CHARACTERIZATION OF COMBAT-INDUCED PTSD IN OEF/OIF VETERANS USING MEG-BASED IMAGING

by

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THESIS

Submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in

Biomedical Imaging

in the

[redacted]

This work is dedicated to my son, Alex.

I'd also like to give special thanks to the following people for their assistance in this work:

Srikantan S. Nagarajan, PhD

Sophia Vinogradov, MD

Susanne Mueller, MD

Thomas Neylan, MD

Danielle Miziuri, BS

Coleman Garrett, BS

Susanne Homna, RT

Megan Thompson, BS

Corby Dale, MPH, PhD

Anne Findlay, MS

Lara Stables, PhD

Alan Leggitt, BS

Abstract

Characterization of Combat-Induced PTSD in OEF/OIF Veterans Using MEG-Based Imaging

by Omar Rutledge

Background: Post-traumatic stress disorder (PTSD) is a mental health disorder characterized by symptoms such as insomnia, irritability, issues with memory, difficulty concentrating, and poor decision-making abilities. With symptoms that closely resemble those of other anxiety disorders, it is very difficult to accurately diagnose. More research is needed to identify structural and functional imaging biomarkers to aid in diagnosis.

Methods: Ten right-handed male subjects (5 combat-exposed veterans, 5 healthy civilian controls) underwent magnetoencephalographic recording for this study. MEG data were acquired with a 275-channel whole-head CTF Omega 2000 system. Resting-state and tasked-based (Stroop Color-Naming Task) data were acquired. Voxel-based time-frequency analysis was subsequently performed using NUTMEG and SPM8.

Results: Significant differences were found between the two groups at rest (in delta, theta, gamma, and high-gamma neural oscillatory frequency bands) and during the Stroop Color-Naming task (in alpha, beta, and gamma, and high-gamma frequency bands).

Conclusions: Despite the small sample size, we were able to replicate some aspects of previous MEG research in veterans with PTSD. Not only does this result substantiate the use of MEG for population studies, but it also shows that PTSD is a mental disorder that is physical in nature and can be characterized through passively observing electromagnetic neuronal activity.

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Introduction

Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is a mental health injury caused by exposure to life-threatening or emotionally traumatic events (Pang et al., 2014). Although the degree and duration of trauma can vary widely among combat veterans, symptoms of PTSD are quite similar across this population. In the United States, the average lifetime prevalence rate of PTSD is around 6.8% (Kessler et al., 2005). As would be expected, this disorder is more common among military service members who have deployed to combat zones (Richardson, Frueh, & Acierno, 2010). Service members who have deployed in support of Operations Enduring Freedom and Iraqi Freedom (OEF/OIF) have an approximate prevalence rate of 15.8% (Dursa, Reinhard, Barth, & Schneiderman, 2014).

The Diagnostic and Statistical Manual of Mental Disorders, or DSM-V (American Psychiatric Association, 2013), describes PTSD as having four distinct symptom clusters: intrusion (flashbacks, recurrent dreams), avoidance (internal thoughts, external triggers), negative affect (negative thoughts of self, detachment from others), and reactivity (irritability, hypervigilance). Clinical manifestations of combat-related PTSD also include non-specific symptoms such as insomnia, irritability, issues with memory, difficulty concentrating, and poor decision-making abilities. With symptoms that closely resemble those of other anxiety disorders and of depression, often co-morbidities of PTSD, it is very difficult to accurately diagnose (Van Boven et al., 2009). With such difficulty in psychological diagnosis, more researchers are attempting to discover novel ways to accurately diagnose PTSD through the identification of structural and functional imaging biomarkers (James et al., 2015).

Structural Imaging of Brain Regions in PTSD

There are a number of imaging modalities that can elucidate the structural and functional differences in various brain regions in individuals with PTSD. Magnetic Resonance Imaging (MRI) is a commonly used imaging modality that utilizes radio wave emission in a powerful magnetic field to excite hydrogen nuclei within the body. The nuclei have quantum properties that resonate at a specific frequency when placed in a strong magnetic field. If a radio pulse is applied to a selected volume at that specific frequency, energy is deposited into the nucleus which becomes excited. The excited nuclei then release that energy which is detected and transformed into pixel information. The strength of the signal received depends on the density of hydrogen nuclei in a given volume element, or voxel. Images generated through this modality contain soft-tissue contrast that is unparalleled compared to other imaging techniques. This property makes MRI an excellent imaging modality to identify structural differences between groups in various brain regions.

One commonly reported symptom of PTSD is difficulty with autobiographical and verbal declarative memory (Buckley, Blanchard, & Neill, 2000). Since the hippocampus is associated with memory encoding (Scoville & Milner, 1957), a number of studies have utilized MRI to measure hippocampal volume changes. An MRI investigation of hippocampal subfields in combat-exposed veterans with PTSD revealed the cornu ammonis 3 (CA3)/dentate gyrus (DG) subfields of the hippocampus are consistently smaller in size in this population (Wang et al., 2010). They suggest hippocampal volume is diminished in individuals with PTSD, although it is not known whether PTSD causes hippocampal atrophy or if smaller hippocampal volume is a risk-factor in the development of the disorder (Van Boven et al., 2009). Further investigations showed that reductions in size of other brain regions, such as the anterior cingulate cortex

(ACC), insular cortex, and corpus callosum, are also correlated with severity of PTSD symptoms (Chao, Weiner, & Neylan, 2013). In this study, there were no significant differences in hippocampal volumes between those with remittance of PTSD symptoms and healthy control subjects. However, this finding was not replicated in a recent study of war veterans (van Rooij et al., 2015). This group of researchers found that those who are combat-exposed have consistently smaller hippocampi, regardless of the presence of active PTSD symptoms, and that the smaller hippocampal size did not change with treatment. Although this is not a comprehensive review of structural MRI studies of structural changes seen in PTSD, these conflicting results show that drawing definitive conclusions based on structural imaging of brain regions associated with mental disorders can be quite difficult.

Functional Imaging of PTSD

Another method to differentiate populations in brain imaging comes in the form of functional imaging. Functional imaging offers researchers the ability to visualize differences based on brain activity rather than the shape of structures within the brain. Functional MRI is a variant on traditional MRI. It is based on the fact that the iron within hemoglobin affects the surrounding magnetic field differently if oxygen is bound to the molecule than if it is not. Brain activity requires more energy and thus more oxygen. As a brain area requires more oxygen, the signal is altered. These alterations are known as the blood oxygenation level-dependent, or BOLD, effect, which can be statistically analyzed to produce functional images.

Differences in brain activation patterns between subjects with PTSD and healthy controls have been observed with fMRI. Evidence shows that people diagnosed with PTSD have exaggerated amygdala and diminished medial prefrontal cortex (mPFC) responses during exposures to emotionally-salient stimuli (Shin et al., 2005). The amygdala is implicated in the

processing of emotion, and is particularly important in linking cortical and subcortical structures during the processing of emotional information (Purves, 2012). This relationship between heightened emotional response and reduced executive function is consistently observed when subjects are exposed to emotionally-salient stimuli (Morey, Petty, Cooper, Labar, & McCarthy, 2008), but not to emotionally-neutral stimuli (Shin et al., 2007). This preferential attention to emotionally-salient stimuli may be a neurological manifestation of the combat experience, where threats must be attended to quickly without much cognitive processing. Adaptive in the combat zone, this change in cognitive processing becomes quite detrimental in the civilian world.

Another modality known as magnetoencephalography, or MEG, is used to infer brain activity by taking advantage of the miniscule magnetic field perturbations generated by firing action potentials to localize their origin. The magnetic field changes are extremely small in magnitude (femtoTesla, $fT = 10^{-15}$ T) and must be detected using magnetometers connected to sensitive superconducting quantum interference devices, or SQUIDs (Sekihara & Nagarajan, 2015). The SQUIDs serve as magnetic/electric transducers and are super-cooled to minimize resistance and maximize sensitivity. An array of sensors is arranged in the shape of a helmet and placed inside a liquid-helium dewar. To reduce external sources of electromagnetic interference, the system must be inside of a magnetically-shielded room, or MSR. Signals obtained through the SQUIDs are amplified and recorded digitally. With the prior knowledge of the arrangement of each sensor in space and the position of the head within the sensor array, the signals can be transformed into a 3-dimensional map of magnetic perturbations with a temporal resolution on the order of milliseconds. Since no anatomic information is obtained with this modality, MEG data is often co-registered with MRI data to create functional images, known as magnetic source

imaging, or MSI (Wheless et al., 2004). MEG-based imaging offers better temporal resolution than fMRI and can reveal activity in different neural oscillation frequency bands as a result.

There have been a number of studies attempting to understand the neural correlates of PTSD using magnetic source imaging techniques, with many reporting similar patterns of activity across various populations diagnosed with PTSD (Anders et al., 2015; Engdahl et al., 2010; Georgopoulos et al., 2010; James et al., 2013). Although they are relatively few in number, most studies find that limbic system structures such as the amygdala are hyperactive and areas in the PFC are hypoactive relative to controls when people with PTSD process emotionally-salient information (M. Huang, Risling, & Baker, 2015).

Resting-State MEG in PTSD

In the field of PTSD research, there have been a few studies that have examined resting-state data with MEG. Comparisons of resting-state neural activity allow researchers to determine if there is a statistically significant difference between groups during a period void of task-dependent cognitive processing. One such study by Kolassa and colleagues reported that abnormally slow delta-wave activity (1-4 Hz) could be observed in those diagnosed with PTSD during a resting-state condition. Increases in delta band activity were localized to the left temporal lobe/insula and right frontal lobe, while decreases in locally-generated slow-wave activity was observed in the parieto-occipital region in both hemispheres (Kolassa et al., 2007). It has been suggested that high densities of low-frequency delta waves are indicative of brain pathology (Wienbruch et al., 2003). Pathology of the insula may be responsible for the inability to regulate responses to emotionally salient stimuli, known as alexithymia (Frewen, Pain, Dozois, & Lanius, 2006). Pathology in the frontal lobe may explain lack of emotional regulation

and extinction to aversive events. Kolassa et al. did not speculate on the meaning of reduced delta-wave activity in the parieto-occipital region.

In another resting-state investigation, Huang et al. (2014) reported that active-duty service members and veterans with PTSD show hyperactivity with respect to controls in the amygdala, hippocampus, and orbitofrontal cortex (fear and memory circuits), hypoactivity in the ventral-medial pre-frontal cortex and dorsal lateral pre-frontal cortex (higher-order inhibition circuits), and that their PTSD assessment scores correlated with the intensity of MEG activity (Huang et al., 2014). This effect is most pronounced in the beta-gamma band (15-80 Hz), where bilateral amygdala/anterior hippocampus hyperactivity and vmPFC hypoactivity can be seen in a resting-state condition (M. Huang et al., 2015). The author suggests these findings are consistent with the theory that reduced behavioral inhibition and an overactive "fear network" are closely related. Dunkley and his group (2014) found that soldiers with PTSD show long-range hyperconnectivity in the high-gamma band during a resting-state MEG acquisition. Healthy controls show a similar pattern only after exposure to emotionally salient stimuli. Hyperconnectivity is also shown to be correlated with measures of anxiety, depression, and PTSD (Dunkley et al. 2014).

Task-based MEG in PTSD

During functional imaging acquisitions, it is common to ask subjects to perform a task designed to activate specific brain regions or induce activation patterns which can be measured and localized (MacLeod & MacDonald, 2000). Researchers measure activity given a set of standard conditions, and perform statistical analyses on the resulting spatio-temporal data. The performance of a subject on a task given during functional imaging acquisition can be evaluated to elucidate group differences in activation (Galer et al., 2015).

Since the spatial resolution of MEG is reduced the deeper the source is in the brain (Sekihara & Nagarajan, 2015), Cornwall and colleagues (2008) wanted to test the ability of MEG to resolve deep brain activations. One popular method for inducing preferential deep-brain activations is exposing subjects to pictures of emotionally-salient faces. Through an adaptive beamformer analysis, they found that healthy subjects had pronounced preferential activation in the amygdala when healthy subjects were exposed to angry and fearful faces versus benign shapes (Cornwell et al., 2008) as what was seen using fMRI. Once spatial resolution of deep brain structures was confirmed, a team of researchers in Canada utilized the excellent temporal resolution of MEG to find that exposure to emotional faces in healthy subjects elicited rapid responses in the amygdala and (ACC) before later activations in the fusiform gyrus, which has been implicated in facial recognition (Hung et al., 2010). They found that this effect occurs even if that information is presented in an unattended area of the visual field. This evidence confirms MEG-based imaging as a reliable functional imaging modality even in deeper subcortical structures as this research shows MEG is consistent with fMRI findings of amygdala responses during exposure to emotionally-salient stimuli.

In subjects with PTSD, Adenauer and colleagues described a biphasic phenomenon in which the increased attention to threatening cues in the orbitofrontal cortex (OFC) experienced by PTSD sufferers precedes hypoactivity in visual processing of affective photographs compared to controls (Adenauer et al., 2010). The authors suggest a model whereby early neural hyperactivity in the OFC is accompanied by *neural avoidance* in the orbito-temporal cortex during the processing of emotionally salient photos. Giving additional support for this model, Rockstroh and Elbert summarized a number of studies from their laboratory, which used a repeated-exposure model (Rockstroh & Elbert, 2010). They note that a “low-road” of rapid

automatic processing of threatening stimuli through the amygdala is always followed by a "high-road" of slower cortical processing. Their work suggests the brain's functional architecture is altered in trauma, moving from a careful analyzer of information to a rapid threat detector with a low threshold for reacting to potentially threatening situations. This is a key symptom of PTSD: reactivity. One interesting result from a study examining the time course of the development of PTSD was that this change in attentional processing of aversive stimuli occurs rather quickly following exposure to traumatic events, with subjects showing this biphasic characteristic within one week after experiencing a traumatic event (Burgmer et al., 2013). Together, these studies show how changes in neural processing of emotionally-salient stimuli may give rise to the two common behavioral symptom clusters that characterize PTSD: reactivity and avoidance.

Interestingly, this effect of neural processing has also been induced in a healthy population by placing them in a condition where they were under a threat of electric shock during a passive auditory oddball task (Cornwell et al., 2007). The task was to passively listen to static tones that would occasionally change in pitch. This task induces neural activity known as mismatch negativity (MMN), indicative of attention to change. As mentioned above, research has shown that people with PTSD are particularly attentive to changes in stimuli (Buckley et al., 2000), and have a higher MMN amplitude than controls (Morgan & Grillon, 1999). Cornwall and colleagues placed their subjects under threat of shock during certain periods of the experiment and designated the others as "safe". They found that they were able to induce the same increase in amygdala activity as had been seen in patients with PTSD during the periods of threat of electric shock, and that the MMN was higher during the deviant stimuli, giving more evidence to the fact that changes in stimuli evoke heightened responses during periods of stress, even in those without PTSD. The implication is that PTSD is a disorder where the normal neural

processing that occurs while evaluating threatening stimuli during periods of high risk never ceases but instead becomes a chronic state.

The Stroop-color task is designed to elicit the interference effect, which is the increase in reaction time (or error rate) when the incongruent stimulus is presented versus the congruent stimulus (Spielberg, Miller, Heller, & Banich, 2015). Tasks such as this examine the neural correlates of conflict detection and attentional control, allowing for statistical comparisons between groups' performance to infer the biological bases of some of the cognitive deficits of PTSD (Dunkley et al., 2015). A massive meta-analysis of several hundred studies in healthy subjects utilizing the Stroop-color task revealed several regions of the brain that show differential activations between the congruent and incongruent stimuli (MacLeod, 1991). Regions of interest included the dorsal anterior cingulate cortex (dACC), lateral PFC, insula, and lateral parietal cortex, some of the same regions that have been previously show to have differential activation in those with PTSD. Although variants of the Stroop-color task have been studied in PTSD, such as the counting-Stroop (Shin et al., 2007) and emotional-Stroop tasks (Metzger, Orr, Lasko, McNally, & Pitman, 1997), to the best of my knowledge, there has never been an investigation using the neutral Stroop-color task in veterans with PTSD.

Present Study

In order to verify published findings and provide additional supporting evidence for a given model of psychopathology, it is important to conduct replication studies. The current study was of a prospective, observational, case-control study design.

There were two aims for this study. The first was to attempt to replicate the resting-state characteristics of PTSD seen in other studies. Based on previous research, it was hypothesized that hypoactivity would be present in the right frontal lobe in the delta band (1-4 Hz), both

frontal lobes for theta (4-7 Hz) and alpha (7-15 Hz) bands, and hypoactivity in the ventromedial prefrontal cortex (vmPFC), dorsolateral prefrontal cortex (dlPFC), and frontal poles in both beta (15-30 Hz) and gamma (30-80 Hz) bands, and hypoactivity in the vmPFC and right dlPFC for the high-gamma (80-150 Hz) band.

Hyperactive areas were hypothesized to be in the left temporal lobe for delta activity, in bilateral posteriolateral orbifofrontal cortices (OFC) and left occipito-temporal-parietal junction for both beta and gamma bands, and hyperactivity in the left OFC, left frontal pole, bilateral occipito-temporal-parietal junctions, and right dorsomedial occipital cortex for the high-gamma (80-150 Hz) band.

The second objective was to characterize the cortical response of veterans with PTSD on the non-emotional Stroop color-naming task to determine if this task proves useful for the characterization of the effects of PTSD on prefrontal and parietal cortical functioning for future MEG studies. As prior research shows areas such as the PFC and parietal cortex are differentially activated in the Stroop-color task, and these areas are closely associated with PTSD, it is my hypothesis that activation patterns should be different between those with PTSD and controls.

Methods

Participant Eligibility Criteria

Subjects participating in this research met specific eligibility criteria. Eligibility for participation was determined using four self-report questionnaires: the Brief Trauma Questionnaire, the PTSD Checklist for the DSM-V, the Ohio State University TBI Identification Method-Short Form, and an MRI safety checklist. These measures are described in detail below.

The Brief Trauma Questionnaire (BTQ) was used to determine eligibility for trauma exposure (Schnurr, Vielhauer, & Findler, 1999). The questionnaire consists of ten inquiries into

the subject's exposure to various types of emotional trauma. A positive answer to any of these questions requires an additional response to the each of the following questions: "Did you think your life was in danger or you might be seriously injured?" and "Were you seriously injured?" Affirmative responses to these secondary questions are interpreted as meeting DSM-V Criterion A for traumatic stress exposure. Healthy control group participants with significant trauma exposure were excluded from participating. Significance was determined as more than one affirmative answer to the secondary questions. Trauma outside of combat had no effect of eligibility for veterans, although the additional level of exposure was noted.

The PTSD Checklist (PCL5) was used to assess the presence and degree of current PTSD symptoms. The measure consists of twenty questions related to PTSD symptoms such as "In the past month, how much were you bothered by feeling jumpy or easily startled". Possible responses were given as a Likert scale ranging from 0 to 4, with 0 being "Not at all" and 4 being "Extremely". Thus, possible total scores ranged from 0-80.

The Ohio State University TBI Identification Method-Short Form was used to determine lifetime history of traumatic brain injuries (Corrigan & Bogner, 2007). The OSU TBI form contains seven questions of possible scenarios that may have resulted in a TBI. For every incident with a positive response, the subject records information about the incident in a table on the form. Any subject who was determined to have a moderate or severe TBI, defined as a loss of consciousness longer than 30 minutes, was excluded from participation.

The MRI Safety form (www.IMRSER.org) was used to determine any contraindications for obtaining the MR images required for co-registration with the MEG data. Subjects with contraindications for the MR environment were excluded from participation.

Participant Recruitment

Subjects were recruited *de novo* through friendships of the author. The author served as one of the veteran subjects. Four other veterans of OEF/OIF were recruited for this study. All five civilian subjects that served as healthy controls were students of the University of California, San Francisco.

Participants

Ten right-handed male subjects (5 combat-exposed veterans, 5 healthy civilian controls) underwent magnetoencephalographic recording for this study. The veteran group consisted only of veterans of OEF/OIF to minimize age effects within the group. The age range for the five veterans was 29-40 (mean: 33.8, SD: 4.55). The control group consisted of civilians that had not experienced any significant lifetime trauma as determined through the BTQ. The age range for the participants was 23-25 (mean: 23.6, SD: 0.89). Every subject provided his written informed consent to participate in the research. All procedures were approved by the Committee on Human Research of the University of California, San Francisco.

Materials

MEG data were acquired inside a magnetically-shielded room (MSR) with a 275-channel whole-head CTF Omega 2000 system (VSM MedTech, Coquitlam, BC, Canada). Each subject had three fiducial marker coils placed on the nasion and 1 cm rostral to the left- and right-periauricular points for head-localization. Operators placed foam padding around the subject's head to increase comfort and reduce head movement. Data were checked prior to processing for excessive head movement. Movement in excess of 5 mm would render the data unusable. Data were recorded at a sampling rate of 1200 Hz.

Subjects were placed in the MEG scanner in a supine position and viewed stimuli on a back-projected screen approximately 1 m from the subject. Resting-state and task-based data were acquired. During the five-minute resting-state condition, the subject was instructed to close his eyes without sleeping and "clear the mind". This was followed by the Stroop-Color task (Stroop, 1935) in which the subject is presented with a word displayed in the colors of either blue or yellow. The words presented were "YELLOW", "BLUE", or "XXXXXX". The goal of the task was to identify the color of the text by pressing a button on a control box corresponding to that color. Recordings were performed in the Biomagnetic Imaging Laboratory, UCSF Parnassus, San Francisco, California, USA.

MEG data must be co-registered with MRI data in order to accurately localize sources within each participant. Structural MRI was obtained using a Magnetom 3T TIM Trio scanner (Siemens AG, Erlangen, Germany) with a T1-weighted 3D volumetric magnetization prepared rapid gradient echo (MPRAGE) sequence, TR/TE/TI=2300/2.98/900ms, 9° flip angle, 1.0 x 1.0 x 1.0 mm^3 spatial resolution, with 256 continuous sagittal slices. The scans were performed at the Neuroscience Imaging Center, UCSF Mission Bay, San Francisco, California, USA.

MEG Data Processing

Prior to co-registration, MEG data were filtered using a third-order gradient, with a notch filter applied from 56-64Hz to remove signals associated with AC-power oscillations. Residual motion and eye-blink artifacts were manually removed from the filtered data. Remaining data were band-pass filtered to correspond to frequencies of interest for further analysis (1-4, 4-7, 7-15, 15-30, 30-80, and 80-150 Hz). A multi-sphere head model was generated using the CTF MEG System Software Package (VSM MedTech, Coquitlam, BC, Canada) that accompanies the

MEG scanner. The head-localization coils of the MEG were spatially registered with the corresponding locations on the subject's MRI.

Statistical Analysis

After the MEG and MRI data were co-registered, voxel-based time-frequency analysis was performed using several software packages. The Neurodynamic Utility Toolbox for MEG (Dalal et al., 2004) is a MATLAB-based program (The Mathworks, Inc, Sherborn, MA) designed to process and visualize MEG data and was used in conjunction with the Statistical Parametric Mapping program, version 8 (SPM8) (Wellcome Trust Centre of Neuroimaging, London, UK), a platform used to visualize functional imaging data onto MR images, to analyze the MEG data. SPM was used to normalize the individual's head space to standard Montreal Neurological Institute (MNI) coordinate space, which allows for a more robust comparison of brain regions across populations.

One minute of continuous resting-state data was selected for analysis for each subject. Selection was made based on the least number of motion and eye-blink artifacts. Each one-minute time course was averaged for each person, and then averaged within each group. A t-test was performed comparing PTSD data to control data with hyperactivity corresponding to PTSD activity greater than that of control subjects. The threshold for visualization was set at $p < 0.05$ using a statistical non-parametric mapping setting, uncorrected for multiple comparisons. This was performed for each frequency band.

Continuous Stroop-color data was broken into stimulus-locked epochs, separated into congruent and incongruent stimulus conditions, then time-averaged for each frequency band. The time averaging was performed with a window of 200 ms, in steps of 25 ms. Only correct responses were used for analysis. Motion and eye-blink artifacts were manually removed prior to

averaging. T-tests were performed between groups for each frequency band. Upon initial processing, it was found that delta and theta bands could not be statistically analyzed for the Stroop-color task due to a large number of motion artifacts. Analyses were performed in two steps: data were first contrasted between the PTSD and control groups for the congruent and incongruent stimulus conditions, and then the incongruent condition was contrasted with the congruent condition within each group. Visualization was made with statistical non-parametric mapping, with a threshold of $p < 0.05$, uncorrected for multiple comparisons. This threshold was selected due to the small sample size. Comparisons were made with processed data at 350 ms, 500 ms, and 650 ms.

Results

Cognitive-Behavioral Assessments

Subject characteristics and results from cognitive-behavioral assessments are summarized in *Table 1*. There was a significant difference in age distribution between the two groups ($p < 0.008$). The amount of lifetime trauma reported for each subject was also significantly different ($p < 0.018$) with an average of 3.8 traumatic events that met DSM-V Criterion A in the PTSD group and 0.2 in the control group. Interestingly, the types of trauma experienced by the PTSD group were not limited to military experiences. Severity of PTSD symptoms was relatively similar within the PTSD group as measured by the PCL-5. The range of PCL scores for the PTSD group was from 29 to 57, with a mean of 43.6, which is considered to be a moderate but clinically significant level of current PTSD symptoms. The control group had an average of 1.6 on the PCL-5. This was the most significant difference between the two groups ($p < 0.002$). Subjects reported varying degrees of potentially traumatic brain injuries with none reaching the threshold for moderate TBI, defined as a loss of consciousness greater than thirty minutes.

Although there was a difference between the group averages, (PTSD = 2.8 (1.3), Control = 1.2 (1.6)), statistical analysis reveals no significant difference between groups on the number of reported minor injuries ($p < 0.132$).

Resting-State Condition

Statistical analyses were performed to examine between-group differences on the delta, theta, alpha, beta, gamma, and high-gamma frequency bands for the resting-state condition. *Figure 1* shows that depressed delta band (1-4 Hz) activity was observed in the PTSD group relative to the healthy control group in a variety of cortical areas, including the right vmPFC, right dlPFC, left temporo-parietal junction, right parieto-occipital cortex. A reduction in theta band activity (4-7 Hz) was observed in the left fronto-temporal junction, left cerebellum, right superior parietal cortex and right temporal cortex. Focal reductions in alpha band activity were seen in the right superior frontal gyrus and right medial temporal gyrus, while a single focal beta band reduction was present in the left cerebellum. Gamma band (30-80 Hz) analysis revealed slight increases in activity in the left superior and inferior temporal region and right medial temporal gyrus, while reductions were seen in the right temporal pole. More significant increases were seen in the high-gamma band (80-150 Hz) with the greatest difference observed across the right temporo-parieto-occipital junction.

Stroop-Color Task: Behavioral Data

Analysis of behavioral performance data on the Stroop-color task revealed no statistically significant difference between the two groups on the number of correct responses ($p < 0.298$), the number of incorrect responses ($p < 0.509$), or the number of missing responses ($p < 0.947$).

This suggests that any group differences observed in the MEG data are not due to behavioral performance differences on the task. Behavioral data are summarized in *Table 2*.

Stroop-Color Task: Between-group Differences

Contrast between the PTSD and the healthy control groups were generated for the congruent and incongruent stimuli at each of three time points (350, 500, and 650 ms) following stimulus presentation. These time points were selected based on the findings of Galer et al. (2015), who found the most significant differences between the congruent and incongruent stimuli within this time frame. We examined group differenced in task-induced neural activity in three frequency bands: alpha band activity, thought to reflect thalamo-cortical communication and functional inhibition; beta band activity, believed to be related to long-range communication; and both gamma and high-gamma activity, indicative of more short-range, local computations.

Group differences in alpha-band activity: Figure 2 shows that in every condition and for every time point, the PTSD group exhibited increases in activation in the alpha band compared to the control subjects. For congruent stimuli at 350 ms, the PTSD group had increased alpha activity in bi-lateral temporo-parietal regions with more temporal activation on the right and more parietal activation on the left. Incongruent stimuli at 350 ms showed the only decreases in activation relative to the control group for the alpha band. These decreases were seen in the right temporal lobe extending into the right central sulcus. A slight decrease was observed in the left fronto-temporal area while a significant increase in activity was seen along the medial occipital lobe. Congruent stimuli at 500 ms showed the PTSD group experienced increases in activity in the right PFC, left parietal lobe, and left temporal pole. For incongruent stimuli at 500ms, the PTSD cohort continued to exhibit increased alpha activation in the occipital lobe, extending into the right parietal lobe. Slight increases were also seen in the left vmPFC, left temporo-parietal

junction and the cerebellum. These activity profiles remained in the same regions, albeit reduced, at 650 ms for both congruent and incongruent conditions.

Group differences in beta-band activity: In the beta band, comparisons of groups for each stimulus type revealed the PTSD group had increased activation in the right frontal lobe and decreases in the right temporal lobe at 350 ms for the congruent condition, followed by sustained increases in both hemispheres of the frontal lobes at 500 ms, followed by increased beta activation in the left PFC at 650 ms. This is seen in *Figure 3*. In the incongruent condition, the PTSD group exhibited large bi-lateral increases in activity in the parietal lobes, with more temporal lobe involvement in the left hemisphere at 350 ms post-presentation. There were also reductions in activity observed near the right superior precentral gyrus and left temporal pole at this time. At 500 ms most differences have been eliminated with the exception of slight increases remaining bi-laterally in the temporal lobes. After 650 ms, temporal lobe increases diminish to a greater exent than at 500 ms, but still remains significant.

Group differences in gamma-band activity: Gamma activity was significantly higher in amplitude and duration over a large area of cortex for the PTSD group in each condition at each time point (*Figure 4*). Primarily, the largest difference in activity for the congruent condition is seen in the right frontal lobe. There were also gamma reductions in activation in the left temporal lobe, with the largest area of reduced activity at 350 ms which continues to diminish through 650 ms. For the incongruent condition, the PTSD group displayed large increases in gamma band activation, with initial widespread bilateral fronto-temporal activity at 350 ms that decreases in size and becomes left-hemisphere dominant at 500 ms. At 650 ms, the left cerebellar and left parietal regions remain hyperactive while temporal activity differences diminish.

Group differences in high-gamma-band activity: In contrasting the PTSD group with the control group in the high-gamma band, there was little difference for the congruent condition (*Figure 5*). A small focal increase in right inferior temporal activation was observed at 350 ms, no perceivable difference was seen at 500 ms, and small focal decreases in the brainstem and left temporo-parietal junction activity were present at 650 ms. For the incongruent condition, PTSD subjects exhibited interspersed increases in cortical activation at 350 ms, mainly in the left temporo-parietal junction, left parietal lobe, and left occipital lobe. At 500 ms, reductions in left vlPFC are seen as well as focal increases in high-gamma activity in bilateral parietal and left temporal lobes. After 650 ms, decreases are observed in the PTSD group in the right vmPFC and right temporal lobe for the incongruent stimulus condition.

Stroop-Color Task: Within-group Differences

In a second set of analyses, comparisons were made between neural activity patterns during the processing of incongruent versus congruent stimuli within the PTSD and control groups. The incongruent condition was contrasted against the congruent condition such that hyperintensities represent incongruent stimulus activations that were greater than congruent stimulus activations.

Differences in alpha-band activity: In *Figure 6*, 350 ms after stimulus presentation, the PTSD group showed significant reductions in alpha activity in the superior medial parietal lobe and right temporal lobe, while the right middle occipital cortex was activated more with respect to the congruent condition. The control group exhibited only positive increases in alpha activity for the incongruent condition in the temporo-parietal cortex of both hemispheres. After 500 ms, the PTSD group displayed increased alpha activity in the left PFC, left lateral parietal lobe, and right vmPFC compared to the congruent condition. The control group revealed only left

temporo-parietal activation during the same timeframe. 650 ms after stimulus presentation, the PTSD group exhibited heightened alpha band activation in the left fronto-parietal cortex, left medial occipital lobe, and left cerebellum, while activation was decreased in the right temporal lobe. This temporal lobe decrease was also seen in controls, along with a decrease in the left cerebellum. The lateralized temporo-parietal increase in activity remained at 650 ms.

Differences in beta-band activity: In the beta band, comparisons of stimuli for each group revealed the PTSD group had widespread increased activation in the right cerebellum, right occipital cortex and right parietal cortex, while there were reductions in the left frontal lobe at 350 ms post-presentation (*Figure 7*). Controls experienced slight increased right frontal lobe activity and slightly increased right occipital activity, and reductions in activation in the left temporal lobe at 350 ms. After 500 ms, the PTSD group showed continued increased beta activity in the right cerebellum with larger reductions in the left frontal lobe that extend into the right parietal lobe, where controls only experienced reductions in the left temporo-parietal junction. At 650 ms, the PTSD group displayed only reductions in beta activation in the left frontal lobe, right superior parietal cortex, and right vlPFC with respect to the congruent condition. For the control group, they exhibited only focal increases in beta activation in the left vlPFC and right occipital cortex, and focal reductions in the left inferior temporal lobe at 650 ms.

Differences in gamma-band activity: In *Figure 8*, we observe the results of contrasting incongruent stimulus activity with congruent stimulus activity in the gamma band for each group. At 350 ms, the PTSD group shows a large increase in gamma activation in the left temporal lobe during incongruent versus congruent processing, while there is a reduction in gamma activation in the left vmPFC. At the same time point, the control group showed widespread gamma reductions in activation in the right cerebellar-occipito-parietal region and

left fronto-temporal junction for the incongruent stimulus compared to the congruent stimulus. At 500 ms, reductions in vmPFC activation increase in size and spread bilaterally while left temporal lobe hyperactivity is diminished in the PTSD group. A new region of hypoactivity emerges in the left parietal lobe. The control group had no significant difference between stimuli for gamma activity at 500 ms. The PTSD group continues to exhibit reduced frontal lobe activation with more left-hemisphere dominance at 650 ms. The area of hyperactivity seen in the left temporal lobe has spread up to the left central sulcus. The parietal focal reduction remains in the left hemisphere. At the same time, the control group only showed widespread gamma reductions in the right occipito-parietal cortex.

Differences in high-gamma-band activity: Figure 9 shows high-gamma activity contrasted between the stimulus conditions for the PTSD and control groups. The PTSD group shows small focal increases in activation in the left temporal and parietal lobes with respect to the congruent condition, which then connect at 500 ms, and spread to adjacent regions at 650 ms. The control group exhibited focal decreases in high-gamma activity at 350 ms in the left temporal, right occipital and right parietal lobes. After 500 ms, the control group only had a small increase in activation in the right OFC, which diminished to no significant difference between conditions at 650 ms.

Discussion

We performed a pilot study using MEG to examine neural activity patterns in PTSD during resting-state and task-based acquisitions. We studied five combat-exposed veterans with an average PCL-5 score of 43.6, compared to five healthy civilian subjects with average PCL-5 score of 1.6. Our overall goal was to replicate and extend upon previous published studies of changes in cortical activity in individuals with PTSD. Despite our small sample size, significant

differences were found between the two groups in cortical activity at rest (in delta, theta, gamma, and high-gamma neural oscillatory frequency bands) and during the Stroop Color-Naming task (in alpha, beta, and gamma, and high-gamma frequency bands). We discuss these findings in detail below.

Resting-State Condition

The reduced delta band (1-4 Hz) resting-state activity observed in the right vmPFC, right dlPFC, left temporo-parietal junction, and the right parieto-occipital cortex in the PTSD group is in contrast to previous findings reported by Kolassa et al. (2007). They noted *enhancement* of delta activity in the left temporal areas in the region of the insula along with fewer slow waves in parieto-occipital regions. Upon analysis of maximal z-values in pre-selected regions, they also found larger absolute values over left temporal, left central, left parieto-occipital and right frontal regions. In another study of delta activity in psychiatric patients, Wienbruch et al. (2003) found that reductions in frontal and prefrontal delta band resting-state activity were highly correlated with depression. It is possible that finding widespread frontal lobe decreases in delta activity was due to depression among subjects in the PTSD group, since depression is often co-morbid with PTSD (Buckley et al., 2000). Future MEG investigations of the resting state should include a depression symptom inventory in order to clarify these findings.

Theta band (4-7 Hz) activity is typically associated with spatial navigation (de Araujo, Baffa, & Wakai, 2002), attentional control (Tesche & Karhu, 2000), working memory (Jensen & Tesche, 2002), and cognitive flexibility (Steinmann & Gutschalk, 2012). In the present study, theta band activity was reduced in the left fronto-temporal, right posterior parietal, right lateral parietal, and right posterior temporal lobes for the PTSD group, with the greatest area of difference in the parietal lobe. This is somewhat consistent with research examining the

functional connectivity in this frequency band in veterans with PTSD (Dunkley et al., 2015); theta band hyperconnectivity in the right superior parietal lobe was associated with poorer performance on a set-shifting task, leading the authors to conclude that hyperconnectivity was detrimental to mental flexibility. Overall, the findings are suggestive of impairments in parietal cortex theta-band neural activity. The resting-state condition does not provide any cognitively-demanding tasks by definition. Therefore, future studies should examine the interplay between lower resting-state theta activity and task-induced hyperconnectivity in the parietal lobe to determine the relationship between these observations and PTSD symptoms.

Focal alpha band activity was reduced in the right dmPFC and right posterior temporal cortex, but these regions of difference were small and may possibly be the result of noise or artifact. M. X. Huang et al. (2014) found more reductions in the frontal lobe that we observed, but also saw alpha activity reductions in the temporal and parietal lobes. In their study, they also found a small region of heightened activation in the left occipito-temporo-parietal junction, an observation that was not seen in the present study. The authors suggest that normal alpha rhythm is linked to functional inhibition: the higher the alpha power, the less functional connectivity required. Regions of hypoactivity in the alpha band would imply overall reductions in behavioral inhibition to emotional stimuli originate through a lack of neuronal inhibition. This was not observed in the present study.

Differential beta activity was observed in the resting-state condition, but consisted only of small, focal reductions in activation in the left cerebellum. Due to the size of the sample, this small region of difference is also probably the result of noise. It is important to note that other studies of the Stroop-color task placed a low-pass filter at 40 Hz (Galer et al., 2015). If the

current finding is in fact significant, how reduced left cerebellar activity relates to PTSD remains unclear and should be pursued further.

There was differential activation observed in the gamma band, with hyperactive regions in the left temporal and lateral parietal cortices and right posterior temporal lobe and a region of hypoactivity in the right temporal pole. These findings were generally consistent with those of M. X. Huang et al. (2014), although they found many more significant regions of differential activity. This is most likely due to the weak statistical power afforded by the small sampling size in the current study, whereas Huang and colleagues used 25 people with PTSD and 30 healthy controls in their study. Despite the small numbers of subjects, it is quite revealing that even with this small sample size, we were able to differentiate those with PTSD from controls in many of the same regions.

Analysis of the resting-state data in the high-gamma bad revealed a large region of hyperactivity in the right posterior temporal lobe and right occipito-temporo-parietal junction, along with increases in the left medial temporal lobe, left ventral occipital lobe, and left cerebellum. We did notice a small region of reduced high-gamma activity in the right temporal pole. Our analysis generally comports with that of M. X. Huang et al. (2014). Differences seen in their research not seen in the present study include increased high-gamma activity in the left OFC and left occipito-temporo-parietal junctions, and decreased activity in the medial PFC and right central sulcus. Again, these differences between the present study and those of M. X. Huang et al. (2014) are most likely due to the small sample size in this study.

Stroop-Color Task

This investigation confirmed much of what has already been published regarding the Stroop-color task in controls, but offered new insight into the effects of PTSD on cognitive

control. Previous research into the Stroop effect using MEG found significant differences between incongruent and congruent stimuli in the left pre-supplementary motor area (pre-SMA) and the posterior parietal cortex (PPC) (Galer et al., 2015). Based on this evidence, we contrasted the PTSD and control groups for each stimulus condition (between groups), then contrasted the incongruent and congruent stimuli for each group (within groups).

Between Groups Comparison: Congruent vs. Incongruent

Differences in alpha-band activation: The PTSD group exhibited larger alpha-band activations during each time point for the congruent condition compared to healthy controls. The majority of the increased activity was lateralized to the left hemisphere. For the incongruent condition, more occipital activation was seen throughout the time course, but the PTSD group exhibited reductions in alpha activation in the temporal lobes at 350 ms. The reduction in alpha activation during a more difficult task is interesting since alpha waves are indicative of functional inhibition. It is reasonable to see these reductions during a more demanding condition in those with PTSD. However, the widespread alpha-band activity increases seen in the present study are novel and require further investigation.

Differences in beta-band activation: Primarily, the PTSD group showed increased beta activation with respect to controls in the left PFC and right vmPFC for the congruent condition. This implies more long-range communication and perhaps less cognitive efficiency than controls. The incongruent condition shows that the PTSD group had increased bilateral temporal and parietal activation and decreased activation in the frontal and motor cortices. During the more challenging incongruent condition, the PTSD group shows reduced activity in areas related to conflict resolution and decision-making. This is generally consistent with the symptoms of PTSD.

Differences in gamma-band activation: Similar to alpha-band comparisons, the PTSD group showed widespread increased gamma activations for both the congruent and incongruent conditions compared to controls. If gamma is indicative of local cognitive processing, we see much more frontal lobe activity during the congruent condition and much more parietal activation for the incongruent condition for the PTSD group. One possible explanation for this would be that those with PTSD have a less efficient processing system, relying more on a broader range of neurons to help evaluate a situation rather than utilizing a few, highly-specialized neurons.

Differences in high-gamma-band activation: There was little difference between groups on the congruent stimuli. The small differences observed are most likely due to noise. The incongruent condition shows larger areas of difference, with the greatest reductions in the right frontal pole and greatest increases in the left fronto-temporal junction. This shows that in the more challenging incongruent condition, those with PTSD are less active in inhibitory regions and more active in language-processing regions.

Within-Groups Comparison: PTSD vs. Healthy Controls

Differences in alpha-band activation: The control group exhibited the expected result of increased left temporo-parietal activation in the incongruent condition compared to the congruent condition. This is most likely as a result of processing of semantic meaning and response selection (West, Jakubek, Wymbs, Perry, & Moore, 2005). In the PTSD group, there were only small local regions of increased activity in the left hemisphere, with a large reduction in alpha activity in the right temporo-parietal junction. This pattern of reduced activation in the 350 ms window is novel, but it is interesting to see that this is the exact opposite activation pattern as controls at this same time point.

Differences in beta-band activation: The healthy controls showed differences in reduced left temporo-parietal junction activation with intermittent increases in the right medial frontal lobe, right occipital lobe, and left OFC in the incongruent condition. The PTSD group displayed large lateralized reductions in beta activation in the left frontal lobe and large increases in right occipital activation. Although these findings are difficult to interpret, it is generally consistent with our resting-state data in the same frequency band.

Differences in gamma-band activation: Contrasting incongruent and congruent stimuli in the gamma band revealed widespread left fronto-temporal and right occipito-temporo-parietal junction activation for the control group, while the PTSD group showed smaller medial frontal lobe reductions and large increases in gamma activation in the left temporo-parietal cortex. It is possible that during the incongruent condition, those with PTSD are unable to suppress the language-processing regions when needed, although it must be noted that there was no statistical difference between the two conditions for the control group during the 500 ms window.

Differences in high-gamma-band activation: Healthy controls displayed little difference between incongruent and congruent stimuli. In fact, the last time window showed no statistically significant difference between conditions. However, the PTSD group showed a large region of increased activation in the left parietal lobe. This may be indicative of large-scale recruitment of neurons to process the incongruent stimuli.

Limitations

When conducting a study examining a particular variable, it is important to minimize the number of extraneous confounding variables and isolate the independent variable. One major flaw in the design of this study was that although age differences were minimized within groups, between groups there was a highly significant effect of age (t-test: $p < 0.009$). Although it is

highly unlikely that the differences observed were due to age alone, future research must utilize age-matched controls. This study design could provide more accurate information on neural differences in PTSD patients if the control group would be as similar to the PTSD group as possible. Ideally, a future study would include combat veterans exhibiting symptoms of PTSD, combat veterans never diagnosed with PTSD, and military veterans without lifetime trauma exposure, and civilians without lifetime trauma exposure. This study would isolate the variable of interest, PTSD, by controlling for other variables such as age, trauma exposure, and military service.

The biggest limitation of this study was the small sample size. Statistically, it is impossible to determine meaningful and reliable differences between groups with only five people in each group. This was evidenced in the processing of the data, in which visualization of significant differences between groups utilizing the statistical non-parametric mapping method ($p < 0.05$) could only be achieved without corrections for multiple comparisons. Corrections for multiple comparisons, such as limiting the false detection rate mathematically separate the "signal" from the "noise". Indeed, many of the observations made from this study could be due to noise. Significant statistical power could be established with sample sizes as small as thirty per group (Schacht & Aspelmeier, 2005), although drawing conclusions about the general population would still be difficult at that sample size.

Conclusion

Despite the small sample size, we were able to replicate some aspects of previous MEG research in veterans with PTSD. Not only does this result substantiate the use of MEG for population studies, but it also shows that PTSD is a mental disorder that is physical in nature and can be characterized through passively observing electromagnetic neuronal activity.

This research aimed to shed light on the neural differences associated with combat-related post-traumatic stress disorder. The motivation behind this research stems from the need to legitimize mental health disorders as real, physical manifestations of psychological injury. Countless veterans have been told that the symptoms they experience are simply "all in their head" and that they just need to "snap out of it". Many military families can attest to the reality of the effects of combat-induced PTSD and have been torn apart as a result. The divorce rate among military service members and veterans is substantial. Homeless veterans are a large portion of the homeless population. Without a doubt, service members who have at one time in their lives written a blank check to this nation for up to and including his or her life have returned home to find themselves dealing with such difficult symptoms such as insomnia and general irritability, leading to social avoidance and being unable to find meaning or purpose in civilian life.

There is a desperate need for a better understanding of the long-term cognitive effects of combat deployments on service members. Mental health is important for everyone, including the men and women of the Armed Forces. We must as a nation dedicate more resources to uncovering the neural correlates of PTSD in order to better understand how to treat the symptoms in those dealing with them, and discover new ways to increase resiliency against the initial development of PTSD for those who will inevitably fight America's future wars.

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Appendix

Table 1. *Cognitive-behavioral assessment measures for PTSD and control participants.*

		PTSD (n=5)	Control (n=5)	*t*-test	*df*	Significance
Age	Mean (SD)	33.8 (4.55)	23.6 (0.89)	4.92	4.31	0.008**
BTQ	Mean (SD)	3.8 (2.05)	0.2 (0.45)	3.84	4.38	0.018*
PCL5	Mean (SD)	43.6 (12.4)	1.6 (1.67)	7.53	4.15	0.002**
OSU TBI	Mean (SD)	2.8 (1.30)	1.2 (1.64)	1.71	7.61	0.132

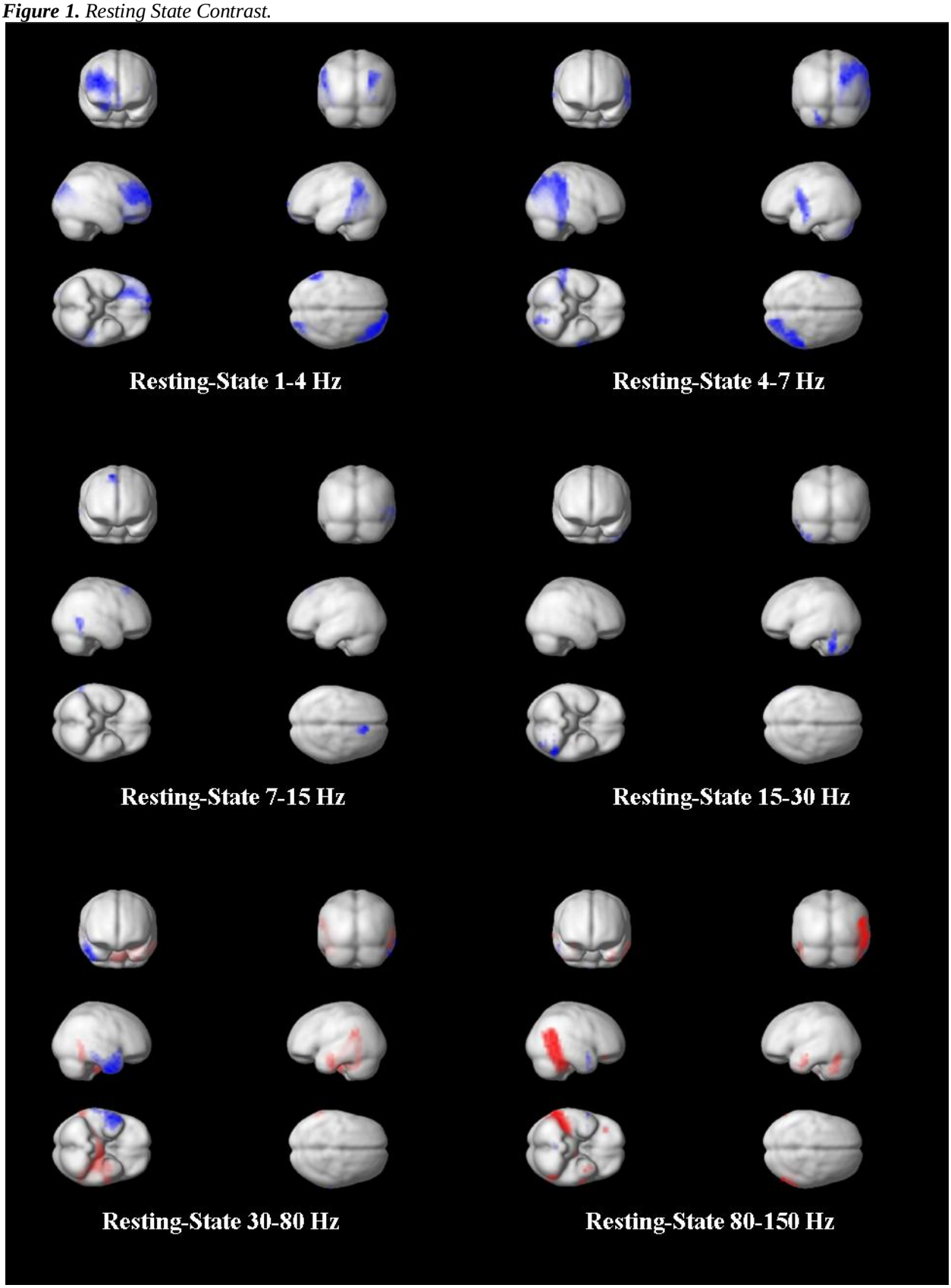
*All statistical tests were performed using Welch's unequal variances t-test. * denotes p < 0.05; * * denotes p < 0.01. BTQ, Brief Trauma Questionnaire; PCL5, Post-Traumatic Stress Disorder Checklist for the DSM V; OSU TBI, Ohio State University TBI Identification Method – Short Form*

Table 2. *Behavioral performance on Stroop-Color Task.*

		PTSD (n=5)	Control (n=5)	*t*-test	*df*	Significance
Inter-stimulus Interval	Mean (SD)	1.367 (0.54)	1.340 (0.83)	0.37	7.24	0.722
Correct Responses	Mean (SD)	202.2 (48.5)	228.6 (9.34)	-1.20	4.30	0.298
	% (SD)	96.63 (2.75)	97.77 (1.70)	-0.78	6.68	0.463
Incorrect Responses	Mean (SD)	7.6 (6.62)	5.2 (3.83)	0.70	6.41	0.509
	% (SD)	3.37 (2.75)	2.24 (1.70)	0.78	6.68	0.463
Missing Responses	Mean (SD)	5.4 (10.43)	5.8 (7.63)	-0.07	7.33	0.947
	% (SD)	2.56 (4.80)	2.57 (3.40)	-0.005	7.21	0.996

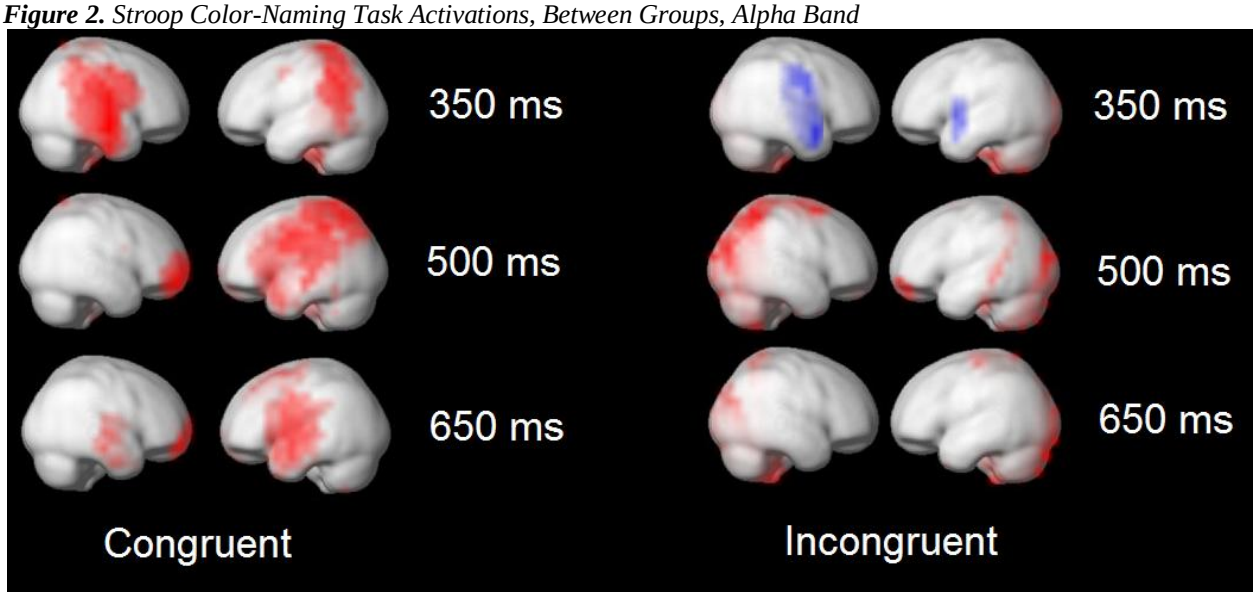
All statistical tests were performed using Welch's unequal variances t-test. Number of trials presented was different between participants.

Figure 1. *Resting State Contrast.*



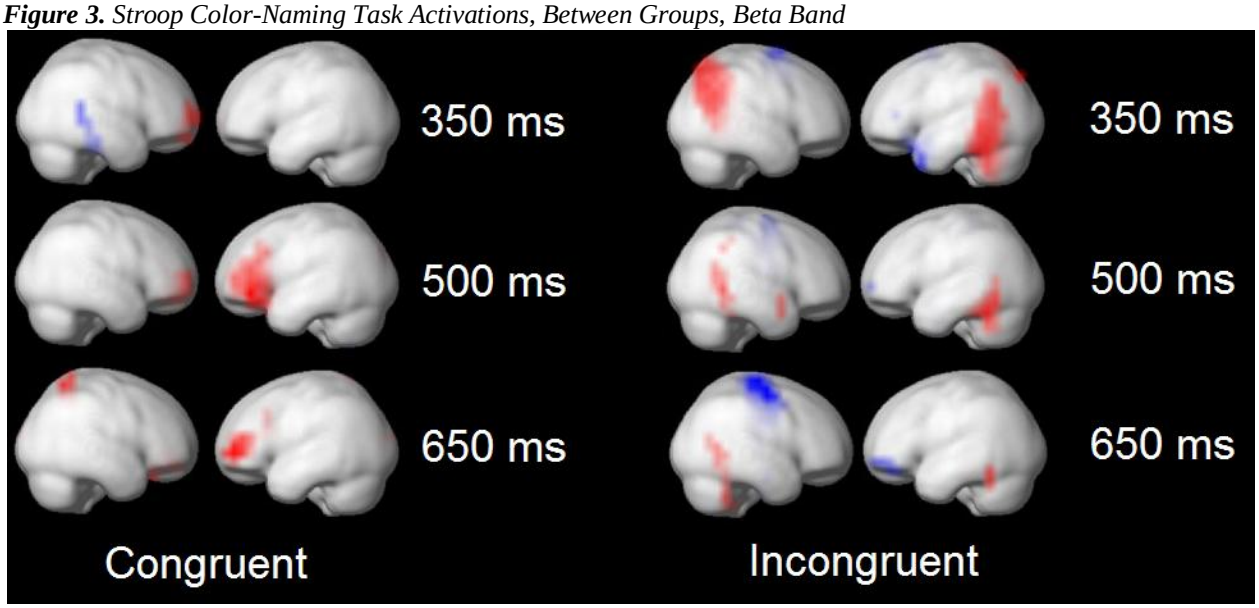
SnPM uncorrected, p < 0.05. Hyperactivity: PTSD > Controls.

Figure 2. *Stroop Color-Naming Task Activations, Between Groups, Alpha Band*



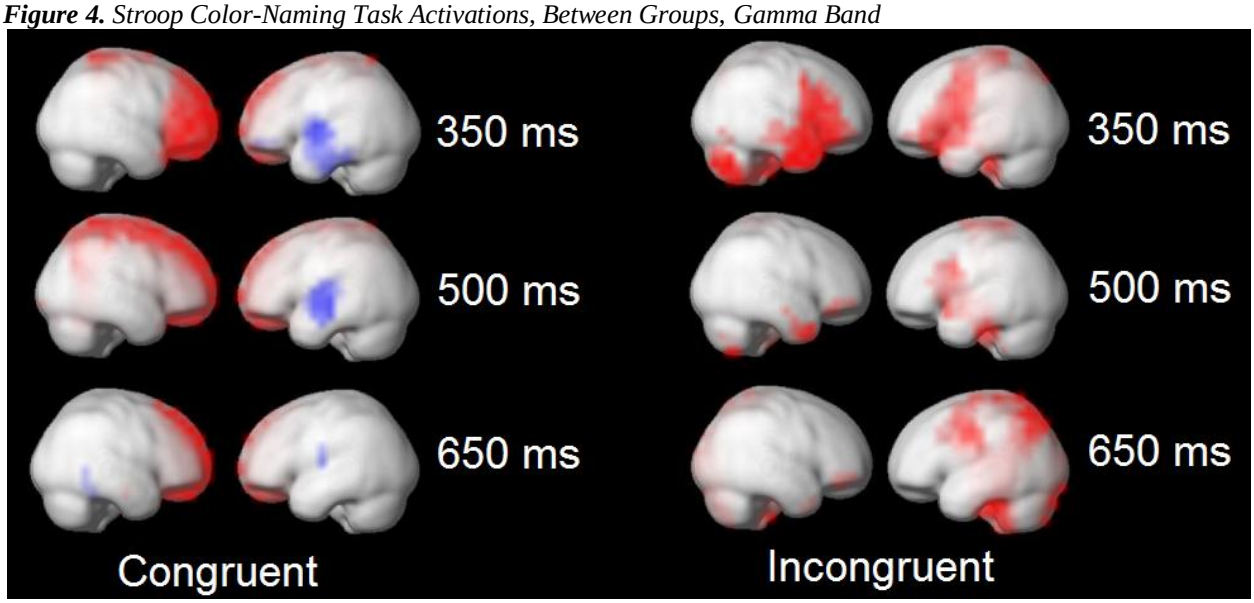
SnPM uncorrected, p < 0.05. Hyperactivity: PTSD > Controls.

Figure 3. *Stroop Color-Naming Task Activations, Between Groups, Beta Band*



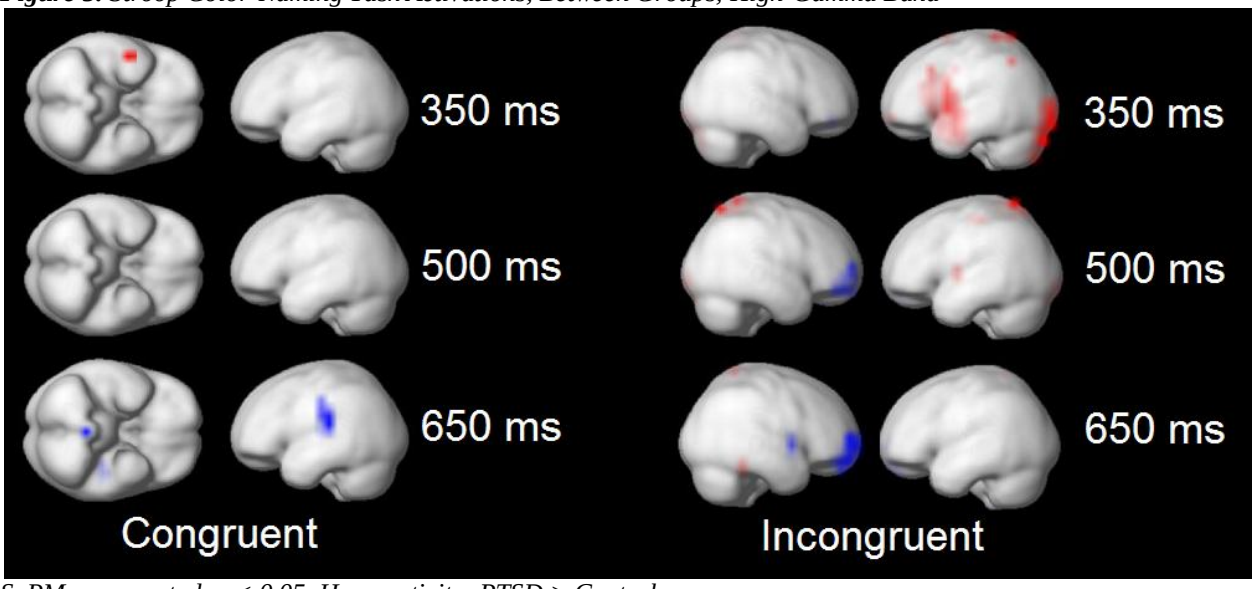
SnPM uncorrected, p < 0.05. Hyperactivity: PTSD > Controls.

Figure 4. *Stroop Color-Naming Task Activations, Between Groups, Gamma Band*



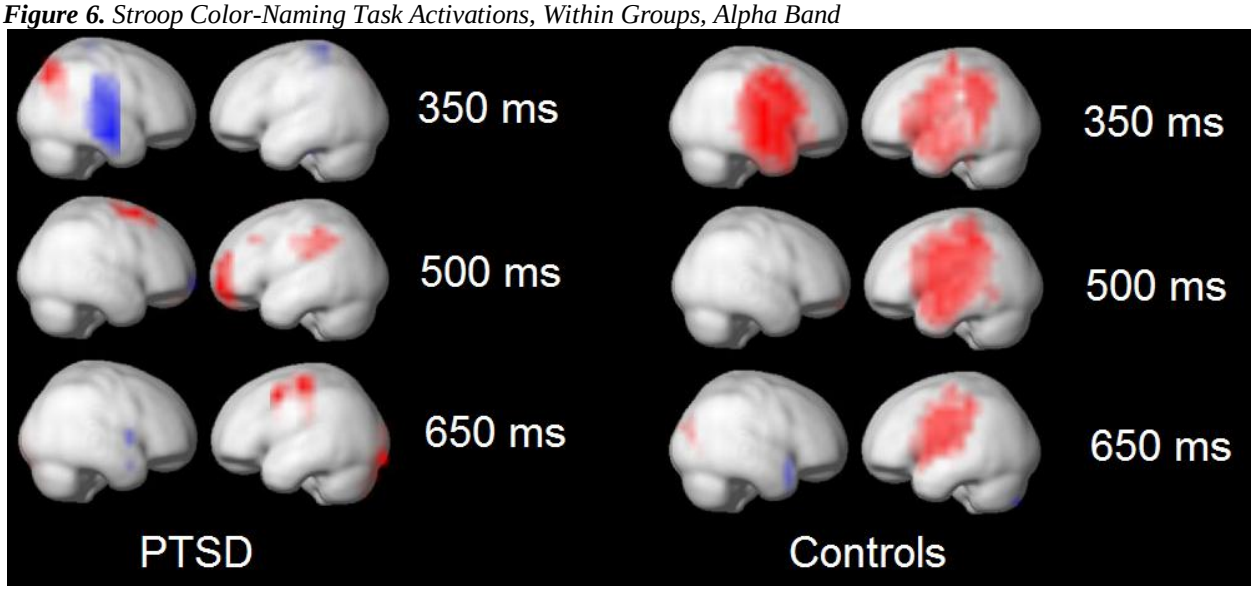
SnPM uncorrected, p < 0.05. Hyperactivity: PTSD > Controls.

Figure 5. *Stroop Color-Naming Task Activations, Between Groups, High-Gamma Band*



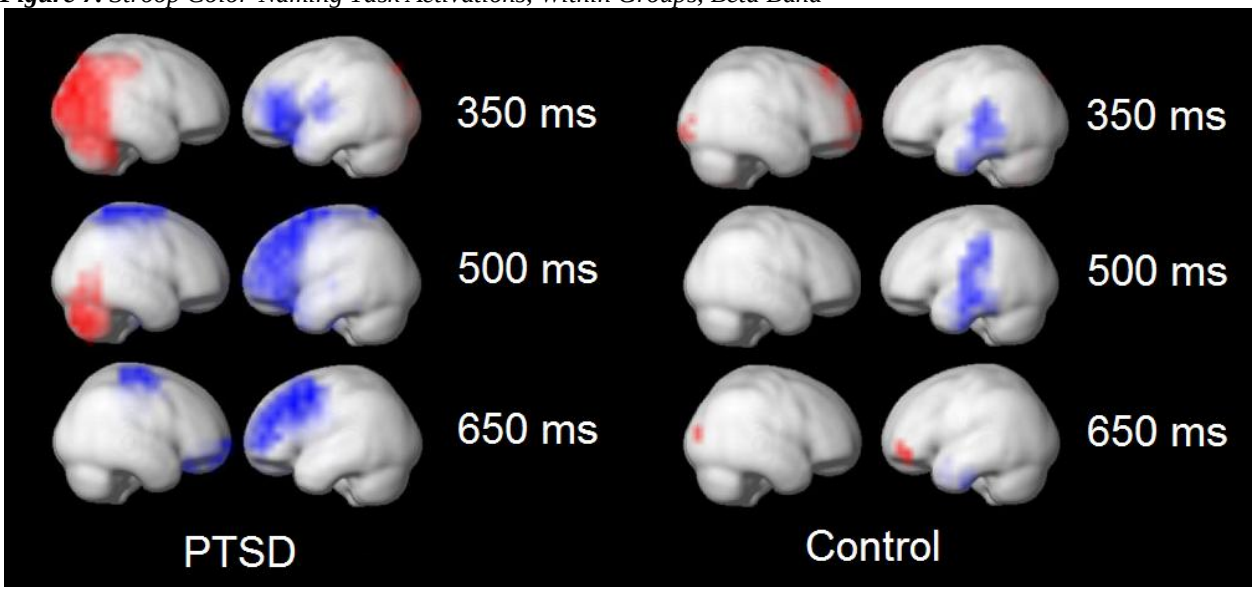
SnPM uncorrected, p < 0.05. Hyperactivity: PTSD > Controls.

Figure 6. *Stroop Color-Naming Task Activations, Within Groups, Alpha Band*



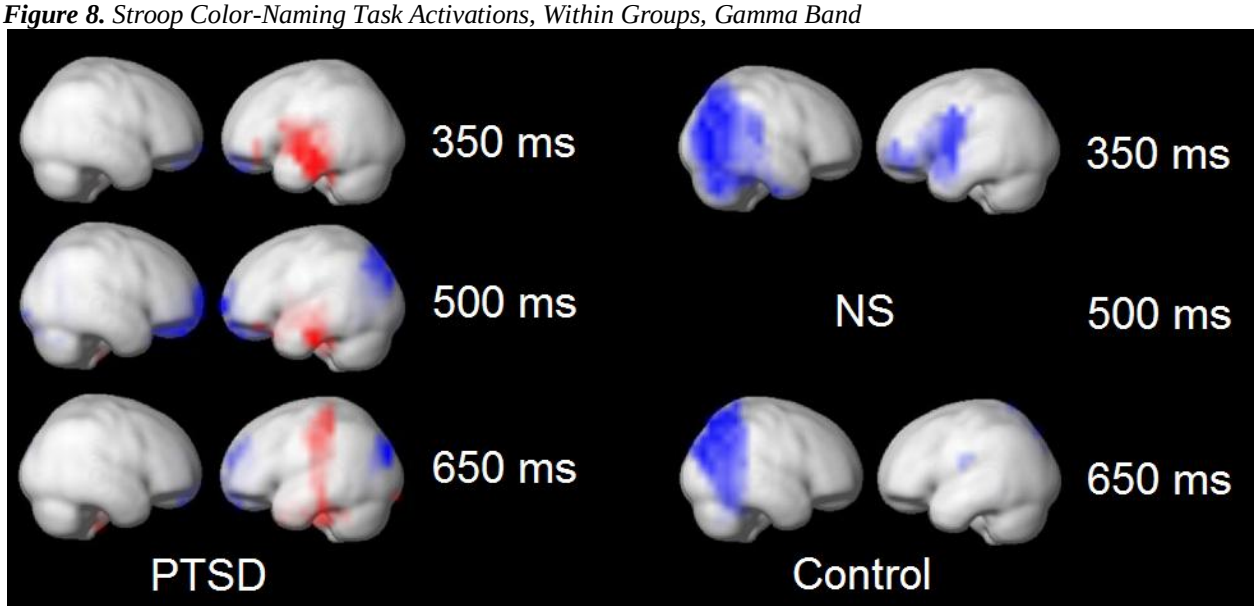
SnPM uncorrected, p < 0.05. Hyperactivity: Incongruent > Congruent.

Figure 7. *Stroop Color-Naming Task Activations, Within Groups, Beta Band*



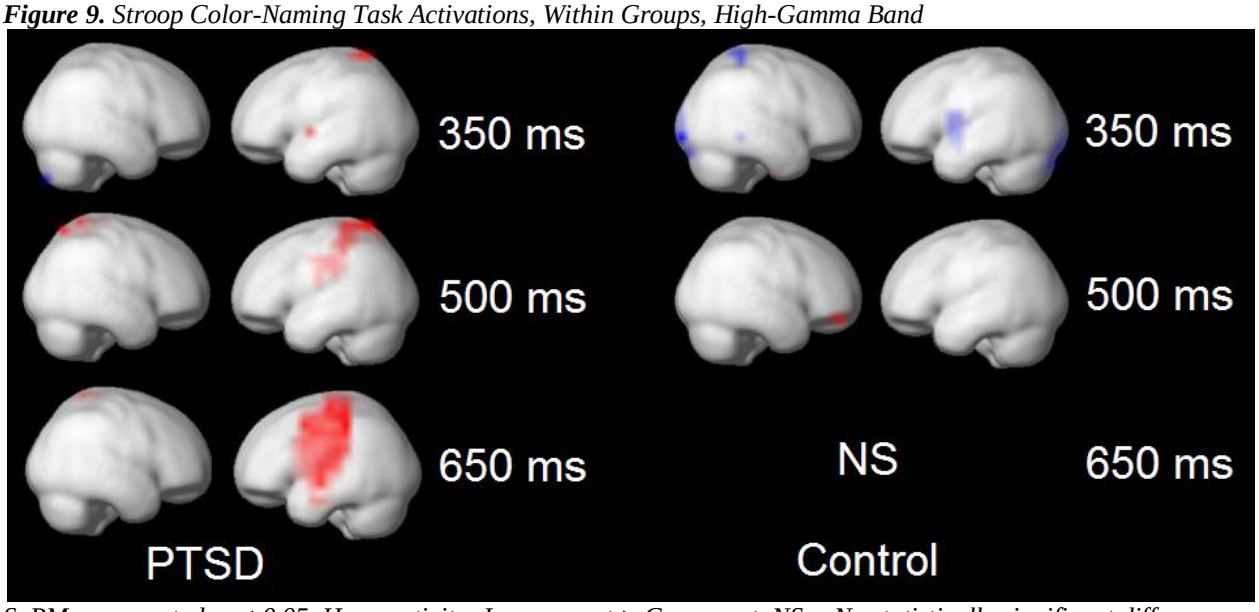
SnPM uncorrected, p < 0.05. Hyperactivity: Incongruent > Congruent.

Figure 8. *Stroop Color-Naming Task Activations, Within Groups, Gamma Band*



SnPM uncorrected, p < 0.05. Hyperactivity: Incongruent > Congruent. NS = No statistically significant difference.

Figure 9. *Stroop Color-Naming Task Activations, Within Groups, High-Gamma Band*



SnPM uncorrected, p < 0.05. Hyperactivity: Incongruent > Congruent. NS = No statistically significant difference.

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