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RESEARCH ARTICLE

Classification of posttraumatic stress disorder and related outcomes in women veterans using magnetoencephalography

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Abstract

Women veterans represent a unique population whose experiences and neurobiology differ from that of their male counterparts. Thus, while previous research has demonstrated the utility of synchronous neural interactions (SNI) as a biomarker of posttraumatic stress disorder (PTSD) in male veterans, the utility of SNI as a biomarker of PTSD in women veterans is unclear. Here we extend that line of research to evaluate classification of women veterans with and without PTSD and other trauma-related outcomes based on functional connectivity using magnetoencephalography (MEG). A total of 121 U.S. women veterans completed diagnostic interviews and underwent a task-free MEG scan from which SNI was computed. Linear discriminant analysis was used to classify PTSD and control groups according to SNI. That discriminant function was then used to classify each individual in the partial recovery and full recovery diagnostic groups as PTSD or control. All individuals were classified correctly (100% accuracy) according to their SNI in their PTSD and control groups. Seventy-seven percent of the full recovery group and 69% of the partial recovery group were classified as control. Individual staging in PTSD recovery was captured by the Mahalanobis D^2 distances from the center of the control and PTSD centroid clusters. These findings provide compelling evidence supporting the utility of task-free SNI as a biomarker of PTSD and related outcomes in women veterans.

Keywords Posttraumatic stress disorder · Recovery · Magnetoencephalography · Classification · Biomarker · Veterans

Introduction

Women veterans are at exceptionally high risk for developing posttraumatic stress disorder (PTSD) and associated trauma-related outcomes given high rates of exposure to potentially traumatic experiences including military sexual trauma, combat and combat-support events (Street et al. 2009; LeardMann et al. 2013; Kearns et al. 2016; Lehavot et al. 2018; Wisco et al. 2014). Trauma exposure and PTSD have been associated with poorer quality of life and significant impacts on physical and psychiatric health among women veterans (Suris et al. 2007; Kelly et al. 2011; Wisco et al. 2014; Goldberg et al. 2019). It is estimated that 13% of women veterans meet lifetime diagnostic criteria for PTSD (Wisco et al. 2014; Lehavot et al. 2018). Many others may experience significant trauma-related distress and impairment, yet may not meet full diagnostic criteria for PTSD and are thus characterized as subthreshold PTSD. Subthreshold PTSD is as common as PTSD among military veterans and service members (Bergman et al. 2017) and, similar to PTSD, is associated with significant comorbidities

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and clinical impairment (Jakupcak et al. 2007; Mota et al. 2016; El-Gabalawy et al. 2018). Taken together, PTSD and subthreshold PTSD impact a significant number of women veterans resulting in a substantial mental health burden for women service members.

Remarkably, although 81–93% of women veterans report exposure to potentially traumatic events (Zinzow et al. 2007), the majority do not experience chronic mental health symptoms. Indeed, extensive research has identified resilience, reflected by the absence of psychological or physical health impacts following exposure to a potentially traumatic event, as the most common outcome following exposure to traumatic events, even among military personnel (Bonanno 2004; Bonanno and Mancini 2012; Bonanno et al. 2012; Donoho et al. 2017; Galatzer-Levy et al. 2018). Those studies have determined that recovery, characterized by a symptomatic period of time followed by return to baseline, has been found to be the second most common outcome, with chronic symptoms representing the third most common outcome following exposure to a potentially traumatic event. Distinguishing between these outcomes is vital for identifying women veterans who may benefit from mental health treatment and guiding clinical service delivery.

Typically, symptoms of PTSD and other mental health conditions are evaluated by subjective measures such as self-report instruments or use of clinician-administered diagnostic interviews; however, subjective measures may be influenced by reporting biases and symptom misattribution (Guina et al. 2016), ultimately impacting diagnostic accuracy and, consequently, treatment planning and delivery. Identification of accurate and replicable objective indicators of PTSD and associated trauma-related outcomes may improve clinical service delivery by enhancing diagnostic accuracy (Lehrner and Yehuda 2014; Yang et al. 2018). Numerous candidate biomarkers of PTSD have been investigated although, to date, no definitive PTSD biomarker has been identified (Zoladz et al. 2013; Linnstaedt et al. 2020; Nisar et al. 2020). Increasing evidence supports task-free synchronous neural interactions (SNI; Georgopoulos et al. 2007) as a promising biomarker of PTSD. Patterns of SNI, which reflect integration of activity across brain areas, are highly conserved across healthy individuals (Langheim et al. 2006) and exhibit disease-specific variations, or "neural signatures" (Georgopoulos et al. 2007, 2010, 2017). With regard to PTSD, our research group and others have documented highly accurate classification of veterans with PTSD compared to community and veteran control participants using SNI computed from magnetoencephalography (MEG) recordings and from functional magnetic resonance imaging (Georgopoulos et al. 2010; James et al. 2015, 2021; Christova et al. 2015; Zhang et al. 2020). However, prior MEG PTSD classification studies have predominantly or solely included male veterans. One MEG SNI classification study, based on an all-male training set, included a small sample of women and found reduced classification accuracy for women compared to men (James et al. 2015). In light of the well-established gender differences in trauma exposure, neurobiology, and PTSD prevalence (Olff et al. 2007; Wisco et al. 2014; Lehavot et al. 2018) and limited inclusion of women in prior PTSD classification studies, this study focused exclusively on women veterans. The aim of the present study is to evaluate the ability of MEG SNI to classify women veterans with PTSD and related outcomes. Accurate classification will provide additional support for the utility of MEG SNI as an objective indicator of PTSD.

Methods

Study participants

A total of 121 women veterans who had not participated in previous PTSD classification studies in our laboratory participated in this study as paid volunteers. The study protocol was approved by the Minneapolis VAHCS institutional review board. All participants provided informed consent prior to participating in the study. Exclusionary criteria included the presence of the cardiac pacemakers or implanted ferrous metal due to magnetic effects on MEG, central nervous system disorders (e.g. Parkinson's disease, cerebrovascular accidents), and diagnoses of psychosis, bipolar disorder, current alcohol or drug dependence, and traumatic brain injury. Women veterans with current or history of uncomplicated PTSD and healthy women control veterans were recruited. All participants were evaluated by doctoral level psychologists according to DSM-5 diagnostic criteria (American Psychiatric Association 2013). Clinical diagnostic interviews including the Clinician Administered PTSD Scale (Weathers et al. 2013) and Structured Clinical Interview for DSM-5 (First et al. 2015) were used to assess current and lifetime PTSD and other psychiatric disorders, respectively. None of the participants included here met criteria for Axis I disorders except for PTSD. Study participants were classified into one of four PTSD-related groups based on the diagnostic interview. The control group ($N=65$) comprised veterans who did not meet current or historic criteria for any mental health condition. Veterans in the PTSD group ($N=30$) met current full diagnostic criteria for PTSD, probable PTSD (one symptom short of full diagnostic criteria for PTSD), or subthreshold PTSD (veterans who reported current symptoms of PTSD that did not meet the full diagnostic criteria for PTSD currently or historically). The partially recovered PTSD group ($N=13$) included women veterans who historically met full criteria for PTSD historically and continue to report PTSD symptoms but below diagnostic threshold. Finally, women veterans in the fully recovered

PTSD group ($N = 13$) historically met full criteria for PTSD and no longer report symptoms consistent with PTSD. Previous MEG SNI findings have shown that the subthreshold PTSD is classified with 100% accuracy as PTSD (James et al. 2021); therefore, the PTSD and subthreshold PTSD cases were combined into one group in the current analyses. The mean (± SEM) age was 50.6 ± 1.46 (25.6–70.7) for the control group, 45.7 ± 2.19 (25.2–68.2) for the PTSD group, 51.1 ± 3.65 (30.8–69.5) for the partially recovered PTSD group, and 41.4 ± 3.25 (27.9–68.6) for the fully recovered PTSD group.

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 were eliminated from further analysis.

Data analysis

The data analytic strategy followed our recent PTSD classification study (James et al. 2021). Specifically, analysis of variance (ANOVA), linear regression, Pearson correlation, and stepwise linear discriminant analysis (LDA) were used to analyze the data with several packages including SPSS (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; Louisville, CO: Rogue Wave Software).

MEG data processing

Python was used to process the raw MEG time series (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 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}^{o} was transformed to Z_{ij}^{o} using Fisher's z-transformation (Fisher 1958) to normalize its distribution:

$$\mathrm{SNI} = z_{ij}^{o} = \operatorname{atanh}\left(PCC_{ij}^{o}\right) \tag{1}$$

Stepwise linear discriminant analysis (LDA)

For each individual, there were 246 SNIs available for each one of the 247 sensors (one sensor was inoperative). For each sensor, we used the maximum and minimum SNI value (Engdahl et al. 2016) of the 246 SNIs available per sensor as input (N = 247 sensors × 2 SNI per sensor = 494 predictors) to a stepwise LDA to classify the brains of veterans diagnosed as PTSD or control, including a cross-validation leave-one-out (LOO) method, similar to the strategy utilized in our recent PTSD classification study (James et al. 2021). This analysis yielded 100% correct classification (see below); therefore, that discriminant function was used to classify veterans in the partially recovered and fully recovered PTSD groups. For each individual, we retained the discriminant score, the probability of classification to a group, and the D^2 Mahalanobis distances of each case from the center of the control and PTSD centroid clusters. Finally, we normalized the D^2 values to be in the 0–1 range:

$$D^2_{\text{control}}{}' = \frac{D^2_{\text{control}}}{D^2_{\text{control}} + D^2_{PTSD}} \tag{2}$$

$$D^2_{PTSD}{}' = \frac{D^2_{PTSD}}{D^2_{\text{control}} + D^2_{PTSD}} \tag{3}$$

Results

Age

Mean group ages did not differ significantly ($P > 0.05$ in all multiple pairwise comparisons in univariate ANOVA; Bonferroni corrected).

Classification of control and PTSD participants

The stepwise LDA yielded a 100% correct classification of veterans diagnosed with PTSD and control veterans: all 65 Control and 30 veterans with PTSD were correctly classified according to their functional connectivity; the same 100% correct classification was obtained by the leave-one-out cross-validation. Of the 494 predictors available, 55 (11.1%) were used by the stepwise LDA for the 100% correct classification; these SNIs came from 52 sensors (3 sensors provided 2 predictors each) depicted in Fig. 1. Wilk's lambda was 0.003 ($P < 0.001$). The frequency

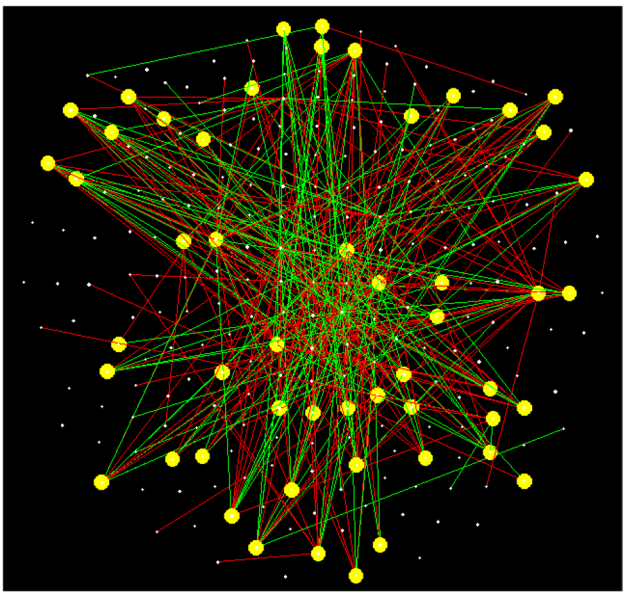

Fig. 1 Functional connectivity networks from the 52 LDA feature-sensors (yellow circles) are shown in a MEG sensor-space map. Green, positive SNI; red, negative SNI. *A* anterior, *P* posterior, *L* left, *R* right

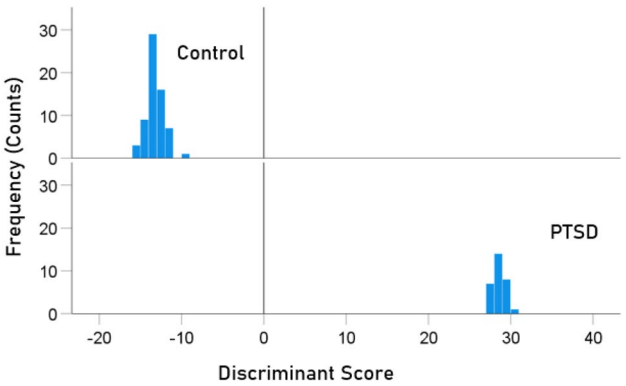

Fig. 2 Frequency distribution of discriminant scores for the PTSD ($N=30$) and control ($N=65$) group

distributions of the discriminant scores for Control and PTSD participants are shown in Fig. 2. The Mahalanobis D^2 distances from the center of the Control and PTSD centroid clusters for each individual are plotted in Fig. 3 for the Control (Fig. 3a) and PTSD (Fig. 3b) participants. Finally, the normalized $D^2_{\text{Control}}{}'$ and $D^2_{PTSD}{}'$ values are plotted against each other in Fig. 4a. These figures demonstrate the excellent classification of all Control and PTSD participants to their actual diagnostic groups.

Classification of partially and fully PTSD recovered participants

Of the 13 women in the partially recovered PTSD group, 9/13 (69%) were classified as Control and 4/13 (31%) as PTSD. The Mahalanobis D^2 distances from the center of the Control and PTSD centroid clusters for each individual in the partially recovered PTSD group are plotted in Fig. 3c. Of the 13 women in the fully recovered PTSD group, 10/13 (77%) were classified as Control and 3/13 (23%) as PTSD. The Mahalanobis D^2 distances from the center of the Control and PTSD centroid clusters for each individual in the fully recovered PTSD group are plotted in Fig. 3d. Finally, the normalized $D^2_{\text{Control}}{}'$ and $D^2_{PTSD}{}'$ values for these two groups are plotted against each other in Fig. 4b, c.

Discussion

The preponderance of PTSD biomarker research involving veterans has involved men; however, women veterans represent a unique population whose risk and protective factors, exposure to traumatic experiences within and outside of the military, and neurobiology differ from their male counterparts. Consequently, it is imperative to formally evaluate whether extant findings in the male-dominated veteran literature extend to women veterans. Previous research has demonstrated highly accurate classification of veterans with PTSD and related outcomes based on SNI in samples of predominantly male veterans (Georgopoulos et al. 2010; James et al. 2015, 2021). Here, we exclusively included veteran women to evaluate the ability of MEG SNI to classify the functional brain status of US women veterans with and without PTSD and related outcomes. The findings documented classification of women veterans with PTSD relative to women veteran control participants and with 100% accuracy and demonstrated the ability of MEG SNI to characterize varying degrees of recovery from PTSD according to brain functional connectivity. The findings, which are discussed below, add to the growing literature supporting the utility of SNI as a biomarker of PTSD.

Although numerous candidate PTSD biomarkers have been proposed, none have garnered sufficient evidence to date to support application outside of research settings. However, the present findings, coupled with previous classification studies of PTSD (Georgopoulos et al. 2010; James et al. 2015, 2021; Zhang et al. 2020), provide mounting evidence suggesting the translational potential of intrinsic functional connectivity as a useful biomarker of PTSD. To that point, task-free SNI has been shown to permit highly accurate classification of veterans with and without PTSD with both MEG and functional magnetic resonance imaging (Georgopoulos et al. 2010; James et al. 2015, 2021;

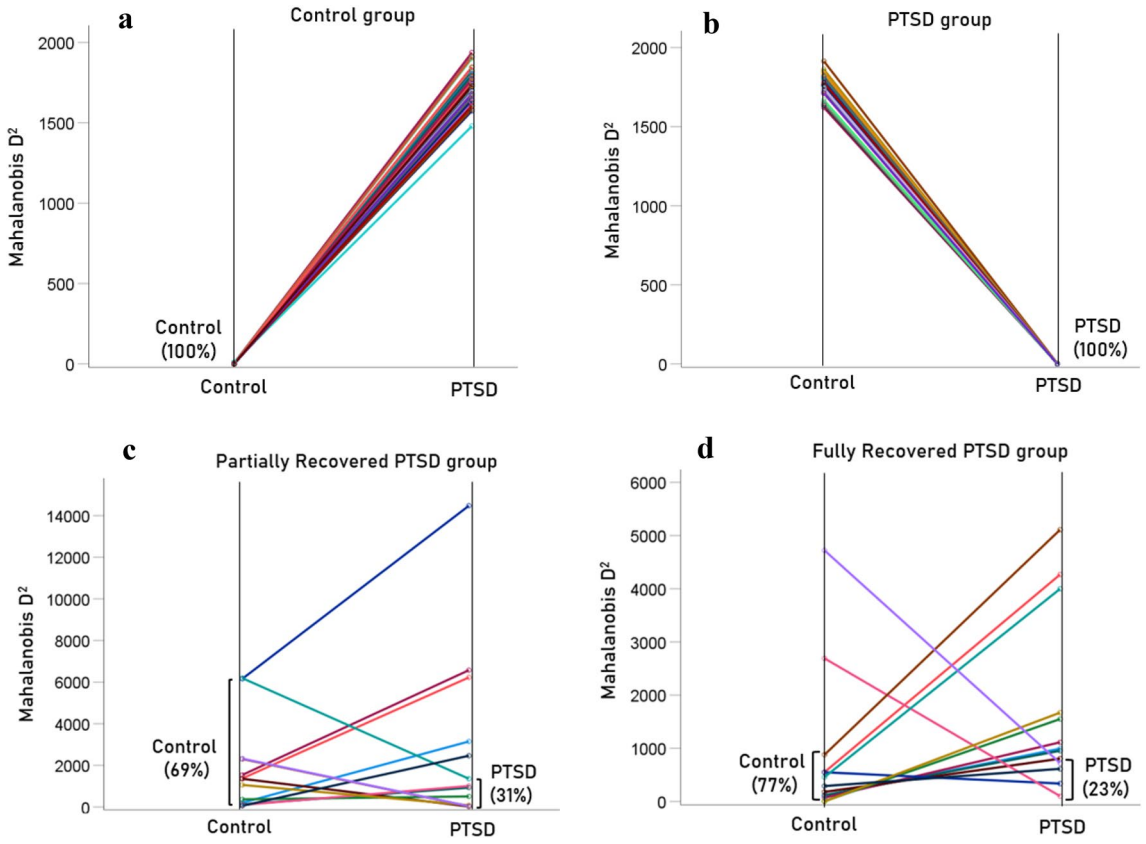

Fig. 3 Mahalanobis D^2 values for the control group (**a**), PTSD group (**b**), partially recovered PTSD group (**c**), and for the fully recovered PTSD group (**d**)

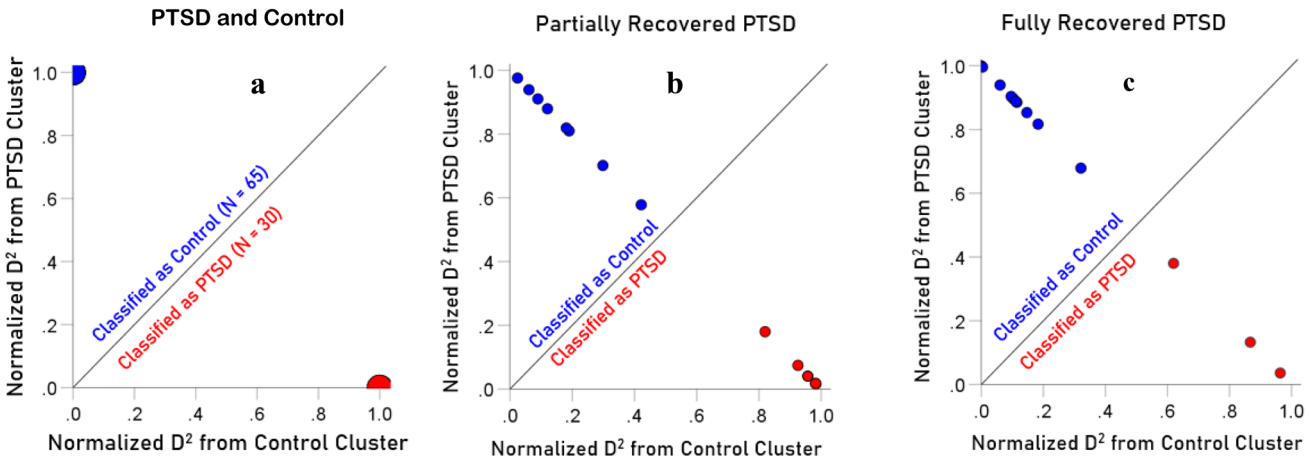

Fig. 4 Normalized Mahalanobis D^2 values for the control and PTSD groups (**a**), the partially recovered PTSD group (**b**), and fully recovered PTSD group (**c**)

Christova et al. 2015), even in the presence of comorbid psychiatric conditions (James et al. 2015). Furthermore, the present findings indicate that recovery from PTSD is reflected in SNI, consistent with findings from previous studies (Engdahl et al. 2010; James et al. 2021), and that recovery can be quantified along a continuum reflecting similarity to PTSD-characteristic functional connectivity versus that of healthy controls. Taken together, there is compelling evidence that SNI reflects a useful objective indicator of PTSD and recovery.

In this sample of women veterans, accurate classification of PTSD and control groups was achieved using just 11% of SNI, involving 55 predictors from a total of 52 sensors. These findings indicate that anomalies in neural interactions involving a relatively small number of sensors distinguish women veterans with PTSD from controls, consistent with previous PTSD classification studies documenting relatively few albeit robust MEG SNI differences among veterans with PTSD compared to healthy controls (Georgopoulos et al. 2010; James et al. 2015, 2021). In previous studies involving primarily male veterans, SNI anomalies involving the right superior temporal gyrus, in particular, have been associated with PTSD (Engdahl et al. 2010; James et al. 2013). Structural and functional right superior temporal abnormalities have also been identified in civilian children, adolescents, and adults with PTSD (De Bellis et al. 2002; Bonne et al. 2003; Flatten et al. 2004). Here, too, the right superior temporal region was indeed involved in the discrimination of women veterans with PTSD vs controls. In addition, several SNI involving additional bilateral temporal, parietal, frontal, and occipital regions were involved in the PTSD vs control discrimination in this sample of women veterans. A recent PTSD classification study of predominantly male veterans similarly showed involvement of several networks distributed across the brain, yet left temporal SNI were conspicuously absent from the PTSD-control discrimination in that study (James et al. 2021). In the current study, a strong focus in the left superior temporal gyrus was present, in keeping with observations that re-experiencing prior events ("experiential" effects) have been documented in women with left temporal lobe epilepsy and have been elicited by electrical stimulation of the temporal lobe during neurosurgical operation (Penfield and Perot 1963). While these studies suggest there may be gender differences in the regional involvement and distribution of anomalous SNI in PTSD, an extensive evaluation of MEG-based sex differences in brain organization related to PTSD is beyond the scope of the present study though certainly merits further evaluation.

The discriminant function obtained from the 55 predictors that correctly classified PTSD and control brains were used to classify functional connectivity of veterans at varying stages of PTSD recovery according to clinical interview. The results indicated that three-quarters of women considered fully recovered from PTSD were indeed classified as controls according to their brain functional connectivity, highlighting strong correspondence between clinical measures and objective indicators for the majority of the fully recovered group. Nonetheless, one quarter of the women who did not report symptoms consistent with a current diagnosis of PTSD were classified as PTSD. Conversely, two-thirds of women in the partially recovered PTSD group (who by definition continue to report some symptoms of PTSD) were classified as controls according to their SNI. Previous findings have shown that veterans with PTSD in remission exhibited neural anomalies that were similar but weaker to those with PTSD (Engdahl et al. 2010). Thus, it is possible that some women who do not experience current symptoms of PTSD (i.e., fully recovered) retain a trauma-related neural scar. Alternatively, reporting biases including under-reporting, over-reporting, social desirability biases, and misattribution of symptoms may result in diagnostic inaccuracies and account for the relatively few discrepancies observed between subjective report and objective indicators (Guina et al 2016).

Overall, the findings of the current study attest to the discriminatory power of MEG SNI and demonstrate the potential clinical utility of functional connectivity in evaluating PTSD and recovery along a continuum, as evidenced by the individual variability in distance from the PTSD and Control centroids. Nonetheless, given the wide-ranging clinical, forensic, and disability implications of PTSD biomarker identification (Lehrner and Yehuda 2014), additional SNI classification research is warranted to further evaluate the applicability of PTSD classification based on SNI to other populations and modalities (e.g., functional magnetic resonance imaging; Christova et al. 2015), and to test the limits regarding sensitivity and specificity. For instance, PTSD and traumatic brain injury (TBI) often co-occur. Recent MEG applications have documented classification of TBI and recovery compared to controls (Thorpe et al. 2020), and the ability of resting-state networks to differentiate PTSD and TBI (Rowland et al. 2017). Similar future studies will be useful for evaluating the power of MEG SNI to discriminate between PTSD and other commonly co-occurring disorders (e.g., depression) and for discerning disease-specific networks.

The present study builds upon a burgeoning field of research demonstrating the utility of resting-state MEG SNI in PTSD classification (Georgopoulos et al. 2010; James et al. 2015, 2021). Though the findings provide compelling evidence supporting SNI as an objective indicator of PTSD and recovery in women veterans, the findings must be considered within the context of study limitations and qualifications. The group sample sizes were relatively small, particularly for the recovery groups, and women veterans with co-occurring mental health conditions were excluded; thus, additional studies with larger, more representative samples are warranted to evaluate the replicability and generalizability of the present findings. In addition, the current study was based on cross-sectional assessment requiring retrospective reporting of symptoms. Longitudinal studies (e.g. before and after trauma-focused treatment) would be useful for evaluating the concordance between subjective change in symptoms and objective indicators such as brain functional connectivity to further evaluate the utility of MEG SNI as an objective indicator of recovery. While

most prior MEG classification studies of PTSD have almost exclusively included male veterans, the present study exclusively focused on women veterans. Future studies evaluating MEG-based sex differences in brain organization of PTSD as well as factors that may contribute to such differences are warranted. Finally, this resting-state study permits characterization of brain function in women veterans with PTSD in the absence of a task; however, as extensively discussed elsewhere (Engdahl et al. 2010), the resting-state approach does not lend itself to source-level analyses which are commonly used following the application of a stimulus, and the present findings may not equate with functional anomalies observed in task-based MEG studies of PTSD (e.g., Badura-Brack et al. 2018; Dunkley et al. 2016; Khana et al. 2017; McDermott et al. 2016).

Conclusions

In summary, the current study provides evidence that brain functional connectivity distinguishes between women veterans with PTSD and control women veterans, and serves as an objective indicator of recovery from PTSD. The findings support the clinical utility of task-free functional connectivity in women with PTSD and related outcomes.

Author contributions Contributed to data collection: LMJ. Contributed to data analysis: APG, LMJ. Wrote the paper: LMJ, APG. Contributed to editing the paper: All.

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Availability of data 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.

Ethical 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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