Sensory Gating in Chronic Posttraumatic Stress Disorder: Reduced Auditory P50 Suppression in Combat Veterans

Thomas C. Neylan, Daniel J. Fletcher, Maryann Lenoci, Keith McCallin, Daniel S. Weiss, Frank B. Schoenfeld, Charles R. Marmar, and George Fein

Background: Posttraumatic stress disorder (PTSD) may be associated with a general impairment of cognitive function that extends beyond the processing of trauma-specific stimuli. Suppression of the auditory P50 response to repeated stimuli occurs in normal subjects and reflects the central nervous system's ability to screen out repetitive stimuli, a phenomenon referred to as sensory gating. This study examines P50 sensory gating to nonstartle auditory stimuli in PTSD subjects and normal controls.

Methods: P50 generation and gating were studied using a conditioning/testing paradigm in 15 male subjects with PTSD and 12 male controls. P50 test/conditioning (T/C) ratios were estimated using the Singular Value Decomposition method.

Results: The amplitude of the P50 response to the conditioning stimulus did not differ in subjects with PTSD compared to normal controls. The P50 T/C ratio is increased in PTSD subjects (mean = .408, SD = .275) as compared to the controls (mean = .213, SD = .126, two tailed t, p = .024).

Conclusions: This study provides evidence that PTSD is associated with impaired gating to nonstartle trauma-neutral auditory stimuli. Biol Psychiatry 1999;46:1656–1664

Key Words: Stress disorders, evoked potentials, electroencephalography, habituation, neural inhibition, hippocampus

Introduction

Posttraumatic stress disorder (PTSD) may be associated with a general impairment of cognitive function that extends beyond the processing of trauma-specific stimuli. It is well established that subjects with PTSD have enhanced physiologic responsiveness to trauma specific cues (Orr et al 1990; Blanchard et al 1991a; Pitman et al 1987, 1990; Orr et al 1993; Shalev et al 1993). In addition, several, but not all, studies have found that PTSD subjects have enhanced responses to acoustic startle (Ornitz and Pynoos 1989; Ross et al 1989; Butler et al 1990; Morgan et al 1996; Morgan et al 1997; Shalev et al 1992). A few studies have studied cognitive processes in PTSD using event related potentials (ERP). ERPs can be measured by repeated sensory stimulation in that stimulus-specific responses are enhanced and background activity is averaged to zero. McFarlane et al (1993) examined the auditory P3 response using a target discrimination task adapted from the methods of Pfefferbaum et al (1984). They found that PTSD subjects had diminished responses to both target and distractor non-startle tones compared to control subjects. They suggested that PTSD subjects had difficulty discriminating relevant from irrelevant stimuli secondary to a general impairment of attentional processing of everyday stimuli. This notion has some support from reports of neuropsychological functioning in PTSD subjects (Everly and Horton 1989; Gil et al 1990; Yehuda et al 1995) that have found cognitive deficits for material that is not cued to traumatic memory.

The P50 wave of the auditory evoked response is particularly useful in studying the phenomenon of sensory gating because it involves a hard wired process that does not vary with voluntary attention or levels of wakeful alertness (Jerger et al 1992; Cardenas et al 1997). Normal subjects presented with two closely paired clicks will have a reduction in amplitude of the P50 wave to the second click. The reduced amplitude is thought to be secondary to inhibitory interneurons involved in habituation and sensory gating (Freedman et al 1996). P50 is usually studied in a conditioning/testing paradigm where responses to pairs of stimuli are recorded, with long intervals between stimulus pairs (e.g., >7 sec) and shorter intervals within stimulus pairs (e.g., 0.5 sec). The conditioning/testing paradigm allows separate measurement of P50 generation at different time points, allowing for the assessment of not only the P50 response itself, but also the gating process. This paradigm has been shown to be sensitive to changes in cognitive function, particularly in the domain of attentional processing, which is thought to be impaired in PTSD.
Sensory Gating in PTSD

and P50 gating, that have been shown to involve separable neural mechanisms.

Sensory gating is of theoretical interest to the study of PTSD because it represents a preattentive form of habituation. Shalev et al. (1992) found that PTSD subjects failed to show habituation in the skin conductance response to acoustic startle in contrast to subjects with other anxiety disorders or normal controls. Orr and colleagues found impaired habituation of skin conductance to loud tones in Vietnam veterans (Orr et al. 1995) and Israeli veterans of the Yom Kippur War (Orr et al. 1997). In contrast, Ross et al. (1989) showed that PTSD subjects did not differ from controls on eye-blink responses to repeated acoustic stimuli. Schwarzkopf et al. (1993) have found that habituation to acoustic startle and suppression of P50 in a paired-click paradigm are highly correlated in normals. Grillon and colleagues found that PTSD subjects had significantly reduced pre-pulse inhibition of the eye blink response to acoustic startle compared to normal controls that suggests that PTSD may be associated with an impairment in sensorimotor gating (Grillon et al. 1996). Habituation to acoustic startle, as measured by heart rate and skin conductance, has been found to have a strong genetic component (Lykken et al. 1988; Kotchoubeï 1987). Reduced habituation predicts increased learning by classical conditioning and reduced capacity for desensitization (Olman and Bohlin 1973). Thus, it is theoretically possible that PTSD subjects with reduced habituation, either by genetic predisposition or developmentally acquired, may be less responsive to exposure based psychotherapies. A major and important difference between the P50 paradigm and the startle paradigm is that the P50 paradigm measures the brain response to affectively neutral, rather than arousing stimuli.

Suppression of P50 has been extensively studied in schizophrenia. Freedman and others have used the conditioning-testing paradigm to demonstrate that schizophrenia is associated with impaired sensory gating (Boutros et al. 1991; Erwin et al. 1991; Judd et al. 1992; Jin et al. 1994; Freedman et al. 1996). Of interest are studies that show that transient increases in noradrenergic activity are associated with reduced P50 suppression (Waldo et al. 1992). Cold stress, that increases sympathetic arousal is associated with reduced P50 suppression (Johnson and Adler 1993). This raises the possibility that other psychiatric disorders associated with increased noradrenergic tone, such as PTSD (Southwick et al. 1993), would be associated with impaired P50 suppression.

Adler and colleagues have completed a study of P50 in of combat veterans with PTSD (Adler et al. 1991). In this study, the patient groups had a high incidence of co-morbid psychiatric and substance dependence diagnoses, although all subjects were abstinent at the time of study. Increased variability of P50 gating in PTSD patients compared to controls was found. On average, there was decreased P50 gating in the patient groups, associated with elevated MHPG levels (Adler, personal communication). Gillette and colleagues (Gillette et al. 1995) have also recently reported reduced P50 gating under baseline conditions in nine PTSD patients compared to five age-matched controls, all drug-, alcohol-, and medication-free for one week before study.

One problem with the P50 measure is its low reliability (on the order of 0.10–0.30) when measured using standard methods. Fein and colleagues have shown that measuring P50 either by Dipole Components Modeling (Cardenas et al. 1993) or Singular Value Decomposition (Cardenas et al. 1997), increases the reliability of the measure to 0.60–0.70. This report of the auditory P50 response of combat veterans with Vietnam-related PTSD is the first study to utilize the singular value decomposition methodology. We hypothesized that PTSD subjects would have impairment in sensory gating as indexed by a relatively high P50 amplitude to the test stimulus (also resulting in an elevated test/conditioning (T/C) ratio) in a conditioning-testing paradigm compared to medication-free nonveteran controls.

Methods and Materials

Fifteen Vietnam combat veterans were recruited from the San Francisco Veterans Affairs Medical Center (SFVAMC) PTSD Outpatient Program and the community at large. Subjects were included in the study if they were medication-free, except selective serotonin reuptake inhibitors (SSRIs), had no history of alcohol or substance abuse in the past year, and met DSM-III-R and DSM-IV criteria for combat-related PTSD based on the Structured Clinical Interview (SCID). Twelve normal control subjects were recruited by newspaper advertisement and were included if they were medication-free, medically healthy, and had no lifetime substance abuse, Axis I disorder, or neurologic disorder. No PTSD or control subject met current or lifetime criteria for organic mental disorder, schizophrenia, schizoaffective disorder, bipolar disorder, panic disorder, obsessive compulsive disorder, or Axis II diagnoses of schizoid, schizotypal, or paranoid personality disorder, neurologic disorder, or systemic illness affecting CNS function. Six PTSD subjects had a prior diagnosis of alcohol or drug abuse (other than cocaine), but all had at least 14 months abstinence before the ERP session. None of the subjects had histories of MDD within the 2 month period preceding the ERP session and all subjects were free of any psychiatric medications except 4 subjects taking SSRIs (3 taking fluoxetine, 1 taking paroxetine) for at least 2 months before participation. All subjects were alcohol-free for two weeks and restricted to having only one cup of caffeinated coffee each morning before the electrophysiologic recordings. Both groups were comparable in level of education (controls 15.6 ± 2.6 years, PTSD subjects 15.1 ± 1.5 years, two-tailed t, p > .05), but experimental subjects were slightly older than controls (PTSD...
subjects 49.6 ± 2.3 years, controls 45.3 ± 6.5 years, two-tailed t, p = .048). PTSD subjects had overall CAPS scores of 56.9 ± 16.7 and overall IES-R scores of 36.2 ± 16.1.

Evoked Potential Recording

Data were recorded from 62 scalp channels using an electrode cap with tin disk electrodes (Electro-Cap International, Eaton, OH) referenced to a tin electrode clipped to the left earlobe. Vertical eye movements were monitored via tin cup electrodes placed above and below the right eye, and horizontal eye movements were monitored via electrodes placed at the lateral canthi. All impedances were below 5000 ohms and signals were amplified 50,000 times by a Contact Precision Instruments amplifier system with analog filters at 1 and 1000 Hz. Stimulus presentations were controlled and data were collected by ERP-SYSTEM Software (Neurobehavioral Laboratory Software) and a Keithley-Metabyte DAS 1800-HC interface card on a 90 MHz Intel Pentium-based personal computer. Data were sampled for 200 msecs at a 2000 Hz within channel resolution beginning 20 msec before stimulus presentation for each click. Individual trials were rejected if activity on either eye movement channel exceeded ± 60 microvolts. Data were collected until there were 100 single trials that did not meet the eye movement channel rejection criteria. This procedure took between 20 and 30 min. The data were then digitally bandpass filtered from 10 Hz to 50 Hz before analysis. This filters out the N100 component from the P50. Click stimuli were created by amplification of a 0.05-msec square wave generated by an Analog Devices D/A converter. The square waves were passed through a Hewlett-Packard 350D Attenuator, amplified by a Pioneer SX-2300 stereo receiver/amplifier and delivered to the subject over Realistic NOVA'20 headphones (Tandy Corporation, Houston). Stimulation was binaural with the same signal delivered to each ear of the headphones. After each subject’s threshold for detecting the click stimulus was established by amplification of a method of limits procedure, stimuli were presented at 55 dB above threshold. Each trial consisted of the presentation of two clicks, 500 msecs apart. The time from the beginning of one trial to the beginning of the next trial varied randomly between 7–8 sec.

During the session, the subjects were relaxed, awake, and seated upright in a room that was quiet but not acoustically isolated. They were instructed to sit quietly, listen to the clicks, and try to keep their eyes still.

The Singular Value Decomposition (SVD) Method for Estimation of P50 T/C Ratios

P50 T/C ratios were estimated using the Singular Value Decomposition (SVD) method (Cardenas et al 1995). We applied the SVD method to data collected from the 5 channels in the electrode array that most clearly contained P50. The SVD Method is a two step process and is represented graphically in Figure 1. In the first step, SVD is applied to a matrix of the individual evoked responses recorded at the 5 scalp electrode locations for both the conditioning and testing conditions. The goal is to extract a single common waveshape that best describes all of the responses from both the conditioning and testing conditions. This generates a weight for each electrode for each condition (labeled \( w_c \) for the conditioning responses and \( w_t \) for the testing responses) reflecting the best-fit magnitude of that common waveshape at that electrode. In the second step, these weights are used to create separate topographies for the conditioning and testing responses. SVD is then applied to these topographies to extract a single common topography, under the assumption that any differences between conditioning and testing topographies are due to noise. This step also results in a pair of weights describing the best-fit amplitude of that common topography for the conditioning and testing responses. The T/C ratio is the ratio of those amplitudes of the common topography in the conditioning vs. testing conditions. For a more thorough, mathematically rigorous description of this method, see Cardenas et al (1995).

SVD is not applied over the entire 200 msecs recording epoch, but is instead applied over a time window chosen for each subject based upon the topography of the P50 response. Topographic maps of the P50 response for all subjects were created using the spherical spline method (Perrin et al 1989). The P50 component was identified based upon latency (approximately 50 msecs post-stimulus) and locality (central), and the time at which the peak amplitude of the component was evident in the map was chosen as the time window center. Figure 2A shows a sample topographic map from one of the subjects in the study. The circled electrodes were those chosen for use in the P50 SVD analysis. The window width was chosen to include as much of the P50 response as possible on the channel in the common montage closest to the peak of the P50 component identified in the topographic map. The average-referenced averages from each channel were inspected and a window of approximately 20 msecs was chosen that included as much of the P50 response as possible, as shown in Figures 2B and 2C. To allow for differences in latency between the conditioning and testing P50 responses, the window for the testing response was allowed to shift with respect to the conditioning response window by a maximum of 10 msecs. In this sample however, the maximum
Figure 2. (A) Step 1 of the SVD analysis involves identifying the P50 component on the topographic map of the conditioning response and selecting the 5 electrodes closest to the peak of the component (i.e., the electrodes on which the P50 response is largest). (B) Step 2 of the SVD analysis involves choosing a time window through which the conditioning response will be examined. The window is chosen to include as much of the conditioning response as possible. (C) Step 3 of the SVD analysis involves shifting the window in time to account for any latency differences between the conditioning and testing responses. The largest shift necessary was 1.5 msec.

One objective measure of the validity of the SVD method as applied to a particular data set is the residual variance. This is the proportion of the variance of the signals recorded at each of the electrodes that is not explained by the waveforms and topographies fit by SVD. Low residual variance indicates that, within the time window examined, the SVD method was able to extract and accurately model a single component, that could explain a large proportion of the variance in the recorded signals. Residual variances were calculated for all of the subjects in this study.

P50 Conditioning Response Amplitude Estimation
Conditioning response amplitudes were estimated by choosing the peak amplitude on each of the 5 recording electrodes within the window defined for the SVD analysis. P50 conditioning amplitude was then defined as the largest of those peak amplitudes. This peak latency was identical to that found in the topographic map. Amplitudes were estimated in 2 ways. First, the difference between the negative N40 peak and the positive P50 peak was examined to report a measure consistent with those reported widely in the literature. In addition, the amplitude of the P50 component with respect to baseline was examined. We believe that this is the more appropriate measure in the context of
identifying characteristics of the P50 component itself. Because the N40 is most likely generated by a separate set of neural generators from those that generate the P50, reporting the conditioning amplitude as the difference between the N40 and P50 peaks confounds P50 characteristics with N40 characteristics. Finally, the peak amplitude of the P50 response to the testing click was estimated in the same way as that for the conditioning click.

**Results**

T/C ratios were estimated for each of the subjects using the SVD method applied to the 5 best electrodes determined from the topographic maps. The scatter plot in Figure 3 shows a significantly increased P50 T/C ratio in PTSD subjects (mean = .407, SD = .275) compared to controls (mean = .213, SD = .126), two-tailed \( t, p = 0.0239 \). Horizontal bars = mean.

![Figure 3. SVD analysis of P50 showed a significantly increased T/C ratio in PTSD subjects (mean = .407, SD = .275) compared to controls (mean = .213, SD = .126), two-tailed \( t, p = 0.0239 \). Horizontal bars = mean.](image)

The mean T/C ratio in the 4 subjects on SSRI’s was slightly higher than the whole sample (T/C = .416). These results replicate in an entirely new sample of PTSD and control subjects the finding from our pilot study that showed a comparably increased T/C ratio in PTSD subjects (mean = .606, SD = .330) (Neylan et al 1996). This pilot study utilized medication-free subjects with Vietnam-related PTSD and non-veteran controls who showed a T/C ratio of mean = .304, SD = .440, (one-tailed \( t, p = 0.047 \)).

Conditioning response amplitudes were also examined using the 2 separate measures described in the methods section and are plotted in Figure 4. Conditioning P50 amplitudes measured to baseline were not significantly different between PTSD subjects (mean = 2.03, SD = 1.64 \( \mu \text{V} \)) and controls (mean = 1.66, SD = .846 \( \mu \text{V} \), Wilcoxon 2-sample test \( p = .942 \)). Similarly, the conditioning amplitudes for the N40-P50 measure were not significantly different for the PTSD subjects (mean = 2.19, SD = 1.85 \( \mu \text{V} \)) compared to controls (mean = 1.70, SD = 1.09 \( \mu \text{V} \), Wilcoxon 2-sample test \( p = .428 \)). Several PTSD subjects had higher conditioning amplitudes than control subjects. If a similar distribution of data was found in a larger sample it is possible that there would be significant differences in the 2 groups. At present, the data suggest that the T/C ratio results cannot be explained simply as a deficit in auditory response amplitude, but in fact that they reflect an impairment in gating of the response to a repeated stimulus.

Residual variances for the SVD fits for all of the subjects were also computed. The maximum residual variance among the control subjects was 19.6% (mean = 5.2%, SD = 5.1%), and the maximum among the PTSD subjects was 30.3% (mean = 7.2%, SD = 7.0%). Although one experimental subject and one control exhibited larger residual variance than the rest of the subjects, clear P50s were present in both sets of data and the SVD method fit a good approximation to the data in both cases. There was no significant difference in residual variance between the groups (two-tailed \( t, p = 0.421 \)). A plot of the distributions of the fit error can be found in Figure 5.

No significant correlations were found between T/C Ratio and IES-R or CAPS total or subscale scores (intrusion, avoidance and hyperarousal).

**Discussion**

Our data suggest that PTSD is associated with an impairment in auditory sensory gating to affectively neutral stimuli. This impairment is of a magnitude similar to that described in schizophrenia (Boutros et al 1991; Erwin et al 1991; Judd et al 1992; Jin et al 1994; Freedman et al 1996). The importance of this finding is that it involves the brain response to neutral nonprovocative stimuli. This finding extends brain abnormalities in PTSD beyond responses to trauma based cues. It also suggests that PTSD subjects are not able to dampen responses to innocuous auditory stimuli. The lack of differences in the conditioning amplitudes between PTSD and controls suggests that at baseline there are no differences across groups. The differences exist in the area of sensorimotor gating that could represent a faster recovery of neurons to process additional information proximal to the conditioning stimulus.

It is theoretically possible, that the difference between test and conditioning responses result from a topographical shift in scalp potentials. This would suggest that the
two responses are served by different generators. This would not be discerned by the SVD method or other methods that assume common conditioning and testing generators (such as analysis of data from a single scalp electrode) because they assume that differences in topography are a result of noise. This seems implausible given the low residual variances in our PTSD and control subjects. If the conditioning and testing response topographies were markedly different, we would expect a poor fit from our model, that assumes a common topography and fits a single topography to both responses. The low residual variances (e.g., good fits) suggest that this assumption is valid.

This reduced P50 gating would implicate an abnormality in PTSD in noradrenergic or cholinergic regulation of GABA mediated inhibitory neurons known to be involved in P50 gating. Several studies have found that the hippocampus (Goff et al 1980) and the entorhinal...
cortex (Reite et al. 1988) have an important regulatory role in the generation of the auditory P50 response. Auditory sensory input from the superior temporal gyrus may be relayed to the hippocampus via the entorhinal cortex (Amaral et al. 1983, Freedman et al. 1996). The N40 response to paired auditory stimuli in the rat has been found to be an analogue to the human P50 response (Adler et al. 1986). The N40 response to auditory stimuli has been recorded in single neurons in the hippocampus of the rat, with the activity of hippocampal pyramidal cells suppressed after the first conditioning auditory stimulus (Bickford-Wimer et al. 1990; Freedman et al. 1996). Freedman and colleagues have developed a model explaining the abnormal P50 response found in schizophrenia. They hypothesize that in normals, hippocampal interneurons release γ-aminobutyric acid in response to cholinergic stimulation of nicotinic receptors that leads to suppression of the pyramidal cells to the test, or second, stimulus (Freedman et al. 1996). Blocking hippocampal nicotinic receptors with alpha-bungarotoxin leads to impaired suppression of auditory responses in the rat (Luntz-Leybman et al. 1992). Recently, Freedman and colleagues found that schizophrenic subjects and relatives with impaired P50 suppression was associated with a polymorphism of the gene coding for the alpha-7 nicotinic receptor (Freedman et al. 1997).

At present, no data exist on hippocampal cholinergic or GABAergic function in PTSD. There are data that suggest that PTSD subjects have reduced hippocampal volume (Bremner et al. 1995, 1997; Gurvitz et al. 1996; Stein et al. 1997; Schuff et al. 1997) and reduced amount of the neuronal marker N-acetyl aspartate in hippocampus (Schuff et al. 1997). Thus, it is possible that damage to hippocampal cholinergic function could contribute to impaired P50 suppression in PTSD.

PTSD subjects have been found to have increased noradrenergic activity to a variety of stressful stimuli (Southwick et al. 1993). Thus, an alternative explanation for this finding is that our PTSD subjects had elevated noradrenergic activity in response to the electrophysiology laboratory experience leading to a reduction in P50 suppression (Waldo et al. 1992; Johnson and Adler 1993). Although we did not directly measure noradrenergic activity, most studies of baseline sympathetic activity show that combat veterans with PTSD are not different from controls. A minority of studies have shown elevated resting heart rate in PTSD subjects compared to normal controls, but not in comparison to controls with other psychiatric disorders (McFall and Murburg 1994). Resting single point plasma epinephrine and norepinephrine is not elevated in PTSD subjects (Blanchard et al. 1991b; Southwick et al. 1993; McFall et al. 1990). In contrast, resting integrative measures reveal increased urinary catecholamines (Davidson and Baum 1986; Kosten et al. 1987; Yehuda et al. 1992), decreased monoamine oxidase activity (Davidson and Baum 1986), and alpha 2 adrenergic receptor down regulation (Perry et al. 1987) in PTSD subjects. The disparity between resting single point and integrative measures may reflect unmeasured, phasic increases in SNS activity in PTSD. Hence, it is possible that our subjects experienced transient increases in sympathetic arousal during the electrophysiology recording. We believe this be unlikely given that we used neutral stimuli with no linkage to combat trauma and our acoustic stimuli were well below that used to provoke startle. Future studies will need to directly assess whether transient increases in noradrenergic activity explain the reduction in P50 suppression.

In summary, these data provide evidence that PTSD subjects have impaired preattentive sensory gating that may lead to reduced ability to screen out trivial or irrelevant stimuli. This may be related to the complaint of hypervigilance frequently reported by PTSD patients. Future studies will be needed to replicate these results, to determine if they are related to performance on neuropsychological measures, if cholinergic, gabaergic, or noradrenergic mechanisms contribute to this phenomenon, and if the phenomenon is associated with structural hippocampal damage.
This work was supported by the Department of Veterans Affairs (Merit Review: GF, TCN); National Institutes of Health (CRM, DSW, GF); National Alliance for Research in Schizophrenia and Depression (TCN); and Solvay Pharmaceuticals (CRM).

A preliminary version of this paper was presented at the International Society for Traumatic Stress Studies 12th Annual Meeting, Nov 9–13, 1996, San Francisco, CA.

References


Cardenas VA, Gerson J, Fein G (1993): The reliability of P50 suppression as measured by the conditioning/testing ratio is vastly improved by dipole modeling. Biol Psychiatry 33:335–344.


