

Health Effects Associated with Self-Optimization of the Brain

Research Summary – August 7, 2014 Update

Numerous studies document that stress, trauma, and disturbed sleep can impact health and performance through influences on the neurological, cardiovascular, metabolic, immune, and other systems. The *brain* is the mediator of these effects, as the organ of “central command.”

Supporting the brain to optimize the activity of its stress response system, on its own terms, should reasonably be the centerpiece for any path to well-being or performance enhancement.

Brainwave Optimization® (BWO) is a computer-guided technology that can be described as a highly precise, sound-based, “brain mirror.” Use of this mirror is intended to support a deeply relaxed or meditative state, of a unique kind. From this relaxed state, the brain tends to optimize its activity patterns. Through self-optimization, other effects are commonly manifest.

Brainwave Optimization is also known as high-resolution, relational, resonance-based electroencephalic mirroring (HIRREM®).

This document is a resource of scientific references related to the BWO/HIRREM model of well-being. It includes a listing of studies reporting on use of HIRREM by individuals with insomnia, traumatic brain injury, post-traumatic stress disorder, migraine, and others conditions.

*These studies should not be interpreted as indications of the direct effect of HIRREM on any disease state. Rather, the studies reflect the **health-promoting potential of the brain itself**, when individuals optimize the activity patterns of the brain.**

Studies involving HIRREM have been led by Professor Charles H. Tegeler, M.D., Department of Neurology, Wake Forest School of Medicine, beginning January 2011. Dr. Tegeler’s research is funded by independent third parties including The Susanne Marcus Collins Foundation, Inc., the United States Department of Defense, and others. Information on the program is available at www.wakehealth.edu/HIRREM.

**Brainwave Optimization is not intended to diagnose or treat medically or psychologically defined diseases or disorders, and it is not a medical device or psychological procedure.*

Selected references that inform BWO model:

Buzsaki G. (2006). *Rhythms of the Brain*. New York: Oxford University Press.

McEwen BS. (2007). Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev.* 87(3): 873-904.

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Sterling P. (2012). Allostasis: a model of predictive regulation. *Physiol Behav.* 106(1): 5-15.

Peer-reviewed publications and presentations related to BWO (HIRREM):

Full-length manuscripts

- Gerdes L, Gerdes P, Lee SW, and Tegeler CH. (2013). HIRREMTM: a non-invasive, allostatic methodology for relaxation and auto-calibration of neural oscillations. *Brain Behav.* Mar; 3(2): 193-205.
- Lee SW, Gerdes L, Tegeler CL, Shaltout HA, and Tegeler CH. (2014). A bihemispheric autonomic model for traumatic stress effects on health and behavior. *Front Psychol.* 5:843. doi: 10.3389/fpsyg.2014.00843.
- Tegeler CH, Kumar S, Conklin D, Lee SW, Gerdes EL, Turner DP, Tegeler CL, Fidali B, and Houle TT. (2012). Open label, randomized, crossover pilot trial of high resolution, relational, resonance-based, electroencephalic mirroring (HIRREM) to relieve insomnia. *Brain Behav.* Nov; 2(6): 814-24.
- Peer-reviewed commentary**
- Tegeler CH, Lee SW, and Shaltout H. (2014). Significance of right anterior insula activation for mental health intervention. *JAMA Psychiatry.* 71(3): 336.
- Abstracts (reverse chronological order)**
- Tegeler CH, Tegeler CL, Cook JF, Lee SW, Gerdes L, Shaltout HA, and Miles CM. (2014). Use of HIRREM is associated with improved symptoms and neural oscillatory balance in athletes with post-concussion symptoms. Accepted for poster presentation at the American Academy of Neurology Sports Concussion Conference, July 11-13, 2014.
- Tegeler CH, Tegeler CL, Cook JF, Lee SW, Franco ME, Nicholas JN, Ray CE, Howard LJ, and Shaltout HA. (2014). A noninvasive approach to improve insomnia in a military cohort. Accepted for poster presentation at the Annual Meeting of the Associated Professional Sleep Societies, May 31 – June 4, 2014.
- Tegeler CH, Tegeler CL, Cook JF, Lee SW, Franco ME, Gerdes L, and Shaltout HA. (2014). Use of a non-invasive neurotechnology, HIRREM, is associated with improved sleep, mood, and baroreflex sensitivity in athletes with persisting post-concussion symptoms. Accepted for poster presentation at the American Academy of Neurology, April 26 – May 3, 2014.
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- Tegeler CL, Fortunato J, Cook J, Lee SW, Franco M, and Tegeler CH. (2014). A noninvasive neurotechnology, HIRREM, is associated with symptom reduction and improved cardiovascular autonomic measures in adolescents with POTS. Accepted for poster presentation at the American Academy of Neurology, April 26 – May 3, 2014.
- Miles CM, Tegeler CL, Lee SW, Franco ME, and Tegeler CH. (2014). A case (series) of improved symmetry. Accepted for poster presentation at the American Medical Society for Sports Medicine, New Orleans, LA, April 7, 2014.
- Tegeler CH, Tegeler CL, Cook JF, Lee SW, Franco ME, Gerdes L, and Shaltout HA. (2014). Use of HIRREM, a noninvasive neurotechnology, is associated with symptom reduction and increased heart rate variability among individuals with traumatic brain injury. Accepted for podium presentation at the International Brain Injury Association, Tenth World Congress on Brain Injury, San Francisco, CA, March 19-22, 2014.
- Fortunato JE, Tegeler CL, Lee SW, Pajewski NM, Franco M, Cook JF, and Tegeler CH. (2013). Case series using high-resolution, relational, resonance-based electroencephalic mirroring (HIRREM) for POTS. *Clin Auton Res.* 23(5):269-70. Presented in poster form at the American Autonomic Society Annual Meeting, Hawaii, October 23-26, 2013.
- Tegeler CH, Tegeler CL, Lee SW, and Cook JF. (2013). High-resolution, relational, resonance-based electroencephalic mirroring (HIRREM) reduces symptoms and EEG asymmetry in an individual with PTSD. *Annals of Neurology.* 74(S17): S77. Presented in poster form at the American Neurological Association Annual Meeting, New Orleans, October 12-15, 2013.
- Tegeler CH, Tegeler CL, Lee SW, Shaltout HA, and Pajewski NM. (2013). Neural-oscillatory intervention for auto-calibration improves EEG asymmetry and heart rate variability (HRV). *Annals of Neurology.* 74(S17): S77. Presented in poster form at the American Neurological Association Annual Meeting, New Orleans, October 12-15, 2013.
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EEG-based technology for auto-calibration of neural oscillations (HIRREM). *Menopause*. (20)12: 1356. Presented in poster form at the North American Menopause Society Annual Meeting, Dallas, October 9-12, 2013.

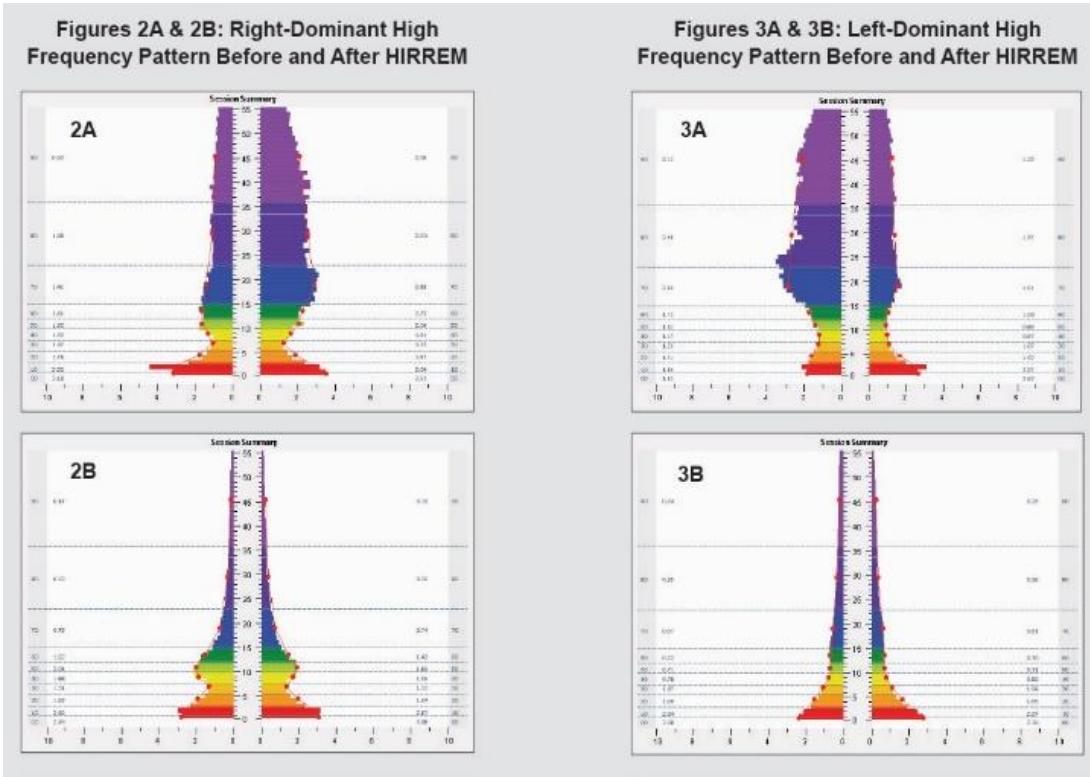
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Figures from Tegeler et al. (2012). Case series of PTSD symptom reduction through a new, non-invasive, EEG-based technology for facilitating self-regulation of neural oscillations (HIRREM).



A bihemispheric autonomic model for traumatic stress effects on health and behavior

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A bihemispheric autonomic model (BHAM) may support advanced understanding of traumatic stress effects on physiology and behavior. The model builds on established data showing hemispheric lateralization in management of the autonomic nervous system, and proposes that traumatic stress can produce dominant asymmetry in activity of bilateral homologous brain regions responsible for autonomic management. Rightward and leftward dominant asymmetries are associated with sympathetic high arousal or parasympathetic freeze tendencies, respectively, and return to relative symmetry is associated with improved autonomic regulation. Autonomic auto-calibration for recovery (inverse of Jacksonian dissolution proposed by polyvagal theory) has implications for risk behaviors associated with traumatic life stress. Trauma-induced high arousal may be associated with risk for maladaptive behaviors to attenuate arousal (including abuse of alcohol or sedative-hypnotics). Trauma-induced freeze mode (including callous-unemotional trait) may be associated with low resting heart rate and risk for conduct disorders. The model may explain higher prevalence of leftward hemispheric abnormalities reported in studies of violence. Implications of the BHAM are illustrated through case examples of a military special operations officer with history of traumatic brain injury and post-traumatic stress disorder, and a university student with persisting post-concussion symptoms. Both undertook use of a noninvasive closed-loop neurotechnology – high-resolution, relational, resonance-based, electroencephalic mirroring – with ensuing decrease in hemispheric asymmetry, improvement in heart rate variability, and symptom reduction. Finally, the BHAM aligns with calls for researchers to use brain-behavioral constructs (research domain criteria or RDoC, proposed by the National Institutes of Mental Health) as building blocks for assessment and intervention in mental health science.

Keywords: autonomic nervous system, hemispheric asymmetry, trauma, traumatic brain injury, post-traumatic stress disorder, polyvagal theory, violence, RDoC

INTRODUCTION AND OVERVIEW

Though studies of the autonomic nervous system (ANS) have historically been dominated by focus on anatomically inferior neural structures or body organs including the heart, gut, skin, and blood vessels, there has also been increasing appreciation for how the ANS is regulated by pathways of the central nervous system that are anatomically and functionally more “upstream” (Saper, 2002; Cechetto and Shoemaker, 2009). The present paper begins on the foundation of multiple studies that have reported lateralization in hemispheric management of arousal or ANS functioning, with the right and left hemispheres being principal managers for the sympathetic and parasympathetic divisions of the ANS, respectively. We propose that the finding of hemispheric laterality in ANS management may be productively integrated with recent thinking that suggests a hierarchical structure in ANS responsivity to stress or trauma (Porges, 2011). The resulting synthesis is a novel ANS model of traumatic stress effects on health and behavior that may have explanatory, predictive,

and interventional implications as a new paradigm in trauma studies.

In one way or another, trauma undoubtedly affects the entire brain. To gain initial traction on this complex problem, the bihemispheric autonomic model (BHAM) explains and predicts traumatic stress effects on health and behavior in terms of shifts in hemispheric asymmetry in the activity of bilateral homologous brain regions responsible for autonomic management. Asymmetrical activation in these regions is associated with different forms of physiological arousal and behaviors. Rightward asymmetry in salient regions is associated with acute threats and sympathetic high arousal (fight-or-flight) behaviors. Leftward asymmetry is associated with repeated or severe traumas (or trauma that produces a sense of futility) and a parasympathetic freeze state (physiological and behavioral immobilization). Production of these asymmetries and their associated arousal states is viewed as the expression of relatively autonomous drives for autonomic auto-calibration. That is to say, when the brain “neurocepts” a

threatening environment, the ANS will tend to calibrate for high arousal without an individual's conscious deliberation. Similarly, if the brain neuroceps a stressful or traumatic state that produces no possibility of successful escape (including serial stressors, an overwhelming stressor, or emotional abandonment), then the ANS will tend to calibrate for a freeze response, again without the subject's thinking or willing.

Autonomic auto-calibration, demonstrable at the level of cerebral hemispheres, may occur in response to trauma, but also as processes or behaviors to support recovery (or attempted recovery) from trauma. Drives for autonomic auto-calibration out of traumatic stress states may explain some behavioral repertoires associated with traumatic life experience, and this aspect of the BHAM is developed in alignment with the hierarchical structure of ANS behavioral responsivity proposed by polyvagal theory (Porges, 2011). Polyvagal theory posits that vagal inhibition of sympathetic arousal, in safe contexts, is the highest-order mode of ANS operation, followed by sympathetic high arousal for acute threats, and finally parasympathetic freeze mode for persistent or severe trauma, as mode of last resort. An inverse view of this hierarchy – in conjunction with postulated existence of autonomous drives for recovery – suggests that individuals in parasympathetic freeze mode may be at risk for generating compensatory high-arousal behaviors to depart the freeze mode, including conduct disorders and substance abuse, to generate greater experience of subjective *feeling*. Individuals in sympathetic high-arousal mode may be at risk for arousal-attenuating behaviors including substance abuse or medication dependence or abuse. Evidence from criminology appears to support the BHAM explanation for history of traumatic life events and high-arousal behavioral risk, in that individuals with propensity for violence have increased prevalence of leftward hemispheric asymmetry or left-hemispheric aberrancy.

The paper illustrates the model through two case examples of individuals with histories of traumatic stress including mild traumatic brain injury, in which reduction of asymmetrical activity in brain regions associated with autonomic management appeared to reflect improved upstream regulation in the ANS. Comment on these cases includes suggestion that the BHAM is in alignment with calls from the National Institutes of Mental Health (NIMH; Cuthbert and Insel, 2013) for researchers to focus on biologically valid brain-behavioral constructs, rather than symptom checklists and population statistical criteria, to make meaningful progress in mental health science. The discussion concludes by proposing that recently proposed hierarchical understanding of ANS responsivity integrated with appreciation of hemispheric lateralization in ANS management, may support a new scientific paradigm (Kuhn, 1962) for research and intervention related to the ANS with broad implications for health and behavior.

STUDIES REPORTING HEMISPHERIC ASYMMETRY IN MANAGEMENT OF AROUSAL OR AUTONOMIC FUNCTIONING

Many studies have reported hemispheric asymmetry in management of arousal levels, either demonstrating or potentially implying a distinct form of ANS activity associated with each hemisphere. We review representative studies in four categories: consequences of unilateral brain dysfunctionality on measures of arousal, studies involving direct stimulation or inactivation of

brain structures, psychophysiological studies in healthy subjects, and studies related to stress effects on hemispheric or neurocardiac functioning. Several of the studies have converged on the bilateral insular cortices as being key sites for lateralization in hemispheric management of the ANS, and implications of this finding are addressed in the case study section. For purposes of this literature review we highlight hemispheric laterality as the common unit of analysis.

Gainotti (1972) compared 80 patients with left-sided lesions to 80 patients with right-sided lesions, with respect to their behaviors during neuropsychological exams. He found that those with left-sided lesions were more likely to demonstrate emotional tendencies for "catastrophic reactions" (anxiety, tears, swearing), and those with right-sided lesions were more likely to show "indifference reactions" (indifference, minimization, or anosognosia). Other teams (Heilman et al., 1978; Morrow et al., 1981) extended his findings with psychophysiological measures showing decreased galvanic skin resistance with a stimulus, indicative of hypoarousal, in patients with right-hemispheric lesions, compared to patients with left-hemispheric lesions or controls without brain injury. The above authors largely refrained from positing a causal role of the left hemisphere to explain findings in patients with right-sided lesions, proposing instead injury to thalamo-cortical loops (Heilman et al., 1978) or disruption of right hemispheric functionality for emotional processing (Gainotti, 1972; Morrow et al., 1981). More recently, Daniele et al. (2002) reviewed electrocardiograms of 352 hospitalized individuals with completed ischemic strokes and found that those with right-hemispheric injuries were more likely to have cardiac arrhythmias than those with left-sided injuries. They postulated that right-sided injuries were more likely to disinhibit right-sided neural mechanisms for sympathetic regulation of heart rate. Finally, Avnon et al. (2004) reported that in a group with unilateral migraine, those with left-sided headache were more likely to have augmented parasympathetic responses – vasodilatation and bradycardia in response to a mild stressor (soapy water to the eye) – than were those with right-sided symptoms. In contrast to the earlier studies, this report suggested a direct role of the left hemisphere in producing parasympathetic responses.

Peri or intra-operative epilepsy surgeries have allowed more direct inferences about the causal role of brain structures. Zamrini et al. (1990) investigated cardiovascular responses from unilateral hemispheric inactivation by intra-carotid amobarbital, in 25 epileptics undergoing preoperative evaluation for epilepsy surgery. Heart rate increased after left hemisphere inactivation, and decreased after right hemisphere inactivation. Spurred by interest in possible mechanisms of cerebrogenic sudden death in epileptics, Oppenheimer et al. (1992) performed intra-operative stimulation of the insular cortex prior to temporal lobectomy for seizure control. They found that stimulation of the left insula (in comparison to the right) produced more bradycardia and blood pressure depressor responses than tachycardia and pressor effects. The opposite was true of right insula stimulation. Other studies (also based on unilateral intra-carotid amobarbital infusion in epileptics) corroborated opposing hemispheric roles for autonomic cardiovascular control using spectral analysis of heart rate (Yoon et al.,

1997) and measures of blood pressure and baroreflex sensitivity (Hilz et al., 2001). Collectively, these studies lend stronger evidence that neural mechanisms in the left hemisphere have an independent, efferent, and parasympathetic role in autonomic modulation.

Evidence that hemispheric lateralization of autonomic management exists for human subjects without neurological disease has been provided through two sets of experiments by Wittling (1990) and Wittling et al. (1998a,b). In the first study, Wittling (1990) and Wittling et al. (1998a,b) showed a romantic film to 50 young adults through a technique of stimulus presentation to a single hemisphere at a time. Right hemispheric film presentations caused significantly greater increases to blood pressure, especially for the female subjects. In the subsequent study, they used the same single hemisphere stimulation technique to show two different films (to control for the effects of emotionality as such, independent of lateralized presentation effects) to 58 young adults. One film was emotionally challenging ("Schindler's List," a film about the pogrom of Jews in Germany), while the second was a scenic film of peaceful pictures. Right hemisphere stimulation was found to be associated with increased ventricular myocardial activity, and left hemispheric stimulation was found to be associated with higher values for the high-frequency spectral component of heart rate variability, a commonly used metric for parasympathetic activation. These studies have represented an important step towards a BHAM by further showing independent roles of the hemispheres, and in subjects without brain injury.

The fourth category of studies supporting a two-hemisphere view of ANS management includes reports that relate to the topic of stress effects on hemispheric or neurocardiac functioning. Rabe et al. (2006) compared electroencephalographic activity of 22 individuals with post-traumatic stress disorder (PTSD) due to motor vehicle accident, 21 individuals who had been through a motor vehicle accident but without PTSD, and 23 healthy controls. Those with PTSD showed greater right-hemispheric activation than the other groups (decreased alpha band on the right compared to the left), when exposed to trauma-related material, and the degree of their asymmetry was correlated with PTSD symptom severity. The same researchers went on to show that rightward asymmetries tended to be reduced after a successful cognitive-behavioral therapy intervention (Rabe et al., 2008). Right-temporal lobe activation has also been reported in a magneto-encephalography study of PTSD (Engdahl et al., 2010), though no inference was made by the authors to associate asymmetry with autonomic mechanisms. In an acute stressor paradigm (performance of rapid calculations), Gray et al. (2007) studied scalp-derived electrical potentials associated with cardiac function, in ten men with heart disease. They found that negativity of a heart-evoked potential (HEP, an electrical signal from the scalp, synchronized with the heart beat) at left temporal and left lateral frontal regions was correlated with changes in cardiac output and cardiac repolarization homogeneity. While this report appears to add to the case for a bihemispheric model of autonomic management, perhaps even more significantly it showed that cortical signals related to autonomic cardiac regulation could be detected

through noninvasive measures at the scalp. And though the authors approached the study as a means to better understand afferent cardiac signaling to the cortex, they were careful to recognize that the cortical potential they measured could instead be representing efferent signaling from the cortex to control the heart rate. Finally, recently we have reported (Tegeler et al., 2013) in a heterogeneous cohort of individuals with stress-associated conditions, that leftward asymmetry in temporal lobe high-frequency electrical activity measured from the scalp is negatively correlated with heart rate and positively with heart rate variability.

It should be noted that not all learned opinion is in agreement regarding the defensibility of a consistent model of lateralized cortical cardiovascular sympathetic and parasympathetic representation. One general refutation of this hypothesis has been presented in the discussion of a retrospective study of individuals hospitalized for video-EEG monitoring whose medical records included evidence of bradycardia or bradycardia-related clinical events (Britton et al., 2006). The authors identified 13 cases that met their inclusion criteria, out of 6168 who underwent video-EEG monitoring over a 14-year period, and they found no consistent hemispheric lateralization of seizure activity in these patients. This study by Britton et al. (2006) is a helpful counterpoint, though it bears mentioning that lack of evidence for correlation between an autonomic effect and a specifically hypothesized form of asymmetry (e.g. lateralized seizure activity) permits a weaker type of inference – only that the autonomic effect being studied was not associated with that specific form of asymmetry – and does not constitute evidence that lateralization in autonomic management does not exist.

THE BIHEMISPHERIC AUTONOMIC MODEL

The studies reviewed in the preceding section collectively suggest that an accurate and comprehensive view of autonomic functioning requires consideration of the independent roles of the left and right hemispheres, and especially patterns of asymmetrical hemispheric activation in brain regions responsible for autonomic management. In this section, we integrate the above data into a BHAM that encompasses the above findings while also proposing a way to understand the dynamics of trauma effects on the brain and brain influences on behavior. We propose the existence of relatively autonomous drives for autonomic auto-calibration that may find expression as shifting forms and degrees of asymmetrical hemispheric activation. For purposes of this paper, the model is deliberately qualitative and conceptual. We hope the model will encourage empirically precise, quantitative, and hypothesis-driven studies, even as we hope it facilitates additional conceptual and theoretical innovations across health and behavioral sciences.

FOUR THESES OF THE MODEL

Thesis One. *Relative symmetry in activation of bilateral cerebral hemispheric regions responsible for management of the autonomic nervous system is likely to be associated with an organismal state of relative autonomic optimality, characterized by relatively small and healthy fluctuations between leftward and rightward asymmetry of activity in those regions.* This state of relative symmetry,

fluctuating towards either leftward or rightward asymmetry but not to extreme degrees or for prolonged lengths of time, corresponds to a relative capacity for healthy and adaptive fluctuation. In a complex and changing environment, it is healthy, needful, and subjectively enjoyable, to move smoothly and fluidly between parasympathetic states of rest and calm, and sympathetic states of increased arousal, action, and overt excitement.

Thesis Two. Rightward dominant asymmetry may arise in hemispheric regions responsible for management of the autonomic nervous system, in association with traumatic experience or perception of threat, producing a tendency for high arousal physiology that is likely to be maladaptive in its persistence. The right hemisphere-dominant autonomic state may be adaptive, for example in a military serviceperson in armed combat, or in an individual living in close quarters with someone who behaves abusively. However, the persistence of such asymmetry and associated high-arousal physiology is likely to be maladaptive for non-threatening contexts. The same soldier returning from war will predictably have difficulties in maintaining the calm and restful parasympathetic state needful for civilian life. Similarly, the individual under threat of abuse in their home may feel maladaptively aroused when they go to the workplace or attempt to enjoy low-risk social encounters. Individuals in this state may be at risk for compensatory behaviors to attenuate the high arousal associated with right-dominant autonomic asymmetry, for example substance abuse or medication dependence or abuse.

Thesis Three. Leftward dominant asymmetry may arise in hemispheric regions responsible for management of the autonomic nervous system, especially in association with severe trauma or perception of futility, producing a risk for compounded maladaptations – tendencies both for persistent immobilization physiology, as well as compensatory high arousal behaviors. A leftward dominant state may be characteristic of an individual faced with stress or trauma that overwhelms the utility of high arousal (for fight or flight) or otherwise presents no exit options, thereby inducing a state of behavioral freeze or shutdown. For example, leftward asymmetry might characterize a soldier who has had severe traumatic stress and is now emotionally numb (frozen), or an individual who feels abandoned by a care-giver or loved one. Such a state may be adaptive as a way to withdraw from complex environments (and decrease risk of further injury), but if persisting it will prevent healthful engagement with life by most any reasonable measure. Paradoxically, high-arousal behaviors may also be expressed by those with immobilization physiology as compensatory processes (to depart the freeze state). Risk for producing these behaviors, which may include conduct disorders, rage, or substance abuse, is predicted to represent a significant burden of suffering for those in the parasympathetic freeze state (see Autonomic Auto-calibration May Explain Increased Risk for High-Arousal Behavior in Individuals who are in a Parasympathetic Freeze State).

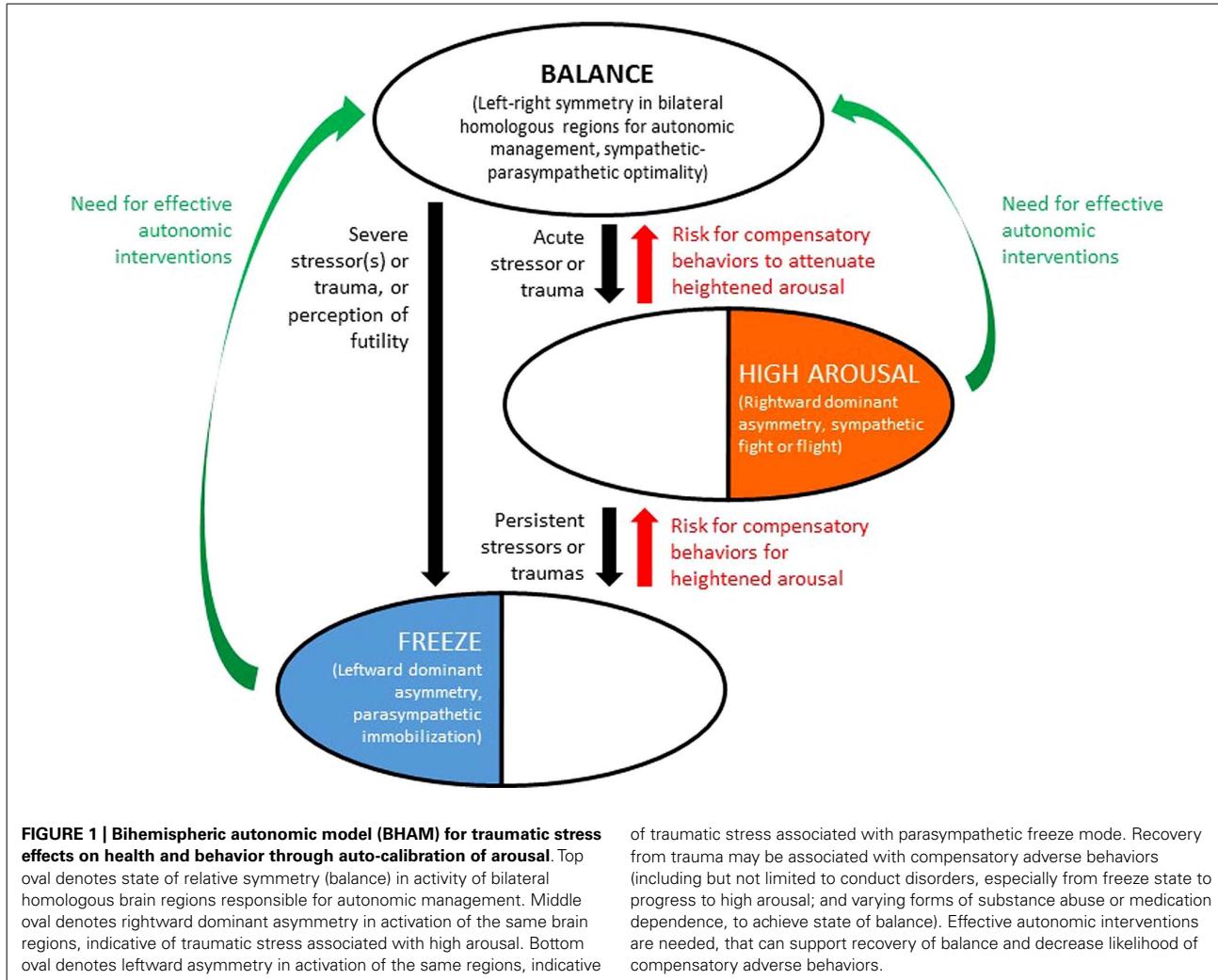
Thesis Four. Movement between the states of symmetry and asymmetry described in Theses One through Three is a function of two main influences – relatively autonomous drives for autonomic auto-calibration, and higher-order self-regulatory processes managed by the prefrontal cortex. Exposure to stressors or trauma will be associated with relatively autonomous drives for autonomic

auto-calibration from relative symmetry to rightward dominance, and/or leftward dominance, whereas processes for recovery will tend to be associated with auto-calibration from leftward or rightward dominance, toward relative symmetry. Autonomous drives for autonomic auto-calibration may be guided by conscious choice-making and other capacities associated with the executive role of the prefrontal cortex, that represent a rudder and decision-making apparatus for navigation and management of environmental contexts and neural energetics that together produce asymmetries.

The distinction made in the model between stresses that produce rightward or leftward asymmetry owes much to polyvagal theory (Porges, 2011), which has reconceptualized autonomic responsivity in hierarchical terms, distinguishing between self-calming (typically healthful) and immobilizing (trauma-induced and typically maladaptive when persisting) functionalities of the vagus nerve. Roughly, the first three theses of the BHAM may be considered to correspond to functionality of the myelinated (“smart” or “social”) vagus, the sympathetic division, and the unmyelinated (“vegetative”) vagus, respectively. Polyvagal theory is discussed further in Autonomic Auto-calibration May Explain Increased Risk for High-Arousal Behavior in Individuals who are in a Parasympathetic Freeze State.

We reiterate that the BHAM as presented in this paper is qualitative and conceptual. It is intended to explain and predict tendencies and risks, not causality, and in its current form is a deliberate simplification. Many individuals in a right-hemispheric autonomic state (Thesis Two) may be “driven high-achievers” without pathological high arousal. Similarly many individuals in a left-hemispheric autonomic state (Thesis Three) may have relatively withdrawn personalities that are not necessarily dysfunctional. Individuals may also have mixed forms of trauma history (producing both sympathetic high arousal and parasympathetic freeze tendencies) associated with mixed forms of right/left overactivation that masks the underlying hemispheric dynamics. With these cautions and caveats, the main elements of the BHAM theses are illustrated in **Figure 1**.

Notably, Craig (2005) has proposed a model of forebrain emotional management that similarly depends on lateralization of hemispheric management of the ANS, and in a broad sense his conceptualization overlaps with Thesis One. The Craig model helpfully articulates the roles of the right and left hemispheres for homeostatic opponent processes, permitting catabolic and anabolic energy management through the sympathetic and parasympathetic divisions, respectively. In contrast to the BHAM, the Craig model tends to focus on afferent over efferent pathways for the brain’s interaction with the peripheral ANS and views the parasympathetic role of the left hemisphere primarily in terms of its role for self-calming and interoception. Thesis Two of the model overlaps with discussion from Rabe et al. (2006), who also propose a model correlating rightward hemispheric asymmetry with increased arousal. Davis et al. (2013) recently showed that individuals with post-traumatic stress disorder and comorbid substance use disorder had decreased startle responses compared to those with post-traumatic stress disorder alone (self-medication hypothesis), lending support to the idea that autonomic auto-calibration to recover from high arousal may



be a driver for adverse compensatory behaviors. We are not aware of other writings that advance the ideas contained in Theses Three or Four.

EXPLANATORY VALUE OF THE MODEL

Model subsumes earlier findings related to hemispheric lateralization of arousal or autonomic management

The BHAM subsumes the reports cited in Section “Studies Reporting Hemispheric Asymmetry in Management of Arousal or Autonomic Functioning.” Gainotti’s (1972) early finding that individuals with right-sided lesions were more likely than those with left-sided lesions to have “indifference” reactions, can be re-interpreted to implicate efferent left-hemispheric influences for freeze behaviors – avoidance or lack of engagement – disinhibited by the right-sided injury. Similar re-interpretations can be offered for the findings of Heilman et al. (1978) and Morrow et al. (1981). The findings of Avnon et al. (2004) also align with the model, suggesting that left-sided migraine carries a burden of greater parasympathetic shutdown physiology – in the form of bradycardia and vasodilatation – after a stressor,

perhaps due to enhanced excitability of left-hemispheric circuits. Bradycardia or vascular depressor responses reported by several of the other studies (Zamrini et al., 1990; Oppenheimer et al., 1992; Hilz et al., 2001; Tegeler et al., 2013) are also consistent with the idea that the left hemisphere mediates a parasympathetic freeze response.

Autonomic auto-calibration may explain increased risk for high-arousal behavior in individuals who are in a parasympathetic freeze state

In this section, we further develop the explanation of behavioral risks associated with a history of trauma exposure (Thesis Three). Fuller explanation of this idea is supported by review of the polyvagal theory. The polyvagal theory proposes that the vagus nerve includes branches that are anatomically and functionally distinct, deriving from different periods of vertebrate evolutionary phylogeny. A myelinated branch is associated with fine-tuned self-calming, social communication skills and physiological regulation, and inhibition of sympathetic arousal in environments perceived to be safe. An unmyelinated branch is associated with

neurogenic bradycardia and other freeze-mode behaviors in the presence of severe stressors, when movement may appear to be futile or dangerous, or in the setting of novel stimuli. In traumatic context, the freeze-mode produces hypoarousal, subjective emotional numbness, avoidant behaviors and social disengagement, and in severe form dissociation.

Polyvagal theory conceives autonomic regulation in hierarchical terms, in contrast to dominant models that view sympathetic and parasympathetic functions as opponent processes (or as being in paired antagonism). The myelinated vagus is normatively “on top,” functional in safe and restful environments and inhibitory of sympathetic mobilization. In the setting of an acute threat that requires mobilization or otherwise overwhelms the capacity for self-calming, sympathetic arousal is “second in command” and can provide fight or flight responses. If sympathetic mobilization behaviors are inadequate for the stressor or otherwise not adaptive for the presented need, then the unmyelinated vagus may be engaged as the mode of last resort, producing freeze or shutdown behaviors and physiology. These relationships are explained to be consistent with the Jacksonian principle of dissolution wherein evolutionarily more primitive structures rise to dominance when the higher are rendered inadequate.

The existence of *relatively autonomous drives for autonomic auto-calibration* has been proposed in our model as a way to describe dynamics of movement between different autonomic states. This postulate overlaps with polyvagal theory’s incorporation of the concept of Jacksonian dissolution. Shifts to sympathetic high arousal or parasympathetic freeze states associated with stress exposures may represent useful, automatic, and calibrated responses to perceived threats. Whereas Jacksonian dissolution explains trauma effects to produce relatively more primitive functioning, the concept of autonomic auto-calibration can also be used to explain behaviors associated with *recovery* (or attempted recovery) from stress or trauma in the direction of reconstitution or greater order. The ubiquity of relaxation strategies (from formal introspective meditation habits to alcohol or sedative-hypnotic use), can be understood as the response to the need of stressed or traumatized individuals to inhibit sympathetic arousal (Thesis Two).

The adverse effects of excess sympathetic arousal – and medical or self-directed strategies to dampen arousal – are commonly recognized by both health professionals and much of popular culture. In contrast the parasympathetic freeze state is less well known, less obviously amenable to intervention, and perhaps even more problematic as a health risk. In extreme cases, neurogenic bradycardia can lead to cardiac arrest (including fetal demise in obstetric contexts), and it may be a mechanism for cerebrogenic sudden death in epileptics. Unmyelinated vagal freeze-mode mechanisms likely contribute to asthma (Porges, 2011). Furthermore, a persisting freeze state may be associated with burdens of suffering independent of the risks of acute cardiac or respiratory shutdown, and also independent of the psychosocial disturbances or discontinuities that accompany emotional numbness or avoidant behaviors as such.

In explication of Thesis Three, we propose that an important burden of suffering associated with the freeze mode is related

to autonomic auto-calibration in the direction of recovery from trauma. The hierarchical logic of polyvagal theory appears to suggest that recovery from a traumatic freeze state that may be associated with disproportionate engagement of the unmyelinated vagus requires some degree of transition through a sympathetic high-arousal state, before one can regain (or gain) the self-calmed state of the myelinated vagus. *Autonomic auto-calibration to depart a parasympathetic freeze state may be expressed as a drive for movement towards high-arousal states, which may be socially dysfunctional but nonetheless experienced as a “step-up” in the hierarchy of autonomic states described by polyvagal theory.* It is established for example that a history of early life abuse or neglect confers a risk of anti-social behaviors or conduct disorder (Weiler and Widom, 1996; Maniglio, 2014). Autonomic auto-calibration may explain this risk as the expression of relatively autonomous drives, in individuals who are in a parasympathetic freeze state, to engage in behaviors associated with heightened arousal. Broadly, we hypothesize that heightened-arousal behaviors driven by a need to depart a parasympathetic freeze state may take a variety of forms, from conduct disorders including rage, to drug abuse (especially, but not only, stimulants) and possibly suicidality.

Autonomic auto-calibration in relation to the freeze state would appear to have specific salience for research on the psychological trait called “callous-unemotional.” Callous-unemotional traits have been found greater in children with experience of trauma, with the relationship being mediated by self-reported numbness to emotions (Kerig et al., 2012). In turn, a higher degree of the callous-unemotional trait in early adolescence has been shown to be a strong predictor of anti-social outcomes during adolescence and adulthood, including delinquency and arrests (McMahon et al., 2010). Callous-unemotional traits may be a function of traumatic stress that produces the parasympathetic freeze state, and the resulting greater risk for conduct disorders may arise from a drive to be unfrozen, to experience *feeling*.

Corroborative evidence for the physiological dimension of Thesis Three appears to exist in the association between low resting heart rate in children and adolescents, and anti-sociality. In reviews spanning nearly twenty years, the criminologist Adrian Raine has concluded that low resting heart rate is the best-replicated biological correlate of anti-sociality in children and adolescents (Raine, 1996, 2002; Glenn and Raine, 2014). Low resting heart rate correlates with anti-sociality independently of multiple other risk factors, and the significance of the relationship has been confirmed in prospective studies. Raine has invoked both psychological and neural functional explanations for this relationship, and his reference to “stimulation-seeking theory” is of special pertinence to the BHAM being proposed in this paper. Low resting heart rate may represent a subjectively unpleasant low-arousal state that encourages behavioral processes including anti-sociality to mitigate or depart the experience of that state. This explanation is essentially identical with the concept of auto-calibration of arousal to depart parasympathetic freeze mode. Intriguingly, Raine (2002) has further noted that the finding of low resting heart rate (increased parasympathetic efferent control) seems to be at odds with other findings showing that anti-social children have decreased vagal tone (decreased

respiratory sinus arrhythmia or heart rate variability, indicative of decreased parasympathetic efferent modulation). However, this paradox is entirely consistent with the existence of two distinct forms of vagal functionality proposed by polyvagal theory. As to the cause for low resting heart rate, the construct of auto-calibration of autonomic arousal encompasses early life traumatic exposures and thus may explain developmental aspects of anti-sociality more robustly than can explanations based on strictly genetic heritability.

The challenge of the freeze state and the relatively autonomous drive for autonomic auto-calibration is perhaps most sharply illustrated by the plight of many US veterans who have returned from the wars in Iraq and Afghanistan. Many or most of these servicemen and women will have experienced significant degrees of stress or trauma. Depending on individual factors, their autonomic physiology is likely to be characterized by significant sympathetic mobilization tendencies, but also marked degrees of parasympathetic freeze mode. Some expressions of high arousal may reflect intrinsic elevation in sympathetic activity, while others may represent a drive to disengage from the freeze state. The latter expressions might include propensity for violence, substance abuse, and suicidality – all of which are highly prevalent in these veterans (Institute of Medicine, 2013).

The bihemispheric autonomic model may explain left-hemispheric asymmetries or abnormalities associated with violence

A recurrent question in criminology is whether or to what degree biological factors may influence propensity for criminal behavior. This topic has been pursued intermittently over the twentieth century with respect to cerebral asymmetry, unilateral hemispheric dysfunctions, and laterality preferences (Nachson and Denno, 1987). One finding that emerged from early work is that left hemispheric EEG abnormalities, especially in the temporal lobe, tend to be more frequent in violent compared to non-violent subjects, and more recent studies have corroborated that finding. Using positron emission tomography, Volkow and Tancredi (1987) reported left temporal lobe metabolic abnormalities in four psychiatric patients with a history of repetitive, purposeless, violent behavior. Convit et al. (1991) recorded EEG's of 21 violent male psychiatric inpatients and found that increased leftward fronto-temporal and temporal asymmetry in the low frequency range (delta band) was correlated with increased violence. Wong et al. (1994) studied 372 subjects in a maximum security mental hospital and reported that those categorized to be in the highest tertile for violence had a markedly higher number of temporal lobe EEG abnormalities (without mentioning whether asymmetries were present). Pillman et al. (1999) reported that, among 222 defendants in a state court who were seen for pretrial psychiatric assessment, the ten individuals with focal left temporal lobe EEG abnormalities had a significantly higher number of violent offenses, than those without abnormalities. More recently, leftward temporal lobe EEG slowing and diminished arousal to emotional stimuli were reported in a case study of a serial killer (Ostrosky-Solis et al., 2008), and leftward temporal lobe high-frequency brain electrical asymmetry was observed in a group of five violent inmates in a medium-security prison (Gerdes, unpublished observations). In some of these studies, left-sided electrical

abnormalities or leftward asymmetries have been interpreted to indicate deficits in language or cognitive processing skills that led the individuals to rely on violence as instrumental means for social interaction.

It should be pointed out that the above studies include reports of both left-sided abnormalities of EEG and leftward asymmetry of electrical activity. While equivalence should not be presumed between abnormalities and asymmetries, nonetheless on a preliminary basis we interpret these studies to suggest that, as with the patients with left-sided migraine symptoms (Avnon et al., 2004), that aberrant or excess left-sided electrical activity represented in these subjects was an indicator of augmented parasympathetic freeze physiology. Review of these data from the perspective of the BHAM, including its concept of autonomic auto-calibration from freeze state, suggests an explanation for the violence of individuals with left-sided defects or excess in brain electrical activity that is independent of the left hemisphere role for language or analytic cognition. Individuals prone to violent behavior may disproportionately have a history of severe life stress adequate to promote the parasympathetic freeze state, associated with leftward asymmetry in the activity of brain regions responsible for autonomic management. A relatively autonomous drive for autonomic auto-calibration may have been expressed, in the individuals in these studies, as propensity for violence.

The BHAM interpretation that risk for violence associated with leftward asymmetry or left-sided abnormality does not contradict the idea that cognitive or language deficits associated with left-sided aberrancy contribute to violent tendency. The combined influence of these factors could easily be greater than either on its own. Furthermore, study design and statistical aspects of the above findings permit a conclusion no stronger than to suggest that leftward dominant asymmetry merits ongoing investigation as a possible relative risk factor for violence, not a determinant of violence. Even if leftward dominant asymmetry is validated as a risk factor for conduct disorder or violence, we hypothesize that only a minority of individuals with leftward dominance will manifest flagrant behavioral disturbance. We reiterate the role of the prefrontal cortex for supporting an individual to steer behaviors and navigate environments, whatever one's prevailing asymmetry. With those caveats, we propose that the BHAM, including the concept of autonomic auto-calibration, may explain previously unexplained portions of the likelihood to enact dysregulated behaviors, among individuals with a history of severe traumatic stress. The model also has implications for intervention, and these are explored in the following section.

ILLUSTRATIONS OF THE BIHEMISPHERIC AUTONOMIC MODEL INCLUDING IMPLICATIONS FOR INTERVENTION A PARADIGM OF INTERVENTIONAL RESEARCH BASED ON THE BIHEMISPHERIC AUTONOMIC MODEL

The two case examples below are drawn from participants enrolled in an IRB-approved, open label, feasibility study at Wake Forest School of Medicine, exploring use of a noninvasive computer-guided neurotechnology for individuals with a variety of conditions, many associated with stress or psychophysiological

dysregulation. The technology is called high-resolution, relational, resonance-based electroencephalic mirroring (HIRREM®, or Brainwave Optimization®), and it is a non-medical device designed to facilitate relaxation and auto-calibration of neural oscillations (Gerdes et al., 2013). The technology produces closed-loop acoustic stimulation (audible tones of variable pitch and timing) such that the brain tends to self-optimize its electrical activity patterns, shifting towards greater symmetry between left and right hemispheres, and more optimized ratios of energy along the brain electrical frequency spectrum. For these subjects, the technology was provided as a series of sessions, typically 90–120 min duration (and up to two sessions per day), with each session composed of a series of 4–9 protocols (6–40 min per protocol), conducted predominantly with eyes closed while at rest. Protocols target multiple brain regions including temporal, frontal, frontal pole, central, parietal, occipital, cerebellar, and occipital lobes and locations. The technology is a “whole-brain” approach, but for purposes of explicating the BHAM, attention is paid in the case illustrations to temporal lobe activity only. As reviewed above, surface readings of brain electrical activity from temporal locations have been found to correlate with peripheral measures of autonomic cardiac control (Gray et al., 2007; Tegeler et al., 2013), and temporal scalp locations have specifically been proposed to be sites for recording or influencing afferent or efferent autonomic activity in the insular cortex (Gray et al., 2007; Montenegro et al., 2011; Gerdes et al., 2013; Okano et al., 2013).

Participants completed a variety of measures at baseline and again after completing the sessions. Self-reported symptom inventories included the Insomnia Severity Index (ISI), a 7-item survey that assesses the severity, nature, and impact of insomnia symptoms on quality of life over the previous two weeks, with possible scores ranging from 0 to 28 (Morin et al., 1993). Scores of ≥ 8 suggest clinically relevant symptoms of insomnia, and a change of seven points reflects a meaningful change. The Center for Epidemiologic Studies Depression Scale (CES-D) is a 20-item survey, with possible scores from 0 to 60, that assesses affective depressive symptomatology to screen for risk of depression (Radloff, 1977). Scores of ≥ 16 suggest clinically relevant symptoms of depression, and a change of eight points reflects a meaningful change. The Post-traumatic stress disorder (PTSD) Checklist-Civilian Version (PCL-C), is a 17-item inventory to evaluate multiple symptoms of post-traumatic stress, with scores ranging from 17 to 85 (Weathers et al., 1993). Scores of ≥ 44 points suggest clinically relevant symptoms of PTSD for the PCL-C, and a change of 16 points reflects a meaningful change.

Baseline data collection also included continuous recordings of blood pressure and heart rate (bpm) data, acquired from noninvasive finger arterial pressure measurements, for a minimum of 5 min while subjects were in the supine position. Systolic blood pressure and RR interval data acquired (BIOPAC acquisition software, Santa Barbara, CA, USA) at 1000 Hz were analyzed using Nevrokard BRS software (Nevrokard BRS, Medistar, Ljubljana, Slovenia) to produce measures of heart rate variability, reported here as the standard deviation of the normal beat to beat interval (SDNN, ms), and baroreflex sensitivity (BRS, ms/mmHg), which we report according to the sequence method.

Each participant had a baseline assessment to obtain information regarding electrical frequencies and amplitudes (Gerdes et al., 2013). The assessment included 3 min recordings obtained from at least six standard locations on the scalp (using placements from the 10–20 system, F3/F4, C3/C4, P3/P4, T3/T4, FZ/OZ, and O1/O2, 1 min each for eyes closed, partially closed, and eyes open), with the participant at rest (eyes closed, partially closed) and while carrying out a cognitive task (eyes open). The assessment is intended to provide a “snapshot” of relative symmetry between homologous brain regions, as well as the distribution of amplitudes among different frequency bands at each location. Data from the assessment were used to identify the protocols for the first intervention session, and data from each intervention session were used to guide protocol selections for subsequent sessions. For purposes of the following case illustrations, spectrographs of 1 min averages of amplitudes at bilateral temporal lobes, eyes closed, are shown for the assessment and the penultimate minute of the temporal lobe protocol for the penultimate HIRREM session.

CASE 1: LEFTWARD TEMPORAL LOBE BRAIN ELECTRICAL ASYMMETRY IN A SPECIAL OPERATIONS MILITARY OFFICER WITH MILD TRAUMATIC BRAIN INJURY AND POST-TRAUMATIC STRESS DISORDER

A 29-year-old man, deployed as part of a US military special operations unit, experienced a mild traumatic brain injury (mTBI) when he was in close proximity to an exploding rocket-propelled grenade. He was diagnosed with mTBI and post-traumatic stress disorder. He had been in good overall health prior to the mTBI, with the exception of several years of insomnia, requiring medications. He reported that his primary symptoms were severe insomnia, headaches, and impaired memory, both short and long term. The traumatic event occurred 15 months prior to enrollment. During the period between the mTBI and enrollment, he reported having tried numerous treatments including both medical therapies and non-traditional approaches (cognitive processing therapy; prolonged exposure; group therapy; anti-depressant medication; adrenal optimization; dietary changes; fitness changes; nerve blocks; nerve ablations; acupuncture; transcranial magnetic stimulation; meditation; massage therapy; pain medication; ketamine infusions; bio-feedback; sleep medications; service dog) from which results had been by his estimation “mixed and relatively limited.” At the time of enrollment, pertinent medications included eszopiclone (3 mg nightly), melatonin (30 mg nightly), venlafaxine XR (225 mg daily), and thyroid hormone (2 grains daily).

On baseline assessment, at homologous temporal lobe regions (T3/T4) with eyes closed (Figure 2), there was a leftward (T3) dominant pattern in the higher frequencies (amplitudes 20–74% greater than the right, at T4). Scores for the ISI, CES-D, and PCL-C were 28, 34, and 78, respectively. Resting heart rate, SDNN, and BRS were 53 bpm, 65 ms, and 19.2 ms/mmHg, respectively. The subject received a total of 22 HIRREM sessions over 12 days, during which time he self-tapered and/or discontinued his various medications. He reported no adverse events in association with the sessions.

Figure 3 shows a one-minute snapshot of temporal lobe (again T3/T4) brain electrical activity from the penultimate minute of a protocol during the penultimate session, to illustrate the

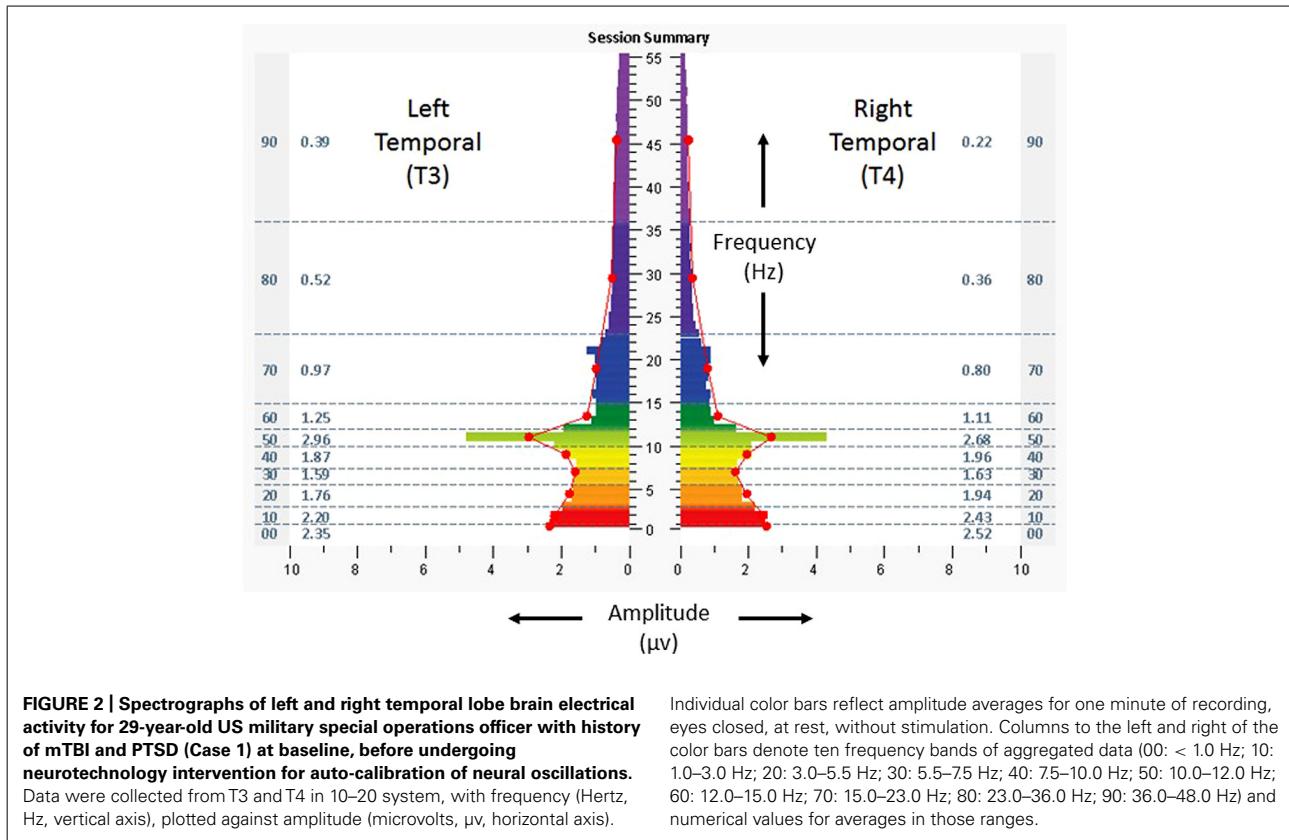
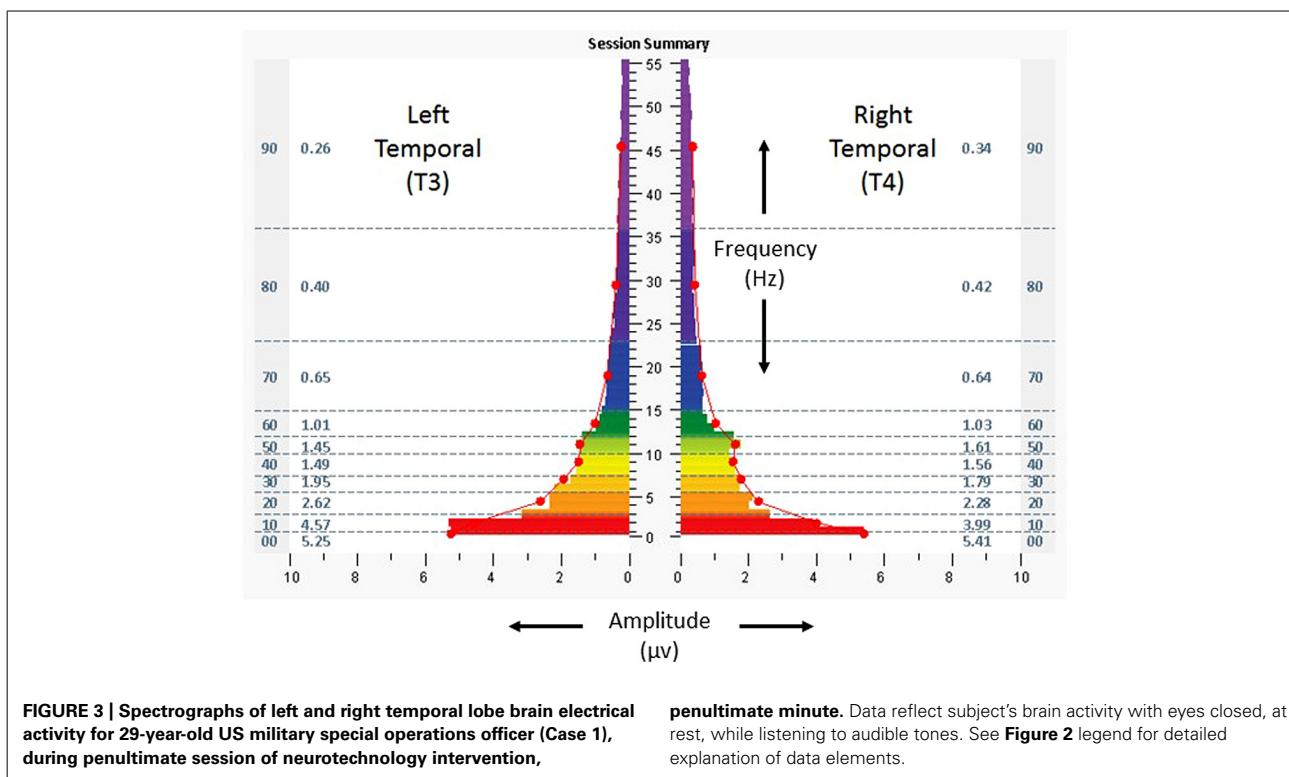


FIGURE 2 | Spectrographs of left and right temporal lobe brain electrical activity for 29-year-old US military special operations officer with history of mTBI and PTSD (Case 1) at baseline, before undergoing neurotechnology intervention for auto-calibration of neural oscillations.

Data were collected from T3 and T4 in 10–20 system, with frequency (Hertz, Hz, vertical axis), plotted against amplitude (microvolts, μ v, horizontal axis).

Individual color bars reflect amplitude averages for one minute of recording, eyes closed, at rest, without stimulation. Columns to the left and right of the color bars denote ten frequency bands of aggregated data (00: < 1.0 Hz; 10: 1.0–3.0 Hz; 20: 3.0–5.5 Hz; 30: 5.5–7.5 Hz; 40: 7.5–10.0 Hz; 50: 10.0–12.0 Hz; 60: 12.0–15.0 Hz; 70: 15.0–23.0 Hz; 80: 23.0–36.0 Hz; 90: 36.0–48.0 Hz) and numerical values for averages in those ranges.



movement towards symmetry which had begun early in the course of sessions (less than 5% asymmetry in higher frequencies). At exit, the subject reported having slept 6 h the preceding night, and scores for the ISI, CES-D, and PCL-C decreased to 19, 22, and 60, respectively. His written comments were that “[I have] discontinued all prescription medication, started sleeping with steady improvement, have reduced pain, increased focus and concentration, and [have had] an improved dynamic with anxiety and depression.” After completing the sessions, the resting heart rate, SDNN, and BRS were 61 bpm, 83.6 ms, and 24.1 ms/mmHg, respectively.

CASE 2: RIGHTWARD TEMPORAL LOBE BRAIN ELECTRICAL ASYMMETRY IN A FEMALE UNIVERSITY STUDENT WITH PERSISTING POST-CONCUSSION SYMPTOMS INCLUDING DEPRESSION

A 23-year-old woman, a graduate student at a local university, enrolled in the same research study referenced in Case 1, due to persisting post-concussion symptoms. She played soccer and suffered from five concussions during a six month period at age of 13. She then suffered additional, non-athletic concussions at 10 and 5 months prior to enrollment in the study, due to a fall and a mishap while dancing, respectively. She reported persisting headaches and dizziness as primary complaints, was unable to exercise at all, and was in the process of dropping out of graduate school since she was not able to read, study, and learn as needed. She mentioned having migraines during high school but denied other medical problems. She had started amitriptyline (25 mg nightly) three days prior to enrollment in the study but discontinued that medication upon beginning the intervention. Her other

medications were oral contraceptives, sumatriptan (25 mg tablet as needed migraine), and ibuprofen (prn).

The baseline assessment at T3/T4, eyes closed (Figure 4), revealed T4 dominance (15–29%) in the highest frequencies. Scores for the ISI, CES-D, and PCL-C were 5, 31, and 22. Resting heart rate, SDNN, and BRS were 79 bpm, 55.5 ms, and 13.5 ms/mmHg. She received 23 HIRREM sessions over 34 days and reported no adverse events.

Figure 5 shows temporal lobe brain electrical activity (eyes closed) from the penultimate minute of a protocol from the penultimate intervention session, with asymmetry reduced to 3–6% in the direction of T3, in the same frequency ranges. During and following the sessions, she reported that she was able to engage in more activities including walking, reading, and watching movies. She also reported improved mood, fewer headaches, increased stamina, better appetite, and improved quality of sleep. Scores for the ISI, CES-D, and PCL-C were 3, 9, and 19. Resting heart rate, SDNN, and BRS were measured at 68 bpm, 83 ms, and 35.7 ms/mmHg.

COMMENT ON CASE ILLUSTRATIONS

The above cases illustrate asymmetries of brain electrical activity measured at temporal scalp locations. In accordance with our findings that brain electrical asymmetry measured at this location appears to allow assessment of relative sympathetic or parasympathetic activation (Tegeler et al., 2013), subjects reported symptoms related to a number of clinical issues that can manifest as dysregulation of arousal, including insomnia, depressiveness, post-traumatic stress, and pain. McGrath et al. (2013) found that

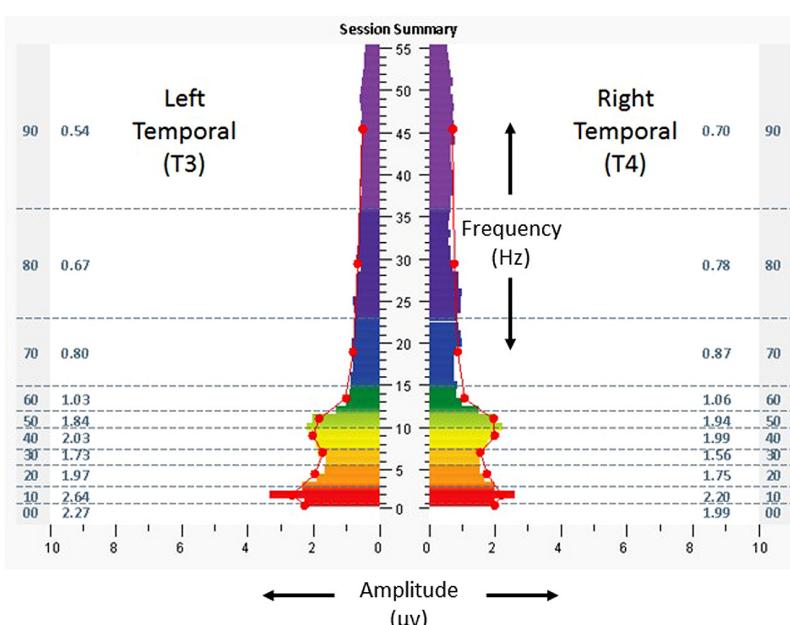


FIGURE 4 | Spectrographs of left and right temporal lobe brain electrical activity for 23-year-old woman with history of persisting post-concussion symptoms (Case 2), before undergoing neurotechnology intervention for auto-calibration of neural

oscillations. Data were collected from T3 and T4 in 10–20 system, with frequency (Hertz, Hz, vertical axis), plotted against amplitude (microvolts, μ V, horizontal axis). See **Figure 2** legend for detailed explanation of data elements.

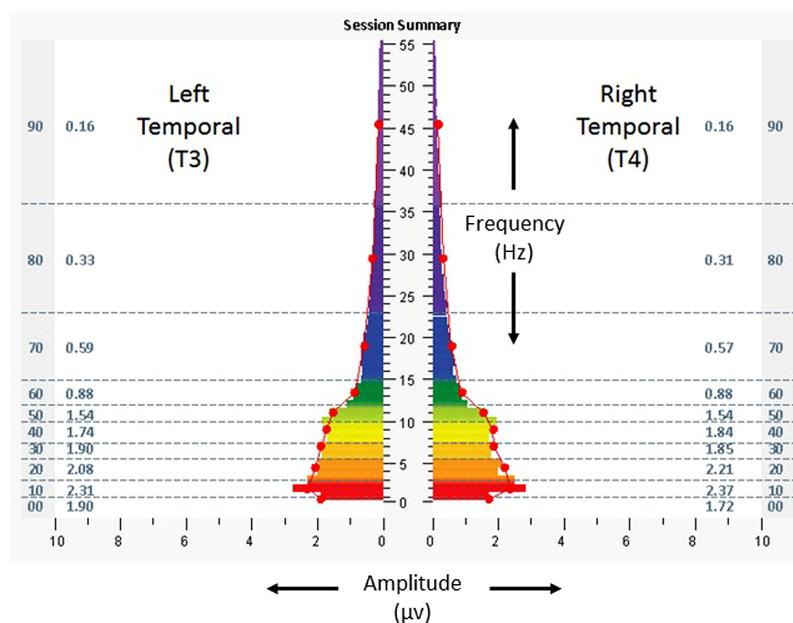


FIGURE 5 | Spectrographs of left and right temporal lobe brain electrical activity for 23-year-old woman (Case 2), during penultimate session of neurotechnology intervention, penultimate minute. Data

reflect subject's brain activity with eyes closed, at rest, while listening to audible tones. See **Figure 2** legend for detailed explanation of data elements.

increased right anterior insula activation helped predict treatment response in major depression, and it has been suggested that the asymmetry reported in that study may have been due to differences in autonomic arousal that are detectable through surface measures of brain electrical activity (Tegeler et al., 2014). Traumatic brain injury itself is well appreciated to be associated with autonomic dysregulation (Hilz et al., 2011). For both subjects, use of a noninvasive neurotechnology for auto-calibration of neural oscillations was associated with shifting of temporal lobe brain electrical activity toward greater symmetry, especially in higher frequency ranges. Both subjects reported significant reductions in clinical symptom inventories and overall improvement in functionality.

Cardiovascular measures were consistent with predictions of the BHAM and its incorporation of polyvagal theory. In Case 1, the subject with leftward (T3) dominance was found to have increased resting heart rate after completing the intervention, possibly reflecting release from the "hold" of a parasympathetic freeze state, allowing increased sympathetic activation. In Case 2, the subject with rightward (T4) dominance was found to have decreased resting heart rate post-intervention, possibly reflecting increased functional parasympathetic inhibition from the left hemisphere. In both subjects, heart rate variability (reflected as higher SDNN values) was increased after the intervention, possibly reflecting greater capacity of the myelinated vagus to maintain calm and emotionally well-regulated states as would be predicted by polyvagal theory. Whereas both heart rate and heart rate variability are known to be under vagal regulation (Task Force for the European Society of Cardiology, and the North American Society of Pacing Electrophysiology, 1996), the

dissociation of the direction of changes in these two variables for the subject in Case 1 is consistent with recovery of a higher level of autonomic functioning as conceived by polyvagal theory. That is to say, the subject may have demonstrated a shift away from unmyelinated toward myelinated vagal activity, permitting both increased resting heart rate and increased heart rate variability.

We do not presume that the epochs of temporal lobe brain electrical activity shown in the figures are exhaustive and unqualified indicators of ANS management. In the first place, other cortical regions may be of interest. Foster et al. (2008) reported a correlation between frontal asymmetry and heart rate, while other investigators have reported null findings when testing for correlation between heart rate variability and frontal asymmetry (Chang et al., 2012; Balle et al., 2013) or parietal asymmetry (Balle et al., 2013). The possibility cannot be excluded that medication or supplement effects (including changes to regimens) contributed to the brain electrical activity findings in these case studies. Differences in asymmetry between the states of eyes closed and eyes open (at task) may be of particular interest, given that both spectral and topographical aspects of brain electrical activity are known to change between those states (Barry et al., 2007). Moreover, the comparison of brain electrical activity "snapshots" from the assessment and the penultimate intervention session is not meant to imply a linear transition from dominant asymmetry to symmetry. Conceptually, the neurotechnology provided to these subjects is allostatic ("stability through change") in its intention (Sterling, 2012), aimed to facilitate brain activity to become "un-stuck" from maladaptive set-points (Gerdes et al., 2013). Though the end result tends to be greater hemispheric symmetry and more optimality of

ratios between low and high frequencies, every recipient is recognized to demonstrate unique and complex neural oscillatory patterns throughout their process. Whether the BHAM may be better defined by the addition of asymmetry measures for regions other than the temporal lobes, to what degree asymmetry in key regions may be influenced by the state of eyes closed or eyes open or concurrent medication use, and the temporal and spectral dynamics of measured asymmetry (including their reproducibility) over the course of an intervention, are all questions for further study.

Being uncontrolled case examples and in consideration of the variables involved, the above case examples are adduced not as proof of the BHAM but rather as illustrations of its application and as preliminary explorations of phenomena that may be meaningful targets for ongoing study. The neurotechnology used in these case studies has also been associated with reduction of insomnia and depressive symptoms in a pilot clinical trial (Tegeler et al., 2012), but to our knowledge there has otherwise been little attempt to leverage hemispheric lateralization of autonomic management for clinical purposes. In trained cyclists, Okano et al. (2013) have reported that transcranial direct current stimulation over left temporal cortex may modulate sensory perception of effort through delay of parasympathetic withdrawal, to permit increased exercise performance.

We propose that the clinical improvements reported by these subjects may be understood in a way that is highly convergent with the imperative for new frameworks to advance mental health sciences. Specifically, we suggest that these subjects' symptom clusters, diagnostically differentiated under the schema of the Diagnostic and Statistical Manual but physiologically related under the BHAM, exemplify the need to reconceptualize mental health as the integrated expression of core and interlocked modules of brain-behavior functionality. The NIMH has been vocal in directing mental health researchers to view individuals in such brain-functional terms, rather than through checklists of behavioral and symptom clusters that are compared to population averages (Cuthbert and Insel, 2013). The NIMH RDoC (Research Domain Criteria) initiative has preliminarily identified arousal, positive valence, negative valence, cognitive systems, and social processes as being five core brain-behavioral domains which are operative in both health and disease, and which may serve as more biologically valid units of analysis for future progress in mental health research. We propose that the BHAM is a promising vehicle for fresh efforts in the direction of RDoC and related endeavors.

DISCUSSION

The present paper has proposed a BHAM that may explain and predict a range of phenomena related to traumatic stress and arousal, mediated partially through relatively autonomous drives toward autonomic auto-calibration. The model proposes that relative symmetry in activity of hemispheric brain regions responsible for autonomic management represents a state of relative optimality in autonomic functioning, whereby sympathetic and parasympathetic functionalities fluctuate naturally and are adaptive for the ongoing needs and changing circumstances of life. Rightward dominant asymmetry in activity of brain regions

responsible for autonomic management may reflect a state of sympathetic mobilization which may develop as an adaptive response to a given context, but is likely to be maladaptive if it is persistent despite changing and especially non-threatening environments. Leftward dominant asymmetry in the same brain regions may be indicative of a parasympathetic freeze mode, also adaptive for certain contexts, but also likely maladaptive if persistent. Exposure of an individual to varying degrees and types of traumatic stress, and recovery from the associated traumatic states, produces (or reflects) processes of autonomic auto-calibration toward and away from varying degrees of dominant rightward or leftward asymmetry.

The BHAM concept of autonomic auto-calibration proposes to explain the increased risk for behavioral disturbances (including conduct disorder and substance abuse) among individuals with a history of traumatic stress. For an individual with a history of severe stress or trauma leaving them in a parasympathetic freeze state, compensatory high-arousal behaviors may represent options for *feeling*, despite being at odds with accepted societal norms. Those in a state of traumatic high arousal may be at risk for compensatory behaviors for arousal attenuation, including substance abuse and medication dependence. The model does not imply that relatively autonomous drives for autonomic auto-calibration are not subject to regulation by the prefrontal cortex.

We have illustrated potential interventional implications of the BHAM through case examples of a military veteran with traumatic stress, and a university student with persisting post-concussive symptoms, both of whom had asymmetries of temporal lobe brain electrical activity, and both of whom experienced symptom reduction after using a noninvasive technology designed for auto-calibration of neural oscillations. The subjects' improvements in arousal-related symptom clusters that cut across diagnostic categories appear to exemplify the value of the RDoC framework proposed by NIMH. Furthermore the traumatic stress history incorporated by the BHAM reflects a sensitivity to neurodevelopmental trajectories that is an advantage of RDoC (Cuthbert, 2014).

Many questions can be asked of the model, to confirm its validity or to explore potential mechanisms or ramifications. We consider that data-collection paradigms based on scalp measures of brain electrical asymmetry are likely to be productive, especially because of their high temporal resolution and ease of implementation, permitting serial measures. Both those advantages may be critical with respect to the capacity of the brain – and the ANS – to shift activity patterns quickly, in the context of rapidly changing and newly anticipated needs. In contrast, some of the core advantages of more complex experimental methodologies, especially their high spatial resolution, are of less consequence if a key parameter of interest is instantaneous hemispheric activation asymmetry.

Within the paradigm of brain electrical measures, it may be asked if there are particular scalp locations most likely to produce reliable indications of autonomic signaling. With respect to the measured signals themselves, studies could be carefully designed to tease apart whether they represent efferent or afferent signals or both, or even one rather than the other depending on the instantaneous context. Spectral components of brain electrical signals

may also hold meaningful information. Just three of the testable hypotheses that derive from the BHAM include the following. Nominally healthy and trauma-free individuals who experience an acute (but not overwhelming) stressor, will have greater rightward hemispheric asymmetry in brain regions responsible for autonomic management and greater peripherally measured heart rate, than matched controls who do not experience the stressor. Individuals who have a history of severe or extended exposure to stress or trauma, or children with a history of severe childhood trauma and evaluated to be callous-unemotional, will be more likely to demonstrate left-hemispheric autonomic asymmetry, and they will have on average a lower resting heart rate, than matched controls. In cases of either rightward or leftward asymmetry, it may be hypothesized that degree of asymmetry will correlate with the magnitude of heart rate differences. Third, one may hypothesize that use of interventions to support greater hemispheric symmetry in brain regions responsible for autonomic management will be associated with more optimal autonomic regulation and associated subjective and behavioral improvements.

If the BHAM is valid, then questions should be raised about its generalizability. A new and non-trivial insight about ANS functioning should have new and non-trivial consequences, given the pervasive and critical role of the ANS across organ systems and behaviors (Rees, 2014). It may be that polyvagal theory represented the beginning of a *paradigm shift* for understanding the ANS. And although the phrase “paradigm shift” is now often used loosely to refer to any subjective shift of perspective, we use the phrase in a manner consistent with its original use by the historian and philosopher of science Kuhn (1962). A scientific paradigm shift begins when normal science is met with an anomaly. In the case of the ANS, understanding of the stress-buffering role of the parasympathetic nervous system did not cohere with understanding about the potential lethality of neurogenic bradycardia. Polyvagal theory explained that anomaly by articulating two different forms of vagal activity, especially identifying distinct features of the parasympathetic freeze state, and proposing that autonomic activity is expressed in a hierarchical way in accordance with environmental context and individual variations. New scientific paradigms require new tools and procedures for collecting and interpreting empirical data, and we suggest that measurement of brain electrical asymmetry may represent a productive new approach for autonomic neuroscience. If a paradigm shift for assessment and intervention on autonomic dimensions of brain-behavior relationships is now in the making, we hope for the BHAM to support productive explorations of the new worldview.

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Letters

COMMENT & RESPONSE

Significance of Right Anterior Insula Activity for Mental Health Intervention

To the Editor We applaud McGrath and colleagues¹ for exploring the use of brain state as a way to predict differential outcomes from either psychotherapy or medication as treatment for depression. Hypometabolism in the right anterior insula correlated with symptom reduction through cognitive behavioral therapy, whereas hypermetabolism in the right anterior insula correlated with symptom reduction through escitalopram. In their discussion, the authors pointed out roles of the anterior insula for interoception, self-awareness, and cognitive control. We wish to highlight additionally that the insulae are loci for lateralized management of autonomic functioning. In particular, the right anterior insula regulates sympathetic activity, and the left insula appears to be responsible for parasympathetic activity.² It may be that depressed individuals with greater right anterior insular activity have higher sympathetic arousal and are thus relatively impaired in their capacity to successfully apply cognitive-behavioral strategies. These individuals may preferentially benefit from psychopharmacological agents, which are known to have effects on autonomic tone.³ In our own work, we have found that hemispheric lateralization of autonomic management may be discerned through surface brain electrical activity recordings, with clinical implications. We recently reported a relationship between temporal high-frequency brain electrical asymmetry, calculated from 2-channel, 1-minute bilateral recordings, and peripheral measures of cardiovascular autonomic regulation. Rightward temporal asymmetry correlated with higher heart rate and lower heart rate variability.⁴ Furthermore, in a clinical trial, we found that autocalibration of right-dominant high-frequency temporal activity toward greater symmetry appeared to correlate with insomnia symptom reduction for individuals with insomnia and depressive symptoms.⁵ We are thus excited that data from positron-emission tomography and surface brain electrical activity recordings may be converging on a unitary conclusion about the role of lateralized activity in temporal lobe-region structures for mental health intervention.

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Schizophrenia, Cognition, and Psychosis

To the Editor *JAMA Psychiatry* recently published an intriguing article by Kahn and Keefe¹ challenging us to reconsider how we conceptualize schizophrenia and providing evidence they felt argues for positioning schizophrenia as a cognitive rather than psychotic disorder. Implicit in their message is the increased focus on functional vs clinical recovery, and they opined that our fixation on psychosis may be holding the field back. In an accompanying editorial, Heckers² mounted a number of challenges that suggest caution in embracing such a position.

We add our voice to this cautionary note for similar, and additional, reasons. One of their arguments centered on evidence that cognitive symptoms predate the onset of psychosis. However, this is also true for negative symptoms,³ a symptom domain not addressed at all in their discussion. Moreover, there is evidence that negative symptoms may be as, if not even more, important in terms of functional outcomes.⁴

Heckers made reference to trivializing the care of schizophrenia, and we take up this point from a slightly different perspective. He highlighted Kraepelin's perception of schizophrenia as a disorder of volition, which we have addressed elsewhere,⁵ but in this case saw the trivialization vis-à-vis psychosis. To diminish the central role of psychotic symptoms in schizophrenia is to ignore the clinical reality of this illness. In terms of biology and pathophysiology, it is imperative that we give equal attention to these other symptom domains, but it is psychosis that fills hospital beds and our current antipsychotic treatments (including clozapine), while reasonable, fall woefully short for many. To this last point, the field seems to have embraced the notion that cognitive and negative symptoms are the rate-limiting factors in schizophrenia recovery, forgetting the comparison is made against individuals treated for psychosis. Were it even ethical, should such comparisons not be made on a level playing field?

Finally, Kahn and Keefe argued that we need to put the "focus back on cognition." They are correct in highlighting our

**Abstract presented in poster form at American Academy of Neurology, Sports Concussion Conference,
July 11-13, 2014**

Use of HIRREM is associated with improved symptoms and neural oscillatory balance in athletes with post-concussion symptoms

Tegeler CH, Tegeler CL, Cook JF, Lee SW, Gerdes L, Shaltout HA, Miles CM

Objective: Explore the use of a noninvasive neurotechnology, HIRREM, in athletes with persisting post-concussion symptoms (PPCS).

Background: Concussed athletes may develop PPCS, including insomnia, depression, and others, many associated with autonomic dysregulation. Brain oscillatory patterns are altered after concussion and may contribute to symptom development. High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM®) generates feedback as audible tones derived from software algorithm-driven analysis of real time changes in brain electrical activity from scalp recordings, measured at high spectral resolutions, to facilitate relaxation and auto-calibration of neural oscillations.

Methods: Twelve athletes (6 female, median age = 17.5 years, 14-23), reported persisting symptoms (median of 6 months, range 9 days to 3 years) after concussion, preventing return to athletic activity. They received a median of 17 (13-36, 90 minutes each) HIRREM sessions over 28 (10-93) days as part of an open label IRB-approved exploratory study of HIRRM for diverse health conditions. Pre- and post-HIRREM symptom inventories included concussion (Rivermead, n=9), insomnia (ISI, n=12), and depression (CES-D, n=7). Asymmetry scores for temporal lobe high frequency amplitudes (TLHFA) were also calculated from 1 minute epochs of temporal (T3/T4, eyes closed) high frequency amplitudes (23-36 Hertz, microvolts) at baseline, the first four, and last four HIRREM sessions according to (T4-T3)/lesser of T3 and T4. Positive numbers show rightward dominance.

Results: Median baseline Rivermead (23, range = 2-57), ISI (7.5, 2-15), and CES-D (22, 10-47) reduced to 2 (0-33, p=0.001), 2 (0-10, p<0.001), 9 (3-33, p=0.009), respectively, post-HIRREM. TLHFA scores decreased from 0.46 (rightward dominance) to -0.13 (slight leftward dominance), suggesting improved neural oscillatory balance. Ten of the 12 returned to full activity, while persistent chronic daily headache precluded return for two.

Conclusion: Use of HIRREM by athletes with PPCS was associated with symptom reduction, improved neural oscillatory balance, and return to athletic activity. Controlled trials are warranted.

awakening durations. There was no association between the self-reported number of awakenings/night vs. any of the objectively-measured awakening durations. Bonferroni-corrected t-test revealed the High-number of self-reported awakening group ($n = 14$ nights) had significantly greater number of sympathetic arousals per hour (33.7 ± 19.7 vs. 13.2 ± 9.1 ; $p < 0.0001$) as compared to the Low-number group ($n = 31$ nights). For the Low-number awakening group, the bias toward patient under-reporting awakenings was decreased from an average difference of 12-per-night with a 30-second awakening duration, to two-per-night with a 300-second awakening duration. For the High-number awakenings group, the average difference decreased from 8-per-night for a 30-second duration, to zero for a 210-second awakening duration.

Conclusion: Patients with chronic insomnia do not accurately estimate awakenings as defined by standard 30-second durations. Longer duration awakenings more closely match subjective experience. Increased heart rate variability during sleep appears more prevalent in patients who self-report greater numbers of awakenings/night.

0549

NIGHT TO NIGHT VARIABILITY IN SLEEP ARCHITECTURE AND CONTINUITY IN PATIENTS WITH CHRONIC INSOMNIA

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Introduction: This study investigates night-to-night variability in sleep architecture and sleep continuity in patients with chronic insomnia.

Methods: Twenty-two patients with chronic insomnia completed a two-night, in-home study with Sleep Profiler (Advanced Brain Monitoring, Carlsbad, CA) prior to CBT-I. This cohort included ten patients with comorbid OSA; eight were studied in-home while on CPAP. The automated sleep staging were manually edited by sleep center staff, prior to computing the percent time by stage. Awakenings were based on a minimum 30-second duration as well as a 90-second duration of wake intrusion/hour. Pearson correlations and Bland-Altman plots were used to assess night-to-night agreement. Automated detection of cortical arousals were based on a 3-second increase in median alpha to sigma power spectra. Sympathetic arousals were based on a six beat-per-minute pulse rate increase compared to the previous 10th beat. Movement arousals exceeded a threshold magnitude of actigraphy change. Snoring arousals were based on a sudden substantial decrease in amplitude after a period of loud snoring. Arousal indexes were derived per hour of sleep.

Results: Strong night-to-night concordance was observed for stages N1 ($r = 0.84$; $p < 0.00001$) and N3 ($r = 0.72$; $p < 0.0001$), and reasonable agreement for stage N2 ($r = 0.56$; $p < 0.01$). Substantial variability in the percent-time REM was attributed to the bias toward increased percent-time N1 and N3, and decreased REM, on Night 2 (bias = 0.8%, 1.4% and -2.1%, respectively). Repeated-measure variability in the awakening index was reduced when the awakening duration was increased from 30- to 90-seconds ($r = 0.66$; $p < 0.001$, and $r = 0.77$; $p < 0.00001$, respectively). Strong night-to-night agreement in the cortical arousal index ($r = 0.84$; $p < 0.000001$), sympathetic arousal index ($r = 0.93$; $p < 0.000001$), movement arousal index ($r = 0.75$; $p < 0.0001$) and snoring arousal index ($r = 0.75$; $p < 0.0001$) suggest fairly stable measures of sleep continuity.

Conclusion: These preliminary results suggest sleep architecture and sleep continuity may be useful in defining sleep trait characteristics.

0550

PRELIMINARY EVIDENCE FOR THE EFFICACY OF ACCEPTANCE AND COMMITMENT THERAPY IN PRIMARY INSOMNIA

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Introduction: In primary insomnia (PI), a discrepancy between severe subjective symptoms and minor objective disruptions of sleep has been described. Current state-of-the-art treatments, cognitive behavior therapy (CBT-I) and hypnotic medication, have been shown to acutely improve sleep, however, an impaired Quality of Life (QoL) often persists after treatment. We posit that Acceptance and Commitment Therapy (ACT) improves the QoL through the enhancement of psychological flexibility. This study hypothesizes that sleep and QoL are partially independent and evaluates the impact of ACT on QoL and sleep quality in individuals with PI.

Methods: Eleven individuals with PI according to DSM-IV criteria who were non- or partial responders to CBT-I were included. They participated in six weekly ACT sessions in an outpatient group setting. Primary outcomes were QoL, as measured by the Glasgow Sleep Impact Index (sleep-related QoL) and the World Health Organization Quality of Life scale (global QoL), and subjective sleep quality, as measured by sleep diaries. Secondary outcomes were subjective sleep data as measured by sleep diaries. Data were collected 6 weeks (T-1) and directly (T0) before the intervention, directly after the intervention (T1) and at three-months-follow-up (T2).

Results: Ten subjects completed the study, one dropped out due to scheduling problems. All outcomes remained stable between T-1 and T0. Significant improvements after the intervention were observed for the sleep-related QoL and global QoL (ANOVA with factor Time, post-hoc contrasts T1 and T2 vs. T0, all $P < .05$, large effects). A trend towards improvement was observed for subjective sleep quality ($p < .1$, large effect). Subjective total sleep time, sleep onset latency and wake time after sleep onset did not significantly change across the study.

Conclusion: The findings provide preliminary evidence that ACT as a group program might expand the therapeutic strategies for PI in terms of improving the patients' QoL.

0551

A NONINVASIVE APPROACH TO IMPROVE INSOMNIA IN A MILITARY COHORT

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Introduction: Insomnia is prevalent in soldiers post-deployment. Autonomic hyperarousal is a key mechanism for insomnia. High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM), a noninvasive neurotechnology for relaxation and auto-calibration of neural oscillations, uses auditory tones to reflect brain frequencies in near real time. We report the effects of HIRREM on insomnia (Insomnia Severity Index, ISI), hyperarousal (temporal high frequency electroencephalic amplitudes, THFEA), heart rate variability (HRV), baroreflex sensitivity (BRS), and mean arterial pressure (MAP) in a military cohort.

Methods: Eight males (7 active duty, median age = 31 years, range = 26-54) with at least one military deployment, enrolled in an open label, IRB-approved pilot study. Median baseline ISI was 15 (range =

10-28). Self-reported co-morbidities included mild TBI (5), and PTSD (5). THFEA was calculated from 1 minute epochs of temporal recordings (T3/T4, eyes closed) of high frequency amplitudes (23-36 Hertz) at baseline, the first 4, and last 4 HIRREM sessions. Serial values for sums of T3 and T4 amplitudes (microvolts, μ V) were calculated. Blood pressure and heart rate were recorded in 7 subjects with spectral analysis for HRV and BRS measures, and calculation of MAP.

Results: Participants received a median of 13.5 (range = 10-22) ninety minute HIRREM sessions over 9 days. Median ISI score was reduced by -9.5 (range = -3 to -13, $p < 0.001$). Sums of T3 and T4 amplitudes decreased from baseline to the final HIRREM session (10.75 to 5.77 μ V). HRV measured as standard deviation of the R-R interval (SDRR) increased by 16% ($p = 0.051$). Parasympathetic BRS by sequence analysis increased by 57% ($p = 0.095$) and MAP dropped (-8 mmHg, $p < 0.05$) without medication change.

Conclusion: HIRREM was associated with improved self-reported sleep as well as HRV, BRS, MAP, and reduced temporal high frequency amplitudes in this series of military participants.

Support (If Any): The Susanne Marcus Collins Foundation, Inc.

0552

TWO IS TWO TOO MANY: A THEMATIC ANALYSIS OF PATIENTS' PERSPECTIVE ON TREATMENT FOR COMORBID INSOMNIA AND OBSTRUCTIVE SLEEP APNEA

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Introduction: Comorbid insomnia and obstructive sleep apnea (OSA) commonly co-occur in patients presenting to sleep disorders clinics. The aim of this study was to examine qualitative data on the patients' perspective of their condition and their experience with treatment at a multidisciplinary sleep clinic.

Methods: Twenty-nine clinic patients, who met criteria for insomnia disorder and OSA (mean age = 54, females = 19), completed a post-treatment interview either in individual or group format. All patients received standard evaluation, and the treatment plan, determined by the clinician, included cognitive-behavior therapy for insomnia (CBT-I) and/or positive airway pressure (PAP) for OSA. Transcribed audio recordings were analyzed using thematic analysis. Two trained raters independently coded each interview and then collated these initial codes into overarching themes. These themes were then refined in an iterative process until consensus was reached between the two raters.

Results: Three main themes were identified: 1) patients consider OSA and insomnia separate disorders, 2) both OSA and insomnia require treatment, and 3) unique considerations influence treatment preference. Insomnia and OSA were considered distinct sleep disorders, where insomnia was classified as a sleep onset and OSA as a maintenance problem. Both disorders required treatment because PAP and CBT-I had no effect on onset insomnia and OSA respectively. Although most patients favored sequential treatment starting with PAP, treatment preference was influenced by unique considerations. Patients emphasized the need for concurrent insomnia treatment, because insomnia could interfere with PAP use and reduce its effectiveness; using PAP while awake does not treat OSA. Furthermore, adhering to stimulus control was challenging whilst wearing a PAP mask.

Conclusion: This is the first study to describe the patients' perspective on having these comorbid sleep disorders. The findings indicate that patients recognize the importance of treating both disorders and articulate important treatment considerations when combining CBT and PAP.

0553

THE FEASIBILITY OF IN-LAB DREAM COLLECTION IN INSOMNIA SUFFERERS: PRELIMINARY DATA

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Introduction: Dream studies are limited in insomnia sufferers (INS). In-lab dream collection is the most reliable procedure to study dreams. This project is aimed at circumscribing the feasibility of in-lab dream collection in INS, considering their reported sleep difficulties and heightened level of hyperarousal.

Methods: Eight INS [Mean age = 39.0 (4.4)] and five good sleepers [GS; 37.0 (4.5)] underwent 5 consecutive PSG nights. At-home ambulatory measures were used during Nights 2 and 4 while Nights 3 and 5 consisted of in-lab REM dream collection. Dream recall frequency (DRF) was calculated while sleep onset latency (SOL) after each awakening was measured and defined as the time elapsed from the beginning of dream collection to the first epoch of stage 2.

Results: Preliminary independent sample t-tests revealed only a marginally significant difference of groups for DRF ($p = 0.11$), DRF being greater in INS than in GS (94% vs. 81%). While longer SOL was observed in INS than GS (51 vs. 22 minutes), groups did not significantly differ ($p = 0.16$). Then, subjective and objective sleep variables were assessed using paired sample t-tests. For GS, at-home and in-lab nights were characterized by significantly higher subjective TST ($p \leq 0.04$) and lower WASO ($p \leq 0.03$) than objective TST and WASO. For INS, lower values were observed for subjective in-lab WASO ($p = 0.04$) and at-home TST ($p = 0.04$). In-lab TST ($p = 0.6$) and at-home WASO ($p = 0.2$) were similar.

Conclusion: Because of the small sample size, caution should be used while interpreting these results. Still, they suggest that in-lab dream collection can be successfully conducted with INS. Higher DRF in INS might reflect their heightened level of hyperarousal. Interestingly, dream collection also appears to contribute to the underestimation of WASO in INS. It is possible that externally induced awakenings attenuate the importance given to sleep difficulties, INS feeling less distressed of being awake since the awakening is attributed to dream collection.

Support (If Any): CIHR (CB#86571).

0554

PERCEIVED STRESS APPEARS TO BE A SECONDARY ISSUE IN THE BEHAVIORAL TREATMENT OF CHRONIC INSOMNIA: MODELING EFFECTS FROM A WEB-BASED TREATMENT PROGRAM

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Introduction: Insomnia is often attributed to stress, but its actual role in clinical improvement is understudied. Results from a web-based sleep program (WBSP), based on behavioral principles, allowed modeling the impact of perceive stress after other treatment effects were controlled for.

Methods: Consenting chronic insomnia participants with internet access were recruited by outreach efforts. Primary insomnia participants were randomized to WBSP or Wait-list control groups. Inclusions and exclusions are described in a companion abstract from our group. Excluded participants were eligible for a observational side-study on the WBSP. Pittsburgh Insomnia Rating Scale (PIRS), Insomnia Severity Index (ISI), and Perceived Stress Scale (PSS) scores were obtained at baseline and 6 weeks. Linear mixed effects models were stepwise developed using Chi-square testing, using ISI scores (pre- and post-intervention) as dependent

[P5.287] Use Of A Non-Invasive Neurotechnology, HIRREM, Is Associated With Improved Sleep And Mood In A Heterogeneous Cohort.

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OBJECTIVE:

To evaluate a non-invasive neurotechnology, High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM), for individuals with insomnia and depressive symptoms.

BACKGROUND:

Studies of brain electrical activity suggest disturbances of neural oscillatory patterns in various neuropsychiatric conditions, which may be more explanatory of underlying neurobiology than DSM-based diagnostic categories. For example excess high frequency amplitudes (hyperarousal) have been reported in insomnia, and right-sided frontal asymmetry in negative mood states. High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM) is a noninvasive feedback technology designed to support auto-calibration of neural oscillations by using auditory tones derived from software algorithms to reflect brain frequencies in near real time.

DESIGN/METHODS:

115 subjects (74 female, median age 50, range 13-83) were enrolled in an open label, IRB-approved feasibility study of HIRREM for individuals with diverse clinical conditions including insomnia, traumatic brain injury, post-traumatic stress disorder, hot flashes, and others. 55 subjects reported moderate to severe insomnia (Insomnia Severity Index, ISI, score ≥ 15), and 56 had clinically relevant depressive symptoms (score ≥ 16 on the Center for Epidemiologic Studies Depression Scale, CES-D). Subjects underwent serial sessions of HIRREM in accordance with standard protocols, which included an average of 14 sessions, 90 minutes each, over 2 to 4 weeks.

RESULTS:

For those with an initial ISI score ≥ 15 , mean ISI reduced from 20.34 (SD=4.07) to 11.00 (SD=6.33, $p < < 0.0001$) post-HIRREM. For those ≥ 16 on the CES-D at baseline, mean scores reduced from 29.36 (SD=9.85) to 14.59 (SD=11.04, $p < < 0.0001$) post-HIRREM. No serious adverse events occurred.

CONCLUSIONS:

Use of HIRREM was associated with clinically relevant, statistically significant reductions in symptoms of insomnia and depression in this heterogeneous cohort, without adverse side effects. Thematic disturbances of brain oscillation patterns may underlie diverse symptoms. Auto-calibration of neural oscillations towards client-unique, self-optimized states is a strategy for facilitating neuropsychiatric health that warrants further exploration.

Study Supported by: The Susanne Marcus Collins Foundation, Inc.

Category - Sleep: Therapeutics

Wednesday, April 30, 2014 3:00 PM

P5: Poster Session V: Sleep: Parasomnias and Measurement Technologies (3:00 PM-6:30 PM)

[P5.313] Use Of A Non-Invasive Neurotechnology, HIRREM, Is Associated With Improved Sleep, Mood, And Baroreflex Sensitivity In Athletes With Persisting Post-Concussion Symptoms

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OBJECTIVE:

To explore effects of a novel non-invasive neurotechnology, HIRREM, on insomnia, depressive symptoms and heart rate variability in athletes with persisting post concussion symptoms (PPCS).

BACKGROUND:

Concussed athletes are at risk for developing PPCS that may include insomnia, depression, and others, many associated with autonomic dysregulation. Brain oscillatory patterns are altered after concussion and may be contributory to symptom development. High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM) generates feedback as audible tones derived from software algorithm-driven analysis of real time changes in brain electrical activity from scalp recordings, measured at high-spectral resolutions, to facilitate auto-calibration of neural oscillations. We report on use of HIRREM by athletes who were unable to return to activity due to PPCS.

DESIGN/METHODS:

Six athletes, (3 male, 3 college, mean age 18, range 15-22) reported persisting symptoms (duration range 3 months to 3 years) following a concussion, preventing return to activity or athletic competition. They received a median of 18.5 HIRREM sessions (range 13-36, 90 minutes each) as participants in an open-label IRB-approved exploratory study of HIRRM for diverse health conditions. Pre- and post-HIRREM assessment included self-reported insomnia and depressive symptoms, as well as blood pressure and heart rate recording for heart rate variability and baroreflex sensitivity calculations.

RESULTS:

Subjects reported significant reductions in insomnia (median change in Insomnia Severity Index of -7, range -3 to -11, p=0.003) and depressive symptoms (median change in CES-D of -8.5 points, range -3 to -30, p=0.03). All returned to full activity. Heart rate variability (Standard deviation of R-R interval, SDRR) increased from 65 to 81 ms (p=0.18) and BRS measured by sequence method was improved from 25.9 to 42.4 ms/mm Hg (p=0.036).

CONCLUSIONS:

Use of HIRREM by athletes with persisting post-concussion symptoms was associated with symptom reduction, improved baroreflex sensitivity, and return to athletic activity. Controlled trials are warranted.

Study Supported by:

The Susanne Marcus Collins Foundation, Inc.

Category - Neuro Trauma, Critical Care, and Sports Neurology: Concussion

Wednesday, April 30, 2014 3:00 PM

P5: Poster Session V: Neuro Trauma, Critical Care, and Sports Neurology: Concussion (3:00 PM-6:30 PM)

[P7.320] A Noninvasive Neurotechnology, HIRREM, Is Associated With Symptom Reduction And Improved Cardiovascular Autonomic Measures In Adolescents With POTS

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OBJECTIVE: Assess effect of High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM) on self-reported autonomic symptoms and cardiovascular measures in POTS.

BACKGROUND: Postural orthostatic tachycardia syndrome (POTS) is characterized by heterogeneous symptoms.

Pharmacological therapy has limitations. HIRREM is a noninvasive neurotechnology for relaxation and auto-calibration of neural oscillations. Reductions in self-reported symptoms and improvements in heart rate variability (HRV) with HIRREM have been reported.

DESIGN/METHODS: Seven adolescents with POTS (age 15-18, 3 males) were enrolled in an IRB-approved open label feasibility study evaluating HIRREM for diverse neuropsychological disorders. Four subjects taking fludrocortisone (FLC) stopped it before or during HIRREM. Subjects rated autonomic symptoms (nausea, vomiting, dizziness, syncope, abdominal pain, constipation, anorexia, fatigue, missing school, flushing, shortness of breath, chest pain, tachycardia, and headaches) from 0 (none) to 4 (severe), before and after a median of 14 (range 10-16) HIRREM sessions (90 minutes each) over 13 (range 8-17) days. Blood pressure and heart rate was continuously recorded and spectral analysis performed for calculating HRV and baroreflex sensitivity (BRS).

RESULTS: A trend was observed for reduction in autonomic symptom scores, from median 18 (range 7-34) to 12 (range 3 to 25), p=0.07. Statistically significant improvements were observed in HRV (standard deviation of the R-R interval, SDRR, increased from 51.4 to 73.7, p=0.03) and BRS (HF alpha increased from 25.9 to 39.8, p=0.04). In exploratory analyses, trends were observed for reductions in temporal lobe high frequency electroencephalic asymmetry (23-36 Hertz). No adverse effects were reported. Subjects remained off FLC.

CONCLUSIONS: HIRREM was associated with reductions in clinical symptoms of POTS and significant increases in HRV and BRS. HIRREM may have a positive influence in POTS by supporting improved upstream central nervous system regulation of peripheral autonomic dysfunction. Controlled clinical trials of HIRREM are warranted.

Study Supported by: The Susanne Marcus Collins Foundation, Inc.

Category - Child Neurology and Developmental Neurology: Other

Thursday, May 1, 2014 3:00 PM

P7: Poster Session VII: Child Neurology and Developmental Neurology VI (3:00 PM-6:30 PM)

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Objectives and methods: The International Collaboration on Mild Traumatic Brain Injury Prognosis (ICoMP) performed a comprehensive search and critical review of the literature from 2001–2012 to update the 2002 best-evidence synthesis conducted by the WHO Collaborating Centre for Neurotrauma, Prevention, Management and Rehabilitation on the prognosis of mild traumatic brain injury (MTBI).

Results: Of 304 relevant studies, 109 were accepted as scientifically admissible. The methodological quality of the research literature on MTBI prognosis has not improved since the 2002 Task Force report. There are still many methodological concerns and knowledge gaps in the literature. This study reports and make recommendations on how to avoid methodological flaws found in prognostic studies of MTBI. Additionally, it discusses issues of MTBI definition and identify topic areas in need of further research to advance the understanding of prognosis after MTBI. Priority research areas include but are not limited to the use of confirmatory designs, studies of measurement validity, focus on the elderly, attention to litigation/compensation issues, the development of validated clinical prediction rules, the use of MTBI populations other than hospital admissions, continued research on the effects of repeated concussions, longer follow-up times with more measurement periods in longitudinal studies, an assessment of the differences between adults and children and an account for reverse causality and differential recall bias.

Conclusions: Well-conducted studies in these areas will aid in understanding of MTBI prognosis and assist clinicians in educating and treating their MTBI patients.

0804

Implementing telemedicine as a viable means of treatment for traumatic brain injury

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Objectives: Traumatic brain injury (TBI) is a leading cause of disability worldwide. Survivors of severe TBI frequently are hospitalized post-injury and experience long-term cognitive and physical impairments. Prognoses for patients who sustain a severe TBI worsen with increased time-to-treatment. Early contact between emergency medical services and the emergency room enables improved preparation. Readily accessible specialists such as neurosurgeons and intensivists can reduce the hospital length of stay and improve patient outcomes. Complications arise when those needing critical care do not have timely access to these and other necessary specialists. This problem is exacerbated at smaller care centres, rural areas and for military members where specialists either are not cost-

effective, the bed count is insufficient to warrant a full-time specialist or when significant travel time is necessary to receive care. Because patients travel further for neurological care than any other type of treatment and costs and length of stay are important factors, the need for improved TBI care in remote areas is in high demand. Telemedicine or the use of computer equipment and technology to provide healthcare, has received increased recognition in an array of health applications. Telemedicine programmes have been implemented in some hospitals as a way to improve access to the expertise of critical care professionals.

Methods: This study developed the Emergency Specialist Programme (ESP) to provide emergent specialty care consultations for STEMI, stroke, trauma and sepsis. In this programme, emergency physicians respond to requests for consults via the RP-7 Robot and the access centre, which serves as a single point of contact for consults, transports and bed control, then joins the consultation by utilizing multiPresence. This allows the access centre staff to see and hear the referring provider, emergency department physician and patient. Including the access centre staff in the telemedicine connection enables them to respond to requests to arrange transport or specialty consults immediately.

Results: This study applied the research focus in TBI in conjunction with experience with the ESP programme to provide a TBI-specific model that can be utilized to implement telemedicine.

Conclusions: In the TBI domain, telemedicine can counteract the challenge of treating TBI in rural areas, to greatly enhance and provide quality care. Programmes enable intensivists and critical care nurses to serve as a resource and support for healthcare providers in communities that would otherwise be without specialty expertise. Audio and video feed capabilities combined with access to x-rays, scans and lab results, provide a physician with the ability to make more informed decisions. Additionally, post-traumatic complications are common in TBI. Real-time monitoring could potentially detect and combat these complications. In the case of rural communities and military members, telemedicine has the potential to expedite TBI diagnosis and treatment from a distance.

0805

Use of HIRREM, a noninvasive neurotechnology, is associated with symptom reduction and increased heart rate variability among individuals with traumatic brain injury

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Objectives: To evaluate high-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM) as an adjunct to usual care for individuals with traumatic brain injury (TBI). TBI may be followed by heterogeneous symptoms including depressed mood, impaired sleep, post-traumatic stress and others, many associated with autonomic dysregulation. Studies of brain electrical activity in TBI report sub-optimal proportionation between high and low frequencies and PTSD, often seen with TBI, has been associated with right temporal lobe over-activation. HIRREM generates feedback as audible tones derived from software algorithm-driven analysis of real time changes in brain electrical activity from scalp recordings, measured at high-spectral resolutions, to facilitate auto-calibration of neural oscillations.

Methods: Twenty-one subjects (mean age = 34.7, range = 15–64, nine women) reporting symptoms relevant to prior TBI (related to sports for six, to military service for five) were enrolled in an IRB-approved, open label feasibility study of HIRREM for diverse clinical conditions. Subjects had a baseline HIRREM assessment followed by a median of 16 (range = 10–36) HIRREM sessions (90 minutes each) over a median of 13 days (range = 9–93). Temporal high frequency electroencephalic asymmetry scores (percentage basis) were calculated at baseline and for serial HIRREM sessions by measuring 1-minute epochs of high frequency (23–36 Hertz) amplitudes (microvolts) at bilateral temporal lobes (T3/T4), subtracting the value at T3 from that at T4 and dividing by the lesser of the two (yielding positive scores for right dominance). Blood pressure and heart rate were measured during recordings at baseline and after completion of the final HIRREM session, to assess cardiovascular autonomic regulation including heart rate variability (HRV).

Results: After completing HIRREM, subjects on average reported reduced symptoms of insomnia (pre- to post-HIRREM change in the Insomnia Severity Index of 13.7 to 7.1, $p < 0.0001$), depression (change in CES-D of 24.3 to 12.7, $p < 0.0001$) and symptoms of post-traumatic stress (change in PCL-C of 44.7 to 32.7, $p = 0.0001$). Measures of HRV improved after HIRREM (SDRR increased from 51.8 to 65.2 milliseconds, $p = 0.009$). In subjects ($n = 8$) who were initially right-temporal (T4) dominant (amplitudes $\geq 10\%$ rightward), temporal asymmetry changed from a median of 49.7% to -2.5% ($p = 0.06$). In those who were initially left-temporal (T3) dominant ($n = 9$), asymmetry scores changed from a median of -30.4% to 18.9% ($p = 0.0004$). For those who were initially $< 10\%$ asymmetrical in either direction ($n = 4$), asymmetry changed from a median of -4.0% to -14.9% ($p = 0.75$).

Conclusions: In this case series, use of HIRREM by individuals with prior TBI was associated with statistically significant reductions in clinical symptoms of insomnia, depression and post-traumatic stress and increased HRV. Trends were found for reduced temporal asymmetry among those who were $\geq 10\%$ asymmetrical at baseline. Controlled clinical trials of HIRREM for TBI are warranted.

0806

The value of neurocognitive and oculomotor testing after mild TBI in the emergency department

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Objective: Traditionally, neuropsychometric testing is performed weeks to months after head injury and mostly in patients who continue to have symptoms or difficulties. This study sought to determine whether these tests, when administered acutely, could assist in predicting short-term outcomes after acute traumatic brain injury (TBI).

Methods: This is an IRB approved retrospective review of all adult (18 years and higher) patients who came to the emergency medicine department of a healthcare facility with a Level-1 trauma centre with the primary diagnosis of TBI. Patients with a head injury from any mechanism that occurred within 24 hours of presentation to the Emergency department (ED), were enrolled prospectively after written informed consent and took two separate neurocognitive tests, the Galveston Orientation Amnesia Test (GOAT) and the Rivermead Post-Concussion Survey Questionnaire (RPCSQ). The GOAT is a 20-question instrument that is scored from 0–100 and the RPCSQ is a 30-question instrument with a score range from 0–65. • Independent variables included raw scores on each of these tests; dependent variables included hospital admission, development of post-concussive syndrome (PCS) and 30-day re-admission rate. Statistical analyses were performed in JMP 10.0.

Results: • The median GOAT score was 99 (IQR = 98–100, range = 84–00). Having a lower GOAT score was significantly associated with being

hospitalized ($p = 0.0139$) and developing post-concussive syndrome (PCS) at the 30–45 day follow-up ($p = 0.0183$, $R^2 = 12.2\%$). • The median RPCSQ score was 12 (IQR = 5–23, range = 0–61). A higher RPCSQ score was significantly associated with hospital admission ($p = 0.0113$), re-admission to hospital within 30 days ($p = 0.0019$) and evidence of PCS at days 3–15 post-injury ($p = 0.0001$, $R^2 = 22.6\%$).

Conclusions: While not commonplace, neuropsychometric testing in the ED in the setting of acute head injury is both feasible and appears to have value in predicting hospital admission and who will suffer from PCS. These data are especially important in terms of helping patients understand what to expect, which in turn aids in their recovery.

0807

Goal-oriented executive function training in veterans with chronic TBI: Short and longer term outcomes

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Objective: Some of the most common and disabling consequences of brain injury are deficits in executive control functions, such as selection, planning, maintenance and execution of goal-relevant activities. Goal-Oriented Attentional Self-Regulation (GOALS) training was designed to target these deficits with attention regulation training applied to participant-defined goals. In a pilot study individuals with chronic acquired brain injury significantly improved post-GOALS, but not brief control training, on measures of attention/executive function, functional task performance and goal-directed control over neural processing on fMRI. The objective of this ongoing study is to assess immediate and long-term effects of GOALS training in Veterans with chronic TBI.

Participants and methods: Twenty-four Veterans with chronic (6+ months) TBI and mild-moderate executive dysfunction were randomized to start with either 5 week of GOALS or an active control Brain-Health (EDU) training matched in time and intensity. Participants that started with EDU switched to GOALS during the second 5 weeks. Assessments at baseline, weeks 5, 10 and 6 months included neuropsychological, complex functional task performance and self-report measures of emotional regulation.

Results: At week 5 post-GOALS, but not EDU training, participants significantly improved from baseline on: (1) overall neuropsychological attention/executive function domain score and the following sub-domain scores: working memory, mental flexibility and generative ability; (2) overall complex functional task performance score and the following sub-domains: planning, self-monitoring, task execution, switching and maintenance of attention; and (3) emotional regulation self-report measures: Profile of Mood States—total mood disturbance, depression, tension, confusion and anger; PCLM-re-experience and avoidance; and BDI-II depression. At follow-up evaluation 6+ months post-GOALS training, participants maintained significant improvements relative to their baseline performance in most of the above domains and the majority reported incorporating trained strategies into their daily life.

Conclusions: GOALS training may be promising in Veterans with chronic TBI. Improving cognitive control functioning may also improve functioning in other domains such as emotional regulation and functional performance. The challenges and importance of: (a) using participant-defined goals applied to relevant training; (b) using

Background: VDD and ID are common, and have been associated with cardiovascular, autoimmune, and osteopenic disease. Recently a retrospective study limited to a pediatric population suggested associations between VDD, ID, and POTS. Because the pathophysiologic nature of POTS remains elusive, such associations—if confirmed in adults—may provide new pathophysiologic insights with treatment implications.

Design/methods: The electronic medical records of 84 cases of well-characterized POTS aged 18 and older were reviewed, and vitamin D and ferritin levels recorded when available. The characteristics of those with VDD and/or ID were compared to those with normal levels, and the prevalence of VDD and ID was compared to established population data.

Results: Subjects were aged 19–56 years, median age 28, including 73 females (87 %) and 11 males (13 %). Vitamin D levels were available in 60 patients (52 females, 8 males), and ferritin levels in 52 patient (48 females, 4 males). 14/60 (23 %) had VDD, a proportion lower than the reported prevalence of VDD (41–70 %). 6/52 (12 %) had iron deficiency, and an additional 15/52 (29 %) had low ferritin, rates greater than those reported in the adult population at large. There was no association found between VDD or ID and age, heart rate increment on head-up tilt, fatigue, or myofascial pain. Those with VDD were found to have lower exercise capacity.

Conclusions: Overall, the results suggest an increased rate of ID in POTS patients. Though several cardinal clinical features of POTS were found to be independent from ID in our sample, ID may add to the symptom burden in POTS and should be screened for. VDD was not seen at a greater rate in POTS compared to the general population.

Poster 9

Differential effects of dietary salt on blood volume regulation in postural tachycardia syndrome and healthy subjects

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Objective: Physicians often prescribe a high-sodium diet to treat postural tachycardia syndrome (POTS), with a goal of fluid retention and blood volume (BV) expansion. The effects of dietary sodium on BV in POTS are unknown. We sought to determine if BV responds differently in patients with POTS than healthy controls.

Methods: POTS patients and controls were assigned, ≥ 1 month apart, to low (LS; 10 mEq Na⁺/day) or high sodium (HS; 300 mEq Na⁺/day) diet for 6 days each (to achieve steady state) in a randomized crossover fashion. BV, measured using radiolabeled albumin, supine and standing heart rate (HR) and blood pressure (BP) were assessed on the last day of study diet. Preliminary data are presented here as mean \pm SD.

Results: Six female POTS patients (35 ± 8 years, BMI 22 ± 3 kg/m²) and 4 healthy female controls (30 ± 5 years, BMI 26 ± 2 kg/m²) were studied. Total BV (TBV) increased in POTS with a HS diet (LS 3703 ± 265 mL vs. HS 4148 ± 205 mL; $p = 0.007$), and this was driven by an increase in plasma volume (PV; LS 2435 ± 185 mL vs. HS 2835 ± 182 mL; $p = 0.007$). In contrast, HS in controls did not increase either TBV (LS 3773 ± 424 mL vs. HS 4013 ± 894 mL; $p = 0.473$) or PV (LS 2511 ± 277 mL vs. 2756 ± 639 mL; $p = 0.373$). There was a trend toward decreased orthostatic tachycardia with HS among POTS patients (LS 55 ± 11 bpm vs. HS 46 ± 7 bpm; $p = 0.066$), but not among controls (LS 33 ± 15 bpm vs. HS 29 ± 13 bpm; $p = 0.430$).

Conclusion: Compared to LS, HS diet increased blood volume in POTS patients but had no effect in controls, with a trend toward reduction in orthostatic tachycardia in POTS. These data suggest either

“salt-sensitivity” in POTS, or an inability to conserve sodium on low salt diets. These data support the use of HS diets in POTS patients. Supported by NIH grants R01 HL102387 and R01 HL071784.

Poster 10

Decreased upright heart rate with increased inspiratory resistance in postural tachycardia syndrome

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Postural tachycardia syndrome (POTS) is characterized by excessive heart rate (HR) increase >30 bpm on standing. Many studies have found that POTS patients have a low stroke volume (SV) that is accentuated with standing, and that this might be driving the HR. One method to acutely increase cardiac venous return and SV might be to increase the negative intrathoracic pressure. Breathing through an impedance threshold device (ITD) can increase the negative intrathoracic pressure required for inspiration. We prospectively tested the hypothesis that breathing through an ITD would increase SV and decrease upright HR in POTS patients. We studied 26 POTS patients ($F = 25$, 30 ± 2 years; BMI 22.8 ± 0.7 kg/m²) on a single-blind crossover of a 10 min head-up tilt test while breathing through an ITD (ResQGARD™, Advanced Circulatory Systems Inc) or a sham (S) resistance device in a randomized order. In the last 2 min of tilt, cardiac output (CO) was measured by inert gas rebreathing, and HR and blood pressure (BP) were measured (arm cuff). SV and total peripheral resistance (TPR) were calculated. Wilcoxon signed rank tests were used for paired analyses between ITD & S. The upright HR was significantly lower with ITD than S (103 ± 4 vs. 111 ± 4 bpm; $P = 0.001$), while the SV was increased with ITD (34 ± 2 vs. 30 ± 2 mL; $P = 0.006$). As a result, there was no change in CO with ITD (3.4 ± 0.2 vs. 3.3 ± 0.2 L/min; $P = 0.318$). TPR was not different between ITD compared with S (2186 ± 157 vs. 2133 ± 113 dyn s cm⁻⁵; $P = 0.732$). Systolic BP was not different with ITD (108 ± 3 vs. 105 ± 2 mmHg; $P = 0.182$). Inspiratory resistance with ITD decreases upright HR in POTS patients, and this is accomplished through an increase in SV without significant change in CO or systolic BP. Inspiratory resistance is a promising acute therapeutic option for POTS, although long-term efficacy and safety requires further study.

Poster 11

Case series using high-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM) for POTS

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Background: Postural tachycardia syndrome (POTS) is known for heterogeneous symptoms, and lacks effective non-drug treatments. High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM) is a noninvasive, sound-based technology for relaxation and

auto-calibration of neural oscillations. Due to proximity of the temporal lobes to the right (sympathetic) and left (parasympathetic) insular cortex, and association of high frequency EEG amplitudes and cortical arousal, asymmetry of temporal lobe high frequency (23–36 Hz) electroencephalic activity (TLHFEA) may provide an index of autonomic balance. HIRREM derived baseline TLHFEA also correlates with measures of heart rate variability.

Aim: Assess effect of HIRREM on autonomic symptoms, and TLHFEA asymmetry, in subjects with POTS.

Methods: Subjects with POTS (4 subjects, 2 males, age 15–18) were enrolled in an IRB-approved protocol. Subjects rated autonomic symptoms (nausea, vomiting, dizziness, syncope, abdominal pain, constipation, anorexia, fatigue, missing school, flushing, shortness of breath, chest pain, tachycardia, and headaches) from 0 (none) to 4 (severe) points before and after a median of 13.5 (SD 2.5) HIRREM sessions over 15.5 (SD 1.7) days. Fludrocortisone (FLC) was stopped before or during HIRREM (3 of 4 subjects). TLHFEA (T3/T4, eyes closed) was analyzed for the baseline and penultimate HIRREM sessions (1 min each). TLHFAE asymmetry scores were calculated by subtracting the lesser from the greater of the amplitudes (microvolts) at T4 and T3, and dividing by the lesser.

Results: HIRREM was well tolerated. Median values for the total autonomic symptom score decreased from 22.5 (SD 10.6) to 10.5 (SD 8.3). TLHFEA asymmetry decreased from 69.1 to 19.4 %.

Conclusion: HIRREM was associated with improved clinical symptoms of POTS and a shift of TLHFEA from relative asymmetry towards symmetry. These findings suggest the potential for POTS treatment by intervening on upstream central nervous system sources of peripheral autonomic dysfunction. Controlled clinical trials of HIRREM are warranted.

Poster 12

The pheochromocytoma that wasn't

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Pheochromocytomas are extremely rare and potentially lethal chromaffin cell tumors that secrete catecholamines into the bloodstream, resulting in episodic symptoms of catecholamine excess including severe hypertension, sweating, and headache. We report the case of a 39-year-old man without a history of hypertension who presented with paroxysms of elevated blood pressure, diaphoresis, tremulousness, palpitations, headache and chest pain, which had led to syncope on several occasions. Blood pressure and heart rate were 144/106 and 92 supine, 152/114 and 100 standing. 24-h urine levels of total metanephrine were 2118 µg, normetanephrine 1944 µg, metanephrine 174 µg, norepinephrine 240 µg. Thyroid function testing and chromogranin A were normal. QSART responses, respiratory sinus arrhythmia, and hemodynamic responses to the Valsalva maneuver were normal. Head-up tilt demonstrated an increase in heart rate from 65 to 98 with little change in blood pressure. Based on clinical suspicion of pheochromocytoma, CT of the abdomen was undertaken and disclosed a 1.4 cm right adrenal mass with stippled calcifications, which had increased in size as compared to a CT from 2 years earlier. The adrenal mass was surgically resected, after which his hypertension persisted. Histopathological examination was consistent with a benign adenoma with prior hemorrhage but not pheochromocytoma. Subsequent whole body MIBG scan revealed no evidence of extra-adrenal pheochromocytoma. In conclusion, the final diagnosis was pseudpheochromocytoma in this patient with a hyperadrenergic state and an incidental adrenal adenoma. Biochemical testing

and imaging of the adrenal glands is usually helpful, but not always definitive, in distinguishing pheochromocytoma from pseudpheochromocytoma, the symptoms of which can be virtually identical. The syndrome of pseudpheochromocytoma falls within the clinical spectrum of hyperadrenergic states.

Poster 13

A failed POTS instrument: what is the message?

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Background: The diagnosis of postural tachycardia syndrome (POTS) is currently based on the findings in a tilt table test (TTT), along with an appropriate clinical presentation. Clearly, a question-set that could approximate this diagnosis with any accuracy would be a welcome addition to both the research and clinical armamentarium.

Methods: Over the last 10 years, this is the third attempt at developing a question set that would separate patients with POTS from those without. The ODYSA was carefully developed with 6 conditions (lightheaded, dizzy, vision change, faint, thinking off, nauseated) repeated across 9 settings (e.g. standing up, standing for 20', lying for 20', randomly, etc.), each using both a frequency and a duration scale. We determined the psychometric properties of this instrument, including its sensitivity and specificity in a POTS (n = 59) and non-POTS (n = 18) population (blindly determined from TTT) both referred for possible autonomic dysfunction.

Results: Although the instrument distinguished the two populations as groups through the composite score ($p < 0.02$ by student's t-test), no combination of the 54 questions (such as subtracting lying scores from standing scores, etc.) could provide good sensitivity and specificity. Logistic regression found that symptoms recorded in the settings of walking, standing for 20 min and while observing a moving object provided the best discrimination with sensitivity as high as 0.93, but specificity remained low at 0.43. Visual inspection revealed that all of these symptoms were voiced by both groups.

Conclusion: These findings call into question the clinical construct of POTS. The seeming impossibility of separating POTS from non-POTS based on symptom presentation suggests that a definition based on tilt table findings may not be capturing the essence of the disorder. Nonetheless, at this writing, TTT still provides the gold standard of diagnosis.

ORTHOSTATIC HYPOTENSION & SYNCOPES

Poster 14

Water ingestion increases plasma somatostatin in the course of the osmopressor response

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Studies in patients with an impaired efferent baroreflex led to the discovery that ingestion of water induces a robust increase in blood

two EEG recordings: one using conventional EEG electrodes and another using epidermal electronic electrodes. The two recordings were de-identified and interpreted by a blinded neurophysiologist.

Results: EEG interpretation in all age groups was the same for recordings obtained from either epidermal electronics or conventional EEG electrodes. Epidermal electronic EEG recordings demonstrated age-specific EEG features, such as the posterior dominant rhythm. For the majority of the recordings, the blinded neurophysiologist could not identify which had been acquired using epidermal electronics.

Conclusions EEG quality acquired by epidermal electronics is indistinguishable to a neurophysiologist from that of conventional electrodes. Epidermal electronics provide an attractive approach to unobtrusive EEG acquisition.

Study supported by: The Gerber Foundation

T1502. Neural-Oscillatory Intervention for Auto-Calibration Improves EEG Asymmetry and HRV

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Reduced vagal tone, inferred from lower heart rate variability (HRV), is associated with neurological and psychophysiological conditions including TBI, insomnia, PTSD, anxiety, and hot flashes. Cross-sectional data show negative correlation between high frequency temporal lobe EEG asymmetry (HFTLA: rightward dominance) and HRV. We tested the effects of high-resolution, relational, resonance-based electroencephalic mirroring (HIRREM), a novel, noninvasive, EEG-based technology for auto-calibration of neural oscillations, on HFTLA and HRV in 31 subjects enrolled in an open-label study for such conditions. Baseline asymmetry scores were calculated from log-transformed high frequency amplitudes (23–36 hertz) at the bilateral temporal lobes (T3/T4: one minute, eyes closed). Subjects, mean age 49.6 (± 16.7 SD), received 16 (± 6.7 SD) ninety-minute HIRREM sessions to explore efficacy and effect sizes. HRV was obtained pre- and post-intervention. Greater temporal lobe asymmetry at baseline strongly predicted reduced asymmetry during the penultimate minute of the penultimate HIRREM session ($r = -0.579$, $p < 0.001$). As a group, the median value for standard deviation of the R-R intervals (SDRR) increased post-intervention (median change = 4ms, $p = 0.037$). Improved HFTLA and HRV suggest a potential role of HIRREM for disorders associated with hemispheric EEG asymmetry and autonomic dysregulation.

Study supported by: The Susanne Marcus Collins Foundation, Inc.; Sung W. Lee, MD, MS, receives salary support from Brain State Technologies, LLC.

T1503. High-Resolution, Relational, Resonance-Based Electroencephalic Mirroring (HIRREM) Reduces Symptoms and EEG Asymmetry in an Individual with PTSD

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Studies link PTSD to right hemispheric over-activation. The right hemisphere manages sympathetic activity. HIRREM is a

novel, noninvasive technology for neural-oscillatory auto-calibration, designed to facilitate greater hemispheric symmetry and more optimized spectral power ratios through high-resolution (0.001 hertz) EEG analysis and auditory tonal resonance. We report the use of HIRREM in a 55 year old woman with PTSD following a transportation accident, without physical injury, enrolled in an open-label pilot trial. Baseline scores on the civilian PTSD Symptom Checklist (PCL-C), Insomnia Severity Index (ISI), and CES-D (depression scale) were 73, 22, and 47, respectively, each exceeding clinical diagnostic thresholds. Baseline temporal lobe (T3/T4: one minute, eyes closed) high frequency (23–36 hertz) EEG asymmetry (TLHFA) was 128.2% (rightward dominance). After sixteen 90-minute HIRREM sessions, over three weeks, scores decreased to 31, 10, and 9, reflecting clinically relevant improvements, which dropped below clinical thresholds. In the penultimate minute of the penultimate HIRREM session, TLHFA was reduced to 18.1%. This supports a model of hemispheric asymmetry in PTSD. Decreased asymmetry may relate to reduced PTSD symptoms. Controlled clinical trials of HIRREM for PTSD are needed.

Study supported by: The Susanne Marcus Collins Foundation, Inc.; Sung W Lee, MD, MS, receives salary support from Brain State Technologies, LLC.

T1504. Ongoing Prospective Multicenter Clinical Studies of Non-Invasive Absolute Value Pressure Measurements

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Background: An innovative non-invasive absolute intracranial pressure (aICP) measurement method, based on two-depth transcranial Doppler technology has been proposed in previous works.

Material and Methods: The aim is to validate the accuracy, precision, sensitivity and specificity of proposed non-invasive aICP measurement method. Ongoing prospective multicenter clinical studies of simultaneous non-invasive aICP and “gold standard” invasive ICP measurements have been conducted on neurological and intensive care unit (ICU) patients. Data were collected from 110 patients (171 independent paired data points). Bland&Altman and ROC analyses have been performed.

Results: Accuracy of non-invasive aICP meter (expressed by the mean systematic error Δ) is $\Delta = 0.03$ mmHg, CL = 0.97. Precision of aICP meter (expressed by SD of random error) is SD = 2.65 mmHg (CL = 0.97). ROC analysis showed an area under ROC curve AUC = 0.94 with sensitivity 73.7 % (CL = 0.95) and specificity 94.7 % (CL = 0.95).

Conclusions: Negligible systematic error and low enough SD of random errors were observed in a wide range of aICP values from 5 mmHg to 30 mmHg. Validated method shows clinically acceptable accuracy, precision, sensitivity and specificity.

Study supported by: Clinical studies and technology development were funded by European Commission EC

pause, and there were no significant differences of EQ-5D index ($p=0.3$) and EQ-VAS ($p=0.827$).

Conclusion: This study concludes that there is no significant association between HRT and QoL in postmenopausal women.

P-106.

Pilot study of menopause-related symptom reduction through a noninvasive EEG-based technology for auto-calibration of neural oscillations (HIRREM)

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Objective: Eighty-eight percent of peri- and postmenopausal women in the United States experience daytime hot flashes or night sweats, which often affect mood and sleep, and can decrease quality of life. Loss of ovarian steroid effects on neurotransmitters and neural circuits, changes in hypothalamic thermoregulation, and autonomic dysregulation have all been implicated as contributing to these symptoms. Since autonomic function is managed by the central nervous system, especially the left and right insular cortex, autonomic dysregulation as a contributor towards menopausal symptoms is consistent with a model that includes a common upstream neural source for diverse menopausal symptoms. High-resolution spectral electroencephalography (EEG) offers a mechanism for data-gathering and noninvasive intervention relative to the central nervous system. Increased electrical amplitudes in the high frequency (beta range) of the EEG are reported in many studies of insomnia. Increased high frequency EEG power during sleep appears to differentiate late peri- and postmenopausal women, from pre- and early perimenopausal women. Hot flash frequency appears to explain much of the relationship between menopausal status and increased high frequency EEG power. High-resolution, relational, resonance-based electroencephalographic mirroring (HIRREM) is a noninvasive technology designed to support the brain to auto-calibrate its neural oscillatory dynamics by using musical tones to reflect brain frequencies in near real time. The primary objective of this pilot study is to evaluate the effect of HIRREM on hot flash symptoms, and high frequency temporal EEG power.

The secondary objective is to evaluate the effect of HIRREM on symptoms of insomnia and depression.

Design: Seven women (median age 54, range=46 to 69) were enrolled in an ongoing, open-label, single site, IRB-approved, feasibility study of HIRREM for individuals with diverse psychophysiological conditions. All reported hot flash symptoms, and completed a daily hot flash diary. EEG frequencies and amplitudes were analyzed from one minute epochs of data collected at baseline, and during the penultimate minute of the final HIRREM session. EEG power analysis focused on high frequency (23-36 hertz) EEG power at the temporal regions (sum of power at T3 and T4) due to the proximity to underlying cortical regions implicated in autonomic regulation. The primary outcomes for this analysis include the median of hot flash scores (total hot flashes multiplied by severity score, calculated daily), and serial values for high frequency EEG power at T3 and T4. Secondary outcomes include self-report insomnia (Insomnia Severity Index, ISI) and depression (Center for Epidemiologic Studies Depression, CES-D) questionnaires at baseline, and following the HIRREM intervention.

Results: Subjects had a median of 14 (range=10 to 23) HIRREM sessions (90 minutes each) over a median of 11 (range=5 to 32) days. At baseline, the median hot flash score was 9 (range=3 to 42), with 6/7 women exhibiting decreased hot flash scores post-intervention (decreases ranging from 61% to 100% of baseline). Median total high frequency power was 11.04 microvolts at baseline and decreased by a median of -2.89 microvolts (range=-11.05 to 0.42, $p=0.031$) at the final HIRREM session. At baseline, participants had a median ISI score of 18 (range=4 to 27), and a median CES-D score of 12 (range=3 to 36). For both symptom inventories, scores decreased post-HIRREM, with a median decrease of -13 (range=-20 to -1, $p=0.022$) for the ISI, and a median decrease of -7 (range=-32 to -1, $p=0.016$) for the CES-D.

Conclusion: These data suggest that menopausal symptoms, including hot flashes as well as associated insomnia and depression, may have a common upstream neural source, and that auto-calibration of neural oscillations through HIRREM may positively impact this group of symptoms. Controlled clinical trials of HIRREM as an intervention for menopausal symptoms are indicated.

P-107.

Trajectory Patterns of Vasomotor Symptoms over the Menopausal Transition in the Study of Women's Health Across the Nation (SWAN)

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Objective: Menopause-related vasomotor symptoms (VMS) are highly prevalent.

Although several studies have shown the time course of VMS over the menopausal transition (MT), these studies are based on group averages and do not consider individual

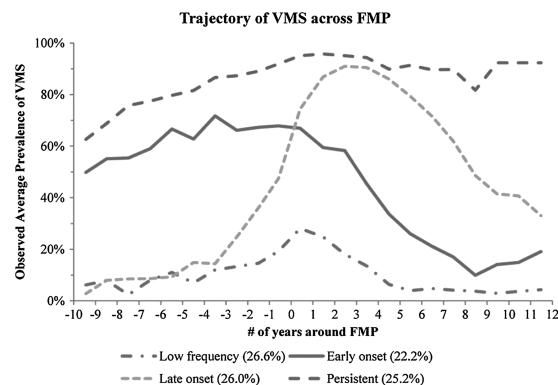
variation or patterns of VMS. We aimed to identify the temporal patterns of VMS over the MT.

Design: We studied annual self-reports of VMS (experiencing hot flashes, night sweats or cold sweats in the past 2 weeks) in SWAN, a multiethnic, multicenter longitudinal observational study. Group-based trajectory modeling was used to identify different temporal patterns of VMS prevalence across the final menstrual period (FMP) using a polynomial relationship between presence of VMS and time before and after FMP. Time stable and time-varying factors were included in the model. A total of 1591 women who experienced natural menopause with up to 13 annual visits were analyzed.

Results: Four distinct VMS trajectories were found: early onset and decline after the FMP (early onset, 22.2%), onset near the FMP then decline (late onset, 26.0%), early onset and persistent (persistent, 25.2%), and consistently low frequency (low frequency, 26.6%).

Compared to women in the early onset group (the reference group), women in the late onset group were more likely to be normal weight and to have a moderate rise in FSH over the MT; while women in the persistent group were more likely to be African American and normal weight, and to have lower educational attainment; and women in the low frequency group were less likely to be obese and to have a moderate FSH rise over the MT. Baseline menopausal stage, overall health, depressive symptoms, symptom sensitivity, alcohol use, perceived stress and change in perceived stress over time were also significant factors associated with membership in a VMS trajectory but not estradiol trajectory over the MT, smoking, anxiety, physical activity, financial hardship or clinical site.

Conclusion: These findings suggest that the pattern of VMS around the FMP varies among women. Distinct VMS trajectories with specific risk factors can be identified to aid in treatment decision making. Future studies can now focus on trajectories of circulating hormones that may provide additional physiological insights.



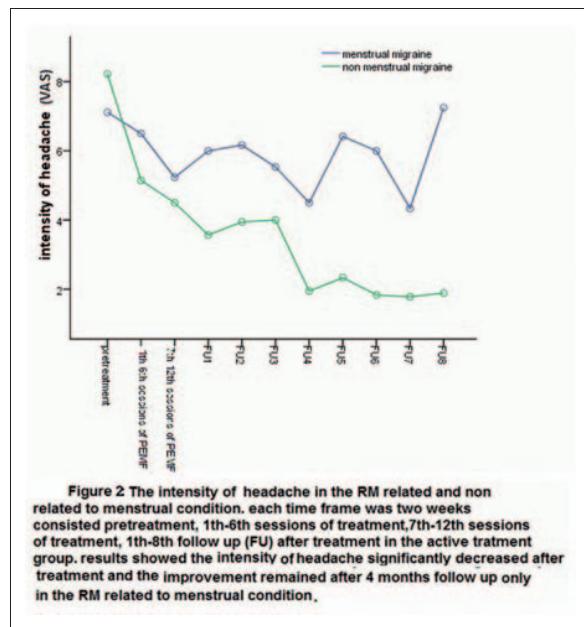
P-108.

In-home S-equol Supplement Sample Survey in Symptomatic Climacteric Women in The US and Japan

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Objective: Equol, which is an active metabolite of soy isoflavone "daidzein", have similar structures to estrogen and exhibit certain aspects of estrogenic activity via the binding to estrogen receptors. Equol can be produced by intestinal bacteria in approximately 50% of Japanese and 20–30% of the US population. Using a lactic acid bacterium, Lactococcus 20-92, that metabolizes daidzein to S-equol, we successfully produced a fermented soy ingredient containing S-equol. The clinical studies have suggested that the daily 10mg S-equol supplement alleviates hot flashes and muscle stiffness of neck and shoulder in both Japanese and US women. Although vasomotor symptoms and/or muscle stiffness are primary symptoms in Japan and the US, menopausal women are various and multiple symptomatic in general and not a few women's situations, like using hormone therapy (HT) or surviving gynecological cancers, were excluded from the clinical studies previously conducted. Thus, in these surveys, the wider range of symptomatic women was enrolled, and then they reported the self-rating menopausal symptoms to indicate their severity at each time point of the surveys.

Design: In the survey in Japan, 1035 women, who were outpatients of 33 clinics or members of a non-profit organization for women's health, were participated. Participants were recommended to take 10mg S-equol supplement daily for 12 wks, then reported the severity of menopausal symptoms using the Climacteric Symptom Evaluation Checklist, which is a questionnaire with 4-point



P128

Rapid Rollout of a Pediatric Migraine Prevention Study Conducted in Academic Research Centers

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Objectives: This study provides a pathway for investigators and institutions who are seeking a successful route for rapid startup of a multicenter pediatric migraine research study. We detail the infrastructure, strategic decisions and processes employed in the startup of an investigator initiated pediatric migraine prevention study funded by NINDS, based at an academic research institution.

Background: Creation of the study infrastructure included recruitment of a committed trial team at the central coordinating center(CCC), development of a collaborative relationship with a co-investigator statistician at an experienced data coordinating center(DCC), recruitment of site investigators committed to migraine research with established research sites and adequate potential subjects, partnering with the funding group to meet the agency's criteria, and recruitment of experienced consultants to provide guidance during planning.

Methods: The principal investigators created ongoing collaboration among the CCC, DCC, the research site investigators and internal and external consultants. This included: weekly teleconferences, clear timelines /accountability for deliverables, project management, IND regulatory, budget management, legal contracting, recruitment/ retention/ marketing, site management, data base development, and a novel statistical plan. Site investigators received frequent updates regarding study development. They contributed opinions regarding study design and became stakeholders. Detailed pre-work resulted in a clinical package that included a complex protocol based upon a novel statistical design allowing for three trials in one. Biweekly contact with the research sites maintained momentum at the sites.

Results: The timeline from date of clinical package delivery to first patient in was 13 weeks. The timeline from delivery to site activation of the initial group of 5 sites was 13-20 weeks, compared to the reported 36 weeks for academic centers. The second group of 10 sites achieved activation at 21 weeks. The remaining 13 sites were activated by 31 weeks, 5 weeks ahead of the industry average. To date, 84 % of site have been activated and open to enrollment, with 50 % of the sites open to enrollment at 24 weeks. The overall average time to site activation was 26 weeks.

Conclusions: A diverse research team in frequent communication with site investigators and complex pre-work with clinical package development enabled the rapid roll out of a multicenter pediatric migraine prevention study. The timeline to site activation for this pediatric migraine prevention study is ahead of industry standards.

P129

Randomized, Placebo-Controlled Pilot Trial of a Novel, Noninvasive EEG-Based Intervention, HIRREM, for Alleviation of Episodic Migraine

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Objectives: To pilot test high-resolution, relational, resonance-based electroencephalic mirroring (HIRREM™) for reduction of headache (HA) frequency and severity in episodic migraine (MI) and to estimate effect sizes for use in a larger trial.

Background: Studies have identified altered proportionation of power across broad-band bins of the EEG

frequency spectrum in MI. HIRREM is a novel, noninvasive technology designed to facilitate relaxation and auto-calibration of neural oscillations. HIRREM involves collection of EEG data from 2-channel recordings, analysis of the data at high spectral resolutions (0.001 hertz), and delivery of auditory tones for resonance in near real time with dynamically varying dominant EEG frequencies.

Methods: Sixty-three subjects were screened, 33 enrolled, and 30 (16 HIRREM, 14 placebo; mean age 51 ± 11, 26 women) completed an IRB-approved, randomized, single-blind, placebo-controlled, pilot trial. Individuals assigned to active HIRREM underwent a series of 90-minute sessions (mean 10.0, range 8-12) over a mean of 2.7 weeks (range 1-5), each of which consisted of listening to near real time auditory feedback derived from their own dynamically varying EEG activity. Individuals assigned to placebo had a comparable number of visits but listened to randomly generated musical tones. Subjects maintained a daily HA diary prior to undergoing intervention (2 weeks), during intervention, and for 2 months afterward. Primary outcome was defined as a joint distribution of HA frequency and intensity during the post-intervention follow up period. Analysis used a mixed effects, mixed distributions model to predict probability of an attack, and, when present, intensity of the attack. Using random effects, the model considers the hierarchical data structure of multiple diary days nested within a person.

Results: Three subjects had malfunctions in electronic daily diary tools and were excluded from analysis. Before the intervention, the HIRREM group tended to have greater likelihood of HA compared to placebo, OR 1.56 (95% CI: 0.97 to 2.53, $p = 0.064$). However, during the post-intervention period, the HIRREM group had a reduction in the likelihood of experiencing headache compared to controls, OR 0.74 (95% CI: 0.55 to 1.03, $p = 0.077$). This clinically meaningful effect size did not reach statistical significance in this pilot sample. No adverse events occurred. A comparable number of subjects in each group (50%) guessed that they received active HIRREM.

Conclusions: In this pilot trial, a promising effect size for reduction in headache frequency was observed for the HIRREM intervention beyond that observed for a placebo condition. The effect size associated with HIRREM as well as its safety and lack of side effects suggest that larger controlled trials are warranted.

P130

Atopic Disorders Are More Common in Childhood Migraine Than TTH

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Objectives: In order to determine and investigate the correlates of atopic disorders in a specific dataset, we performed this retrospective cross-sectional clinical based study.

Background: There are supportive clinical and pathophysiological data about the relationship between migraine and atopic disorders far from a coincidence.

Methods: Data set was composed from three tertiary center web based data (www.childhoodheadache.org). Headache diagnosis and differential diagnosis had been made according to ICHD-II and DSV-IV. Migraine (MwA, MwoA and chronic migraine) and TTH (episodic TTH and chronic TTH) patients included and all other causes of headache disorders also comorbid headache disorders like migraine plus TTH or “possible” causes of headache had been excluded.

Results: Out of 765 patients, identical age and gender distributed 293 migraine and 178 TTH, totally 471 patients included the study. After descriptive statistics accordingly, 49 migraine (16.7%) and 3 TTH (1.7%) reported specific atopic disorders ($p=0.000$). Among migraine sufferers MwA (21.6 %) were more frequent association than MwoA and CTTH ($p=0.000$). Most common types of atopic disorders were seasonal rhinitis, conjunctivitis and asthma. There were also a close relationship between atopic disorders and generalized anxiety disorders of the patients and positive atopic disorders or migraine history of the families, especially mothers.

Conclusions: Atopic disorders are common pathophysiological mechanisms with migraine. Although ICHD-II did not require, atopic disorders have to be questioned in all patients and relatives, not only accurate diagnosis but also planning to prophylactic medications such as beta blockers.

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Case Series of PTSD Symptom Reduction through a new, non-invasive, EEG-based Technology for Facilitating Auto-calibration of Neural Oscillations (HIRREM)

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Background

Normally, cortical oscillatory frequencies are distributed rather evenly throughout homologous cortical regions (balance), and exhibit a predictable pattern among component frequency bands in any given cortical region (harmony). Patients with post-traumatic stress disorder (PTSD) exhibit characteristic lateral imbalances and frequency spectrum disharmony.¹⁻³ Such patterns tend to be characterized by right-lateralized fronto-temporal and parietal dominance that resemble but remain distinct from patterns reported in comorbid conditions like traumatic brain injury (TBI), insomnia, and depressive disorders.⁴⁻⁶ Additionally, polyvagal theory presents a basis for the possibility that left-lateralized patterns reflect a parasympathetic freeze state, which could contribute to the numbing and dissociative components of PTSD.⁷



High-resolution, relational, resonance-based electroencephalic mirroring (HIRREM) is a novel, non-invasive electroencephalographic technology that aims to facilitate auto-calibration of cortical neural oscillations. HIRREM has already been shown to palliate primary insomnia symptoms in a randomized,

wait list controlled pilot study.⁸ This case series explores its benefit to PTSD symptomatology as well as secondary insomnia and depressive symptoms in subjects receiving HIRREM plus usual care, and includes case examples regarding changes in oscillatory balance and harmony in two subjects with right- and left-dominant activity prior to HIRREM.

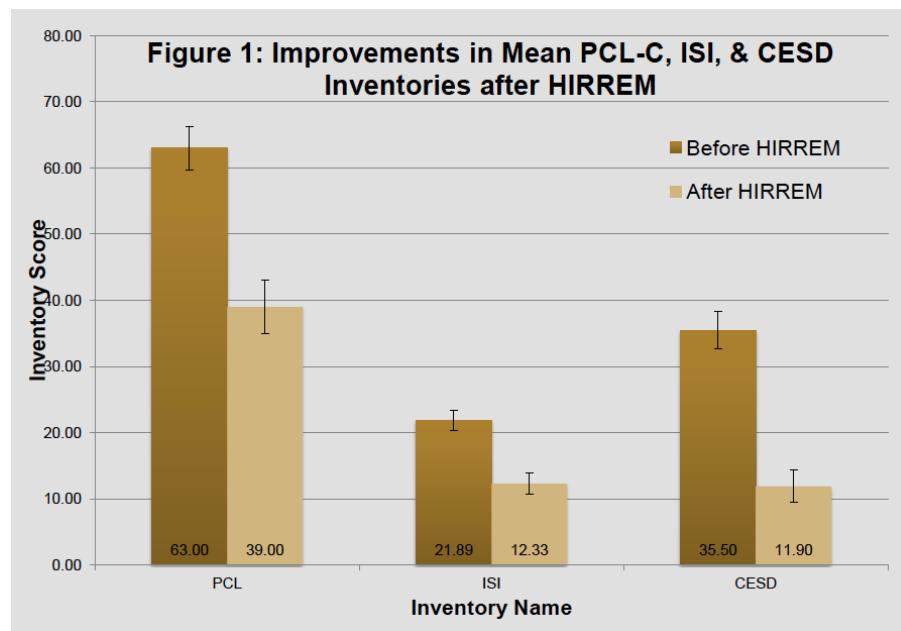
Methods

Participants (N = 10, 5 men) with a mean age of 45.5 (SD = 14.9) and self-reported PTSD diagnoses, whom also met a cut-off score of 44 or higher on the Post-Traumatic Stress Disorder Checklist - Civilian (PCL-C), were identified from an exploratory, IRB-approved, open-label protocol of HIRREM.⁹ Participants received a baseline EEG brain pattern assessment followed by a mean of 16.1 sessions of HIRREM over 11.9 days in addition to usual care. Post-intervention data were collected at an exit interview within two weeks after the final session. Pre- and post-HIRREM data inventories included the PCL-C (primary outcome), Insomnia Severity Index (ISI), and Center for Epidemiologic Studies Depression Scale (CESD). Exclusion criteria included ongoing treatment with opiates, benzodiazepines, or anti-psychotics as well as use of recreational drugs or alcohol. Due to missing pre-HIRREM data, one participant was excluded from ISI analyses.

Results

Significant drops ($p \leq 0.001$) in scores for our primary and secondary inventories were observed, along with large unbiased effect sizes (Cohen's d 95% CI > 1.4). PCL-C scores, the primary outcome for this case series, decreased from a pre-intervention mean of 63, to 39 for a mean decrease of 24 points $t(9) = 6.11$, $p = .001$, 95% CI [-12.31, -35.68], $d = 1.95$. The secondary outcome measures of ISI & CESD achieved similar improvements, as seen in Table 1. Mean scores for all three measures fell to below clinically relevant thresholds (PCL-C: 44, ISI: 15, CESD: 16) [Fig. 1].

Electroencephalographic data from the HIRREM system also demonstrated substantial tempering of signature PTSD oscillatory imbalances. In Case #1, the right-dominant high frequency disharmonized temporal pattern was reduced substantially during HIRREM, resulting in a symmetrical pattern by the penultimate session [Fig. 2]. Case #2 shows similar balancing and harmonization of a left-dominant high frequency initial pattern [Fig. 3].



Bar graph demonstrating score improvements in pre- and post-HIRREM inventory collection for the Post-Traumatic Stress Disorder Checklist - Civilian (PCL-C), Insomnia Severity Index (ISI), and Center for Epidemiologic Studies Depression Scale (CESD). Bars represent standard error.

Table 1: Statistical Tests			
	PCL-C	ISI	CES-D
Mean Improvement	-24.00	-9.56	-23.60
95% CI	[-12.31, -35.68]	[-5.65, -13.46]	[-13.22, -34.00]
T Statistic	6.11	6.90	9.00
Degrees of Freedom	9	8	9
p Value (Bonferroni)	0.001	< 0.001	< 0.001
Cohen's d	1.95	1.97	3.60
95% CI	[1.41, 2.48]	[1.43, 2.52]	[2.71, 4.49]

Paired Student's T-tests with Bonferroni corrections yielded statistically significant changes in scores after HIRREM treatment for all three inventories. Cohen's d effect size and 95% confidence intervals were > 1.4, even after adjustment for sample size.

Figure 2A & 2B: Right-Dominant High Frequency Pattern Before and After HIRREM

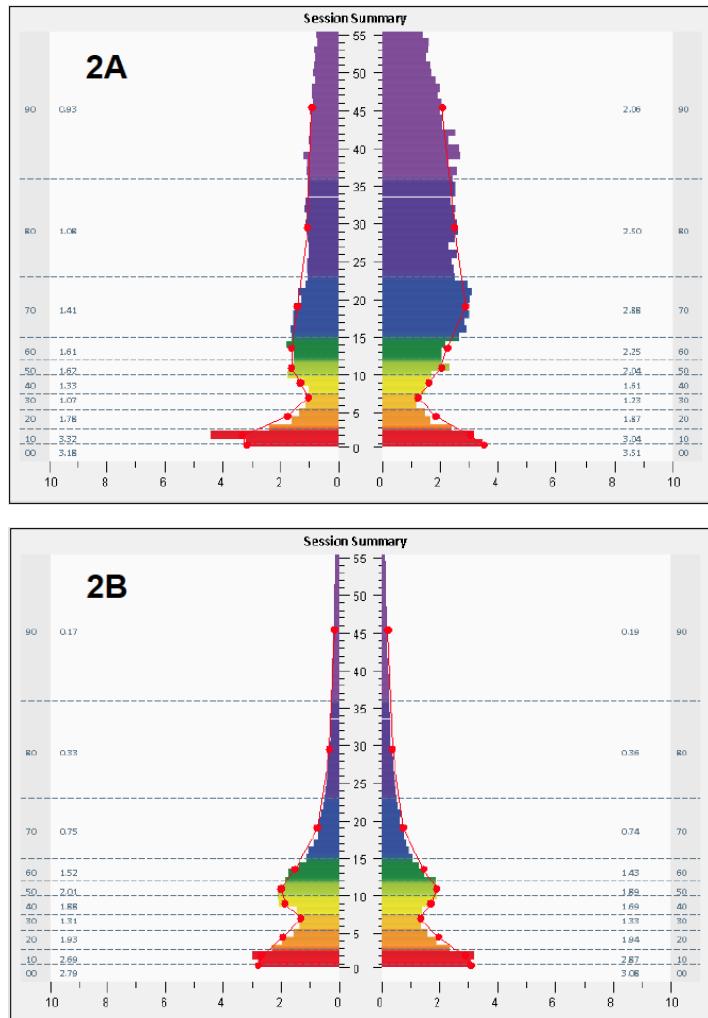
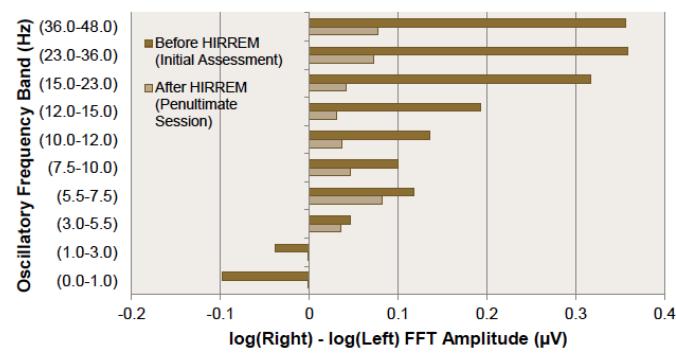


Fig. 2C: HIRREM Restores Temporal Balance in a Right-Dominant Participant
(Logarithm differences between right and left hemispheric amplitudes by frequency band)



Figs. 2A-C: FFT spectral display of EEG data with frequency (central Y axis) plotted against transformed amplitude (μ V, X axis). Data represents one minute of the T3-T4 montage (eyes closed) at the initial assessment before HIRREM (July 1, **A**) and the penultimate (15th) HIRREM session (Aug 10, **B**) for a 55 year old female. **C** Differences of the logarithm of electroencephalographic power of data by frequency band. Amplitude differences were calculated $\log(\text{Right}) - \log(\text{Left})$; negative values indicate left-lateralization.

Figures 3A & 3B: Left-Dominant High Frequency Pattern Before and After HIRREM

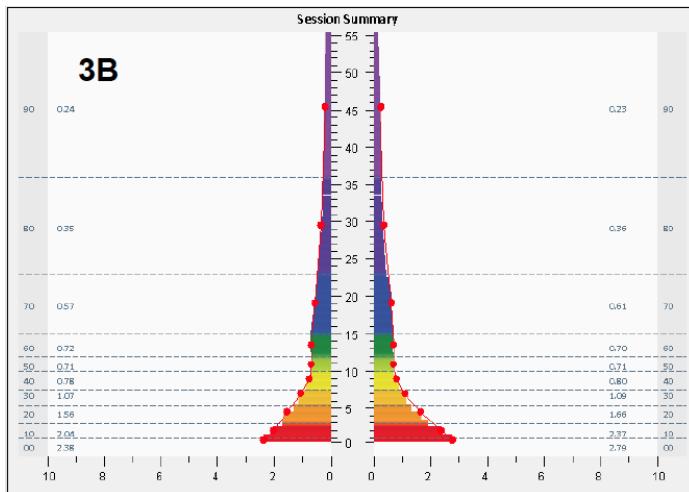
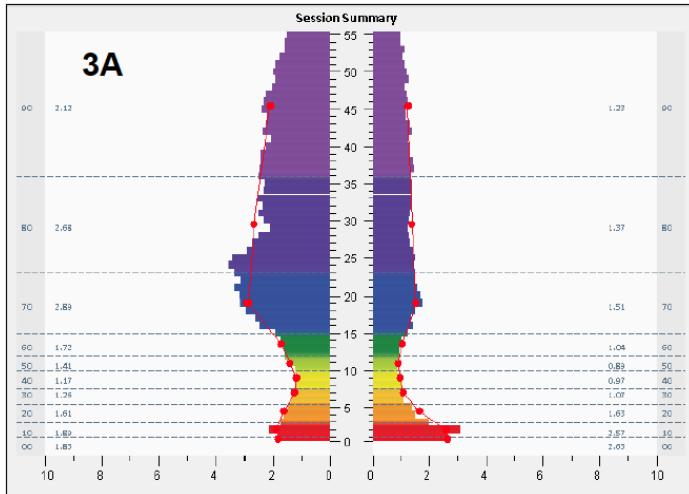
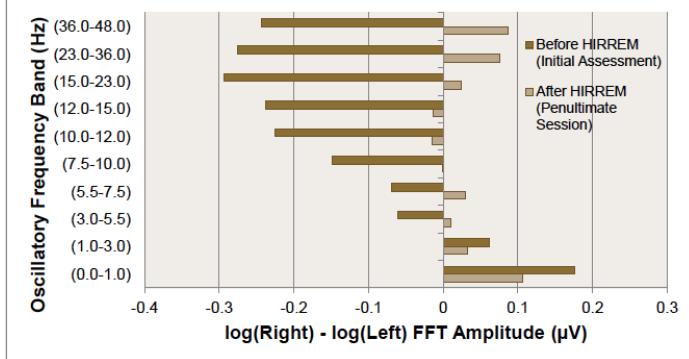


Fig. 3C: HIRREM Restores Temporal Balance in a Left-Lateralized Participant
(Logarithm differences between right and left hemispheric amplitudes by frequency band)



Figs. 3A-C: FFT spectral display of EEG data with frequency (central Y axis) plotted against transformed amplitude (μ V, X axis). Data represents one minute of the T3-T4 montage (eyes closed) at the initial assessment before HIRREM (Aug 13, **A**) and the penultimate (16th) HIRREM session (Aug 29, **B**) for a 54 year old male. **C** Differences of the logarithm of electroencephalographic power of data by frequency band. Amplitude differences were calculated $\log(\text{Right}) - \log(\text{Left})$; negative values indicate left-lateralization.

Conclusions

HIRREM appears to be a feasible intervention for those with PTSD, demonstrating significant, clinically-relevant improvements in our pilot subjects' symptom scores. Secondary analyses suggest that HIRREM also improves comorbid insomnia and depression symptoms in subjects with PTSD. These data suggest potential importance for clinical care. The drop of 24 points on the PCL-C represents clinically relevant change , with 7 subjects falling to sub-clinical screening scores.¹⁰ Similarly, the 7 of 9 subjects with "clinically significant" or higher rated insomnia, dropped to "not clinically significant" or "sub-threshold" insomnia levels on the ISI. Finally, 7 of 10 subjects' CESD scores fell to below the cut-off for depression screenings. Additional research is warranted to confirm these results in a larger cohort, using a controlled study design and elucidate the specific effect of HIRREM on the core PTSD and comorbid insomnia and depressive symptoms.

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Conflicts of Interest

Co-authors Lee Gerdes and Sung Lee are compensated by Brain State Technologies, LLC, Scottsdale, AZ. All other authors have no conflicts to report.

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HIRREM™: a noninvasive, allostatic methodology for relaxation and auto-calibration of neural oscillations

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Keywords

Allostasis, auto-calibration, biofeedback, electroencephalography, hemispheric asymmetry, HIRREM, insomnia, neural oscillation, relaxation, stochastic resonance

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Abstract

Disturbances of neural oscillation patterns have been reported with many disease states. We introduce methodology for HIRREM™ (high-resolution, relational, resonance-based electroencephalic mirroring), also known as Brainwave Optimization™, a noninvasive technology to facilitate relaxation and auto-calibration of neural oscillations. HIRREM is a precision-guided technology for allostatic therapeutics, intended to help the brain calibrate its own functional set points to optimize fitness. HIRREM technology collects electroencephalic data through two-channel recordings and delivers a series of audible musical tones in near real time. Choices of tone pitch and timing are made by mathematical algorithms, principally informed by the dominant frequency in successive instants of time, to permit resonance between neural oscillatory frequencies and the musical tones. Relaxation of neural oscillations through HIRREM appears to permit auto-calibration toward greater hemispheric symmetry and more optimized proportionation of regional spectral power. To illustrate an application of HIRREM, we present data from a randomized clinical trial of HIRREM as an intervention for insomnia ($n = 19$). On average, there was reduction of right-dominant temporal lobe high-frequency (23–36 Hz) EEG asymmetry over the course of eight successive HIRREM sessions. There was a trend for correlation between reduction of right temporal lobe dominance and magnitude of insomnia symptom reduction. Disturbances of neural oscillation have implications for both neuropsychiatric health and downstream peripheral (somatic) physiology. The possibility of noninvasive optimization for neural oscillatory set points through HIRREM suggests potentially multitudinous roles for this technology. Research is currently ongoing to further explore its potential applications and mechanisms of action.

Introduction

This study introduces a novel, noninvasive electroencephalography-based interventional technology, called high-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM™), or Brainwave Optimization™. The purpose of HIRREM is to facilitate relaxation and auto-calibration of neural oscillations through dynamic, auditory resonance with electroencephalic activity measured at high spectral resolutions. To contextualize HIRREM as an intervention with potentially multitudinous roles, in this section, we briefly review the array of diseases associated with neural oscillatory disturbance,

share an overview of HIRREM and its development, and adduce the model of *allostasis* for explaining physiological regulation. Materials and Methods section describes procedures for provision of HIRREM. In Results section, data are presented from a clinical trial of HIRREM for individuals with insomnia, to illustrate a clinical application for HIRREM and associated changes in neural oscillatory symmetry.

Disturbances of neural oscillation

Oscillation is a fundamental feature of physics and biology, and appreciation of the brain as a network of

oscillators provides a highly integrative framework for understanding brain functionality (Buzsaki 2006). Neural oscillations can be impacted by stimuli which span a range of intensity from the subtle to the near lethal. Blast injuries sustained in warfare can produce disturbance of oscillatory synchrony (Sponheim et al. 2011). At the other extreme, weak signals can alter neural oscillations through the phenomenon of stochastic resonance (see HIRREM and EEG artifact or noise), whereby an increase in a neural system's noise level can, perhaps counterintuitively, enable the detection of an otherwise subthreshold periodic signal (Moss et al. 2004; McDonnell and Ward 2011).

Disturbances of synchronization of neural oscillation have been described in association with clinical disorders including epilepsy (Margineanu 2010), Parkinsonism (Gale et al. 2008), schizophrenia (Uhlhaas and Singer 2010), Alzheimer's disease (Dauwels et al. 2010), autism (Isler et al. 2010), and insomnia (Marzano et al. 2008). At the level of the cerebral hemispheres, oscillatory disturbances may manifest as imbalances of left-right EEG symmetry. Frontal EEG asymmetry has been described as a marker for affective style, with left and right frontal cortex associated with approach and withdrawal tendencies, respectively (Davidson et al. 1990). Other reports have associated hemispheric oscillatory asymmetry with posttraumatic stress disorder (Rabe et al. 2006; Engdahl et al. 2010), insomnia (St-Jean et al., 2012), attention-deficit disorder (Hale et al. 2010), autism (Stroganova et al. 2007; Lazarev et al. 2010), dyslexia (Spironelli et al. 2008), and schizophrenia (Swanson et al. 2010). Whether there could be a physiologic disturbance common to these asymmetries has not been much considered, but the hemispheric lateralization of management of the autonomic nervous system functioning (Yoon et al. 1997; Avnon et al. 2004; Craig 2005) – sympathetic and parasympathetic divisions by the right and left hemispheres, respectively – seems to raise the possibility that hemispheric oscillatory asymmetry may be an indicator of dysregulation of autonomic nervous system functioning.

Given that neuronal populations oscillate over a range of low to high frequencies, it is also possible to describe neural oscillatory disturbances as suboptimal proportionation of spectral EEG power across those frequency ranges, usually discerned through comparison of average amplitudes of broadband EEG ranges (i.e., delta, 0.5–4 Hz; theta, 4–8 Hz; alpha, 8–12 Hz; beta, 12–30 Hz; gamma, >30 Hz). Attention-deficit spectrum disorders (Barry et al. 2003), mild cognitive impairment (Babiloni et al., 2010), dementia (Dauwels et al. 2010), and traumatic brain injury (Moeller et al. 2011) have been associated with relative excess power in low frequencies (i.e., delta and/or theta) in comparison with high frequencies. Other

forms of suboptimal proportionation of spectral EEG power have been reported with insomnia (Perlis et al. 2001; Wolynczyk-Gmaj and Szelenberger 2011), alcoholism (Campanella et al. 2009), and chronic fatigue syndrome (Decker et al. 2009).

The existence of an array of conditions which share thematic forms of neural oscillatory disturbance – asymmetry and suboptimal proportionation of spectral power – suggests that a positive role may exist for technologies that may constructively impact neural oscillations in the direction of greater symmetry and optimized proportionation.

Definition and development of HIRREM

Through serendipity, one of the authors of this article (L. Gerdes) found that near real time reflection of neural oscillatory activity back to the brain through the medium of audible sound appeared to facilitate a state of relaxation wherein the brain, itself, would tend to change its own activity patterns toward greater hemispheric EEG symmetry and more optimized proportionation of regional spectral EEG power. We thus described the process facilitated as one of relaxation and auto-calibration for neural oscillations. The methodology has been continuously refined since its development in 2000–2002, and since 2010, it has been described technically as high-resolution, relational, resonance-based electroencephalic mirroring or HIRREM. The technology is based on provision of auditory musical tones corresponding to dominant frequencies detectable in individual spectral EEGs, to permit resonance between neural oscillatory frequencies and auditory tones. It requires no direct energetic input to the brain, no cognitive guidance or education from a clinician, nor any referencing against population norms for the EEG.

Allostatic regulation of neural oscillations through HIRREM

Because of the variety of conditions, including "somatic," that have been reported to benefit from HIRREM on an anecdotal basis (see Overview section), we infer that HIRREM facilitates self-guided and healthful reorganization of neural oscillations at some level(s) of primary neural process, with consequences for both neuropsychiatric health and downstream peripheral physiology. To model the larger theoretical role of HIRREM, we adduce the concept of *allostasis* as defined by Sterling (2004, 2012). Allostasis refers to stability (stasis) through change (allo). Allostasis highlights the centrality of the brain as the master control center for human physiology, whose primary function is to serve as an instrument for optimal predictive regulation. The concept of allostasis may be

clarified through comparison with the more commonly used biomedical concept of homeostasis.

Homeostasis as a model of physiological regulation through maintenance of predetermined and normative set points

Homeostasis refers to stability (stasis) through constancy (homeo) and is a model of physiological regulation in which various systems are described in terms of their requirement to maintain various set points at constant values. These values are deemed normative, and systematic deviations are generally considered disease states. The objective of biomedicine is to identify the mechanisms underlying regulation of set points. The guiding assumption is that *mechanisms are dysfunctional* in states of disease and therefore are the cause of deviated set points. Therapeutics thus consists of intervention to correct dysfunctionality of local mechanisms. The system set points being “defended” in homeostasis are typically defined based on prespecified level of demand, calculated on norms derived from historical or other controlled influences. Homeostasis thus focuses on functionality (or dysfunctionality) of local mechanisms without a nuanced appreciation for how complex environmental contexts drive system needs or set points in the first place. The seeds for the concept of homeostasis were developed before the dissemination of evolutionary theory (Sterling 2012), and thus, the homeostasis model reflects an understanding of life itself as being fundamentally unchanging.

Allostasis as a model of brain-guided predictive regulation through dynamic optimization of system set points

Allostasis conceives the brain as the master regulator which, when well-functioning, anticipates changing needs in a constantly changing environment and recalibrates system set points in accordance with present or anticipated demands. The brain dynamically allocates and re-allocates the body’s energetic resources in order to *optimize fitness*. In the Sterling model of allostasis, activities of the present should meet the needs of the present; they should not be organized to meet the demands of the past or other non-salient norms; and they must also include anticipation and preparation for the needs of the future. In the allostasis model, deviations of system set points may be indicative of disease states, but local mechanisms are not viewed as being intrinsically dysfunctional – rather they are simply responding to a different level of demand.

Figure 1 (adapted from Sterling 2004) illustrates a simplified general model for how a healthy system will adjust its output set points to respond dynamically for the

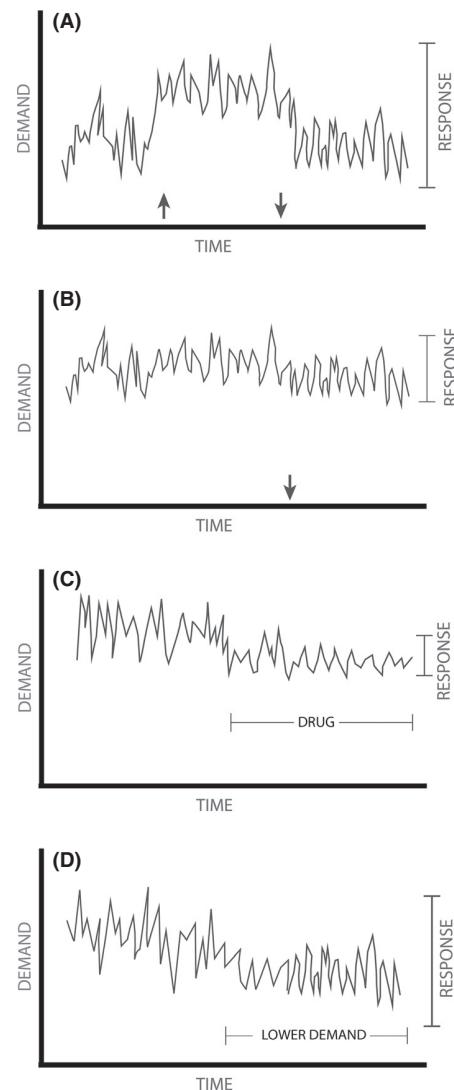


Figure 1. Rhythmic output of a model system under conditions of health and fluctuating demand (A); “stuckness” due to prolonged or possibly acutely potent demand (B); pharmacotherapy (C); and an idealized health intervention, associated with gradual reduction of demand (D). Black vertical arrows denote changes in demand on the system. Adapted from Sterling (2004).

changing levels of ambient demand (Fig. 1A). The system set point can become stuck (Fig. 1B), for example, because of an acutely potent demand or elevated demand over time (e.g., a trauma or chronic stress), to produce outputs which are calibrated for the historical level of demand, despite the emergence of a new and lower level of demand. Pharmacological therapy (Fig. 1C) can alter and clamp the system set point at an output level which appears more congruent with the present demand, but at the expense of depriving the system of its dynamic range

of action. An ideal intervention (Fig. 1D) would encourage a diseased system to relax, become “unstuck,” and recalibrate output for the true and present (not historical) level of demand.

Allostasis would appear to be consistent with the view of physiology from nonlinear dynamical theory, which considers system complexity to be a hallmark of health (Goldberger et al. 2002). It may be that it is the loss of complexity, rather than the loss of regularity, which is associated with disease states. Decreased neural functional complexity has been described in Alzheimer’s disease (Jeong 2004), mild cognitive impairment (Cantero et al. 2009), posttraumatic stress disorder (Chae et al. 2004), and autism (Bosl et al. 2011; Catarino et al. 2011). Decreased EEG complexity can be observed in epileptic seizure (Babloyantz and Destexhe 1986), and increased variability of synchrony has been shown to be associated with recovery from pediatric traumatic brain injury (Nenadovic et al. 2008). Increased complexity appears to be a normal and perhaps healthy feature of the EEG over the course of human development from infancy to older age (Meyer-Lindenberg 1996; Anokhin et al. 2000; McIntosh et al. 2008; Muller and Lindenberger 2012).

Allostasis and disease

The difference between the homeostasis and allostasis models of physiological regulation can be illustrated through the ways they explain blood pressure management (Sterling 2004). Homeostasis portrays blood pressure as a set point managed by blood volume, vascular resistance and cardiac output, and medical interventions aim to impact mechanisms related to the management of those variables. Allostasis portrays blood pressure as a set point influenced proximally by vascular resistance, volume, and cardiac output among other factors, but ultimately managed by the brain (Fig. 2). Under the allostasis model, the ultimate way for blood pressure to change is for the brain itself to adopt a different set point. Adoption of new (and changing) blood pressure set points that are more optimally calibrated for complex (and changing) environmental demands likely necessitates high-level integration of information at the level of the cortex.

The concept of allostasis has been especially developed to explain the deleterious effects of chronic stress on health (McEwen 1998, 2007). *Allostatic load* may manifest when otherwise helpful and adaptive neural response mechanisms, especially the response of the hypothalamus–pituitary–adrenal (HPA) axis to an environmental challenge, have been highly activated over time. For example, circulation of effectors related to the HPA axis including cortisol, epinephrine, and norepinephrine may be helpful in the setting of an acute stressor, but their extended

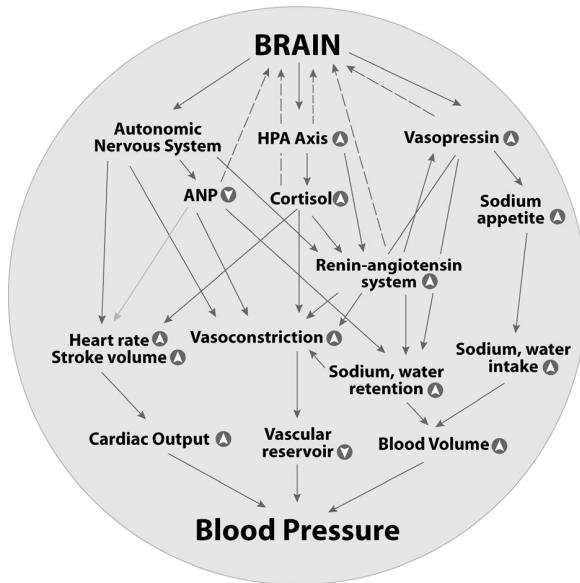


Figure 2. Allostatic model of blood pressure regulation (adapted from Sterling 2004).

presence (weeks, months, or years) may cause damage to the tissues they would otherwise protect. Allostatic load may explain the relationship between low socioeconomic status and poor health outcomes (Seeman et al. 2010).

Various other health and disease phenomena have also been re-contextualized with the model of allostasis and allostatic load, including migraine (Borsook et al. 2012), sleep deprivation (McEwen 2006), glucose regulation (Stumvoll et al. 2003), fibromyalgia (Martinez-Lavin and Vargas 2009), perinatal health outcomes (Shannon et al. 2007), aging (Karlamangla et al. 2006), asthma (Bahreini et al. 2012), nonalcoholic fatty liver disease (Baffy 2012), substance abuse (Koob and Le Moal 2001; George et al. 2012), and bipolar disorder (Kapczinski et al. 2008).

HIRREM as a precision-guided technology for allostatic therapeutics

Allostatic therapeutics is a field yet to be systematized. Nonetheless, it stands to reason that allostatic therapeutics will invoke, for example, the need for multicomponent and behavioral interventions (e.g., Ornish et al. 1998; Loizzo et al. 2009; Streeter et al. 2012) which are intended to change demand levels, so that neural functioning can recalibrate toward more healthful set points in subject-specific increments. Yet, considering the inertia often associated with these domains, the objectives of allostatic therapeutics may be more effectively realized if the brain itself is facilitated to calibrate its oscillations to desirable set points. Thus, HIRREM technology may be well suited

to serve as a catalyst for neural changes underpinning healthful behavior change.

Materials and Methods

Overview of HIRREM requirements and application

The physical requirements for provision of HIRREM include a standard PC-based desktop or laptop computer, a specialized EEG amplifier and preamplifier, EEG sensors, standard earbud headphones, a specialized software program, and a reclining chair. EEG sensors connected to the preamplifier (powered by a 9 V, 400 mAh rechargeable lithium ion battery) filter 50 and 60 Hz activity so as to reduce the contribution of environmental electromagnetic noise. Sampling rate is 256 Hz. The amplifier is powered by a standard Windows-based laptop computer and uses a 16-bit A/D converter with a notch filter for rejection of signal >50 dB at 50 or 60 Hz. Signal processing is done in a 64-bit computer processor. Technologists are trained to identify EEG evidence of grossly recurring artifact (e.g., eye-blinking) or sensor displacement from the scalp, but the software does not attempt to identify artifact or other forms of noise (see HIRREM and EEG artifact or noise).

Provision of HIRREM for an individual consists of EEG and questionnaire-based assessment, active HIRREM sessions (generally 60–90 min each, 3–10 sessions or more), and software-supported data analysis by a technologist. Questionnaires capture data related to symptoms, medical history, and objectives for undergoing the HIRREM procedure. Data are collected in a master database (see below), which is used to help guide ongoing innovations of HIRREM technology. Based on clinical experience suggesting a deleterious effect on outcomes, subjects are strongly advised to abstain from alcohol and recreational drugs for the period of their HIRREM sessions and for at least 3 weeks thereafter.

Procedure for HIRREM assessment

Assessment consists of serial measurements of two-channel EEG using active sensors, with scalp locations identified based on the International 10–20 EEG system. Two recording sensors, two reference sensors, and one ground sensor are used. Measurements are taken at homologous regions of the hemispheres (F3/F4, C3/C4, T3/T4, P3/P4, O1/O2) for eyes closed (1 min), partially closed (1 min), and eyes open (1 min), with subject in an upright, seated position. For eyes closed, subjects are asked to rest and relax quietly. For eyes open, subjects are given standardized tasks involving numerical digit-recall (F3/F4), reading silently (C3/C4), calculations (P3/P4), listening comprehension

(P3/P4), and visual observation (O1/O2). A sixth measurement is taken along the midline of the scalp at FZ/OZ. The reference sensors are connected at A1/A2 and linked. The EEG portion of the assessment takes approximately 45–60 min to complete.

Procedure for HIRREM exercises

With the subject comfortably at rest, sitting or reclining in a zero-gravity chair, sensors are placed over specific target areas on the scalp. As with the assessment, up to two recording sensors, two reference sensors, and one ground sensor are used. Most HIRREM protocols (defined as a combination of sensor montage and the specific software design) capture two channels of electroencephalic data between homologous regions of the hemispheres. Two-channel single-sided protocols may be used to focus attention on apparently recalcitrant oscillatory activity localizing in a particular region. One-channel protocols may also be used to focus attention, especially in “alpha” and “beta” frequency bands, on single regions without a particular interest in symmetry with the homologous region of the contralateral lobe.

Initial placements for the sensors are recommended by the HIRREM software based on cortical regions and spectral frequency ranges exhibiting the greatest asymmetries and/or suboptimal proportionations of spectral power, based on data collected during the assessment. Single HIRREM sessions generally consist of 5–8 protocols, each lasting 5–15 min. In general, sessions are provided on a relatively compressed schedule, that is, as intensively as two per day, or generally no more slowly than three per week, with 10 sessions typically being completed within 3 weeks. A typical HIRREM session lasts 60–90 min.

During all HIRREM protocols, subjects wear standard earbud headphones, through which they listen to the musical tones generated by the HIRREM software algorithms. Subjects are encouraged to relax in the zero-gravity chair at a near-prone angle so as to maximize cerebral blood flow, and they may be encouraged to visualize themselves in a peaceful setting in nature or simply to pay attention to their breathing. The majority of exercises take place with eyes closed. For exercises with eyes open, subjects may read a book or relax while watching changing graphics on a computer monitor.

High-resolution spectral analysis of electroencephalic data and dynamic, iterative engagement of dominant frequencies

The HIRREM system includes proprietary preamplifiers and filters which allow collection of electroencephalic data

to the nearest 0.01 Hz, at the level of the sensor attached to the scalp. HIRREM software analytics then identify dominant frequencies in specific spectral brackets, in up to 48,000 bins of spectral data for any given bracket. Brackets are assigned by the software based on a proprietary algorithm. The software compares the two channels of data to ascertain the symmetry between channels of EEG information and proportionation of spectral power within the channels. From the bracket of frequencies assigned for the subject's exercise, the HIRREM software translates the dominant EEG frequency in a given instant of time to an audible musical tone, which is received by the subject through earphones. Depending on algorithm calculations, the delay between measurement and analysis of neural oscillatory activity and consequent presentation of corresponding musical tones can be as narrow as an estimated 12 msec. The process then iterates.

The HIRREM mathematical algorithms to define specifically how and when the dominant EEG frequencies are selected for resonance are informed by relationships among the parameters of the individual's own unique spectral EEG. The specific tone is produced from a proprietary mathematical algorithm principally informed by the dominant frequency within the observed spectral bracket. A sample sequence of tones produced during 1 min of a HIRREM exercise and the corresponding notes on the pentatonic scale are available as Internet resources, in the form of audio, and pdf files.

Application of HIRREM exercises to the bilateral temporal lobes is emphasized, as we theorize that comparison of spectral EEG amplitudes in simultaneous recordings at

the bilateral temporal lobes (T3 and T4 in the 10–20 International EEG system) may provide an opportunity to engage the degree of balance between the sympathetic and parasympathetic divisions of the autonomic nervous system. As noted in Introduction, numerous studies have found that management of the autonomic nervous system is lateralized in the cerebral hemispheres. Specifically, right insular cortex appears to drive sympathetic functioning, whereas left insular cortex drives parasympathetic functioning (Craig 2005). T3 and T4 are located over Brodmann areas 21 and 22, respectively, at the middle and superior gyri of the temporal lobes (Homan et al. 1987) and are therefore in the proximity of insular cortex. Apart from a focus on the temporal lobes, HIRREM exercises take place for major regions of the cortex including frontal, parietal, occipital lobes, central strip, and the midline, and across the EEG frequency spectrum in each of those locations.

At the conclusion of a single HIRREM session, the provider runs an analysis program which shows summary data for the session. Comparative amplitudes and coherence of the two channels of data collected during various protocols can be evaluated in the following 10 broadband frequency ranges: 0–1, 1–3, 3–5.5, 5.5–7.5, 7.5–10, 10–12, 12–15, 15–23, 23–36, and 36–48 Hz. Cortical regions and spectral frequency ranges of interest can be chosen for subsequent HIRREM sessions. Examples of the output from this analysis program are shown in Figure 3, which depicts changing amplitudes in the 0–1 and 36–48 Hz frequency bands, over five successive HIRREM exercises at the temporal lobes. As of the time of this writing, new

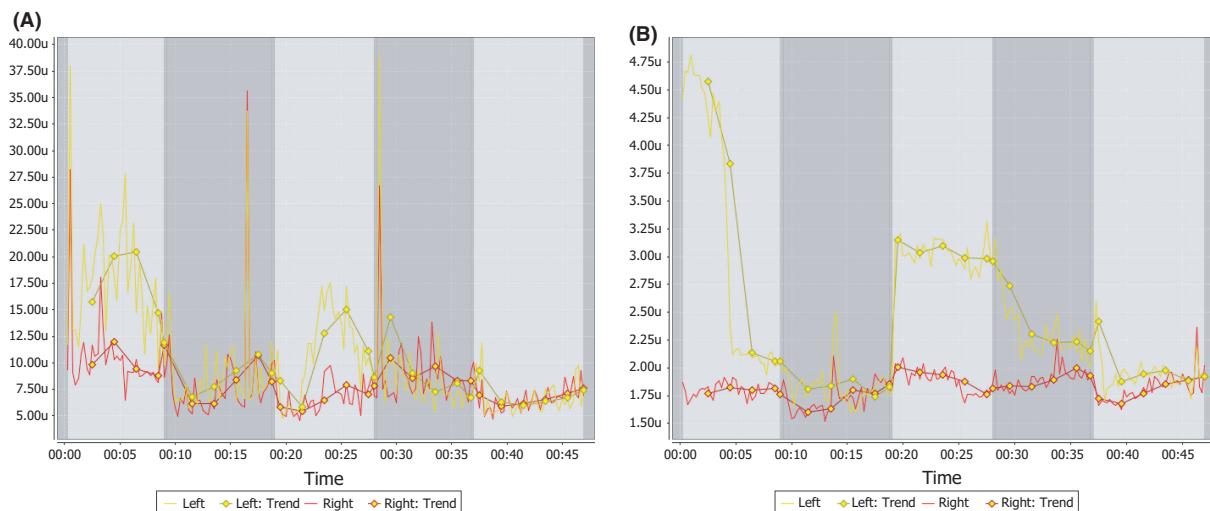


Figure 3. Changing asymmetry at the bilateral temporal lobes over the course of five successive HIRREM exercises, in the 0–1 Hz (A) and 36–48 Hz (B) frequency bands. Yellow line represents amplitudes at T3, and red line represents amplitudes at T4. Each HIRREM exercise is represented by a background with alternating shades of gray.

analytic software is being developed to enable computer-guided recommendations for protocols to implement in successive HIRREM sessions. The new session-to-session analytic tool performs primarily time-domain analysis of amplitudes in the 10 aforementioned ranges, aggregated over 15-sec intervals after removing the first and last 30 sec to eliminate artifacts related to the start or end of the exercise. Data are fitted using regression analysis to determine trends of symmetry and proportionation of spectral power. Based on the identified trends, HIRREM protocol suggestions are made for the next session.

Use of HIRREM master database to guide iterative innovations in hardware and software

All data associated with the HIRREM procedure including responses to the questionnaires, the assessments, and all HIRREM exercises are stored locally on computers at various locations throughout the world where HIRREM is provided. These locations are linked by Internet to the corporate headquarters of the developers of HIRREM technology (Brain State Technologies, Scottsdale, AZ). On a nightly basis, these data are uploaded without personal identifiers into a master database located at the corporate headquarters.

The information in this database allows for exploratory hypothesis testing to identify possible correlations between symptom clusters and EEG patterns, thereby facilitating the refinement of HIRREM software designs and protocol options. Thus, HIRREM technology is continuously adjusted and refined to selectively provide resonance for cortical regions and EEG spectral ranges which may better assist the subject's own unique self-regulatory process. Notably, the master database is not used to generate normative values for EEG parameters, against which subjects would be compared and which would be held as a basis for therapeutic goals.

Results

Overview

As of September 2012, HIRREM technology is being used by over 200 providers in North America, Europe, South Africa, Asia, and Australia. Over 50,000 subjects have undergone HIRREM worldwide and are contained in the database. Case series of outcomes have been reported for individuals with neurodegenerative disease (Singh and Gerdes 2009a) and depression (Singh and Gerdes 2009b). Anecdotally, a range of benefits are reported including relief from sleep disorders, depressive symptoms and anxiety, reduced symptomatology related to trauma,

improved cognitive functioning, relief from addictive urges, improvement in cardiovascular and gastrointestinal conditions, and others. A randomized, wait-list controlled pilot trial has shown efficacy of HIRREM for relieving symptoms of insomnia (Tegeler et al. 2012), and a placebo-controlled trial testing efficacy for migraine has been completed.

Changes in temporal lobe EEG asymmetry associated with use of HIRREM as an intervention for insomnia

We present changes in temporal lobe asymmetry for 19 subjects enrolled in a randomized, wait-list, controlled pilot trial of HIRREM as an intervention for insomnia. Methods and main clinical outcomes for this study have been reported elsewhere (Tegeler et al. 2012). Mean age of subjects was 45 (70% women), and at baseline, mean score on the Insomnia Severity Index (Bastien et al. 2001) was 18.8, indicating, on average, clinical insomnia of moderate severity. Subjects also reported substantial depressive symptomatology (average CES-D score 14.9). All subjects underwent an average of nine (range 8–13) HIRREM sessions, beginning either immediately after enrollment into the study or after a waiting period (usual care) of 6 weeks. At the primary endpoint, subjects undergoing HIRREM reported a reduction of 10.3 points in the ISI, while those undergoing usual care reported no change.

Though HIRREM exercises were conducted at the temporal, occipital, parietal, central, and frontal lobes, and anterior and posterior midline, temporal lobes were chosen for the present analysis on an a priori basis, because of the proximity of the insula and limbic structures related to autonomic functioning (see High-resolution spectral analysis of electroencephalic data and dynamic, iterative engagement of dominant frequencies). Data for calculation of asymmetry scores were derived from the HIRREM exercise conducted at the bilateral temporal lobes, for each subject and for each session. For those sessions in which two exercises were conducted at the temporal lobes, the first exercise was used for calculation of the asymmetry score. Asymmetry scores were calculated based on the log of the average spectral power (23–36 Hz) at T4 over the course of the 8-min HIRREM exercise, minus log of the average spectral power (23–36 Hz) at T3. The high frequency (23–36 Hz) range of the EEG was chosen for the present analysis because of evidence of high-frequency arousal as being contributory to insomnia (Perlis et al. 2001; Wolynczyk-Gmaj and Szelenberger 2011).

Figure 4 shows the average asymmetry score for T3 in comparison with T4, for all 19 subjects over the course of their HIRREM sessions. Rightward asymmetry ($T4 > T3$) diminished over the course of six HIRREM sessions, fol-

lowed by a shift to average leftward asymmetry ($T_3 > T_4$) for session 7, and a return to rightward asymmetry for session 8. To test whether change in asymmetry was correlated with improvement in insomnia symptoms, an individual asymmetry change value was computed for each individual, by fitting a simple linear equation to the serial asymmetry scores of each subject. A positive slope for this equation indicated a trend of higher asymmetry scores over the course of the sessions, or greater dominance of T_4 over T_3 , whereas a negative slope indicated a trend of lower asymmetry scores, or diminishing dominance of T_4 over T_3 . A plot of individual change of asymmetry scores against individual change in insomnia as measured by the Insomnia Severity Index (Bastien et al. 2001) is shown in Figure 5. There was a trend for reduction of temporal lobe high-frequency EEG asymmetry in the direction of less dominance of T_4 over T_3 to correlate with greater reduction of insomnia symptoms.

Safety and side effects

HIRREM has been found to be a safe procedure. Based on experience with provision of case management support (by Brain State Technologies), feedback from clients and the HIRREM provider community, and three IRB-approved studies based at a tertiary medical center, the developers and researchers are not aware of any serious adverse events resulting from undergoing HIRREM.

On an anecdotal basis, individuals undergoing HIRREM may report an apparent “release of emotions” or paradoxical effects especially initially, which can manifest as brief periods of increased awareness of emotional states, both positive and negative. These experiences are typically transient, that is, lasting intermittently over

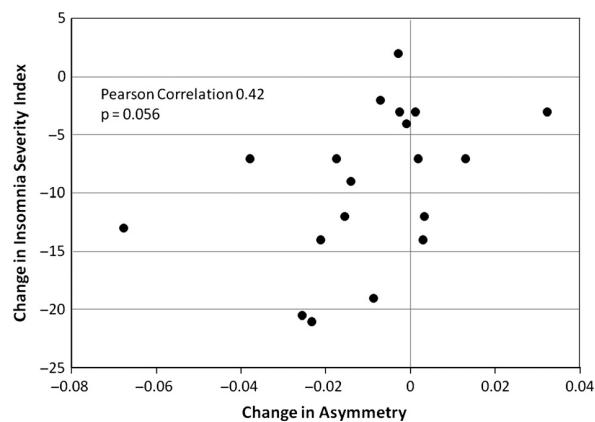


Figure 5. Correlation between individual change in asymmetry between T_3 and T_4 in 23–36 Hz range over eight serial HIRREM exercises, and change in insomnia symptoms as measured by change in ISI score. More negative change in asymmetry scores indicates lesser dominance of amplitudes at T_4 over T_3 . More negative ISI change scores indicate greater reduction in insomnia symptoms. Change in asymmetry is calculated as the slope of a linear equation fitted to the series of asymmetry scores over eight serial HIRREM exercises, for each individual.

the course of one to several days. In the course of provision of HIRREM to 118 subjects participating in three university-based IRB-approved studies, subthreshold changes in emotional symptomatology (not requiring additional clinical intervention or necessitating discontinuation of sessions) were estimated by the principal investigator to occur in approximately 5–10% of subjects. All HIRREM sessions are administered by technologists who have been certified in the procedure, including guidelines for addressing emotional releases that may occur. If emotional releases are prolonged or intense, individuals are

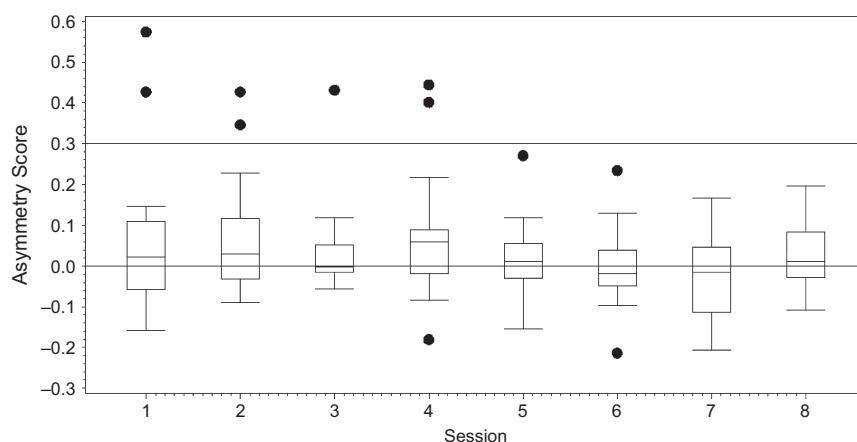


Figure 4. Tukey plot of average asymmetry scores between T_3 and T_4 in the 23–36 Hz range, over the course of eight successive HIRREM exercises for 19 subjects enrolled in a clinical trial evaluating efficacy of HIRREM as an intervention for insomnia. Whiskers extend to last observation not more than 1.5 times the interquartile range. Dots represent observations more than 1.5 times the interquartile range.

advised to see a mental health professional for additional evaluation or treatment.

Discussion

Comparison with other interventions to remediate disturbances of neural oscillations

There is no absolute schema for the classification of interventions that can impact neural oscillations, nor is there a logical consensus for terminology. For example, while the term “neuromodulation” is used by some providers to refer specifically to surgically implanted devices for direct stimulation of neural tissue, there is no doubt that myriad other interventions can act as modulators of neural function either through stimulation of the cortex through the skull, pharmacological action (e.g., influencing neuronal membrane potentials or ion channel function), or sensory stimulation of the peripheral nervous system from consumer-oriented or computer-based technologies.

A variety of device-based interventions exist which can impact neural oscillations. Electroconvulsive therapy, transcranial magnetic stimulation, and transcranial direct current stimulation can impact neural oscillations through delivery of electromagnetic energy from a device to the cortex through the skull. Deep brain stimulation, transcutaneous electrical nerve stimulation, vagus nerve stimulation, and others impact neural oscillations by delivery of electrical impulses through implanted devices that are in direct contact with neural tissue. Stimulation devices available in the consumer marketplace can entrain neural oscillations toward specific and predetermined frequencies through delivery of rhythmic light and/or sound.

EEG operant conditioning (also known as EEG biofeedback or neurofeedback) is a collection of techniques for measuring neural oscillations in broadband EEG ranges and teaching individuals how to consciously increase or decrease the amplitudes in those ranges. Individuals are presented with visual and/or auditory stimuli as feedback when average amplitudes of the selected ranges cross a predetermined threshold. These stimuli are thus presented as either “rewards” for movement of energy toward the specified parameter or “inhibits” if the energy moves in the nonnormative direction. To set parameters of training, providers may access databases of EEG assessments to formulate a normative basis for evaluation and treatment. Clinical studies of EEG operant conditioning have been reported for a number of disorders including epilepsy (Sterman 2010) and attention-deficit disorder (Arns et al. 2009). The technology is noninvasive and generally considered a low-risk procedure with minimal side effects.

A limitation of EEG operant conditioning (conscious associative learning) to change average amplitudes of broadband spectral EEG ranges (i.e., delta, theta, alpha, beta, gamma) is that it is likely associated with collateral, nonuseful learning. That is to say, learning to change amplitudes across these broad ranges will entail learning to change amplitudes for some segments of those frequency ranges that are likely nonproblematic for that individual (Salansky et al. 1998). Relatedly, use of broadband EEG ranges entails a relative blurring of large quantities of EEG information. Szava et al. (1994) found that broadband analysis could obscure peaks of energy detectable in narrower frequency ranges that appeared to be associated with pathology. Also, the precise spectral location of the peak frequency for the alpha (8–12 Hz) range is variable across individuals, and the location of this peak is a meaningful parameter that has been correlated with development (Cragg et al. 2011) and cognitive performance (Angelakis et al. 2004). Engagement with an individual’s unique spectral EEG fingerprint is not possible with technologies that rely on standard broadband EEG frequency ranges.

HIRREM and EEG artifact or noise

Artifact identification and rejection are thematic to the field of EEG. EEG artifacts may include a variety of discrete phenomena including abnormalities of the EEG tracing which are due not to neural oscillation but rather to scalp muscular contraction, eyeblinking, or head or sensor movement.

For the practice of EEG operant conditioning, the identification of EEG artifact is mission-critical, because the presentation of reward or inhibit signals in response to peripheral muscular contractions (for example), rather than neuronal oscillations, is subversive to the purpose and basis of the enterprise. (Likewise, artifact identification is critical for medical EEG especially insofar as definitive diagnosis depends on accurate characterization of EEG waveforms which are abnormal but may manifest inconsistently.)

Because HIRREM technology does not aim to consciously teach the individual through signals of reward or inhibition, we postulate that there is little if any jeopardy associated with providing auditory signals which are informed by nonneural sources and are therefore “meaningless.” (Nor does HIRREM aim to diagnose disease.) Rather we infer that the brain responds to epochs of HIRREM sounds generated from grossly noisy EEG artifact in the way that it would respond to grossly noisy sounds. Furthermore, artifact-associated data will tend to be distributed symmetrically, and because HIRREM algorithms are based on the relationship of activity between homolo-

gous brain regions, artifactual signals will tend to cancel one another out in the algorithmic equation.

We also hypothesize that, paradoxically, a possible mechanism for benefit of HIRREM could be the engagement between HIRREM and what is generally considered background noise or randomness in the EEG. The core technical aim of HIRREM is to resonate with dynamically changing dominant frequencies in the spectral EEG. Variations of amplitudes in these frequencies are typically characterized in stochastic terms. That is, *the energies of interest to HIRREM are in the category of apparently random fluctuations in the EEG, or noise*.

Variations in system noise levels can change the probability that a weak periodic signal will cross a threshold for sensory processing. The presence of an optimal noise level in a system can improve detection of a weak periodic signal, by boosting the signal sufficiently to cross the output threshold. For example, small increments in the luminance of a square presented to the right eye are better detected when there are tiny random fluctuations in the luminance of a square presented to the left eye than when the square presented to the left eye has constant luminance (Kitajo et al. 2003). This phenomenon has been referred to as stochastic resonance or stochastic facilitation, and it has been demonstrated for visual, auditory, and tactile sensory modalities (McDonnell and Ward 2011).

An implication of stochastic facilitation is that the system noise level may be a critical parameter for neural information processing (McIntosh et al. 2010; McDonnell and Ward 2011). If noise levels systematically change through HIRREM, it could be hypothesized that HIRREM impacts endogenous noise levels and thereby impacts overall efficiency of information processing.

Possible contribution of placebo effects or other nonspecific factors

Delivery of HIRREM entails up to 10 or more visits (90 min each) with HIRREM technologists, instruction to relax while listening to musical tones, and being recumbent in a comfortable chair situated in a quiet environment. This combination of social interaction and relaxation induction might be predicted to produce improvements in self-reported well-being irrespective of the specific pitch or timing of musical tones produced through the HIRREM software algorithms. To establish definitively that clinical improvements associated with HIRREM are attributable to the specificity of software algorithms and not placebo effects or other nonspecific factors, placebo-controlled trials are indicated.

As a preliminary illustration of the contrast between nonspecific relaxation induction and HIRREM, Figure 6

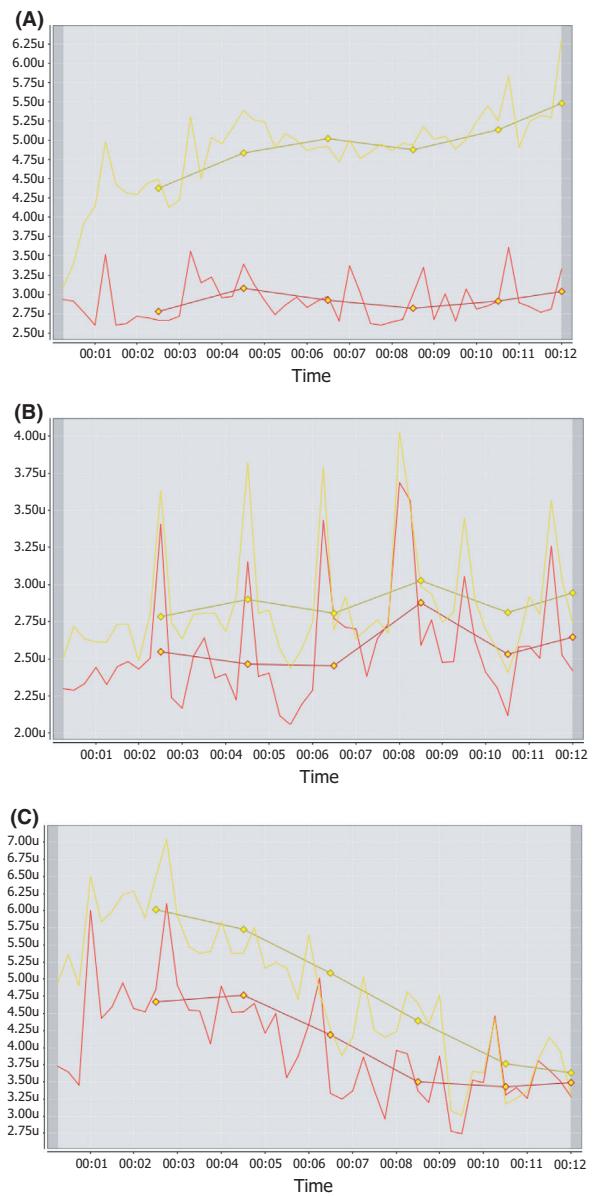


Figure 6. High-frequency (23–36 Hz) amplitudes (microvolts) in bilateral temporal lobes (T3 yellow, T4 red), for a 37-year-old man with insomnia, obtained from continuous EEG recordings (eyes closed) while listening to 12 min of white noise (A), random musical tones (B), and musical tones generated from HIRREM software algorithms (C).

shows high-frequency (23–36 Hz) amplitudes in bilateral temporal lobes during exposure to three different types of sounds for a 37-year-old man with insomnia (Insomnia Severity Index Score 18, indicating moderate clinical insomnia) who presented to a community-based setting for HIRREM provision. Prior to beginning the standard HIRREM assessment and proceeding with the HIRREM

intervention, the subject agreed to listen to three consecutive sets (12 min each) of “relaxing sounds” while undergoing continuous EEG recording (using HIRREM technology as described in High-resolution spectral analysis of electroencephalic data and dynamic, iterative engagement of dominant frequencies). The first two sound sets were commercially available sound generators for white noise (<http://www.simplynoise.com>) and random musical tones (Winchime 3.0; <http://www.sagebrush.com>). The third sound set was a HIRREM protocol for the temporal lobes. In the interval before the second and third sound sets, the subject rested (1 min) and participated in a digit-recall task (1 min). Figures 6A and B demonstrate a consistent left hemispheric dominance while the subject listened to white noise and random musical tones, and no change in the amplitudes over the course of the sound sets. Figure 6C demonstrates gradual quieting, with progressive reduction of amplitudes beginning at minute 1 and continuing through minute 9, as well as disappearance of the asymmetry midway through minute 9, while listening to the HIRREM tones.

Conclusion

Disturbances of neural oscillation have been reported with a variety of disease states, and there is a need for expansion of the repertoire of interventions which can positively impact oscillatory dynamics. The model of allostasis implies that brain functioning has consequences not only for neural systems but also for peripheral physiology, and thus further highlights the imperative for optimization of brain functional set points. Use of HIRREM, a noninvasive technology that creates sequences of resonance between neural oscillatory frequencies and musical tones, was associated with reduction of temporal lobe high-frequency asymmetry and fewer insomnia symptoms among individuals in a controlled clinical pilot trial. Studies are currently ongoing to further investigate potential applications of HIRREM and elucidate biophysical mechanisms of action.

Acknowledgments

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Conflict of Interest

L. Gerdes is the inventor of HIRREM technology, and CEO of Brain State Technologies LLC. P. Gerdes and S. W. Lee are employees of Brain State Technologies. C. H. Tegeler was the Principal Investigator for a pilot

clinical trial in 2011, evaluating HIRREM for insomnia. That study was supported by an unrestricted research grant to the Department of Neurology at Wake Forest School of Medicine from Brain State Technologies. The PI has received no salary support or other tangible benefits related to HIRREM technology, and has no other conflicts to report related to this work.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. List of sequential tones for a sample HIRREM exercise.

Audio File. Sample of HIRREM musical tones (1 min).

Open label, randomized, crossover pilot trial of high-resolution, relational, resonance-based, electroencephalic mirroring to relieve insomnia

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Abstract

Effective noninvasive interventions for insomnia are needed. High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM™) is a non-invasive, electroencephalography (EEG)-based method to facilitate greater client-unique, autocalibrated improvements of balance and harmony in cortical neural oscillations. This study explores using HIRREM for insomnia. Twenty subjects, with an Insomnia Severity Index (ISI) score of ≥ 15 (14 women, mean age 45.4, mean ISI 18.6), were enrolled in this randomized, unblinded, wait-list control, crossover, superiority study. Subjects were randomized to receive 8–12 HIRREM sessions over 3 weeks, plus usual care (HUC), or usual care alone (UC). Pre- and post-HIRREM data collection included ISI (primary outcome), and many secondary, exploratory measures (CES-D, SF-36, HR, BP, neurocognitive testing, and VAS scales). The UC group later crossed over to receive HIRREM. ISI was also repeated 4–6 weeks post-HIRREM. All subjects completed the primary intervention period. Analysis for differential change of ISI in the initial intervention period for HUC versus UC showed a drop of 10.3 points (95% CI: -13.7 to -6.9, $P < 0.0001$, standardized effect size of 2.68). Key secondary outcomes included statistically identical differential change for the crossed-over UC group, and persistence of the effect on the ISI up to > 4 weeks post-HIRREM. Differential change in the HUC group was also statistically significant for CES-D (-8.8, 95% CI: -17.5 to -0.1, $P = 0.047$), but other exploratory outcomes were not statistically significant. For all receiving HIRREM ($n = 19$), decreased high-frequency total power was seen in the bilateral temporal lobes. No adverse events were seen. This pilot clinical trial, the first using HIRREM as an intervention, suggests that HIRREM is feasible and effective for individuals having moderate-to-severe insomnia, with clinically relevant, statistically significant benefits based on differential change in the ISI. Effects persisted for 4 weeks after completion of HIRREM. Larger controlled clinical trials are warranted.

Introduction

Insomnia is the most prevalent sleep disorder and is associated with significant psychosocial and somatic pathology. Up to 50% of the U.S. adult population reports symptoms of insomnia on a weekly basis and approximately 12% meets criteria for insomnia disorder (Ohayon 2002). Cross-sectional studies demonstrate that 40–60% of individuals with insomnia exhibit depressive symptoms

(Foley et al. 1995; Ohayon et al. 1998), 10–25% may have clinical depression, and 20–30% have anxiety disorder (Ohayon and Roth 2003; Taylor et al. 2005). Chronic insomnia is associated with reduced quality of life, higher absenteeism, impaired job performance, and higher healthcare utilization (Kuppermann et al. 1995; Simon and VonKorff 1997). In a large population-based study, a linear relationship was demonstrated between insomnia prevalence and number of self-reported comorbid medical

disorders (Budhiraja et al. 2011). Insomnia severity has been correlated with suicidal thinking in a clinical trial population (McCall et al. 2010).

Although these cross-sectional associations are often interpreted to suggest that a variety of pathologies can result in secondary insomnia, prospective studies have found insomnia to be a risk factor for acute myocardial infarction (Laugsand et al. 2011) and depression (Jaussett et al. 2011). In long-term follow-up of 1741 individuals who had undergone polysomnography, insomnia was found to confer an independent and significantly increased risk for mortality (Vgontzas et al. 2010). The question of how or why insomnia should be a risk factor for other pathologies likely overlaps with the question of what processes are responsible for the pathogenesis of insomnia itself. To answer one or both of these questions, conceptualizations and data from several lines of inquiry may be helpful.

The “hyperarousal” theory (Perlis et al. 1997) highlights interplay between psychological and physiological factors in the etiology and perpetuation of chronic insomnia, including increased autonomic activity (Monroe 1967; Adam et al. 1986); activation of neuroendocrine and neuroimmunological axes (Vgontzas et al. 2001; Burgos et al. 2006), and altered brain metabolism, especially during the night (Nofzinger et al. 2004). For instance, compared with normal controls, insomnia patients show significantly increased ratio of low- to high-frequency spectral power (LF/HF, sympathetic activation) of heart rate variability (Bonnet and Arand 1998), increased production of cortisol (activity of the hypothalamic–pituitary–adrenal axis) and interleukin-6 (IL-6, activation of neuroimmunological axes) (Riemann et al. 2009), and increased power in higher frequencies as measured by spectral analysis of the sleep electroencephalogram (EEG) at sleep onset (Perlis et al. 2001a) and during nonrapid eye movement (REM) sleep (Perlis et al. 2001b). Greater amplitudes, as measured by event-related EEG potentials, were observed in several latency ranges prior to, during, and on awakening (Devoto et al. 2005; Steiger 2007; Yang and Lo 2007; Bastien et al. 2008). Taken together, these data suggest that heightened cortical arousal may be either part of the pathogenesis of chronic primary insomnia or a consequence of it, or both.

Disruption of biological rhythms is another way to model the etiology and sequelae of insomnia (Reid and Zee 2009). Virtually all physiological systems function on a rhythmic basis, and timing of their cycles is entrained through the influences of ambient light, physical activity, and feeding. Forced desynchronization of these systems by prolongation of a normal “day” from 24 to 28 h has been shown to cause reversal of the usual pattern of diurnal cortisol release, increases of insulin and post-

prandial blood glucose, and alterations in levels of epinephrine, norepinephrine, and leptin (Sheer et al. 2009). Technological advances with cultural and economic shifts encouraging round-the-clock stimulation may exacerbate or cause insomnia in susceptible individuals through desynchronization of physiological mechanisms from their otherwise endogenous rhythms. Individuals with shift-work sleep disorder, for example, have been found to have electrophysiological evidence of reduced sensory memory and hyperattention to novel sounds, compared with healthy day workers (Gumenyuk et al. 2010).

In convergence with the hyperarousal theory, it is well established that sleep disturbances including insomnia are common sequelae of traumatic stress (Spoormaker and Montgomery 2008; Charuvastra and Cloitre 2009; Pigeon et al. 2011). A review of polysomnographic studies found that individuals with post-traumatic stress disorder (PTSD) have reduced slow wave sleep (Kobayashi et al. 2007). Furthermore, it appears that pretraumatic sleep disturbance is a predictor for development of psychiatric morbidity after a traumatic event (Bryant et al. 2010). Thus, with respect to traumatic pathology as well, it appears that sleep disturbance may be not only a secondary phenomenon but possibly also a causal factor.

Fundamentally, the nature of what sleep itself “is,” has not been established with definitive consensus. A long tradition of investigation has conceptualized sleep as a global state under top-down, central regulatory control (e.g., Saper et al. 2005). This model describes competing homeostatic drives for sleep versus wakefulness and focuses on biochemical mediators of sleep including “sleep regulatory substances.” In contrast, a view of sleep focusing on synchronization of activity in local neural networks has been recently proposed (Krueger et al. 2008). In this model, local assemblies of neurons (individual cortical columns) synchronize with one another in an activity-dependent way (i.e., following a period of stimulation). Perhaps counterintuitively, some regions of the brain can be described as being in a “sleep-state” while other regions are “awake.” Global, whole-organism sleep is explained as an emergent property of the local networks.

Although the local network synchronization model does not exclude the role of metabolic factors (and pharmacological interventions) as primary initiators of local sleep states, it would appear that the model has potential to re-frame the approach to therapeutics in sleep medicine, given the physics of oscillatory synchronization (as well as the relative ease of measuring phenomena related to neural synchronization, e.g., through EEG). Therapeutic strategies that target neural oscillatory aspects of sleep, through nonpharmacological mechanisms, may be particularly attractive, in consideration of the risk of side effects

and dependency associated with many pharmacological interventions for sleep disorders.

High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREMTM, Brain State Technologies, LLC, Scottsdale, AZ) is a noninvasive approach to enhancing neurodynamic self-regulation by giving the brain an opportunity to perceive its own oscillatory pattern. HIRREM, also known as Brainwave OptimizationTM, uses sound (musical tones) to reflect the brain's changing pattern of frequency-specific electrical activity back to itself. In essence, the individual is given an opportunity to "listen" to his or her own brain. HIRREM musical tones are chosen on the basis of pattern-recognition algorithms in HIRREM software. Because of the identity between the dominant EEG frequency and the frequency of the musical tone, the phenomenon of resonance occurs between the individual's brain and the musical tones. The operational theory is that neural-musical resonance may be a mechanism for autocalibration of neural networks. Because the technology does not rely on entraining the brain toward operator-defined norms for the neural energetic ratios, HIRREM is considered a procedure for autocalibration of neural oscillations. Provision of the technology does not depend on clients' active cognitive engagement.

Use of HIRREM has been anecdotally associated with amelioration of a variety of symptoms including sleep complaints (L. Gerdens, pers. comm.), and so the aim of this pilot clinical trial was to evaluate the efficacy of HIRREM for relieving symptoms of insomnia. Our primary hypothesis was that the addition of HIRREM to usual care would be superior to usual care alone, for reduction of self-reported insomnia severity.

Methods

Participants

This single site study was carried out in the Department of Neurology at Wake Forest Baptist Health, an academic medical center in Winston-Salem, NC. A total of 20 men and women over the age of 18 having a clinical diagnosis of insomnia and an Insomnia Severity Index (ISI) score ≥ 15 were recruited by physician referral and by advertisements throughout the institution. This was a pilot superiority trial with no previous randomized clinical trials of HIRREM available on which to base power calculations. Subjects were excluded if they had a history of known sleep apnea, restless legs/periodic limb movement disorder, seizure disorder, urinary problems such as benign prostate hypertrophy, severe hearing impairment, or ongoing treatment with opiates, benzodiazepines, or antipsychotic medications. Subjects were requested to abstain from using alcohol or recreational drugs during,

and for 3 weeks following the HIRREM study period. Subjects were also advised not to undergo selected health care cointerventions including manual therapies during, and for 3 weeks following the HIRREM portion of the study. Additionally, participants were requested to refrain from caffeine consumption after 1:00 PM. All subjects were also instructed to continue their usual care, which was defined as whatever other medications or therapies, outside of those listed above as exclusions, that subjects were using prior to enrollment.

Study design

A randomized, unblinded, wait-list control, crossover, superiority study design was utilized, and the protocol was approved by the Institutional Review Board of Wake Forest School of Medicine, which did not require data safety and monitoring board oversight. The 20 subjects were randomly allocated using a blocked randomization design, with a block size of four, and a 1:1 ratio. The randomization scheme, utilizing sequentially numbered sealed envelopes containing group assignments, was created independently by a team member having no contact with the subjects, and was maintained secure by the principal investigator. Group assignments were made independent of team members enrolling the subjects. This resulted in 10 subjects being assigned to the wait-list usual care control group (UC) and 10 assigned to HIRREM plus usual care (HUC) groups. All subjects provided informed consent during an enrollment visit (V1), initial measures obtained, and past medical history obtained. During week #1, the HUC group received a HIRREM assessment and began HIRREM sessions which continued until week #4 (Fig. 1). During weeks #4 and #5, the HUC group returned for the study completion visit where post-treatment measures were obtained (V2). During weeks #5 and #6, the UC group returned for another data collection visit (V2). During week #7, the UC group had their brain energy assessments and began HIRREM sessions which lasted until week #9. During weeks #10 and #11, the UC subjects returned for study completion visits and HUC subjects were contacted for a telephone follow-up at least 4 weeks after their study completion visit. As usual care was maintained throughout the study, there was no washout period and no carryover effect needed to be calculated. There were no rules or restrictions placed on sleep hygiene or naps.

Primary intervention

The HIRREM intervention began with an initial assessment (45 min), which enabled identification of relative balance or symmetry between homologous brain regions,

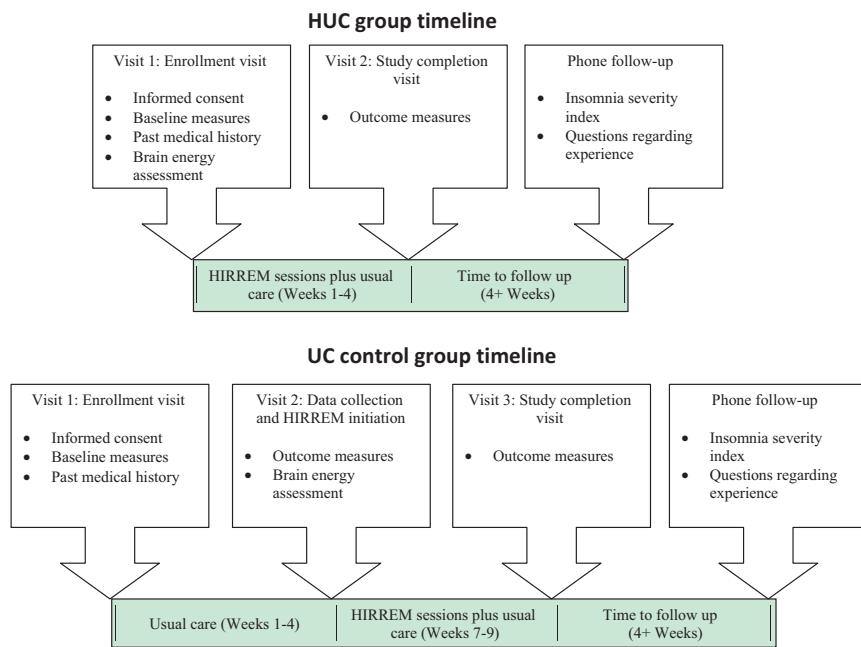


Figure 1. Timelines for occurrence of specific activities in the two groups (HUC and UC).

as well as the harmony or proportionation of energy among different frequency bands. The assessment was followed by a series of active HIRREM sessions (90 min each). The system uses unique sensors placed on the scalp according to standard International 10–20 EEG locations (Jasper 1958), and is held in place using standard EEG conductive paste. The sensors measure the frequencies (Hz) and amplitudes (μ V) of brain energy overlying the major lobes. The sensors utilize embedded computer chips to filter electromagnetic interference and artifact, allowing collection of precise frequency data to enhance resolution of the functional aspects of the brain. Two recording leads, two reference leads, and one ground were used in conjunction with an EEG preamplifier. Data were recorded and viewed with a Dell Precision T3500 PC running Windows Vista, and proprietary data collection software (Brain State Technologies, LLC, Scottsdale, AZ). For the assessment, measurements were taken at homologous regions of the bilateral hemispheres (F3/F4, C3/C4, T3/T4, P3/P4, O1/O2 for both eyes closed (EC; 1 min), eyes partially open (1 min), and eyes open (EO; 1 min) conditions, while the subject was seated. For EC, and eyes partially open assessments, subjects were asked to take a deep breath and relax. For EO assessments, subjects were given standardized tasks involving numerical digit recall (F3/F4), reading silently (C3/C4), math calculations (P3/P4), listening comprehension (T3/T4), and to relax with eyes open (O1/O2). A sixth midline measurement was taken at FZ/OZ, with an EO task to count number of

appearances of a specific word as they read a standardized printed passage. The reference sensors were connected at A1/A2 and linked for assessments (Fig. 2).

HIRREM sessions generally consisted of between four and eight individual HIRREM protocols, lasting between 6 and 10 min each. Protocols were intended to facilitate balance and harmony between and within brain regions. Individual protocols included up to two recording leads, two reference leads, and one ground lead using the same equipment as for the assessment. Most protocols (a combination of sensor montage and the specific software design) were two channel and recorded homologous regions of the contralateral hemispheres, but occasionally two channel, single-sided protocols or one channel protocols were used. The sensor locations and names largely corresponded to the expanded international 10-20 system; the 10-5 system (Oostenveld and Praamstra 2001).

During a protocol, and with sensors in place over the desired scalp locations, a mathematical algorithm selected the musical tone to be reflected back to the user by identifying the dominant frequency of the individual's EEG spectrum in a floating middle range, at a given instant of time. The dominant EEG frequency was then translated to a musical tone based on that frequency. The musical tone was played back to the individual through earphones, and presented binaurally with less than a 25-msec delay. Resonance between the musical tones and oscillating neural circuits was presumed to facilitate autocalibration and movement toward improved balance and harmony. Some

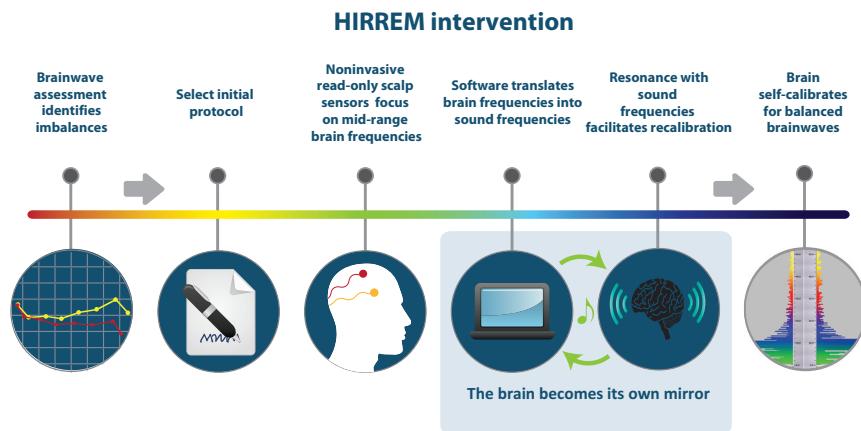


Figure 2. Schematic of key components of the HIRREM intervention.

protocols were accomplished with eyes open (rostral brain regions) and some with eyes closed (caudal brain regions).

Subjects received 8–12 HIRREM sessions, of up to 90 min per session. The number of sessions was guided by the balance and stability of the energetic pattern and neurodynamics seen during HIRREM sessions. Subjects had two HIRREM sessions in a half day, separated by a 30- to 60-min break. The majority of clients underwent four sessions in a 2-day period, and all clients completed their HIRREM sessions within 3 weeks of beginning, with most administered during the day. Each HIRREM session comprises 4–8 protocols focused on balancing specific frequencies in targeted locations on the scalp. HIRREM sessions were administered by experienced technologists who were certified in the methodology by Brain State Technologies. During sessions, subjects were encouraged to recline in a zero gravity chair (PC⁶, Human Touch, LLC, Long Beach, CA).

Outcome measures

The primary outcome measure was the ISI (Bastien et al. 2001). All other outcomes were secondary, or exploratory. Outcome measures were obtained during the enrollment visit, post-treatment visit, and for the UC group at the repeat data collection visit (V3). Patients responded to the pencil and paper tests: ISI (primary outcome), the Center for Epidemiologic Studies Depression Scale (CES-D), the SF-36 health and well-being survey, the Medical Outcomes Survey Sleep Scale (MOS-SS), the Connor–Davidson Resilience Scale, and Visual Analogue Scales (VAS) for stress, depression, anxiety, fatigue, pain, relaxation, and overall well-being. A computerized battery of neuropsychological measures, was also administered to assess neuropsychological and psychophysiological function in multiple domains including verbal memory, visual memory, finger

tapping, symbol digit coding, Stroop testing, shifting attention, and continuous performance (CNS Vital Signs, Morrisville, NC). Physiological data collected included blood pressure (BP) and a 10-min continuous recording of heart rate recording with the subject at rest. The heart rate recordings were made using the Bioharness (Biopac Systems, Inc., Goleta, CA), a noninvasive chest strap worn by the participants. The heart rate recordings included beat to beat intervals, and the data could be processed to obtain heart rate variability (HRV) data. HRV statistics which could be generated included mean, variance, standard deviation of normal to normal RR intervals (SDNN), square root of the mean squared difference of successive normal to normal RR intervals (RMS-SD), very low frequency (VLF), LF, HF, total power (TP), LF/HF, sample asymmetry, sample entropy, and coherence. All of the algorithms for computation of these parameters are derived from information or source code from the Physionet archive (Goldberger et al. 2000).

Follow-up and safety

All outcome measures were recorded before the study began and before crossover for both groups. Only the UC group repeated all measures after the crossover intervention. Both groups had repeated ISI at a final phone follow-up at 4 or more weeks after completion of the HIRREM intervention. No adverse events or side effects were reported by any participant at any point in the study.

Statistical analysis

All analyses were conducted using SAS 9.2 (SAS, Inc., Cary, NC). Because this is a pilot trial, no a priori power calculations were conducted prior to initiating enrollment; sample sizes were selected based on a sufficient number to

estimate the treatment effect size. The primary and secondary analyses were conducted using multilevel random effects models. For the primary outcome, ISI score was modeled specifying random intercepts for participants (i.e., accounting for variance in the initial levels of insomnia across participants at baseline) with group (HUC vs. UC) and time (baseline vs. post-treatment) as fixed effects. The group \times time interaction was interpreted as the differential change of the HUC group compared with the UC group. Secondary outcomes were similarly modeled, with the follow-up period added to examine the duration of change. To estimate the size of effect, Cohen's d was calculated for all outcome measures to index the size of the group differences in terms of within-group standard deviations (e.g., 1.2 standard deviation difference between the groups). Although arbitrary ranges, standard deviation differences ≤ 0.2 are often considered "small," $d = 0.5$ are considered "medium," and $d > 0.80$ are "large." Descriptive statistics are presented as means (SD) or frequency counts (%) as appropriate. All point estimates of differential change are presented with 95% confidence intervals. Where appropriate, all hypothesis testing is two-tailed with $P < 0.05$ interpreted as statistical significance.

Results

Baseline data and subject flow

A total of 28 subjects were enrolled in the study at Wake Forest Baptist Health (Fig. 3). Recruitment took place from March 1, 2011, through May 1, 2011. Twenty participants were assigned to either the wait-list UC or HUC group. Demographics and baseline characteristics (Table 1) were not statistically different between the two groups. There were slightly more comorbidities noted in the HUC group (Table 2). Antidepressants were used by three subjects in the HUC group, and one in the UC group. All patients continued their usual care throughout the course of the study; HIRREM was added to usual care during the primary intervention epoch. All subjects completed the primary intervention period, and primary data collection visits. All 10 participants in the HUC group received HIRREM (mean of 10.3 sessions) and nine of 10 UC subjects subsequently received HIRREM after crossover. One in the UC group had a job change and the schedule prevented further participation. One subject from each group receiving HIRREM was not available for the late telephone follow-up.

Primary outcome

Mean baseline ISI for each group was identical, at the enrollment visit (mean = 18.6, $P = 1.0$). The primary

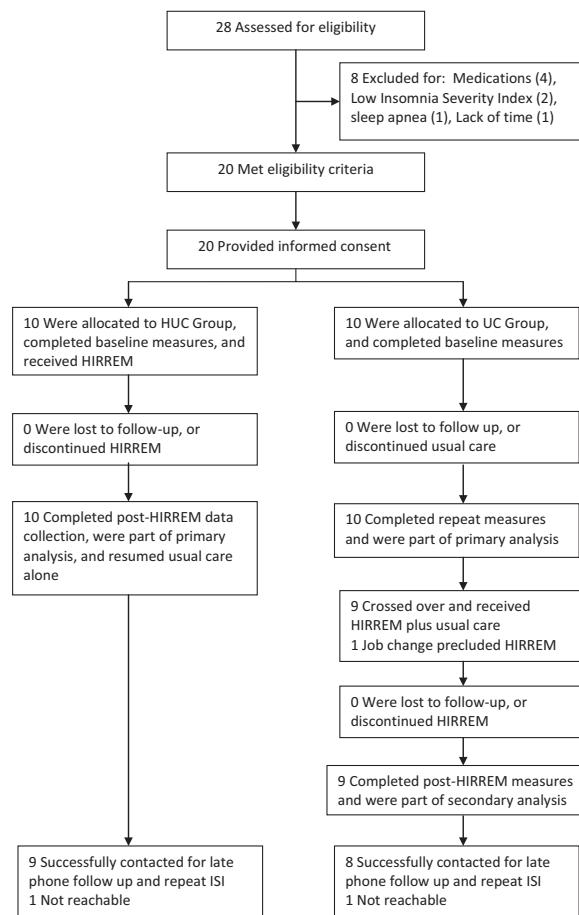


Figure 3. Subject recruitment and flow through the study.

Table 1. Baseline demographics.

	HUC intervention group (SD)	UC control group (SD)
N	10	10
Mean age	41.3 (17.5)	49.5 (8.1)
Women/Men	8/2	6/4
Ethnicity	9/10 Caucasian	10/10 Caucasian
Mean baseline ISI	18.75 (2.7)	18.9 (3.2)
CES-D	17.1 (11.1)	12.6 (7.1)
SF-36: General health	72 (28.0)	69 (20.4)
Systolic blood pressure	115.7 (9.6)	116.2 (9.4)
Heart rate	74.4 (12.8)	71.6 (9.5)

HUC, HIRREM plus usual care; UC, usual care; ISI, Insomnia Severity Index; CES-D, Center for Epidemiologic Studies Depression Scale.

outcome for the study, analysis for differential change in the ISI at V2 (Fig. 4), showed a statistically significant drop of 10.3 points (-13.7 to -6.9 ; $P < 0.0001$). Standard effect size (Cohen's d) was 2.68 for change in ISI.

Table 2. Self-reported comorbidities.

Medical condition/Comorbidity	HUC intervention group	UC control group
Hypertension	2	2
Hyperlipidemia	3	1
Headaches/Migraine	3	0
Stress/Anxiety disorder	2	1
Depression	3	2
Trauma/TBI	1	1

HUC, HIRREM plus usual care; UC, usual care; TBI, traumatic brain injury.

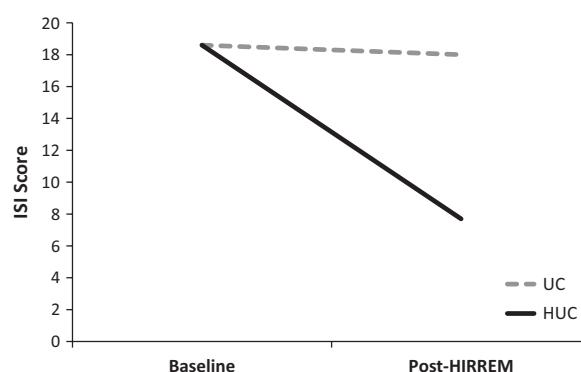


Figure 4. Baseline and post-HIRREM Insomnia Severity Index (ISI) scores for usual care (UC) and HIRREM plus usual care (HUC) groups. Differential change: -10.3 (95% CI: -13.7 to -6.9), $P < 0.0001$.

Secondary outcomes

The UC group was then offered crossover to receive HIRREM. There was no statistical difference for analysis of differential change in the ISI following HIRREM intervention between the HUC group and the crossover UC group. The ISI was also administered at a telephone follow-up at least 4 weeks following completion of the HIRREM intervention. The improvement in insomnia symptoms reported following completion of the HIRREM sessions persisted through that period (Fig. 5).

Considering clinical threshold correlates for insomnia, based on the differential change in mean ISI, the HUC group improved to just under the cut point for subthreshold insomnia category, while the UC group remained in the moderate insomnia category (Table 3). As a way to consider clinically relevant changes for individual subjects, the number of subjects in each category, before and after each study epoch, shows that 9/10 in the UC group remained in the moderate-to-severe insomnia category, while 9/10 in the HUC group moved to the no insomnia or subthreshold categories following HIRREM. Following crossover and receipt of HIRREM, 6/9 in the

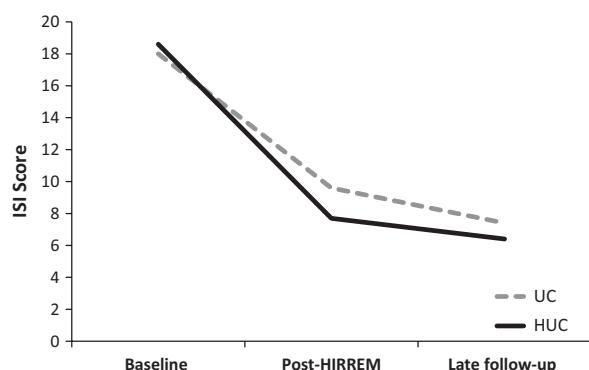


Figure 5. Baseline to post-HIRREM changes in Insomnia Severity Index (ISI) scores for usual care (UC) and HIRREM plus usual care (HUC) groups after cross-over, with 4- to 6-week late follow-up ISI scores.

UC group also improved to no insomnia or subthreshold insomnia, and the effects persisted with late follow-up after HIRREM for both groups.

Differential change in the CES-D score during the primary intervention period reached statistical significance with a drop of 8.8 points (-17.5 to -0.1 ; $P = 0.047$). Differential change was not statistically significant for the total SF-36 score, which increased by 4.0 (-6.8 to 14.8 ; $P = 0.446$), but there were small effect sizes for some components of the SF-36, with effect size values ranging from 0.07 for physical function to 0.58 for energy and fatigue. There were also no statistically significant changes for the neurocognitive measures, although several domains, psychomotor speed (0.38), neurocognitive index (0.24), and complex attention (0.22) showed small effect sizes. Due to the small sample size, there was inadequate power for analysis of other secondary and exploratory outcome measures. Poor technical quality of recordings precluded analysis of HRV measures.

Exploratory analysis of changes in the brain pattern following HIRREM, for all those who received HIRREM ($n = 19$), suggested that there was a decrease in the overall power in high frequencies (23–36 Hz) at the temporal lobes in the T3/T4 location (Fig. 6), over the course of the required minimum of eight HIRREM sessions. The median for log transformed mean power values showed a steady decline over the first four HIRREM sessions. The median for high-frequency power then appeared to oscillate, seemingly around a lower set point, for the remaining sessions.

Discussion

This study represents the first use of HIRREM in a randomized clinical trial. HIRREM was a feasible, effective

Table 3. Changes in clinical category for insomnia after HIRREM based on ISI scores.

Clinical category by ISI score	HUC intervention group			UC control group			
	Pre	Post	Late phone F/U	Pre	Post	After crossover HIRREM	Late phone F/U
No clinically significant insomnia (0–7)	0	5	5	0	0	2	5
Subthreshold insomnia (8–14)	0	4	4	0	1	4	1
Moderate insomnia (15–21)	9	1	0	7	8	3	3
Severe insomnia (22–28)	1	0	0	3	1	0	0

HIRREM, high-resolution, relational, resonance-based, electroencephalic mirroring; HUC, HIRREM plus usual care; UC, usual care; ISI, Insomnia Severity Index.

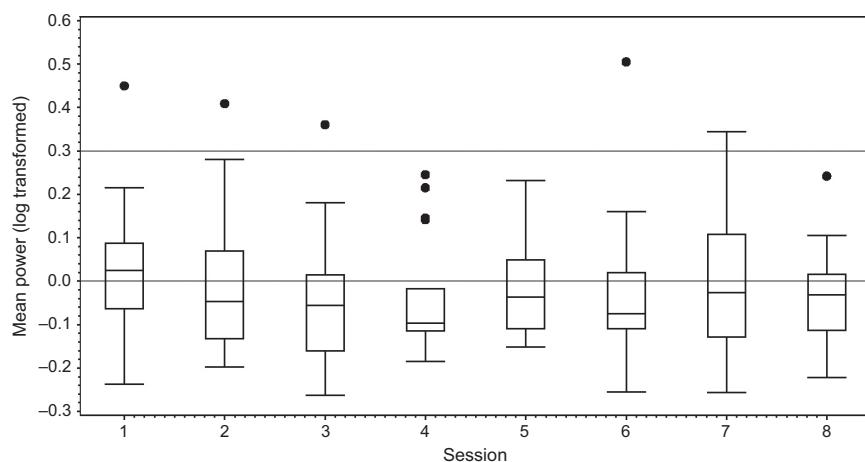


Figure 6. Tukey box plot of mean power (log transformed) in the high-frequency (23–36 Hz, "80") range at the temporal locations (T3 and T4, averaged together), over the course of eight HIRREM sessions, $n = 19$ subjects.

intervention for such an outpatient population, and appeared both safe and well tolerated. Based on our primary outcome measure of differential change in the ISI score, as an addition to usual care, use of HIRREM was associated with an improvement of insomnia symptoms in this study population of subjects with moderate-to-severe insomnia. The standard effect size suggested that as applied during this study, HIRREM had a strong effect. Based on telephone follow-up done at least 4 weeks following HIRREM, the improvement in ISI persisted. When crossed over to receive HIRREM, those in the UC group showed similar differential change in the ISI, with similar persistence of the effect on late telephone follow-up. When considered in light of clinical correlates with the ISI, nine of 10 subjects in the HUC group moved to an ISI score in the no insomnia or subthreshold insomnia categories. Following crossover, and receipt of HIRREM intervention, six of nine in the UC group also moved to no insomnia or subthreshold insomnia categories, suggesting clinically relevant changes in this population following HIRREM.

Among other secondary outcomes, differential change (improvement) in the CES-D measure of depression just reached statistical significance, while there was no significant change in formal measures of overall health and well-being (SF-36), or neurocognitive function, as measured by a computerized neurocognitive battery. Depression is closely intertwined with insomnia, and future studies may help elucidate whether improvement in either sleep or mood appears to be causal to improvement in the other. The small sample size and the specific measures used do not allow identification of a specific effect for depression.

Although the exact mechanism of action of HIRREM has not yet been confirmed, the secondary finding of a decrease in overall high-frequency power in the temporal lobes may provide some insights. Exploratory analysis of brain changes was focused on the temporal lobes based on the supposition that temporal lobe activity may reflect autonomic functioning. Craig (2005) has reported a neuroanatomical basis for lateralization of autonomic nervous system management by the right and left insula for the

sympathetic and parasympathetic divisions, respectively. Thus, increased overall power in the temporal lobes, if reflective of activation of autonomic functioning, is consistent with the hyperarousal theory regarding the underlying mechanism for insomnia. Quieting of high-frequency power in the temporal lobes could be understood as mitigating an underlying driver of insomnia.

Limitations

The limitations of this study include a small sample size, as well as the use of a wait-list usual care control group rather than an active control, or sham-placebo group. Because the study design entailed usual care for the control group, without blinding as to the intervention, it is not possible to rule out placebo or expectation effects as contributors to the improvements associated with the HIRREM intervention. HIRREM, like other interventions which entail social interaction and relaxation induction, may facilitate improvements not only through auditory tonal mirroring of dominant electroencephalic frequencies but also through nonspecific mechanisms. Placebo biofeedback interventions, for example, have in some cases been shown to offer benefits comparable to true biofeedback (Nicassio et al. 1982; Hunyor et al. 1997). Nonetheless other studies have reported that true biofeedback is more efficacious than placebo biofeedback (Henderson et al. 1998; Aramagan et al. 2003; Becerra et al. 2006; Rao et al. 2007; Basta et al. 2011). The degree of improvement, and the standard effect size, coupled with persistence of benefit for at least 4 weeks following completion of HIRREM suggests the presence of a real change. In addition, subjects in both groups continued their usual care throughout the course of the study. It is unclear whether HIRREM alone would achieve the results observed or if combination is necessary. Placebo-controlled studies of HIRREM are warranted, and future studies should include physiological outcomes and follow-up to evaluate persistence of effect.

Conclusion

In this pilot clinical trial, the use of HIRREM in subjects with insomnia was feasible and effective and was safe and well tolerated. Based on differential change for a subjective clinical insomnia outcome measure, HIRREM improved insomnia compared with continuation of usual care alone. This appeared to be a strong effect based on the standard effect size, and the effect persisted for at least 4 weeks following HIRREM. The CES-D also showed improvement. Exploratory analysis suggested changes in brain pattern having relevance to the hyperarousal theory of insomnia, with potential implications

for understanding the mechanisms of HIRREM for individuals with insomnia. This study suggests a need for additional controlled clinical trials to both confirm the effect and further explore possible mechanisms of action.

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Conflict of Interest

None of the authors from Wake Forest School of Medicine have conflicts of interest, nor any direct financial relationships, or hold positions with Brain State Technologies, LLC. Sung Lee, MD, MSc, is Research Coordinator for Brain State Technologies. Lee Gerdes is the inventor of the HIRREM technology, and CEO of Brain State Technologies, LLC.

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