Post-traumatic stress disorder: a right temporal lobe syndrome?

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Abstract
In a recent paper (Georgopoulos *et al* 2010 *J. Neural Eng.* **7** 016011) we reported on the
power of the magnetoencephalography (MEG)-based synchronous neural interactions (SNI)
test to differentiate post-traumatic stress disorder (PTSD) subjects from healthy control
subjects and to classify them with a high degree of accuracy. Here we show that the main
differences in cortical communication circuitry between these two groups lie in the
miscommunication of temporal and parietal and/or parieto-occipital right hemispheric areas
with other brain areas. This lateralized temporal-posterior pattern of miscommunication was
very similar but was attenuated in patients with PTSD in remission. These findings are
consistent with observations (Penfield 1958 *Proc. Natl Acad. Sci. USA* **44** 51–66, Penfield and
Perot 1963 *Brain* **86** 595–696, Gloor 1990 *Brain* **113** 1673–94, Banceaud *et al* 1994 *Brain* **117**
71–90, Fried 1997 *J. Neuropsychiatry Clin. Neurosci.* **9** 420–8) that electrical stimulation of
the temporal cortex in awake human subjects, mostly in the right hemisphere, can elicit the
re-enactment and re-living of past experiences. Based on these facts, we attribute our findings
to the re-experiencing component of PTSD and hypothesize that it reflects an involuntarily
persistent activation of interacting neural networks involved in experiential consolidation.

1. Introduction

Post-traumatic stress disorder (PTSD) is a psychiatric disorder defined by an enduring set of maladaptive symptoms that arise after exposure to one or more potentially life-threatening events (DSM-IV-TR) [7, 8]. These include unwanted re-experiencing of persistent painful trauma memories through nightmares, daytime intrusive memories and psychological distress or physiologic arousal when reminded of the trauma. Other symptoms include avoidance of trauma reminders, withdrawing from one's environment and a general numbing of responsiveness. Persistent arousal through sleep disturbances, irritability, exaggerated startle response, and/or hypervigilance also contribute to the functional impairments of the disorder. A recent replication of the US National Comorbidity Survey of over 5600 adults indicated a lifetime risk for PTSD of 6.8% [9], and a 12 month prevalence of 3.5% [10]. In addition, PTSD is often diagnosed comorbidly with depressive disorders, other anxiety disorders and substance use disorders [10].

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The polymorphous symptomatology associated with PTSD is partially responsible for the lack of a clear understanding of its underlying pathophysiology. However, the widely varying experimental designs, imaging methods and patient samples also generate findings that can be difficult to interpret. For example, structural neuroimaging studies typically employ magnetic resonance imaging (MRI), while functional neuroimaging studies commonly use functional MRI (i.e. fMRI) or positron emission tomography (PET) to localize the activations triggered by symptom provocation (e.g. by script-driven imagery) and/or cognitive performance tasks (see [11] for a review).

In contrast, we and other research groups investigate brain function in PTSD patients in the absence of a task (task-free). A recent fMRI study by Lanius *et al* [12] evaluated the blood oxygen level dependent (BOLD) interactions between posterior cingulate/precuneus (PCC) and other brain areas in PTSD during rest. However, without adequately accounting for the inherent nonstationarities in time-series data (such as the BOLD signal), their findings are not easily interpretable or comparable with other studies[11]. In another task-free study, Shin *et al* [13] detected enhanced resting metabolic activity in the dorsal anterior cingulate cortex/mid-cingulate cortex of veterans with PTSD and their identical co-twins relative to identical twin pairs without PTSD. They concluded that this represented a familial risk factor for developing PTSD.

Most recently, we used MEG to investigate the fine-grain (1 ms) temporal interactions among small neuronal ensembles during a task-free state [1]. We relied on the synchronicity of these neuronal ensembles as a basis for optimizing individual PTSD subject classification. As in our previous investigation, a 1 min long, task-free condition was employed in the present study. Here, we sought to assess differences in cortical communication circuitry in steady-state brain function among PTSD ($N = 80$), recovered PTSD ($N = 18$) and control subjects ($N = 284$). To our knowledge, this is the largest study of brain function in PTSD yet reported.

2. Materials and methods

2.1. Subjects

All subjects participated in the study after providing informed consent, in adherence to the Declaration of Helsinki, and were

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[11] The study by Lanius *et al* [12] was based on a metabolic signal (blood oxygen level dependent, BOLD, activation), was restricted to very low frequencies (0.012–0.1 Hz) and was focused on the relations of a specific brain area (PCC) to other areas. Correlation analyses were performed on time series data without prewhitening, rendering the results difficult to evaluate because the correlation between two time series is strongly influenced by nonstationarities (with respect to the mean and variance) and autocorrelation within the individual series. For example, a significant correlation between times series A and time series B can very well be due to a highly autocorrelated series A without any true association between A and B. This pitfall was first noted several decades ago [18, 19, 25]. The remedy [18, 19, 25–29] is to render the time series stationary and nonautocorrelated by suitably modelling the series and taking the white noise, stationary and non-autocorrelated residuals, $R(A)$ and $R(B)$: the correlation between these residuals is the true correlation between the two time series. This preprocessing is called 'prewhitening' of the series and is typically accomplished by fitting an autoregressive integrative moving average (ARIMA) model [18]. Without prewhitening, the correlations between raw time series are very likely to be spurious.

financially compensated for their time. All study protocols were approved by the respective Institutional Review Boards.

2.1.1. PTSD group. Subjects were recruited from a database of veterans with a PTSD diagnosis living in Minnesota and Wisconsin. We reviewed their medical records, contacting those with a likely current PTSD diagnosis, and not contacting those with indicators of instability within the last 6 months (e.g. inpatient medical or mental health treatment, significant changes in health or medications). Candidates for recruitment were free of current Axis I disorders other than PTSD and nicotine dependence, pacemakers or other imbedded ferrous metal (due to magnetic effects on MEG) and histories of mild to severe brain injury, We also excluded veterans with active substance use disorders, serious chronic pain and other CNS disorders (e.g. Parkinson's disease, dementia, cerebral vascular accidents, etc). Recruitment letters were then sent and the study coordinator followed up with phone calls to determine interest in participation. Interested veterans were invited to the VA Medical Centre for an interview and MEG scan participation. Approximately 45% of those contacted agreed to participate. Our sample was not designed to be representative of PTSD cases in the general population—where many cases exhibit comorbidity—rather, we developed a sample of relatively 'pure' PTSD cases, uncomplicated by other disorders.

Diagnostic status was determined using structured clinical diagnostic interviews. PTSD diagnosis was based either on the CAPS [14] or DSM-IV-TR SCID PTSD module [15]. Non-PTSD Axis I diagnoses were determined using the non-PTSD portions of the SCID [15]. Ultimately, we included only subjects ($N = 80$) with confirmed PTSD as their primary diagnosis. All were free of current depressive disorders, current anxiety disorders other than PTSD, current substance dependence disorders and lifetime psychotic disorders.

Of the 80 PTSD subjects studied, 73 were men (51.9 $\pm$ 1.7 y, mean $\pm$ SEM) and seven were women (48.7 $\pm$ 3.7 y). Several had PTSD linked to childhood abuse or non-military trauma experienced as an adult (e.g. sexual assault). Those with combat trauma served in various wars, including World War II and the wars in Iraq and Afghanistan; most had fought in the Vietnam War. With respect to medications, 66 patients received medications related to PTSD, whereas the remaining 14 were not receiving any such medications. We previously reported [1] that comparisons of the medicated to non-medicated groups revealed no differences in their MEG scan results. Finally, 18 additional subjects were studied with PTSD in remission (rPTSD). Of those, 15 were men (54.7 $\pm$ 4.8 y) and three women (26.3 $\pm$ 2.5 y). Ten met criteria for anxiety disorder, not otherwise specified, related to their trauma exposure. Eight had met criteria for PTSD at some point in the past, but no longer met criteria for PTSD or any other Axis I disorder.

2.1.2. Control subjects. Healthy subjects ($N = 284$) within the age range of the PTSD patients were recruited from the general public. 171 were men (49.3 $\pm$ 1.4 y, mean $\pm$ SEM) and 113 were women (45.8 $\pm$ 1.8 y). Health was assessed

by clinical interview of the subject upon initial contact and again in more detail at the time of consent. This included a general medical history, medication use and a detailed review of neurologic and psychiatric history.

2.2. Task and data acquisition

As in previous work [1], a simple fixation task was employed to engage the brain in a stable condition. Subjects lay supine within the electromagnetically shielded chamber and fixated their eyes on a spot ~ 65 cm in front of them, for 60s. MEG data were acquired using a 248-channel axial gradiometer system (Magnes 3600 WH, 4D Neuroimaging, San Diego, CA), sampled at 1017.25 Hz and band filtered between 0.1 and 400 Hz.

2.3. Data pre-processing

Prior to the main analyses, cardiac correction of the MEG signals was performed using synchronous event subtraction [16, 17]. Subsequently, single trial MEG data from all sensors underwent 'prewhitening' [18, 19] using a (25, 1, 1) ARIMA model. Residuals were estimated using the SPSS statistical package (SPSS for Windows, version 15, SPSS Inc., Chicago, IL, 2006). Interpolated plots were set up using Matlab, version 2009b.

2.4. Crosscorrelations

All possible pairwise zero-lag crosscorrelations ($N = 30\,628$, given 248 sensors) were computed using the DDCCF routine of the IMSL statistical library (Compaq Visual Fortran Professional edition version 6.6B). Next, the partial zero-lag crosscorrelations PCC_{ij}^0 between i and j sensors 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_{ij}^0 was then transformed to z_{ij}^0 using Fisher's z-transformation [20] to normalize its distribution:

$$z_{ij}^0 = 0.5 \left[\log_e \left(1 + PCC_{ij}^0 \right) - \log_e \left(1 - PCC_{ij}^0 \right) \right]. \quad (1)$$

In total, there were 30 628 such Z predictors; we denote by z_{ij}^0 the specific value of Z for a particular subject.

2.5. Analysis of covariance (ANCOVA)

This analysis assessed the effect of the fixed group factor (PTSD versus control subjects, or rPTSD versus control) on z_{ij}^0 with age and gender as covariates. Since 30 628 assessments were made in total, an adjusted threshold for statistical significance of the group factor was set at $a = \frac{0.05}{30\,628} = 0.000\,001\,63$. This level was used to count and plot significant differences between the control versus PTSD (and control versus rPTSD), as well as between subsamples of the control and PTSD populations. In addition, the value of the F statistic for the group factor in the ANCOVA was used as a quantitative measure of the magnitude of the effect.

3. Results

3.1. Tests between groups

3.1.1. Control versus PTSD.
In the control versus PTSD ANCOVA, 261/30 628 z_{ij}^0 (0.852%) exceeded the threshold above; the highest $F_{1,360}$ value was 152.2. The locations of these significant values in sensor space are shown in figure 1. It can be seen that there is a preponderance of sensors with significant effects over the right hemisphere. A flattened two-dimensional (2D) contour plot is shown in figure 2, and a 3D plot in figure 3. In figure 3, the sensors that differed most from the control group are denoted by capital letters. Based on the 3D sensor layout in the MEG helmet and typical brain surface reconstructions from brain MRIs using the integrated BESA (version 5.06, MEGIS Software GmbH, Gräfelfing, Germany) and Brain Voyager (Electrical Geodesics, Inc., Eugene, OR, USA) package, these sensors are closest to the right superior temporal gyrus (A), right posterior parietal cortex (B) and right parieto-occipital cortex (C). This pattern was also observed when handedness was included as a covariate in the ANCOVA. Finally, subjects were classified as described in [1]. For this dataset, the sensitivity was 96% and the specificity 95%.

3.1.2. Control versus rPTSD.
In the control versus rPTSD ANCOVA, 27/30 628 z_{ij}^0 (0.088%) exceeded the threshold; the highest $F_{1,298}$ value was 65.5. This proportion differed significantly from the aforementioned control versus PTSD ($P < 0.001$, normal deviate $z = 13.8$). The locations of the 27 significant values in sensor space are shown in figures 4–6. It can be seen that the sensors with significant effects are in the same locations as in the corresponding figures 1–3, although the counts are much smaller.

3.2. Tests within groups

The same ANCOVA as above was performed between permuted subsamples of the control and the PTSD groups to find out how homogeneous these groups were with respect to significant differences in the z_{ij}^0 space. (No such test was run for the rPTSD group due to the small number of subjects in that group.)

3.2.1. Control group.
The control group comprised 284 subjects. First, the subjects were randomly permuted and then split into two subsets with $n_1 = n_2 = 142$. The ANCOVA was performed between these two subsets, and the number of z_{ij}^0 values (out of 30 628 available) for the group effect exceeded noted. This procedure was repeated 100 times, each based on a different random permutation. No comparisons exceeded the threshold in any of these 100 runs.

3.2.2. PTSD group.
The PTSD group comprised 80 subjects. The subjects were randomly permuted and then split into two subsets with $n_1 = n_2 = 40$. The ANCOVA was performed between these two subsets, and the number of predictors for the group effect exceeded noted. This procedure was repeated 100 times, each based on a different random permutation. No comparisons exceeded the threshold in any of these 100 runs.
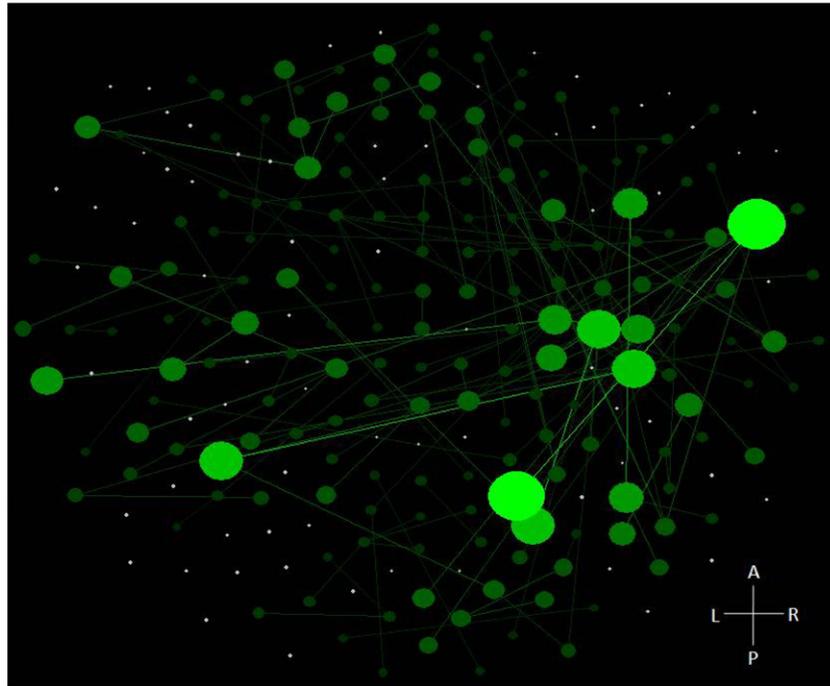
Figure 1. 2D sensor-space plot depicting the SNI differences between PTSD and control groups. White dots indicate the MEG sensor location on a plane. Lines ($N = 261$) indicate the presence of a statistically significant effect (at the threshold specified in section 2); the color intensity of a line is proportional to the value of the F statistic for the group in the ANCOVA. The radius of the ellipses and color intensity are proportional to the maximum F-value related to the specific sensor (out of 247 possible). A, anterior; P, posterior; L, left; R, right.
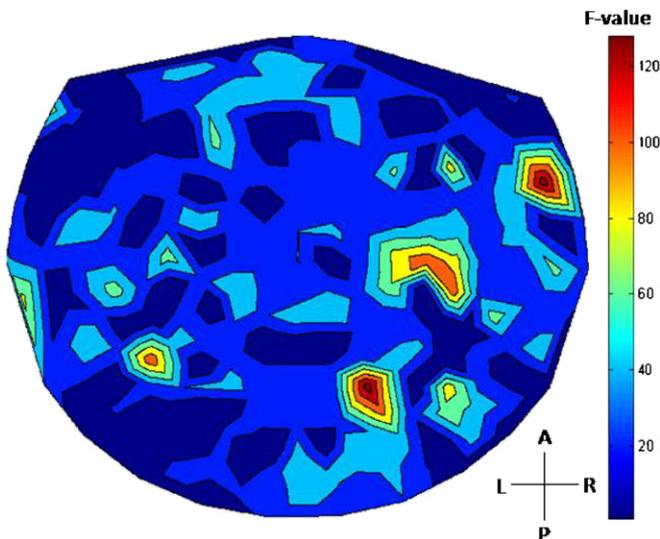

Figure 2. 2D contour plot of color-coded ANCOVA F-values (above threshold) interpolated linearly in sensor space for PTSD versus controls.
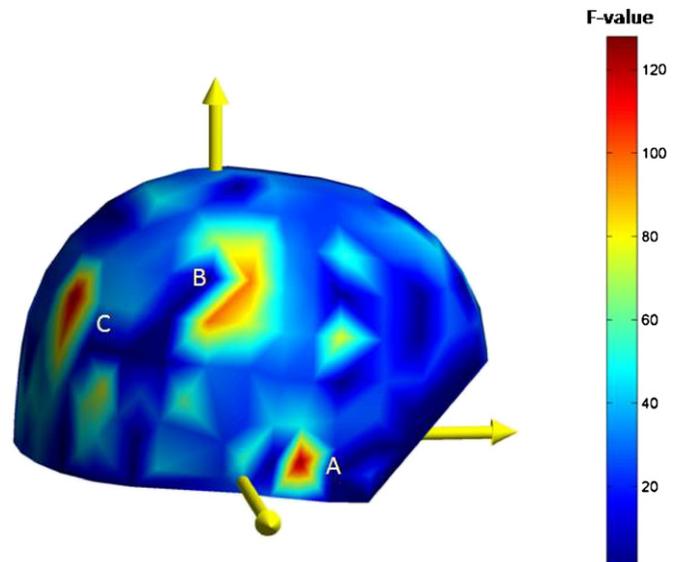

Figure 3. 3D surface plot using Delaunay triangulation of MEG sensor coordinates with interpolated, color-coded ANCOVA F-values (above threshold) for PTSD versus controls.

4. Discussion

4.1. Methodological considerations

4.1.1. MEG signal. The results of this study revealed significant differences between the PTSD and control groups in synchronous correlations between specific sensor pairs. We discuss below differences in MEG signal analysis between this study and other more conventional methods of MEG analysis [21]. 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.
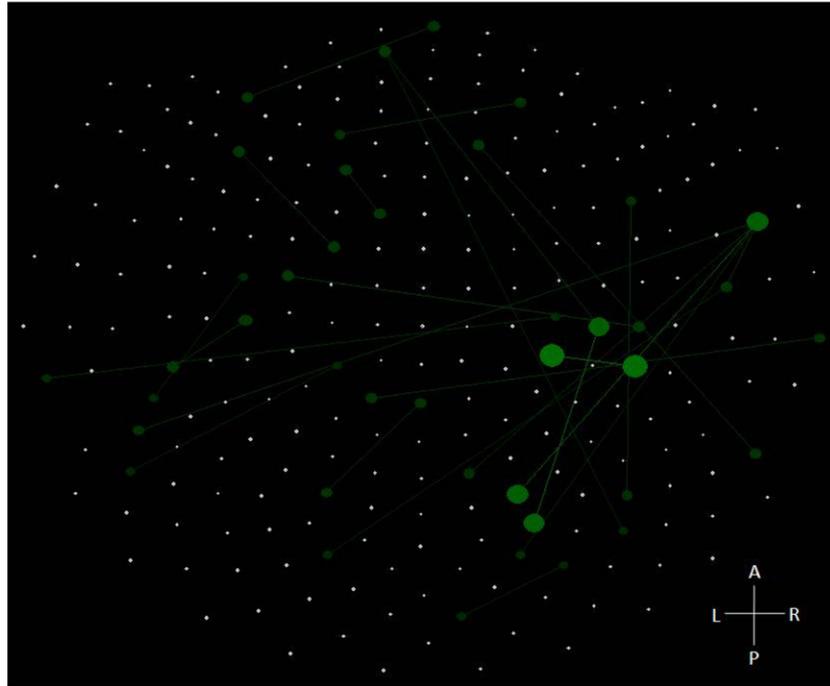
Figure 4. SNI differences between rPTSD and control groups ($N = 21$ statistically significant differences). Conventions as in figure 1.

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, 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 [21]. However, recent work [22] 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 and our previous study [1] is different, mainly because we acquire spontaneous MEG activity in a task-free state. Therefore, it is reasonable to suppose that the MEG signal in this case comes from widely distributed, small intensity cortical generators reflecting
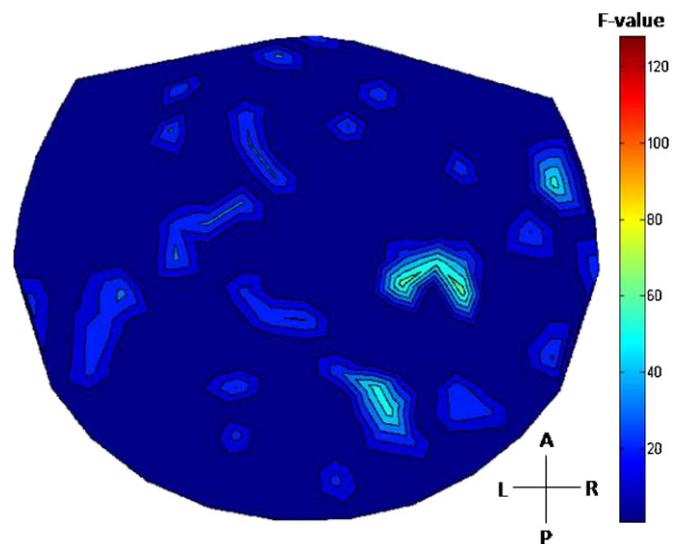

Figure 5. 2D contour plot of color-coded ANCOVA *F*-values (above threshold) interpolated linearly in sensor space for rPTSD versus controls.

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.
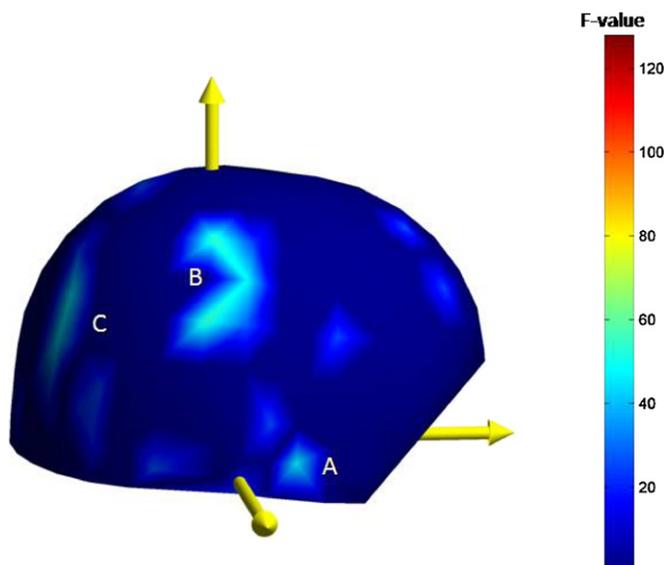
Figure 6. 3D surface plot using Delaunay triangulation of MEG sensor coordinates with interpolated, color-coded ANCOVA *F*-values (above threshold) for rPTSD versus controls.

4.1.2. Prewhitening. The essence of our approach in this and our previous studies [1, 23] lies in the hypothesis that a key aspect of the brain function lies in the synchronous interactions of neuronal populations. These interactions can be estimated by correlating time courses of the MEG signal recorded by different sensors. However, since these time courses are typically nonstationary and highly autocorrelated [24], correlating the raw time courses is inadvisable as it would yield spurious, erroneous and typically inflated correlations [25]. In order to correctly assess the correlation between time series, the removal of nonstationarities and autocorrelations is imperative [18, 19, 26–29]. We accomplished this task by 'prewhitening' the MEG time series, i.e. performing ARIMA modeling [18, see methods], taking the residuals (also called 'innovations' by Priestley [19]), and calculating from them correct estimates of their correlation. These correlations between pairs of sensors, after partialing out effects of other sensors, proved very effective in differentiating and correctly classifying subjects suffering form various brain diseases [23] and PTSD [1].

4.2. General

Remarkably, the differences we found between the PTSD and the control groups were documented in a task-free state, without evoking traumatic experiences, and, therefore, reflect the status of steady-state neuronal interactions. In addition, they reflect mostly cortical interactions, given the limited capacity of MEG to record signals from deep brain structures. What might these differences signify? They certainly do not correspond to all aspects of the diagnostic construct we call PTSD. This disorder, as currently defined in DSM-IV, is often conceptualized as consisting of four components [30]: re-experiencing of painful memories, effortful avoidance of trauma cues, emotional numbing and hyperarousal. Based on our findings, we offer an alternative view and hypothesize

that the observed differences in neuronal interactions reflect the re-experiencing component, which we further substantiate below.

Whereas there is general agreement that PTSD involves altered neural circuitry, others have hypothesized that PTSD is primarily a trauma-induced disorder of fear circuitry [31]. The two hypotheses are not mutually exclusive. Neuroimaging research generally indicates that the amygdala, medial prefrontal cortex and hippocampus play prominent roles in PTSD; it is likely that this reflects abnormalities in fear circuitry [31], but abnormalities have also been found outside of fear circuits. For example, Bremner *et al* [32] reported functional abnormalities in the right visual association cortex, the cuneus and the right parietal lobe in women with PTSD. Obviously, much more investigation is needed.

4.3. Hemispheric differences

We found significant differences between the PTSD and control groups in only a small percentage of synchronous correlations. The sensors associated with the most significant changes formed four distinct nodes, three in the right hemisphere and one in the left hemisphere (figure 2). The right-hemispheric preponderance is in accord with other findings in the literature pointing to alterations in the right hemispheric function in PTSD [32]. More importantly, however, it is reminiscent of findings by several investigators on the effects of electrical stimulation of the cortex during brain surgery [2–6], namely the elicitation of re-living or re-enacting past experiences, which Penfield called 'experiential' responses, including what he called 'flash-backs' [3]. These re-enactments are evocative of the flashbacks experienced by patients suffering from PTSD.

Experiential responses were mostly elicited by stimulation of the right temporal lobe, notably the superior temporal gyrus [3, 5]. Interestingly, the most significant effect in our study was also observed in a sensor in close proximity to the right superior temporal gyrus. This congruence in the approximate location of the 'experiential node' between the effects of electrical stimulation and the results of this study suggests that our findings could be attributed mostly to the flashbacks and/or painful, intrusive memories experienced in PTSD. In a more general sense, it seems that it is the repetition of these flashbacks and memories as such, and not their negative valence, that underlies our results, for the experiences elicited by electrical stimulation typically do not have a negative valence. The negative valence of re-experiencing in PTSD may be related to activation of fear circuitry. Therefore, a simple explanation of our findings would be that we are picking up a hyperactive brain network involved in re-experiencing the traumatic event(s), in a similar, qualitative sense as witnessing a hyperactive arm-movement network in the case of involuntary movements (e.g. hemiballismus).

Penfield [2, 3] and Gloor [4] were very careful to point out that the experiential responses elicited by stimulating the temporal lobe reflected a distributed neural network, and not just interference with local events (pages 689–690 in [3]). Indeed, the lines linking sensors in figure 1 reflect

such a distributed network, and the color coding in figures 2 and 3 denotes the magnitude of the statistical significance of the group difference for a particular network interaction. Given that experiential responses and PTSD flashbacks both contain perceptual (visual, auditory), speech/language and interpretive components, we hypothesize that the posterior parietal and parieto-occipital nodes we observed (figure 3, B and C) relate to a functional interaction between the temporal lobe (figure 3, A) and the 'perceptual-plus' content of the flashbacks. Indeed, Gloor [4] pointed out that temporal lobe epileptic discharge (as well as electrical stimulation of temporal lobe structures) can trigger experiential phenomena encompassing perceptual and mnemonic features usually based on a person's experience through elaboration of patterns of excitation and inhibition in widely distributed neuronal networks that include temporal isocortex and limbic structures (amygdala, hippocampus and parahippocampal gyrus).

An additional intriguing possibility is that our findings may indicate a particular kind of memory disturbance. Brewin *et al* proposed a dual representation theory of PTSD [33]. They posited two distinct memory systems. The first consists of well organized, flexible, contextualized representations (C-reps) that can be retrieved intentionally. The second is made up of inflexible, sensory-bound representations (S-reps) that can be triggered by environmental cues or can intrude spontaneously into awareness. According to the authors, intrusive traumatic memories and flashbacks contribute to both the onset and maintenance of PTSD when sensation-based memories of extreme events are primarily or exclusively represented as S-reps that have not been fully integrated with contextual memory. The locus of integration is hypothesized as a connection between temporal and parietal networks. In this context, it is interesting that a recent study in rats suggests that secondary sensory cortices may support memory storage and retrieval of sensory stimuli that have acquired a behavioral salience with the experience [34].

4.4. PTSD in remission

It is remarkable that the same effects we observed for the PTSD versus controls comparison were also observed for the rPTSD versus controls comparison, but are much attenuated. This finding suggests that a central network abnormality in PTSD can be scaled and evaluated using the SNI test, as indicated in our previous study [1]. The possibility of deriving continuous measures of brain network abnormalities in PTSD remains to be investigated. Such measures would have obvious implications for treatment research and for charting the longitudinal course of PTSD.

4.5. Conclusions

It should be pointed out that the PTSD subjects in the present study were veterans; further studies are needed to confirm these findings in other groups, such as children and non-veteran adults. In future work, PTSD subjects could be compared with more closely matched control groups, such as trauma-exposed veterans who have not developed PTSD. In addition, MEG studies using activation (e.g. fear induction) would probably

be informative, as would studies of subjects with PTSD and comorbid disorders (i.e. mild brain injury, depression). Indeed, longitudinal studies of PTSD subjects who are recovering are also clearly needed.

Finally, we agree with Shin and Handwerger [28] that biomarkers in general (such as our SNIs) are expected to play important roles in refining diagnostic constructs such as PTSD. The continuous revision of psychiatric diagnoses is not uncommon given that they are regarded as 'open constructs'. In fact, almost without exception, diagnostic constructs were established without knowledge of the underlying pathophysiology. As such, it is natural to expect that when such knowledge becomes available, these constructs will evolve accordingly. In addition to their role in refining diagnostic constructs, biomarkers will also improve treatment research by providing objective indicators of diagnostic status and stimulate the development of treatments targeted to specific brain circuits.

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