

Effects of an Allostatic Closed-Loop Neurotechnology (HIRREM) on Brain Functional Connectivity Laterality in Military-Related Traumatic Stress

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ABSTRACT

BACKGROUND AND PURPOSE: Brain asymmetries are reported in posttraumatic stress disorder, but many aspects of laterality and traumatic stress remain underexplored. This study explores lateralization changes in resting state brain network functional connectivity in a cohort with symptoms of military-related traumatic stress, associated with use of a closed-loop neurotechnology, HIRREM.

METHODS: Eighteen participants (17 males, mean age 41 years [SD = 7]) received 19.5 (1.1) HIRREM sessions over 12 days. Whole brain resting magnetic resonance imaging was done pre- and post-HIRREM. Laterality of functional connectivity was assessed on a whole brain basis, and in six predefined networks or regions. Laterality of connectivity within networks or regions was assessed separately from laterality of connections between networks or regions.

RESULTS: Before HIRREM, significant laterality effects of connection type (ipsilateral for either side, or contralateral in either direction) were observed for the whole brain, within networks or regions, and between networks or regions. Post-HIRREM, there were significant changes for within-network or within-region analysis in the motor network, and changes for between-network or between-region analyses for the salience network and the motor cortex.

CONCLUSIONS: Among military service members and Veterans with symptoms of traumatic stress, asymmetries of network and brain region connectivity patterns were identified prior to usage of HIRREM. A variety of changes in lateralized patterns of brain connectivity were identified postintervention. These laterality findings may inform future studies of brain connectivity in traumatic stress disorders, with potential to point to mechanisms of action for successful intervention.

Keywords: Functional MRI, HIRREM, laterality, network connectivity, posttraumatic stress.

Acceptance: Received April 8, 2019, and in revised form November 30, 2020. Accepted for publication December 1, 2020.

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Acknowledgments and Disclosures: Katelyn McNab provided assistance with statistical analyses. Nancy C. Buchheimer assisted with the IRB approval and research grant management. Lindsay J. Howard and Krystal D. Schmidt helped with provision of the HIRREM intervention and the organization of data for analysis. Dr. Hossam A. Shaltout created Figures 2-4. The primary financial support for this study was through the Joint Capability Technology Demonstration Program within the Office of the Under Secretary of Defense (Acquisition, Technology, and Logistics) via a contract with the U.S. Special Operations Command (H92222-14-P-0012). It is also supported by a research grant from The Susanne Marcus Collins Foundation, Inc. Sean L. Simpson was supported by NIBIB R01EB024559, and Wake Forest Clinical and Translational Science Institute (WF CTSI) NCATS UL1TR001420. Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the Department of Defense. All coauthors affiliated with Wake Forest University or Wake Forest School of Medicine have no conflicts to report. Dr. Sung W. Lee was previously an employee of Brain State Technologies, and Lee Gerdes is employed by Brain State Technologies.

J Neuroimaging 2021;31:287-296.

DOI: 10.1111/jon.12825

Introduction

Numerous studies have reported relative brain asymmetries in populations with posttraumatic stress disorder (PTSD), compared to controls with or without a history of trauma. Structural neuroimaging has shown asymmetrical volumes of the hippocampus, amygdala, and other limbic regions,¹⁻⁵ as well as in the cerebellum.⁶ Researchers have demonstrated asymmetrical patterns of activity, in frontal regions⁷⁻¹¹ and also temporoparietal regions.^{7,8,12-15} Some of these investigations have been mo-

tivated by a model positing that the left and right prefrontal cortices mediate approach and withdrawal behavioral tendencies, respectively,¹⁶ and more recent studies have examined asymmetry with a focus on specific symptom clusters within PTSD¹⁰ or on the basis of trait versus state physiology.¹¹ Another impetus for such studies is provided by the bihemispheric autonomic model (BHAM) that suggests that traumatic stress may produce dominant and maladaptive asymmetries in the activity of homologous brain regions responsible for efferent autonomic

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signaling.¹⁷ BHAM posits that arousal producing stressors may be associated with rightward dominance in brain regions related to autonomic management, whereas chronic stress may produce parasympathetic immobilization mediated by leftward dominance in those same regions, and therefore predicts that facilitation of adaptive symmetry across critical brain regions could be an important target for clinical interventions.

The current investigation extended the study of brain asymmetries associated with chronic stress by focusing on the lateralization of functional connectivity rather than structural or brain activation asymmetries per se. This reflects what Menon¹⁸ has characterized as a paradigm shift in the understanding of psychiatric and neural disorders based on the analysis of alterations in functional connectivity within and between large scale intrinsic (resting state) brain networks. Studies of functional connectivity emphasize correlations in activity over time between different brain regions or nodes. Application of the tools of graph theory and network science to these data has identified relatively stable and consistent patterns of connectivity that have been used to define the large scale intrinsic brain networks Menon refers to (see Bullmore and Sporns¹⁹ for a review of network science applications to brain imaging).

Menon's triple network model of pathology¹⁸ highlights alterations in functional connectivity and interactions between the default mode (DMN), salience (SN), and central executive (CEN) networks as key to understanding disturbed psychological and cognitive functioning. The default mode network includes medial prefrontal cortex, the precuneus and posterior cingulate, lateral temporoparietal cortex, and the medial temporal lobe. It is implicated in self-referential thought and interoceptive processing.²⁰ The salience network includes the insula, amygdala, dorsal anterior cingulate, and the frontal poles. SN detects and processes autonomic and emotional information and directs behavior toward relevant events.²¹ The central executive network includes dorsolateral prefrontal and posterior parietal cortex and is implicated in attention and executive functioning.^{21,22} In general, the model assumes co-activation of the SN and CEN, and deactivation of the DMN, when attention is directed outward, and the opposite pattern during inwardly focused thoughts. Consistent with this model, alterations in connectivity and interactions between the default mode network, the salience network, and the central executive network have been observed in depression,²³ Alzheimer's disease,²⁴ and schizophrenia.²⁵

Also consistent with Menon's model, multiple studies have reported altered functional connectivity patterns within and between these networks during resting states and while viewing emotionally salient stimuli in PTSD samples.²⁶⁻³⁰ Among relevant findings are disturbances in the connectivity of the DMN, disturbances in switching between DMN and CEN while viewing salient stimuli, and altered SN and CEN connectivity. However, research specifically looking at the lateralization of functional connectivity in this population is lacking. The present study offers a first step toward filling this void by examining the lateralization of brain functional connectivity during a resting state observed in a cohort with symptoms of military-related traumatic stress, before and after use of a neurotechnological clinical intervention designed to support symmetry in brain activation patterns.

The intervention used for this study, High-resolution, relational, resonance-based electroencephalic mirroring

(HIRREM[®], Brain State Technologies, Scottsdale, AZ), is a noninvasive, closed-loop feedback, acoustic stimulation neurotechnology.³¹ Two-channel scalp recordings monitor brain electrical activity at high spectral resolutions. Specific frequencies are translated in real time into auditory tones of varying pitch and timing, and are echoed back via ear buds with as little as 4-8 milliseconds delay. The intention is to support autocalibration, self-adjustment, and relaxation of neural oscillatory dynamics, and shifts are observed toward improved hemispheric balance, as well as reduced hyperarousal.³² The theoretical basis for HIRREM is supported by the paradigm of allostasis.³³

The use of HIRREM has been associated with significant reduction of self-report symptoms of insomnia,³⁴ persisting symptoms following athletic concussion,³⁵ and perimenopausal symptoms,³⁶ as well as improved objective measurements of autonomic cardiovascular regulation (heart rate variability and baroreflex sensitivity).³⁷ Clinical outcomes associated with application of HIRREM for participants enrolled in the present study included significant improvements in multiple measures of autonomic cardiovascular regulation (SDNN, rMSSD, high frequency, low frequency, and total power, HF Alpha, sequence all, and systolic, diastolic, and mean arterial pressure) and significant reductions in self-reported symptom inventory scores to 6 months following intervention completion (PTSD, insomnia, depression, and anxiety).

The PTSD Checklist–Military inventory (PCL-M)^{38,39} was used to evaluate symptoms of traumatic stress, which was of primary interest for this cohort. A drop of 10 points is considered as a clinically meaningful difference.⁴⁰ Through the follow-up data collection 1 month following intervention completion, 83% of subjects reported PCL-M scores that were at least 10 points lower than their baseline score. Significant reductions were durable through 6 months postintervention. There were also changes in network connectivity on whole brain, rest functional magnetic resonance imaging (fMRI).⁴¹

Based on the observed clinical changes, a theoretical orientation such as BHAM might predict a corresponding shift toward a more symmetric laterality profile. That prediction would be based on activity per se. Because the present study instead assessed the laterality of functional connectivity, the predictions are more tenuous. Previous assessments of the lateralization of brain networks assessed using functional connectivity analyses in a normal population have found differences both between networks and within networks. In one comprehensive study of normal, functional connectivity of the default mode, network was left lateralized, whereas the visual network was strongly right lateralized. Different components of the attention network and the frontal networks were left and right lateralized. Components of the sensorimotor network were left and right lateralized, although the degree of left lateralization was more pronounced. Finally, a basal ganglia network was symmetrical.⁴² Given the exploratory nature of the present study, the strongest a priori predictions would be that there would be an imbalance in networks specifically associated with alterations in PTSD such as the salience network prior to treatment, and that such imbalance would be decreased posttreatment.

In the present report, the lateralization of functional connectivity was assessed using the networks in Menon's triple model (DMN, SN, and CEN) as possible loci, along with the basal ganglia because of previous research linking it to PTSD,⁴³ as

well as motor cortex and visual cortex areas included in order to provide more complete coverage of the brain. Each of these areas was composed of multiple nodes in the network analysis. Lateralization of functional connectivity was determined by counting the number of links from all nodes in a given network or region to other nodes in the same network or region, to the homologous network or region on the contralateral side of the brain, or to other nodes outside of the network or region on the ipsilateral or contralateral side of the brain. These analyses were performed before and after the HIRREM clinical intervention in order to determine whether that intervention affected the lateralization of functional connectivity.

Methods

Participants

Eighteen participants (17 male; mean age = 41 years, SD = 6.9) were enrolled in an IRB-approved open label pilot study conducted in the Department of Neurology at Wake Forest School of Medicine (Clinicaltrials.gov registration NCT03230890). Participants were either active duty members of the military (15) or recent Veterans (3). All participants were over the age of 18, and all had been either formally diagnosed with PTSD, had received medical treatment for traumatic stress symptoms, or had current symptoms indicative of PTSD based on a PCL-M score of 50 or greater. Participants reported a mean of 20.5 years in service (8-33), with eight deployments (2-19), and reported having had symptoms of PTS lasting from 1 to 25 years. Of the 11 individuals who reported previous use of a psychoactive or sleep-related medication, 10 had made recent adjustments to their regimen (withholding or discontinuing a medication that would entail exclusion) under the guidance of their medical provider. Eight participants had previously received cognitive behavioral therapy or psychotherapy. The most prevalent self-reported co-morbid health conditions included prior traumatic brain injury or concussion (15), insomnia (11), impaired memory or cognitive ability (10), depression (9), stress or anxiety (9), and tinnitus (9). Participants were recruited from a variety of sources: The Care Coalition, which serves the needs of the Special Operations community, physician referral from military facilities, physician referral from the community, referral from prior participants, or response to posted advertisement. Exclusion factors included severe hearing impairment, known seizure disorders, or the need for ongoing use of benzodiazepines, antipsychotics, antidepressants, opiates, sleep medications, stimulants, or thyroid hormones. Participants were instructed to refrain from recreational alcohol or drug use during the course of the study. There were no dropouts or serious adverse events reported.

HIRREM Sessions

Following informed consent, and as part of the enrollment data collection, baseline recordings were initially obtained for each participant in an assessment session of 45 minutes using two-channel, three-minute recordings from at least six paired locations on the scalp (F3/F4, C3/C4, P3/P4, T3/T4, FZ/OZ, O1/O2, FP1/FP2, and CB1/CB2). Recording for each location entailed 1 minute with eyes closed, 1 minute with eyes partially closed, and 1 minute with eyes open and performing cognitive tasks such as recalling numerical stimuli or reading from a passage.

Brainwave data from the baseline recordings were used to create individualized protocols for the initial HIRREM sessions, whereas review of data from the prior session was used for subsequent sessions. Duration of sessions was approximately 1.5-2 hours. Typically, two sessions were completed daily, with a short break (20-60 minutes) between them. Each session consisted of between four and 10 HIRREM protocols lasting between 5 and 40 minutes each. In these protocols, specific brain frequencies are translated into audible tones in real time that are echoed back to the participant through headphones in as little as 4 microseconds. Protocols were received with the participant sitting or reclining in a chair (Human Touch PC-6). Some protocols were received with eyes open and others with eyes closed, depending mostly upon the function of the lobe being observed based on scalp location during that particular protocol. The majority of the protocols received were with eyes closed to support the brain's internal regulation and reset. Specific protocols (varying scalp locations, design, and duration) were chosen by trained Technologists with an aim of supporting increasing hemispheric symmetry and optimal proportions of oscillation in specified frequency ranges, while keeping session duration to about 1.5-2 hours. The mean number of sessions was 19.5 (SD = 1.1) administered over a period of 12 days.

MRI Data Acquisition

Brain imaging was done using MRI two times: once before and once just prior to departure, after completion of the HIRREM intervention. Due to scheduling needs, one participant's second scan was performed just prior to the final HIRREM session, but after completion of 18 of his 19 sessions. MRI data were acquired in a 3T Siemens Magnetom Skyra using a 32 channel head coil. Anatomical images were collected using a Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence. fMRI images based on the blood oxygenation level-dependent signal were acquired using echo planar imaging. Data used in the present report were acquired while the participants were in an eyes open resting state while focusing on a fixation point. Data were also collected in an eyes-closed resting state, but these were not explored further because previous analyses of the present population found no difference between the eyes open and eyes closed conditions.⁴⁴ The MPRAGE was acquired in a sagittal plane using TR = 2,300 ms; voxel dimensions = .98 × .98 × 1.22 mm; 256 × 256 voxels; slice thickness = 1 mm. fMRI data were acquired in the axial plane using 187 images with TR = 2,000 ms and voxel dimensions of 4 × 4 × 4 mm with a resulting total scan time of 6 minutes and 14 seconds.

Brain Network Generation

Image processing used SPM8 software (<http://www.fil.ion.uel.ac.uk/spm/>) and MATLAB scripts previously developed in house. The MPRAGE was transformed into the axial plane and warped to fit Montreal Neurological Institute (MNI) space using SPM8. The initial 8 volumes were removed from the fMRI data. Images were subsequently realigned to the first image in the series and coregistered with the structural image. The fMRI images were then normalized into MNI space using the transformation that was applied during warping of the structural image. Only voxels that overlapped with gray matter in the Automated Anatomical Labeling (AAL) atlas were retained in order to limit the analyses to gray matter. Physiological noise and

low-frequency drift were removed using a band-pass filter of .009-.08 Hz.⁴⁵ The six rigid-body transformation parameters created during the realignment process and global mean time course for whole brain, whiter matter, and cerebrospinal fluid were regressed out of the functional data,⁴⁵ and image volumes with excessive motion were removed.⁴⁶

Network analyses used MATLAB scripts. Gray matter voxels obtained from the preprocessed functional data were used to create voxel-based networks for each participant. The Pearson correlations between the time series for each voxel and every other voxel were calculated. The resulting correlation matrices were thresholded to remove weak links based on formula $N = K^S$ where N = number of nodes in the network, K = average degree or number of connections per node in the network, and $S = 2.5$. Analyses in the present paper focused on the networks created using the threshold of 2.5 based on previous research showing that that value yields networks with size to density ratios comparable to other naturally occurring networks.⁴⁷ This yielded networks that were undirected and unweighted with approximately equal densities across participants.⁴⁸

The regions of interest (ROIs) selected for individual network and region analyses were selected as follows: The attention network (analogous to the Central Executive Network per Menon), default mode network, and salience networks were derived from Menon's triple network model¹⁷ and defined using the coordinates in Shirer and colleagues.⁴⁹ These consisted of large-scale and overlapping brain regions. The basal ganglia, visual, and motor networks were defined using the scaled inclusivity from Moussa et al.⁵⁰ These maps identify functional communities across a population of 194 people and a minimum scaled inclusivity of 25 was used to threshold the networks. All left-right assignments for these regions were based on the AAL atlas. The ROIs are shown in Figure 1.

Analyses

The laterality of functional connectivity was assessed first on a whole brain basis, and then in the six different specific networks or regions previously noted. For those networks or regions, the laterality of within-network or region connectivity was analyzed separately from the lateral connections between networks or regions. Because of previous findings that gender may affect the lateralization of functional connectivity,⁴⁴ the analyses reported below were performed both with and without the one female participant. The exclusion of this participant did not change any of the statistical conclusions and therefore the analyses reported include the data from all participants.

Results

Whole Brain Connectivity Pre- and Post-HIRREM

Connections across the whole brain were characterized in terms of whether they were between two left hemisphere nodes, two right hemisphere nodes, or between a left and a right hemisphere node. The mean number of connections of each type is shown in Figure 2. Because the networks constructed were undirected, the contralateral connections do not differentiate between left to right and right to left connections.

A 3 (type of connection: ipsilateral LL, ipsilateral RR, or contralateral LR or RL) \times 2 (time of testing, pre- vs. post-HIRREM) repeated measures analysis of variance was used to analyze lateralized differences in connectivity at the whole

brain level. This analysis yielded a significant main effect of connection type ($F(2,34) = 4.41, P < .05$), but no effect of time and no interaction of type of connection with time. Subsequent paired t -tests averaging across time showed that there were significantly more contralateral connections than L-L connections in the whole brain data ($t(17) = -3.55, P < .01$). In addition, there were marginally more R-R connections than L-L connections ($t(17) = -1.94, P < .10$).

Laterality of Within Region and Within Network Connectivity Pre- and Post-HIRREM

For each of the three specific networks and three ROIs in this study, the pattern of laterality of connectivity within that network or region was assessed. Node edges or connections were characterized as ipsilateral within network or region left hemisphere (LL), ipsilateral within region or network right hemisphere (RR), or within region or network across hemispheres (LR or RL). As was the case for the whole brain analyses, LR and RL connections were equivalent because the networks are undirected. The mean number of connections of each type for each region at each time is shown in Figure 3.

Laterality effects were statistically evaluated using 3 (type of connection) \times 2 (time, pre- and post-HIRREM) repeated measures analyses of variance. Separate ANOVAs were conducted for each brain network or region. Main effects or interactions not specifically noted below were not significant.

Within the networks associated with Menon's triple network model, there were differences in lateralization of functional connectivity consistent with previous reports based on activation, but no changes in that pattern over time. The attention network was strongly connected to itself ipsilaterally but not contralaterally, the default mode network showed a tendency toward left lateralization, and the salience network showed a tendency toward right lateralization. In the attention network, a main effect of type of connection ($F(2, 34) = 42.56, P < .0001$) reflected fewer contralateral connections than connections within the left hemisphere ($t(17) = 8.29, P < .001$) or connections within the right hemisphere ($t(17) = 7.38, P < .001$). The default mode network analysis yielded a main effect of type of connection ($F(2, 34) = 14.98, P < .001$) reflecting fewer within right hemisphere default mode connections compared to within left hemisphere default mode connections ($t(17) = 5.15, P < .001$) and between hemisphere default mode connections ($t(17) = 4.47, P < .001$). The analysis of the salience network showed a main effect of type of connection ($F(2, 34) = 23.87, P < .001$) reflecting more ipsilateral right hemisphere connections, followed by more bilateral connections, and then ipsilateral left hemisphere connections. The differences in the number of connections were significantly different between each type ($t(17) \geq 2.77, P \leq .02$).

For the other three regions analyzed, there were differences in the types of connections, but the only effect of time (pre-HIRREM vs. post-HIRREM) occurred in the motor cortex. Connection type varied significantly within the basal ganglia ($F(2,34) = 25.64, P < .001$), reflecting more contralateral connections than ipsilateral connections within the left hemisphere ($t(17) = 6.08, P < .001$) or ipsilateral connections within the right hemisphere ($t(17) = 3.21, P < .01$). There also were more ipsilateral right hemisphere than left hemisphere connections ($t(17) = 4.78, P < .001$). A somewhat similar pattern occurred within the visual region: A significant main effect of connection type ($F(2, 34) = 10.65, P < .001$) reflected more contralateral

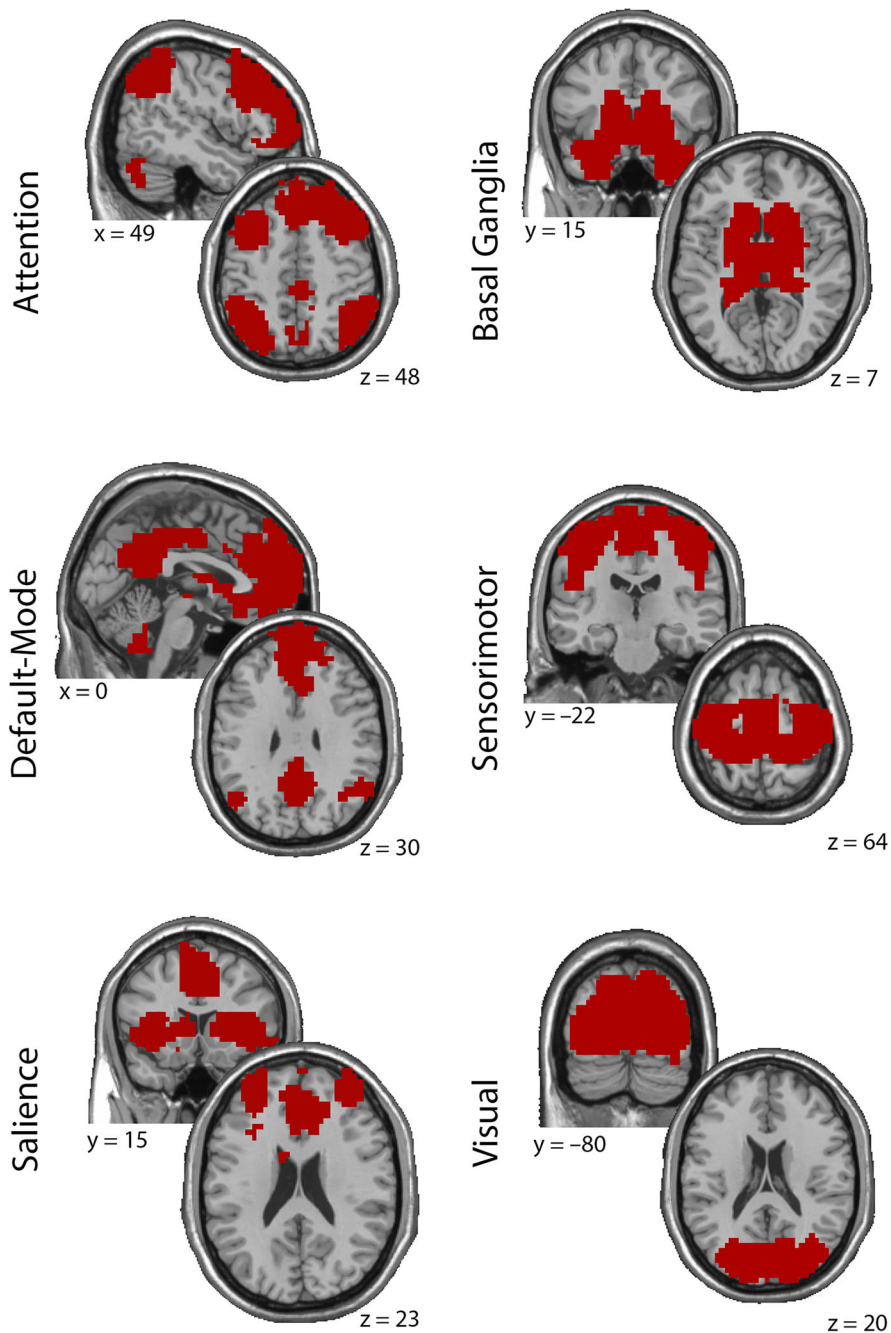


Fig 1. Maps showing location and extent of the regions of interest used in this study. Montreal Neurological Institute coordinates are listed below each slice.

connections than ipsilateral left hemisphere connections ($t(17) = 4.31, P < .001$). There were also more ipsilateral right hemisphere connections than left hemisphere connections ($t(17) = 2.70, P < .02$).

The motor region showed a main effect of connection ($F(2,34) = 4.23, P < .05$), reflecting significantly more contralateral connections than ipsilateral left hemisphere connections ($t(17) = 2.22, P < .05$). In addition, there was a main effect of time ($F(1,17) = 5.15, P < .05$) and an interaction between type and time ($F(2,34) = 3.75, P < .05$). The overall number of motor cortex connections decreased significantly at the second time of testing. Additionally, there were significantly more bilateral connections prior to HIRREM compared to ipsilateral

left hemisphere connections ($t(17) = 2.20, P = .05$), whereas there were no significant differences in types of connections post-HIRREM.

Laterality of Specific Region and Network Connectivity to Other Areas Pre- and Post-HIRREM

The final set of analyses assessed the laterality of connections between the networks and specific ROIs to nodes outside of those networks or regions. Thus, analyses were based on the number of connections from a hemispheric location of a network or region (eg, left hemisphere salience network), whether the connections for the nodes from that region or network were to somewhere else in the same hemisphere, or elsewhere in

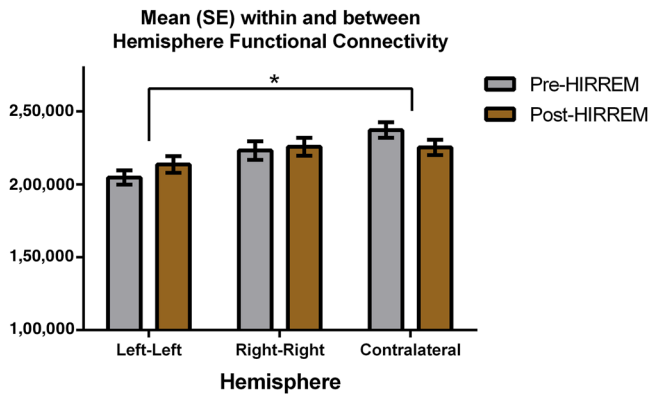


Fig 2. Mean (Standard Error) within and between hemisphere functional connectivity. More contralateral connections than Left-Left connections were observed based on repeated measures ANOVA and subsequent paired *t*-tests, but no effects of time or interactions were significant. * = $p < 0.05$.

the contralateral hemisphere (ipsilateral vs. contralateral). The mean number of connections of each type for each network or ROI is shown in Figure 4.

Statistical evaluation of these effects used 2 (hemisphere of network or region being evaluated) \times 2 (type of connection, ipsilateral or contralateral) \times 2 time (pre- vs. post-HIRREM) repeated measures ANOVAs. Separate ANOVAs were performed for each network or region. Main effects or interactions not described below were not statistically significant.

The salience network showed significant main effects of hemisphere and ipsilateral/contralateral connectivity, and most importantly, an interaction of hemisphere with time (pre- vs. post-HIRREM intervention). More connections involved the right hemisphere salience network ($F(1,17) = 25.21, P < .001$) and there were more ipsilateral than contralateral connections ($F(1,17) = 7.51, P < .02$). The interaction of hemisphere with time of testing ($F(1,17) = 5.08, P < .05$) reflected an increase in connections involving the left salience network post-HIRREM compared to pre-HIRREM, whereas the opposite pattern was true for the right salience network, although more connections involved the right salience network at both times. More specifically, the salience network in the left hemisphere increased an average of 2,470 connections, or 6.5%, whereas the salience network in the right hemisphere decreased an average of 2,127 connections, or 4.0%.

The analyses of the attention and the default mode networks showed no effects of hemisphere being evaluated, but did yield significant, although contrasting, main effects of the ipsilateral versus contralateral factor. The attention network had more ipsilateral connections than contralateral ($F(1,17) = 22.94, P < .001$). In contrast, the default mode network had more contralateral than ipsilateral connections ($F(1,17) = 17.40, P \leq .001$).

The analyses of the other ROIs showed similar effects for all three: A main effect of hemisphere occurred for each region ($F(1,17) = 11.35, P < .01$ for the basal ganglia; $F(1,17) = 15.74, P < .01$ for the motor cortex; and $F(1,17) = 15.82, P < .01$ for the visual cortex), with each showing more right than left hemisphere connections. A main effect of type of connection also occurred for each region ($F(1,17) = 72.14, P < .001$ for the basal ganglia; $F(1,17) = 12.23, P < .01$ for the motor cortex; and $F(1,17) = 47.98, P < .001$ for the visual cortex), with each region hav-

ing more contralateral than ipsilateral connections. No main effect of time was significant. Hemisphere \times type of connection interactions also occurred for the motor ($F(1,17) = 17.10, P < .001$) and visual regions ($F(1,17) = 9.23, P < .01$). In both cases, this reflected more right than left hemisphere ipsilateral connections ($t \geq 3.87, P < .001$), along with no significant difference in contralateral connections. Finally, an interaction of time and type of connection occurred for the motor cortex ($F(1,17) = 5.11, P < .05$), reflecting a large decrease in contralateral connections along with a slight increase in ipsilateral connections.

Post-HIRREM Brain Lateralization and PTSD Symptoms

In a further check of the relationship between brain lateralization and PTSD symptoms in this sample, we correlated the symptoms reported on the PCL-M inventory with whole brain lateralization, and with lateralization in the SN. PCL-M scores were from baseline and immediately after the HIRREM sessions.

The whole brain analyses correlated type of connection (L-L, R-R [or L-R]) as a percent of the total number of connections (L-L + R-R + L-R) with PCL-M scores. Pre-HIRREM L-L scores were unrelated to symptoms at any point. However, pre-HIRREM R-R scores correlated significantly with symptoms at baseline ($r(16) = .53, P = .02$) and after the HIRREM sessions ($r(16) = .59, P = .01$). Pre-HIRREM L-R scores were significantly negatively correlated with symptoms at baseline ($r = -.48, P = .04$) and after the HIRREM sessions ($r = -.54, P = .02$). There were only trends in the correlations of post-HIRREM type of connection scores with symptoms: L-L scores were negatively correlated with symptoms after HIRREM ($r(16) = -.46, P = .053$), whereas R-R scores were positively correlated ($r(16) = .44, P = .07$).

The relationship between symptoms and lateralization in the SN was analyzed in analogous manner, but no significant relationships were observed.

Discussion

Extensive evidence indicates a relationship between traumatic stress and hemispheric lateralization of brain activity.⁷⁻¹⁵ To date, however, there has been little investigation regarding the presence of laterality patterns in network or brain regional connectivity under such conditions, and whether laterality patterns may change after a successful therapeutic intervention. The present study reports preliminary findings with respect to these questions based on a sample of military service members and recent Veterans with symptoms of military-related traumatic stress who undertook usage of HIRREM, a closed-loop, allostatic, echoing neurotechnology that has previously been shown to decrease asymmetries in brain activity.³²

At baseline, there were numerous main effects of connection type (ipsilateral for either side, or contralateral in either direction), for the whole brain as well as within networks or regions, and between networks or regions. In populations with no history of trauma, asymmetries of lateralization in functional networks have been demonstrated for the default mode,^{51,52} motor regions,^{53,54} and other networks,^{55,56} and it may be that baseline findings shown in this study were within the range of "healthy variability." Alternatively, most of the participants were affiliated with special operations and these changes may have been a consequence of neuroplastic changes from the

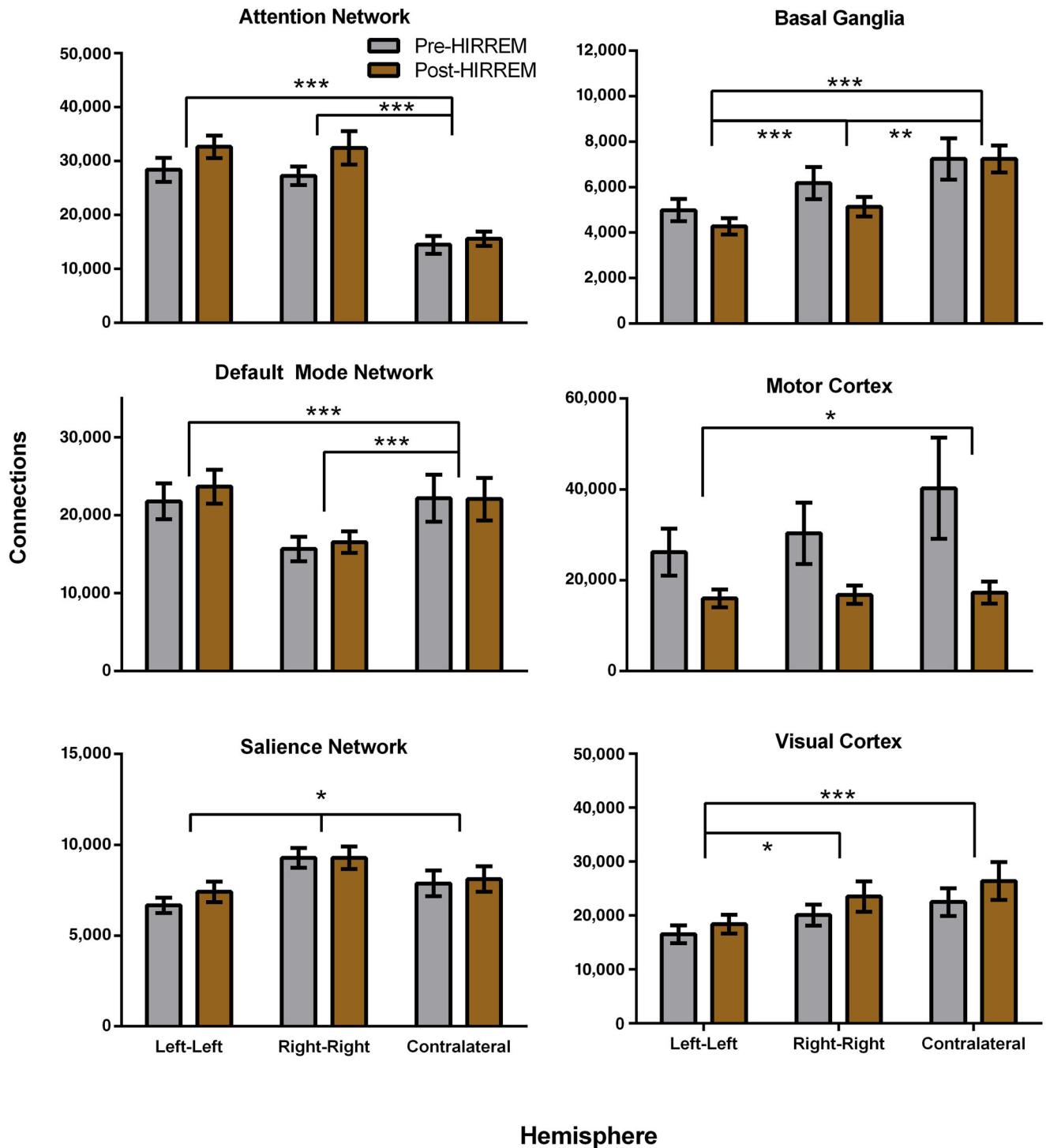


Fig 3. Mean (Standard Error) within-network or within-region functional connectivity by hemisphere. Repeated measures ANOVAs and subsequent paired t-tests showed (1) Attention Network Left-Left (LL) and Right-Right (RR) > contralateral; (2) DMN LL > RR, LL > contralateral; (3) Salience Network RR > contralateral, contralateral > LL; (4) Basal Ganglia contralateral > LL and RR, RR > LL; (5) Motor Cortex contralateral > LL; main effect of time and interaction of time and type of connection (not annotated on graph); and (6) Visual Cortex contralateral > LL, RR > LL. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

intensive training required to become a special operations officer. Or, some portion of the baseline findings may have been related to the subjects' traumatic stress history. Adjudication of these interpretations may be possible by comparison of the presently reported asymmetries with results from future hypothesis-driven studies.

Regarding the outcomes that could be related to the intervention, a finding of particular interest was in between the network analysis: After HIRREM, there was a reduction in connections between the right hemispheric nodes of the salience network, and other regions. The salience network serves to detect and attend to goal relevant stimuli in the

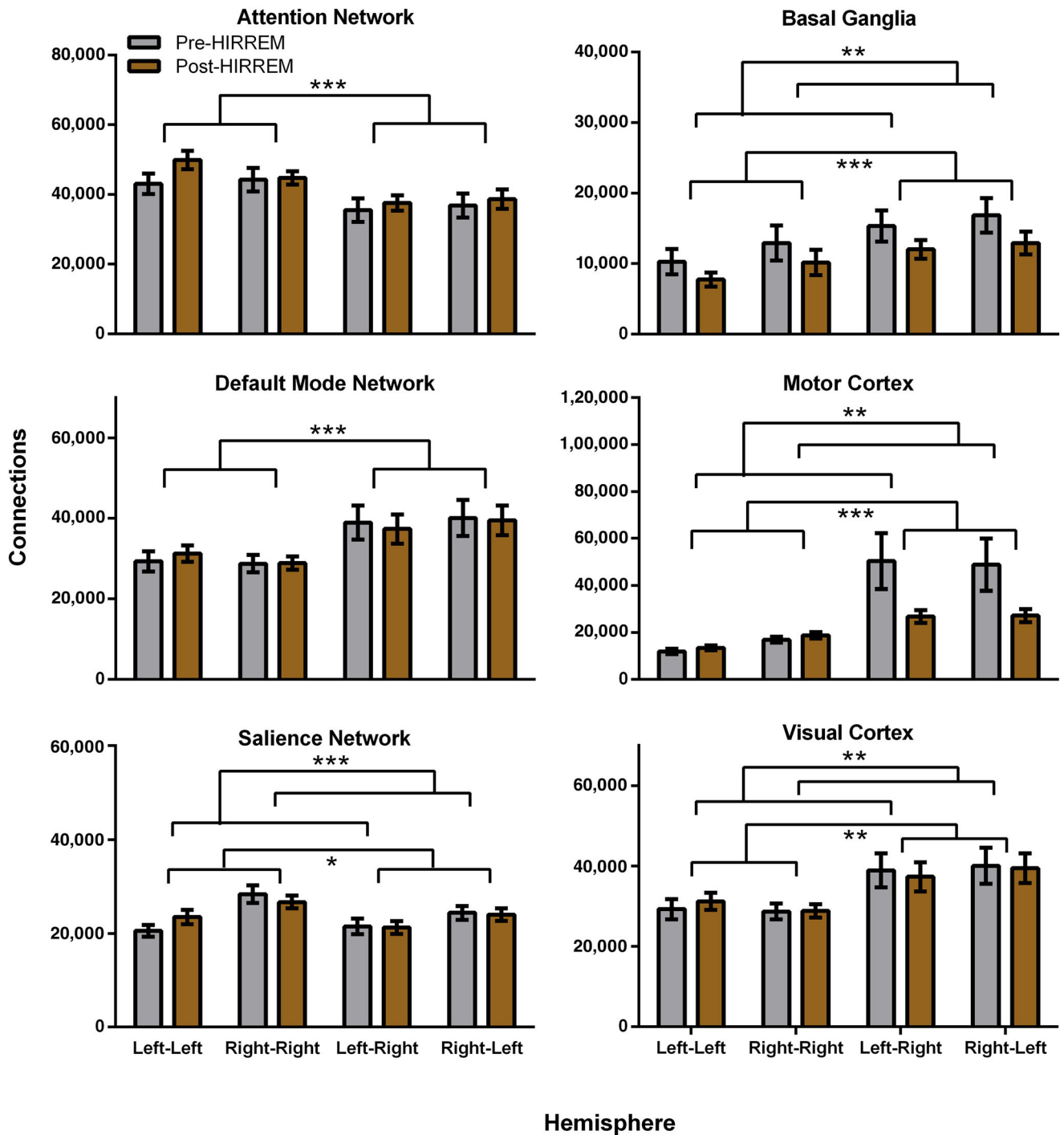


Fig 4. Mean (Standard Error) between-network or between-region functional connectivity by hemisphere. Repeated measures ANOVAS and subsequent paired t-tests showed: (1) Attention Network ipsilateral > contralateral; (2) DMN contralateral > ipsilateral; (3) Salience Network ipsilateral > contralateral, right > left, and hemisphere \times time interaction (not annotated on graph); (4) Basal Ganglia contralateral > ipsilateral, right > left; (5) Motor contralateral > ipsilateral, right > left, type of connection interactions with time and hemisphere (not annotated); and (6) Visual contralateral > ipsilateral, right > left, hemisphere \times type of connection interaction (not annotated). * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

environment,⁵⁷ and it appears to show hyperconnectivity in PTSD.⁵⁸ Postinterventional decrease in connectivity between the right side of the salience network and other regions may have reflected decreased triggering of the sympathetic nervous system, potentially consistent with previously reported trends for decrease in rightward dominant temporal lobe electrical asymmetry, or improved HRV.^{32,37,59} However, the correlations

between symptoms reported on the PCL-M and lateralization of the SN were not significant and thus suggest caution in this interpretation. The correlations between whole brain lateralization scores and the PCL-M scores were significant in a manner consistent with the BHAM framework.¹⁷ The percentage of R-R connections was positively correlated with symptoms, which fits with the postulate of linkage between sympathetic

hyperarousal and many high arousal state symptoms associated with PTSD. The percentage of bilateral L-R connections showed a negative correlation with symptoms. This, along with the trend for negative correlation of L-L connections with symptoms post-HIRREM, also supports the BHAM postulate that better balance and improved parasympathetic influence is associated with reduced symptoms and the observed improvement in autonomic cardiovascular regulation (heart rate variability).

Alternatively, yet not mutually exclusively, the significance of these changes may rest in their indication of a change in dynamics at larger scales. It may be that, consistent with the allostasis model for “whole-brain” therapeutic strategy⁴¹ as well as other data from the study of EEG-based intervention,^{60,61} successful remediation of traumatic stress effects should be demonstrated as an array of changes across circuits or subsystems. As noted previously, numerous studies now characterize PTSD as a disorder of connectivity rather than abnormality of a specific neural area, and they point to the need for treatments that impact connectivity patterns,⁶⁰ and assessment of effects that take such changes into account.

These preliminary findings must be qualified by the limitations of the present study. The principal limitation of this study lay in its single-arm design. A comparison arm was impractical because of the nature and timing of the training regimen of special operations officers as well as the reality that there is significant underreporting of symptomatology in military service members.⁶² This was a small sample with associated issues such as limited power. We did not apply statistical techniques to adjust for multiple comparisons in that such an approach may have been excessively conservative for our exploratory objectives, and could obscure changes that might arise as correlated biological effects. It should also be noted that the method of counting the number of connections between nodes is relatively coarse, and moreover many of the ROIs used were relatively large such that other changes in connectivity may not have been detected. Because a majority of the participants reported prior traumatic brain injury or concussion as comorbid medical conditions, it is possible that this may have been the etiology of some of the baseline laterality findings. Finally, this study assesses changes in connectivity before and after the HIRREM intervention at the group level rather than at the individual level.

In conclusion, this study showed numerous asymmetries of network and brain region connectivity patterns at baseline in a group with symptoms of military-related traumatic stress, mostly from special operations, prior to usage of HIRREM. After intervention, there were several changes compared to their baseline patterns, including a reduction in connections between the right hemispheric nodes of the salience network and other networks and regions. These findings provide further evidence for the value of using network connectivity analysis, including laterality, to understand traumatic stress effects, and may point to mechanisms of action for successful clinical intervention.

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