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AUDITORY INHIBITORY GATING IN MEDIAL PREFRONTAL CORTEX: SINGLE UNIT AND LOCAL FIELD POTENTIAL ANALYSIS

R. P. MEARS, A. C. KLEIN AND H. C. CROMWELL*

Department of Psychology and the J.P. Scott Center for Neuroscience, Mind and Behavior, Psychology Building, Bowling Green State University, Bowling Green, OH 43403, USA

Abstract—Medial prefrontal cortex is a crucial region involved in inhibitory processes. Damage to the medial prefrontal cortex can lead to loss of normal inhibitory control over motor, sensory, emotional and cognitive functions. The goal of the present study was to examine the basic properties of inhibitory gating in this brain region in rats. Inhibitory gating has recently been proposed as a neurophysiological assay for sensory filters in higher brain regions that potentially enable or disable information throughput. This perspective has important clinical relevance due to the findings that gating is dramatically impaired in individuals with emotional and cognitive impairments (i.e. schizophrenia). We used the standard inhibitory gating two-tone paradigm with a 500 ms interval between tones and a 10 s interval between tone pairs. We recorded both single unit and local field potentials from chronic microwire arrays implanted in the medial prefrontal cortex. We investigated short-term (within session) and long-term (between session) variability of auditory gating and additionally examined how altering the interval between the tones influenced the potency of the inhibition. The local field potentials displayed greater variability with a reduction in the amplitudes of the tone responses over both the short and long-term time windows. The decrease across sessions was most intense for the second tone response (test tone) leading to a more robust gating (lower T/C ratio). Surprisingly, single unit responses of different varieties retained similar levels of auditory responsiveness and inhibition in both the short and long-term analysis. Neural inhibition decreased monotonically related to the increase in intertone interval. This change in gating was most consistent in the local field potentials. Subsets of single unit responses did not show the lack of inhibition even for the longer intertone intervals tested (4 s interval). These findings support the idea that the medial prefrontal cortex is an important site where early inhibitory functions reside and potentially mediate psychological processes.

Key words: evoked potential, sensory gating, prelimbic, electrophysiology, variability, schizophrenia.

Neural inhibition and prefrontal cortex (PFC) have been linked in numerous studies examining diverse groups from patient populations to a variety of mammalian animal models (Swerdlow et el., 2005; Egner and Hirsch, 2005; Shoemaker et al., 2005; Likhtik et al., 2005; Knight et al., 1999). Evidence that the PFC is important for neural inhibition is very well supported yet the functional significance of the intrinsic or extrinsic PFC inhibitory control remains mostly unknown. Relevant work on the functional role has investigated patients or animals with PFC damage and found that this region is important for short-term attention to external stimuli (Carli et al., 2006; Bailey and Mair, 2004; Knight et al., 1995). In human patients with focal lesions to the PFC or animals with experimental PFC damage inhibitory control of sensory processing is significantly impaired (Knight et al., 1989; Yamaguchi and Knight, 1990, 1991; Rosenkranz and Grace, 2001). These same populations have severe problems in attending to relevant versus irrelevant stimuli (Woods and Knight, 1986; Christakou et al., 2001). PFC dysfunction leads to defective identification of novel stimuli (Knight, 1984) and causes a loss of inhibitory control over internal processes involved in integrating cognition and emotion (Rule et al., 2002; Phan et al., 2005; Maren and Quirk, 2004; Runyan et al., 2004). Additionally, PFC damage can lead to a dramatic loss of behavioral inhibition that initiates a syndrome of impulsive behavior and maladaptive choice behavior (Carli et al., 2006; Chudasama et al., 2005).

Alterations to PFC function are thought to play a role in the etiology of schizophrenia (Cannon et al., 2005; Selemon, 2001; Weinberger et al., 2001). Schizophrenic patients similar to the patients with focal damage to the PFC have problems with attention and stimulus discrimination (Elliot et al., 1995; Pantelis et al., 1997, 1999). Moreover, a common symptom that schizophrenics express has been termed “sensory flooding” with a loss of input filtering that would normally “gate” incoming input from the various sensation sources (Venables, 1964, 1969). Other psychological disorders such as obsessive compulsive disorder, post-traumatic stress disorder and drug addiction have sensory filtering problems that could be described as “sensory flooding”(Rossi et al., 2005; Ghisolfi et al., 2004; Adler et al., 2001) and may all involve PFC dysregulation (Richert et al., 2006; van den Heuvel et al., 2005; Self, 1998). Each of these disorders has been examined using one particular index of inhibition, labeled P50 (positive wave at 50 ms) suppression or sensory inhibitory gating (IG). Several clinical groups are now using the paradigm as a way to gauge symptom progression and potentially diagnose certain psychological impairments (Louchart-de la Chapelle et al., 2005; Freedman et al., 1996).

*Corresponding author. Tel: +1-419-372-9408; fax: +1-419-372-6013.
E-mail address: hcc@bgsu.edu (H. C. Cromwell).

Abbreviations: A/D, analog-to-digital; cAmp, amplitude of response to C_{tone}; CTI, condition-test interval; C_{tone}, conditioning tone; ELD, excitatory long-duration; EP, evoked potential; ESD, excitatory short-duration; IG, inhibitory gating; Inh, inhibitory response; LFP, local field potential; mPFC, medial prefrontal cortex; PFC, prefrontal cortex; PPT, pedunculopontine nucleus; P50, positive wave at 50 ms; tAmp, amplitude of response to T_{tone}; T_{tone}, test tone; VTA, ventral tegmental area.

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Sensory IG is partially similar to other gating paradigms and differs in that it is not necessarily linked to a particular reflexive behavioral response. In this way, IG can be more of a pure index of sensory input gating rather than necessarily sensorimotor gating (Swerdlow et al., 2005). To measure IG in the clinical setting, the subject is placed in a quiet room and presented with pairs of sensory stimuli. In almost all the previous work, auditory stimuli have been used and the tone pairs are presented with a 500 ms intertone interval and a 10 s interval between tone pairs (Adler et al., 1998). Subjects are asked to relax but not to sleep and listen to the tones while evoked potentials (EPs) are recorded from the scalp. In normal subjects, a sharp reduction in the response to the second tone of the pair is observed (Waldo and Freedman, 1986). The second tone is labeled the test tone (T_{tone}) because it tests the integrity of the inhibitory network. The initial tone has been labeled the conditioning tone (C_{tone}) (see Freedman et al., 1996). In schizophrenic, PTSD, OCD patients and drug addicts the inhibition is reduced so that the responses appear much more similar in amplitude throughout the session period (Freedman et al., 1987; Adler et al., 2001; Rossi et al., 2005; Ghisolfi et al., 2004).

Using EPs to auditory stimuli, IG has been found in numerous locations throughout the CNS including brainstem, septum, hippocampus (Adler et al., 1986; Moxon et al., 1999; De Bruin et al., 2001) as well as primary auditory cortex (Moxon et al., 1999). EP recording has been the primary tool used to measure IG in both patients (Adler et al., 1982; Freedman et al., 1994; Boutros et al., 2004) and normal human and animal subjects (Boutros et al., 1995, 1997; Kisley et al., 2004). This technique pools information from a large number of neural elements. The P50 or positive wave at 50 ms following the stimulus has been the focal point of most investigations (Patterson et al., 2000; Olincey et al., 2000). Other potentials, including mid-latency potentials, have been shown to gate as well but not as robustly under certain conditions (Grunewald et al., 2003; Boutros and Belger, 1999).

Gating has been measured by single-unit tone responses in different brain regions such as the hippocampus (Bickford-Wimer et al., 1990; Miller and Freedman, 1995; Moxon et al., 1999), amygdala (Cromwell et al., 2005), and reticular nucleus of the thalamus (Krause et al., 2003). Interestingly, IG is weak to non-existent in a major relay in the lemniscal auditory pathway, the medial geniculate nucleus of the thalamus (Bickford-Wimer et al., 1990). The single unit analysis has provided a unique window into the basic properties of IG. For instance, IG is observed to different types of tone responses in the amygdala (Cromwell et al., 2005). These types of analyses of the precise details of IG suggest that it can be a pervasive and consistent mechanism in certain brain structures. These basic properties of IG using local brain region recording in freely moving animals have not been investigated in the PFC, a region thought to be crucial to IG.

Our primary goal with this research was to describe and examine the parametric qualities of IG in the medial prefrontal cortex (mPFC) using chronic recording wires to monitor both single unit and local field potential (LFP) responses simultaneously. By demonstrating and characterizing mPFC single-units, it was possible to establish IG as an inherent property of distinct subregions of the PFC. Another goal was to ascertain that IG was relatively stable over the course of multiple recording sessions and within the segments of a single recording session for LFPs and single-units. We hypothesized that both levels of neural activity would show a high degree of stability due to the fact that these tones were irrelevant and highly predictable. A final goal was to test IG for both LFPs and single-units at different intervals of separation between first and second tones in order to determine that an interval of optimal IG exists. We hypothesized that as the intervals increased, the strength of gating would decrease. These changes should be graded between the different delays and similar between the single unit and LFP level of activity within the mPFC.

EXPERIMENTAL PROCEDURES

Chronic microelectrode implantation

Animals were anesthetized with xylazine (10 mg/kg) and ketamine (100 mg/kg), and surgery was conducted according to procedures as described in protocols approved by nationally approved guidelines for the care and use of animals (USDA and PHS). All procedures were approved by the Bowling Green State University Animal Care and Use Committee. A stereotaxic apparatus was used for the implantation of recording microwires (NB Laboratories, Denison, TX, USA) into mPFC (A +2.7, M ±0.7, D −3.0) according to the standard rat stereotaxic atlas (Paxinos and Watson, 1998). Anchor screws were affixed to the skull surface to be used in the protective headstage. Rats were bilaterally implanted in mPFC with 16 microwires in two bundles of eight (one bundle in each hemisphere). Grounding wires were implanted bilaterally near bregma, but 3 mm lateral and 2–3 mm below dura. The recording electrodes were cemented into permanent placement using dental acrylic. After surgery, rats were allowed one week to recover before the beginning of testing.

Experimental apparatus

The testing chamber (20×28×35 cm) was located in a small sound attenuating room. The chamber floor had parallel rods that suspended the rat 5 cm above a removable pan. Piezoelectric tone generators were attached to the top of the chamber, and holes were drilled to allow sound to pass into the chamber. A tone generator produced a distinctive tone pitch of 4.1 kHz. A potentiometer on the tone generator was manually adjusted in order to produce brief tones that were 75 dB in intensity (i.e. measured from a height of 15 cm at two or more points above the chamber floor bars). The tone generator was controlled using Med-PC IV software (Med Associates, Inc., St. Albans, VT, USA) on a computer outside the room.

Gating protocols

In four separate sessions, two different IG protocols were used. In each session, the stimuli were presented in blocks of identical tone pairs. The protocols were used to examine the stability of gating and the effects of stimulus timing.

Protocol 1: paired-stimulus tests

The stability of gating was investigated by recording for three consecutive sessions. Prior to the first exposure to the paired

stimulus paradigm, rats were habituated to handling and to the experimental chamber. At the beginning of each recording session, the rat's headstage was connected to the preamplifier, and 60 s passed before the beginning of the session in order to allow the rat to acclimate to the chamber. After this, 100–360 stimulus pairs were presented to the rats. Stimuli consisted of 4.1 kHz tones (10 ms, 75 decibels) presented at a condition-test interval (CTI) of 500 ms. There was a 10 s interval between pairs of stimuli. On the first-day of recording, 360 stimulus pairs were presented to a subgroup of animals. For later analysis, the first session would be divided into three segments of 120 stimulus pairs for a within session analysis of LFPs and single-units. For a between session analysis of all animals, the first 100 trials would be analyzed from three consecutive sessions for LFPs and single-units.

Protocol 2: CTI tests

In a fourth session, pairs of tones were presented at different CTIs in order to study the effects of stimulus timing on gating-out. Four different CTIs (150 ms, 500 ms, 1 s, 4 s) were presented. Pairs of identical stimuli were presented throughout the session, but CTIs were varied in blocks of 100 trials. The order of the different CTI blocks was counterbalanced across animals.

Electrophysiological apparatus

Electrical activity received by each of the 16 recording electrodes in the mPFC was passed through op-amps (1×) that were located where the cable attached to electrode wires in the protective headstage. The signal was then passed along an electrically shielded cable, to the rotational commutator. The signals were then further amplified (100×) before being sent to the data acquisition system. The amplified signal was then split to two different analog-to-digital (A/D) data acquisition cards. For the single-unit signal, high frequencies were sent through bandpass filters (0.15 kHz–9 kHz) before being passed to the single-units A/D card (Plexon Inc., Dallas, TX, USA). For the field potential signal, low frequencies were sent through bandpass filters (3 Hz–90 Hz) before being passed to the field potential A/D card (National Instruments, Austin, TX, USA).

Data acquisition

Single-units and LFPs were received using a computer with data acquisition software (MAP System, Plexon Inc.). Signals from both the single-units and field potential A/D cards were received on the acquisition computer. Single-units spikes were detected off line in MAP and transported to the Neuroexplorer program (NEX, System, Plexon Inc.). Field potentials were imported to Matlab (The Mathworks, Nantic, MA, USA) for online averaging and monitoring of LFP responses to tones. Using the MAP Sort Client application it was possible to independently adjust the gain for individual channels on both the field potential and single-units A/D cards. For single-units it was possible to adjust the electrode grounding references and waveform voltage thresholding for each channel. Individual single-units were discriminated according to a variety of methods including thresholding windows, waveform templates, and independent components clustering. Additional MAP software applications that were used for online, real-time monitoring of data acquisition included: Sort Client, PeriEvent Client (PEC), Graphical Activity Client (GAC), and an Event-triggered Field Potential GUI. Using the available array of techniques it was possible to discriminate up to four single-units on each channel. Single-units spikes were detected on-line in MAP and transported to the Neuroexplorer software application (NEX, System, Plexon Inc.) for further real-time analyses including: rate-histograms, autocorrelograms, interspike intervals, perievent rasters, and perievent histograms. Two single-units were discriminated from a single electrode using the principal components sorting algorithm. Off-line fine-tuning and even re-sorting, when necessary, of single-units discrimination was possible using an off-line sorter application. Further off-line analyses were possible using the Neuroexplorer software application. Field potentials were imported to Matlab (The Mathworks) for off-line averaging of LFP responses to tones.

LFPs: data analysis

Within each session, extracellular field potentials corresponding to trials of stimulus pairs were aggregated according to the onset for each stimulus, and EP were generated through waveform averaging. EPs were analyzed after waveform peaks were quantified through amplitude measurements for certain negative peaks and positive peaks in the average waveform. The peaks were identified according to the local maxima (or minima) in predefined time windows, and the peaks were measured according to the peak's amplitude difference from the baseline amplitude at the time of stimulus onset. With sliding-window *t*-tests, LFP peaks were compared with activity during a 1 s control period that was three seconds before each C_{tone}. Only LFP peaks that differed from the control period at the 0.01 level of significance were used for further analysis, and the responses that differed significantly from the control period were designated as cAmp or tAmp, respectively, for the amplitude of response to C_{tone} or T_{tone}. T/C ratios of tAmp divided by cAmp served as a crucial comparison for field potential gating. Repeated-measures ANOVAs were used to assess differences in the latencies of LFP responses to C_{tone} or T_{tone}, cAmp, tAmp, and T/C ratio for *within* and *between sessions* analyses.

Additionally, the responses of single-units to C_{tone} and T_{tone} were compared with the responses of LFPs. For single-units that were found to have tone responses, relationships between the single-units and the LFPs were examined for LFPs from the same channel as the responding single-unit. Single-units were grouped into classes based on the pattern of response to the C_{tone}. To compare single-units and LFPs regression analysis was performed within each class and each LFP. Finally, the T/C ratios for each single-unit were compared with the T/C ratios for the LFP recorded from the same channel as the single-unit. This comparison of single-unit and LFP ratios gave us a good measure of the degree of correspondence between these two types of neuronal activity.

Single-units: data analysis

On each recording electrode, single-units were recorded and sorted using waveform amplitude thresholding and clustering. A variety of clustering procedures, both during recording and after, was used to sort waveforms including a principal components analysis of the amplitude, shape, and duration of spike waveforms. Single-units were further examined using autocorrelograms and interspike intervals. In order to be considered for analysis, units from a given wire were required to exhibit an absence of firing for the 1–5 ms refractory period surrounding the reference spike in interspike intervals. Single-units with the same interspike interval distributions and with closely similar waveform shape and duration were identified across sessions using WaveTracker or Matlab. Peri-event time histograms and raster plots of single-unit firing were generated centering on the times of stimulus onset. Data were analyzed using several custom-made analyses in Matlab. These analyses included several sliding-window significance tests for bins (i.e. time windows) of 5–25 ms in width. The bin width depended on the baseline firing rate of the single-unit. The 25 ms bin was used for single-units with low firing rates of 1 Hz or less. The 5 ms bin was used for neurons with high firing rates of 40 Hz or more. The 10 ms bin was used for all the other single-units with moderate firing rates. For the majority, however, 25 ms bins were used for single-units.

Table 1. Between-sessions neuronal database for three types of single-unit response to paired-stimuli

	Session 1			Session 2			Session 3		
	ESD	ELD	Inh	ESD	ELD	Inh	ESD	ELD	Inh
Significant responses	12	6	15	12	6	15	12	6	15
C-response (ms)	65±23	64±20	42±7	28±6	82±26	91±15	38±11	67±18	72±15
T-response (ms)	56±16	97±32	81±21	37±9	102±40	78±13	80±27	95±34	78±15
Baseline firing rate (Hz)	3.3±1.1	5.8±2.9	1.6±0.5	3.4±1.2	5.8±3.6	1.8±0.6	2.8±1.0	7.8±3.4	1.4±0.4
cAmp (% baseline)	992±324	1071±616	−40±41	590±123	562±212	−90±9	811±260	620±270	−109±8
tAmp (% baseline)	361±91	449±202	−25±25	199±45	228±69	−45±8	316±154	193±86	−61±8
T/C ratio	0.53±0.09	0.71±0.11	0.50±0.09	0.35±0.05	0.53±0.09	0.48±0.09	0.54±0.14	0.59±0.16	0.57±0.07

In the analysis of baseline activity (Table 1) we used *t*-tests to compare activity from a 3 s control window in order to test the amount of single-unit activity activated or suppressed by each stimulus. The control period was taken from baseline activity beginning 3.5 s and ending 0.5 s before the onset of the C_{tone}. The single-unit activity in the bins 300 ms before C_{tone}, 300 ms after C_{tone}, and 300 ms after T_{tone} was compared with the control period using sliding-window *t*-tests. This analysis indicated activity in response to tone stimuli that was significantly increased or decreased from the baseline level. Only single-units with activations that differed from the control window at the 0.05 level of significance were used for further analysis. For significant differences, the maximum or minimum difference from baseline firing rate within each block was used to represent activation or suppression in firing rate. Similar to the designations used for LFPs, the responses that differed significantly from the control period were cAmp or tAmp, respectively, for the magnitude of response to C_{tone} or T_{tone}. For each tone-responsive unit, T/C ratios were generated for each session, and ratios were compared between sessions. A repeated-measures ANOVA was used to compare the latencies of peak responses to C_{tone} or $T_{tone,}$ C_{tone} activation or suppression, T_{tone} activation or suppression, and T/C ratios across sessions. A repeated-measures ANOVA was also conducted to compare the latencies of peak responses to C_{tone} or $T_{tone,}$ C_{tone} activation or suppression, T_{tone} activation or suppression, and T/C ratios within-session for the three segments corresponding to the 1st, 2nd, and 3rd segments of the session. For both analyses post hoc *t*-tests were completed for pairwise comparisons.

Additionally, the responses of single-units to C_{tone} and T_{tone} were compared with the responses of LFPs. For single-units that were found to have tone responses, relationships between the single-units and the LFPs were examined for LFPs from the same channel as the responding single-unit. Single-units were grouped into classes based on the pattern of response to the C_{tone}. Finally, the T/C ratios for each single-unit were compared with the T/C ratios for the LFP recorded from the same channel as the single-unit. This comparison of single-unit and LFP ratios gave us a good measure of the degree of correspondence between these two types of neuronal activity.

Electrode mapping

After the completion of the last session of the study rats were anesthetized with pentobarbital (100 mg/kg, i.p.) and then perfused with 0.9% saline solution followed by a 10% solution of phosphate buffered formalin. Just prior to perfusion, 10 mA of current was passed for 15 s through every other microwire of each bundle of recording electrodes to mark their placement. After perfusion the brains were removed and stored in the perfusion solution for one week. The brains were then transferred to a 30% sucrose/10% formalin solution for one day. The brains were then sliced into 40 μm coronal sections on a freezing microtome. The relevant sections were mounted on glass slides and stained with Cresyl Violet. The sections were scanned under digitizing microscope and analyzed to determine the position of each electrode in the mPFC. Electrode placements were identified using a rat atlas.

RESULTS

LFP database

A neuronal database was created for LFP responses. Across the entire set of recording wires, only one positive-going peak was consistently measured to satisfy criteria for significance. This potential, P60, was initially recorded with a 60 ms latency following the onset of tone stimuli (Fig. 1). As indicated in the Experimental Procedures section, LFP responses tone stimuli from each wire were required to be significantly ($P<0.01$) different in amplitude compared with a 1 s control window that was three seconds before the onset of each trial. On some wires, other potentials were occasionally found to meet criteria for a significance, but the amplitude of these peaks varied greatly from wire to wire. Due to issues of reliability only the P60 was included for further analysis.

Single-unit database

A neuronal database was created for single-units that were simultaneously recorded from the same electrodes used to record LFPs. Of single-units recorded in mPFC, 77/145 (53%) met the criterion for significant activation above the baseline levels on at least one of the first three recording sessions. Of the single-units with significant activations, 33/77 had activations on all three consecutive recording sessions. These single-units were grouped according to three classes of tone response (Cromwell et al., 2005). Single-units that were found to have a tone-related increase in firing rate that lasted less than 50 ms were classified as excitatory short-duration (ESD) units (Fig. 2A). Single-units with a tone related increase in firing rate lasting more than 50 ms were classified as excitatory long-duration (ELD) units (Fig. 2B). A third category of single-units responded to tones with a decrease in firing rate, and these single-units were classified as inhibitory response (Inh) single-units (Fig. 2C). The properties of the three classes of single-units are included in Table 1.

There were a variety of latencies for single-unit tone stimulus responses in mPFC. ESD units tended to have earlier latencies, with an average latency as early as 28 ms

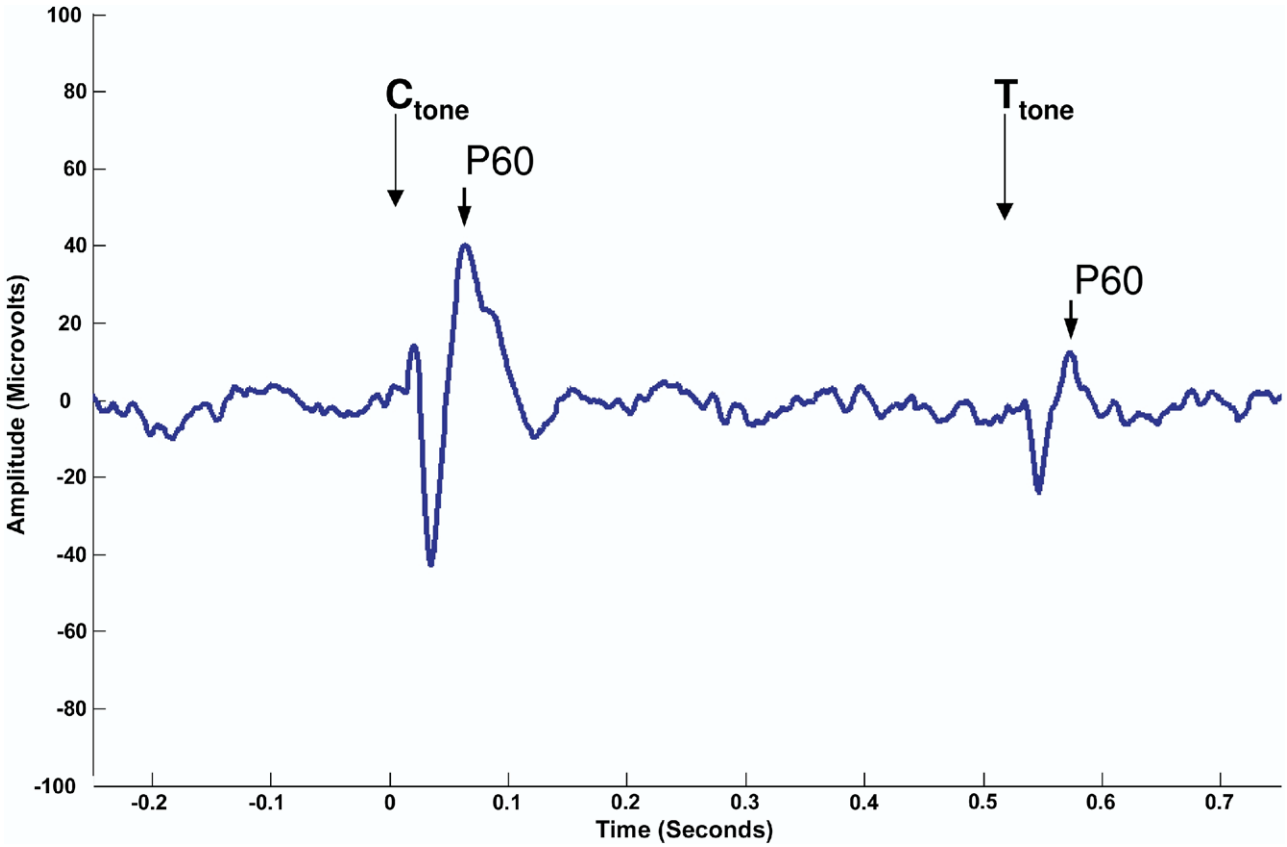

Fig. 1. An example of a LFP recorded from a single microwire yields waveforms for both tones in a block of trials (n=360). A P60 potential occurred as a positive going peak 60 ms after the first tone (C_{tone}) at 0 s. Another P60 occurred at 60 ms after the second tone (T_{tone}) at 0.5 s. Gating of the second tone is apparent in the diminished amplitude of P60 when compared with P60 following the first tone.

in one session (Table 1). A subset of these neurons had latencies as early as 15–20 ms (Fig. 3). Other single-units, ELD and Inh responded with longer latencies.

Electrode mapping revealed fairly restricted placement of the electrode arrays. A majority of electrodes were placed in prelimbic mPFC (Fig. 4). The range of placements spanned all cortical layers in mPFC. In the anteroposterior plane, recording electrodes ranged between +1.6 to +3.2 mm anterior to bregma, but the majority of electrodes were placed between +2.2 and +2.7 mm anterior to bregma.

Analysis of variability: LFPs

Between session variability. Field potentials from the majority of the single wires were retained over the three day period in which testing took place. A one-way ANOVA was completed on the neural data acquired between sessions with session number (1st, 2nd or 3rd) as the repeated measures factor. Separate ANOVAs were completed for the P60 latencies, cAmp, tAmp and T/C ratio. For latencies of P60 to C_{tone} in sessions 1, 2 and, 3 there was a significant effect ($F(2,246)=21.40$, $P<0.001$). Post hoc *t*-tests showed that the average latency of P60 following C_{tone} in session two was significantly shorter than in sessions 1 and 3 (sess 1 M=64.48 ms±0.64, sess 2 M=59.78 ms±0.37, sess 3 M=62.91 ms±0.80, $P<0.001$). For P60 latencies after T_{tone} in sessions 1, 2 and, 3 there was a significant effect ($F(2,246)=25.21$, $P<0.001$). Post hoc *t*-tests showed that the average the P60 T_{tone} latency in session 1 was significantly longer than in sessions 2 and 3 (session 1 M=65.56 ms±0.80, session 2 M=61.02 ms±0.55, session 3 M=60.16 ms±0.66, $P<0.001$). A main effect was found for the cAmp data ($F(2,246)=3.54$, $P<0.05$). We conducted post hoc *t*-tests to find a significant difference between sessions 1 and 3 (sess 1 mean=112.50±9.07 S.E.M. versus 100.05±6.65, $P<0.01$). This finding reflects a decrease in the amplitude of the first tone response over the three sessions (Figs. 5 and 6). Similar results were obtained for the tAmp (session main effect, $F(2, 246)=16.88$, $P<0.01$) with post hoc *t*-tests showing a decline in the amplitude from session 1 to session 3 (sess 1 mean=72.52±6.46, sess 2 mean=62.15±4.16 and sess 3 mean=55.88±4.68, $P<0.01$; see Figs. 5 and 6). Finally, the overall ANOVA on the T/C ratios revealed a main effect for sessions ($F(2,246)=32.78$, $P<0.001$). Post hoc *t*-tests between the sessions determined that the ratio significantly decreased from session 1 to sessions 2 and 3 (sess 1 M=0.63±0.01 vs. sess 2 0.55±0.01 and sess 3 M=0.53±0.01, $P<0.001$; see Figs. 5 and 6). Overall, the three measures decreased across the three day testing period. The decrease in the T/C ratio reflects a greater difference between the first and second tone response poten-

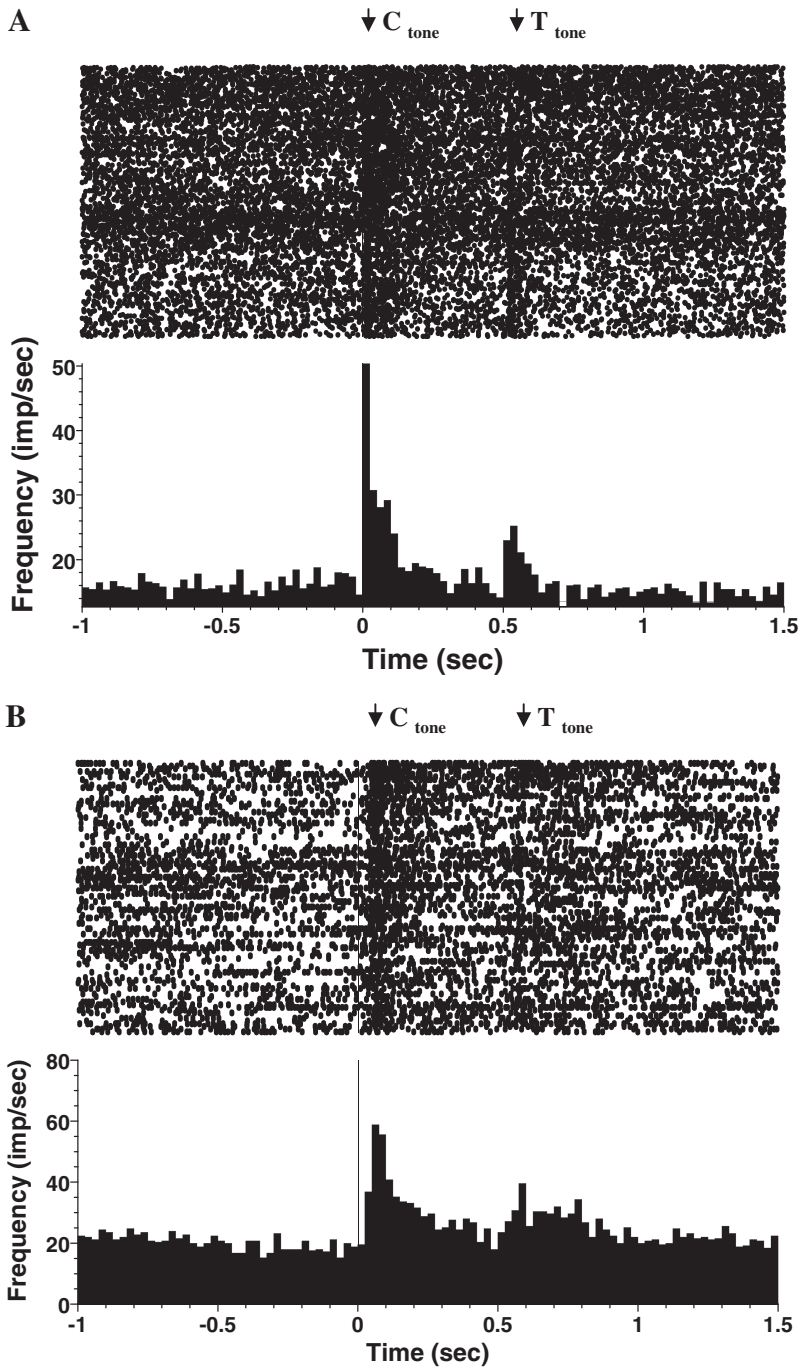

Fig. 2. Single-units that responded significantly to tone stimuli revealed three major classes of tone response. As indicated by raster plots in the top half of each figure, activity to the first tone (C_{tone}) was stronger than activity to the second tone (T_{tone}). (A) ESD single-units responded to tone stimuli with a brief increase in impulses per second above background firing rate. (B) ELD single-units often had a sustained response lasting hundreds of milliseconds. (C) Inh single-units decreased their firing rate below baseline in response to tone stimuli. Bin sizes are 50 ms.

tials from session 1 to session 3. The decrease in T/C ratio for the later sessions was due to a proportionally larger decrease in tAmp compared with the decrease in cAmp.

Within session variability. In order to determine how consistent IG is within a single session, LFP cAmp, tAmp, and T/C ratios were analyzed according to three different time segments during the initial gating session. We conducted a repeated-measures ANOVA for C_{tone} latencies of P60 in segments 1, 2 and, 3, and there was a significant effect ($F(2,306)=89.24$, $P<0.001$). Post hoc *t*-tests showed that the average latency of P60 following C_{tone} in segment 1 was significantly shorter than in segments 2 and 3 (segment 1 M=63.20 ms±0.55, segment 2 M=77.24 ms± 1.22, segment 3 M=79.26 ms±1.25, $P<0.001$). For P60

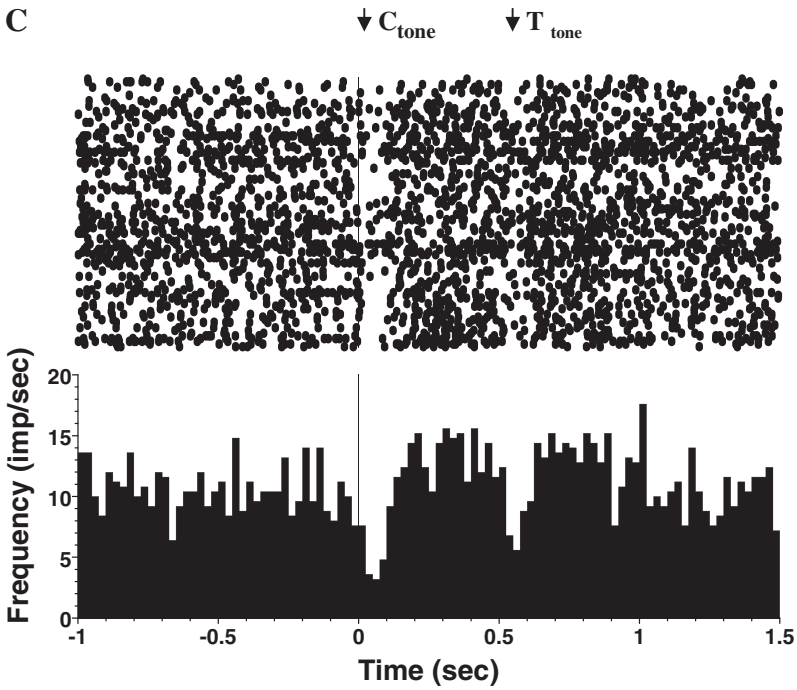

Fig. 2. (*Continued*).

latencies after T_{tone} in segments 1, 2 and, 3 there was a significant effect ($F(2,306)=96.28$, $P<0.001$). Post hoc *t*-tests showed that the average the P60 T_{tone} latency in segment 1 was significantly shorter than in segments 2 and 3 (segment 1 M=64.76 ms±0.82, segment 2 M=72.43 ms±0.95, segment 3 M=81.53 ms±1.27, $P<0.001$). P60 T_{tone} latency in segment 2 was significantly shorter than in segment 3 ($P<0.001$). We conducted a repeated-measures ANOVA in which segments (segment 1: trials 1–180, segment 2: trials 181–270, and segment 3: trials 271–360) served as the repeated-measures factor. We conducted the ANOVA for cAmp and found a main effect for segment ($F(2,185)=27.19$, $P<0.001$). Post hoc *t*-tests revealed that cAmp for segment 1 (M=106.13±4.04) was significantly greater than cAmp for segment 2 (M=86.09±3.37, $P<0.001$) and segment 3 (M=90.30±3.20,

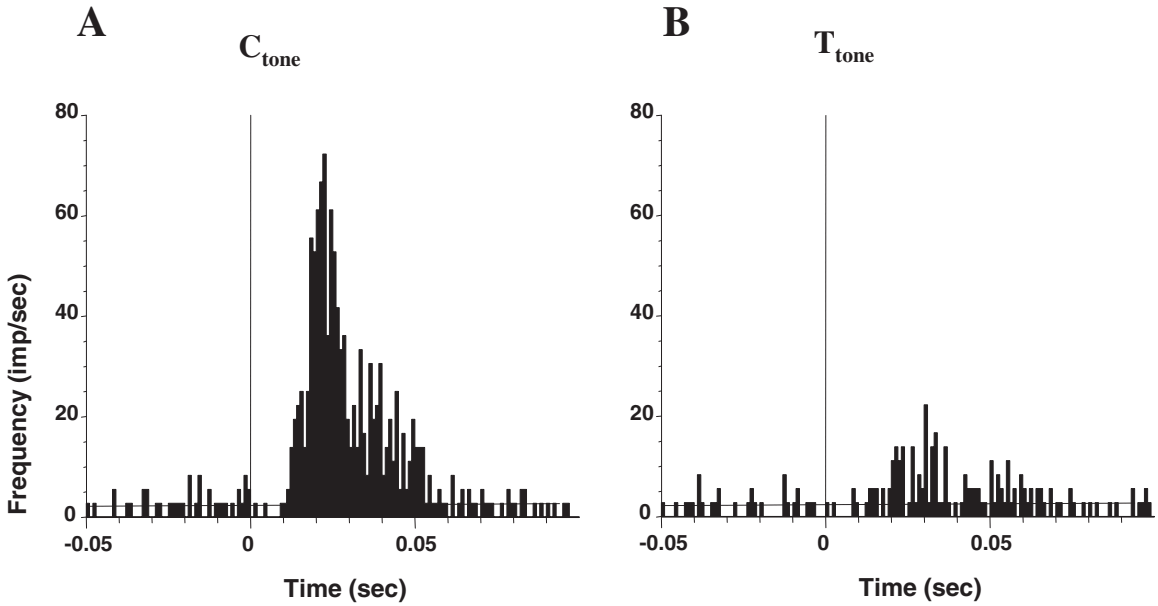

Fig. 3. The firing rate increase for one ESD single-unit reveals a very short latency of onset (13–17 ms) for an increase in firing rate following C_{tone}. This increase in firing rate is apparent for a single unit response to (A) C_{tone}, but the response following (B) T_{tone} is less clearly defined. Bin sizes are 0.5 ms.

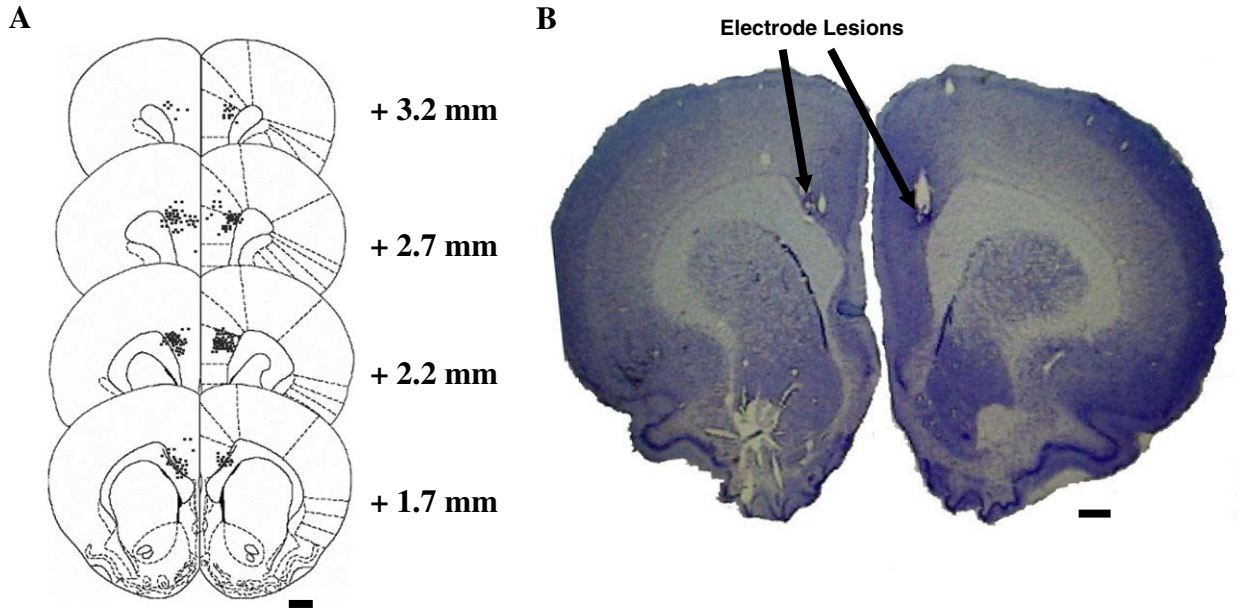

Fig. 4. Electrode mapping revealed that (A) a majority of electrodes were placed in prelimbic mPFC. Diagrams are adapted from Paxinos and Watson (1998). Most electrodes were placed between +2.7 mm and +2.2 mm anterior to bregma. A scale bar=1 mm. (B) electrode lesions are indicated for bilateral pairs of electrodes placed +2.2 mm anterior to bregma. A scale bar=1 mm.

$P<0.001$). In the ANOVA for tAmp we found a significant main effect for segments ($F(2,185)=23.01$, $P<0.001$). Post hoc *t*-tests demonstrated that tAmp for segment 1 (M=65.85±3.06) was significantly greater than tAmp for segment 2 (M=52.46±2.21, $P<0.001$) and segment 3 (M=59.31±2.26, $P<0.05$). Segment 2 tAmp was significantly less than segment 3 tAmp. In the ANOVA of T/C ratios we found a significant main effect for segments ($F(2,185)=10.45$, $P<0.001$). Post hoc *t*-tests showed that segment 1 T/C (M=0.59±0.01) was significantly less than segment 2 T/C (M=0.68±0.02, $P<0.001$) and segment 3 T/C (M=0.66±0.01, $P<0.001$). Overall, T/C ratios and amplitudes for conditioning and test were relatively consistent during the course of the extended trials session. There was an increase in T/C ratio in segments 2 and 3 compared with segment 1. In contrast, there was a slight decrease for both cAmp and tAmp in segments 2 and 3 compared with segment 1, but the increase in T/C ratio in segments 2 and 3 indicated that the decrease was proportionally greater for cAmp than for tAmp.

Analysis of variability: single units

Between session variability. We conducted repeated measures ANOVAs for all three neuron types, but no significant effects observed for session with latencies following C_{tone} and T_{tone}, cAmp, tAmp, or T/C ratios. This consistency across session days contrasted with the alterations in these measures seen for the LFPs. We present the data for each of the response types for each day in Table 1. In order to represent overall patterns of response for the three classes of single-units in the first three sessions, population averages were produced. Group mean histograms are shown in Fig. 7.

Within session variability. In order to understand the consistency of gating within a session, single-unit cAmp, tAmp, and gating ratios were analyzed according to three segments within a session. A subgroup of animals was tested in extended sessions lasting 360 trials. A repeated-measures ANOVA was conducted in which segments (segment 1: trials 1–180, segment 2: trials 181–270, and segment 3: trials 271–360) served as the repeated-measures factor. We conducted repeated-measures ANOVAs for all three neuron types, but no significant effects observed for session for latencies following C_{tone} and T_{tone}, cAmp, tAmp, or T/C ratios.

CTIs: LFPs

We analyzed P60 latencies, cAmp, tAmp, and T/C ratios from the four blocks of CTI in order to understand the influence of CTI on sensory gating (Fig. 8). We performed a repeated-measures ANOVA whereas the different blocks of CTIs (150 ms, 500 ms, 1 s, and 4 s) served as the repeated-measures factor. For C_{tone} latencies of P60 in the 150 ms, 500 ms, 1 s and 4 s CTI blocks there was a significant main effect ($F(3,540)=22.29$, $P<0.001$). Post hoc *t*-tests showed that P60 latency was shorter in the 150 ms block (M=71.21 ms±1.07) than in the 500 ms (M=79.25 ms±1.10, $P<0.001$), 1 s (M=76.87 ms±1.07, $P<0.01$), and 4 s (M=83.06 ms±1.10, $P<0.001$) blocks. P60 latency was longer in the 4 s block than in the 500 ms ($P<0.05$) and 1 s blocks ($P<0.001$). For P60 latencies after T_{tone} in the four CTI blocks there was a significant effect ($F(2,540)=40.31$, $P<0.001$). Post hoc *t*-tests showed that the average the P60 T_{tone} latency in the 150 ms block was significantly shorter than in the other blocks (150 ms M=65.11±0.91, 500 ms M=79.48 ms±1.25, 1 s

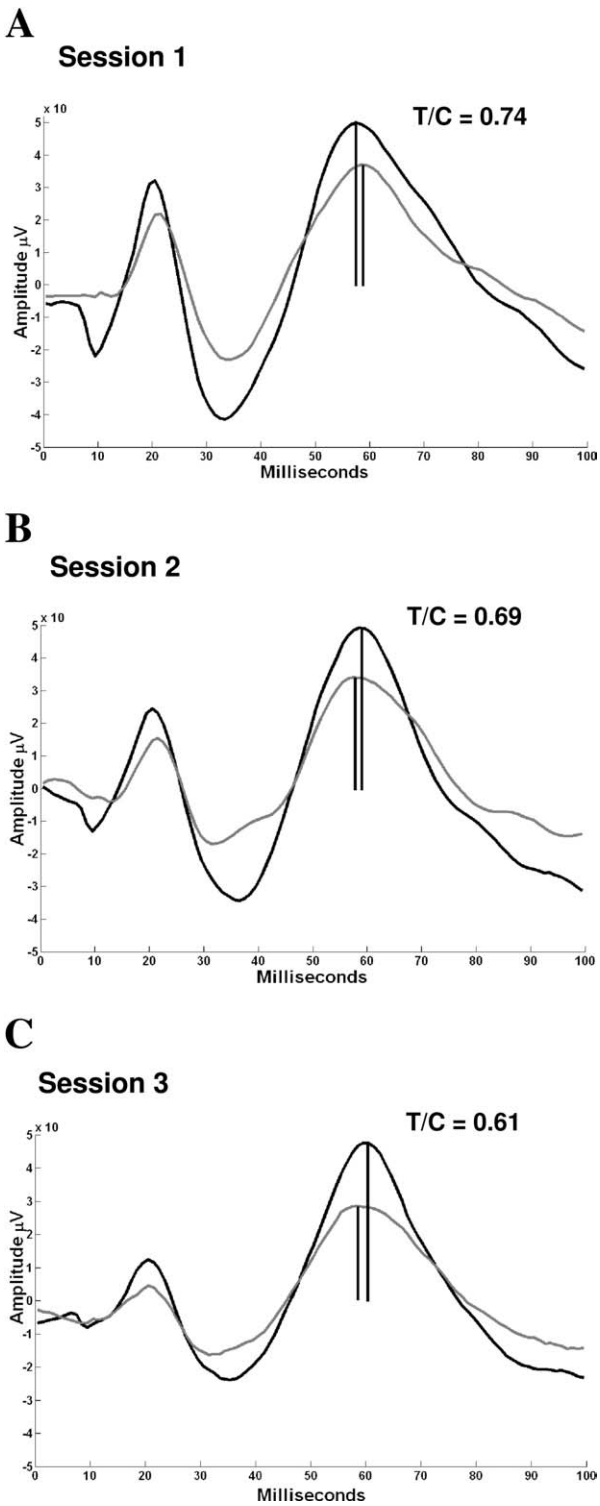

Fig. 5. LFP for C_{tone} (dark line) and T_{tone} (light line) are overlaid in order to compare relative amplitudes. (A) P60 for session 1 reveals a T/C ratio of 0.7 for indicating that tAmp is 74% of cAmp. T/C ratios for (B) session 2 and (C) session 3 indicate that gating of P60 is relatively stable, if not strengthening for following recording sessions.

M=75.16 ms±1.01, 4 s M=77.27 ms±0.93, $P<0.001$). P60 T_{tone} latency in segment 2 was significantly shorter than in segment 3 ($P<0.01$). For the cAmp ANOVA there was a significant main effect for CTI ($F(3,540)=7.1$, $P<0.001$). Post hoc analysis of cAmp showed that there was greater amplitude at the 150 ms CTI than the 1 s CTI ($P<0.01$), and the 4 s CTI ($P<0.01$). The ANOVA for tAmp revealed a significant main effect for CTI ($F(3,540)=252.0$, $P<0.001$). Post hoc analysis of tAmp illustrated a scheme of amplitude increase according to increasing length of CTI ($P<0.001$): 150 ms<500 ms<1 s<4 s. The ANOVA for T/C ratio revealed a significant main effect for CTI ($F(3,540)=428.6$. $P<0.001$). Similar to the post hoc analysis of tAmp, post hoc analysis of T/C ratios also illustrated a scheme of increase according to increasing length of CTI ($P<0.001$): 150 ms<500 ms<1 s<4 s (Fig. 8). LFPs demonstrated a category I change in IG with each increase in CTI. This means that each decrease in T/C ratio at different CTIs was primarily due to a proportionally greater increase in tAmp than in cAmp.

CTIs: single units

We compiled a neuronal database of all units that produced significant activations or suppressions in response to the C_{tone} in all four CTI blocks of tone pairs. A summary of these results is shown in Table 2. In order to represent overall patterns of response for the three classes of single-units in the first three sessions, population averages were produced. Group mean histograms are shown in Fig. 9.

For the ESD units there were six units that had significant activations for at least three of four CTI blocks. We conducted repeated-measures ANOVAs for latencies following C_{tone} and T_{tone} and for cAmp, and we found no significant results. For responses to tAmp, we found a significant main effect for CTI ($F(3,15)=4.78$, $P<0.05$). With post hoc *t*-tests we found that tAmp for the 1 s CTI (M=811±158, $P<0.05$) and the 4 s CTI (M=1557±403, $P<0.05$) were significantly greater than the tAmp for the 500 ms CTI (M=329±72). We conducted a repeated-measures ANOVA for T/C ratio, and we found a significant effect for CTI ($F(3,15)=15.21$, $P<0.01$). Post hoc *t*-tests showed that T/C ratios for the 4 s CTI (M=1.04±0.15, $P<0.001$) were significantly greater than T/C ratios for the 150 CTI (M=0.17±0.04, $P<0.01$), the 500 ms CTI (M=0.32±0.06, $P<0.01$), and the 1 s CTI (M=0.55±0.08, $P<0.05$). The T/C ratio for 1 s CTI was also greater than the T/C ratio for 150 ms CTI ($P<0.01$). Overall for ESD units, there was an increase in tAmp for the 1 s and 4 s CTI compared with the 500 ms CTI, and this increase in tAmp was responsible for the increase in T/C ratio at these CTIs.

For the ELD units there were seven units that had significant activations for at least three of four CTI blocks. We conducted repeated-measures ANOVAs for latencies following C_{tone} and T_{tone}, and for cAmp for the CTIs, but there were no significant results. We found that for tAmp there was a significant effect for CTI ($F(3,18)=5.11$, $P<0.05$). We conducted post hoc *t*-tests to find that tAmp for the 4 s CTI (M=464±110) was greater than tAmp ratio for the 500 ms CTI (M=248±70,

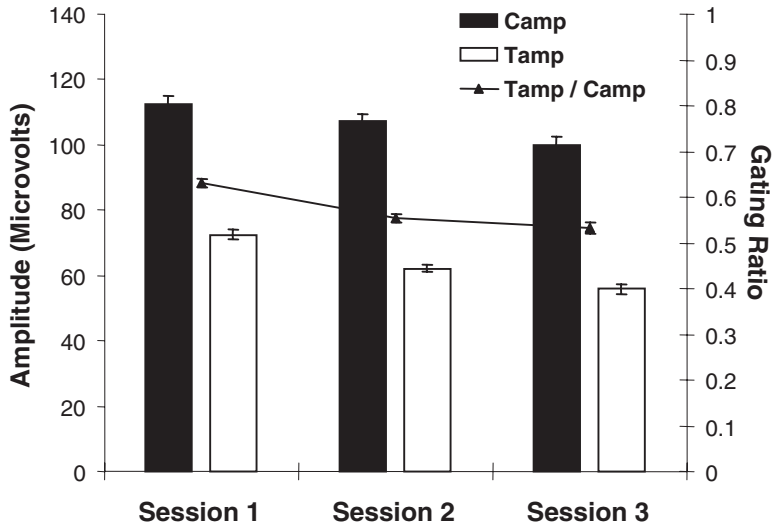

Fig. 6. Results of LFP for three sessions are indicated with amplitudes of response for cAmp and tAmp (microvolts) represented on the right-side axis. T/C ratios for each session are represented on the left-side axis. S.E.M. markers are shown for all data.

$P<0.05$) and tAmp for the 1 s CTI ($M=139\pm27$, $P<0.01$). For T/C ratio, there was a significant effect for CTI ($F(3,18)=11.59$, $P<0.001$). Post hoc *t*-tests showed that the tAmp for the 4 s CTI ($M=0.95\pm0.10$) was significantly different from the 150 ms CTI ($M=0.50\pm0.13$, $P<0.001$), 500 ms CTI ($M=0.44\pm0.07$, $P<0.001$), and 1 s CTI ($M=0.49\pm0.09$, $P<0.01$). Overall for ELD neurons, the increase in T/C ratio at the 4 s CTI compared

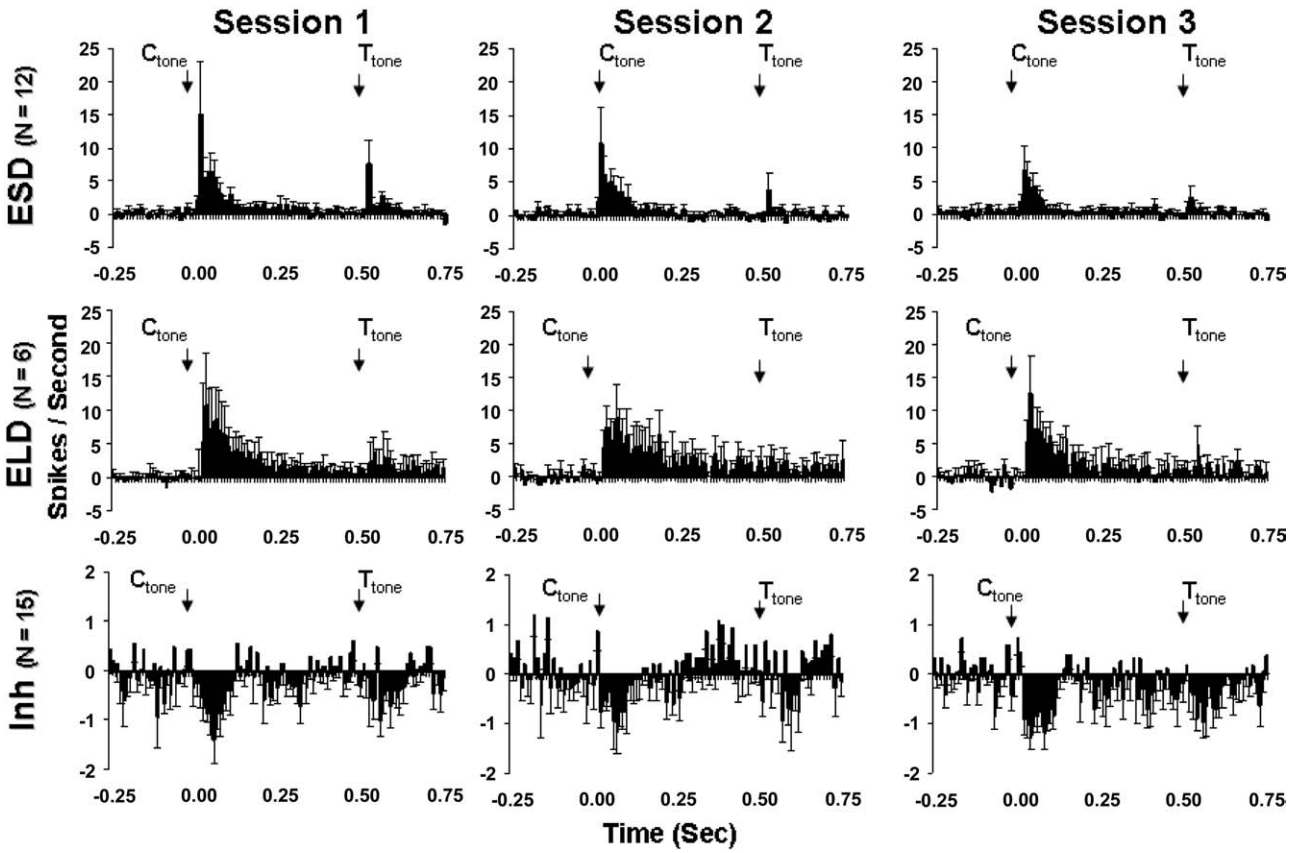

Fig. 7. Group mean histograms represent population averages for each class of single-unit that responded to pairs of tones for the first 100 trials for three sessions. Histogram bin sizes are 10 ms, and S.E.M. markers are presented for each bin. The numbers of units incorporated are indicated beside the title of each class of single-unit response.

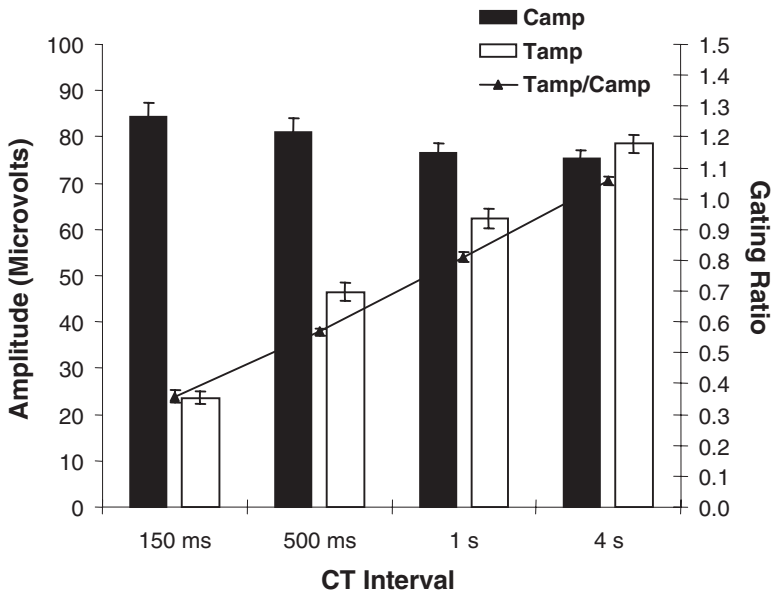

Fig. 8. Results for LFP from four CTIs of separation are indicated on the right-side axis for cAmp and tAmp (microvolts). The left-side axis marks T/C ratios for each CTI. S.E.M. markers are shown for all data. Although, T/C ratios increase monotonically with increasing CTIs, the relationship is not necessarily linear.

with shorter intervals was due to the increase in tAmp at the 4 s CTI.

For the Inh single-units there were seven units that had significant activations for at least three of four CTI blocks. We conducted repeated-measures ANOVAs for latencies following C_{tone} and T_{tone} and for cAmp, and we found no significant results. In a repeated-measures ANOVA for tAmp, we found a significant effect for CTI ($F(3,18)=3.60$, $P<0.05$). Post hoc *t*-tests showed that tAmp for the 150 ms CTI ($M=-72\pm9$, $P=0.05$) and the 4 s CTI ($M=-77\pm5$, $P=0.05$) were nearly increased compared with the 500 ms CTI ($M=-42\pm10$). We conducted a repeated-measures ANOVA for T/C ratios, and we found a significant effect for CTI ($F(3,18)=4.49$, $P<0.05$). Post hoc *t*-tests revealed that T/C ratios for the 150 ms CTI ($M=0.84\pm0.10$, $P<0.05$) and the 4 s CTI ($M=0.91\pm0.06$, $P<0.05$) were increased compared with the 500 ms CTI ($M=0.51\pm0.12$). Overall for the Inh units, the increases in T/C ratio at the 150 ms and 4 s CTIs compared with T/C for the 500 ms CTI, were due to increases in tAmp at the 150 ms and 4 s CTIs.

Comparing LFP and single unit activity

In order to compare LFP and single-unit neuronal activity we chose a subset of neural responses that were recorded from the same wire and yielded both P60 and excitatory-profile single unit activities. We then performed two-factor repeated-measures ANOVAs in order to compare gating between these two levels of activity.

First, a (3×2) ANOVA ($n=16$ wires) was conducted for the between-sessions data collected in the paired-stimulus tests over the course of three consecutive recording sessions. The two factors in this ANOVA were session and activity. When we conducted this ANOVA we found a main effect for session ($F(1,30)=12.2$, $P<0.001$). Post hoc pairwise comparisons of marginal means demonstrated that sessions 2 and 3 were significantly different from session 1 (session 1 $M=0.6\pm0.05$; session 2 $M=0.46\pm0.04$; session 1 $M=0.39\pm0.04$, $P<0.01$). The lack of a main effect for activity points toward the possibility that the variability of gating is actually similar between LFPs and single-units. However, a low sample size and high variances between individual cases within the sample of single-units might mask any potential differences between LFPs and single-units.

Fig. 10 depicts single unit and LFP activity recorded simultaneously from the same microwire during the CTI tests. In order to compare these two levels of neuronal activity, we completed a second (4×2) ANOVA ($n=13$) on the conditioned-test interval data collected over four separate blocks of intervals between stimulus pairs (150 ms, 500 ms, 1 s, 4 s). The two factors in this ANOVA were CTI and activity. We found a significant main effect for activity ($F(1,24)=6.04$, $P<0.05$), and we also found a significant main effect for CTI ($F(1,24)=59.25$, $P<0.001$). There was also a significant interaction of activity and CTI ($F(1,24)=6.35$, $P<0.01$). Using paired *t*-tests, we found that for the 500 ms CTI the T/C ratio for P60 ($M=0.65\pm0.08$) was significantly greater than the T/C ratio for the excitatory single-units ($M=0.38\pm0.05$, $P<0.05$). At the 1 s CTI the T/C ratio for P60 ($M=0.83\pm0.05$) was significantly greater than the T/C ratio for the excitatory single-units ($M=0.51\pm0.06$, $P<0.001$).

DISCUSSION

The results of the present study provide direct support for mPFC in sensory IG and show that the inhibition can persist over an extended period at both the LFP and single unit level. These data are critical in order to expand in the

Table 2. CTI neuronal database for three types of single-unit response to paired-stimuli

	150 ms Interval			500 ms Interval			1000 ms Interval			4000 ms Interval		
	ESD	ELD	Inh	ESD	ELD	Inh	ESD	ELD	Inh	ESD	ELD	Inh
Significant responses	6	7	7	6	7	7	6	7	7	6	7	7
C-response (ms)	27±4	45±19	43±13	28±4	42±19	34±13	27±4	55±22	34±12	26±4	35±13	18±11
T-response (ms)	100±42	104±31	45±24	47±15	81±33	26±7	38±15	72±29	19±4	30±4	42±13	24±9
Baseline firing rate (Hz)	1.1±0.4	11.1±4.6	8.7±7.4	1.0±0.3	10.2±3.4	7.7±5.9	1.2±0.2	11.4±3.8	3.7±1.8	1.1±0.3	10.7±3.9	7.3±5.7
cAmp (% baseline)	5160±2694	502±147	−87±6	1069±219	587±140	−88±6	1743±492	351±81	−89±5	1483±237	548±164	−86±5
tAmp (% baseline)	650±353	193±83	−72±9	329±72	248±70	−43±10	811±158	139±27	−65±6	1557±403	446±110	−77±5
T/C ratio	0.17±0.04	0.50±0.13	0.84±0.10	0.32±0.06	0.44±0.07	0.51±0.12	0.55±0.08	0.49±0.09	0.74±0.05	1.04±0.15	0.95±0.10	0.91±0.06

analysis of IG toward investigating the functional significance of IG within the mPFC regions. Our general idea related to the functional properties of IG is that each brain region and subregions contain sets of intrinsic inhibitory circuits and these circuits utilize the inhibition on different information. Additionally, the criteria for IG should vary from neural structure to neural structure with the basic patterns of inhibition appearing very similar. For example, we know that around 80% of the tone responsive neurons in the amygdala display IG and that these neurons can be grouped into similar subtypes observed in the mPFC (Cromwell et al., 2005). That is, we see neural responses that follow the tone onset of short and long duration that are excitatory and inhibitory and all of them show a reduction in amplitude after the second tone. One subtype of response that was observed in the amygdala that was not observed in the present study was an anticipatory tone response that also displayed IG (Cromwell et al., 2005). These responses were infrequent and showed the most deterioration over time. Other single unit studies are finding similar pervasive IG even when the frequency of the tone responsiveness is very low (Moxon et al., 1999; Klein et al., 2005). The results of the present study as well as the basic description of IG in connected regions will allow us to reveal functional properties of gating in neural systems. Proposed ideas include primary functions related to "emotional or behavioral or cognitive" gating in which the inhibition would work on different forms of information and interact with different psychological processes.

Variability of IG in mPFC

Understanding how gating changes over time will enable the use of IG as a clinical tool (Boutros et al., 1998). Previous work has shown IG to be altered depending upon arousal state (Kisley et al., 2001). In order to interpret variability of IG, it is essential to completely describe alterations in neural activity at all relevant time points. This includes changes occurring prior to and following each sensory stimulus. Primarily, IG has been quantified as a ratio of neuronal activity, the response to the second stimulus divided by the response to a first stimulus (T/C ratio) (Adler et al., 1985; Freedman et al., 1991; Clementz et al., 1997). This general method lacks precision due to the many possible combinations of alteration in both cAmp and tAmp that can occur. The different types of alterations can result in similar increases or decreases in T/C ratios or even no change in T/C ratio (Oranje et al., 2004). To clarify this issue, we have introduced three categories of changes in IG in order to summarize and interpret the variability of gating.

In this new classification scheme, statistically significant changes in cAmp or tAmp are used to interpret changes in the T/C ratio (Table 3). The first category (I) of IG change was designated as an increase or decrease in tAmp that contributes primarily to a change in T/C ratio. We characterized this change as an increase or decrease in tAmp that was proportionately greater than a complimentary increase or decrease of cAmp. The second category (II) of change in IG was designated as a difference in T/C

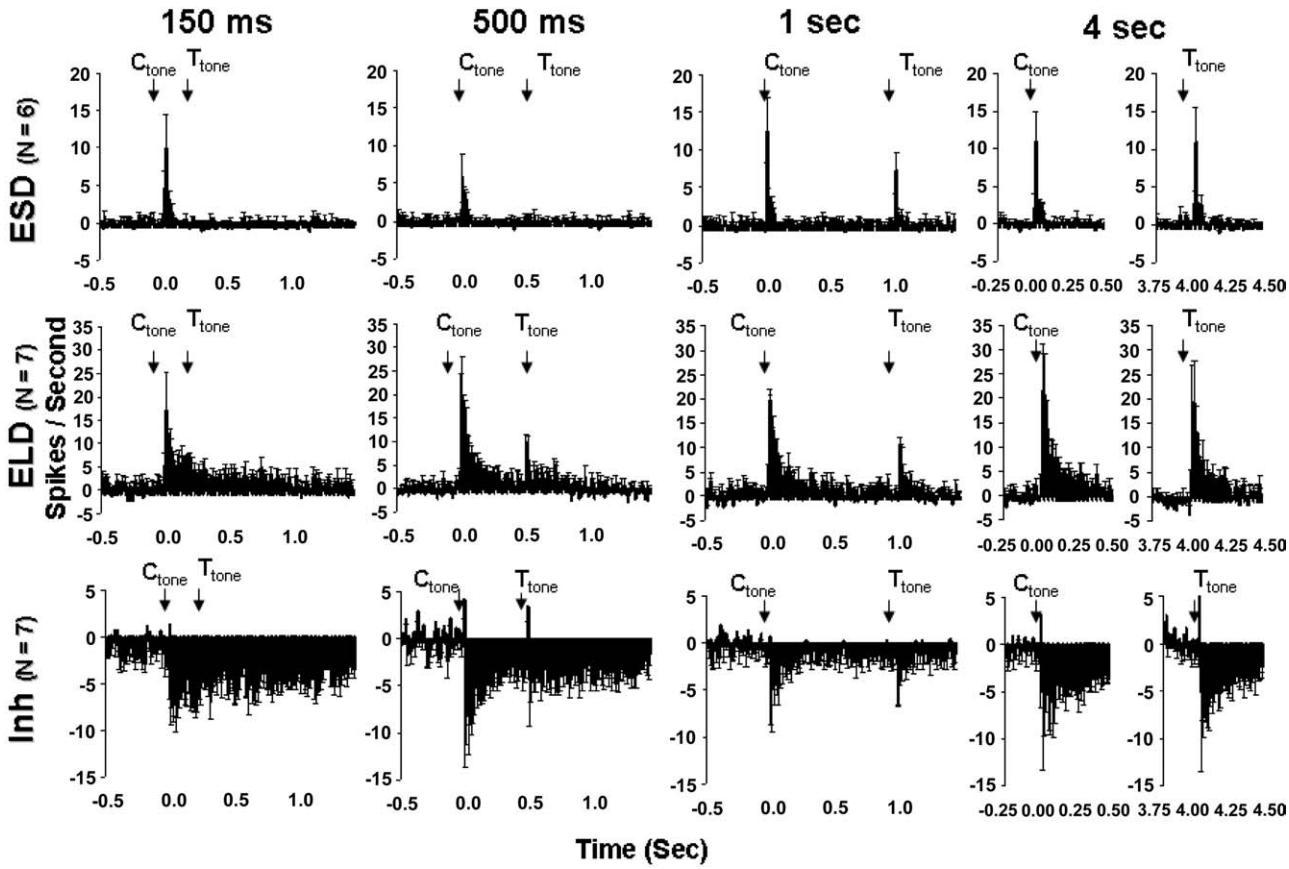

Fig. 9. Group mean histograms represent population averages for each class of single-unit that responded to pairs of tones at four different CTIs. Histogram bin sizes are 10 ms, and S.E.M. markers are presented for each bin. The number of units incorporated into each average is listed beside the class designation.

ratio that is due to a proportionately greater increase or decrease in cAmp than a complimentary increase or decrease of tAmp. The third category (III) of gating change was designated for inverse (or opposing) changes in both cAmp and tAmp.

Between-sessions analysis for LFPs showed that there was a decrease in T/C ratio, cAmp, and tAmp in sessions 2 and 3 compared with session 1. We propose that the decrease in T/C ratio was due to a proportionately greater decrease in the tAmp than cAmp, and we label this type of change a category I strengthening of sensory gating, to compare with the other types of changes that could lead to similar results. Single-units followed the same pattern of results, but perhaps the small sample size or high variance between the single-unit measurements prevented a significant finding. This pattern of results suggested that gating was stable for single-units over the course of multiple sessions. In the case of LFPs, sensory gating was stable, and gating strengthened slightly over the course of multiple sessions.

The within-session analysis of LFPs demonstrated a decrease of the magnitude of cAmp and tAmp over segments 2 and 3 compared with segment 1. We designated this as category II weakening of sensory gating, as the decrease in cAmp was proportionally greater than the decrease in tAmp, resulting in an increase in T/C ratio. Other studies have found that the P50 in humans is affected by repetitive presentation of individual, i.e. non-paired, stimuli (Cacace et al., 1990). Research using a paired-stimulus paradigm to examine human P50 found a coincident decrease in both cAmp and tAmp after many repeated presentations of paired stimuli (Naber et al., 1992; Clementz et al., 1997). Another study found a decrease in cAmp, an increase in tAmp, and a resulting decrease of sensory gating (Lamberti et al., 1994). A study of EPs in rats has found a weakening in sensory gating of the N40 potential that was primarily due to a reduction of cAmp (de Bruin et al., 2001).

Our analysis of CTIs was designed to examine the duration of sensory gating. For LFPs there was category I weakening of gating as the length of CTI increased. With each increase in length of CTI (150 ms, 500 ms, 1 s, and 4 s) there was an increase in LFP tAmp and a consequent increase of T/C ratio. Studies of P50 gating in humans have examined the effects of CTIs (Freedman et al., 1983; Adler et al., 1986; Nagamoto et al., 1989, 1991; Zouridakis and Boutros, 1992; Dolu et al., 2001). One study limited the gating of P50 to CTIs less than 1 s. Two studies of rat EPs have examined the effects of CTIs (Jongsma et al., 1998; de Bruin et al., 2001). One study limited gating to CTIs less than 1–2.5 s (de Bruin et al., 2001).

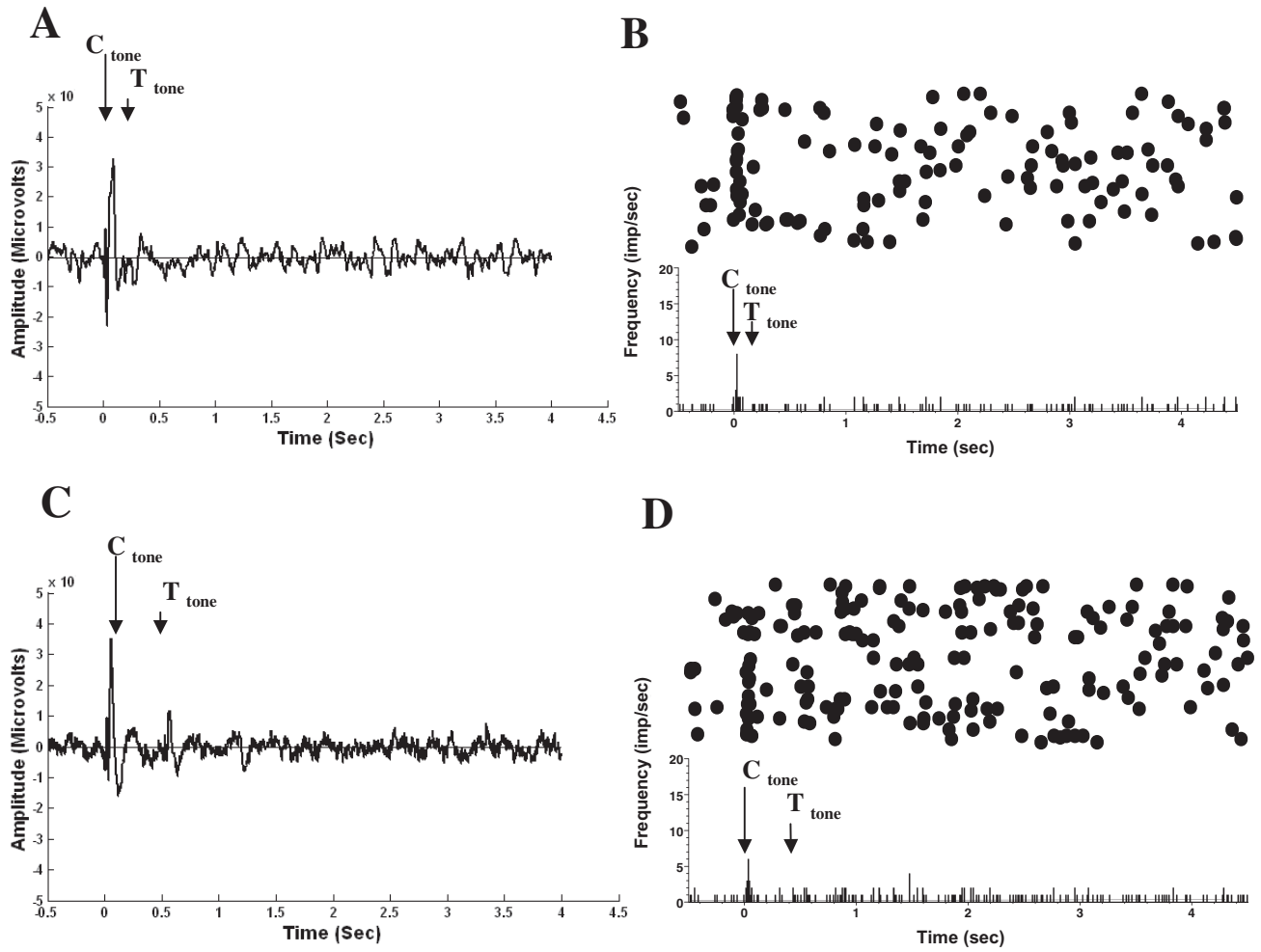

Fig. 10. Examples of LFP and a single-unit recorded simultaneously from the same wire are shown with responses to pairs of tones presented at four different CTI. At a CTI of 150 ms responses of (A) LFP and (B) single-units are very strongly gated following T_{tone}. A CTI of 500 ms responses of (C) LFP is strongly gated following T_{tone}, yet responses for (D) single-units are very strongly gated following T_{tone}. The CTIs of 1 s (E) LFP responses are weakly gated following T_{tone}, indicated by tAmp nearly equal to cAmp. For the (F) single-unit responses at 1 s CTI strong gating is evidenced by much smaller increases in firing rate following T_{tone} than following C_{tone}. At a CTI of 4 s gating is weak for (G) LFP. For the (H) single-unit at a CTI of 4 s IG is nonexistent, evidenced by a facilitation of firing rate increase following T_{tone}.

To our knowledge no other studies have examined the effects of CTIs on single-units. The single-units in mPFC demonstrated considerable variability. Single-units responded to tones with either excitation or inhibition of firing rate, and the duration of the excitation varied from unit to unit. The variability in response profile might reflect different aspects of a gating mechanism intrinsic to mPFC. Furthermore, when classified according to three subgroups, ESD, ELD and Inh, IG varied depending on CTI. For all single-units in this study there was category I weakening of gating, but the pattern of alteration depended on both the type of single-unit and the CTI. For the ESD single-units there was category I weakening of gating with increasing CTI, as each increase in T/C ratio occurred along with an increase in tAmp. For ELD single-units, only the 4 s CTI was different from the other CTIs. We interpreted this change as a category I weakening of gating as the increase in T/C ratio for the 4 s CTI was entirely due to an increase in tAmp for the 4 s CTI compared with tAmp at other CTIs. For Inh single-units, there was weakening at both the 150 ms and 4 s CTIs compared with the 500 ms CTI. The increases in T/C ratios at the 150 ms and 4 s CTIs were due to an increase in the magnitude of tAmp.

Comparisons of CTI effects between LFPs and single-units reveals that, at the 1 s CTI, LFPs and single-units had different response properties. At the 1 s CTI, single-units were gated, and LFPs were only weakly gated. These two levels of neuronal information might represent distinct sources or influences. Between LFPs and single-units, this mismatch in the strength of gating at the 1 s CTI might favor a hypothesis that sensory gating of single-units is generated by some intrinsic mechanism within mPFC local circuitry. If category I changes in gating represent inhibition of the neural response to T_{tone} then the duration of inhibition differs between LFPs and the excitatory subsets of single-units. In the case that LFPs might be considered to be related to dendritic potentials or information incoming to neurons of the rat mPFC, then single-unit activity

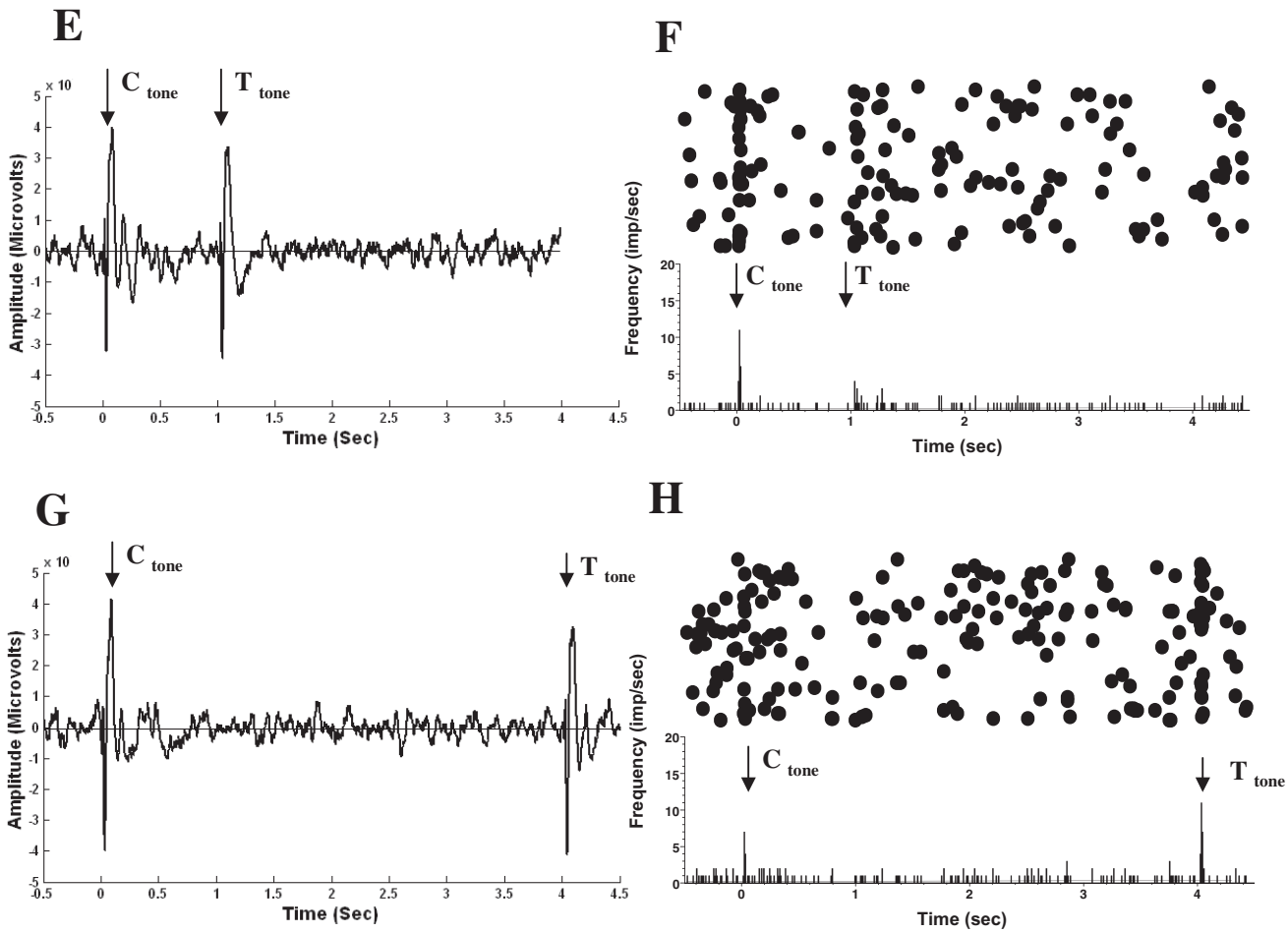

Fig. 10. (*Continued*).

would correspondingly be related to information outgoing from a mPFC neuron. The fact that P60 T/C ratios at the 1 s CTI are significantly different from single-unit T/C ratios at the 1 s CTI raises the possibility that for the T_{tone}, P60 tAmp does not correspond with single-unit tAmp. While P60 LFP (dendritic current) for tAmp is more nearly equivalent to cAmp, as evidenced by mean T/C ratio of 0.8 at the 1 s CTI, this relationship does not hold for single-unit activity. Single-unit excitatory activity for tAmp is still half of that for cAmp, evidenced by T/C ratios just above 0.5.

Functional neuroanatomy of IG in mPFC

An investigation into the functional anatomy of IG should incorporate two streams of information flow: one stream is the flow of auditory sensation and the other stream is the input trigger that activates inhibition. Of course, these two streams could arise from the same external source, removing the need for synchronizing independent inputs to the mPFC. There are a number of potential sources for auditory input into the mPFC. Primary auditory cortical regions send projections to the PFC in primates (Romanski, 2003). Temporal lobe to prefrontal connections are more sparse in the rodent (Reep et al., 1990; Conde et al., 1995). Surprisingly, auditory gating is weak to nonexistent in primary auditory cortex and medial geniculate nucleus of the rat (Moxon et al., 1999) and these factors make the cortico-cortical or MGN-cortical connections less likely to be the primary projection involved in the rapid responses and

Table 3. Different categories for the alterations in sensory gating decreases in the amplitude of the test tone (tAmp)

Sensory gating	T/C ratio	tAmp	cAmp
Category I			
Strengthening	↓	↓	
Weakening	↑	↑	
Category II			
Strengthening	↓		↑
Weakening	↑		↓
Category III			
Strengthening	↓	↓	↑
Weakening	↑	↑	↓

Category I changes in gating are due to alterations of tAmp. Category II changes in gating arise from alterations in the amplitude of the cAmp. Finally, category III alterations in gating come about when opponent tAmp and cAmp changes occur together. This type of classification scheme could help to delineate the diverse causal factors involved in alterations of inhibitory gating.

gating examined in the present study. Auditory information could arrive from non-lemniscal sensory structures such as brainstem regions (Saper, 1982; Saper and Loewy, 1982; Semba and Fibiger, 1992; Hur and Zaborszky, 2005), non-auditory thalamus (Thompson and Robertson, 1987; Reep et al., 1999; Krause et al., 2003), amygdala (Krettek and Price, 1977; McDonald, 1991) and hippocampus (Swanson, 1981; Ferino et al., 1987; Verwer et al., 1997). The brainstem input seems to be the most reasonable choice for incoming auditory information that mediates the fast response of the ESD single unit activity due to rapid conduction (Shaw, 1995). Subsets of single units had onset of activity increase between 15 and 20 ms following the tone stimulus. A number of brainstem regions send input directly to the mPFC including the pedunculopontine nucleus (PPT), lateral dorsal tegmentum (LDT), and the ventral tegmental area (VTA) (Semba and Fibiger, 1992; Hur and Zaborsky, 2005). Glutamate fibers have been shown to emanate from these regions to the mPFC (Hur and Zaborsky, 2005) and a well-known dopaminergic projection ascends from the VTA (Groenewegen et al., 1997). The dopamine input has been found to synapse directly onto GABA neurons within the mPFC (Ohara et al., 2003). There is evidence for some of these brainstem sites influencing auditory information. For example, the PPT receives auditory input (Reese et al., 1995a,b) and lesions to this structure significantly reduce the P50 EP (Harrison et al., 1990). In general, other regions of the reticular nuclear region have been shown to receive auditory information (Cant and Benson, 2003) and recording from these brainstem sites revealed IG of the tone responses (Moxon et al., 1999). Previous work showed that stimulation of the brainstem reticular region could actually substitute for the auditory input to induce IG in the hippocampus (Bickford et al., 1993). This evidence supports the role of ascending brainstem inputs in activating the inhibitory circuitry related to the gating.

Inputs from other neural regions such as the amygdala and the hippocampus could be important in the auditory responses that occur at longer latencies. Our earlier findings that the amygdala neurons in the lateral and central nuclei show rapid tone responses and demonstrate gating suggest that the amygdala could be an important source for this sensory information in this paradigm (Cromwell et al., 2005). The hippocampus could also be an important region in producing tone activations and in mediating inhibitory circuits but conduction time would limit the influence to mid or late latency activations (see Thierry et al., 2000 for estimated conduction time between hippocampus and mPFC at ~15 ms). Inputs or local neurons could activate an intrinsic inhibitory network within mPFC. Future work will need to be completed on the composition of the internal circuits within mPFC that enable IG. In other structures, GABA interneurons have been proposed as the critical cell group producing a type of lateral inhibition (Lewis et al., 2004; Tepper and Bolam, 2004; Gisabella et al., 2005). These types of interneurons are prevalent in medial cortex at multiple sites and layers (Gabbott et al., 1997). Our initial pharmacological examination points to a strong GABAergic component to the IG in mPFC (Mears and Cromwell, 2003, 2004). An understanding of the fundamental neuropharmacology of IG will enable more effective clinical applications of IG as a neurophysiological tool.

Clinical implications

Recent data have found a relationship between the degree of IG and the intensity of symptoms in schizophrenic patients (Louchart-de la Chapelle et al., 2005). IG could be used as an endophenotypic marker of schizophrenia as well as other psychiatric disorders (Gottesman and Gould, 2003; Braff and Light, 2004). IG has enabled the development of a quite sophisticated model for impairments in schizophrenia based upon genetic and molecular research (Freedman et al., 1994, 2003). Basically, the gating impairment has been proposed to be due to defective nicotinic receptors within the hippocampus and nicotine activation could restore normal gating and the subsequent cognitive and perceptual deficits. This idea has expanded into recent clinical and therapeutic work (Harris et al., 2004; Martin et al., 2004). How changes to mPFC function become integrated into the model will depend on detailed analysis of the properties of gating with this brain region. Another major idea making an impact on clinical practice is the recent examination on the effects of early brain damage on cognition, emotion and behavior in animal models (Wong et al., 2005; Powell et al., 2006). Early hippocampal or mPFC damage has been proposed as a model for diseases like schizophrenia (Lillrank et al., 1995; Schneider and Koch, 2005) and early amygdala damage has been proposed as a model for autism (Diergaarde et al., 2005a,b). IG could be potent neurophysiological assay in which to examine the validity of these models and as a marker for the effects of certain pharmaceutical manipulations. These future studies will benefit from basic research findings elucidating the functional nature of IG, and the current study initiates this essential groundwork. Christakou et al., 2004; Conde et al., 1990; Cullum et al., 1993; Fuster, 1990; Groenewegen, 1988; Light and Braff, 1998; Patterson et al., 2000; Paxinos and Watson, 1998; Posner and Petersen, 1990.

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