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RESEARCH ARTICLE

MEG neural signature of sexual trauma in women veterans with PTSD

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Abstract

Previous research has documented the utility of synchronous neural interactions (SNI) in classifying women veterans with and without posttraumatic stress disorder (PTSD) and other trauma-related outcomes based on functional connectivity using magnetoencephalography (MEG). Here, we extend that line of research to evaluate trauma-specific PTSD neural signatures with MEG in women veterans. Participants completed diagnostic interviews and underwent a task-free MEG scan from which SNI was computed. Thirty-five women veterans were diagnosed with PTSD due to sexual trauma and sixteen with PTSD due to non-sexual trauma. Strength of SNI was compared in women with and without sexual trauma, and linear discriminant analysis was used to classify the brain patterns of women with PTSD due to sexual trauma and non-sexual trauma. Comparison of SNI strength between the two groups revealed widespread hypercorrelation in women with sexual trauma relative to those without sexual trauma. Furthermore, using SNI, the brains of participants were classified as sexual trauma or non-sexual trauma with 100% accuracy. These findings bolster evidence supporting the utility of task-free SNI and suggest that neural signatures of PTSD are trauma-specific.

Keywords Posttraumatic stress disorder · Magnetoencephalography · Biomarker · Sexual trauma

Introduction

Posttraumatic stress disorder (PTSD) commonly occurs as a result of exposure to potentially traumatic events including combat, physical or sexual assault, natural or human-made disasters, and life-threatening illness or injury (American Psychiatric Association 2013). Female veterans experience particularly high rates of trauma exposure both within and outside of the military and, consequently, have significantly higher rates of lifetime and past-year PTSD than male veterans and civilians of either sex (Lehavot et al. 2018; Street et al. 2009; Wisco et al. 2014; Zinzow et al. 2007). Although estimates vary, up to 93% of female veterans report lifetime exposure to any potentially traumatic event with up to 64% reporting lifetime sexual assault (Suris et al. 2007; Zinzow et al. 2007). Interpersonal trauma is particularly likely to be associated with PTSD (Kessler et al. 2017). An estimated 13% of women veterans meet lifetime criteria for PTSD (Lehavot et al. 2018) which includes persistent intrusive re-experiencing, avoidance of trauma-related stimuli, negative alterations in mood and cognition, and marked physiological arousal and reactivity (APA 2013). PTSD is also associated with significant physical and psychiatric health impacts and reduced quality of life among women veterans (Dobie et al. 2004; Suris et al. 2007; Kelly et al. 2011; Wisco et al. 2014; Goldberg et al. 2019).

Decades of neuroimaging research have documented neurobiological alterations associated with PTSD. As summarized in recent reviews, brain structures and networks involved in fear learning, memory, salience detection, and contextual processing have been widely implicated in PTSD (Harnett et al. 2020; Liberzon and Abelson 2016; Neria 2021; Ross and Cisler 2020). Recently,

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magnetoencepahography (MEG) has been applied to the study of PTSD. MEG studies have shown that resting-state neural network alterations distinguish veterans with PTSD from control participants with remarkable accuracy (Georgopoulos et al. 2010; Engdahl et al. 2010; James et al. 2021, 2022; Zhang et al. 2020). MEG studies investigating almost exclusively male veterans have documented few albeit robust anomalous resting-state synchronous neural interactions (SNI) in veterans with PTSD involving the right superior temporal and parieto-occipital areas, as well as bilateral medial temporal areas, sensorimotor, and prefrontal regions (Engdahl et al. 2010; James et al. 2021; Badura-Brack et al. 2017). In the only prior MEG PTSD study of exclusively women veterans, women were classified as PTSD or control with 100% accuracy, and additional involvement of left temporal involvement was documented (James et al. 2022). These MEG studies provide compelling evidence regarding the discriminatory power of MEG and the potential utility of intrinsic functional connectivity as a useful biomarker of PTSD.

Here, we extend that line of research beyond characterizing neural signatures of PTSD to evaluate trauma-specific alterations using MEG. A recent meta-analysis documented trauma-specific gray matter alterations in individuals with PTSD compared to trauma-exposed controls, in addition to general alterations involving the prefrontal-limbic-striatal system associated with PTSD (Meng et al. 2016). Similarly, a functional magnetic resonance imaging (fMRI) activation-likelihood meta-analysis found a common neural substrate of PTSD shared across various trauma types in addition to evidence of trauma-specific networks (Boccia et al. 2016). Those analyses, however, were based on studies evaluating activation during experimental paradigms aimed at invoking affective responses or investigating specific cognitive domains; consequently, it is unclear whether the trauma-specific neural patterns reflect underlying neural alterations or capture task-related processes. Here, we use resting-state MEG to evaluate trauma-specific PTSD neural signatures in the absence of task influence in a sample of women veterans with sexual trauma or non-sexual trauma.

Methods

Study participants

A total of 51 women veterans with PTSD were included in the present study. Current and lifetime mental health diagnoses were evaluated by doctoral level psychologists with the Clinician Administered PTSD Scale (Weathers et al. 2013) and Structured Clinical Interview for DSM-5 (First et al. 2015) according to DSM-5 diagnostic criteria (American Psychiatric Association 2013). All participants met current full diagnostic criteria for PTSD, probable or subthreshold PTSD. Participants were characterized according to the index trauma reported during the CAPS interview as either sexual trauma (ST; $N=35$) or non-sexual trauma (NST; $N=16$) for subsequent analyses. Seven of the 16 NST participants (43.5%) and 14/35 (40%) of ST also met criteria for depressive disorder. Participants also completed the Sexual Harassment scale of the Deployment Risk and Resilience Inventory–2 (DRRI-2; Vogt et al. 2012) which evaluates exposure to unwanted sexual contact or harassment during deployment. The study protocol was approved by the Minneapolis VAHCS institutional review board. All participants provided informed consent prior to participating in the study and were paid for their participation.

MEG data acquisition

All participants underwent a MEG scan. As described previously (Georgopoulos et al. 2007), subjects lay supine within the electromagnetically shielded chamber and fixated their eyes on a spot 65 cm in front of them, for 60 s. MEG data were acquired using a 248-channel axial gradiometer system (Magnes 3600WH, 4-D Neuroimaging, San Diego, CA), band-filtered between 0.1 and 400 Hz, and sampled at 1017.25 Hz. Data with artifacts (e.g., from excessive subject motion) were eliminated from further analysis.

Data analysis

Standard statistical methods were used to analyze the data, including analysis of variance (ANOVA), linear regression, Pearson correlation, and linear discriminant analysis (LDA). The following packages were employed: (IBM SPSS Statistics for Windows, Version 27.0, 64—bit edition. Armonk, NY: IBM Corp; 2020), MATLAB (MATLAB and Statistics Toolbox Release 2015b. Natick, MA: The MathWorks, Inc. 2015), and ad hoc Fortran computer programs employing the International Mathematics and Statistics Library (IMSL; Rogue Wave Software, Louisville, CO, USA) statistical and mathematical libraries.

MEG data processing

Processing of the raw MEG series was performed using programs in Python (Mahan et al. 2015). Single trial MEG time series from all sensors underwent 'prewhitening' (Box and Jenkins 1976) using a (50,1,3) ARIMA model to obtain practically white noise innovations (i.e., residuals) (Mahan et al. 2015). All possible pairwise zero-lag crosscorrelations ($N=30{,}628$, given 248 sensors) were computed between the prewhitened MEG time series. Finally, the partial zero-lag crosscorrelations PCC_{ij}^{0}(SNI) between i and j sensors were computed for all sensor pairs. PCC_{ij}^{0} was transformed to z_{ij}^{0} using Fisher's z transformation (Fisher 1958) to normalize its distribution:

$$\mathrm{SNI} = z_{ij}^{0} = \mathrm{atanh}(\mathrm{PCC}_{ij}^{0}) \quad (1)$$

Comparison of SNI strength between NST and ST groups

For this comparison, we used the absolute value of SNI, |SNI|, as a measure of the strength of pairwise association of MEG time series. The difference between the two groups on this measure was evaluated using an independent samples t test for each one of the 247 sensors, and the P value was adjusted for 247 comparisons using the Bonferroni inequality. The results of these 247 tests further served to identify the pattern of ST vs. NST differences in sensor space by using the signed t value (ST-NST).

Linear discriminant analysis (LDA)

In this analysis, we used the functional brain patterns (SNI; Georgopoulos et al. 2007) to classify brains of participants with PTSD due to sexual trauma (ST, $N=35$) or non-sexual trauma (NST, $N=16$) groups. For that purpose, we used the SNIs in a stepwise LDA analysis, as follows. For each brain, there were 247 SNIs available for each one of the 248 sensors (one sensor was inoperative). For each sensor, we used the maximum and minimum SNI value (Engdahl et al. 2016) as input ($N=247\times2=494$ predictors) to a stepwise LDA to classify NST and ST brains, including a Leave-One Out (LOO) cross-validation procedure. For each case (brain), we retained the discriminant score, the probability of classification to a group, and the Mahalanobis D^2 distances (Mahalanobis 1936) of each case from the center of the ST and NST centroid clusters.

Results

Age

The age did not differ significantly between the NST and ST groups (NST, mean ± SEM: 43.8 ± 2.53, $N=16$; ST: 46.3 ± 2.0, $N=35$; $P=0.486$, independent samples t test).

DRRI-2 sexual harassment

DRRI-2 Sexual Harassment scale score was available for 13/16 NST and 28/35 ST participants. The Sexual Harassment score was significantly higher in the ST (vs NST) group (NST: 7.23 ± 1.41, $N=13$; ST: 11.64 ± 1.22, $N=28$; $P=0.0036$, independent samples t test) (Fig. 1).

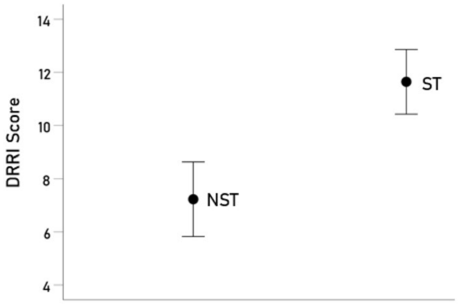

Fig. 1 Group differences on DRRI-2 Sexual Harassment score for ST and NST groups

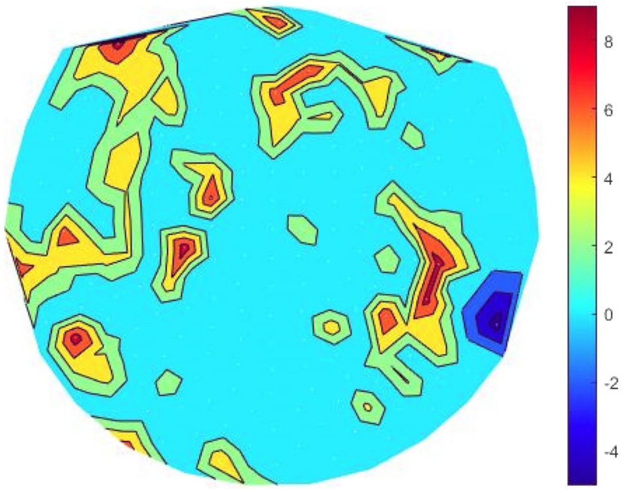

Fig. 2 Brain pattern of signed t values of ST-NST comparison with absolute values corresponding to $P<0.000202$, Bonferroni corrected for 247 multiple comparisons. See text for details

Comparison of SNI strength between NST and ST groups: brain networks involved in ST vs NST discrimination

For each t test on the difference between the two groups on |SNI| in a given sensor, there were 12,597 values available in total (NST group: $N=247$ sensors × 16 brains = 3952; ST group, $N=247\times35=8645$), and, hence, 12,595 degrees of freedom for the test. Since 247 comparisons were made, for a Bonferroni corrected test, the nominal P value of $P<0.05$ was adjusted to a corrected $P<0.05/247$ ($P<0.000202$), corresponding to a t value of $t_{[12595]}=3.717$ (for $P<0.000202$). The distribution of signed t values (for ST-NST comparisons) in sensor space meeting these criteria is shown in Fig. 2. It can be seen that ST is associated with widespread SNI hypercorrelation, involving several brain areas, including prominent involvement of left frontal and temporo-occipatal cortex, midline frontal, left central sulcus, and bilateral posterior parietal areas.

Classification of ST and NST brains

The stepwise LDA yielded a 100% correct classification of NST and ST brains: All 16 NST and 35 ST brains were correctly classified; the same 100% correct classification was obtained by the leave-one-out cross-validation. The frequency distribution of the discriminant scores is shown in Fig. 3; it can be seen that they were well separated without any overlap. Of the 494 predictors available, only 26 (5.3%) were used by the LDA for the 100% correct classification, a very small percentage. Wilk's lambda was 0.001, a highly statistically significant value (chi-square = 261.2, $df = 26$, $P = 1.1 \times 10^{-40}$). The Mahalanobis D^2 distances from the center of the ST and NST centroid clusters for each subject are plotted in Figs. 4 and 5 for the NST and ST groups, respectively.

Association between sexual harassment and mahalanobis D^2 distances

The DRRI-2 Sexual Harassment score was significantly positively associated with Mahalanobis D^2 from the NST centroid ($r = 0.322$, $P = 0.04$, $N = 41$) and negatively associated with D^2 from the ST centroid ($r = -0.332$, $P = 0.034$, $N = 41$).

Discussion

Methodological considerations: MEG

The results of this study revealed significant SNI differences between the NST and ST groups. We discuss below differences in MEG signal analysis between this study and other, more conventional methods of MEG analysis (Hämäläinen et al. 1993). Such methods commonly aim at source modeling following the application of an adequate stimulus. The stimulus is thought to elicit the simultaneous activation of tens of thousands of pyramidal cells in the cerebral cortex through excitatory postsynaptic potentials on their apical dendrites. These potentials produce large electromagnetic fields that are detected by the MEG sensors and collected as a sampled time-varying MEG signal. Now, this signal contains components that are time-locked to the stimulus as well as others that are not. Source modeling relies on the former which, however, are very weak in single trials. For that purpose, many traces from a large number of trials (e.g., 100 or more) are typically averaged to obtain a stimulus-locked waveform from which the location and strength of the source are derived. This is made possible because the stimulus-aligned averaging cancels substantial brain activity asynchronous to the stimulus. In fact, this is the basis for various applications in neuroscience, including sensory-evoked and event-related potentials in electroencephalography, spike-triggered averaging in neurophysiology, event-related designs in fMRI, etc. In summary, conventional source modeling makes use of only a small part of the signal,

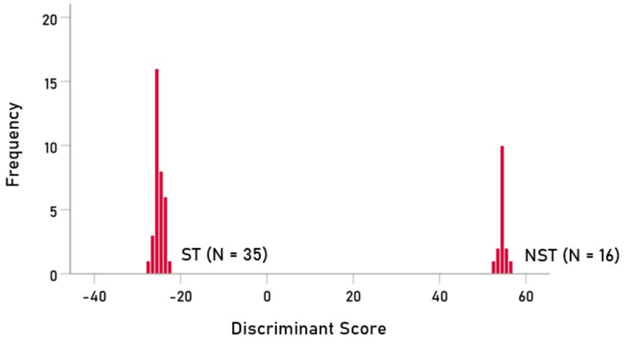

Fig. 3 Frequency distribution of discriminant scores

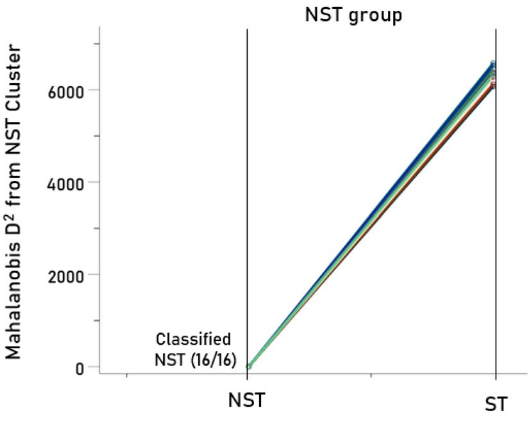

Fig. 4 Mahalanobis D^2 values for NST group

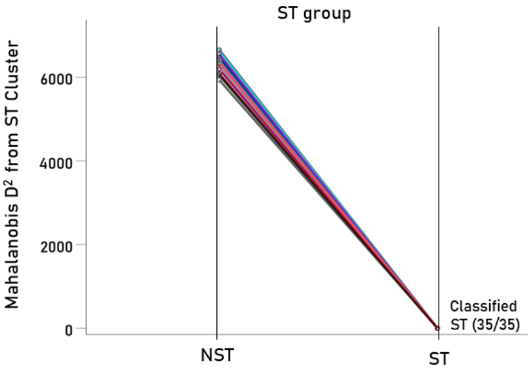

Fig. 5 Mahalanobis D^2 values for the ST group

namely that which is stimulus time-locked. The averaged MEG waveform that comes from such stimulus-locked activity reflects a mixture of interrelated neural processes thought to occur in apical dendrites with a spatial extent of the order of ~ 10 mm^2 (Hämäläinen et al. 1993). However, more recent work (Murakami and Okada 2006) indicates that significant contributions to the MEG signal may also come from generators other than the apical dendrites of pyramidal cells. Some of these sources may not survive the averaging process, and, therefore, may not contribute to source modeling.

The situation in the present study is different, mainly because we acquire spontaneous MEG activity in a resting state, i.e., in the absence of any stimulus. Therefore, it is reasonable to suppose that the MEG signal in this case comes from widely distributed, small intensity cortical generators reflecting integrated synaptic activity in small neuronal populations. Moreover, the analysis used in this paper does not require individual generators to reach the strength of a modelable source to contribute to the results; in fact, smaller events that are frequently recurring may be easily seen. In addition, the differencing, millisecond-by-millisecond, of the MEG time course performed as part of the ARIMA modeling in this study will further attenuate the stronger generators manifested as low-frequency components in the MEG signal, thus allowing smaller sources to contribute. Finally, it should be mentioned that the axial gradiometers used in this study pick up MEG signals coming from subcortical areas. However, we believe that, given the task-free resting state design, those contributions are small and that the bulk of the signal recorded is of cortical origin.

Methodological considerations: LDA

The LDA was introduced by Fisher in 1936 as a method by which to discriminate objects and classify them to specific groups based on available measurements (Fisher 1936). As Fisher put it, "When two or more populations have been measured in several characters, x_1, …, x_s, special interest attaches to several linear functions of the measurements by which the populations are best discriminated." (Fisher 1936, p. 466). Assume *M* objects belonging to *N* different groups, and let *k* be the number of attributes of each object for which we have measurements (values). LDA finds coefficients (weights) for each *k*th attribute, such that the linear sum of the weighted attributes ("characters" in Fisher's quote above) separate (i.e., discriminate) the different groups and classify each object to a group. The outcome is evaluated by calculating what percent of the objects were correctly classified: if all of them are classified correctly to the group they truly belong, we have a 100% correct classification outcome. In LDA, all attributes can be used or only a fraction of them, namely those that provide the best discrimination (classification percentage); the latter method is called "stepwise LDA" because attributes are entered and/or removed from the analysis based on the goodness (accuracy) of the outcome, and those attributes are ultimately retained that yield the best outcome. This procedure is particularly useful in applications where there are many attributes (predictors), of which only some possess useful information to discriminate groups; in this case, stepwise LDA functions, additionally, as a dimension reduction procedure. For example, in its specific application in this study, only 26 out of 494 (5.3%) available SNI predictors were used to yield a 100% correct classification of 51 brains to NST and ST groups, which means that a 494-dimensional predictor space was reduced to a 26-dimensional one, a substantial dimension reduction of 94.3%. Let *L* be the number of attributes ultimately retained by the stepwise LDA; this defines the final *L*-dimensional discrimination space where each one of the *M* objects is placed according to its distance from the *L* axes. This then yields *N* clusters ("group centroids") of *M* objects, where a cluster contains objects classified (assigned) to its group. Now, we know in which group each object belongs, by definition; if every object is classified to the group to which it truly belongs, then we have a 100% correct classification. The results of LDA are typically presented in a Classification Table, where the numbers (and percentages) of "actual" and "predicted" group memberships are given. Finally, a cross-validation procedure is typically carried out, in which LDA is performed using all but one object ("Leave-One-Out cross-validation"), which is then classified to a group based on the discriminant functions derived from the rest of the objects; thus, in this procedure, the object to be classified does not contribute to the calculation of the discriminant functions, and the result attests to the robustness of the outcome.

LDA provides, at the end, three measures pertaining to each object: (1) the discriminant score, which is the linear sum of the weighted attribute contributions, (2) the probability of classification (assignment) of the object to the different groups, and (3) the Mahalanobis D^2 which is the number of standard deviations an object point is away from the mean of a group centroid. If all predictor axes are rescaled to unit variance, then Mahalanobis D^2 corresponds to standard Euclidean distance. In this study, we found that the DRRI score (a sexual trauma score) was positively correlated with Mahalanobis D^2 from the NST centroid and negatively correlated with the Mahalanobis D^2 from the ST centroid, as expected.

MEG outcomes

The goal of the present study was to evaluate the MEG neural signature of sexual trauma in women veterans with PTSD. We found that resting-state MEG distinguishes between PTSD due to sexual trauma and non-sexual trauma with 100% accuracy using only 5.3% of sensors, and that PTSD due to sexual trauma is associated with widespread hypercorrelation relative to PTSD associated with non-sexual trauma. These findings, which document trauma-specific neural involvement and provide additional evidence regarding the discriminatory power of MEG, are discussed below along with potential treatment implications.

Brain mechanisms of PTSD

The findings documented here with MEG are consistent with previous structural and functional MRI studies in which trauma-specific neural alterations associated with PTSD were reported (Meng et al. 2016; Boccia et al. 2016). We have previously documented that relatively few SNI (11%) discriminate women veterans with PTSD from control women veterans (James et al. 2022). Here, only 5% of SNI distinguish PTSD due to sexual trauma and non-sexual trauma, attesting to a more focused ST-related neural substrate. Compared to non-sexual trauma, PTSD related to sexual trauma was associated with widespread SNI hypercorrelations, particularly involving left frontal and temporo-occipatal cortex, midline frontal, left central sulcus, and bilateral posterior parietal areas. Previous research has similarly documented hypercorrelated neural networks in PTSD compared to controls (Engdahl et al. 2010; James et al. 2013), a finding that was interpreted as reflecting constraints on information processing that presumably underlie maladaptive cognitive functioning in PTSD (James et al. 2013). The present study suggests that sexual trauma has more robust effects on neural network correlations than non-sexual trauma, potentially indicating greater impacts on information processing associated with sexual trauma compared to other types of trauma. Indeed, interpersonal trauma has been associated with cognitive impairment (Twamley et al. 2009). Numerous structural and functional frontal lobe anomalies have been documented in PTSD and are implicated in impairments in conditioned fear extinction, mood, and salience networks as well as executive dysfunction (Selemon et al. 2019). Similar to the current findings, hyperconnectivity involving the right parietal cortex has been documented in male veterans PTSD and associated with impaired attention (Dunkley et al. 2015). The stronger SNI involving frontal and parietal areas among those with sexual trauma that was observed here suggests that impairments in fear extinction, mood, executive function, and attention may be enhanced among those with sexual trauma compared to other trauma types. Greater involvement of the central sulcus/midline region observed in women with sexual trauma suggests greater sensorimotor involvement relative to non-sexual trauma. Indeed, other studies have implicated the sensorimotor cortex in PTSD (Badura-Brack et al. 2017) and in individuals with sexual trauma, in particular (Bremner et al.1999). Finally, with regard to the preponderance of left hemispheric involvement observed here, a recent study found that primarily left hemispheric alterations were characteristic of those with prolonged vs single-event trauma (Meng et al. 2016). Taken together, the present study confirms neural alterations identified in previous studies and bolsters evidence of trauma specific neural alterations associated with sexual assault (Bremner et al. 1999; Cisler et al. 2013; Kim et al. 2012; Quidé et al. 2021).

A reasonable implication of the present findings involves the potential influence of trauma-specific neural anomalies on treatment considerations. For instance, the benefit of exposure therapy has been documented for various trauma types (Rauch et al. 2012); the more intense involvement of sensorimotor cortices and frontal regions associated with sexual trauma relative to non-sexual trauma suggests that exposure therapy may be particularly well suited for treating sexual trauma. If and how the involvement of these areas changes with treatment remain to be seen; however, previous research has documented that recovery from PTSD is reflected in SNI (Engdahl et al. 2010; James et al. 2021, 2022). As such, inclusion of MEG could enhance future treatment studies by providing an objective indicator of symptom improvement and recovery from PTSD.

To our knowledge, this is the first study to document trauma-specific neural anomalies associated with PTSD using MEG. Furthermore, since the data were acquired during a task-free resting-state, the trauma-specific neural signatures observed here reflect underlying neural network characteristics rather than task-related neural anomalies. Additional strengths of this study include the use of gold-standard diagnostic interviews and focus on women veterans for whom trauma exposure, neurobiology, and PTSD prevalence differ from their male counterparts (Olff et al. 2007; Wisco et al. 2014; Lehavot et al. 2018). Several limitations, however, must also be considered. First, the group sample sizes are relatively small, particularly for the non-sexual trauma group. Among women using Veterans Affairs health care services, one in four report military sexual assault and half report sexual harassment (Skinner et al. 2000); furthermore, nearly two-thirds of women veterans report lifetime sexual trauma (Zinzow et al. 2007). Since sexual trauma is associated with exceptionally high risk of PTSD (Kessler et al. 2017; Wisco et al. 2014; Zinzow et al. 2007), it is perhaps not surprising that relatively few women veterans experienced PTSD due to non-sexual trauma. Among women veterans in particular, PTSD and depression are highly comorbid (Dobie et al. 2004). Indeed, a substantial number of women veterans with PTSD in the present study also met criteria for depression. However, since the rates of depression were identical for both the sexual trauma and non-sexual trauma groups, depression is unlikely to significantly influence the differences observed here in relation to trauma type. Finally, in contrast to task-based studies, the resting-state approach does not lend itself to source-level analyses (discussed in Engdahl et al. 2010) and reflects cortical neural interactions (vs those involving deep structures commonly associated with PTSD). Nonetheless, the cortical anomalies documented with MEG provide robust discriminatory power and the current study provides compelling evidence of trauma-specific neural signatures of PTSD in women veterans.

Author contributions LMJ, AFL contributed to data collection. APG, LMJ contributed to data analysis. LMJ, APG wrote the paper. All authors contributed to editing the paper.

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Data availability The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request pending local IRB approval.

Code Availability Not applicable.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethics approval The Institutional Review Board at the Minneapolis VAHCS approved the research protocol.

Consent to participate All participants in the present study gave informed written consent to participate in this study.

Consent for publication All participants in the present study gave consent for the publication of the result of this study.

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