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Lateralized abnormalities in auditory M50 sensory gating and STG cortical thickness in PTSD: Preliminary results

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1. Introduction

Post-traumatic stress disorder (PTSD) is characterized by unique symptoms resulting from the exposure of a traumatic event. These symptoms include persistent re-experiencing of the event, avoidance of stimuli associated with the event, numbing of general responsiveness, and increased arousal (DSM-IV-TR). Neurophysiological research in PTSD has shown impairments in essential mechanisms underlying information processing (for review see Karl et al., 2006a), particularly within the inhibitory network (Paige et al., 1990; Gillette et al., 1997; Neylan et al., 1999; Skinner et al., 1999; Mennings et al., 2008).

Sensory gating of the auditory evoked potential (EP) P50 has been used as a neurophysiological measure of sensory filtering that occurs so early in the processing stream that it has been described as pre-attentive (Adler et al., 1982). In healthy participants, when two auditory clicks are presented in close proximity (500 ms), the response amplitude to the second click (S2) is significantly smaller in relation to the response amplitude to the first click (S1). The process involved in the inhibition of S2 is referred to as sensory gating, which is usually expressed as the ratio of S2 to S1 (Adler et al., 1982).

Previous studies have shown that patients with schizophrenia did not exhibit this filtering effect to the extent of healthy controls: the response amplitude for S2 was equal or only slightly smaller than S1 (Adler et al., 1982; reviewed in Patterson et al., 2008). This phenomenon evinces a physiological impairment in filtering out redundant stimuli, and has been termed a sensory gating deficit (Adler et al., 1982). Previous EP studies in PTSD

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secondary to combat exposure (Paige et al., 1990; Gillette et al., 1997; Neylan et al., 1999); rape (Skinner et al., 1999); and urban violence (Ghisolfi et al., 2004) reported impaired P50 auditory gating (with the exception of Metzger et al., 2002).

Since P50 is best observed in the midline Cz site using EEG and its generators are bilateral, investigation of possible lateralized differences in the latency and response magnitude of the hemispheric generators may help to specify the nature of P50 sensory filtering deficits found in PTSD. Magnetoencephalography (MEG) is a neuroimaging technique that records the brain's magnetic fields by using an extremely sensitive array of superconducting quantum interference devices (SQUIDs). Since magnetic fields are less distorted by the skull and scalp, and is more sensitive to tangentially oriented generators, MEG allows for better source localization than standard EEG protocols, which has been used extensively to investigate the M50 generators (M50 is the MEG equivalent to P50) of auditory sensory gating within each hemisphere (Huang et al., 2003, Thoma et al., 2003, Hanlon et al., 2005). The left and right M50 response has been localized to Heschl's gyrus and planum temporale of the superior temporal gyrus (STG) in both healthy controls and individuals diagnosed with schizophrenia (Huang, et al., 2003; Thoma et al., 2003; Hanlon et al., 2005). Moreover, it has been shown in healthy controls that the bilateral M50 STG sources accounted for 97% of the variance in P50 responses at electrode Cz, which demonstrated that the P50 auditory EP can be attributed to the bilateral M50 STG source localizations (Huang et al., 2003). In addition, Thoma and colleagues (2004) observed that ipsilateral STG cortical thickness at the M50 dipole sources were negatively related to M50 gating ratios in individuals diagnosed with schizophrenia; that is, thinner cortex predicted worse auditory sensory gating only in the patient group.

To our knowledge, the relationship between STG cortical structure and M50 sensory gating has not been studied in the PTSD population. In the current study, MEG in conjunction with structural magneticresonance imaging (sMRI) were employed to investigate the mechanisms involved in auditory sensory gating in a sample of PTSD subjects. The objectives of this study were to explore: 1) potential lateralization of M50 auditory sensory gating; 2) any relationship between STG cortical thickness and M50 gating; and 3) possible associations between PTSD symptom severity and M50 components.

2. Methods and Materials

2.1 Participants

Seven unmedicated male Vietnam War veterans with combat-related PTSD (M age=57.43, SD =2.23; M years of education=14.57, SD =1.72), and eleven controls matched for age, sex, and education (M age=57.25, SD =3.54; M years of education=14.75, SD =1.48; $t(13)=-0.115$, $P=0.91$ and $t(12)=0.324$, $P=0.75$, respectively) participated in this study. All participants were right handed, assessed with the Edinburgh Handedness questionnaire (Oldfield, 1971).

Diagnosis of PTSD was established with the Clinician-Administered PTSD Scale for DSM-IV (CAPS-DX, Blake et al., 1995). Patients had no history of other Axis I psychiatric diagnoses other than depression or substance abuse/dependence in remission for at least 6

months on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID, First et al., 1997). The patient sample diagnoses are displayed in Table 1. Controls were free of Axis I diagnoses on the SCID (First et al., 1997). Exclusionary criteria for both groups included hearing impairment (e.g., the need for hearing devices), history of psychosis, head injury with loss of consciousness for more than five minutes, or other neurological disease, and alcohol/substance abuse in the prior 6 months. This study was approved by the Human Research Review Committee at the University of New Mexico and the Albuquerque VA Medical Center Office of Research and Development and all participants signed approved consent forms prior to participation.

2.2. MEG and sMRI data collection

MEG data were collected using a whole-head 122-channel biomagnetometer (NeuroMag Ltd., Helsinki, Finland) and analyzed using NeuroMag analysis software. Binaural clicks (3ms duration) were presented in pairs (S1 and S2) with a 500 ms inter-stimulus interval and a variable inter-trial interval of 7–11 s (Adler et al., 1982). The clicks were delivered through entymotic earphones placed in each ear canal. All subjects' hearing thresholds were assessed by decreasing the dB level until they reported that they could no longer hear the clicks. The dB level that the subject last heard was recorded as the hearing threshold. Then, the intensity in each ear was set 35dB above the subject's hearing threshold. The left and right ear hearing thresholds were assessed individually. The hearing thresholds for the PTSD group ranged from 30–45dB, which was in range with the control group. One-hundred fifty uncontaminated paired-click trials were collected over approximately 30 minutes. To identify eye-blink and muscle artifacts, electro-oculogram (EOG; bipolar oblique, upper right and lower left sites) and electro-cardiogram (ECG; placed on collarbone) were collected simultaneously with MEG. There was some variability in the number of trials automatically rejected by Neuromag software online due to artifact (peak-to-peak signal strength for the entire epoch collected [-300 to 500 ms] exceeding 150 μ V in any EOG or ECG channel or 3000fT in any MEG channel). MEG data were digitized at 500Hz after 0.03–150Hz analog bandpass filtering.

After the MEG session, structural magnetic resonance imaging (sMRI) data were acquired using a 1.5T Picker Edge Imager for localization of the MEG functional data. The pulse sequence was a Field Echo 3-D Sagittal (Picker) with the following parameters: TR=15ms, TE=4.4ms, FOV=256mm, flip angle=25 degrees, matrix 192 $\times$ 256, slice thickness=1.5mm, no gap. One-hundred twenty-eight slices were obtained in six minutes.

2.2.1 MEG data processing and source modeling—MEG data were superimposed over sMRI images for data co-registration using NeuroMag software. Prior to M50 source localization, a 5–55Hz bandpass filter and a -100 to -10ms baseline were applied to the data. A spherical MEG headmodel (Sarvas, 1987) was used in which a single homogeneous sphere was fitted to the inner surface of the skull (obtained from the participants' MRI) with standard NeuroMag software. Peak source strength, location, and latency of M50 sources (40–80ms post-stimulus) in left and right hemispheres were determined by fitting a single dipole separately over the left and right hemispheres using subsets of 34 planar gradiometers over each temporal lobe; where M50 was defined as the first upward-oriented dipole

occurring within 40–80ms post-stimulus (Huang et al., 2003; Thoma et al., 2003). For modeling M50 S1, 10ms of data surrounding the M50 peak were selected (see Figure 1). Participant's MEG data were excluded from the analysis if S1 source strength was below 5 nanoAmpere-meters (n-Am). M50 S2 measures were identified using a procedure outlined in a previous study (Cardenas, Gerson, and Fein, 1993) in which the location of the S2 dipole was assumed to be the same as that of the S1 dipole. Ratio scores for left and right M50 gating were calculated by dividing S2 source strength by S1 source strength (S2/S1). All dipoles analyzed in the present study had a goodness of fit greater than 70%. One control subject was omitted from the MEG analysis because the data did not meet the outlined criteria.

2.3 Cortical thickness measures

Cortical reconstruction and parcellation were performed with the FreeSurfer image analysis suite (Fischl and Dale, 2000). This method uses both intensity and continuity information from three dimensional magnetic resonance (MR) volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl and Dale, 2000). The cortical thickness for the STG cortices were obtained using the parcellation method outlined previously (Fischl et al., 2004). This method bases the cortical parcellation procedure on class statistics, which are tabulated regionally throughout an atlas space, using a registration procedure that optimally aligns cortical folding patterns (Fischl, Sereno and Dale, 1999). Prior probabilities were computed via a frequency histogram in the atlas space, allowing the calculation of the probability that each parcellation label occurs at every atlas location. The STG cortices obtained by FreeSurfer were Heschl's gyrus, planum temporale, and lateral aspect (for the location of these structures on the FreeSurfer brain, see Figure 2). If a STG thickness measure was 2.5 SD away from its corresponding group, it was omitted from any STG statistical analyses. One control participant was omitted who had extremely small values for all 3 structures on the left- ($>2.5SD$) and right- ($>3SD$) hemisphere.

2.4 Clinical assessment

The CAPS-DX was used for measuring the symptom severity (Blake et al., 1995). The CAPS is composed of the three subscales: 1) re-experiencing of the traumatic event; 2) persistent avoidance of stimuli associated with the trauma and numbing of the responsiveness; and 3) persistent hyperarousal symptoms. The PTSD Symptom Scale Self Report (PSS-SR, Foa, 1993) was also administered.

2.5 Statistical methodology

The data distributions for all variables in this study were tested for normality using the Shapiro-Wilk test. All statistical tests were applied on distributions that had p-values greater than 0.05, indicating normality; no transformations were required. To assess dipole position differences in each hemisphere between groups a repeated measures multivariate analysis of variance (MANOVA) was obtained with x, y, z as the dependent within-subjects factor and diagnosis as between subjects factor. Repeated measure ANOVAs were conducted to compare M50 S1 and S2 latencies, source strengths, S2/S1 ratio scores, and STG cortical

structures. Group was the between subjects factor and hemisphere was the within subjects factor. Each STG structure was analyzed separately. Linear regressions were used to examine the extent to which STG cortical thickness predicted M50 gating within each group; the three STG structures were modeled separately. Diagnostics were assessed for all the regressions reported. Lastly, Pearson correlations were obtained to explore the possible associations between clinical scores (CAPS and PSS-SR) with left and right S1 and S2 source strength measures and S2/S1 gating in the PTSD group. To reduce the likelihood of a Type I error a Bonferroni family-wise correction was applied to the significance level of the reported correlations ($\alpha_b = 0.04$).

3. Results

3.1. M50 dipole position

In all cases, the M50 source dipole location fell on posterior Heschl's gyrus or planum temporale, or within an accepted 15 mm margin of error (Huang et al., 2003; Thoma et al., 2003; Hanlon et al., 2005). The M50 source dipole position was expressed in distance (mm) on the x-(medial/lateral, left lateral<0, right lateral>0), y- (anterior/posterior), and z- (dorsal/ventral) axes from the center of a spherical-head model. There were no group differences in source position for the left ($F(1, 16)=0.01$, $P= 0.935$) or right ($F(1, 16)=0.51$, $P=0.49$) hemisphere.

3.2. M50 S1 and S2 latencies and source strengths

Means and SD for latencies, source strength, and ratios are listed in Table 2. For latency, there were no significant between subjects' effect ($F(1,15)<0.01$, $P=0.99$), within hemisphere effect ($F(1,15)=0.26$, $P=0.62$), nor significant interaction. For the S1 and S2 source strengths (i.e., components), the interaction effect of hemisphere $\times$ component $\times$ group reached a trend level significance ($F(1,15)=4.11$, $P=0.06$). When group was compared for hemisphere and component, there was a significant difference in source strength for S1 in the right hemisphere only, where the PTSD group had reduced source strength ($F(1,15)=5.15$, $P=0.04$). When hemispheres were compared for group and component, the right hemisphere S1 source strength was significantly smaller than the left hemisphere in the PTSD group only ($F(1,15)=6.95$, $P=0.02$). Both tests suggest an attenuated lateralized S1 source strength in the PTSD group. Lastly, when component was compared for group and hemisphere, there was a significant difference between S1 and S2 in both groups and hemispheres, where S2 was significantly reduced in comparison to S1 ($P<0.005$), except for the right hemisphere in the PTSD group ($F(1,15)=3.14$, $P=0.10$), which indicates that S2 inhibition is deficient within the right hemisphere of the PTSD group (see Table 2).

3.3. M50 sensory gating ratios

There was a significant main effect for group ($F(1,15)=7.24$, $P=0.01$), with the PTSD group showing higher S2/S1 ratio scores (see Table 2). There was no significant difference for hemisphere ($F(1,15)=0.22$, $P=0.64$). Although the group $\times$ hemisphere interaction was not significant ($F(1,15)=1.65$, $P=0.22$), one of the objectives in the current study was to explore the potential lateralization of M50 auditory gating. Therefore, a one-way ANOVA was conducted between groups for each hemisphere. The right M50 gating ratio was

significantly larger in the PTSD group ($F(1,15)=11.31, P<0.01$). The left hemisphere M50 gating ratio group difference was not significant ($F(1,15)=0.67, P=0.43$, see Table 2).

3.4. STG cortical thickness

Means and SD are reported in Table 3. For Heschl's gyrus and lateral aspect cortices there was a trend-level main effect for group ($F(1,15)=3.37, P=0.08$; $F(1,15)=3.75, P=0.07$, respectively), where the PTSD group had thinner cortex. For all three structures there was a significant within subjects' effect for hemisphere, where the right hemisphere was significantly reduced in comparison to the left ($P<0.05$). Also, for all three structures, there was no group $\times$ hemisphere interactions observed. There were no significant correlations with age and STG cortical thickness (all 3 regions).

3.5. STG cortical thickness and M50 sensory gating regressions

The goodness of fit, computed as R^2 for each regression model, is presented in Figure 3. In the PTSD group regressions, the right hemisphere Heschl's gyrus cortical thickness explained 72% of the variance in right hemisphere M50 gating ($Beta=-0.85, SE=0.21, P=0.02$). The right hemisphere planum temporale cortical thickness explained 80% of the variance in right hemisphere M50 gating ($Beta=-0.90, SE=0.16, P<0.01$; see Figure 3). The right STG lateral aspect had no significant linear relationship with right M50 gating in the PTSD group ($P=0.27$). No significant relationships were found for the left hemisphere STG thickness and left M50 gating in PTSD group (all with $P>0.39$). No significant relationships between STG thickness and M50 gating were observed for the control group (all with $P>0.41$). When combining both groups ($n=18$), there were no associations observed for left or right hemisphere gating ratios and STG cortices ($p>0.22$).

3.6. Associations between PTSD symptom severity with M50 measures

In the PTSD group, a significant positive correlation was found between right S1 source strength and the CAPS hyperarousal score (see Figure 4). The PSS-SR total score (PTSD symptom severity) was negatively correlated with right hemisphere M50 gating ratio ($r(7)=-0.86, P=0.01$). However, right hemisphere M50 gating ratios did not correlate with CAPS total scores, $r(6)=-0.13, P=0.81$.

4. Discussion

The overall objective in the current study was to investigate early information processing in a combat-related PTSD sample by assessing M50 auditory sensory gating and its relationship to STG cortical thickness and PTSD symptom severity. Reliable evidence has accrued in support of impaired P50 gating in PTSD (Paige et al., 1990; Gillette et al., 1997; Neylan et al., 1999; Skinner, 1999; for review see Karl et al., 2006a), but to our knowledge there have been no studies that examined the hemispheric M50 generators of sensory gating in this population. The use of magnetic source imaging (MSI) allowed localization of the auditory M50 to Heschl's gyrus and planum temporale on STG in both PTSD and control groups. No group differences were observed for dipole positions, indicating normal localization of auditory processing in both groups. The M50 ratio scores (S2/S1) were significantly larger in the right hemisphere of those diagnosed with PTSD in comparison to

the healthy controls, demonstrating a lateralized deficit in M50 auditory gating. Our major finding was that in PTSD subjects, the extent of right hemisphere thinning of the cortex at Heschl's gyrus and planum temporale predicted worse right hemisphere M50 gating, suggesting that the lateralized M50 gating impairment is modulated by STG structural changes.

We observed that the source strength for S1 in the right hemisphere was significantly reduced in the PTSD group compared to the control group. To our knowledge, this attenuation of S1 has not been previously reported in PTSD P50 literature. Nonetheless, this finding is generally consistent with other auditory EP reports in PTSD. Several studies found that the amplitude of the P200 auditory EP was sensitive to the manipulation of the intensity of auditory tones (Paige et al., 1990; Lewine et al., 1993; Metzger et al., 2008). Specifically, as the tones became more intense, the PTSD group significantly attenuated, or suppressed, the P200 response amplitude in comparison to the control group (Paige et al., 1990, Lewine et al., 2002). However, Metzger and colleagues (2002) reported opposite findings in female veterans. Paige and colleagues (1990) suggested that the PTSD brain dampened the auditory response in order to render the stimuli more tolerable. This phenomenon was termed "protective inhibition", which was hypothesized to be an "appropriate adaptive mechanism to allow people with PTSD to better cope with environmental stimuli" (Paige et al., 1990). More recently, other studies have investigated this phenomenon by utilizing the mismatch negativity (MMN) protocol, which examines the auditory EP activity that is generated between 100 and 250ms by the brain's adjusted response from contiguous to deviant stimuli (Menning et al., 2008). Menning and colleagues (2008) reported that PTSD subjects had significantly decreased MMN amplitude as compared to the non-PTSD group, but Morgan et al., (1999) found increased MMN amplitude. One explanation to account for these opposite findings is that there may be gender, trauma or other sample-specific factors, which determine the presence of a "protective inhibition" mechanism within PTSD. Both negative studies assessed EPs from females diagnosed with PTSD (Morgan et al., 1999 and Metzger et al., 2002). Thus, our finding of decreased M50 S1 source strength is consistent with the hypothesis of a protective inhibition network and is generally consistent with other studies of early auditory EPs in males with combat-related PTSD. However, our results suggest that M50 S1 changes are specific to the right auditory cortex.

The association between auditory gating and the structural integrity of its cortical generators has yet to be understood in the PTSD literature. In the current study, the PTSD group displayed a trend level reduction in cortical thickness in Heschl's gyrus and planum temporale in comparison to healthy matched controls. Furthermore, the cortical thinning in those cortices which primarily generate the right M50 response predicted worse right M50 gating in the PTSD group. Due to the cross-sectional nature of this study, it is not possible to determine if the origin of thinner STG cortices in the PTSD group is developmental or neurodegeneratively related to the onset of PTSD. Healthy subjects experience an age-dependent reduction in cortical thickness that is evident by middle age and is more prominent in the prefrontal cortex, with relative sparing of the temporal cortex (Salat et al., 2004). This, normal age-related atrophy is thought to result from the shrinkage of dendritic trees, not from the loss of neurons (Morrison & Hof, 1997; Salat et al., 2004). Recent

structural studies in PTSD, which also utilized automated techniques, found significantly thinner STG and prefrontal cortices in comparison to age matched healthy controls (Geuze et al., 2008; Woodward et al., 2009; Mollica et al., 2009). It can be speculated that the onset of PTSD spawns deleterious effects on a set of specific brain regions, with a pattern affecting the normally spared STG (Geuze et al., 2008; Woodward et al., 2009; Mollica et al., 2009), however, longitudinal studies are needed to address this question. To this end, the current results suggest that a functional consequence of STG thinning is poor preattentive M50 auditory gating in the right hemisphere of PTSD subjects.

The associations between reduced P50 suppression and PTSD symptomatology in previous studies have also remained sparse and disparate (for review, see Karl et al., 2006a). We found two counter-intuitive correlations in the PTSD group. First, there was a strong correlation with hyperarousal symptoms assessed with the CAPS and the right hemisphere M50 S1 source strength. Since the right hemisphere S1 source strength was significantly dampened in PTSD subjects in comparison to controls, we expected to find an inverse association between higher arousal symptoms and lower S1 source strength. However, we found that those subjects with more normal, or larger M50 S1 source strengths tend to have worse symptoms. This suggests that subjects who are able to dampen M50 tend to have less intense hyperarousal symptoms. Although speculative, one possible explanation is that the dampening of S1 has a “protective inhibition” mechanism that plays a role in reducing arousal symptoms.

The second unanticipated result was a negative correlation between lower (better) right hemisphere M50 ratio scores and higher PTSD symptom severity on the self report PSS-SR. We expected that better gating would correlate with fewer symptoms. This finding may suggest that poor gating is a protective mechanism and perhaps has upstream effects reducing PTSD severity. However, we did not find significant correlations between right S2/S1 gating ratios and total CAPS scores, the gold standard measure to assess PTSD severity. Another possibility is that this correlation was actually driven by S1 serving as a proxy for the ratio scores. Altogether, the associations between P50 gating and clinical measures have also been inconclusive in previous studies and in the current study with M50. For example, Gillete and colleagues (1997) found that reduced P50 suppression correlated with re-experiencing symptoms, but Metzger et al (2002) found no correlations between P50 gating and PTSD symptoms, but with general psychopathology. Future P50 and M50 studies should continue to explore the correlations of gating ratio scores, individual S1 and S2 components and PTSD symptom severity in larger samples to further understand the association between STG neurophysiology and PTSD symptomatology.

The pathophysiological significance of our lateralized STG structural/functional findings in PTSD has yet to be determined. There are conflicting reports of lateralized hemispheric deficits in the PTSD literature. Several studies report that mixed handedness is associated with PTSD, suggesting less hemispheric dominance is a risk factor in this population (Spivak et al., 1998; Chemtob et al., 2003; Saltzman et al, 2006; Choudhary et al., 2007; and Boscarino et al., 2007). Structural brain imaging studies do not show consistent lateralized changes in PTSD (reviewed in Karl, 2006b), nor have there been consistent lateralization findings in functional neuroimaging studies. Some studies reported increased right limbic

activation and left hemisphere deactivation during symptom provocation; however these findings are not consistent (for review see Rauch, 2006). Electroencephalographic studies also report conflicting lateralization results. Schiffer and colleagues (1995) found that subjects with a history of childhood trauma had a significant left dominant asymmetry of the auditory EP during a neutral memory, which markedly shifted to the right when the unpleasant memories were elicited. A more recent report of resting EEG found no differences in hemispheric asymmetry between PTSD subjects and controls (Shankman et al., 2008). Metzger and colleagues (2004) reported that increased right hemisphere parietal activation was associated with PTSD arousal symptoms, and a study in maltreated children with PTSD found an association between increased left frontal activity and resilience (Curtis et al., 2007). Thus, more comprehensive research encompassing neurocognition, neurophysiology and neuroimaging should continue to investigate the potential role of right hemisphere dysfunction in the pathophysiology of PTSD.

The generalizability of our preliminary results is limited due to the small sample size and an older subject population. Nevertheless, the current study is the first, to our knowledge, to provide evidence of right hemisphere M50 auditory sensory gating deficit in a sample of righthanded Vietnam veterans with combat-related PTSD. Our major finding suggests that there is a relationship between abnormal M50 auditory information processing and thinning of its cortical generators (Heschl's gyrus and planum temporale) in the right hemisphere for the PTSD group. Evinced by the strong correlations between PTSD symptomatology and M50 processing, we propose that this abnormal inhibitory mechanism has a protective function that perhaps modulates, or ameliorates, PTSD symptom severity. Further electrophysiological and structural research is necessary in PTSD in order to establish whether thinning of STG and gating deficits are risk factors to developing PTSD or if the observed changes in structure/function occur as a consequence of the onset of PTSD. To this end, future studies should also investigate the neuronal sources of M50 sensory gating in PTSD and their relation to anatomy, symptom severity and neuropsychological function. This may ultimately provide new insights for the development of better treatment and prevention strategies for those diagnosed with PTSD.

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References

- Adler LE, Pachtman E, Franks RD, Pecevic M, Waldo MC, Freedman R. Neurophysiological evidence for a defect in neuronal mechanisms involved in sensory gating in schizophrenia. *Biological Psychiatry*. 1982; 17:639–654. [PubMed: 7104417]
- Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM. The development of a Clinician-Administered PTSD Scale. *Journal of Traumatic Stress*. 1995; 8:75–90. [PubMed: 7712061]

- Boscarino JA, Hoffman SN. Consistent association between mixed lateral preference and PTSD: confirmation among a national study of 2490 US Army Vietnam veterans. *Psychosomatic Medicine*. 2007; 69:365–369. [PubMed: 17510288]
- Cardenas VA, Gerson J, Fein G. The reliability of P50 suppression as measured by the conditioning/testing ratio is vastly improved by dipole modeling. *Biological Psychiatry*. 1993; 33:335–344. [PubMed: 8471691]
- Chemtob CM, Taylor KB. Mixed lateral preference and parental left-handedness: possible markers of risk for PTSD. *Journal of Nervous and Mental Disease*. 2003; 191:332–338. [PubMed: 12819553]
- Choudhary CJ, O'Carroll RE. Left hand preference is related to posttraumatic stress disorder. *Journal of Traumatic Stress*. 2007; 20:365–369. [PubMed: 17598139]
- Curtis WJ, Cicchetti D. Emotion and resilience: a multilevel investigation of hemispheric electroencephalogram asymmetry and emotion regulation in maltreated and nonmaltreated children. *Developmental Psychopathology*. 2007; 19:811–840.
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV)*. Washington, DC: American Psychiatric Press; 1997.
- Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences U S A*. 2000; 97:11050–11055.
- Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage*. 1999a; 9:195–207. [PubMed: 9931269]
- Fischl B, Sereno MI, Tootell RB, Dale AM. High-resolution intersubject averaging and a coordinate system for the cortical surface. *Human Brain Mapping*. 1999b; 8:272–284. [PubMed: 10619420]
- Fischl B, van der Kouwe A, Destrieux C, Halgren E, Segonne F, Salat DH, Busa E, Seidman LJ, Goldstein J, Kennedy D, Caviness V, Makris N, Rosen B, Dale AM. Automatically parcellating the human cerebral cortex. *Cerebral Cortex*. 2004; 14:11–22. [PubMed: 14654453]
- Foa EB, Riggs DS, Dancu CV, Rothbaum BO. Reliability and validity of a brief instrument for assessing posttraumatic stress disorder. *Journal of Traumatic Stress*. 1993; 6:459–473.
- Geuze E, Westenberg HG, Heinecke A, de Kloet CS, Goebel R, Vermetten E. Thinner prefrontal cortex in veterans with posttraumatic stress disorder. *Neuroimage*. 2008; 41:675–681. [PubMed: 18445532]
- Ghisolfi ES, Margis R, Becker J, Zanardo AP, Strimlitz IM, Lara DR. Impaired P50 sensory gating in post-traumatic stress disorder secondary to urban violence. *International Journal of Psychophysiology*. 2004; 51:209–214.
- Gillette GM, Skinner RD, Rasco LM, Fielstein EM, Davis DH, Pawelak JE, Freeman TW, Karson CN, Boop FA, Garcia-Rill E. Combat veterans with posttraumatic stress disorder exhibit decreased habituation of the P1 midlatency auditory evoked potential. *Life Sciences*. 1997; 61:1421–1434. [PubMed: 9335232]
- Hanlon FM, Miller GA, Thoma RJ, Irwin J, Jones A, Moses SN, Huang MX, Weisend MP, Paulson KM, Edgar JC, Adler LE, Canive JM. Distinct M50 and M100 auditory gating deficits in schizophrenia. *Psychophysiology*. 2005; 42:417–427. [PubMed: 16008770]
- Huang MX, Edgar JC, Thoma RJ, Hanlon FM, Moses SN, Lee RR, Paulson KM, Weisend MP, Irwin JG, Bustillo JR, Adler LE, Miller GA, Canive JM. Predicting EEG responses using MEG sources in superior temporal gyrus reveals source asynchrony in patients with schizophrenia. *Clinical Neurophysiology*. 2003; 114:835–850. [PubMed: 12738429]
- Karl A, Malta LS, Maercker A. Meta-analytic review of event-related potential studies in post-traumatic stress disorder. *Biological Psychology*. 2006a; 71:123–147. [PubMed: 15961210]
- Karl A, Schaefer M, Malta LS, Dorfel D, Rohleder N, Werner A. A meta-analysis of structural brain abnormalities in PTSD. *Neuroscience and Biobehavioral Review*. 2006b; 30:1004–1031.
- Lewine JD, Thoma RJ, Provencal SL, Edgar C, Miller GA, Canive JM. Abnormal stimulus-response intensity functions in posttraumatic stress disorder: an electrophysiological investigation. *American Journal of Psychiatry*. 2002; 159:1689–1695. [PubMed: 12359674]
- Menning H, Renz A, Seifert J, Maercker A. Reduced mismatch negativity in posttraumatic stress disorder: a compensatory mechanism for chronic hyperarousal? *International Journal of Psychophysiology*. 2008; 68:27–34.

- Metzger LJ, Carson MA, Paulus LA, Lasko NB, Paige SR, Pitman RK, Orr SP. Event-related potentials to auditory stimuli in female Vietnam nurse veterans with posttraumatic stress disorder. *Psychophysiology*. 2002; 39:49–63. [PubMed: 12206295]
- Metzger LJ, Paige SR, Carson MA, Lasko NB, Paulus LA, Pitman RK, Orr SP. PTSD arousal and depression symptoms associated with increased right-sided parietal EEG asymmetry. *Journal of Abnormal Psychology*. 2004; 113:324–329. [PubMed: 15122952]
- Metzger LJ, Pitman RK, Miller GA, Paige SR, Orr SP. Intensity dependence of auditory P2 in monozygotic twins discordant for Vietnam combat: associations with posttraumatic stress disorder. *Journal of Rehabilitation Research Development*. 2008; 45:437–449. [PubMed: 18629752]
- Mollica RF, Lyoo IK, Chernoff MC, Bui HX, Lavelle J, Yoon SJ, Kim JE, Renshaw PF. Brain structural abnormalities and mental health sequelae in South Vietnamese ex-political detainees who survived traumatic head injury and torture. *Archives of General Psychiatry*. 2009; 66:1221–1232. [PubMed: 19884610]
- Morgan CA, Grillon C. Abnormal mismatch negativity in women with sexual assault-related posttraumatic stress disorder. *Biological Psychiatry*. 1999; 45:827–832. [PubMed: 10202569]
- Morrison JH, Hof PR. Life and death of neurons in the aging brain. *Science*. 1997; 278:412–419. [PubMed: 9334292]
- Neylan TC, Fletcher DJ, Lenoci M, McCallin K, Weiss DS, Schoenfeld FB, Marmar CR, Fein G. Sensory gating in chronic posttraumatic stress disorder: reduced auditory P50 suppression in combat veterans. *Biological Psychiatry*. 1999; 46:1656–1664. [PubMed: 10624547]
- Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*. 1971; 9:97–113. [PubMed: 5146491]
- Paige SR, Reid GM, Allen MG, Newton JE. Psychophysiological correlates of posttraumatic stress disorder in Vietnam veterans. *Biological Psychiatry*. 1990; 27:419–430. [PubMed: 2310797]
- Patterson JV, Hetrick WP, Boutros NN, Jin Y, Sandman C, Stern H, Potkin S, Bunney WE. P50 sensory gating ratios in schizophrenics and controls: a review and data analysis. *Psychiatry Research*. 2008; 158:226–247. [PubMed: 18187207]
- Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research—past, present, and future. *Biological Psychiatry*. 2006; 60:376–382. [PubMed: 16919525]
- Salat DH, Buckner RL, Snyder AZ, Greve DN, Desikan RS, Busa E, Morris JC, Dale AM, Fischl B. Thinning of the cerebral cortex in aging. *Cerebral Cortex*. 2004; 14:721–730. [PubMed: 15054051]
- Saltzman KM, Weems CF, Reiss AL, Carrion VG. Mixed lateral preference in posttraumatic stress disorder. *Journal of Nervous and Mental Disorders*. 2006; 194:142–144.
- Sarvas J. Basic mathematical and electromagnetic concepts of the biomagnetic inverse problem. *Physical and Medical Biology*. 1987; 32:11–22.
- Schiffer F, Teicher MH, Papanicolaou AC. Evoked potential evidence for right brain activity during the recall of traumatic memories. *Journal of Neuropsychiatry and Clinical Neuroscience*. 1995; 7:169–175.
- Shankman SA, Silverstein SM, Williams LM, Hopkinson PJ, Kemp AH, Felmingham KL, Bryant RA, McFarlane A, Clark CR. Resting electroencephalogram asymmetry and posttraumatic stress disorder. *Journal of Traumatic Stress*. 2008; 21:190–198. [PubMed: 18404640]
- Skinner RD, Rasco LM, Fitzgerald J, Karson CN, Matthew M, Williams DK, Garcia-Rill E. Reduced sensory gating of the P1 potential in rape victims and combat veterans with posttraumatic stress disorder. *Depression and Anxiety*. 1999; 9:122–130. [PubMed: 10356650]
- Spivak B, Segal M, Mester R, Weizman A. Lateral preference in post-traumatic stress disorder. *Psychological Medicine*. 1998; 28:229–232. [PubMed: 9483701]
- Thoma RJ, Hanlon FM, Moses SN, Edgar JC, Huang M, Weisend MP, Irwin J, Sherwood A, Paulson K, Bustillo J, Adler LE, Miller GA, Canive JM. Lateralization of auditory sensory gating and neuropsychological dysfunction in schizophrenia. *American Journal of Psychiatry*. 2003; 160:1595–1605. [PubMed: 12944333]

- Thoma RJ, Hanlon FM, Sanchez N, Weisend MP, Huang M, Jones A, Miller GA, Cañive JM. Auditory sensory gating deficit and cortical thickness in schizophrenia. *Neurobiology and Clinical Neurophysiology*. 2004; 62:1–7.
- Woodward SH, Schaer M, Kaloupek DG, Cediell L, Eliez S. Smaller global and regional cortical volume in combat-related posttraumatic stress disorder. *Archives of General Psychiatry*. 2009; 66:1373–1382. [PubMed: 19996042]

Figure 1.

M50 dipolar source waveforms for 1 control (left column), and 1 PTSD patient (right column) for left hemisphere (top) and right hemisphere (bottom). The arrow is pointing to the center of the epoch that was modeled for M50. Comparing S1 (blue) with S2 (red) waveforms illustrates considerable gating bilaterally for the controls, whereas for the PTSD patient in the right hemisphere, S2 is nearly the same strength as S1, indicating a sensory gating deficit.

Figure 2.

Parcellated brain obtained by *FreeSurfer* highlighting defined STG cortices.

Heschl's gyrus (HG) is colored in green; planum temporale (PT) is colored in yellow; and lateral aspect (LA) is colored in purple. The M50 response was generated no more than 15mm from primary auditory cortex, displayed here as HG, PT, and posterior LA. (a) Corresponds to the pial brain within the skull. (b) Displays the white matter of the cortex. (c) Represents the pial brain inflated, which reveal the fissures within the brain. The dark green lines represent the gyri and the maroon lines represent the sulci. (d) The inflated brain (c) rotated 30 degrees.

Figure 3. Scatterplots with fitted regression lines and R^2 displaying the right hemisphere associations between gating ratios (S2/S1) and cortical thickness of STG cortices (mm) in the PTSD group.

Figure 4. Scatterplot showing the significant correlation between hyperarousal symptoms and right hemisphere S1 source strength in the PTSD group.

Table 1

Clinical Characteristics of PTSD Sample

<i>Comorbid Psychiatric Diagnoses</i> [*]	<u>PTSD (n=7)</u>
Major Depressive Disorder	5
Dysthymic Disorder	1
Depression NOS	1
Alcohol or Substance Abuse/Dependence in remission	4
<i>Medication History</i> ^{**}	
< 1 week ^{***}	1
> 1 month	6
<i>CAPS Scores</i>	<i>Mean (SD)</i>
Hyperarousal	25 (3.8)
Avoidance	32 (3.7)
Re-experience	16 (5.8)
Total	73 (7.8)
<i>PSS-SR Scores</i>	
Hyperarousal	12 (1.6)
Anxiety	13 (3.6)
Re-experience	9 (4.3)
Total	34 (6.0)

* All PTSD subjects were male and had combat related trauma, all diagnosis are listed as current.

** Medication history prior to MEG scan.

*** Lorazepam (0.5mg), no subjects were taking antidepressants or antipsychotics.

Table 2

Mean(SD) for M50 S1 and S2 source strength, latency, and S2/S1 ratio scores for controls (Cnrl) and PTSD Vietnam Veterans (PTSD) for both hemispheres.

	Source Strength (n-Am)		Latency (ms)		Ratio Scores	
	S1	S2	S1	S2	S2/S1	
Cnrl, n=10						
M50L	18.3(10.2)	9.9(6.3)	55.1(10.1)	56.3(11.5)	0.52(0.21)	
M50R	18.3(7.4)*	8.3(4.1)	56.2(10.5)	56.4(10.8)	0.46(0.14)**	
PTSD, n=7						
M50L	22.4(7.5)	13.6(6.2)	58.3(8.5)	57.0(9.6)	0.62(0.30)	
M50R	11.4(3.7)*	8.7(3.9)	55.2(11.9)	53.8(12.3)	0.76(0.24)**	

* ANOVA between subject comparisons significant at the 0.05 level;

** 0.01 level.

Table 3

Mean (SD) STG cortices obtained by FreeSurfer for Controls (Cnrl) and PTSD Vietnam Veterans (PTSD) for both hemispheres measured as thickness (mm).

	Heschl's gyrus	Afa Planum temporale	Lateral aspect
Cnrl, <i>n</i> =10			
Left	1.97(0.28)	2.37(0.26)	2.86(0.28)
Right	2.10(0.36)	2.25(0.24)	2.80(0.22)
Total	2.04(0.27)*	2.31(0.21)	2.83(0.21)*
PTSD, <i>n</i> =7			
Left	1.72(0.11)	2.23(0.10)	2.71(0.19)
Right	1.87(0.27)	2.10(0.29)	2.54(0.19)
Total	1.79(0.26)*	2.17(0.21)	2.63(0.21)*

* Trend-level main effect for group was observed $0.05 < p < 0.09$.