment/scanning session.

At baseline, participants will complete a comprehensive neuropsychological test battery, including personality and psychodiagnostic testing, a modified sleep latency test (MSLT), and will undergo two scanning sessions, including 3T fMRI, structural MRI, and DTI scans.

Over the next 7 weeks, participants will wear a wrist actigraph for sleep monitoring and complete daily sleep diaries. During the 6 weeks between the second and third session participants will use a commercially available light therapy device for 30 minutes daily, within 2 hours of awakening, but prior to 10:30 A.M. each day. Subjects will be contacted by phone about once per week for a brief follow up to make sure that everything is progressing well and to answer any questions that arise.

After the treatment period, participants will return for a follow-up assessment/scanning session similar to that conducted at baseline.

Optional Sleep Follow-up Monitoring:

Subjects may choose to participate in an additional 6 weeks of sleep monitoring. Willing subjects who indicate their agreement on the consent document will continue wearing the wrist-worn actigraph and complete daily sleep diaries for up to 6 weeks after termination of the light exposure period.

One year post-participation in the study, subjects who consent will have a follow-up phone call where they will be administered the RPCSQ, the PHQ-9, and be asked about general sleep problems using the ESS.

Telephone Screening

All potential volunteers will initially be screened via telephone interview with a trained research technician. Screening will include basic information about the study and its requirements. Potential volunteers will be asked a series of screening questions to determine eligibility. These questions will assess the length of time since the suspected mTBI incident, general health, medications, and contraindications for MRI scanning or light therapy, and the presence of sleep disruption. Eligibility will require an mTBI within the past 18 months, with either no loss of consciousness (LOC) or LOC lasting less than 30 minutes and (if scores are available) a Glasgow Coma Scale of 13-15. Furthermore, half of the subjects assigned to each group will be required to show evidence of sleep onset insomnia or delayed sleep phase, as identified though screening and questionnaires. Additionally, participants engaging in shift-work, night work, or those with substantially desynchronized work-sleep schedules (i.e., sleeping later than 10:00 a.m. more than once a week) will be excluded. Individuals meeting basic eligibility requirements will be instructed how to provide physician/medical/professional verification of their head injury and will be scheduled for an initial assessment session.

Initial Assessment

Upon arrival, all participants will have the procedures thoroughly explained and will complete verbal and written informed consent procedures. Participants will complete the Mini-International Neuropsychiatric Interview (MINI), the Screen Time Questionnaire, Personality Assessment Inventory (PAI), the Wechsler Abbreviated Scale of Intelligence II (WASI™ II) as a measure of

intelligence and the VA National Traumatic Brain Injury Neurobehavioral Symptom Inventory (NSI). The first visit is still considered part of the initial screening portion of the study and the subject's responses to the assessments and questionnaires will be evaluated to determine his or her eligibility for subsequent portions of the study. For example, if significant psychopathology or other disqualifying condition is discovered during the psychiatric assessment 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. If the participant is deemed ineligible for continuation, compensation will be provided for the time he or she participated according to a prorated schedule. At the conclusion of the initial assessment, eligible participants will be fitted with a wrist actigraph (Actiwatch AW-Spectrum) for measuring sleep-wake patterns and trained in its use. In addition, participants will be given a sleep diary to be completed upon awakening each morning. Subjects will wear the wrist actigraph and complete sleep diaries and scales for the week prior to their baseline assessment/scanning session.

Personality and Psychodiagnostic Assessment

At the Baseline and Post-Treatment sessions, further assessment of psychopathology will be made via administration of the Beck Depression Inventory (BDI-II); the patient health questionnaire (PHQ); Rivermead Post-Concussion Symptoms Questionnaire (RPCSQ), Buss Perry Aggression Questionnaire (BPAQ), and Spielberger State-Trait Anxiety Inventory (STAI). Risk-taking propensity will be assessed with the Evaluation of Risks Scale (EVAR) and Invincibility Beliefs Index (IBI). Participants will also complete basic questionnaires regarding sleep history, caffeine use, Morningness-Eveningness traits (MEQ), Stanford Sleepiness Scale (SSS), Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS), the Satisfaction with Life Scale (SWLS), and the Functional Outcome of Sleep Questionnaire (FOSQ)(Weaver et al., 1997). These measures of sleep parameters and mood state will permit comparison of the effects between treatment with MBLT and SPLT on mood and sleep (OBJECTIVE 1) and will be correlated with other measures of neurocognition and neuroimaging (OBJECTIVE 3).

Neurocognitive Assessment

All participants will complete a comprehensive neuropsychological assessment battery. This battery will assess whether neurocognitive abilities on the ANAM are improved by the MBLT treatment relative to placebo (OBJECTIVE 2) and will be correlated with changes in sleep and neuroimaging parameters (OBJECTIVE 3). 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. The recording will then be deleted. This assessment will include:

1. ANAM4® TBI Battery. Participants will complete a comprehensive neurocognitive assessment using the ANAM4® Core battery. The specific tests assess different basic functions (or domains) of cognition such as attention, reaction time, memory, and concentration which are often affected

by mTBI. This battery will be administered to assess improvement in cognitive abilities in each group (OBJECTIVE 2). The full ANAM4® can be self-administered by the user and takes approximately 60 minutes to complete. The ANAM Core modules that will be tested include:

a. Modified Stanford Sleepiness Scale. This test permits self-assessment of the user's sleep/fatigue state (and/or trait). The user is presented with seven different statements of alertness/sleepiness, ranging from "Feeling very alert, wide awake, and energetic" to "Very sleepy and cannot stay awake much longer." The user is instructed to select the one statement that best matches the current state.

b. Symptoms Checklist. This test assesses frequency and severity of subjective symptoms frequently reported following mild TBI and other emotional and physical conditions. The user is asked to rate each of 21 symptoms on a scale from 0 (Not Present) to 6 (Severe). Included within these 21 symptoms are 12 symptoms that make up the Concussion Symptom Inventory reported by Randolph and colleagues (2009) to be particularly sensitive to identifying individuals with a history of concussion.

c. Mood Scale II – Revised. This test permits self-assessment of the user's mood state in seven categories: Vigor (high energy level), Happiness (positive disposition), Depression (dysphoria), Anger (negative disposition), Fatigue (low energy level), Anxiety (anxiety level), and a new subcategory of Restlessness (motor agitation). The user is presented with a scale of numbered blocks ranging from 0 to 6, with "0" having the verbal anchor "Not at all," the midpoint "3" labeled "Somewhat" and "6" labeled "Very much." The user is presented a series of adjectives, each adjective contributing to one of the mood categories, and is instructed to select the box/number that best represents the current state with respect to the presented adjective.

d. Simple Reaction Time. This test measures simple reaction time by presenting the user with a series of "*" symbols on the display. The user is instructed to respond as quickly as possible by pressing a button each time the stimulus appears.

e. Procedural Reaction Time. This test measures the reaction time and processing efficiency associated with following a simple set of mapping rules. There are three possible blocks of trials for this test. In the Basic Block, the user is presented with a number constructed on the display using a large dot matrix (either a 2, 3, 4, or 5). The user is instructed to press one designated button for a "low" number (2 or 3) and another designated button for a "high" number (4 or 5). In the Coded Block, the user is presented with the same numbers and mapping rules, but the numbers are visually distorted by the presence of noise in the matrix and are more difficult to read. In the Time-Uncertainty Block, the user is presented with the same undistorted stimuli and mapping rules as in the Basic Block, but at longer, irregular interstimulus intervals.

f. Code Substitution. This test assesses visual search, sustained attention, and working memory by asking the user to compare a displayed digit-symbol pair with a set of defined digit-symbol pairs (the key). The user presses designated buttons to indicate whether the pair in question represents a correct or incorrect mapping. In the Learning phase (simultaneous presentation mode), the defined pairs are presented on the screen simultaneously with the digit-symbol pair in question. In the Immediate Memory test that follows the learning phase, the comparison stimuli are presented individually without the key. In the Delayed Memory test presented later in the battery, the comparison stimuli are again presented individually without the key.

g. Matching to Sample. This test assesses spatial processing and visuo-spatial working memory. The user views a pattern produced by eight shaded cells in a 4x4 sample grid. The sample is then removed and two comparison patterns are displayed side by side. One grid is identical to the sample grid and the other grid differs by one shaded cell. The user is instructed to press a designated button to select the grid that matches the sample.

h. Mathematical Processing. This test assesses basic computational skills, concentration, and working memory. An arithmetic problem involving three single-digit numbers and two operators is displayed (e.g., "5 - 2 + 3 ="). The user presses buttons to indicate whether the answer to the problem is less than five or greater than five.

2. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The RBANS is a brief battery of well-normed neuropsychological tests. The test is commonly used for assessing individuals with traumatic brain injury. The RBANS has two alternate forms to permit repeated testing. Subtests include: List Learning, Story Memory, Figure Copy, Line Orientation, Digit Span, Coding, Picture Naming, Semantic Fluency, List Recall, List Recognition, Story Recall, and Figure Recall. The test provides several index scores, including: Total Score, Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory. Alternate forms will be counterbalanced across the two groups. This battery will be administered to assess improvement in cognitive abilities in each group (OBJECTIVE 2).

3. Psychomotor Vigilance Test (PVT). To assess simple reaction time/psychomotor speed, a modified 10-minute version of the PVT will be administered on a computer at three time points during the assessment session (approximately every two hours). This version has been shown to provide valid and reliable estimates of psychomotor vigilance during sleep deprivation (Thorne et al., 2005). During this task, participants will monitor a screen and press a response button on the hand held unit each time an “x” target appears. The interstimulus interval will be varied pseudorandomly between presentations to minimize anticipation of the stimulus. Average reaction time from all trials will be scored for each administration. This task will be administered to assess improvement in cognitive abilities in each group (OBJECTIVE 2).

4. Balloon Analogue Risk Task (BART). A computerized task that requires the participant to fill a simulated balloon with air (Lejuez et al., 2002). Points are given for maintaining the flow of air

and keeping volume of the balloon at as full as possible. The more expanded the balloon gets, the more points are gained. However, all points are lost if the balloon is over-inflated and pops. Thus, the goal is to earn as many points as possible by keeping the balloon inflated safely. The task provides a measure of the willingness to take risks versus "playing it safe." Administration time is approximately 10 minutes.

5. Go/No-Go Task (GNG). This is a computerized measure of response inhibition. Subjects will see two different geometric shapes (circles and squares) that are either large or small. Participants are instructed to press the spacebar (i.e., "go") to all stimuli types except one (e.g., small circle), which is the "no-go" stimulus. Because the "go" stimuli occur much more frequently than the "no-go" stimuli, participants must inhibit their prepotent response when confronted with the less frequent "no-go" stimuli. Task administration time is approximately 8 minutes.
6. Tower of London (TOL). This computerized task measures visuospatial planning and sequencing abilities that depend heavily upon prefrontal cortex executive functions. Participants will use the computer mouse to rearrange a stack of "beads" among three "pegs" of differing size on the computer screen. Ten trials will be given. Administration time is approximately 8 minutes.

Neuroimaging Tasks

Diffusion Weighted Imaging (DWI)

Standard MRI techniques are often insensitive to the axonal injuries common to mTBI. However, a recently developed technique known as Diffusion Weighted Imaging (DWI) has shown particular sensitivity to the types of diffuse white matter damage associated with mTBI. DWI is an MRI technique that measures the directional diffusion of intra- and extracellular water on a cellular scale in an MRI system. This non-invasive measure of water mobility can be used to assess white matter/axonal health through its indirect assessment of cell wall shape, size, and orientation (Mori & Zhang, 2006). DWI is achieved by applying second order calculations to a diffusion weighted MR acquisition. Diffusion weighted scans are MRI images in which the image intensity at a given position has been attenuated according to the amount of microscopic diffusion occurring along a selected direction within that position. This attenuation is controlled by applying sensitizing fields along the selected direction during image acquisition. In a DTI acquisition, several diffusion weighted images are acquired, each with the weighting along one of a selected set of directions. The resulting images are combined to produce an Apparent Diffusion Coefficient (ADC) tensor for each image location. Quantities can be calculated from these ADC components that correspond to physiological characteristics (Alexander, Lee, Lazar, & Field, 2007). Two of these quantities are the Fractional Anisotropy (FA) and the mean diffusivity (MD) which together provide a measure of axonal size and density (Basser, 1995; Budde et al., 2007).

FA and MD have been used for assessment of brain damage following mTBI (Huang et al., 2009; Miles et al., 2008; Rutgers, Fillard et al., 2008). Recent work has suggested that indices of MD are significantly higher in mTBI patients compared to controls, whereas FA indices are typically lower

(Miles et al., 2008). Moreover, these indices have been shown to correlate with cognitive performance in patients (Miles et al., 2008). FA reductions are most commonly found in the corpus callosum, cingulum, and cerebral lobar white matter (Rutgers, Toulgoat et al., 2008). These changes are often most evident within the first 3 months post injury (Rutgers, Fillard et al., 2008). Here, we hypothesize that mTBI patients undergoing MBLT will show greater improvement (i.e., reduction in FA and MD) during the treatment period than patients receiving SPLT, and that this will correlate with sleep improvement and cognitive/symptom improvement.

Diffusion acquisitions will be taken with two separate 72 direction-weighting scheme. These acquisitions have been found to provide sufficient angular resolution of the composite apparent diffusion coefficient in areas of fiber crossings for possible use in a tractography analysis, while having a short enough acquisition time to be clinically effective. Scans will be acquired on a 3T MRI system (Siemens Skyra Syngo) using a standard single shot, spin echo, echo planar acquisition with diffusion weighting gradient pulses.

Functional Neuroimaging:
Blood Oxygen Level Dependent (BOLD) functional magnetic resonance imaging (fMRI) will be collected at UAMC. Functional brain responses during cognitive challenge tasks will permit quantification of brain function changes between the MBLT and SPLT treatment groups (OBJECTIVE 2) and will be correlated with measures of sleep (OBJECTIVE 3). A Trio 3.0 Tesla whole body high-speed imaging device equipped for echo planar imaging (EPI) 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 will be collected for spatial normalization, positioning the slice prescription, and for subsequent morphometric analysis (see below). Then a T1-weighted and a T2-weighted 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.

The following paradigms will be administered to volunteers during fMRI scanning. These tasks are visual in nature and will involve back-projection of stimuli onto a screen via a shielded LCD projector and viewed through a mirror mounted on the head coil. The three functional tasks include:

1. Multi-Source Interference Task (MSIT) (Bush & Shin, 2006): This task presents the subject with two alternating conditions. In each trial, three numbers are shown on the screen. For the control condition, subjects simply make a button press using the index, middle, or ring finger of their dominant hand to indicate the spatial location of the "number 1" on the screen (left, middle, or right). For the "interference" condition, subjects again see three numbers on the screen, but two numbers are the same and one is different. The subject must press the key that identifies the numeral (1, 2, or 3) that is different from the other two. The interference task has been shown to reliably activate the anterior cingulate gyrus in previous studies (Bush & Shin, 2006).

2. N-Back Task. The n-back task is a widely used task in functional neuroimaging for probing working memory (Drobyshevsky, Baumann, & Schneider, 2006; Jansma, Ramsey, Coppola, & Kahn, 2000). Participants will continuously monitor a series of letters as they appear on a screen and will be required to indicate when a pre-specified target letter appears in the sequence. During the control portion of the task (0-back), the subject merely responds when the prespecified letter appears on the screen. During the experimental task (2-back), the subject responds when the current letter is the same as on displayed 2-letters previously. The task has been shown to reliably activate the dorsolateral prefrontal cortex (Drobyshevsky et al., 2006).

3. Resting State fMRI. 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 (Shehzad et al., 2009; Voss & Schiff, 2009; Zhang et al., 2008; Zhong et al., 2009). Therefore, subjects will also be scanned for 6 minutes with eyes closed and instructed to let their "mind wander." Functional connectivity will be evaluated from pre- to post-treatment for the two groups.

4. (HC Arm Only) Food Activity Decision Task & Food Rating Task. This will be administered to subjects during MRI to determine foods subjects may find appetizing and if healthier or unhealthier choices are made. The FADT is done during the MRI in scanner and the FRT is done afterwards outside the MRI scanner.

Modified Sleep Latency Test (MSLT)

At each session, participants will undergo an MSLT with polysomnographic (PSG) recording. A trained technician will fit each participant with a standard electrode montage for PSG recording. Standard PSG will be recorded using an ALICE system. The participant will be escorted three times to a private sound attenuated bedroom where they will attempt to take a brief nap. Participants will be given up to 20 minutes to fall asleep. PSG recordings will be scored by a trained technician using Somnologica software to determine the latency to fall sleep.

Six-Week Light Exposure Treatment

At the conclusion of the assessment and scanning session, all main study arm participants will also be given a Phillips goLITE device and WattsUp? Pro® power usage meter. This is a power usage meter used to instantly display the wattage being used. This device is being used to measure wattage use for subjects to help track study compliance. The goLITE BLU is a commercially available device that provides controlled exposure to narrow band blue wavelength light with a peak wavelength of 464-467 nm. The device consists of a table-mounted, 13.5 x 14 cm plastic encased device with a 10-by-6 LED array. The WattsUp? Pro® power usage meter will be used in conjunction with the Phillips go LITE device to measure compliance. Specifically, the WattsUp? Pro® meter will be used to measure: times of day during which the Phillips goLITE device was used, duration of use, and intensity setting at which it was used. Participants will be given a demonstration about how to use the instrument and will also be provided with written instructions. Each morning, within 2 hours of awakening, but prior to noon each day, participants will use the light device for 30 minutes. This will allow added flexibility and reduce subject burden by permitting subjects the opportunity to choose

whether to use the light immediately upon arising, or after morning hygiene, meals, drive, etc., but will still ensure that all treatment occur in the morning hours. The instrument is equipped with a timer to ensure 30 minutes of exposure. Appropriate use will involve placing the light device at a distance between 12-24 inches, offset from center to reduce glare. Participants will be instructed not to look directly at the light source, but to allow the light to enter from their peripheral vision. Each morning, within 2 hours of arising from sleep, participants will 1) document the time, indicate sleepiness using the Stanford Sleepiness Scale (SSS), activate the light device, and document the sleep and wake times from the previous day. At the completion of the light period, participants will again indicate sleepiness using the SSS. To further monitor compliance, the wrist actigraph will also include a light monitor. Participants will be instructed to ensure that the light sensor of the actigraph is exposed to the light source for the full 30-minute duration in order to verify compliance. This will permit cross-verification that subjects have in fact used the blue wavelength light at the specified times (and will allow co-variation for additional light effects in statistical analyses). MBLT exposure will be conducted daily for 6-weeks for all participants. Participants will also be contacted weekly by phone to ensure compliance, answer questions, and collect a weekly Epworth Sleepiness Scale.

Half of the participants will be randomly assigned to the morning MBLT or a sham placebo light treatment (SPLT). Participants in the MBLT group will be administered blue light therapy using the standard goLITE BLU device, whereas participants in the SPLT group will be given identical appearing goLITE devices where the standard bright blue-wavelength LEDs have been replaced with amber LEDs. The goLITE BLU has been shown to have 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 SPLT devices, but will peak at $\lambda = 566$ nm, at 180 Lux, and total irradiance (mW/cm^2) = 0.58.

Safety. The Philips goLITE BLU device is a commercially available product marketed for relief of "winter blues" and improvement of mood. The device has been used off label for treatment of SAD and jet lag and has undergone extensive safety testing based on U.S. and international standards for photobiological safety of light devices. An independent optical safety analysis was provided to the manufacturer of the devices on 30 August 2009, and is attached as an appendix to this application. The analysis indicated that the averaged radiance of the array of LEDs is below hazardous standards set by the Illuminating Engineering Society of North America (IESNA) and the International Commission on Illumination, and International Electrotechnical Commission, and meets criteria for an Exempt product without photobiological risk when used as indicated."

The goLITE AMBER units have lower total irradiance levels and include significantly less blue wavelength light than the blue active condition. A safety analysis was conducted on the AMBER lights (20 April 2006, attached) and these were found to pose no meaningful optical hazard when used as indicated. The safety analysis concluded that the emission levels of the amber device are so far below recommended safe exposure limits that even photosensitive individuals would not be at risk.

Actigraphic Sleep Measurement:

Daily sleep, activity, and light exposure will be collected via the Respironics Actiwatch. This actigraphic wrist-watch device uses a built-in accelerometer to 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 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. 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 downloaded using the Actiwatch-2 communication dock after week 7 of the study.

Participants will also keep a daily sleep log during the 7-week period.

Optional Sleep Follow-up Monitoring:
Subjects may choose to participate in an additional 6 weeks of sleep monitoring. Willing subjects who indicate their agreement on the consent document will continue wearing the wrist-worn actigraph and complete daily sleep diaries for up to 6 weeks after termination of the light exposure period.

Follow-Up: One year post-participation in the study, subjects who consent will have a follow-up phone call where they will be administered the RPCSQ, the PHQ9, and be asked about general sleep problems using the ESS.

Healthy Control/Effect Localization Arm:
Following the initial assessment, subjects will have a saliva sample collected via a small plastic tube placed in the lower part of their mouth. This is being done to measure melatonin levels and is not painful. Once subject eligibility has been determined, they will be fitted with a heart rate monitor that has 2 leads to attach to the chest which will be worn for the duration of the visit, save the MRI scanner. They will complete study assessments and then subjects will have electrodes attached for EEG (electroencephalography) recordings during their light exposure period. This is being done to measure changes in beta, alpha and theta over the light exposure period and only takes a few minutes to attach the EEG headset. Subjects will sit in a dark room while being exposed to 30 minutes of amber (placebo) light. For 10 minutes of this time, subjects will be asked to sit quietly, and fixate on a cross on the opposite wall. After this time, these subjects will be exposed to either blue wavelength light per the goLITE BLU, or they will be exposed to amber wavelength placebo/sham light for 30 minutes. They will be asked to repeat the cross fixation for another 10 minutes during the light exposure period (amber/blue) in order to help get clean EEG data. Total light exposure time will be 60 minutes. Once this is complete, another saliva sample will be collected. Subjects will then undergo an MRI scanning session. A third saliva sample will then be collected. Following this, subjects will be given an Actiwatch and instructed in its use to wear until their follow-up appointment for around 8:30pm the same day.

While wearing the EKG device, a final melatonin sample will be collected at this follow-up appointment and the Actiwatch will be collected. This follow-up visit saliva sample is being performed to measure the difference in melatonin levels for subjects who received the active versus sham light exposure during their initial visit. Melatonin levels should be higher later at night as levels

stay flat during the day and increase exponentially in the evening just prior to when subjects are predisposed to sleep.

All saliva samples will be stored in protected access freezers in CaTS until they are processed and analyzed. Analysis will be done in the UACC lab by our study team per the Melatonin Assay Protocol. Transport will occur the day of analysis in a sealed Styrofoam container from CaTS storage directly to the lab by study personnel.

Post-Treatment Assessment and Scan:
At the completion of 6-weeks of MBLT or SPLT, participants will return to the laboratory and turn in the light device. Participants will undergo a comprehensive neurocognitive assessment virtually identical to the pre-treatment assessment. A series of functional and structural neuroimaging scans will be repeated to evaluate the impact of treatment on brain function and structure. Finally, in order to provide an objective measure of sleep latency, an MSLT with polysomnography will be performed at the same time of day as during the first visit.

Healthy Control/Effect Localization Arm:
Following exposure to the blue or amber wavelength light, participants will undergo a comprehensive neurocognitive assessment akin to the pre-treatment assessment. A series of functional and structural neuroimaging scans will be repeated to evaluate the impact of treatment on brain function and structure.

I. BIOSTATISTICAL ANALYSIS

Several global outcomes and their interpretations include:

1) "If the effects of MBLT versus SPLT are not different and improvement is observed in both groups"—this would suggest that nonspecific effects (practice, maturation, recovery) occurred but were unrelated to the MBLT treatment. Thus there is no specific benefit to the use of MBLT versus placebo. Based on such an outcome, there would be no recommendation for the use of MBLT for treatment of post-concussive symptoms. Secondary analyses correlating cognitive/symptom improvement with changes in brain structure and function may identify new avenues of research and would still contribute valuable knowledge regarding these relationships.
2) "If effects of MBLT versus SPLT are not different and no significant improvement is observed in either group"-- this finding is less likely, as continued improvement between the two sessions would be expected due to gradual recovery during the first year and due to practice effects associated with repeated assessment. While such a finding would clearly suggest that there is no specific benefit to the use of MBLT versus placebo, it would raise suspicion that the assessments were invalid or insensitive.
3) "If MBLT is better than SPLT"—this is the hypothesized effect. This would support the hypothesis that MBLT is beneficial in the treatment of post-concussive symptoms relative to placebo. Regression analysis between the change in symptoms/neurocognitive function and measures of sleep and mood would identify whether this was due to sleep related changes or whether the changes were due to the mood altering effects of MBLT, or both. Similarly, changes in one condition and not the other will also be examined for their relationship to

specific functional and structural changes. Such information will identify target regions that are most affected by MBLT.

4) "If SPLT is better than MBLT"—it would be unexpected to find the placebo group outperforming the MBLT group. However, such a finding would argue against melatonin suppression as the likely candidate for improvement. Such an intriguing finding would necessitate follow on research to identify the causal factors, and if replicated, could in itself lead to new discovery of an alternative treatment approach. Again, secondary correlational analyses with imaging and neurocognitive measures and analysis of the direction of the effects will guide such interpretations.

Per the Department of Defense, all study data will be deposited on the Federal Interagency Traumatic Brain Injury Research Informatics System (FITBIR) database. This is a protected database that provides training approximately monthly.

The National Institutes of Health (NIH), in partnership with the Department of Defense (DoD), is building a secure, centralized informatics system (database) for TBI research. It will serve as a central repository for new data, link to current databases and allow valid comparison of results across studies. The database builds upon an effort to create common data elements for the study of TBI - which are essentially definitions and guidelines about the kinds of data that should be collected, and how to collect these data in clinical studies.

The Federal Interagency Traumatic Brain Injury Research (FITBIR) informatics system is a collaborative effort involving the NIH Institutes and Centers (ICs) and the US Army Medical Research and Material Command (USAMRMC) to develop a biomedical informatics system and data repository for Traumatic Brain Injury (TBI) research.

The FITBIR Informatics System is an extensible, scalable informatics platform for TBI relevant data (medical imaging, clinical assessment, environmental and behavioral history, etc.) and for all data types (text, numeric, image, time series, etc.). FITBIR was developed to share data across the entire TBI research field and to facilitate collaboration between laboratories, as well as interconnectivity with other informatics platforms.

Data submitted to the FITBIR Informatics System will be de-identified such that the identities of data subjects cannot be readily ascertained or otherwise associated with the data by the FITBIR staff or secondary data users. In addition, de-identified data will be coded using a unique code known as a Global Unique Identifier (GUID). Use of the GUID minimizes risks to study participants because it keeps one individual's information separate from that of another person without using names, addresses, or other identifying information. The unique code also allows FITBIR to link together all submitted information on a single participant, giving researchers access to information that may have been collected elsewhere. The GUID is a computer-generated alphanumeric code [example: 1A462BS] that is unique to each research participant (i.e., each person's information in FITBIR—or each subject's record—has a different GUID). FITBIR will assist investigators in how to create the GUID, which is an essential requirement for uploading data to FITBIR.

8) Risks to subjects

The psychological, social, economic and legal risks of the assessment, light exposure, and MRI acquisition components of this study are minimal, and no physical or economic harm is anticipated. The questionnaires and brief clinical interview may ask questions that produce discomfort in some participants, but this is not expected. The instruments used here are all published and have been used with large numbers of human participants without ill effect.

The Philips goLITE device is a commercially available product that has no significant known harmful effects. The device has been used for treatment of SAD and jet lag and has undergone extensive safety testing based on U.S. and international standards for photobiological safety of light devices. As shown in the appendix to this protocol, an independent optical safety analysis was provided to the manufacturer of the devices on 30 August 2009. The analysis indicated that the averaged radiance of the array of LEDs is below hazardous standards set by the Illuminating Engineering Society of North America (IESNA) and the International Commission on Illumination, and International Electrotechnical Commission, and meets criteria for an Exempt product without photobiological risk when used as indicated. During normal use of the device, as will be standard procedure in the present study, participants will only view the LED array at an indirect angle (i.e., the subject will be instructed NOT to look directly at the LEDs but to keep them visible in the periphery). When the LED panel is viewed off axis, at an indirect angle as directed, the LED radiances fall below internationally recognized levels for indefinite viewing. Thus, when viewed as directed, the goLite device can be safely viewed at maximum intensity for as long as desired (although participants will be instructed to use it for no longer than 30 minutes each day).

Although normal usage of the device has no known hazards, the primary and most extreme health concern, which is an issue with any form of blue wavelength light exposure, is photoretinitis, or "blue-light hazard", which may occur when exposure surpasses internationally recognized limits ($10 mW cm^2 sr^{-1}$). Photoretinitis involves photochemical damage to the retina as a result of prolonged exposure to extremely bright light (e.g., excessive sun exposure; snow blindness) and can have symptoms that are minor and dissipate quickly (e.g., afterimages), or less commonly, long-term degradation of vision. The risk of photoretinitis is influenced by the wavelength, brightness, and duration of light exposure. According to the ocular safety analysis and safety information provided by the manufacturer, the goLITE BLU produces only 8.9% of the long-term exposure limit, and therefore there is no specified limit to viewing, even for direct fixation. When used as directed, as will be the standard procedure in the present study, the goLITE has been shown to be safe even at a factor of 100 times the normal usage recommendations. The safety analysis, which was reportedly reviewed and concurred with by the FDA, suggests that the exposure to hazardous light from the goLITE falls below all internationally recognized standards and meets criteria for a non-risk, exempt category device. According to the ocular safety analysis, even the most extreme example of staring directly at a single unshielded diode would require 27.8 minutes of direct fixation before long term fixation exposure limits could be reached. However, this eventuality is extremely unlikely for the following reasons:

1) The high luminance of the diodes would be discomforting to stare at for more than a brief time. Humans find direct staring directly at bright light sources aversive, and the discomfort would

likely preclude an individual from voluntarily gazing directly at a single diode for more than a few moments.
2) Participants will be informed about the potential for visual discomfort and possible hazards of long term direct staring at the diodes. This information will be listed prominently in the informed consent document and will be described orally to the participant as well.
3) Participants will be given a hands-on demonstration about how to use the device. During the interactive demonstration, the participant will practice the correct method for viewing and will be warned about not staring for prolonged periods at the diodes.
4) Participants will be given written instructions with a visual diagram outlining normal safe positioning and use of the device.
5) A warning label will also be printed and taped to the face of each device which states "WARNING: DO NOT STARE DIRECTLY AT THE LED SCREEN"
Participants will be instructed on proper use of the device and the importance of not looking directly at the LEDs for extended periods. Of course, individuals differ in their sensitivity to light and it is possible that unanticipated eye fatigue or irritation could occur. Direct staring at the diodes could lead to the presence of temporary afterimages. Participants will be instructed to discontinue use and contact the principal investigator immediately if any unusual sensations or discomforts are noticed.

The MR imaging procedure does not pose a significant risk to subjects meeting the entry criteria for this study. There is no known hazard associated with MR imaging. Nuclear magnetic resonance imaging does not involve ionizing radiation such as that associated with X-ray or radionuclide techniques. All studies will use radiofrequency power deposition and gradient switching which have been approved by the FDA. We do not know if MRI scanning presents a risk to unborn fetuses, so we will ask all females of childbearing potential to complete a urine pregnancy test immediately prior to the scan. This pregnancy test will be performed in the Department of Psychiatry.
Although MR imaging is thought to be hazard free, some subjects may experience discomfort. Noise from the MRI machine can cause discomfort. Even though most subjects tolerate the scanning session, some subjects may find the enclosed space of the MRI device to be physically uncomfortable or anxiety producing. Some subjects may experience tingling in the extremities or numbness caused from remaining in the same position for a long duration. Measures will be taken to minimize these discomforts.

Risks and discomforts during PSG are generally minimal. On rare occasions some mild skin irritation or rash may emerge while wearing the electrodes, but this normally resolves upon removal of the electrodes. Participants will wear the electrodes for less than an hour, so such irritation is highly unlikely in such a short time.
6) There is the risk of some skin irritation from the EEG/EKG leads being attached to the skin. This can be alleviated by application of lotion/cream.
7) There are no anticipated risks associated with saliva collection. These samples will be collected via a small plastic tube placed in the lower part of your mouth. These samples will be labeled with a unique study ID number only and will be kept in the research suite only accessible to authorized study personnel.
8) Subjects will see images they may find distressing during one task while in the scanner.

Participants are informed of the disturbing images at two distinct junctures during their visit: 1) During the consenting process, the experimenter mentions that some disturbing images will be shown on a screen while the participant is in the scanner, 2) The experimenter again reminds the participant that they will be asked to view some disturbing images on a screen just prior to entering the scanner. Participants are reminded at both of these times that their participation is voluntary and that they may withdraw their participation at any time and for any reason without penalty. If the participant expresses any discomfort, the experimenter will have a brief conversation about the subject's discomfort. If any indication is given from the participant that they do not feel comfortable viewing the images, their participation will be withdrawn from the study. Participants may also push a button that they are given while in the scanner to immediately stop the study if they decide upon viewing one or more images that they do not wish to continue their participation.

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 mTBI and sleep disorders.

The study will provide basic scientific information about the effects of short wavelength light on sleep patterns and potential rate of recovery from mTBI. Such information may improve the ability to treat sleep disorders and cognitive performance among patients with mTBI.

The diagnostic assessment and heart rate measures may reveal previously unidentified psychiatric and/or cardiac abnormalities subjects 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, they should not rely on our analyses to reveal abnormalities in your data, and our lab claims no responsibility for abnormalities that go undetected during their participation in any research related activities.

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

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

name, social security number, date of birth) will not be included on any research record that has the subject's ID number.

Communication through the 3rd party marketing campaign (Twilio) will connect interested individuals to study staff via a their medadmin email accounts and to dedicated secure study phone lines. The company retains a call log and SMS message history, which is also sent to the SCAN Lab. All call and SMS message history will be wiped from the company's servers every 24 hours and removed from the SCAN Lab's database as soon as study staff respond to any calls or text messages (no later than the next business day). At no point does any subject "subscribe" or "opt-in" to any system. This is voluntary and participants may elect to not receive SMS-based communication.

All information regarding experimental subjects will be kept in a locked file cabinet in the University of Arizona Department of Psychiatry. The signed consent forms will be 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) will be 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 to avoid creating any additional PHI. MR Records will be kept indefinitely in a locked office. Subject identifying codes such as the subject's MRN (medical record number) will not be used for research data. All HIPAA requirements will be followed.
Research data will be stored in a secure area indefinitely.

A Certificate of Confidentiality has been obtained from NHLBI (National Heart, Lung and Blood Institute) for this study.

11) Cost to subjects

Subjects will not incur any costs for participation in this study, save for their time. Their participation is expected to last 7 weeks if they see their participation to conclusion, or up to 13 weeks if they participate in all 6 weeks of follow-up sleep monitoring.

12) Subject compensation

Main Study Arm:

Subjects will receive $1000 for completion of both study sessions and successful adherence to the daily light exposure treatment. This payment is also intended to cover all transportation expenses to and from the hospital.

If subjects choose to withdraw from the study prematurely, they will be compensated at a rate of $25/hour for the time they were undergoing scanning and testing, according to the following schedule:

- Discontinuation during or following the initial visit, subjects will be paid $50 for completing the initial clinical assessment and questionnaires.
- Discontinuation before the end of second visit (i.e., first testing and scanning session): $25/hour, up to a maximum of $250 total, following return of all study-related equipment.
- Discontinuation any time during the 6-week light exposure period: $275 maximum total payment, following return of all study-related equipment.
- Discontinuation during but before the end of the third visit: $275 plus $25/hour during the third visit, up to a maximum total payment of $475, following return of all study-related equipment.
- Completion of study procedures up to the end of the third visit and return of all study equipment: $900.
- Completion of all study procedures up to the end of the third visit, return of all study equipment, and evidence that all at-home study procedures were followed (i.e., regular compliance with the use of wrist activity monitors, sleep diaries, and light exposure device): $1,000. If subjects fail to return the Actiwatch and/or Light Device, subjects will receive no compensation.

If subjects choose to participate in the 6-week follow-up period after the initial 7 weeks:

- Discontinuation at any time during the 6-week period post light therapy: $1,000 plus $33.33/week for each week of participation after the end of the third visit.
- Completion of all study procedures for the entire duration of the study (13 weeks), including return of all study equipment within 10 days and evidence that all at-home procedures were followed (i.e., regular compliance with the use of wrist activity monitors and sleep diaries): $1,200.

Healthy Control/Effect Localization Arm:

Subjects will receive $200 for completion of the assessment, light exposure, brain imaging scans and return of the Actiwatch. This payment is also intended to cover all transportation expenses to and from the hospital.

If subjects choose to withdraw from the study prematurely, they will be compensated at a rate of $8.05/hour for the time they were undergoing scanning and testing (up to a maximum of $40.00).

Compensation will mirror current minimum wage. The initial visit is expected to take approximately 5 hours at $8.05/hour. Subjects will receive a bonus of $160.00 for returning for the follow-up visit, expected to take approximately 30 minutes, the same day for final saliva collection and returning the Actiwatch. Should the subject not return for the follow-up visit or return for the follow-up, but not return the Actiwatch, they will not receive compensation. In the event the subject returns for the follow-up, but the Actiwatch is broken, the subject will still receive the maximum compensation of $200.00.

All reasonable steps will be taken to prevent undue influence, and the study team feels that the compensation schedule reflects reasonable compensation for participation given the study activities involved.

Subjects who are recruited from the PSY101 course will receive up to 4 credits as part of their compensation for participation. Their financial compensation will not be affected.

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.

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.

Additionally, a medical monitor. Alex Hishaw, M.D., has been designated for this study. Dr. Hishaw is required to review all anticipated problems involving risk to volunteers or others, serious adverse events and all volunteer deaths associated with the protocol and provide an unbiased written report of the event to the USAMRMC Office of Research Protections (ORP) Human Research Protection Office (HRPO). At a minimum the medical monitor should comment on the outcomes of the event or problem and in the case of a serious adverse event or death comment on the relationship to participation in the study. The medical monitor should also indicate whether he/she concurs with the details of the report provided by the study investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death should be promptly forwarded to HRPO.

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.

Females 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.

The subject may request a copy of the report or the films. If this request is made, subjects will be warned that the information released may not remain confidential.

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

The diagnostic assessment and heart rate measures may reveal previously unidentified psychiatric and/or cardiac abnormalities subjects 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, they should not rely on our analyses to reveal abnormalities in your data, and our lab claims no responsibility for abnormalities that go undetected during their participation in any research related activities.

15) Withdrawal of subjects

If significant psychopathology or other disqualifying condition is discovered during the psychiatric assessment 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.

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.** 06/16/15
2. Protocol	**2.** 04/14/14
3. Bright Light Treatment Protocol Schema	**3.** N/A
4. Informed Consent & PHI Form	**4.** 06/16/15
5. Payment Form	**5.** 04/08/14
6. Phone Screening Form	**6.** 06/16/15
7. Phone Script	**7.** 06/16/15
8. UAMC SRA Approval Letter	**8.** 04/03/14
9. Grant Application	**9.** AWAITING
10. Notice of Recommendation for Funding	**10.** 11/22/13
11. PI CV	**11.** 04/04/14
12. goLITE Blu Pamphlet	**12.** 2013
13. Screen Time	**13.** N/A
14. Day of Scan Info Questionnaire	**14.** 05/21/13
15. Second Day of Scan Questionnaire	**15.** 05/21/13
16. Sleep Diary	**16.** N/A
17. Watch & Light Subject Guide	**17.** N/A
18. Print Ad	**18.** 06/10/15
19. Flyer Ad	**19.** 06/10/15
20. Radio Ad	**20.** 06/10/15
21. Questionnaire Task List	**21.** 04/02/14
22. ANAM4 Scale	**22.** March 2007
23. BART	**23.** N/A
24. BDI-II	**24.** N/A
25. EVAR	**25.** N/A
26. FOSQ	**26.** N/A
27. GNG	**27.** N/A
28. IBI	**28.** N/A
29. MEQ	**29.** N/A
30. MINI 6.0	**30.** 01/01/09
31. MSIT	**31.** N/A

32. N-Back	**32.** N/A
33. NSI	**33.** N/A
34. PAI	**34.** N/A
35. PHQ-9	**35.** 1999
36. PSG	**36.** N/A
37. PSQ1	**37.** 1989
38. PVT	**38.** N/A
39. RBANS	**39.** 1998
40. Rivermead Questionnaire	**40.** 2006
41. STAI	**41.** N/A
42. SSS	**42.** N/A
43. TOL	**43.** N/A
44. WASI	**44.** 2011
45. Medical Monitor CV (Alex Hishaw)	**45.** 2013
46. FITBIR Data Sharing Policy	**46.** 03/27/14
47. Instructions for using light device	**47.** 06/16/15
48. Flyer – BL2 General	**48.** 06/16/15
49. Flyer- BL2 mTBI Short Flyer	**49.** 06/16/15

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:

- **Data Collection Tools** – surveys, questionnaires, diaries not included in the protocol, data abstraction form for records 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.
- **Site Authorizations** for research purposes and/or access to administrative records/samples
  - UAHN University Campus, South Campus and clinics Site Review Authority (SRA) approval

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