Abnormal Mismatch Negativity in Women with Sexual Assault-Related Posttraumatic Stress Disorder

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Background: *Disturbances in sensory processing have been hypothesized in individuals with posttraumatic stress disorder (PTSD). The authors investigated this possibility by using mismatch negativity (MMN), an event-related potential (ERP) that reflects the operation of a preconscious cortical detector of stimulus change.*

Methods: *Thirteen medication-free women with sexual assault-related PTSD were compared with 16 age-matched, healthy comparison women without PTSD. ERPs were elicited by regularly presented "standard" auditory stimuli and by infrequently occurring "deviant" auditory stimuli, which differed slightly in frequency. The MMN was identified in the subtraction waveforms as the difference between ERPs elicited by the deviant and standard stimuli. Group comparisons of P50, N1, P2, and N2 to the standard and to the deviant stimuli, and of the MMN in the subtraction waveform were performed.*

Results: *The amplitude of the MMN was significantly greater in the PTSD compared to the non-PTSD women. MMN was significantly correlated with the total Mississippi PTSD Symptom Scale score in the PTSD group. No significant group differences were noted in P50, N1, or P2 responding. Significant group differences in N2 were due to the increased MMN in PTSD subjects.*

Conclusions: *The data provide evidence for abnormalities in preconscious auditory sensory memory in PTSD, whereas earlier studies have reported abnormalities in conscious processing. These data suggest an increased sensitivity to stimulus changes in PTSD and implicate the auditory cortex in the pathophysiology of the disorder.* Biol Psychiatry 1999;45:827–832 © *1999 Society of Biological Psychiatry*

Key Words: Women, stress, evoked potentials, posttraumatic stress disorder, sexual assault

Introduction

Over the past decade, clinical investigations have provided evidence of substantial alterations in information processing, as evidenced by event-related potential (ERP) abnormalities, in individuals with combat- and non–combat-related posttraumatic stress disorder (PTSD) (Attias et al 1996; Charles et al 1995; McFarlane et al 1993; Metzger et al 1996; Paige et al 1990). ERPs can be grossly divided into early sensory components and late cognitive components. For example, auditory stimuli evoke P50, N1, P2, and N2 components that mostly reflect the physical characteristics of the stimulus. The P300 component, which usually follows N2, is elicited in response to a significant stimulus. Most ERP studies in PTSD have evaluated P300. Using auditory "oddball" tasks, investigatiors have reported significantly reduced, or increased, P300 amplitudes to target and distractor tones. Because P300 represents attention-dependent, controlled sensory processing of events, these investigators have hypothesized that diminished P300 amplitudes may be an index of disturbed concentration found in individuals with this disorder.

Although P300 has been relatively well characterized in PTSD, less is known about some of the earlier sensory ERPs in this patient population. An ERP component that precedes P300 is the mismatch negativity (MMN), a frontocentral negative waveform with an onset latency as short as 50 msec following stimulus delivery. The MMN is elicited by stimuli that deviate from a train of identical stimuli (Naatanen et al 1982; Naatanen 1990; Naatanen and Alho 1995). Although it overlaps with early sensory ERP components such as P50, N1, P2, and N2, the MMN can be extracted by subtraction of the ERPs from standard and deviant stimuli. Like P300, MMN is believed to reflect a discrete stage of information processing. Unlike P300, however, MMN does not represent attention-dependent processes, but rather reflects automatic brain processing that is largely not under direct subject control (Baddeley 1992). The discrete stages of an "acoustic sensory memory system" that builds traces of the acoustic environment against which new stimuli can be compared are seen in MMN (Naatanen and Picton 1986). The mismatch

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negativity differs from "immediate-recall" type memory or "short-term" memory that are often part of the clinical mental-status evaluation of patients in that the acoustic sensory memory or "template" that underlies MMN is preconscious and maintained without conscious awareness or rehearsal (Baddeley 1992; Naatanen 1990; Naatanen et al 1980; Novak et al 1992).

Because some investigations have demonstrated that certain individuals with PTSD have deficits in attentional processes, this study examined the possibility that individuals with PTSD may exhibit abnormalities in preattentional, nonconscious sensory processing. Hence, this study was designed to assess MMN in civilian women with PTSD.

Methods and Materials

Subjects

Thirteen right-handed, female civilian subjects with sexual assault-related PTSD (mean age 38.1 years, SD = 7.5) and 16 right-handed, healthy female civilian comparison subjects (mean age 37.6 years, SD = 10.5) were recruited for participation in the study. Subjects with PTSD were recruited from the outpatient Woman's Trauma Program at the Yale Psychiatric Institute. Each subject with PTSD met full symptom criteria for PTSD per Structured Clinical Interview for DSM-III-R Diagnosis (SCID) (Spitzer et al 1989). The mean time since sexual assault trauma in the PTSD group was 8.46 years (SD = 7.21 years: range = 1–27 years). Six of the 13 PTSD patients had a comorbid diagnosis of panic disorder with agoraphobia, and 11 patients had a history of major depression. No subject met criteria for illicit drug abuse or dependence.

PTSD patients also were administered the Mississippi PTSD Symptom Scale for civilian trauma. The Mississippi PTSD scale (range: 35–175) is a self-report inventory consisting of 35 items derived from DSM-III and associated features. It measures both symptom severity and the effects of those symptoms on an individual's life (Keane et al 1988; Vreven et al 1995). In addition, all subjects were administered the Spielberger State/Trait Anxiety Inventory (STAI), a self-report assessment that evaluates state and trait anxiety (Spielberger 1983).

Comparison subjects were recruited through responses to advertisements from the Biological Studies Division of the National Center for PTSD. None of the healthy comparison subjects met criteria for any psychiatric or substance abuse disorders per SCID–Non Patient criteria. None of the PTSD or comparison subjects reported a history of serious medical illness. All of the subjects underwent successful audiologic testing (500, 1000, 2000, 4000 Hz) prior to participation in the study. All participants in the study were free of substance use as determined by urine toxicology screens, and none of the subjects was taking medication. Written and informed consent was obtained from all participants.

Brain electrical activity was recorded from 9 locations (Fz, Cz, Pz, F3, C3, P3, F4, C4, P4) using an electro-cap (Electro-Cap International). Thus, the electrodes formed a grid with a coronal (left, central, right) and sagittal (frontal, central, parietal) distribution. Eye movements were monitored via an electrode located under the lower orbital ridge of the left eye. All electrodes were referred to linked mastoids. The ground electrode was placed on the forehead. Electrode impedance did not exceed 5 kΩ. Electrical activity was amplified with a filter setting of 0.03–40 Hz and digitized at a rate of 500 Hz.

Two types of auditory stimuli, frequent "standard" 1000 Hz tones (p = .90) and infrequent "deviant" 1064 Hz tones (p = .10), were delivered binaurally at 60 dB (SPL) (stimuli were delivered every 600 msec and were 100 msec in duration). Each participant was presented with three blocks of 389 auditory stimuli while they were reading a magazine. Subjects did not perform a task, such as hitting a button, in response to the deviant stimuli.

Data Analysis

Trials in which the electro-oculogram (EOG) or electroencephalogram (EEG) exceeded 80 mV were excluded during averaging. The remaining artifact-free EEGs were averaged separately for the two types of stimulus. There were no significant differences in the rejection rates between the PTSD (19%) and non-PTSD (21%) groups.

The peaks of the major components were identified at the midline electrodes in the grand average waveforms. Peak amplitude (relative to 100 msec prestimulus baseline) and latency were calculated in the following windows: P50: most positive peak between 30 and 90 msec; N1: most negative peak between 70 and 130 msec; P2: most positive peak between 120 and 190 msec; and N2: most negative peak between 200 and 270 msec. To better examine the MMN, difference waveforms were constructed by subtracting point by point the ERPs to the standard stimuli from the ERPs to the deviant stimuli. The peak amplitude and the peak latency of the MMN in the difference waveforms was calculated over the 100–300-msec latency range.

The raw ERP data were analyzed using analyses of variance (ANOVAs) with repeated measures. Reduced degrees of freedom (Greenhouse–Geisser) were used to counter violations of the sphericity assumption underlying ANOVA with repeated measures. Midline and lateral sites were analyzed separately. In midline sites, there were factors of Group (PTSD, non-PTSD), Stimulus Type (standard, deviant), and Electrode (Fz, Cz, Pz). At lateral sites, the factor Hemisphere (left, right) was added to the preceding ANOVA. Results at lateral sites are reported only when they were significant. The MMN in the difference waveform was analyzed with similar ANOVAs, except that the factor Stimulus Type was not included. Preplanned analyses of significant interactions with the factor Electrode examined responses at the Fz electrode, where the MMN is usually the largest. Spearman rho correlations were performed between the magnitude of the MMN at Fz and the STAI scores and the Mississippi PTSD scores.

Results

Table 1 shows the Spielberger anxiety and Mississippi scores. State and trait anxiety were significantly higher in

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Table 1. Mean (SD) STAI and Mississippi PTSD Symptom Scale Scores

	State anxiety[a]	Trait anxiety[a]	Mississippi score
PTSD subjects	48.7[b] (9.5)	52.8[b] (8.8)	120.5 (20.5)
Non-PTSD subjects	30.6 (6.1)	34.0 (8.5)	NA

[a]From the Spielberger State/Trait Anxiety Inventory.
[b]$p < .0009$.

the PTSD compared to the non-PTSD group ($t_{27} = 5.7$, $p < .0009$ and $t_{27} = 6.0$, $p < .0009$, respectively). Figure 1 and Figure 2 present the grand average ERPs to the standard and deviant stimuli in the two groups. The standard stimuli elicited an initial positive peak, P50 (peak latency of about 65 msec) that was followed by N1 (latency = 110 msec), P2 (latency = 160 msec), and N2 (latency = 240 msec). Similar components were elicited by the deviant stimuli, excepting that the entire waveform tended to be more negative, due to an overlapping negative component, the MMN.

The ERPs to standard stimuli were similar in the PTSD and non-PTSD groups; however, as shown in Figure 3, the MMN elicited by the deviant stimulus was greater in the PTSD, compared to the non-PTSD group. These impressions were confirmed by the statistical analysis. P50 peak amplitude and latency were similar for frequent and deviant stimuli at the midline sites (amplitude: $F_{1,27} = 1.8$; latency: $F_{1,27} = 2.5$) and did not significantly differ between groups (amplitude: $F_{1,27} = 1.4$; latency: $F_{1,27} = 0.3$). Because of the underlying MMN, N1 was more negative when elicited by the deviant, compared to the standard stimuli (−2.06 μV vs. −0.90 μV; Stimulus Type: $F_{1,27} = 18.7$, $p < .00009$). This effect did not significantly differ between the two groups (Group × Stimulus Type: $F_{1,27} = 0.39$). For N1 latency, the Stimulus Type ($F_{1,27} = 2.8$) and Group ($F_{1,27} = 0.6$) factors were not significant. P2 was also less positive when elicited by the deviant, compared to the standard stimuli (0.79 μV vs. 2.6 μV; Stimulus Type: $F_{1,27} = 26.5$, $p < .0009$). This effect tended to be more pronounced in the PTSD, compared to the non-PTSD group (Group × Stimulus Type: $F_{1,27} = 3.1$, $p = .09$). P2 latency to the deviant stimuli was earlier than P2 latency to the standard stimuli (158.0 msec vs. 163.1 msec; Stimulus Type: $F_{1,27} = 7.9$, $p < .009$). This effect also tended to be more pronounced in the PTSD group (Group × Stimulus Type: $F_{1,27} = 2.9$, $p = .1$). N2 amplitude was larger to deviant than to standard stimuli (Stimulus Type: $F_{1,27} = 72.0$, $p < .00009$). The magnitude of this effect was greater in the PTSD (4.5 μV) compared to the non-PTSD (2.5 μV) group (Group × Stimulus Type: $F_{1,27} = 6.0$, $p < 0.02$). Post hoc analyses indicated that N2 amplitude to the standard stimuli did not significantly differ between the two groups ($F_{1,27} = 1.1$), but that N2 amplitude to the deviant stimuli was significantly greater in the PTSD, compared to the non-PTSD group ($F_{1,27} = 5.2$, $p < .03$). There was also a Hemisphere main effect ($F_{1,27} = 6.2$, $p < .02$) at the lateral sites that was due to the fact that N2 was greater over the left (2.9 μV), compared to the right (2.4 μV) hemisphere. The Hemisphere × Group interaction was not significant. N2 latency was earlier to the deviant than to the standard stimuli (226.2 msec vs. 241.3 msec; $F_{1,27} = 21.6$, $p < .0009$). This effect did not significantly differ in the two groups ($F_{1,27} = 0.3$).

A specific analysis of the MMN in the difference waveforms also confirmed that the MMN was greater in the PTSD, compared to the non-PTSD group (Group: $F_{1,27}$

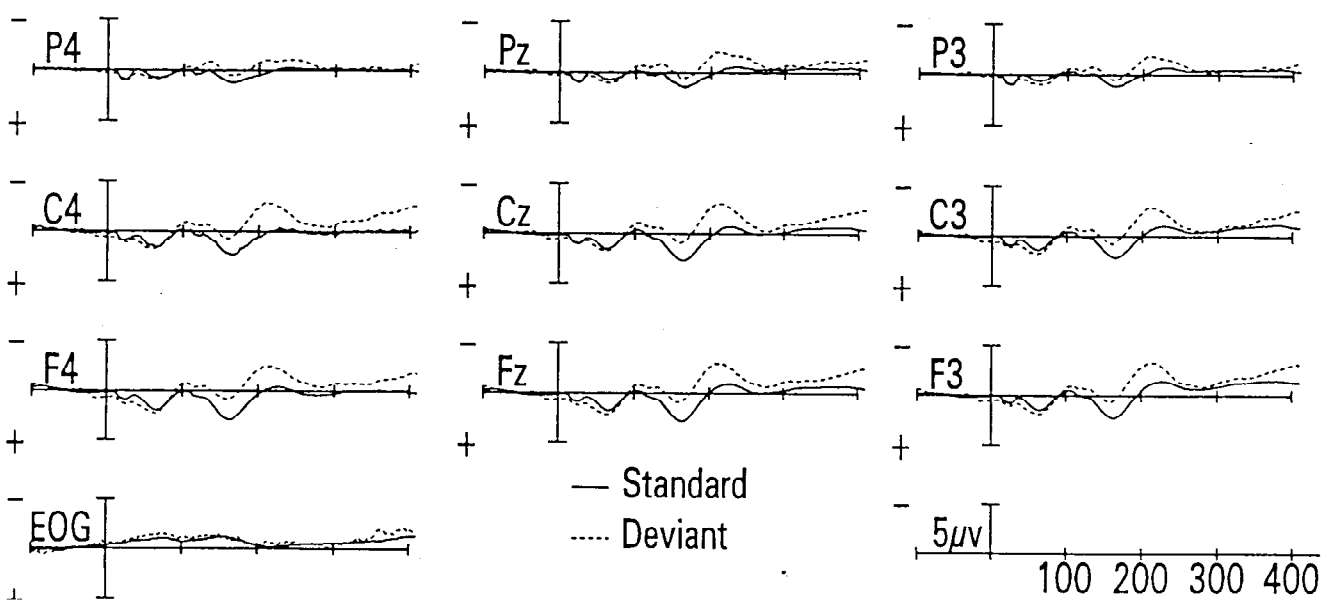

Figure 1. The grand average ERPs to the standard and deviant stimuli in healthy comparison subjects.

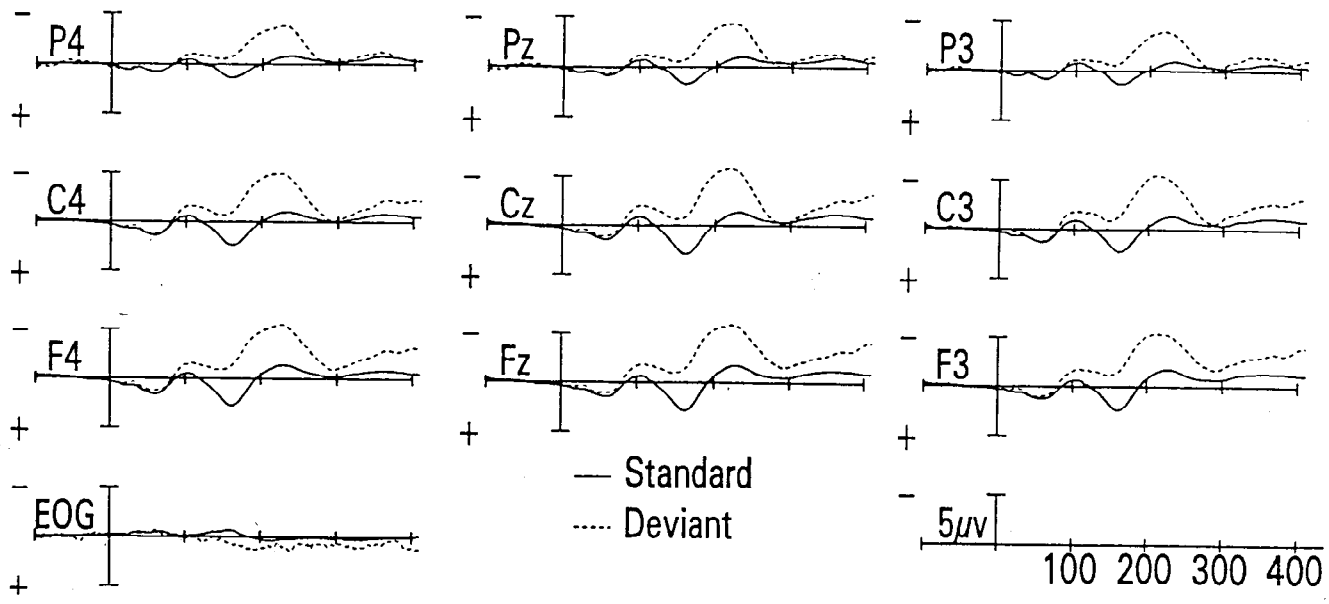

Figure 2. The grand average ERPs to the standard and deviant stimuli in individuals with PTSD.

= 4.1, $p < .05$). The Group × Electrode interaction was also significant ($F_{2,54} = 3.4$, $p < .05$). Post hoc analyses based on preplanned analyses indicated that MMN at Fz was larger in the PTSD (−2.9 μV), compared to the non-PTSD (−1.5 μV) group ($F_{1,27} = 5.7$, $p < .02$). The Hemisphere main effect and the Group × Hemisphere interaction were not significant. The latency of the MMN did not significantly differ between the two groups ($F_{1,27} = 0.4$).

In the PTSD group, there was a significant correlation between the magnitude of the MMN at Fz in the difference waveform and the Mississippi score ($R = .60$, $p < .05$). The trait and state anxiety scores were not significantly correlated with the amplitude of the MMN.

Discussion

The present findings suggest the existence of preattentional, cortical sensory processing abnormalities in female patients with PTSD. These patients exhibited significantly increased MMN amplitude compared to the non-PTSD subjects.

In contrast, there were no significant group differences in the amplitude or latency of the ERP components thought to be associated with the transmission of sensory information (i.e., P50, N1, or P2 to the standard stimuli). This suggests that the enhanced mismatch negativity in the PTSD subjects was specific to the neural mechanisms sensitive to stimulus change. It is generally thought that being able to detect unusual or possibly dangerous events in the environment is a fundamental ability that helps ensure the survival of biological organisms. Novelty detection requires a memory system that assembles neural representations of events in the environment so that changes are detected because they violate the predictions of the established neural schema. The MMN is believed to reflect such a process (Naatanen 1992; Schroger and Winkler 1995).

The generation of MMN is dependent on the ability of the auditory cortex to maintain a brief, modality-specific representation of recent auditory stimuli. Investigators have referred to this neural representation as a "mnemonic template" or as a "short-term sensory memory" (Javitt et al 1995). When an auditory stimulus differs, or deviates, from the working neural representation formed by preceding stimuli, MMN is elicited. If the deviance is large enough, the MMN reaches a threshold and a N2b–P3 complex, sign of conscious awareness, is activated (Naatanen 1992; Sams et al 1985). The presence of abnormally enhanced MMN in individuals with PTSD supports the hypothesis that abnormalities in environment novelty detection may play a significant role in the clinical symptomatology of this disorder. Symptoms of hypervigilance, feelings of being "on alert," "on guard for the possibility of danger," or being "keyed-up without knowing why" are commonly reported by patients with PTSD. It is possible that the root of these experiences may be found, to some degree, in the precognitive, sensory processing abnormalities manifested in MMN generation.

An alternative explanation for the increased MMN in the subjects with PTSD is that it is a consequence of the symptom of hyperarousal that characterizes individuals

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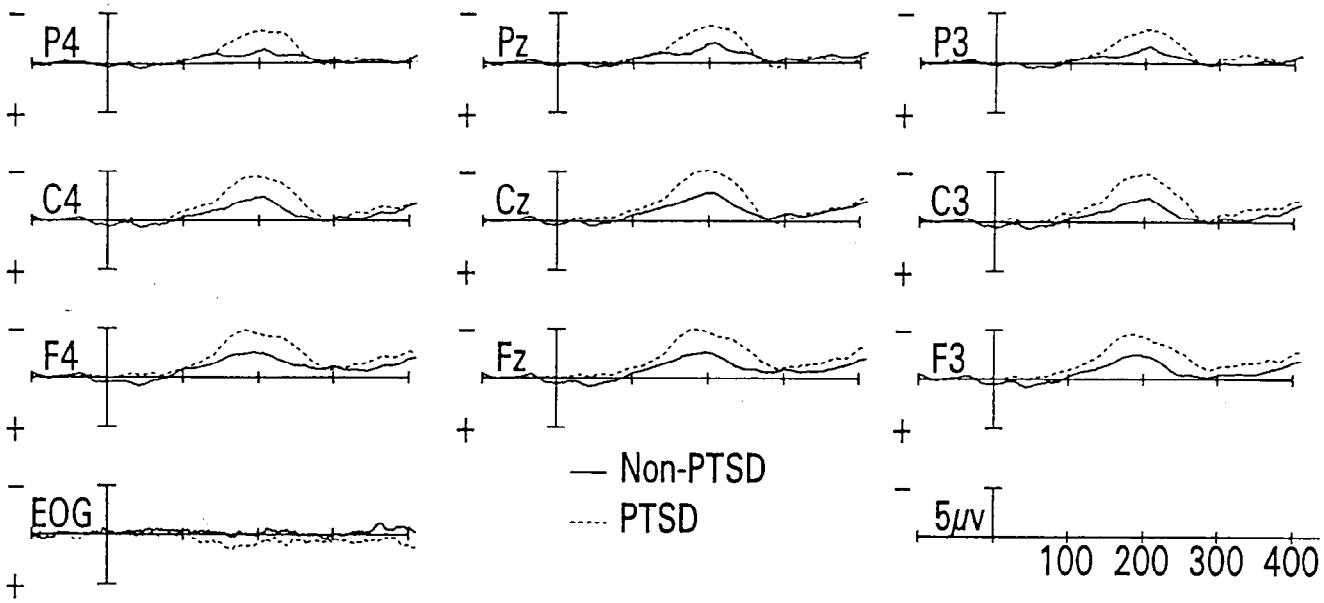

Figure 3. Mismatch negativity (MMN) is better seen in the difference waveforms obtained by subtracting the ERPs to the standard stimuli from the ERPs to the deviant stimuli. MMN was significantly larger in the PTSD group.

with this condition. This hypothesis seems to be unlikely, however, because other ERP components known to be sensitive to arousal, such as N1 (Kropotov et al 1987), did not significantly differ in the PTSD and non-PTSD groups. No significant differences were detected in MMN latency between groups. Latency and reaction times are often used in the assessment of alertness. Although the clinical relationship between latency and alertness may not be applicable to preconscious processing (MMN) and the symptoms of hypervigilance seen in PTSD, the lack of significant differences in latency is noteworthy.

Mismatched negativity reflects activation of local, modality-specific, neural mechanisms in the primary auditory cortex, or the adjacent supratemporal auditory cortex, which automatically (i.e., independently of attention) react to changes in a repetitive sound (Kropotov et al 1995). The neuronal populations in the temporal cortex that generate MMN to sound change are spatially separate from the attention-dependent neuronal populations that generate N2b and P300 responses to sound changes when they are to be discerned (Halgren et al 1980; Puce et al 1989; Wood et al 1980). The increased MMN in the subjects with PTSD suggests that the neurophysiological dysfunction associated with this disorder extends to the level of the sensory cortex.

Preclinical literature suggests that the generation of MMN is dependent upon *N*-methyl-d-aspartate (NMDA) type glutamate receptor functioning. For example, in primates, intracortical injections of NMDA antagonists into auditory cortex have been shown to result in a selective disruption of MMN generation (Javitt et al 1994). Hence, there is a possibility that enhanced NMDA receptor-mediated neurotransmission might account for the MMN abnormalities in the PTSD subjects of the current study.

The increased MMN in the PTSD group stands in contrast to clinical reports of low mismatch negativity in patients with schizophrenia and with depression, and also in contrast to the finding of normal MMN in patients with bipolar disorder (Catts et al 1995; Ogura et al 1993; Sandman et al 1987). Earlier reports of significant negative correlations between MMN and the total score of the Scale for the Assessment of Negative Symptoms (Andreasen 1982), as well as the subscale score for affective flattening, have lead previous investigators to speculate that low mismatch negativity in patients with schizophrenia may be a trait or chronicity marker (Andreasen 1982). It is similarly possible that the enhanced MMN seen in the PTSD patients may be a chronicity or trait marker, rather than an index of PTSD. Future studies involving family members and sexual assault victims without PTSD would be able to test this possibility.

There are certain limitations to this study. As alluded to above, these data do not permit the investigators a conclusion as to whether or not enhanced MMN is due to the presence of PTSD, exposure to trauma, or a premorbid trait marker. Nevertheless, the data do provide strong evidence for the existence of dysfunction in the primary auditory cortex and adjacent anterior auditory association areas of the superior temporal gyrus in the pathophysiology of PTSD. Second, this was a small study in a select population of patients. It represents an initial step toward

understanding sensory processing in women with sexual assault-related PTSD, and the results should be interpreted in light of this fact.

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