Behavioral Neuroscience
2009, Vol. 123, No. 2, 315–327

0735-7044/09/$12.00 DOI: 10.1037/a0014364

Reduction of Prelimbic Inhibitory Gating of Auditory Evoked Potentials After Fear Conditioning

Ryan P. Mears and Nash N. Boutros
Wayne State University School of Medicine

Howard C. Cromwell
Bowling Green State University

Inhibitory gating (IG) is a basic central nervous system process for filtering repetitive sensory information. Although IG deficits coincide with cognitive and emotional dysfunction in a variety of neuropsychiatric disorders, limited research has been completed on the basic, functional nature of IG. Persistent IG occurs in rat prelimbic medial prefrontal cortex (mPFC), a crucial site for modulating emotional learning. To investigate the interaction of affect and IG, we recorded local field potentials (LFP) directly from prelimbic mPFC and examined the influence of tone-shock fear conditioning (FC) on IG. Behavioral reactions during IG were observed before and after FC, and increase of orienting response after FC indicated induction of tone-shock association. After FC, some components of LFP response exhibited short-term weakening of IG. On a subsequent day of recording, IG strengthened for all LFP components, but individual components differed in their particular changes. Affective regulation of IG represents an important factor influencing within-subject IG variability, and these results have implications for understanding the role of rapid, implicit neural coding involved in emotional learning and affective disruption in psychiatric disease.

Keywords: evoked potentials, prefrontal cortex, sensory gating, negative affect, acute stress

Inhibitory gating (IG) is a neurophysiological mechanism proposed to be involved in elemental information filtering (Adler et al., 1982; Boutros & Belger, 1999). Neurophysiological assays that gauge IG have been used in basic science fields (Bock & Goode, 2002; Eccles, 1969) and in clinical neurophysiology (Adler et al., 1990; Boutros, Korzyukov, Jansen, Feingold, & Bell, 2004). Clinical research has indicated that IG could be used as a marker or potential neuroendophenotype for specific psychiatric disorders (Cadenhead, Light, Shafer, & Braff, 2005; Gottesman & Gould, 2003). It is well known that IG when tested in an elemental fashion is disrupted in patients from a diverse set of disorders including schizophrenia (Adler et al., 2001; Boutros et al., 2004; Freedman et al., 1996), Alzheimer's disease (Jessen et al., 2001), obsessive–compulsive disorder (OCD; Rossi et al., 2005), addiction (Adler et al., 2001; Boutros et al., 2002; Boutros, Uretsky, Lui, & Millana, 1997), panic disorder (Ghisolfi et al., 2006), and posttraumatic stress disorder (PTSD; Ghisolfi et al., 2004; Neylan et al., 1999; Skinner et al., 1999). IG is typically tested in clinical settings using a standard two-tone paradigm in which two identical tones are presented with a 500-ms interstimulus interval (Adler et al., 1982). Normally, the neural response to the second or "test" tone is reduced relative to initial or "conditioning" tone. IG is similar to habituation or adaptation except that the response to the initial tone is preserved whereas the main impact reflects the "inhibitory trace" that bridges the two stimuli and inhibits subsequent information. A "gating ratio" is usually calculated by dividing the test tone response by the conditioning tone response: scores approaching 0 or 1 reflect respectively greater or less inhibition. Patients with diverse neuropsychiatric illnesses have been found to have potential impairment of the typical degree of inhibition reflecting disruption of basic inhibitory circuits (Freedman et al., 1994, 1996), and gating of auditory evoked potentials (AEPs) at various stages of auditory processing (i.e., P1, N1, and P2) are independently affected in neuropsychiatric disease (Boutros et al., 2004, 2006). Complications in interpretation can arise for multiple reasons with changes in the computed gating ratio observed in clinical (Patterson et al., 2000) and preclinical studies (Hajos, 2006). Alterations in gating ratios might be due to changes primarily in the response to the second tone, to the first tone, or to inverse or parallel changes in both responses (Mears, Klein, & Cromwell, 2006).

A second major issue in the clinical studies of IG includes the influence of state alteration on IG (Boutros & Kwan, 1998; Boutros, Overall, & Zouridakis, 1991; Smith, Boutros, & Schwarzkopf, 1994). These state changes can involve arousal, sleep-wakefulness, attention, and emotion. These diverse state-related influences on IG are only beginning to be analyzed (Kisley, Olincy, & Freedman, 2001). It is known that all of the disorders in which IG is altered are characterized by emotional alterations. However, unaccounted within-subject variability is an obstacle to establishing the reliability of gating as an assessment tool, regard-

Ryan P. Mears and Nash N. Boutros, Department of Psychiatry and Brain Research and Imaging Neuroscience, Wayne State University School of Medicine; Howard C. Cromwell, Department of Psychology and J. P. Scott Center for Neuroscience, Mind, and Behavior, Bowling Green State University.

Ryan P. Mears is now affiliated with Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts.

This work was partially supported by the J. P. Scott graduate fellowship and Joe Young Sr. Research in Psychiatry funds. We thank Holly Moore and Matthew Galloway for helpful comments and guidance on this article. Andrew Klein, Dorcie Gray, Sarah Echols, and Nick Baldwin assisted with some behavioral assessments and histological preparations.

Correspondence concerning this article should be addressed to Ryan P. Mears, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, CLS 07M1, Boston, MA 02215. E-mail: rmears@bidmc.harvard.edu

less of clinical status (Fuerst, Gallinat, & Boutros, 2007). Also, recent data reveals relationships between certain symptoms and the degree of gating impairment (Cullum et al., 1993; Louchart-de la Chapelle et al., 2005). For example, greater negative symptomatology is positively correlated with gating ratio scores meaning that as negative-type symptoms become more intense, reductions between sensory stimuli becomes less pronounced (Louchart-de la Chapelle et al., 2005). Emotional problems of anxiety are prevalent in all of the disorders in which gating is impaired, and IG defects could arise from elevated anxiety states or play a role in the etiology of high anxiety observed in schizophrenia, OCD, panic disorder, or PTSD.

Rapid processing of stimuli is fundamental for the production of emotional states (Lang & Davis, 2006) and IG is a potential screening process that could aid in normal emotional functioning. Ongoing investigation of AEP components has established groundwork for cross-species comparisons (Cromwell, Mears, Wan, & Boutros, 2008). Parallels between human AEP components and P1, N1, and P2 components recorded in mice led authors to conclude that as analogue counterparts, these components are shortened in latency due to the shorter conduction distances in the rodent brain (Siegel et al., 2003; Umbricht et al., 2004). In preclinical investigations of IG, single-unit and/or local field potential activity have further defined components of a functional gating network including amygdala (Cromwell, Anstrom, Azarov, & Woodward, 2005), hippocampus (Bickford, Luntz-Leybman, & Freedman, 1993; Bickford-Wimer et al., 1990; Moxon et al., 1999), thalamus (Krause, Hoffmann, & Hajos, 2003; Moxon et al., 1999), brainstem (Moxon et al., 1999), striatum (Cromwell, Klein, & Mears, 2007), and medial prefrontal cortex (Mears et al., 2006). These brain regions have all been implicated in modulating emotional states as part of a larger limbic system network (Morgane, Galler, & Mokler, 2005). For example, the striatum is thought to regulate reward information as it is linked with motor output (Berridge & Cromwell, 1990) and IG in the striatum has been shown to be influenced by shifts in reward value and motor output (Cromwell et al., 2007). The hippocampus is thought to be a critical location in the brain where IG signals could originate and propagate to local inhibitory networks located in diverse brain regions (Freedman et al., 1994, 1996). Convergent clinical and basic research points to crucial processing in the hippocampus and frontal cortex (Boutros et al., 2008; Grunwald et al., 2003; Korzyukov et al., 2007) related to IG deficits observed in schizophrenia (Lawrie, McIntosh, Hall, Owens, & Johnstone, 2008; Wood et al., 2008) and that could also be related to emotional impairment in other disorders.

IG in the amygdala and mPFC could more directly be involved in processes related to fear conditioning and the regulation of emotional states (LeDoux, 2003; Quirk & Beer, 2006; Quirk, Garcia, & Gonzalez-Lima, 2006). It is known that amygdala single-unit responses that show IG are altered by acute stress (Cromwell et al., 2005) and single-unit responses that show gating have similar time scales in the amygdala and mPFC (Cromwell et al., 2005; Mears et al., 2006). The previous work on IG in the prelimbic region of the mPFC in rats demonstrated that the inhibition is mostly persistent within a session and across several days of recording. Slight decreases in response amplitudes were observed, but gating ratios were preserved, if not strengthened. Single-unit responses were diverse and included both inhibitory and excitatory responses. Excitations between the tones appeared similar to prelimbic excitatory responses observed during trace fear conditioning (Gilmartin & McEchron, 2005). Local field potential (LFP) P2 AEP responses from the prelimbic region of mPFC displayed relatively stable gating in both the short-term (single 1-hr session) and long-term (72-hr period). Amplitudes of the components did decrease over time and gating weakened in a linear fashion between interstimulus intervals of 150 to 4,000 ms (Mears et al., 2006).

What role might IG within the mPFC play in processing emotionally meaningful stimuli and what impact might emotional state changes have on this basic elemental process observed in brain regions evaluated thus far? The aim of the present work was to address these issues by examining IG after a session of standard tone-shock conditioning. LFPs from the mPFC were focused on because these responses are more stable and more directly relevant to the clinical neurophysiology used to evaluate patient populations. We predicted that IG would be disrupted in that the gating ratio would be closer to 1 after the conditioning. This would reflect an equalization of the response amplitudes between the two tones and could occur different ways depending on the relative shifts (or lack thereof) in the initial and subsequent responses to the auditory stimuli.

Method

Subjects

Five male Sprague–Dawley rats between 300 and 450 *g* were implanted with intracranial microelectrodes. Surgery, recovery, and testing were conducted according to Institutional Review Board approved guidelines at Bowling Green State University. Animals were anesthetized with xylazine (10 mg/kg) and ketamine (100 mg/kg), and surgery was conducted according to sterile procedures as described in approved protocols. A stereotaxic apparatus guided bilateral implantation of 16 recording microwires (two arrays of 8 microelectrodes; NB Labs, Denison, TX) into prelimbic mPFC (A + 2.7, M ± 0.7, D − 3.0 mm, 3-D coordinates based on skull lambda and dura membrane) according to the standard rat stereotaxic atlas (Paxinos & Watson, 1998). Surgery methods and postexperiment euthanasia and histology have been previously described, see (Mears et al., 2006). Animals were previously subjected to at least 1 week of IG testing with standard paired-tone paradigm. IG had been stable over many days before the present experiment. The placement of electrodes in prelimbic cortex (see Figure 1) was later confirmed by mapping of cresyl violet stained tissue slices photographed under a digital microscope. Before the start of testing in the paired-tone protocol, the electrode wires for each animal were connected to a cable, leading to the electrophysiology apparatus. Experimental procedures began with continuous and uninterrupted three-part testing, conditioning, and testing protocol and then, ended with an additional testing session on a subsequent day.

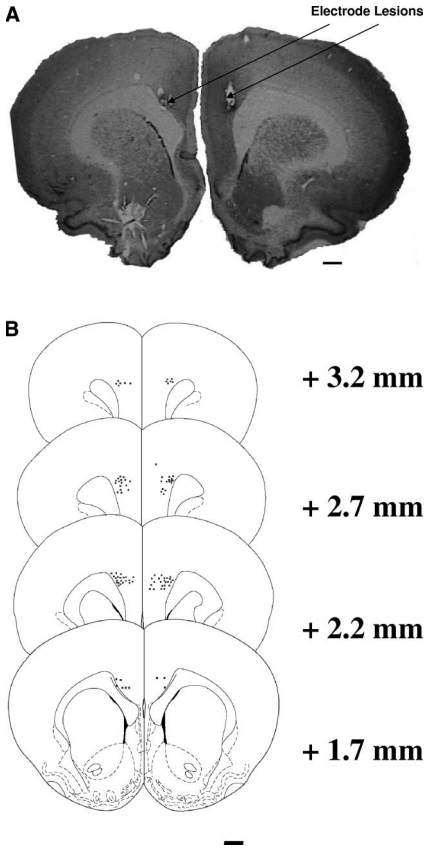

Figure 1. Anatomical mapping of (A) electrode lesions indicated that (B) microelectrode placements ($n = 80$) centered primarily in dorsal prelimbic mPFC. Horizontal bar below slices represents 1 mm. Panel B is adapted from *The Rat Brain in Stereotaxic Coordinates* (4th ed.), G. Paxinos and C. Watson, 1998. Copyright 1998, with permission from Elsevier.

Gating and Fear Conditioning Protocols

Before Fear Conditioning Session

All experimental protocols proceeded in a clear Plexiglas box (20 × 28 cm at base, 35 cm tall) with parallel rods that suspended the rat 5 cm above a removable pan. A piezoelectric tone generator attached to the top of the chamber produced auditory stimuli. Testing for each animal consisted of a block of 100 identical pairs of 4.1 kHz tones. Auditory stimuli (10 ms duration, 75 decibels) sounded from the tone generator with 0.5 s and 10 s intervals, respectively, within and between stimulus pairs.

Footshock Conditioning Period

After pretesting, each animal was disconnected from the electrophysiology cable, taken out of the testing chamber, and placed into a Plexiglas footshock chamber (15 × 20 × 25 cm) that was small enough to be placed inside the recording chamber. The footshock chamber was then placed back into the testing chamber, and footshock conditioning ensued for 1 hr. During conditioning, 30 separate tone-footshock pairings consisted of single 4.1 kHz tones (3-s duration, 75 dB SPL) that were paired with a footshock via the electrified footshock chamber floor. A footshock (0.5 mA) began 2.5 s after the onset of each tone and coterminated with the tone. All tones occurred 1 to 3 min apart with 2 min mean separation between tones.

After Fear Conditioning Session

The postconditioning test session occurred after the reconnection of the animal to the electrophysiology apparatus. The stimulus pairs were identical to those before footshock conditioning.

Extinction Session

An additional session of paired-stimulus testing assessed gating on a different day than aversive conditioning to examine the effects of extended trials on gating. The stimulus pairs were identical to those of before and after conditioning sessions.

Data Analysis

Behavior Analysis

Videotape recording of behavior during before, after, and extinction sessions permitted a later evaluation of the relation of behavior to inhibitory gating. Behavioral coding entailed 100 observations per session for each paired-tone testing session. Videotape reviewers coded animal behavior during each paired-tone trial into three classifications: nonmovement, orient, and movement. Nonmovement included every trial that the animal remained perfectly motionless. Orienting trials included pinna or head movement, in response to the tone pairs (Gallagher, Graham, & Holland, 1990). The movement category included locomotion, rearing, sniffing, and grooming.

Local Field Potential Analysis

Waveform averaging of extracellular LFPs generated auditory evoked potentials (AEPs) for the first (C_{tone}) and second (T_{tone}) tone from each session. AEP data analysis began with single-trial, sliding-window *t* tests of LFP to distinguish electrodes with significant tone response for each session. The *t* tests compared AEP components (i.e., at a .001 level of significance) to activity during a 1-s baseline period 2 s before each C_{tone}. AEP components from electrodes with significant tone response in at least one trial block during any session and T/C ratios below 3.0 (see White & Yee, 1997; Yee & White, 2001) were retained for further analysis. All AEP components were baseline corrected according to the 1-s baseline period for each electrode. Some or all of three components typically attained significance on each electrode, and for P1, N1, and P2 AEP components, respectively, 31, 33, and 74 out of 80 channels ($n = 5$ animals) met selection criteria to be retained for final analysis. This selection process based on selecting evoked responses that attained significance (i.e., compared to baseline) was independently verified with visual inspection of AEP. Whereas the majority of electrode placements produced large P2 evoked potential components, only a subset of electrodes typically produced P1 and N1 of appreciable amplitude for analysis. Future experiments will be necessary to establish the precise neuroanatomical relationships of sites that produce P1 and N1.

AEP analysis between and within sessions. Across the three sessions of paired-tone tests (see Figure 2), responses to first and second tones consisted of the peak amplitude measurements,

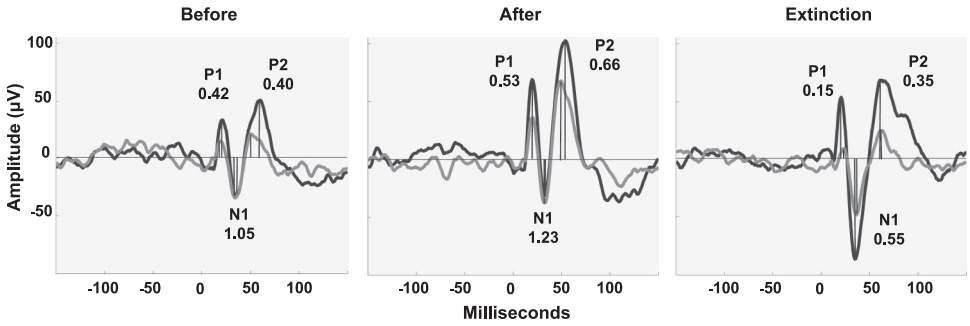

Figure 2. Waveforms are representative LFP cases recorded from the same microelectrode for averages of all trials in each session. T/C ratios indicate the proportional relationships for each AEP component in response to C_{tone} (black trace) and T_{tone} (gray trace) in before FC, after FC, and extinction sessions.

cAmp and tAmp, for P1, N1, and P2 AEP components. Inhibitory gating was assessed as the ratio of tAmp to cAmp (T/C) and thus a measure of the degree of suppression of the second response relative to the first response. N1 T/C ratios were calculated using absolute magnitude of the evoked response. Separate 3 × 3 repeated-measures ANOVAs with three levels of session (before, after, and extinction) and three levels of trial block (Blocks 1, 2, and 3) permitted analysis of cAmp, tAmp, or T/C ratios from each component. Pairwise *t* tests of marginal means permitted further examination of main effects. In cases in which significant interactions were present, post hoc *t* tests were performed for each level of each factor, and Bonferroni corrections were applied to minimize family wise errors due to multiple comparisons.

Behavior-based AEP analysis. A secondary analysis of local field potential data revealed the relation of behavior to inhibitory gating. As mentioned above, reviewers of the videotaped behavior classified the activity of each subject during individual trial sweeps of LFP, and waveform averaging of the sorted LFPs generated new behavior-based AEP for P1, N1, and P2 components for each session. For behavior-based AEP components there were respectively 31, 33, and 74 out of 80 channels for P1, N1, and P2 AEP components that met selection criteria to be retained for analysis. Nonmovement and orient behavioral classifications were retained for further analysis, but the movement trials were excluded from further analysis based on the poor signal quality of these averages. Separate 3 × 2 repeated-measures ANOVAs with three levels of session (before, after, and extinction) and two levels of behavior type (nonmovement and orient) permitted analysis of cAmp, tAmp, or T/C ratios from each component. Pairwise comparisons of marginal means and post hoc *t* tests were conducted similarly to the session by trial block analysis.

Results

Behavior

Analysis of behavioral activities revealed significant effects of fear conditioning (FC) on the proportion of movement and nonmovement behavior episodes across before (BFC), after (AFC) and extinction sessions. A chi-square analysis was completed to determine how behavior changed between sessions. Results of the analysis showed that FC led to a shift in behavior with an increase in orienting, $\chi^2(2, N = 5) = 7.60$, $p < .05$. The median number of trials in which animals oriented increased AFC (see Figure 3), and this reflects an attribution of emotional significance to the stimulus. Furthermore, there was a significant shift in the nonmovement category across sessions, $\chi^2(2, N = 5) = 6.40$, $p < .05$. Nonmovement increased during the extinction session relative to the BFC and AFC sessions. The particular method of videotape behavioral assessment in this study precluded the reviewers' discrimination of resting and freezing behavior, so increased nonmovement in the extinction session must be taken simply as nonmovement. We found no significant difference for the distribution of the movement trials, $\chi^2(2, N = 5) = 1.20$, $p = .55$, between the different sessions.

Fear Conditioning Effects on AEPs

Fear Conditioning and P1 Gating

Analysis of each component of the AEP occurred in three parts: (a) cAmp or initial tone response, (b) tAmp or second tone response, and (c) T/C ratio. Two factor ANOVA (3 × 3) for each portion of analysis permitted assessment of the effects of fear conditioning between sessions and with a finer temporal resolution within sessions.

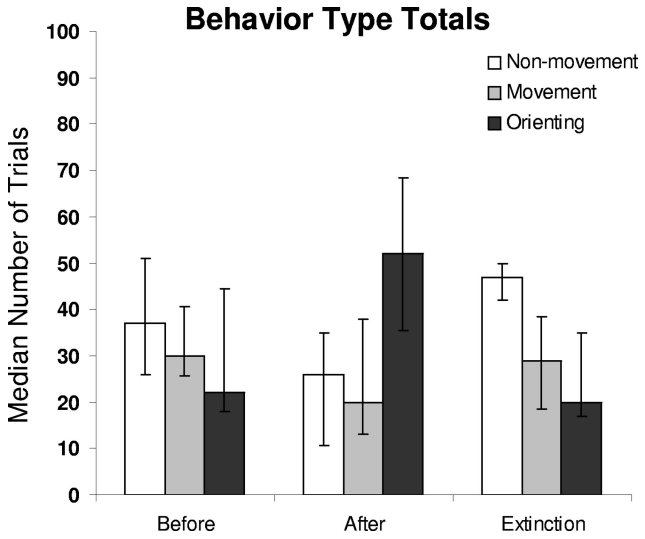

Figure 3. Median (bar) and interquartile ranges (whisker) indicate the numbers of trials (i.e., out of 100) for each behavior type from subjects ($n = 5$) in each session.

Table 1
Analysis of cAmp, tAmp, and T/C Ratios for Sessions and Trial Blocks or Behavior-Based AEPs

	cAmp		tAmp		T/C ratio		
	F	*p*	*F*	*p*	*F*	*p*	*df*
P1							
Session	2.83	.093	42.79	.000	24.28	.000	(2, 60)
Block	26.68	.000	15.25	.000	7.70	.005	(2, 60)
Session × Block	36.60	.000	2.53	.072	5.24	.007	(4, 120)
Session	6.35	.011	41.91	.000	85.49	.000	(2, 60)
Behavior	33.97	.000	0.26	.613	6.69	.014	(1, 30)
Session × Behavior	0.67	.468	31.66	.000	19.33	.000	(2, 60)
N1							
Session	5.09	.029	0.52	.514	11.31	.000	(2, 64)
Block	117.98	.000	23.66	.000	12.28	.000	(2, 64)
Session × Block	19.33	.011	2.42	.100	3.29	.055	(4, 128)
Session	12.50	.000	6.83	.007	4.13	.033	(2, 64)
Behavior	13.37	.001	178.30	.000	6.52	.016	(1, 32)
Session × Behavior	20.81	.000	17.05	.000	1.44	.245	(2, 64)
P2							
Session	14.00	.000	79.90	.000	46.98	.000	(2, 146)
Block	73.83	.000	116.77	.000	1.00	.353	(2, 146)
Session × Block	120.46	.000	43.89	.000	42.98	.000	(4, 292)
Session	3.31	.063	58.38	.000	36.78	.000	(2, 146)
Behavior	27.05	.000	10.98	.001	0.63	.431	(1, 73)
Session × Behavior	60.71	.000	2.97	.068	19.33	.000	(2, 146)

Note. T/C = ratio of tAmp to cAmp; AEP = auditory evoked potential.

For P1 cAmp, we found that the response varied significantly within the different sessions (block factor) and this depended on the session (Session × Block interaction; see Table 1). Between sessions, cAmp increased dramatically in the beginning of the session AFC compared to BFC or extinction sessions (see Table 2). Within-session *t* tests indicated that P1 cAmp increased for each successive trial block in BFC and extinction sessions, that is, Block 1 > Block 2 > Block 3. In contrast, AFC P1 cAmp decreased across successive blocks of trials.

For the analysis of tAmp, we found significant main effects for Session and block (see Table 1). The pairwise analysis of marginal

Table 2
P1 Trial Block Amplitudes and Ratios for Each Session

	Sessions							
	Before		After		Extinction		Total sessions	
	M	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*
P1 cAmp (μV)								
Trials 1 to 33	35.28	4.82	81.33_{a}	6.85	60.35_{b}	6.81	57.96	4.84
Trials 34 to 66	50.58^{*}	4.92	58.56^{*}	5.09	64.85^{*}	8.31	57.99^{*}	4.55
Trials 67 to 100	$67.63^{*,**}$	4.70	$49.40^{*,**}$	4.25	$86.30^{*,**}_{b}$	10.50	$65.97^{*,**}$	5.33
Total blocks	51.21	4.74	62.59	5.24	68.12	8.58		
P1 tAmp (μV)								
Trials 1 to 33	19.93	3.20	40.35_{a}	4.23	21.63_{b}	2.41	26.71	2.58
Trials 34 to 66	12.02	2.16	40.96_{a}	2.63	17.72_{b}	1.80	23.57	1.81
Trials 67 to 100	10.77	2.50	27.47^{**}_{a}	3.44	16.20	3.20	18.18^{*}	2.04
Total blocks	14.09	1.88	35.91_{a}	3.00	18.46_{b}	2.32		
P1 T/C ratio								
Trials 1 to 33	0.76	0.16	0.48	0.03	0.37	0.02	0.52	0.05
Trials 34 to 66	0.38	0.08	0.77^{*}_{a}	0.04	0.31_{b}	0.02	0.49	0.03
Trials 67 to 100	0.21	0.03	0.56_{a}	0.05	0.23^{*}_{b}	0.02	0.43^{**}	0.02
Total blocks	0.43	0.05	0.60	0.02	0.31_{b}	0.01		

Note. Mean and standard error values for cAmp, tAmp, and T/C ratios are displayed for each cell and marginal mean. Significant *t*-test differences ($p < .001$) between sessions are indicated: subscript a = before fear conditioning (FC); subscript b = after FC. Significant differences ($p < .001$) within sessions are indicated: * Block 1 (Trials 1–33); ** Block 2 (Trials 34–66).

means showed that FC produced an increase in the T_{tone} response amplitude (AFC tAmp) compared to BFC or extinction. The within-session analysis showed that the response amplitude progressively decreased within each session. The between-session result is very interesting in that an elevation of tAmp, or the response to the T_{tone}, could lead to a significant increase in the T/C ratio. This would suggest weakening of sensory gating.

The T/C ratio analysis did find significant main effects for session and block and Session × Block interaction, and pairwise tests revealed this increase in ratio AFC (see Table 2 and Figure 4). The T/C shifts depended on the time period within a session, so that the middle and last blocks AFC had the greatest shift compared to the similar blocks BFC. For extinction, T/C ratios returned to lower levels and this was most prominent for the later part of the extinction trial (Block 3) compared to the earlier portions of the session (see Table 2).

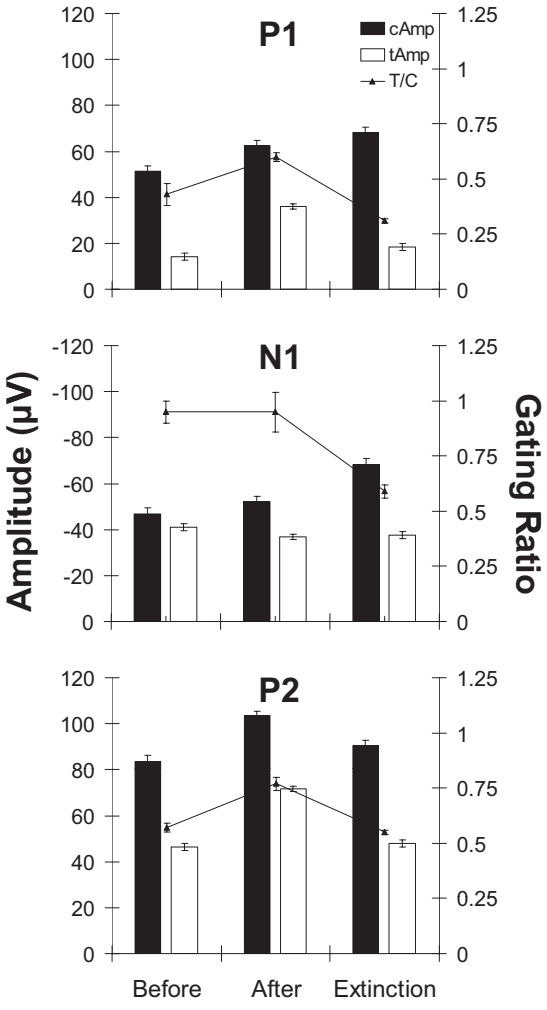

Figure 4. Side-by-side presentation of session marginal means (with *SE* whiskers) for cAmp, tAmp (bars), and T/C (lines) clearly indicate that change of P1 and P2 tAmp brings about T/C change across sessions. P1 tAmp and T/C ratios increased after fear conditioning and decreased in the extinction session. N1 marginal means indicate that increased cAmp mediates the decrease of T/C ratio in the extinction session. P2 marginal means clearly show that tAmp determines the T/C effects of fear conditioning and extinction.

P1 and behavior. Similar to the trial blocks analysis, analysis of behavior-based AEP took place in 3 parts for cAmp, tAmp, and T/C. However, the second factor of each ANOVA (3 × 2) had levels of orient and nonmovement based AEP types. Our analysis of P1 cAmp revealed main effects of session and behavior (see Table 1). P1 cAmp decreased in the extinction session, and orient cAmp was always greater than nonmovement cAmp (see Table 3). Analysis of P1 tAmp revealed a main effect of session, and a significant interaction of Session × Behavior for tAmp. P1 tAmp AFC was greater than BFC and extinction for both behavior AEP types. However, nonmovement tAmp increased more than orienting in the AFC session. Analysis for P1 T/C ratios revealed main effects of session and behavior and a significant Session × Behavior interaction. Nonmovement T/C increased greatly in AFC, but both nonmovement and orienting T/C decreased during the extinction session. Overall, the increase of nonmovement P1 tAmp indicated weakened suppression AFC and decreased nonmovement and orienting tAmp indicated strengthened suppression in the extinction session.

Fear Conditioning and N1 Gating

Our analysis for N1 cAmp resulted in significant main effects for session, block, and a significant Session × Block interaction (see Table 1). Within each session, the largest magnitude N1 cAmp occurred at the end of each session, and N1 cAmp was augmented most in the extinction session (see Table 4).

Analysis of N1 tAmp produced a significant main effect for block. N1 tAmp was greater in magnitude during the third block compared to the first block.

With the analysis of N1 T/C ratio we found significant main effects for session and block. N1 T/C ratios were significantly decreased in the extinction session compared to BFC. N1 T/C ratios were decreased during the third block compared to the first block.

N1 and behavior. Analysis of N1 cAmp revealed main effects of session and behavior and a significant Session × Behavior interaction (see Table 1). N1 cAmp increased magnitude in the extinction session for both behavior types, particularly for orient cAmp (see Table 5). Nonmovement N1 cAmp was greater than orient cAmp BFC and AFC, but this relation was reversed in the extinction session. For N1 tAmp there was a main effect for session, a main effect of behavior, and a significant interaction of Session × Behavior. Nonmovement tAmp decreased, and orienting tAmp increased during the extinction session compared to AFC. For ANOVA of N1 T/C ratios, there was a significant main effect for session and behavior. T/C ratios for both behavior types decreased significantly during the extinction session compared to prior sessions, and orient T/C was always less than nonmovement T/C. The extinction session was the only session to have appreciable IG for N1, indicated by T/C ratios less than .75 for both behavior types.

Fear Conditioning and P2 Gating

The analysis of P2 cAmp produced significant main effects for session and block, and a significant interaction occurred for Ses-

Table 3
P1 Behavior-Based AEP Amplitudes and Ratios for Each Session

	Sessions							
	Before		After		Extinction		Total sessions	
	M	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*
P1 cAmp (μV)								
Nonmovement	71.43	8.33	66.68	6.45	46.48	3.77	61.53	4.70
Orient	81.83*	8.84	77.43*	5.42	53.27_{b}	4.48	70.84*	4.09
Total behaviors	76.63	8.47	72.06	5.80	$49.87_{a,b}$	3.94		
P1 tAmp (μV)								
Nonmovement	21.01	3.24	45.54_{a}	3.12	11.34_{b}	1.45	25.96	2.12
Orient	26.24*	2.32	37.96^{*}_{a}	3.24	$15.30_{a,b}$	2.15	26.50	1.64
Total behaviors	23.62	2.70	41.75_{a}	3.16	$13.32_{a,b}$	1.60		
P1 T/C ratio								
Nonmovement	0.26	0.02	0.78_{a}	0.05	0.26_{b}	0.03	0.43	0.02
Orient	0.39	0.03	0.47*	0.02	0.28_{b}	0.03	0.38*	0.01
Total behaviors	0.32	0.01	0.62_{a}	0.02	0.27_{b}	0.02		

Note. Mean and standard error values for cAmp, tAmp, and T/C ratios are displayed for each cell and marginal mean. Significant t-test differences ($p < .001$) between sessions are indicated: subscript a = before fear conditioning (FC); subscript b = after FC. Significant mean differences ($p < .001$) between behavioral categories, within sessions are indicated with an asterisk.

sion × Block (see Table 1). Changes of P2 cAmp depended on the session. P2 cAmp increased during the final trial block BFC, but in the AFC session a pattern of decreasing cAmp was observed from the maximum P2 cAmp in Block 1 to the minimum P2 value in Block 3 (see Table 6).

Analysis of P2 tAmp indicated significant main effects for session and block, and there was a significant interaction of Session × Block. P2 tAmp was greater for AFC than BFC or extinction sessions. Similar to P2 cAmp, in latter trial blocks of AFC and extinction sessions tAmp decreased.

We found that analysis of P2 T/C ratio revealed a significant main effect for session and a significant Session × Block interaction. Between sessions, the AFC T/C ratio was greater than BFC or extinction sessions in Blocks 2 and 3 (see Table 6). Within sessions for the BFC and extinction conditioning sessions there was a pattern of decreasing T/C ratio for successive trial blocks. However, the converse pattern occurred for AFC, as T/C ratio increased in latter blocks.

P2 and behavior. Analysis of P2 cAmp revealed a main effect of behavior, and there was a significant interaction of Session ×

Table 4
N1 Trial Block Amplitudes and Ratios for Each Session

	Sessions							
	Before		After		Extinction		Total sessions	
	M	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*
N1 cAmp (μV)								
Trials 1 to 33	−34.24	5.56	−32.23	3.69	-49.12_{b}	3.65	−38.53	3.10
Trials 34 to 66	−44.63	3.73	−60.29*	8.56	-59.97_{a}	4.58	−54.96*	3.67
Trials 67 to 100	−61.22*	7.66	−64.20*	7.70	$-96.02^{*,**}_{a}$	5.68	−73.82*,**	3.54
Total blocks	−46.70	5.06	−52.24	6.35	-68.37_{a}	3.77		
N1 tAmp (μV)								
Trials 1 to 33	−33.59	4.31	−30.66	3.46	−31.10	2.01	−31.79	2.52
Trials 34 to 66	−36.65	5.65	−41.16	2.50	−37.24	3.77	−38.35	2.67
Trials 67 to 100	−52.62*,**	6.44	−38.80	4.15	−43.85	3.54	−45.09*	2.93
Total blocks	−40.95	5.06	−36.87	2.62	−37.40	2.20		
N1 T/C ratio								
Trials 1 to 33	1.19	0.12	1.01	0.12	0.67	0.04	0.96	0.04
Trials 34 to 66	0.79	0.10	1.11^{*}_{a}	0.13	0.64	0.06	0.85	0.07
Trials 67 to 100	0.87*	0.06	0.73	0.09	$0.48^{*}_{a,b}$	0.03	0.69*	0.04
Total blocks	0.95	0.05	0.95	0.09	0.59_{a}	0.03		

Note. Mean and standard error values for cAmp, tAmp, and T/C ratios are displayed for each cell and marginal mean. Significant t-test differences ($p < .001$) between sessions are indicated: subscript a = before fear conditioning (FC); subscript b = after FC. Significant mean differences ($p < .001$) within sessions are indicated: * Block 1 (Trials 1–33); ** Block 2 (Trials 34–66).

Table 5
N1 Behavior-Based AEP Amplitudes and Ratios for Each Session

	Sessions							
	Before		After		Extinction		Total sessions	
	M	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*
N1 cAmp (μV)								
Nonmovement	−52.22	5.17	−69.46	7.07	-76.43_{a}	4.58	−66.04	3.43
Orient	-30.98^{*}	3.55	-56.25^{*}	8.27	$-90.35^{*}_{a,b}$	7.71	-59.20^{*}	3.95
Total behaviors	−41.60	3.78	-62.86_{a}	7.54	$-83.39_{a,b}$	6.09		
N1 tAmp (μV)								
Nonmovement	−45.25	3.68	−54.83	3.90	-47.06_{b}	2.98	−49.05	2.65
Orient	-20.64^{*}	2.85	-31.39^{*}	2.26	$-42.20^{*}_{a,b}$	3.25	-31.41^{*}	1.79
Total behaviors	−32.95	2.99	-43.11_{a}	2.79	-44.63_{a}	3.01		
N1 T/C ratio								
Nonmovement	1.37	0.28	0.99	0.01	0.63_{b}	0.03	1.00	0.09
Orient	0.86	0.11	0.83	0.02	0.53	0.05	0.74^{*}	0.07
Total behaviors	1.11	0.17	0.91	0.13	$0.58_{a,b}$	0.04		

Note. Mean and standard error values for cAmp, tAmp, and T/C ratios are displayed for each cell and marginal mean. Significant t-test differences ($p < .001$) between sessions are indicated: subscript a = before fear conditioning (FC); subscript b = after FC. Significant mean differences ($p < .001$) between behavioral categories, within sessions are indicated with an asterisk. AEP = auditory evoked potential.

Behavior for P2 cAmp (see Table 1). Orient P2 cAmp increased for AFC and extinction session compared to BFC, and orient P2 cAmp was greater than nonmovement cAmp for AFC and extinction sessions (see Table 7). For both behavior AEP types there was an increase of cAmp in AFC compared to BFC, and the increase of cAmp continued in the extinction session compared to BFC, possibly indicating an effect of learning. Analysis of P2 tAmp revealed a main effect for session and for behavior. The increase of nonmovement P2 tAmp in AFC, compared to BFC, indicated weakened suppression of T_{tone} response. In addition, during extinction the decrease of P2 tAmp for both behavior-based AEP types, indicated strengthened suppression of T_{tone} response. Analysis of P2 T/C ratios revealed a main effect of session, and a significant interaction of Session × Behavior for P2 T/C ratios. The increase of T/C ratio in the AFC session depended on the behavior category. For nonmovement, P2 T/C AFC increased compared to T/C BFC. Extinction P2 T/C decreased compared to AFC T/C at both levels of behavior. Although there was not significant weakening of gating during orienting behavior in the AFC session, weakened suppression of

Table 6
P2 Trial Block Amplitudes and Ratios for Each Session

	Sessions							
	Before		After		Extinction		Total Sessions	
	M	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*
P2 cAmp (μV)								
Trials 1 to 33	73.14	3.45	149.25_{a}	3.62	$98.86_{a,b}$	5.54	107.68	3.42
Trials 34 to 66	71.84	2.82	90.72^{*}_{a}	3.07	84.19^{*}	4.86	82.25^{*}	2.39
Trials 67 to 100	$106.41^{*,**}$	3.78	$69.18^{*,**}_{a}$	2.51	87.27_{b}	2.97	87.70^{*}	1.50
Total blocks	83.75	2.87	103.42_{a}	2.55	90.46	3.79		
P2 tAmp (μV)								
Trials 1 to 33	47.83	2.30	88.90_{a}	2.87	$59.54_{a,b}$	3.61	66.00	2.39
Trials 34 to 66	40.89^{*}	2.51	70.45^{*}_{a}	1.85	43.92^{*}_{b}	2.74	51.75^{*}	1.94
Trials 67 to 100	49.03^{**}	2.62	$54.75^{*,**}$	1.42	$39.93^{*}_{a,b}$	1.50	$48.22^{*,**}$	1.32
Total blocks	46.35	2.34	71.57_{a}	1.81	48.06_{b}	2.44		
P2 T/C ratio								
Trials 1 to 33	0.67	0.02	0.59	0.01	0.60	0.01	0.63	0.01
Trials 34 to 66	0.55^{*}	0.03	0.84^{*}_{a}	0.03	0.55_{b}	0.03	0.64	0.02
Trials 67 to 100	$0.48^{*,**}$	0.02	0.88^{*}_{a}	0.05	0.49^{*}_{b}	0.02	0.62	0.02
Total blocks	0.57	0.02	0.77_{a}	0.03	0.55_{b}	0.01		

Note. Mean and standard error values for cAmp, tAmp, and T/C ratios are displayed for each cell and marginal mean. Significant t-test differences ($p < .001$) between sessions are indicated: subscript a = before fear conditioning (FC); subscript b = after FC. Significant mean differences ($p < .001$) within sessions are indicated with an asterisk.

Table 7
P2 Behavior-Based AEP Amplitudes and Ratios for Each Session

	Sessions							
	Before		After		Extinction		Total sessions	
	M	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*
P2 cAmp (μV)								
Nonmovement	102.17	3.72	95.95	3.00	91.30_{a}	4.24	96.48	2.62
Orient	93.67	5.47	121.65^{*}_{a}	3.33	107.88^{*}_{a}	6.20	107.73^{*}	4.20
Total behaviors	97.92	4.34	108.80_{a}	2.93	99.60	5.16		
P2 tAmp (μV)								
Nonmovement	49.90	2.71	77.39_{a}	3.19	46.68_{b}	3.24	57.99	2.28
Orient	55.96^{*}	3.44	78.68_{a}	2.37	$49.52_{a,b}$	3.76	61.39^{*}	2.85
Total behaviors	52.93	3.03	78.03_{a}	2.62	$48.10_{a,b}$	3.46		
P2 T/C ratio								
Nonmovement	0.50	0.02	0.85_{a}	0.04	0.47_{b}	0.02	0.61	0.02
Orient	0.68^{*}	0.04	0.66^{*}	0.02	$0.44_{a,b}$	0.02	0.59	0.01
Total behaviors	0.59	0.03	0.75_{a}	0.02	$0.46_{a,b}$	0.02		

Note. Mean and standard error values for cAmp, tAmp, and T/C ratios are displayed for each cell and marginal mean. Significant t-test differences ($p < .001$) between sessions are indicated: subscript a = before fear conditioning (FC); subscript b = after FC. Significant mean differences ($p < .001$) between behavioral categories, within sessions are indicated with an asterisk. AEP = auditory evoked potential.

tAmp might have been obscured by a parallel and proportional increase in cAmp.

Discussion

Inhibitory Gating and Suppression Versus Activation

The results of this investigation point toward a variety of influences on auditory evoked potentials of prelimbic cortex. Weakened IG of P1 and P2 after fear conditioning was primarily caused by a large increase of tAmp (see Figure 4), meaning that change in gating is due to weakened suppression of the T_{tone} response (i.e., conventionally defined as gating). Strengthened IG of N1 in the extinction session was primarily mediated by large increase of cAmp, and there was essentially no change of N1 tAmp across sessions.

Classification of IG changes into categories based on proportionally greater changes in tAmp (category I), cAmp (category II), or inverse changes in both cAmp and tAmp (category III) provides a means to identify some influences of T/C ratio changes (Mears et al., 2006). Category I and II changes of gating might point toward independent mechanisms related to sensory activation or suppression in mPFC (see Figure 5). Activation results from increased rate and/or number of active inputs to prelimbic cortex in response to all tones. Suppression is the product of rapid but transient inhibition of T_{tone} response. P1 and P2 tAmp changes in the after FC and the extinction sessions produce category I gating changes (see Tables 8 and 9). Category I gating change indicates that fear conditioning modulates suppression of P1 and P2 T_{tone} response. On the other hand, category II strengthening of N1 gating in extinction session indicates an alteration of sensory activation of C_{tone} response (Boutros & Belger, 1999; Hajos, 2006). Activation and suppression might simultaneously, but independently, change to magnify (category III) or to obscure changes of gating (i.e., P1 or P2 in AFC Block 1). Finally, considering activation and suppression as potentially separate factors would clarify future investigations of within-subject variability.

Negative Affect, Stress, and IG

Acute stress increases T/C ratios in animal and human subjects. Mild physical discomfort produces transient weakening of P50 (i.e., P1) inhibitory gating for up to 30 min following the cold pressor test in human subjects (Johnson & Adler, 1993). Psychological stress weakens IG and increases electrodermal response and heart rate measures of stress (White, Kanazawa, & Yee, 2005; White & Yee, 1997). The weakening of IG by psychological stress

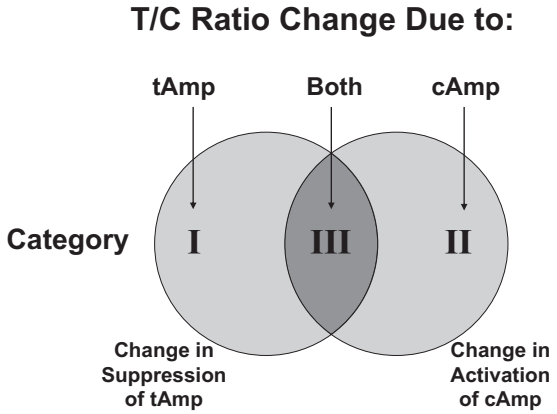

Figure 5. A descriptive model for changes of gating indicates that proportional changes of mainly tAmp suppression (category I) or cAmp activation (category II) contribute to T/C ratio change. Furthermore, the largest change in T/C ratio can come from combined, reciprocally proportional changes in both tAmp and cAmp (category III). This model accounts for weakening or strengthening of gating.

Table 8
Categories of Gating Changes for Trial Blocks

	After versus before fear conditioning			Extinction versus after fear conditioning		
	P1	N1	P2	P1	N1	P2
Block 2	Category I weaken	Category I weaken	Category I weaken	Category I strengthen		Category I strengthen
Block 3	Category I weaken		Category III weaken	Category III strengthen	Category II strengthen	Category III strengthen

depends on whether the experimental manipulation is perceived to be stressful (White et al., 2005; Yee & White, 2001). In many of these experiments in humans there was cAmp decrease along with T/C ratio increase. For mice subjected to restraint stress, IG weakened for hippocampal N40 (i.e., N1; Suer, Dolu, & Ozesmi, 2004). The aversive experience of forceful restraint weakened gating in mice, and weakening of gating corresponded with decreased cAmp and increased tAmp. Similar to the present investigation, previous investigations of P1 and N1 in human and animal subjects found that gating weakened following acute stress. The weakening of gating in these other investigations would be classified as category II, or in some cases category III. In the present study, weakened prelimbic IG for P1 and P2 always accompanied an increase of tAmp, and thus, fear conditioning weakens prelimbic cortex suppression of T_{tone} response.

Role of mPFC in Aversive Conditioning

Prefrontal cortex, hippocampus, and amygdala form part of a widespread network of structures involved in fear conditioning (LeDoux, 1998; Pezze & Feldon, 2004). For example, trace fear conditioning involves amygdala, medial prefrontal cortex, and hippocampus (McEchron, Bouwmeester, Tseng, Weiss, & Disterhoft, 1998; McLaughlin, Skaggs, Churchwell, & Powell, 2002). Hippocampus and mPFC participate in a functional system for maintaining conditioned stimulus information during short gaps of time prior to the unconditioned stimulus (Lee & Kesner, 2003). Opposite patterns of delay-bridging single-unit activity predominate in prelimbic and infralimbic regions during trace fear conditioning (Gilmartin & McEchron, 2005). Interactions between structures of this network mediate fear learning in stages of formation, consolidation, expression, and extinction. Prefrontal cortex contributes particularly in the latter two stages (Pezze & Feldon, 2004). Dorsal and ventral regions of mPFC play important roles, respectively, in the expression (Corcoran & Quirk, 2007) and extinction of fear memory (Quirk & Mueller, 2008). Prelimbic and infralimbic cortex (i.e., corresponding to dorsal and ventral mPFC regions) often operate in a reciprocal fashion (Moghaddam & Homayoun, 2008; Quirk & Mueller, 2008), and electrical stimulation of prelimbic or infralimbic cortex produces opposite effects, respectively resulting in the enhancement or suppression of fear learning and fear expression (Vidal-Gonzalez, Vidal-Gonzalez, Rauch, & Quirk, 2006). The present experiment involved a combination of fear conditioning expression and then extinction of fear conditioning. In AFC Block 1, increased P1 and P2 activation (i.e., increased cAmp) reflects expression of fear potentiated AEP response immediately after footshock conditioning. The decrease of P1 and P2 activation throughout the remainder of the session indicates extinction or habituation.

Functions of mPFC

Dorsal mPFC appears to encode a fundamental type of activity related to sensory events, and prelimbic cortex need not be restricted to exclusively encoding fear-related information. Dorsal mPFC single units (Mears et al., 2006) and LFP AEPs (i.e., P1 and P2 before fear conditioning in this study) respond to stimuli of no particular emotional or cognitive relevance, and these data support the conclusion that dorsal mPFC encodes some more general aspect of information. Gating of repetitive, irrelevant tones occurs in human DLPFC (Grunwald et al., 2003; Korzyukov et al., 2007; Oranje, Geyer, Bocker, Leon Kenemans, & Verbaten, 2006; Tregellas et al., 2007; Weisser et al., 2001), and human DLPFC plays a significant role in a network of brain structures that mediate gating (Knight, Staines, Swick, & Chao, 1999). Furthermore, some data substantiates the premise that gating prefrontal cortex might be differentially affected in particular disorders, such as schizophrenia (Judd, McAdams, Budnick, & Braff, 1992). Functional parallels between rat dorsal mPFC and primate dorsolateral PFC (DLPFC) have been drawn for short-term or working memory and executive function (Birrell & Brown, 2000; Brown & Bowman, 2002; Dalley, Cardinal, & Robbins, 2004; Marquis, Killcross, & Haddon, 2007; Moghaddam & Homayoun, 2008; Otani, 2003; Vertes, 2006). Further, IG in prelimbic mPFC (Mears et al., 2006) reinforces the analogy between rat prelimbic mPFC and human DLPFC. Due to the functional implications for prelimbic cortex,

Table 9
Categories of Gating Changes for Behavior-Based AEPs

	After versus before fear conditioning			Extinction versus after conditioning		
	P1	N1	P2	P1	N1	P2
Nonmovement	Category I weaken		Category I weaken	Category I strengthen	Category III strengthen	Category I strengthen
Orient				Category I strengthen	Category II strengthen	Category I strengthen

Note. AEP = auditory evoked potential.

alterations of AEP magnitude might reveal something about attention and monitoring of auditory stimuli. Increased N1 activation throughout the extinction session, particularly during orienting, might indicate increased attention and monitoring of tones. Provided that animals had been previously exposed to tones before this experiment (see Method), tone-shock association might have provided increased salience of the tones during the extinction session. Gating of N1 was observed during initial exposure during prior testing (Mears et al., 2006). Whereas gating of P1 and P2 remained stable, activation of the N1 appeared to habituate with repeated testing. The meaning of this finding in relation to human N1 gating is uncertain because no studies so far have examined the relation of fear conditioning, or extinction, to gating measured over prefrontal locations.

Strong Acute Stressors and mPFC Function

Increased catecholamine release in prefrontal cortex after fear conditioning might explain IG weakening in this investigation. Acute, strongly aversive stressors produce mPFC elevations of numerous neurotransmitters including glutamate, dopamine, and norepinephrine (Abercrombie, Keefe, DiFrischia, & Zigmond, 1989; Finlay, Zigmond, & Abercrombie, 1995; Jackson & Moghaddam, 2004; Moghaddam, 1993; Moghaddam, Roth, & Bunney, 1990), and footshock conditioning, as a strongly aversive paradigm, produces excessive mPFC dopamine (DA) and norepinephrine (NE) release (Feenstra, Vogel, Botterblom, Joosten, & de Bruin, 2001). Optimal performance of PFC dependent tasks requires a level of prefrontal DA receptor stimulation that is neither too low nor excessive (O'Donnell, 2003; Williams & Castner, 2006). PFC working memory function follows a bell-shaped curve in relation to DA release (Seamans & Yang, 2004), and acute stress elevates DA sufficiently to produce PFC mediated cognitive deficits in rats and in nonhuman primates (Arnsten, 1998; Arnsten & Goldman-Rakic, 1998; Murphy, Arnsten, Goldman-Rakic, & Roth, 1996; Murphy, Arnsten, Jentsch, & Roth, 1996). Prefrontal gating might be affected by excessive DA release following strongly aversive experiences. Numerous investigations of auditory gating in hippocampus demonstrate that systemic pharmacological compounds that increase catecholamine neurotransmitter release (Adler, Rose, & Freedman, 1986; Stevens, Fuller, & Rose, 1991) weaken gating. Given the functional effects of excessive catecholamine release in prefrontal cortex, further research is necessary to assess manipulations of dopamine or norepinephrine receptor systems in relation to prefrontal gating mechanisms. Results of the present research contribute to our understanding of basic patterns of neural dysfunction that may underlie cognitive and emotional impairment in schizophrenia and PTSD as well as many other human brain disorders.

Clinical Implications: State or Trait Deficit in IG

Some clinical investigations have considered implications of whether gating should be characterized as predominantly determined by the individual's state or by trait. Because of the discovery of compromised gating in schizophrenic individuals (Adler et al., 1982) gating has been hypothesized to be an indicator of an underlying heritable attribute. This finding was reinforced when unaffected first degree relatives of schizophrenics were found to have high likelihood of weakened gating (Clementz, Geyer, & Braff, 1998). However, studies of other clinical populations have demonstrated more transient changes of gating. Patients with bipolar disorder have poor gating during mania but not during remission of manic symptoms (Franks, Adler, Waldo, Alpert, & Freedman, 1983). Weakened inhibitory gating occurs in anxiety disorders such as PTSD (Ghisolfi et al., 2004; Neylan et al., 1999; Skinner et al., 1999) and panic disorder (Ghisolfi et al., 2006). Future preclinical or clinical investigations should examine inhibitory gating within-subjects at multiple-time points to examine interaction of the trait related aspects of IG with the emotional state of the subject.

References

Abercrombie, E. D., Keefe, K. A., DiFrischia, D. S., & Zigmond, M. J. (1989). Differential effect of stress on in vivo dopamine release in striatum, nucleus accumbens, and medial frontal cortex. *Journal of Neurochemistry, 52,* 1655–1658.

Adler, L. E., Olincey, A., Cawthra, E., M. Hoffer, Nagamoto, H. T., Amass, L., & Freedman, R. (2001). Reversal of diminished inhibitory sensory gating in cocaine addicts by a nicotinic cholinergic mechanism. *Neuropsychopharmacology, 24,* 671–679.

Adler, L. E., Pachtman, E., Franks, R., Pecevich, M., Waldo, M. C., & Freedman, R. (1982). Neurophysiological evidence for a defect in neuronal mechanisms involved in sensory gating in schizophrenia. *Biological Psychiatry, 17,* 639–654.

Adler, L. E., Rose, G., & Freedman, R. (1986). Neurophysiological studies of sensory gating in rats: Effects of amphetamine, phencyclidine, and haloperidol. *Biological Psychiatry, 21,* 787–798.

Adler, L. E., Waldo, M. C., Tatcher, A., Cawthra, E., Baker, N., & Freedman, R. (1990). Lack of relationship of auditory gating defects to negative symptoms in schizophrenia. *Schizophrenia Research, 3*(2), 131–138.

Arnsten, A. F. (1998). The biology of being frazzled. *Science, 280*(5370), 1711–1712.

Arnsten, A. F., & Goldman-Rakic, P. S. (1998). Noise stress impairs prefrontal cortical cognitive function in monkeys: Evidence for a hyperdopaminergic mechanism. *Archives of General Psychiatry, 55,* 362–368.

Berridge, K. C., & Cromwell, H. C. (1990). Motivational-sensorimotor interaction controls aphagia and exaggerated treading after striatopallidal lesions. *Behavioral Neuroscience, 104,* 778–795.

Bickford, P. C., Luntz-Leybman, V., & Freedman, R. (1993). Auditory sensory gating in the rat hippocampus: Modulation by brainstem activity. *Brain Research, 607,* 33–38.

Bickford-Wimer, P. A., Nagamoto, H. T., Johnson, R., Adler, L. E., Egan, M., Rose, G., et al. (1990). Auditory sensory gating in hippocampal neurons: A model system in the rat. *Biological Psychiatry, 27,* 183–192.

Birrell, J. M., & Brown, V. J. (2000). Medial frontal cortex mediates perceptual attentional set shifting in the rat. *Journal of Neuroscience, 20,* 4320–4324.

Bock, G., & Goode, J. (2002). *Sodium channels and neuronal hyperexcitability.* Chichester, England: Wiley.

Boutros, N. N., & Belger, A. (1999). Midlatency evoked potentials attenutaion and augmentation reflect different aspects of sensory gating. *Biological Psychiatry, 45,* 917–922.

Boutros, N. N., Gelernter, J., Gooding, D. C., Cubells, J., Young, A., Krystal, J. H., et al. (2002). Sensory gating and psychosis vulnerability in cocaine-dependent individuals: Preliminary data. *Biological Psychiatry, 51,* 683–686.

Boutros, N. N., Korzyukov, O., Jansen, B., Feingold, A., & Bell, M. (2004). Sensory gating deficits during the mid-latency phase of information processing in medicated schizophrenia patients. *Psychiatry Research, 126,* 203–215.

Boutros, N. N., & Kwan, S. W. (1998). Test-retest reliability of the rat N40

auditory evoked response: Preliminary data. *Psychiatry Research, 81,* 269–276.

Boutros, N. N., Mears, R., Pflieger, M. E., Moxon, K. A., Ludowig, E., & Rosburg, T. (2008). Sensory gating in the human hippocampal and rhinal regions: Regional differences. *Hippocampus, 18,* 310–316.

Boutros, N. N., Overall, J., & Zouridakis, G. (1991). Test–retest reliability of the P50 mid-latency auditory evoked response. *Psychiatry Research, 39,* 181–192.

Boutros, N. N., Trautner, P., Korzyukov, O., Grunwald, T., Burroughs, S., Elger, C. E., et al. (2006). Mid-latency auditory-evoked responses and sensory gating in focal epilepsy: A preliminary exploration. *Journal of Neuropsychiatry and Clinical Neurosciences, 18,* 409–416.

Boutros, N. N., Uretsky, N. J., Lui, J. J., & Millana, R. B. (1997). Effects of repeated cocaine administration on sensory inhibition in rats: Preliminary data. *Biological Psychiatry, 41,* 461–466.

Brown, V. J., & Bowman, E. M. (2002). Rodent models of prefrontal cortical function. *Trends in Neurosciences, 25,* 340–343.

Cadenhead, K. S., Light, G. A., Shafer, K. M., & Braff, D. L. (2005). P50 suppression in individuals at risk for schizophrenia: The convergence of clinical, familial, and vulnerability marker risk assessment. *Biological Psychiatry, 57,* 1504–1509.

Clementz, B. A., Geyer, M. A., & Braff, D. L. (1998). Poor P50 suppression among schizophrenia patients and their first-degree biological relatives. *American Journal of Psychiatry, 155,* 1691–1694.

Corcoran, K. A., & Quirk, G. J. (2007). Activity in prelimbic cortex is necessary for the expression of learned, but not innate, fears. *Journal of Neuroscience, 27,* 840–844.

Cromwell, H. C., Anstrom, K., Azarov, A., & Woodward, D. J. (2005). Auditory inhibitory gating in the amygdala: Single-unit analysis in the behaving rat. *Brain Research, 1043,* 12–23.

Cromwell, H. C., Klein, A., & Mears, R. P. (2007). Single unit and population responses during inhibitory gating of striatal activity in freely moving rats. *Neuroscience, 146,* 69–85.

Cromwell, H. C., Mears, R. P., Wan, L., & Boutros, N. N. (2008). Sensory gating: A translational effort from basic to clinical science. *Clinical EEG and Neuroscience, 39,* 69–72.

Cullum, C. M., Harris, J. G., Waldo, M. C., Smernoff, E., Madison, A., Nagamoto, H., et al. (1993). Neurophysiological and neuropsychological evidence for attentional dysfunction in schizophrenia. *Schizophrenia Research, 10,* 131–141.

Dalley, J. W., Cardinal, R. N., & Robbins, T. W. (2004). Prefrontal executive and cognitive functions in rodents: Neural and neurochemical substrates. *Neuroscience and Biobehavioral Reviews, 28,* 771–784.

Eccles, J. C. (1969). *The inhibitory pathways of the central nervous system.* Springfield, MA: Thomas.

Feenstra, M. G., Vogel, M., Botterblom, M. H., Joosten, R. N., & de Bruin, J. P. (2001). Dopamine and noradrenaline efflux in the rat prefrontal cortex after classical aversive conditioning to an auditory cue. *European Journal of Neuroscience, 13,* 1051–1054.

Finlay, J. M., Zigmond, M. J., & Abercrombie, E. D. (1995). Increased dopamine and norepinephrine release in medial prefrontal cortex induced by acute and chronic stress: Effects of diazepam. *Neuroscience, 64,* 619–628.

Franks, R. D., Adler, L. E., Waldo, M. C., Alpert, J., & Freedman, R. (1983). Neurophysiological studies of sensory gating in mania: Comparison with schizophrenia. *Biological Psychiatry, 18,* 989–1005.

Freedman, R., Adler, L. E., Bickford, P., Byerley, W., Coon, H., Cullum, C. M., et al. (1994). Schizophrenia and nicotinic receptors. *Harvard Review of Psychiatry, 2,* 179–192.

Freedman, R., Adler, L. E., Myles-Worsley, M., Nagamoto, H. T., Miller, C., Kisley, M., et al. (1996). Inhibitory gating of an evoked response to repeated auditory stimuli in schizophrenic and normal subjects. Human recordings, computer simulation, and an animal model. *Archives of General Psychiatry, 53,* 1114–1121.

Fuerst, D. R., Gallinat, J., & Boutros, N. N. (2007). Range of sensory gating values and test-retest reliability in normal subjects. *Psychophysiology, 44,* 620–626.

Gallagher, M., Graham, P. W., & Holland, P. C. (1990). The amygdala central nucleus and appetitive Pavlovian conditioning: Lesions impair one class of conditioned behavior. *Journal of Neuroscience, 10,* 1906–1911.

Ghisolfi, E. S., Heldt, E., Zanardo, A. P., Strimitzer, I. M. Jr., Prokopiuk, A. S., Becker, J., et al. (2006). P50 sensory gating in panic disorder. *Journal of Psychiatric Research, 40,* 535–540.

Ghisolfi, E. S., Margis, R., Becker, J., Zanardo, A. P., Strimitzer, I. M., & Lara, D. R. (2004). Impaired P50 sensory gating in post-traumatic stress disorder secondary to urban violence. *International Journal of Psychophysiology, 51,* 209–214.

Gilmartin, M. R., & McEchron, M. D. (2005). Single neurons in the medial prefrontal cortex of the rat exhibit tonic and phasic coding during trace fear conditioning. *Behavioral Neuroscience, 119,* 1496–1510.

Gottesman, I. I., & Gould, T. D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry, 160,* 636–645.

Grunwald, T., Boutros, N. N., Pezer, N., von Oertzen, J., Fernandez, G., Schaller, C., et al. (2003). Neuronal substrates of sensory gating within the human brain. *Biological Psychiatry, 53,* 511–519.

Hajos, M. (2006). Targeting information-processing deficit in schizophrenia: A novel approach to psychotherapeutic drug discovery. *Trends in Pharmacological Sciences, 27,* 391–398.

Jackson, M. E., & Moghaddam, B. (2004). Stimulus-specific plasticity of prefrontal cortex dopamine neurotransmission. *Journal of Neurochemistry, 88,* 1327–1334.

Jessen, F., Kucharski, C., Fries, T., Papassotiropoulos, A., Hoenig, K., Maier, W., et al. (2001). Sensory gating deficit expressed by a suppression of the P50 event-related potentials in patients with Alzheimer's disease. *American Journal of Psychiatry, 158,* 1319–1321.

Johnson, M. R., & Adler, L. E. (1993). Transient impairment in P50 auditory sensory gating induced by a cold-pressor test. *Biological Psychiatry, 33,* 380–387.

Judd, L. L., McAdams, L., Budnick, B., & Braff, D. L. (1992). Sensory gating deficits in schizophrenia: New results. *American Journal of Psychiatry, 149,* 488–493.

Kisley, M. A., Olincy, A., & Freedman, R. (2001). The effect of state on sensory gating: Comparison of waking, REM and non-REM sleep. *Clinical Neurophysiology, 112,* 1154–1165.

Knight, R. T., Staines, W. R., Swick, D., & Chao, L. L. (1999). Prefrontal cortex regulates inhibition and excitation in distributed neural networks. *Acta Psychologica (Amsterdam), 101,* 159–178.

Korzyukov, O., Pflieger, M. E., Wagner, M., Bowyer, S. M., Rosburg, T., Sundaresan, K., et al. (2007). Generators of the intracranial P50 response in auditory sensory gating. *NeuroImage, 35,* 814–826.

Krause, M., Hoffmann, W. E., & Hajos, M. (2003). Auditory sensory gating in hippocampus and reticular thalamic neurons in anesthetized rats. *Biological Psychiatry, 53,* 244–253.

Lang, P. J., & Davis, M. (2006). Emotion, motivation, and the brain: Reflex foundations in animal and human research. *Progress in Brain Research, 156,* 3–29.

Lawrie, S. M., McIntosh, A. M., Hall, J., Owens, D. G., & Johnstone, E. C. (2008). Brain structure and function changes during the development of schizophrenia: The evidence from studies of subjects at increased genetic risk. *Schizophrenia Bulletin, 34,* 330–340.

LeDoux, J. (1998). Fear and the brain: Where have we been, and where are we going? *Biological Psychiatry, 44,* 1229–1238.

LeDoux, J. (2003). The emotional brain, fear, and the amygdala. *Cellular and Molecular Neurobiology, 23,* 727–738.

Lee, I., & Kesner, R. P. (2003). Time-dependent relationship between the dorsal hippocampus and the prefrontal cortex in spatial memory. *Journal of Neuroscience, 23,* 1517–1523.

Louchart-de la Chapelle, S., Levillain, D., Menard, J. F., Van der Elst, A., Allio, G., Haouzir, S., et al. (2005). P50 inhibitory gating deficit is correlated with the negative symptomatology of schizophrenia. *Psychiatry Research, 136,* 27–34.

Marquis, J. P., Killcross, S., & Haddon, J. E. (2007). Inactivation of the prelimbic, but not infralimbic, prefrontal cortex impairs the contextual control of response conflict in rats. *European Journal of Neuroscience, 25,* 559–566.

McEchron, M. D., Bouwmeester, H., Tseng, W., Weiss, C., & Disterhoft, J. F. (1998). Hippocampectomy disrupts auditory trace fear conditioning and contextual fear conditioning in the rat. *Hippocampus, 8,* 638–646.

McLaughlin, J., Skaggs, H., Churchwell, J., & Powell, D. A. (2002). Medial prefrontal cortex and pavlovian conditioning: Trace versus delay conditioning. *Behavioral Neuroscience, 116,* 37–47.

Mears, R. P., Klein, A. C., & Cromwell, H. C. (2006). Auditory inhibitory gating in medial prefrontal cortex: Single unit and local field potential analysis. *Neuroscience, 141,* 47–65.

Moghaddam, B. (1993). Stress preferentially increases extraneuronal levels of excitatory amino acids in the prefrontal cortex: Comparison to hippocampus and basal ganglia. *Journal of Neurochemistry, 60,* 1650–1657.

Moghaddam, B., & Homayoun, H. (2008). Divergent plasticity of prefrontal cortex networks. *Neuropsychopharmacology, 33,* 42–55.

Moghaddam, B., Roth, R. H., & Bunney, B. S. (1990). Characterization of dopamine release in the rat medial prefrontal cortex as assessed by in vivo microdialysis: Comparison to the striatum. *Neuroscience, 36,* 669–676.

Morgane, P. J., Galler, J. R., & Mokler, D. J. (2005). A review of systems and networks of the limbic forebrain/limbic midbrain. *Progress in Neurobiology, 75,* 143–160.

Moxon, K. A., Gerhardt, G. A., Bickford, P. A., Austin, K., Rose, G. M., Woodward, D. J., et al. (1999). Mulitple single units and population responses during inhibitory gating of hippocampal auditorey response in freely-moving rats. *Brain Research, 825,* 75–85.

Murphy, B. L., Arnsten, A. F., Goldman-Rakic, P. S., & Roth, R. H. (1996). Increased dopamine turnover in the prefrontal cortex impairs spatial working memory performance in rats and monkeys. *Proceedings of the National Academy of Sciences of the United States of America, 93,* 1325–1329.

Murphy, B. L., Arnsten, A. F., Jentsch, J. D., & Roth, R. H. (1996). Dopamine and spatial working memory in rats and monkeys: Pharmacological reversal of stress-induced impairment. *Journal of Neuroscience, 16,* 7768–7775.

Neylan, T. C., Fletcher, D. J., Lenoci, M., McCallin, K., Weiss, D. S., Schoenfeld, F. B., et al. (1999). Sensory gating in chronic posttraumatic stress disorder: Reduced auditory P50 suppression in combat veterans. *Biological Psychiatry, 46,* 1656–1664.

O'Donnell, P. (2003). Dopamine gating of forebrain neural ensembles. *European Journal of Neuroscience, 17,* 429–435.

Oranje, B., Geyer, M. A., Bocker, K. B., Leon Kenemans, J., & Verbaten, M. N. (2006). Prepulse inhibition and P50 suppression: Commonalities and dissociations. *Psychiatry Research, 143,* 147–158.

Otani, S. (2003). Prefrontal cortex function, quasi-physiological stimuli, and synaptic plasticity. *Journal of Physiology Paris, 97,* 423–430.

Patterson, J. V., Jin, Y., Gierczak, M., Hetrick, W. P., Potkin, S., Bunney, W. E., et al. (2000). Effects of temporal variability on P50 and the gating ratio in schizophrenia. *Archives of General Psychiatry, 57,* 57–64.

Paxinos, G., & Watson, C. (1998). *The rat brain in stereotaxic coordinates* (4th ed.). San Diego, CA: Academic Press.

Pezze, M. A., & Feldon, J. (2004). Mesolimbic dopaminergic pathways in fear conditioning. *Progress in Neurobiology, 74,* 301–320.

Quirk, G. J., & Beer, J. S. (2006). Prefrontal involvement in the regulation of emotion: Convergence of rat and human studies. *Current Opinion in Neurobiology, 16,* 723–727.

Quirk, G. J., Garcia, R., & Gonzalez-Lima, F. (2006). Prefrontal mechanisms in extinction of conditioned fear. *Biological Psychiatry, 60,* 337–343.

Quirk, G. J., & Mueller, D. (2008). Neural mechanisms of extinction learning and retrieval. *Neuropsychopharmacology, 33,* 56–72.

Rossi, S., Bartalini, S., Ulivelli, M., Mantovani, A., Di Muro, A., Goracci, A., et al. (2005). Hypofunctioning of sensory gating mechanisms in patients with obsessive-compulsive disorder. *Biological Psychiatry, 57,* 16–20.

Seamans, J. K., & Yang, C. R. (2004). The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Progress in Neurobiology, 74,* 1–58.

Siegel, S. J., Connolly, P., Liang, Y., Lenox, R. H., Gur, R. E., Bilker, W. B., et al. (2003). Effects of strain, novelty, and NMDA blockade on auditory-evoked potentials in mice. *Neuropsychopharmacology, 28,* 675–682.

Skinner, R. D., Rasco, L. M., Fitzgerald, J., Karson, C. N., Matthew, M., Williams, D. K., et al. (1999). Reduced sensory gating of the P1 potential in rape victims and combat veterans with posttraumatic stress disorder. *Depression and Anxiety, 9,* 122–130.

Smith, D. A., Boutros, N. N., & Schwarzkopf, S. B. (1994). Reliability of P50 auditory event-related potential indices of sensory gating. *Psychophysiology, 31,* 495–502.

Stevens, K. E., Fuller, L. L., & Rose, G. M. (1991). Dopaminergic and noradrenergic modulation of amphetamine-induced changes in auditory gating. *Brain Research, 555,* 91–98.

Suer, C., Dolu, N., & Ozesmi, C. (2004). The effect of immobilization stress on sensory gating in mice. *International Journal of Neuroscience, 114,* 55–65.

Tregellas, J. R., Davalos, D. B., Rojas, D. C., Waldo, M. C., Gibson, L., Wylie, K., et al. (2007). Increased hemodynamic response in the hippocampus, thalamus and prefrontal cortex during abnormal sensory gating in schizophrenia. *Schizophrenia Research, 92,* 262–272.

Umbricht, D., Vyssotky, D., Latanov, A., Nitsch, R., Brambilla, R., D'Adamo, P., et al. (2004). Midlatency auditory event-related potentials in mice: Comparison to midlatency auditory ERPs in humans. *Brain Research, 1019,* 189–200.

Vertes, R. P. (2006). Interactions among the medial prefrontal cortex, hippocampus and midline thalamus in emotional and cognitive processing in the rat. *Neuroscience, 142,* 1–20.

Vidal-Gonzalez, I., Vidal-Gonzalez, B., Rauch, S. L., & Quirk, G. J. (2006). Microstimulation reveals opposing influences of prelimbic and infralimbic cortex on the expression of conditioned fear. *Learning & Memory, 13,* 728–733.

Weisser, R., Weisbrod, M., Roehrig, M., Rupp, A., Schroeder, J., & Scherg, M. (2001). Is frontal lobe involved in the generation of auditory evoked P50? *NeuroReport, 12,* 3303–3307.

White, P. M., Kanazawa, A., & Yee, C. M. (2005). Gender and suppression of mid-latency ERP components during stress. *Psychophysiology, 42,* 720–725.

White, P. M., & Yee, C. M. (1997). Effects of attentional and stressor manipulations on the P50 gating response. *Psychophysiology, 34,* 703–711.

Williams, G. V., & Castner, S. A. (2006). Under the curve: Critical issues for elucidating D1 receptor function in working memory. *Neuroscience, 139,* 263–276.

Wood, S. J., Pantelis, C., Velakoulis, D., Yucel, M., Fornito, A., & McGorry, P. D. (2008). Progressive changes in the development toward schizophrenia: Studies in subjects at increased symptomatic risk. *Schizophrenia Bulletin, 34,* 322–329.

Yee, C. M., & White, P. M. (2001). Experimental modification of P50 suppression. *Psychophysiology, 38,* 531–539.

Received April 15, 2008
Revision received August 11, 2008
Accepted September 24, 2008 ■