Psychiatry Research: Neuroimaging 231 (2015) 1–7

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Development and application of a diagnostic algorithm for posttraumatic stress disorder

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ARTICLE INFO

Article history:
Received 13 March 2014
Received in revised form
12 September 2014
Accepted 7 November 2014
Available online 15 November 2014

Keywords:
Posttraumatic stress disorder
Biomarker
Magnetoencephalography
ROC curve
Regression analysis
Veterans

ABSTRACT

Intact cognitive functions rely on synchronous neural activity; conversely, alterations in synchrony are thought to underlie psychopathology. We recently demonstrated that anomalies in synchronous neural interactions (SNI) determined by magnetoencephalography represent a putative PTSD biomarker. Here we develop and apply a regression-based diagnostic algorithm to further validate SNI as a PTSD biomarker in 432 veterans (235 controls; 138 pure PTSD; 59 PTSD plus comorbid disorders). Correlation coefficients served as proximities in multidimensional scaling (MDS) to obtain a two-dimensional representation of the data. In addition, least absolute shrinkage and selection operator (LASSO) regression was used to derive a diagnostic algorithm for PTSD. Performance of this algorithm was assessed by the area under the receiver operating characteristic (ROC) curves, sensitivity, and specificity in 1000 randomly divided testing and validation datasets and in independent samples. MDS revealed that individuals with PTSD, regardless of comorbid psychiatric conditions, are highly distinct from controls. Similarly, application of the LASSO regression-derived prediction model demonstrated remarkable classification accuracy (AUCs $\geq$ 0.93 for men, AUC = 0.82 for women). Neural functioning in individuals with PTSD, regardless of comorbid psychiatric diagnoses, can be used as a diagnostic test to determine patient disease status, further validating SNI as a PTSD biomarker.

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1. Introduction

Posttraumatic stress disorder (PTSD) is a common and debilitating psychiatric disorder (Kessler et al., 2005). Within the last decade there has been a surge of interest in identification of biomarkers to facilitate diagnosis of PTSD. To that end, a number of neuroendocrine, genetic, and structural or functional brain abnormalities associated with PTSD have been identified (Lanius et al., 2002; Yehuda et al., 2002; Karl et al., 2006; Pitman et al., 2006; Geuze et al., 2008; Kovacic et al., 2008; Eckart et al., 2011; Zolad and Diamond, 2013); however, identification of putative biomarkers has largely been hampered by poor reliability and validity (Yehuda et al., 2013; Zolad and Diamond, 2013).

Recently, it was demonstrated that veterans with posttraumatic stress disorder (PTSD) can be reliably distinguished from community controls with > 90% accuracy based on differences in neuromagnetic signals recorded with magnetoencephalography (MEG) (Georgopoulos et al., 2010). Subsequent research using MEG revealed a PTSD neural signature characterized by miscommunication of cortical circuitry primarily involving temporal and parieto-occipital right hemispheric areas (Engdahl et al., 2010). In particular, neural amomalies involving the right superior temporal gyrus, a region associated with re-experiencing phenomena (Penfield and Perot, 1963) have been observed (Engdahl et al., 2010; James et al., 2013) in veterans with PTSD. These findings add to the growing work highlighting the utility of MEG in identifying

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http://dx.doi.org/10.1016/j.pscychresns.2014.11.007
0925-4927/Published by Elsevier Ireland Ltd.

functional biomarkers of brain disease (Georgopoulos et al., 2007), and provide compelling preliminary evidence of a PTSD biomarker identified from anomalies in synchronous neural interactions (SNI).

Synchronous neural activity is a ubiquitous phenomenon of cortical networks that is central to numerous cognitive functions including attention, memory, sensory integration, and sensory-motor coordination (for review, see Singer (2004)). Though the mechanisms underlying SNI are not fully understood, the putative function is integration of activity across distributed brain areas that operate in parallel. Notably, patterns of correlated network activity are virtually identical across healthy subjects (Langheim et al., 2006). In contrast, deviations in neural synchrony have been linked to several neuropsychiatric disorders (Uhlhaas and Singer, 2006; Georgopoulos et al., 2007, 2010), presumably reflecting dysfunctional cognitive processing. Indeed, impaired working memory, attention, and perceptual organization have been tied to alterations in neural synchrony in schizophrenia (Uhlhaas et al., 2009). Regarding PTSD, the most prominent deviations in SNI are hypothesized to underlie aberrant memory processing associated with re-experiencing symptoms (Georgopoulos et al., 2010; Engdahl et al., 2010; James et al., 2013).

We have previously demonstrated disease-specific deviations in SNI (Georgopoulos et al., 2007) and have proposed that SNI anomalies can be used as a diagnostic indicator (Georgopoulos et al., 2010; Engdahl et al., 2010). In the present study we used least absolute shrinkage and selection operator (LASSO) regression (Tibshirani, 1996) to derive a diagnostic algorithm for PTSD based on MEG SNIs. The diagnostic performance of this classification algorithm was measured by the area under the ROC curves in 1000 randomly divided testing and validation datasets. The performance of the diagnostic algorithm was also evaluated in female veterans and veterans with comorbid psychiatric disorders, patient samples that were not used in generating diagnostic algorithm.

2. Methods

2.1. Subjects

Four-hundred-thirty-two U.S. veterans ($n=235$ controls; $n=138$ PTSD without co-morbidities, 74 of whom were included in Georgopoulos et al., 2010; 59 PTSD with co-morbidities) participated in the study as paid volunteers. Study participants were recruited from October 2008 to November 2012. Inclusion criteria were either a primary diagnosis of PTSD or, for the control group, no lifetime history of subthreshold or greater PTSD symptoms and absence of any current clinically significant mental health symptoms. Individuals were excluded from participating if their medical chart indicated current suicidal ideation, recent psychiatric hospitalization, history of psychotic disorder, presence of cardiac pacemakers or other imbedded ferrous metal (due to magnetic effects on MEG), serious chronic pain, or other central nervous system disorders (e.g. Parkinson's disease, dementia, cerebral vascular accidents, etc.). Eligible veterans completed diagnostic interviews, the Edinburgh Handedness Inventory (Oldfield, 1971), and underwent a MEG scan. The study protocol was approved by the Institutional Review Board at the Minneapolis VA Medical Center and subjects provided written informed consent prior to the study. Provided in Table 1 are demographic and clinical characteristics of the study participants.

2.2. Diagnostic measures

PTSD was assessed using the Clinician-Administered PTSD Scale for *DSM-IV* (CAPS; $n=332$) (Blake et al., 1995) or the Structured Clinical Interview for *DSM-IV*-TR (SCID; $n=100$) (First et al., 2002) PTSD module. The CAPS provides a continuous measure of symptom severity; to categorize participants' PTSD status, severity of each symptom was scored according to the SCID Symptom Calibration method, which minimizes false positives and false negatives and is the preferred scoring method for the CAPS when differential diagnosis is the goal (Weathers et al., 1999). The SXCAL scoring rule provides empirically-derived cut-points for determining the presence or absence of each of the 17 PTSD symptoms. To facilitate compatibility with the SCID, CAPS symptom scores were converted to SCID-equivalent scores as follows: a symptom score that met or exceeded the SXCAL cut-point was considered full symptom endorsement (i.e., SCID score of 3); absence of the symptom was considered a 'no' response (i.e., SCID score of 1); all other values were considered subthreshold (i.e., SCID score of 2). Thus, the range of possible values for the sum of the 17 PTSD symptoms was 17–51. Because reactions to trauma are wide-ranging (Brewin et al., 2000; Breslau and Kessler, 2001; Adler et al., 2008), emotional responses other than intense fear, helplessness, or horror were accepted for Criterion A2 (e.g., anger, guilt, shame, absence of emotional response). Most males with PTSD (94.6%) reported combat-related events as their index trauma. In contrast the majority of women with PTSD (71.4%) reported sexual assault as their index trauma. The majority of control participants (77%) reported exposure to potentially traumatic events; of those, military and civilian events were equally represented (48% and 50%, respectively). Lifetime history of non-PTSD Axis I diagnoses were evaluated with the SCID (First et al., 2002) using *DSMIV-TR* criteria. Co-morbidities are detailed in Table S1 in Supplement 1. None of the control participants met current diagnostic criteria for any Axis I disorder.

2.3. MEG data acquisition

As described previously (Georgopoulos et al., 2007; 2010), 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., eyeblinks, saturation, etc.) were eliminated from further analysis. Subjects were monitored during MEG acquisitions using a video camera to detect possible motion of the head; no such motion was detected.

2.4. Data pre-processing and analysis

All MEG data underwent 'prewhitening' (Box and Jenkins, 1976; Priestley, 1981) using a (50,1,1) ARIMA model. Matlab (version 2011b) was used to fit the model and obtain innovations (i.e. residuals). All possible pairwise zero-lag cross-correlations ($N=30{,}628$, given 248 sensors) were computed between the prewhitened MEG time series. Finally, the partial, full-rank zero-lag cross-correlations PCC^0_{ij} between i and j sensors (SNI) were computed for all sensor pairs; thus, for any given pair of sensors (from a total of 248) the effects of the remaining 246 sensors were partialed out. The PCC^0_{ij} were transformed to z^0_{ij} using Fisher's (1958) z-transformation to normalize its distribution

$$z^0_{ij} = \frac{1}{2}\ln\frac{1+PCC^0_{ij}}{1-PCC^0_{ij}} \quad (1)$$

2.4.1. Unsupervised analysis

Pearson's correlation coefficient was used to compare the distributions of z^0_{ij} among subject groups. For each pair of subjects, correlation coefficient was computed over all

Table 1
Demographic and clinical characteristics of the 432 study participants.

		Controls ($n=235$)	PTSD w/o co-morbidities ($n=138$)	PTSD with co-morbidities ($n=59$)
Males (%)		222 (94%)	121 (88%)	43 (73%)
Age (mean ± S.D.)	Males	60 ± 14 ($n=222$)	52 ± 15 ($n=121$)	47 ± 16 ($n=43$)
	Females	42 ± 16 ($n=13$)	45 ± 10 ($n=17$)	42 ± 14 ($n=16$)
PTSD score (mean ± S.D.)	Males	17.7 ± 1.8	40.2 ± 4.5	41.7 ± 5.1
	Females	17.6 ± 2.1	41.9 ± 4.0	42.5 ± 3.6
Psychotropic medication		26 (11%)	88 (64%)	10 (17%)
Trauma exposure		181 (77%)	138 (100%)	58 (98%)

30,628 z_{ij}^{0} between the subjects. These correlation coefficients were used as the similarity measure in a classical multidimensional scaling algorithm (MDS) to obtain a two-dimensional representation of the data (Gower, 1966).

2.4.2. Missing data methods

Cross-correlations with any missing values among the 432 subjects were excluded. Alternatively, missing cross-correlations could be imputed using the *K*-nearest neighbor approach (Troyanskaya et al., 2001), implemented in the R package *imputation* for sensitivity analysis.

2.4.3. Age adjustment

Since the PTSD subjects were significantly younger than the control subjects (Wilcoxon test p-Value < 0.0001 for all subjects and for males only), we implemented an age-adjustment procedure, similar to that proposed in Lu et al. (2006), prior to analysis, as described in the Supplemental material.

2.4.4. Time adjustment

Since PTSD and control subjects were not recruited at equal rates throughout the course of the study, we adjusted for the potential confounding effect of time by excluding those cross-correlations that were significantly associated with recruitment time.

2.4.5. Supervised analysis

The Lasso penalized regression analysis was used to fit a prediction model for PTSD (Tibshirani, 1996; Friedman et al., 2010). LASSO is a form of regularized regression that performs model selection by imposing an L^1 penalty on the size of the coefficients. LASSO is especially effective in problems where the number of predictors far exceeds the number of observations (Wu and Lange, 2008; Wu et al., 2009). Details of the LASSO method are provided in the Supplementary material. The men (222 controls and 121 pure PTSD) were randomly divided into training and test sets (stratified by group). The test set consisted of 25 PTSD and 25 control males. Age-adjusting weights were computed for the training and test sets separately. Cross-correlations that were significantly associated with recruitment time in the training set were excluded. The Lasso with 10-fold cross-validation was used to select the optimal model based on the training data. The predicted probability of PTSD (or a PTSD score) was calculated for each subject in the training set. In order to classify patients into PTSD and control groups based on their estimated probability of PTSD, a threshold was chosen to maximize the sum of sensitivity and specificity in the training data. The optimal model was validated using the test set. The predicted probability of PTSD was calculated for each subject in the test set based on the optimal model. A subject was classified as PTSD if his/her PTSD score was above the threshold; otherwise, the subject was classified as control. The optimal model was also applied to classify the male PTSD veterans with co-morbidities, and the female veterans. This procedure was repeated 1000 times, including random allocation of the men into training and test sets (stratified by group, control vs PTSD without co-morbidities), the computation of the age-adjusting weights, time adjustment, and the selection and validation of the optimal model. The area under the curve (AUC), sensitivity and specificity of the classifiers, and the correlation between the predicted and the actual PTSD scores were estimated using the test set by averaging over the 1000 iterations. The sensitivity of the optimal models in PTSD males with co-morbidities was also assessed by averaging over 1000 iterations.

3. Results

3.1. Unsupervised analysis

Fig. 1 displays the classical MDS representation of the data in two dimensions. Shown in Panel A is the two-dimensional representation of all subjects. Datapoints were colored to distinguish the PTSD and control groups, males and females, and subjects with co-morbidities. Panel B displays men without co-morbidities. The PTSD and control groups appear distinct; in addition, the control males group into two distinct clusters. Panel C displays the same two-dimensional plot as in Panel A, but the subjects are now colored to show age groups. The median age of 60 was used as the cutoff point for age. The subjects do not appear to group into clusters based on age. Finally, Panel D displays datapoints for all subjects, colored to represent gender. Males and females appear as markedly distinct groups, although some of the female controls overlap with male controls (see Panel A).

3.2. Supervised analysis

Sixteen percent of the 30,628 cross-correlations had at least one missing value among the 432 subjects. The median and mean numbers of missing values were 1 and 7, respectively, among the cross-correlations with missing values. In particular, over 10% of the 432 subjects had missing values for all 247 cross-correlations involving sensor 19, indicating that this sensor could be dysfunctional. All cross-correlations with any missing values were excluded, leaving 25,878 cross-correlations for analysis. When missing cross-correlations were imputed using the *K*-nearest neighbor approach, the results and conclusions reported here remained unchanged and were not sensitive to the number of nearest neighbors used (data not shown).

The male veterans without co-morbidities ($n=343$) were randomly divided into a training and test set stratified by group (controls vs PTSD). That is, 25 subjects were randomly selected from each the PTSD male and the control male groups without co-morbidities to form the test set ($n=50$). The rest of the male veterans without co-morbidities were assigned to the training set ($n=293$). Cross-correlations that were significantly associated with recruitment time in the training set ($p<0.05$) were excluded, leaving 14,583 cross-correlations for analysis. Using the training data, a prediction model was constructed using the Lasso penalized regression analysis that included a 10-fold cross-validation procedure to select the optimal model. The cross-validation plot is provided in Fig. S1, panel A of Supplement 1. The full solution paths of the Lasso coefficients are displayed in Fig. S1, panel B of Supplement 1. The optimal model, corresponding to lambda$=0.0324$ (log(lambda)$=-3.43$), consisted of 97 non-zero coefficients. Thus, most of the 14,583 coefficients were shrunk to zero.

The optimal model was validated on the training data themselves ($n=293$), the test data ($n=50$), and was applied to female veterans without co-morbidities ($n=30$) and veterans with co-morbidities (43 males and 16 females). Shown in Fig. S2 in Supplement 1 are receiver operating characteristic (ROC) plots for the optimal model applied to training data, test data and the female veterans without co-morbidities. AUC were 1.00, 0.96 and 0.79 for the training data (Fig. S2, panel A in Supplement 1), test data (Fig. S2, panel B in Supplement 1), and females without co-morbidities (Fig. S2, panel C in Supplement 1), respectively.

Fig. 2 shows the estimated PTSD (red circles) and control scores (green circles) for each subject in the training data (Fig. 2A), test data (Fig. 2B), and for women (Fig. 2C), with and without co-morbidities. Note that for each subject, the PTSD and control scores add up to one. In the training set, 100% of PTSD males without co-morbidities and 98% of controls were correctly classified. In the test set, 92% of PTSD males without co-morbidities and 92% of controls were correctly classified. Among PTSD males with co-morbidities, 88% were correctly classified. Lastly, the optimal model correctly classified 77% of female controls, 63% of PTSD females without co-morbidities and 60% of PTSD females with co-morbidities.

The data were then divided into training/test sets 1000 times and each time the above model building procedure was repeated using the training set and validated using the test set. The number of non-zero coefficients in the 1000 optimal Lasso models ranged from 20 to 135 with a median of 58.

Table 2 shows AUC, sensitivities and specificities of the Lasso classifier as well as the correlation between the predicted and the actual PTSD scores in the training set, test set, and in females without co-morbidities averaged over the 1000 iterations of the procedure. Provided in Table 2 is also the average sensitivity of the Lasso classifier in veterans with co-morbidities, calculated over the 1000 iteration of the model-building procedure.

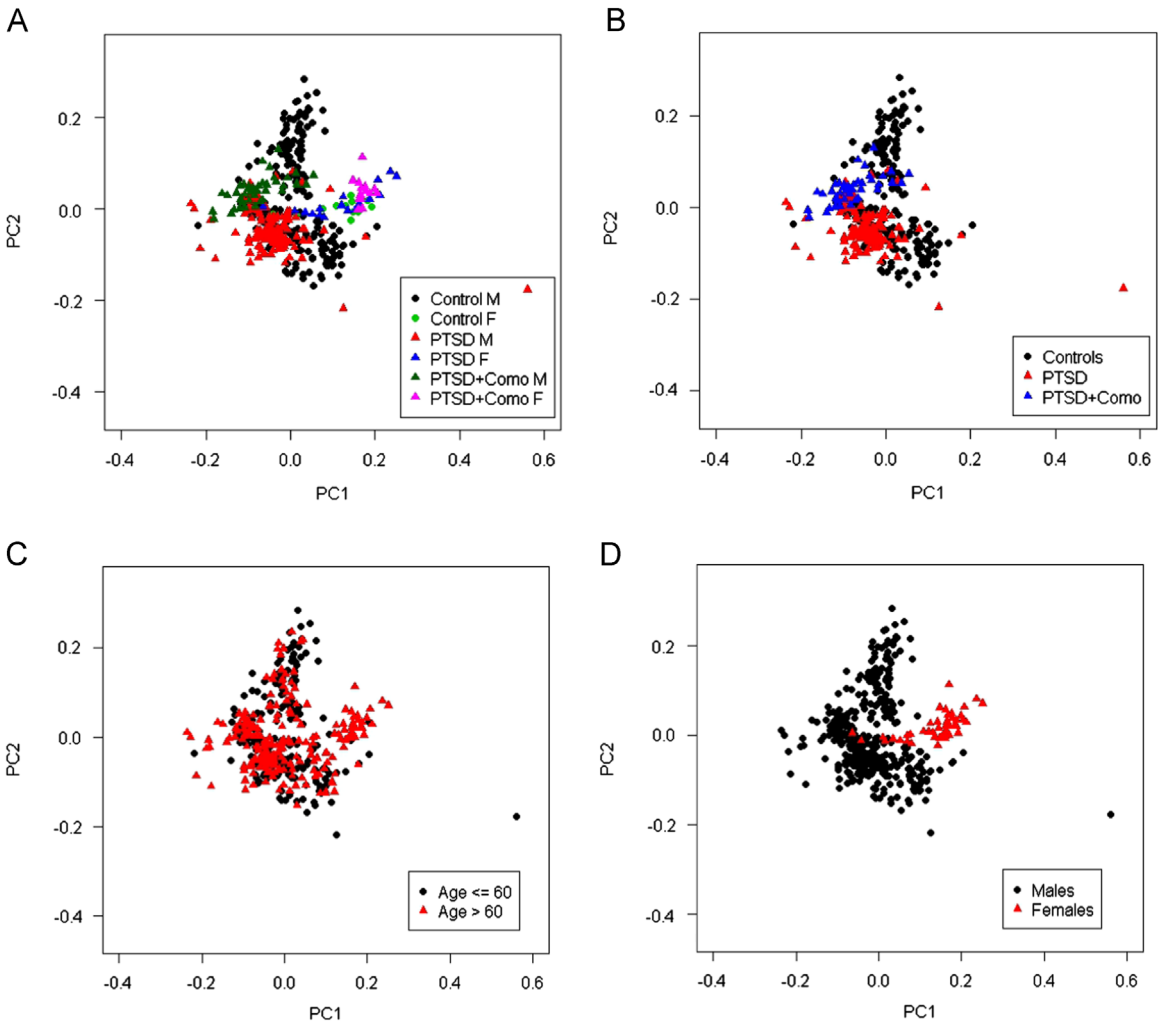

Fig. 1. Classical multidimensional scaling representation for all 432 subjects (Panel A), men only (Panel B), all 432 subjects, by age (Panel C), and all 432 subjects, by gender (Panel D). (A) All 432 subjects. (B) Males only. (C) All 432 subjects, by age. and (D) All 432 subjects, by gender.

Similar results were obtained for both medicated and unmedicated participants and when missing cross-correlations were imputed instead of being excluded (data not shown).

4. Discussion

The present study was aimed at developing and evaluating a PTSD diagnostic algorithm based on MEG SNIs. Results of the present study demonstrate that SNIs provide a highly accurate objective means of differentiating veterans with PTSD from healthy control veterans, demonstrating robust evidence of a PTSD diagnostic algorithm. These findings corroborate and extend prior research indicating that anomalies in SNIs reflect a putative biomarker of PTSD (Engdahl et al., 2010; Georgopoulos et al., 2010; James et al., 2013).

Results of both the classical MDS representation of the data and the classification analyses revealed several intriguing findings. First, regarding the MDS analyses, individuals with PTSD appear to be highly distinct from controls. Second, this distinction is more pronounced in male versus female veterans. Third, individuals with PTSD plus comorbid disorders cluster together and overlap with individuals with pure PTSD. Finally, regardless of diagnostic status, individuals clustered together based on gender but not age, suggesting significant gender differences in SNI. In parallel, the supervised classification analyses revealed a remarkably high correct classification rate, providing further evidence of a distinct difference in SNIs for veterans with PTSD and controls. Classification accuracy was good, albeit somewhat reduced, when comorbid conditions were included, suggesting that the PTSD neural signature can be detected among neural anomalies associated with other psychiatric disorders. Last, correct classification rates were higher for males than females, although relatively few women were included in the present study. Taken together, results of the MDS and the supervised classification analyses demonstrated that neural functioning in individuals with PTSD, regardless of comorbid psychiatric diagnoses, is highly distinct from controls, particularly among male veterans, and can be used as a diagnostic test to determine patient disease status.

Both the gender distinctions observed in the MDS analyses and relatively weaker classification accuracy among women compared to men were unexpected. Regarding the MDS, female controls overlapped with male controls, suggesting minimal differences in SNIs between the two control groups. In contrast, females with PTSD (regardless of comorbid psychopathology) formed a distinctly different cluster from men with PTSD with relatively no overlap, suggesting significant differences in SNI between men and women with PTSD. This difference likely underlies the relatively weaker classification accuracy among women, particularly since the classification training data included only men. The observed gender differences in SNI may be attributable, in part, to differences in trauma type. Indeed, combat-related traumatic events

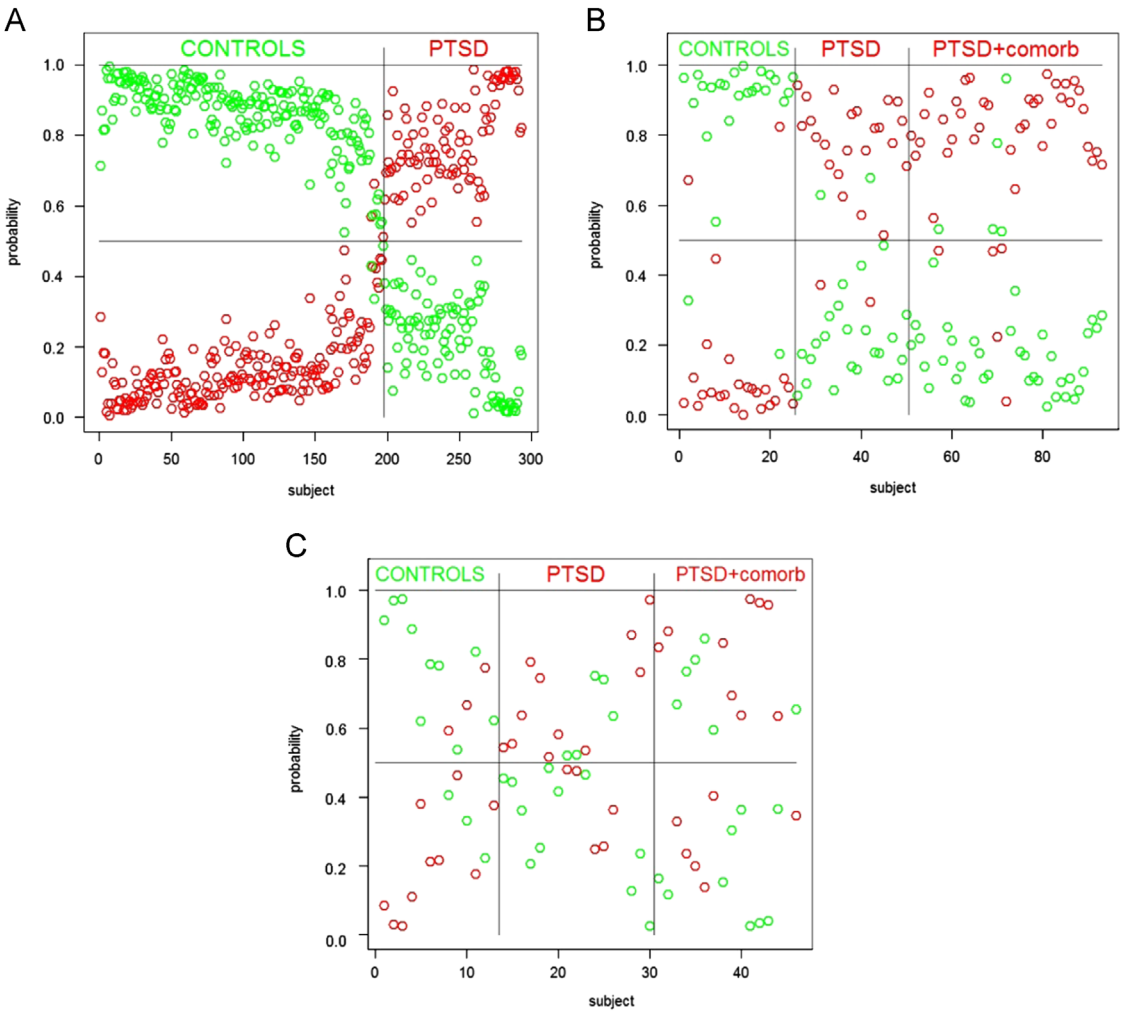

Fig. 2. Predicted PTSD scores (red circles) and control scores (1-PTSD score, green circles) for each subject in the training set, test set and for females, with and without co-morbidities. (a) MALES, training set, (b) MALES, test set, (c) FEMALES, test set.

Table 2
Area under the curve, sensitivity and specificity of the Lasso classifier and correlation between the predicted and the actual PTSD scores, in the training and test data, averaged over 1000 iterations.

		AUC	Sensitivity	Specificity	Correlation with PTSD score
		Mean [95% CI]	Mean [95% CI]	Mean [95% CI]	Mean [95% CI]
Veterans w/o co-morbidities	Training ($n=293$)	0.981 [0.955, 1.00]	0.989 [0.948, 1.00] $n=96$	0.945 [0.878, 1.00] $n=197$	0.839 [0.739, 0.943]
	Test ($n=50$)	0.934 [0.859, 995]	0.874 [0.719, 1.00] $n=25$	0.894 [0.760, 1.00] $n=25$	0.750 [0.603, 0.875]
	Females ($n=30$)	0.819 [0.725, 0.906]	0.737 [0.471, 0.941] $n=17$	0.719 [0.498, 0.923] $n=13$	0.483 [0.340, 0.609]
Veterans with co-morbidities (all PTSD)	Males ($n=43$)	NA	0.879 [0.721, 0.953]	NA	NA
	Females ($n=16$)	NA	0.669 [0.533, 0.800]	NA	NA

were most prevalent among male veterans whereas sexual assault was the most common trauma type for female veterans. Future studies including a larger sample of women with diverse traumatic experiences are imperative to parse whether the gender differences observed here reflect gender-specific or trauma-specific PTSD neural signatures. Nonetheless, the classification rate of females with PTSD was still high, strongly suggesting that correlated brain network activity (i.e., SNIs) is a definitive biomarker of PTSD, regardless of gender.

Several potential PTSD biomarkers including disturbances in hormones or neurotransmitter systems, impaired physiological responses to stimuli, and structural or functional brain abnormalities have been investigated (Lanius et al., 2002; Yehuda et al., 2002; Karl et al., 2006; Pitman et al., 2006; Geuze et al., 2008; Kovacic et al., 2008; Eckart et al., 2011; Zolad and Diamond, 2013); yet, none have previously emerged as definitive PTSD biomarkers. Indeed, to be useful, a PTSD biomarker must first be both reproducible and highly accurate; many previously proposed biomarkers meet one but not both of these criteria. In contrast, in conjunction with Georgopoulos et al. (2010), we have now demonstrated that SNIs distinguish PTSD from control participants with highly accurate ($>$ 90%) results in two studies (it should be noted that some of the PTSD participants here overlap with Georgopoulos et al. (2010); however, the majority of study participants [83%] were original to the present analyses). The fact that supervised classification analyses based on SNI yielded $>$ 93% accuracy in the present study is remarkable, particularly for a disorder that historically was considered primarily a psychological

rather than biological phenomenon. Ideally, evaluation of a biomarker must also be relatively non-invasive. The findings in the present study are based on 1-min recordings of MEG resting-state brain activity without evocation of traumatic memories, consistent with that characteristic. The ability of such a short, non-invasive test to provide highly accurate results firmly attests to the power of MEG and suggests that evaluating correlated neural network activity (i.e., SNI) is the optimal approach for extracting information from resting-state brain activity.

The neurobiological underpinnings of SNI, and alterations thereof, are not fully understood but appear to be genetically influenced. We have previously demonstrated that different forms of the apolipoprotein E (apoE) genotype systematically affect SNI (Leuthold et al., 2013). Furthermore, we have demonstrated an influence of apoE on PTSD symptomatology (Peterson et al., in press). Thus, alterations in SNI observed in those with PTSD may be partially accounted for by genetic variations; however, neural network properties are likely multiply determined and additional research is needed to identify other biological contributors.

There are several notable strengths of the present study. First, a relatively large sample of veterans with PTSD, both with and without comorbid psychiatric disorders, participated in the study thereby increasing generalizability of the findings to other veteran populations. Second, unlike many other imaging techniques that rely on metabolism or blood flow, MEG provides a direct measure of brain function and is ideally suited to evaluate neural interactions, the essence of brain functioning. Finally, the study used a rigorous statistical analysis approach to construct the classification algorithm and develop its diagnostic performance.

4.1. Limitations

The present study reinforces the utility of MEG SNI as a PTSD biomarker and highlights the application of a diagnostic algorithm based on SNIs with remarkable accuracy; however, the findings must be considered in the context of limitations. For instance, a relatively small sample of female veterans were included in the present study, and the classification accuracy for those women was lower than in men, raising questions about observed gender differences. In addition, veterans with uncomplicated PTSD and control veterans were the focus of recruitment efforts; consequently, comorbidity rates were relatively low and may not represent the majority of veterans with PTSD. Similarly, though individuals with subthreshold PTSD symptoms are quite common clinically, they were not included in the present analyses. Additional research addressing these limitations is important for evaluating real-world applicability of the SNI biomarker. The present study replicates and extends findings from Georgopoulos et al. (2010); however, due to overlap in some of the PTSD participants, replication of the findings in an independent sample is needed. Finally, given the cross-sectional nature of the present study, an important characteristic of a PTSD biomarker – namely, clinical utility, or change in relation to an individual's clinical status – was not evaluated. Longitudinal studies tracking SNI in relation to treatment response will be beneficial in further cementing SNI as a PTSD diagnostic biomarker.

4.2. Conclusions

The present study demonstrates the development and application of a highly accurate PTSD diagnostic algorithm based on SNIs. The findings validate SNI as a PTSD biomarker and offer evidence that SNI anomalies associated with PTSD are manifest regardless of comorbid psychiatric diagnoses. Although the findings were robust across gender, they were somewhat stronger among men. Additional research is required to illuminate the nature of the gender differences in SNI identified in the present study.

Acknowledgments

This work was partially supported by a service directed grant from the United States Department of Veterans Affairs. The authors thank Kari Johnson, Emily Van Kampen, Ann Marie Winskowski, Ryan Miller, Alina Shub, and Alex Alcorn for their help in participant recruitment, consent, and data entry.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2014.11.007.

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