NEUROPHYSIOLOGY OF AUDITORY INHIBITORY GATING IN RAT MEDIAL PREFRONTAL CORTEX

Ryan Phillip Mears

A Dissertation

Submitted to the Graduate College of Bowling Green State University in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

August 2006

Committee:

Howard Casey Cromwell, Advisor

Timothy Brackenbury

Graduate Faculty Representative

Verner Bingman

William O'Brien

ABSTRACT

Howard Casey Cromwell, Advisor

Medial prefrontal cortex (mPFC) is a crucial region involved in inhibitory processes. Damage to mPFC leads to loss of normal inhibitory control over motor, sensory, emotional and cognitive functions. The present study was designed to examine basic properties, influence of aversive conditioning, and neuropharmacology of inhibitory gating in mPFC. Inhibitory gating is 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 findings that gating is dramatically impaired in individuals with emotional and cognitive impairments (i.e., in schizophrenia, PTSD, and drug abuse). In the present research, single-units and local field potentials (LFPs) were measured using chronic microwire arrays implanted in rat mPFC. The stability of gating was first examined using paired tone tests in short-term (within session) and long-term (between session) analyses of auditory gating. LFPs displayed reduction in amplitudes of tone responses and increase of gating over both short and long-term time windows. A variety of single-unit responses retained similar levels of auditory responsiveness and inhibition in both short and long-term analysis. Next, altering the interval between tones in each tone-pair influenced the potency of inhibition. Neural inhibition decreased monotonically related to the increase in intertone interval for both LFPs and single-units. The influence of fear conditioning was investigated by administering 30 footshock pairings with tones similar to those normally used to test gating. Inhibitory gating of LFPs weakened, and animals' orienting behavior to tones increased after, compared to before, the session of footshock and tone pairings. Systemic neuropharmacological manipulations were used to investigate effects of dopamine and GABA neurotransmitter systems on inhibitory gating of LFPs in mPFC. For effects of

dopaminergic manipulations, the drugs haloperidol and apomorphine respectively strengthened and nearly eliminated inhibitory gating, and the drugs had completely opposite effects of respectively decreasing and increasing evoked response to the first tone. For effects of GABA manipulations, the drugs baclofen and pentobarbital strengthened gating to varying degrees. This set of experiments lays essential framework for investigation of inhibitory gating in mPFC and the network of connected brain structures that also display inhibitory gating.

DEDICATION

I would like to dedicate this work to Susan, for her confidence in and inspiration to me, and to my entire family for their constant guidance and support.

ACKNOWLEDGEMENTS

I would like to acknowledge Casey Cromwell as my advisor and mentor. I aspire to follow his example as a scientific researcher and a teacher.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter 1

INTRODUCTION

Inhibitory gating is a rapid, transient suppression of neural responsiveness to stimuli, occurring for a short time following a prior stimulus. This particular phenomenon was first observed in auditory-evoked potentials (AEP) recorded from the scalp of humans (Davis et al, 1966) and, later, from rats (Knight et al, 1985) that were presented with sets of consecutive auditory stimuli. The construct of inhibitory gating depicts neural inhibition that measured as an attenuation of response to a stimulus that is conditioned by the occurrence of a prior stimulus (Eccles, 1969). Inhibitory gating is commonly measured in a conditioning-testing paradigm, in which a brief conditioning tone-click is paired with a test tone-click that occurs 0.5 seconds later (Adler et al, 1982). The purpose of the second tone is to test the effect of inhibition from the first tone. The amount of attenuation in the amplitude of the second neural response is measured as a ratio of the amplitude of second stimulus response divided by the amplitude of first stimulus response. Inhibitory gating has been interpreted to be an active inhibitory process (Adler et al, 1982; Boutros and Belger, 1999) rather than a passive, momentary incapacity of neurons to fully respond to stimuli (Davis et al, 1966).

The purpose of this investigation was to examine the occurrence, dynamics, and emotional and neuropharmacological influences of inhibitory gating in prelimbic medial prefrontal cortex (mPFC). Two neurophysiological techniques, local field potentials and single-units were utilized to assess simultaneously the occurrence and dynamics of inhibitory gating. The local field potentials were used to compare inhibitory gating in mPFC with existing literature regarding inhibitory gating of AEP in humans and rats. Single-units were used to uncover the elemental constituents of neural response to auditory tones in mPFC. Next, local

field potentials were used to examine the influence of aversive conditioning on inhibitory gating in mPFC. Finally, local field potentials were utilized to examine the influence of two principal mPFC neurotransmitters systems, dopamine and GABA. Prior to a description of the research it is important to briefly review the neuroanatomy, functions, and significance of mPFC. Next, the relation of inhibitory gating to mPFC, aversive conditioning, and dopamine and GABA neurotransmitter systems will be delineated.

1.1. Neuroanatomy and Functional Significance of Medial Prefrontal Cortex

1.1.1 Neuroanatomy of Medial Prefrontal Cortex

A number of brainstem areas project inputs to all prefrontal regions in the rat. Fibers from ventral tegmentum, basal forebrain, locus coereulus, and dorsal raphe respectively containing dopamine, acetylcholine, norepinephrine, and serotonin project to both medial and lateral areas of PFC. Limbic structures such as the amygdala (Krettek and Price, 1977) and hippocampus (Verwer et al, 1997; Thierry et al, 2000) send projections to particular regions of PFC.

Projections from the mPFC to many other brain regions have been found. The mPFC has been shown to project to neuromodulatory regions such as ventral tegmental area (Carr and Sesack, 1999; Carr and Sesack, 2000), basal forebrain (Zaborsky et al, 1997), locus coeruleus (Jodo and Aston-Jones, 1997; Jodo, Chiang, and Aston-Jones, 1998), and raphe nuclei (Vertes, 2004). The rat PFC also projects to the amygdala (McDonald et al, 1996; McDonald, 1998), dorsomedial dorsal striatum (McGeorge and Faull, 1989) and the nucleus accumbens (O'Donnell et al, 1997; Gronewegen et al, 1999; Sesack and Carr, 2002; Vertes, 2004). Electrical

stimulation of the mPFC in the rat has been shown to inhibit dopamine release in the nucleus accumbens (Jackson, Frost, and Moghaddam, 2001). Electrical stimulation of the mPFC has also been shown to inhibit neuronal activity in the amygdala (Quirk et al, 2003; Rosenkrantz, Moore, and Grace, 2003). Given the extensive connectivity of the mPFC with many other brain regions, this cortical region directly or indirectly modulate or otherwise influence the activity of a multitude of other brain regions.

1.1.2. Comparative Neuroanatomy of Medial Prefrontal Cortex

The mammalian brain has a continuum of functionally segregated, topographically organized cortico-striato-thalamo-cortical feedback loops (Groenewegen et al, 1997 Uylings et al, 2003). Alexander and colleagues (1990) defined four semi-parallel functional circuits in the primate brain that are characterized by specific anatomical and functional characteristics. The motor, oculomotor, prefrontal, and anterior cingulate circuits were defined by their starting points in frontal cortex (Alexander et al, 1990). Uylings and colleagues (2003) have described similar circuits beginning in rat frontal cortex. In primates and rodents, motor and oculomotor circuits are important for integration of sensory information with motor routines. Prefrontal and anterior cingulate circuits integrate limbic and sensory information with motivation and attention.

Some researchers have asserted that homologous regions of prefrontal cortex and anterior cingulate exist in the primate and rat (Uylings and VanEden, 1990; Uylings et al. 2003). Comparisons of patterns of neuronal connectivity and function in frontal cortex of the primate and rat provide support in the case for homology. Mediodorsal (MD) thalamus projects to prefrontal and anterior cingulate cortex in rats (Leonard, 1969; Krettek and Price, 1977;

Groenewegen, 1988) and primates (Rose and Woolsey, 1948; Alexander et al, 1990). The specific routes that prefrontal and anterior cingulate cortico-striato-thalamo-cortical circuits follow through medial and ventral striatum to then project to MD thalamus is similar in rats and primates (Uylings and VanEden, 1990; Uylings et al. 2003).

On the basis of topographically layered connections through MD thalamus, other thalamic areas and limbic areas numerous researchers have recently attempted to establish a case of homology between various rat and primate PFC areas. Kesner (2000) has presented evidence that rat prelimbic and infralimbic prefrontal cortex are homologous to primate ventrolateral prefrontal cortex, and rat dorsal anterior cingulate is homologous to primate dorsolateral PFC. Uylings and colleagues (2003) contend that rat dorsal anterior cingulate/FR2 correspond to primate dorsolateral PFC, and rat prelimbic/infralimbic correspond to primate anterior cingulate and orbitomedial PFC. Vertes (2005) has asserted that, on the basis of limbic and thalamic connections, rat prelimbic and infralimbic PFC cortex respectively correspond to primate dorsolateral and orbitomedial PFC.

1.1.3. Functional Significance of Medial Prefrontal Cortex

The possibility exists that anatomical methods might be insufficient to establish homology between rat and primate PFC (Preuss, 1995), but currently much evidence is accumulating for analogies between functional characteristics of various prefrontal areas in the two species. Certain supervisory, or executive, functions have been shown to depend on intact PFC in the human or non-human primate (Shimamura, 2000). Two examples of executive functions are attentional set-shifting and working memory. These functions have been localized

to primate dorsolateral PFC, and current research is showing that rat prelimbic cortex might be functionally analogous if not homologous to primate dorsolateral PFC.

Regions of rodent mPFC have been demonstrated to have functional correspondences to executive functions in the primate PFC (Brown and Bowman, 2002; Otani, 2003). Birrell and Brown (2000) have shown that lesions centered on rat prelimbic mPFC brought about specific deficits in attentional set-shifting but not feature specific attention. The function of attentional set shifting is defined as the attending to a perceptual set that must be later ignored when the subject is faced with a shift in some perceptual dimension. In primates, attentional set-shifting is required for satisfactory performance of the Wisconsin Card Sorting Task (Heaton, 1981). The WCST depends on using error related information to make rules that allow successful sorting of cards, and WCST is often used as a clinical test of dorsolateral PFC function (Milner 1963; Berman and Weinberger, et al, 1990; Andreason et al, 1992). Individuals with schizophrenia or lesions of the dorsolateral PFC have poor performance on the WCST (Goldberg et al, 1987). Primates with lesions of dorsolateral PFC, but not orbital PFC, have deficits in an analogue of the WCST (Dias et al, 1997). Orbital PFC is required for reversal learning in primates (Dias et al, 1997 and humans (Bechara et al, 1998).

Similar to primate dorsolateral PFC, prelimbic mPFC in the rat has been shown to be necessary for performance of tasks that involve short term delays or behavioral flexibility. The primate dorsolateral PFC has been shown to participate in the maintenance of sensory information during a short delay, in order make correct responses in delayed spatial match to sample and non-match to sample tasks (Goldman-Rakic, 1995; 1996). Furthermore, lesions of dorsolateral PFC in the primate has been shown to produce impairment in similar working memory tasks (Petrides, 1995). Similar to dorsolateral PFC in primates, working memory

deficits are produced by lesions of rat prelimbic PFC. Rats with prelimbic lesions demonstrated behavioral inflexibility in delayed spatial navigation tasks (Granon and Poucet, 1995; Delatour and Gisquet-Verrier, 2000). In the rat Seamans (1995) and colleagues demonstrated that temporary inactivation of prelimbic cortex was sufficient to disrupt performance on a delayed 8-arm radial maze task. In all of these working memory tasks, internal representations of spatial relationships per se was not disrupted, but there was a decrement of flexible behavior based on short term maintenance and manipulation of this information (Delatour and Gisquet-Verrier, 2000). Hippocampal and subicular neurons have been shown to project to prelimbic cortex (Ferino et al, 1987; Jay et al, 1989), and such projections have been shown to produce synaptic plasticity (i.e., long tem potentiation) in prelimbic neurons (Laroche et al, 2000) Rat hippocampal projections are essential to normal function of prelimbic mPFC in these working memory tasks, for disconnection of hippocampal afferents to prelimbic mPFC has the same effect as prelimbic lesions during delayed responding (Floresco et al, 1997).

Given bidirectional connectivity with brainstem regions and given unidirectional and bidirectional connectivity with other cortical, sub-cortical regions, the prefrontal cortex is situated to integrate information and modulate the activity of many other brain regions. These other brain regions are involved in perception, affect, cognition, and behavior and the prefrontal cortex has been shown to maintain an important inhibitory influence on these other regions (Knight et al, 1989, 1999). Since the prelimbic prefrontal cortex has been shown to play a role in two types of supervisory or "executive" functions there is evidence to suggest that the inhibitory influence of prefrontal cortex is important carry out such functions. The first part of this investigation was to first demonstrate that inhibitory gating does occur in prelimbic mPFC.

Next, it was important to show how the phenomenon of gating might be involved in the affective neuronal systems in which mPFC is known to participate.

1.2 Neural Inhibition and Prefrontal Cortex

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 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., 2005; 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; Correll et al, 2005). 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). Medial PFC (mPFC) in the rat has been posited to operate as an inhibitory interface between brain regions important for voluntary goal-directed actions and brain regions important for habitual stimulus-response actions (Kilcross and Coutreau, 2003). 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., 2005; Chudasama et al., 2005).

PFC has been shown to play an important role in inhibitory brain processes, as patients with lesions of PFC have enhanced evoked potential responses in auditory cortex, suggesting that the PFC is involved in the inhibitory modulation of sensory inputs to auditory cortex (Knight et al, 1989; Knight et al, 1999). Auditory cortex and PFC are reciprocally connected in humans and other primate species (Romanski et al, 2003; Romanski & Goldman-Rakic, 2002). Based on the pattern of afferent and efferent connections there is substantial evidence that mPFC in the rat might correspond in many ways to the human PFC (Uylings and van Eden, 1990; van Eden et al, 1990; Uylings, Groenewegen, and Kolb, 2003).

1.3. Inhibitory Gating and Prefrontal Cortex

Inhibitory gating has been linked to PFC in humans. Patients with PFC damage lack inhibitory gating of AEPs in the paired-tone paradigm (Knight et al, 1999). The most extensively studied human AEP with inhibitory gating is the human P50 (Adler et al, 1982; Freedman et al, 1993; Siegel et al, 1984; Waldo and Freedman, 1986; Boutros et al 1991; Clementz et al, 1997). The P50 has been shown to have multiple generators, bilateral temporal sources (Liegeois-Chauvel et al, 1994) and a possible frontal source (Weisser et al, 2001). Further, compared to the other sources, inhibitory gating of P50 is heightened in this putative frontal source (Weisser et al, 2001), and there is evidence that inhibitory gating of P50 in this frontal source is most strongly disrupted in schizophrenia (Judd et al, 1992). Inhibitory gating of auditory evoked potential components has been observed using intracranial electrodes in human mPFC (Grunwald et al, 2003). The rudimentary aspects of inhibitory gating in PFC have been established in human

subjects, but a detailed analysis of the local origins, dynamics, and influences of inhibitory gating remained to be explored. The purpose of the present research has been to conduct such fine-grained analyses, as such investigation is most suitable to the animal model.

1.4. Inhibitory Gating and Mental Dysfunction

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., 2005; van den Heuvel et al., 2005; Self, 1998). Each of these disorders has been examined using one particular index of inhibition, labeled P50 suppression or sensory inhibitory gating (IG). Several clinical groups are now using inhibitory gating paradigms as a way to gauge symptom progression and potentially diagnose certain psychological impairments (Louchart-de la Chapelle et al., 2005; Freedman et al., 1996).

A large amount of research on inhibitory gating impairment in mental disorders has focused on schizophrenia (Adler et al, 1982; Clementz et al, 1997; Boutros et al, 1999; Ghisolfi et al, 2004). Schizophrenia has been presumed to have independent groupings of symptoms: positive, negative, or disorganized (Andreasen et al, 1995; Grube et al, 1998). Inhibitory gating

is affected in patients with either predominantly positive, negative, or disorganized subtypes of symptoms (Adler et al, 1990; Louchart-de la Chapelle et al, 2005; Ringel et al, 2004). Gating deficits in humans have been found in schizophrenic patients and their first-degree relatives (Clementz, Geyer, and Braff, 1998). The fact that gating deficits are found in the non-schizophrenic relatives of individuals diagnosed with schizophrenia suggests that gating deficits might be related to some fundamental genetic factor predisposing some individuals to schizophrenia (Freedman et al, 2000).

Other research by Freedman and colleagues (1997) has shown genetic linkage of families with schizophrenia to chromosome 15q14-15. This linked chromosome region has been shown to relate to a subunit gene for the alpha-7-nicotinic receptor (Freedman et al, 1997). Studies of this region have revealed that the presence of the linked allele variant might reduce expression levels of the nicotinic receptor (Leonard et al, 2006). Other studies in humans have shown that nicotinic drugs influence inhibitory gating (Adler et al, 1992; 1997; 2001). In a parallel line of research with a particular breed of mouse, a reduced expression of the nicotinic acetylcholine receptor was shown to have a reduction of inhibitory gating of hippocampal AEPs in the paired-tone paradigm (Stevens et al, 1996). Restoration of gating using peripherally administered nicotinic drugs in this mouse breed (Stevens et al, 1998), bolsters the case that a neural deficit linked to reductions of inhibitory gating in schizophrenia can be pinpointed and studied in detail in the animal model.

1.5. Inhibitory Gating in the Animal Model

The animal model is essential for conducting neurophysiological research at a variety of levels of detail. Using auditory evoked potentials, IG in the rat animal model has been found in

numerous locations throughout the central nervous system 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). Evoked potential 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; Boutros et al., 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 other mid-latency potentials, have inhibitory gating as well but not as robustly under certain conditions (Boutros and Belger, 1999; Boutros et al, 1999; Grunewald et al., 2003).

In the rat, inhibitory gating has been measured in single-unit tone responses in different brain regions such as the hippocampus (Bickford-Wimer et al, 1990; Miller & Freedman, 1995; Moxon et al, 1999), amygdala (Cromwell et al, 2005), striatum (Klein et al, 2005), and reticular nucleus of the thalamus (Krause et al, 2003). Interestingly, inhibitory gating is weak to non-existent in a major relay in the lemniscal, central 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 was found to have different types of single-unit 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 being crucial to IG in humans.

1.6. Negative valence and gating

A number of variables associated with aversive experience have dampening effects on inhibitory gating. Negatively valenced stimuli (Yamashita et al, 2005) and acute stress in humans (White and Yee, 1997; Yee and White, 2001) and acute stress in mice (Suer et al, 2004) reduce inhibitory gating of the AEP. The etiology of Post-Traumatic Stress Disorder (PTSD) has underpinnings in episodes of severe acute stress, and PTSD is a mental disorder associated with inhibitory gating deficits (Skinner et al, 1999; Neylan et al, 1999; Ghisolfi et al, 2004).

The prefrontal cortex and the amygdala form an important circuit in the function of fear memory (Quirk and Gehlert, 2003), and the prefrontal cortex might participate in a larger fear conditioning network that centers on the amygdala as its functional node (Ledoux, 1998; Pezze and Feldon, 2004). There are thought to be four stages of fear memory: formation, consolidation, expression and extinction, and prefrontal cortex is important in the latter two stages (Pezze and Feldon, 2004). There is evidence suggesting that PFC exerts an inhibitory action on the amygdala. Lesions of the mPFC produce increases in fear related behaviors (Morgan and Ledoux, 1995; Correll et al, 2005). Dopamine profoundly affects the ability of prefrontal neurons to influence amygdala activity (Pezze et al, 2003; Pezze and Feldon, 2004). Chronic stressors have been shown to reduce prefrontal inhibition of the amygdala (Correll et al, 2005). There is evidence to suggest that an aberrant interaction between the amygdala and frontal brain regions might be involved in the etiology of PTSD (Shin et al, 2005). Furthermore, stress may take advantage of vulnerabilities to dopamine system instabilities in schizophrenia (Finlay and Zigmond, 1997) and drug abuse (Sato, 1992; Sinha et al, 1999). Stimulation of the prefrontal cortex inhibits neural activity in response to auditory stimuli in the amygdala (Rosenkranz and

Grace, 2002; Rosenkranz et al, 2003; Quirk et al, 2003; Milad et al, 2004), and a reciprocal effect of amygdalar activity has been suggested to produce inhibition of activity in prefrontal cortex (Garcia et al, 1999).

Finally, inhibitory gating has been shown to be a reliable and robust feature of amygdala single-unit response to stimuli in the paired-tone paradigm (Cromwell et al, 2005). IG has been suggested to function as a filter for uninformative and repetitive stimuli (Freedman et al, 1994; Moxon et al, 1999). Amygdala and PFC both have been implicated as neural structures important in IG and involved in the expression of fear related memory (Quirk and Gehlert, 2003; Maren and Quirk, 2004). A test of the functional role of IG in mPFC is to impart negatively valenced meaning to tone pairs.

1.7. Neuropharmacology of Inhibitory gating

The relationship of dopamine systems to inhibitory gating has been a topic of recent debate (Boutros, 1998; Oranje et al, 2004), yet numerous studies have found links between psychosis and decreased inhibitory gating (Adler et al, 1982; Clementz et al, 1997; Boutros et al, 1999; Ghisolfi et al, 2004). Psychosis has been linked to dysfunction of dopamine systems (Snyder, 1973, 1976), and the clinical efficacy of antipsychotic drugs have been found to be directly related to their D_2/D_4 dopamine receptor binding properties (Creese et al, 1976; Creese et al, 1996). Reductions in gating in human subjects have also been found after administration of certain psychotomimetic drugs. Such reductions have been found after dopamine influencing drugs such as amphetamine (Light et al, 1999). Furthermore, gating deficits have been found in chronic abusers of cocaine, which also has a powerful modulatory effect on dopamine systems (Fein et al, 1996).

Gating in rats has been hypothesized to involve different ERP components than in humans, but the mechanisms behind gating are hypothesized to be the very similar (Adler et al, 1986; deBruin et al, 2001). Gating deficits have also been found in rats treated with psychotomimetic drugs (deBruin et al, 1999). Rats treated with amphetamine (Adler et al, 1986), cocaine (Boutros, 1997) and phencyclidine (Adler et al, 1986) have large reductions in gating. Furthermore, different strains of rats have been found to have differences in gating related to their genotypic dopamine system profiles (deBruin et al, 2001).

Antipsychotic drug treatments have been found to reverse gating deficits in both rats and humans. As previously described, schizophrenics have deficits in gating (Cullum et al, 1993). Atypical antipsychotics have been shown to restore gating in schizophrenics (Light et al, 2003). In rats treated with psychotomimetic drugs, gating was restored after additional administration of the antipsychotic drug haloperidol (Adler et al, 1986).

GABA neurotransmitter systems are altered in schizophrenia (Benes and Beretta, 2001). Further, postmortem examination of schizophrenic brains has revealed altered neurocircuitry in prefrontal cortex (Goldman-Rakic and Selemon, 1997; Selemon and Goldman-Rakic, 1999; Selemon et al, 2002). This altered neurocircuitry has been shown to be dysfunctional due to defects in a particular interneuron that inhibits prefrontal pyramidal projection neurons (Lewis and Volk, 2002; Gonzalez-Burgos et al, 2005). Researchers have hypothesized that inhibitory neuronal mechanisms involved in information processing utilize local GABAergic inhibitory networks (Eccles, 1969; Gupta, 2000). These GABAergic inhibitory networks in conjunction with local glutamatergic and incoming monoamine fibers might play an important role in gating. Pribram (1966) proposed that two types of inhibition, collateral and recurrent, contribute to neuronal processing. Collateral inhibition involves a suppression of neuronal activity

surrounding the active unit. This type of inhibition tends to contrast individual units of activity with the surrounding activity. Recurrent inhibition involves a suppression of nearby or distant collateral inhibition. Boutros and Belger (1999) hypothesized that inhibitory gating might involve a general suppressive mechanism such as collateral inhibition, and the reduction of inhibitory gating might involve recurrent inhibition. Through collateral inhibition, the first stimulus could create local inhibitory activity that would specifically gate or inhibit a second, identical stimulus. In certain situations, for example when the stimulus acquires meaning, recurrent inhibition would inhibit collateral inhibition. This type of disinhibition would result in an unsuppressed or even enhanced response to meaningful stimuli.

1.8. Research Goals

There has been a three-fold objective in this investigation of mPFC inhibitory gating in the rat. A first objective was to identify and understand the occurrence, temporal limits and dynamics of gating in rat medial prefrontal cortex. A second objective was to observe the influence of emotional learning on IG in mPFC. A third objective was to examine mPFC gating using neuropharmacological models of mental disorders

It has been essential to the first objective in this research to demonstrate inhibitory gating of sensory signals in mPFC single-units and LFPs. By finding and characterizing mPFC single-units, it would be possible to establish whether inhibitory gating is local to mPFC. Another goal was to ascertain whether inhibitory gating would be relatively stable over the course of multiple recording sessions and within segments of a single recording session for both LFPs and single-units. An analysis of the stability of gating would establish whether inhibitory gating is a typical feature of mPFC response to repetitive, irrelevant stimuli. Another goal was to test inhibitory

gating for both LFPs and single-units at different intervals of separation between first and second tones in order to discover whether an interval of optimal inhibitory gating exists. By comparing single-units and LFPs it would be possible to observe similarities and differences in the optimal intervals of inhibitory gating at these two neuronal levels.

The second objective of this research was to observe the influence of emotional learning on IG in mPFC. Acute and chronic stressors have been implicated in the reduction of inhibitory gating, but no studies have directly examined the effects of stimulus conditioning on inhibitory gating. If gating acts as a filter for meaningless and repetitive stimuli then inhibitory gating should be reduced by meaningful, negatively valenced stimuli.

The third objective of this research was to use neuropharmacological manipulations of inhibitory gating in mPFC to attain a better understanding of neurochemical dysregulation in mental disorders that are associated with weakening of gating. Two neurotransmitter systems that are fundamentally altered in mental disorders with associated gating deficits are dopamine and GABA. Pharmacological manipulations of these neurotransmitter systems have been shown to produce potent alterations of inhibitory gating. An understanding of two important neurotransmitter systems will yield valuable insights about the mechanisms of gating in mPFC, and it is hoped that this understanding will guide future research of inhibitory gating.

Chapter 2

DYNAMICS OF INHIBITORY GATING IN MPFC

2.1. Introduction

The objective of the present chapter was to characterize the basic properties of IG in the mPFC by analyzing single-unit and LFP responses to auditory stimuli presented in the paired-tone paradigm. In order to understand the dynamics of gating it was necessary to localize gating to the mPFC using electrophysiological methods to record both single-units and LFPs from chronically implanted microwires. Neural responses to tone stimuli have previously been found in mPFC (Watanabe, 1992; Jodo et al, 1999). Our first goal was to determine if IG was in operation in prefrontal cortex. Our second goal was to better define this IG process by examining whether IG varied over time. Using the standard paired-tone paradigm, IG has been found in human mPFC (Grunwald et al, 2003). The prefrontal area has been hypothesized to be relevant to IG of various sensory modalities (Knight et al, 1999; Staines et al, 2000). These studies in humans have used gross measurements of brain activity such as field potentials, and until now, nothing has been known about the small-scale details that constitute the large-scale IG phenomenon that has been observed.

We began by examining the profile, intensity, duration, and shape of single-unit and field potential responses to tone stimuli. Next, we directly measured IG by comparison of the neural responses to the first and second tones in the paired-tone paradigm. We utilized the standard paired-tone paradigm so that our findings would be relevant to previous and current studies on IG in humans (Adler et al, 1982; Grunwald et al, 2003) and in rats (Adler et al, 1986; Moxon et al, 1999). It was necessary to understand the basics of IG prior to initiating manipulations that are more complex. Some of these initial steps have been completed in other

brain regions such as the hippocampus, amygdala, and reticular thalamus. Once the stability or variability of IG in mPFC was known then it would be possible to clearly study the effects of manipulation of other more complex parameters on IG in mPFC.

As gating has been hypothesized to represent a temporary suppression of neural response to stimuli, it was necessary to examine the optimal intervals of separation between the conditioning and test tones. In this goal the intervals between the stimuli in each pair were methodically varied in order to examine the influence of stimulus timing on gating. A number of studies in humans involving field potentials have investigated the effects of varying the interval between stimuli in order to observe changes in IG (Davis et al, 1966; Cardenas et al, 1997; Boutros & Belger, 1999; Dolu et al, 2001). A few studies in rats have examined the effects of varying the interval between stimuli in order to observe changes in field potentials (Jongsma et al, 1998; deBruin et al., 2001). It is important to examine the temporal limitations of IG, for the rapid and transient nature of inhibition might vary from structure to structure and at different neuronal levels.

The objective of the following set of experiments was to localize inhibitory gating to mPFC using single-units and LFPs. In so doing, it was predicted that the basic properties of inhibitory gating would be relatively stable over short and longer periods of time. Furthermore, it was predicted that the optimal intervals of inhibitory gating would be similar between single-units and LFPs.

2.2. Methods

2.2.1. Chronic microelectrode implantation

Animals were anesthetized with xylazine (10mg/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 & PHS). A stereotaxic apparatus was used for the implantation of recording microwires (NB Labs, Denison, TX) into mPFC (A + 2.7, M +/-0.7, D -3.0) according to the standard rat stereotaxic atlas (Paxinos & Watson, 1997). 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 8 (1 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.

2.2.2. Experimental apparatus

The testing chamber (20 X 28 X 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 kiloHertz (kHz). A potentiometer on the tone generator was manually adjusted in order to produce brief tones that were 75 decibels (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) on a computer outside the room.

2.2.3. Gating protocols

In four separate sessions, two different inhibitory gating 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.

2.2.3.1. 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 sec passed before the beginning of the session in order to allow the rat to acclimate to the chamber. After this, 100 to 360 stimulus pairs were presented to the rats. Stimuli consisted of 4.1kHz tones (10 ms, 75 decibels) presented at a Condition-Test Interval (CTI) of 500 milliseconds. There was a 10 seconds 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.

2.2.3.2. Protocol 2: CT interval tests

In a fourth session, pairs of tones were presented at different CTI in order to study the effects of stimulus timing on gating. Four different CTI's (150 ms, 500 ms, 1 sec, 4 sec) 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.

2.2.4. Electrophysiological apparatus

Electrical activity received by each of the 16 recording electrodes in the mPFC was passed through op-amps (1X) 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 (100X) 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). 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).

2.2.5. Data acquisition

Single-units and LFPs were received using a computer with data acquisition software (MAP System, Plexon Inc., Dallas, TX). 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., Dallas, TX). Field potentials were imported to Matlab (The Mathworks, Nantic, MA) 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 4 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., Dallas, TX) 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, Nantic, MA) for off-line averaging of LFP responses to tones.

2.2.6. Local Field Potentials: Data analysis

Within each session, extracellular field potentials corresponding to trials of stimulus pairs were aggregated according to the onset for each stimulus, and evoked potentials (EP) were generated through waveform averaging. EP's 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 to activity during a 1 second 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 local field potentials. 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 to 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.

2.2.7. 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, were 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 was 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.

In the analysis of baseline activity (Table 1) we used t-tests to compare activity from a 3 second 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 sec and ending 0.5 sec 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 to 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 1^{st}, 2^{nd}, and 3^{rd} 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 local field potentials. 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 to 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.

2.2.8. 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 seconds 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 micron 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.

2.3. Results

2.3.1. Local Field Potential Database

A neuronal database was created for local field potential (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 (Figure 1). As indicated in the methods section, LFP responses tone stimuli from each wire were required to be significantly ($p<0.01$) different in amplitude compared to a 1 sec 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.

2.3.2. 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 3 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 (Figure 2A). Single-units with a tone related increase in firing rate lasting more than 50 ms were classified as excitatory long-duration (ELD) units (Figure 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 (Figure 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. E-SD units tended to have earlier latencies, with an average latency as early as 28 ms in one session (Table I). A subset of these neurons had latencies as early as 15-20 ms (Figure 3). Other single-units, E-LD 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 (Figure 4). The range of placements spanned all cortical layers in mPFC. In the antero-posterior 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.

2.3.3. Analysis of Variability: Local Field Potentials

2.3.3.1. 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 (1^{st} , 2^{nd} or 3^{rd}) 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 2 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 Ttone 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 Ttone latency in session 1 was significantly longer than in sessions 1 and 2 (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 SEM 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 (Figure 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 Figure 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 Figure 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 potentials 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 to the decrease in cAmp.

2.3.3.2. 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 2 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 latencies after Ttone 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 Ttone 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 Ttone 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, $p < 0.001$). 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, $p < .001$) and segment 3 (M = 59.31±2.26, $p < .05$). 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 < .001) and segment 3 T/C (M = 0.66±0.01, p < .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 to segment 1. In contrast, there was a slight decrease for both cAmp and tAmp in segments 2 and 3 compared to 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.

2.3.4. Analysis of Variability: Single Units

2.3.4.1. 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 local field potentials. 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 Figure 7.

2.3.4.2. 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.

2.3.5. Conditioned-Test Intervals: Local Field Potentials

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 (Figure 8). We performed a repeated-measures ANOVA whereas the different blocks of CT intervals (150 ms, 500 ms, 1 sec, and 4 sec) served as the repeated-measures factor. For C_{tone} latencies of P60 in the 150 ms, 500 ms, 1 sec and 4 sec 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 $\pm$ 1.07) than in the 500 ms ($M = 79.25$ ms $\pm$ 1.10, $p < 0.001$) , 1 sec ($M = 76.87$ ms $\pm$ 1.07, $p < 0.01$) , and 4 sec ($M = 83.06$ ms $\pm$ 1.10, $p < 0.001$) blocks. P60 latency was longer in the 4 sec block than in the 500 ms ($p < 0.05$) and 1 sec blocks ($p <0.001$). For P60 latencies after Ttone in the 4 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 Ttone latency in the 150 ms block was significantly shorter than in the other blocks (150 ms $M = 65.11 \pm 0.91$, 500 ms $M = 79.48$ ms $\pm$ 1.25, 1 sec $M = 75.16$ ms $\pm$ 1.01, 4 sec $M = 77.27$ ms $\pm$ 0.93, $p < 0.001$). P60 Ttone 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 sec CTI ($p < 0.01$), and the 4 sec 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 CT interval

($p<0.001$): 150 ms < 500 ms < 1 sec < 4 sec. 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 CT interval ($p<0.001$): 150 ms < 500 ms < 1 sec < 4 sec (Figure 8). LFPs demonstrated a category I change in inhibitory gating with each increase in CT interval. 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.

2.3.6. Conditioned-Test Intervals: 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 CT interval 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 Figure 9.

For the E-SD units there were 6 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 sec CTI ($M = 811\pm158$, $p < 0.05$) and the 4 sec CTI ($M = 1557\pm403$, $p < 0.05$) were significantly greater than the tAmp for the 500 ms CTI ($M = 329\pm72$). 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 sec CTI ($M = 1.04\pm0.15$, $p < .001$) were significantly greater than T/C ratios for the 150 CTI ($M = 0.17\pm0.04$, $p < .01$), the

500 ms CTI (M = 0.32±0.06, $p < .01$), and the 1 sec CTI (M = 0.55±0.08, $p < .05$). The T/C ratio for 1 sec CTI were also greater than the T/C ratio for 150 ms CTI ($p<0.01$). Overall for E-SD units, there was an increase in tAmp for the 1 sec and 4 sec CTI compared to the 500 ms CTI , and this increase in tAmp was responsible for the increase in T/C ratio at these CT intervals.

For the E-LD units there were 7 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 sec CTI (M = 464±110) was greater than tAmp ratio for the 500 ms CTI (M = 248±70, $p <0.05$) and tAmp for the 1 sec CTI (M = 139±27, $p < 0.01$). 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 sec CTI (M = 0.95±0.10) was significantly different from the 150 ms CTI (M = 0.50±0.13, $p < .001$), 500 ms CTI (M = 0.44±0.07, $p < .001$), and 1 sec CTI (M = 0.49±0.09, $p < .01$). Overall for ELD neurons, the increase in T/C ratio at the 4 sec CTI compared to shorter intervals was due to the increase in tAmp at the 4 sec CTI.

For the Inh single-units there were 7 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±9, $p = 0.05$) and the 4 sec CTI (M = -77±5, $p = 0.05$) were nearly increased compared to the 500 ms CTI (M = -42±10). 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±0.10, $p < 0.05$)

and the 4 sec CTI (M = 0.91±0.06, $p < 0.05$) were increased compared to the 500 ms CTI (M = 0.51±0.12). Overall for the Inh units, the increases in T/C ratio at the 150 ms and 4 sec CTIs compared to T/C for the 500 ms CTI,, were due to increases in tAmp at the 150 ms and 4 sec CTIs.

2.3.7. Comparing Local Field Potential and Single Unit Activity

In order to compare local field potential 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.

For a first (3 X 2) ANOVA (n=16 wires) was for the *between-sessions* data collected in the paired-stimulus tests over the course of three sequential 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±0.05; session 2 M = 0.46±0.04; session 1 M = 0.39±0.04, $p<0.01$). 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.

Figure 10 depicts single unit and local field potential 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 X 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 sec, 4 sec). 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±0.08) was significantly greater than the T/C ratio for the excitatory single-units (M =0.38±0.05, $p < 0.05$). At the 1 sec CTI the T/C ratio for P60 (M = 0.83±0.05) was significantly greater than the T/C ratio for the excitatory single-units (M = 0.51±0.06, $p < 0.001$).

2.4. Discussion

Analysis of *between-session* effects for LFPs demonstrated that inhibitory gating is relatively stable, if not strengthening, over the course of multiple sessions. There was a gradual decline in both cAmp, tAmp, and T/C ratios from session 1 to session 2 and 3. The effect of decreasing T/C ratios for sessions 2 and 3 might be interpreted as an effect of proportionally greater suppression of tAmp relative to habituation of cAmp. Analysis of *within-session* effects for LFPs showed that inhibitory gating was relatively stable, yet weakening over the course of an initial, extended session of 360 trials. A slight habituation of LFP cAmp *between-session* and *within-session* is consistent with other LFP findings in both humans (Boutros et al, 1991; Clementz, et al, 1997) and rats (Boutros and Kwan, 1998; deBruin et al; 2001). The possibility exists that there were differences in the state of alertness of the animals over the course of multiple sessions or over the course of the extended trials session. However, studies in humans have shown that gating ratios are unaffected by variation within a normal range wakeful alertness. Gating of the P50 does not change significantly due to variations in state of

wakefulness (Cardenas et al, 1997). Furthermore, gating ratios do not vary significantly between wakefulness and REM or non-REM (stage 2) sleep (Kisley et al, 2001). Gating of P50 was also shown to be unaffected by variations in seated vs. supine posture of subjects as they are tested (McCallin et al, 1997) or by conditions of non-movement vs. active or passive movement (Waldo and Freedman, 1986).

Analysis of *between* and *within-session* effects for single-units did not generate significant effects although this is not surprising given the relatively low sample size within each subset of excitatory or inhibitory neurons. Overall, the pattern of single-units with an excitatory-long duration response profile resembled the LFP *between-session* effects for cAmp and T/C ratios.

In order to understand the dynamics of inhibitory gating it was necessary to find the optimal intervals at which suppression of response to T_{tone} occurred. For LFP it was possible to understand differences in T/C ratio and different CTIs by examining differences in cAmp and tAmp. There was a slight decrease for cAmp at the 1 and 4 sec CTI compared to the shorter CTIs, and this slight decrease for cAmp that these intervals has been seen in other studies of LFP in rats (deBruin et al, 2001). There was a far larger increase in tAmp at each successively larger CTI. The increases in T/C ratio are due primarily to increases in tAmp. This type of weakening of inhibitory gating reflects the classical explanation of gating as a rapid, transient suppression of tAmp (Adler, 1982). Studies of human P50 have shown that CT intervals of 0.5, 1, and 2 sec produced T/C ratios of 0.2, 0.6, and 0.7 respectively (Franks et al, 1983) Another study of human P50 demonstrated that CT intervals of 6 sec produced T/C ratios of less than 1.0 and that CTIs need to be 8 to 10 seconds to be closer to T/C ratios that equal 1 (Zourdakis and Boutros, 1992).

Thus, the inhibitory effects of individual tones or pairs of tones might last for as long as 8-10 seconds for human P50.

The results of this first set of experiments establish that inhibitory gating can be localized to mPFC using LFP, and single units. The fact that inhibitory gating a stable, if not slightly strengthening, suggests that inhibitory gating is an inherent property of mPFC that is quickly and robustly established. The fact that optimal intervals have been found and that, surprisingly, the optimal intervals of gating differ between single-units and LFPs suggests that there is some complexity to the mechanisms of the inhibition at a local neurocircuitry level. Now that inhibitory gating has been defined in terms of normal mPFC neuronal activity it will be possible to go on to other manipulations that will provide further information about the function and mechanisms of inhibitory gating in mPFC.

Despite the lack of *between-sessions* and *within-sessions*, statistically significant findings for single-units, there were significant findings for single-unit CTIs. Increases in T/C ratio were due to increases in tAmp. The ESD single-unit T/C ratios increased at each successively larger interval, similar to LFP but with much lower T/C ratios at each interval. The ELD single-unit T/C ratios increased only at 4 sec CTI. The Inh single-unit T/C ratios were similar to LFPs except at the 150 ms CTI.

Chapter 3

INHIBITORY GATING IN MPFC AND FEAR CONDITIONING

3.1. Introduction

Paradigms that test inhibitory gating of AEP in humans and animals are typically very repetitive and emotionally neutral. A few studies of inhibitory gating that have incorporated manipulations of negative affect or acute stress found disruptions of inhibitory gating. Until the present research, no studies have examined direct association of the tones in the inhibitory gating paradigm with negative or stressful experimental conditions.

The purpose of this experiment was to examine how inhibitory sensory gating in rat medial prefrontal cortex (mPFC) can be altered by affective properties associated with a primary aversive event. The mPFC has been shown to be involved in aversive conditioning and fear memory (Quirk and Gehlert, 2003; Maren and Quirk, 2004). In the present experiment, animals were tested gating before and after aversive footshock conditioning. The goal of this research was to address interpretations of variability in gating due to negative properties of the stimuli that were used to test inhibitory gating. No previous studies of gating have directly examined effects related to directly aversive properties of stimuli.

To address the role of aversive footshock conditioning on gating, we examined this potential influence of meaning attribution by studying how aversive conditioning influences gating within mPFC. When stimuli predict punishment or reward they acquire relevance and are attended. Evidence supports the role of mPFC in meaning attribution and attention (Watanabe, 1992; Fuster, 1989; Jodo et al, 1999; Broersen, 2000). Neurons in the mPFC in rabbits have been shown to be responsive to aversively conditioned stimuli (Powell et al, 1996). Furthermore, mPFC appears to play an important role in maintenance of trace fear conditioning in the rat

(Runyan, et al, 2004). It is possible that selective protection occurs for conditioned stimuli, and this protection might manifest itself as a change in inhibitory gating.

In mPFC, increases in single-unit activity have been shown to occur after conditioned tone stimuli (Pirch and Peterson, 1981; Jodo et al, 1999; Shinba, 2002). Research in rabbits has shown that certain cells in the mPFC are activated by stimuli that are aversively conditioned (Powell et al., 1996). Aversive conditioning of an auditory stimulus was found to bring about increases of dopamine and norepinephrine in the mPFC (Feenstra et al, 2001).

Gating might functionally operate to filter out repetitive, uninformative stimuli (Freedman et al, 1994; Moxon et al, 1999). Protocols for gating typically use repetitive stimuli of low informational value. Alternatively, gating might function as a filtering mechanism to inhibit or to enhance processing of incoming stimuli depending on information value (Boutros et al, 1997; Boutros & Belger, 1999). Various studies in humans have been designed in order to account for the effects of attentional manipulations on inhibitory gating of P50. In one study, subjects performed a reaction time task to discriminate the presence of paired or singly presented tones (Jerger et al, 1992). P50 gating was compared to a condition where the presence of a second tone was meaningless. There were no effects on P50 gating regardless of the status of the pair of tones as attended or non-attended.

Very recent research in humans suggests that subjects who observe negatively valenced visual stimuli have reductions in gating of auditory stimulus responses as measured by magnetoencephalographic techniques (Yamashita et al, 2005). Viewing of negative versus neutral visual stimuli was inferred to influence the affective state of the subject which indirectly altered information processing of auditory stimuli as measured by gating. Another study in humans demonstrated that subjects had altered P50 gating while subjected to psychological stress

(White and Yee, 1997). Gating was weakened while subjects listened to pairs of tones and performed oral or silent mental arithmetic. A later study demonstrated that it was the subjects' experience of social stress in the oral arithmetic task that determined the aversive nature of the oral arithmetic task (Yee and White, 2001).

The objective of this experiment was to observe the influence of emotional learning on IG in mPFC. Previously, it was hypothesized that IG depends on neutral and repetitive stimuli (Freedman et al, 1994; Moxon et al, 1999). Acute and chronic stress and manipulations that produce negative affect have been shown to disrupt gating. In light of the existing literature, it was predicted that inhibitory gating would be disrupted if tones used to test gating were associated with negatively valenced conditions.

3.2. Methods

3.2.1. Subjects. The six rats tested in this experiment were the same animals that had been previously tested in Chapter 2. 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. The rat then was tested in a three part gating and fear conditioning protocol that was conducted continuously and without interruption for each subject.

3.2.2. Gating and Fear Conditioning Protocol

3.2.2.1. Pre-conditioning Test: Each animal was tested with a block of 100 identical pairs of 4.1 kHz tones. Stimuli (10 milliseconds duration, 75 decibels) were presented 500 ms apart within each pair, and there was a 10 sec interval separating stimulus pairs.

3.2.2.2. Aversive Conditioning: After pre-testing, each animal was disconnected from the electrophysiology cable, taken out of the testing chamber, and placed into a plexiglass footshock chamber (15 X 20 X 25 cm). The footshock chamber, with rat, was then placed back into the testing chamber. Aversive conditioning took place in a plexiglass footshock chamber that was small enough to be placed inside the recording chamber. During conditioning 30 separate 4.1 kHz tones were presented. Footshock conditioning 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 seconds after the onset of each tone. The footshock was 500 ms in duration, and the footshock co-terminated with the tone. All tones were presented 1-3 minutes apart with the mean separation of two minutes between each tone.

3.2.2.3. Post-conditioning Test: After the aversive conditioning the animal was reconnected to the electrophysiology apparatus, and then post-testing was conducted. The stimulus pairs were identical to those in pre-conditioning.

3.2.3. Data Analysis

3.2.3.1. Local Field Potential Analysis: Evoked potentials were generated through waveform averaging of extracellular local field potentials from each block of trials. Data analysis for LFPs began with t-tests to detect significant activations using a within session comparison. With sliding-window t-tests, P60 was compared to activity during a 1 second control period that started three seconds before each C_{tone}. Only electrode data for P60 that differed from the control period at the 0.001 level of significance were used for further analysis. T-tests were then used to compare cAmp, tAmp, and T/C ratios before and after fear conditioning.

3.2.3.2. Behavior Analysis: In order to assess the behavioral effects of footshock conditioning animals were videotaped during the paired tone testing before and after footshock conditioning. In later observation of the videotapes, animal behavior was coded during delivery of each pair of tones. For sessions before and after footshock conditioning there were 100 observations for each session. These observations were coded according to one of six mutually exclusive classifications: non-movement, non-movement with pinna orientation, head movement / orientation, locomotion, rearing, and grooming. There were two analyses of the coded data. In an analysis of freezing behavior, data were grouped into non-movement and movement categories. The non-movement category included behavior coded as non-movement, non-movement with pinna orientation, and head movement / orientation. The movement category included locomotion, rearing, and grooming. The percentage of trials classified as non-movement out of total trials for each subject served as the functional measure of freezing in the t-test before and after conditioning. In the analysis of orienting responses the coded behavior were alternately grouped into two categories orienting and non-orienting trials. Orienting trials corresponded to trials previously coded as non-movement with pinna orientation and head movement / orientation (Gallagher et al, 1990; Sebastiani et al, 1994). The percentage of orientation trials out of total trials for each animal served as the measure of orienting response for each session. A paired t-test was conducted comparing orienting response before and after conditioning.

3.3. Results

3.3.1. Neuronal Activity Database

A neuronal activity database was compiled for all local field potentials. Evoked potential maxima and minima were compared to baseline at a 0.001 significance level. For subjects in fear conditioning experiment there were 88 out of 96 channels that met selection criteria to be retained for analysis. For recording channels that met criterion, cAmp, tAmp, and T/C ratios were computed and analyzed.

3.3.2. Analysis of Gating: Before and After Fear Conditioning

For 4.1 kHz tone pairs, footshock conditioning produced increases in cAmp, tAmp, and T/C ratios in the after conditioning session compared to before conditioning (Figure 9). There were significant increases of P60 cAmp after aversive footshock conditioning compared to before (before conditioning $M = 77.15 \pm 1.84$; after conditioning $M = 96.60 \pm 2.60$; $t = -7.08$, $p > 0.001$, $df = 87$). There was also a significant increase for tAmp after conditioning compared to before (before conditioning $M = 44.34 \pm 2.04$; after conditioning $M = 64.94 \pm 2.14$; $t = -9.58$, $p > 0.001$, $df = 87$). For T/C ratios there was a decrease in inhibitory gating for the 4.1 kHz tone pairs (before conditioning $M = 0.56 \pm 0.02$; after conditioning $M = 0.68 \pm 0.02$; $t = -6.22$, $p > 0.001$, $df = 87$) after aversive footshock conditioning compared to before conditioning.

3.3.3. Analysis of Behavior: Before and After Fear Conditioning

Separate behavioral analyses of freezing and orienting behavior provided further information on the effects of footshock conditioning. In analysis with paired t-tests, freezing was not significantly affected after ($M = 67 \pm 6$) compared to before ($M = 60 \pm 10$) footshock

conditioning ($p = 0.5$, $df = 5$). Footshock conditioning produced an increase in orienting behavior in the session of paired tone tests after footshock conditioning (Figure 10). Paired t-tests of the percentage of orienting behaviors in each session showed that orienting to tones did increase after footshock conditioning ($t = 5.05$, $p < 0.01$, $df = 5$). This increase in orienting behavior showed that animals were more responsive to tone stimuli after footshock conditioning.

3.4. Discussion

In rat mPFC, fear conditioning leads to a weakening of inhibitory gating. The increase in T/C ratio is rapidly established by the time immediately following after the fear conditioning session. The increase in cAmp and tAmp occurred with as few as thirty footshock pairings of the tone that was used in the paired-tone test. The thirty footshock pairings also led to an increase in orienting to stimuli during the after conditioning paired stimulus test. Although an increase in freezing behavior was not measurable, the increase in orienting response indicates that rats were more aroused and more responsive to tone stimuli.

Stress and arousal have been shown to alter inhibitory gating in humans and animals. Mice subjected to restraint stress have reduced inhibitory gating following restraint stress (Suer et al, 2004). However, in contrast to the present research, the reduction of inhibitory gating was accompanied by a decrease in cAmp following restraint stress. Mild physical discomfort produces reductions of inhibitory gating in humans. Adler and colleagues (1993) found a weakening of inhibitory following the cold pressor test in human subjects. The increase of T/C ratio following the application of the cold bar produced a reduction of cAmp, rather than an increase of cAmp. Normal individuals have decreased inhibitory gating when subjected to a mild psychological stressor (White & Yee, 1997). This study with human subjects also found that cAmp was decreased as T/C ratios increased. All of the acute, mild stressor manipulations of

animal and human subjects produced decrease in cAmp along with an increase in T/C ratio. The present research contrasts with these studies. Although T/C ratios increased following footshock conditioning, there was also an increase, rather than decrease, in cAmp.

Research of inhibitory gating in patients with PTSD has found inhibitory gating deficits (Neylan, et al 1999; Skinner et al 1999; Ghisolfi et al, 2004). Two of the studies of PTSD found an increase in cAmp along with the increase of T/C ratio (Neylan, et al 1999; Skinner et al 1999), and the other study found a negligible decrease in cAmp (Ghisolfi et al, 2004). The post-conditioning decrease of inhibitory gating in rats in the present research is similar to that observed in humans diagnosed with PTSD. The present research bears a closer resemblance to PTSD than the other changes of inhibitory gating. Perhaps, fear conditioning produces a more robust form of stress than the in the other studies of non-disordered populations. A difference between the current research and PTSD is the chronic nature of the disorder of PTSD. Future research of fear conditioning manipulations should examine inhibitory gating at multiple timepoints and at smaller increments of time in order to examine the course of time to establish and to extinguish of this weakening of inhibitory gating.

Chapter 4

NEUROPHARMACOLOGY OF INHIBITORY GATING IN MPFC

4.1 Introduction

The normal functioning of prefrontal cortex depends on a variety of neurochemicals. Besides primary neurotransmitters such as glutamate and GABA that convey information into and within the prefrontal region, there are numerous modulators of neuronal activity. Neurotransmitters and neuromodulators have a variety of receptor types. Often, the normal flow of neuronal information depends on a balance of neurotransmitter binding to certain receptor types, and an imbalance of effect on a particular neuromodulator type can lead to alterations in other neurotransmitter types. Alteration of any one transmitter system can determine alterations in another transmitter system. Countless interactions are possible from the combinations of neurotransmitter types, so a systematic approach is essential to manipulation of prefrontal neurotransmitter systems. We have selected two important prefrontal neurotransmitter systems, dopamine and GABA, to examine the effects of neuropharmacological manipulation of inhibitory gating in mPFC.

4.1.1. Dopamine systems manipulations

Dopamine input has been proposed to have a profound modulatory influence on glutamate systems of the mPFC (Goldman-Rakic & Selemon, 1998; Tzschentke, 2001). Administration of dopaminergic agents, haloperidol and apomorphine, have been shown to respectively increase and decrease power spectra of EEG activity in prefrontal cortex (Sebban et al, 1999a,b). Single-units in the mPFC increase baseline firing rates when haloperidol and clozapine are administered (Kim et al, 2001). Alterations in dopaminergic systems have been

shown to change inhibitory gating as measured by scalp recorded evoked potentials in humans (Light et al, 1999: Adler et al., 2001) and in rats (Adler et al, 1986; Stevens et al, 1996; deBruin et al, 1999). The aim of this experiment was to alter dopamine systems by administration of a dopamine agonist or antagonist and to determine the effects that these dopamine system alterations produced on inhibitory gating in mPFC.

Reduced or enhanced inhibitory gating can occur as a result of independent effects upon either the initial tone response or the second tone responses or as a consequence of a shift in the two tone responses together. The ventral tegmental area (VTA) sends a major dopamine projection to the mPFC (VanEden et al, 1987; Williams and Goldman-Rakic, 1998). Other researchers have found neural responses to visual cues or during delay periods to be altered by dopaminergic manipulations (Murphy et al, 1996).

Drug infusions affecting dopamine neurotransmitter receptors have been shown to influence field potential measures of inhibitory gating. Complementary pairs of neuropharmacological agents were administered to reduce and then restore gating. The broad-spectrum dopaminergic agonist, apomorphine, was shown to eliminate gating in the hippocampus, and then the antagonist, haloperidol, restored gating by countering the action of apomorphine (Stevens et al., 1996; deBruin et al., 2001b). The present experiments add to the findings on inhibitory gating of scalp potentials or hippocampal LFPs by testing the influences of the dopamine system alterations on LFPs in a region that is dependent upon dopamine input for appropriate neural signaling (Seamans et al., 2001; Yang and Seamans, 2004; Trantham-Davidson, et al., 2005).

4.1.2. GABA systems manipulations

Neural communication in the mPFC is influenced by intrinsic inhibitory networks mediated by GABAergic interneurons (Kawaguchi & Kubota, 1997; Kubota & Kawaguchi, 1998; Benes & Beretta, 2001; Gonzalez-Burgos et al, 2005). Specifically, a $GABA_B$ antagonist was administered into the lateral ventricles of rats and there was a reduction of gating measured in the hippocampus (Hershman et al, 1995). $GABA_B$ receptors have figured prominently in hypotheses and explanations (Adler et al., 1998;Martin et al, 2004) and computer models of inhibitory gating (Moxon et al, 2003ab). Local manipulations of $GABA_B$ receptors alter the neural communication in the mPFC (Santiago et al, 1993; Doherty & Gratton, 1999), and changes in the inhibitory dynamics of mPFC should lead to alterations in inhibitory gating. Pentobarbital and other barbiturates have been shown to potentiate the ionotropic, $GABA_A$ receptor (Steinbach and Akk, 2001. The binding of pentobarbital to a specific binding site on the $GABA_A$ receptor has been shown to enhance the conductance of the chloride ion channel that is associated with the receptor. One study of scalp recorded electroencephalographic (EEG) activity demonstrated that a low (sub-anesthetic) dose of pentobarbital (25 mg/kg) altered the profile of EEG power spectra (Sato et al, 1995).

The goal of this experiment was to examine how altering GABA systems with administration of $GABA_B$ agonist or an modulator of $GABA_A$ influenced mPFC mechanisms related to inhibitory gating. GABAergic drugs might also alter inhibitory gating through a number of potential mechanisms. The VTA sends a GABAergic projection to mPFC (Swanson, 1982; Carr & Sesack, 2000). Further, there are an abundance of GABA containing interneurons in the mPFC (Kawaguchi & Kubota, 1997). Manipulations of $GABA_B$ receptors in the mPFC have been shown to produce changes in mPFC dopamine release and in mPFC function (Santiago et al, 1993; Doherty & Gratton, 1999). The $GABA_B$ antagonist, baclofen, has been

used to study inhibitory gating in the hippocampus (Hershman et al, 1995). Administration of pentobarbital was necessary to examine whether manipulations of particular GABA receptors only or modulation of GABA receptors in general would influence inhibitory gating.

The objective of this set of experiments was to examine the neuropharmacology of dopamine and GABA, two neurotransmitter systems that have been shown to influence inhibitory gating in humans and rats. It was predicted that apomorphine would produce an effect similar to the conditions of dopamine excess that have been shown to disrupt IG. Both excesses of dopamine (Stevens et al, 2004) and psychoticism have been shown to disrupt gating (Boutros, 1998). On the other hand, haloperidol has been shown to restore the IG that is disrupted after administration of psychotomimetics. Our predictions were that haloperidol would produce either no effect or enhancement of inhibitory gating. GABA systems have been shown to be disrupted in Schizophrenia (Lewis and Volk, 2002, and the inhibition in IG is likely to be GABA mediated (Boutros and Belger, 1999; Moxon et al, 2003a,b). In light of the existing literature, it was predicted that both baclofen and pentobarbital would enhance inhibitory gating.

4.2. Methods

4.2.1. Subjects

The ten rats tested in this experiment were the same animals that were previously tested in Chapter 2..The animals in these experiments were the same animals that had been previously tested in Chapter 2. Before the start of testing in the paired-tone protocol, the drug or saline was first administered, and then, immediately, the electrode wires for each animal were connected to a cable, leading to the electrophysiology apparatus.

4.2.2. Pharmacology

Drugs were administered by intramuscular injection, and recordings began 5 minutes after injection. The broad-spectrum dopaminergic agonist, apomorphine (1.0 mg/kg), dopaminergic antagonist, haloperidol (1.0 mg/kg), the $GABA_B$ agonist, baclofen (4.0 mg/kg), and the $GABA_A$ potentiator, pentobarbital (25 mg/kg). were administered before drug treatment sessions. Each animal received all four of the drug treatments. In order to prevent contamination of effects, two to four days separated drug treatment sessions. Two sessions occurred for each drug treatment. First, in a pre-drug session, animals received a saline injection, and recordings began 5 minutes after injection. Second, in the drug session one of the four drugs was administered and followed by testing 5 minutes after injection. Pairs of stimuli were presented in blocks of 360 trials at 500 ms CTI similar to the extended session testing in Chapter section 2.2.3.1.

4.2.3. Data Analysis

For analysis, evoked potentials were generated through waveform averaging of extracellular field potentials. Tone responses for LFP recorded from each microwire were analyzed with t-tests to compare the pretrial baseline with LFP activity after C_{tone} and after T_{tone} for each saline or drug treatment session. With sliding-window t-tests, P60 was compared to activity during a 1 second control period that started three seconds before each C_{tone}. A 3X2 repeated measures ANOVA was conducted for P60 cAmp, tAmp and T/C ratio. There were three levels of the segment factor and two levels of treatment factor.

4.3. Results

4.3.1. Neuronal Activity Database

A neuronal activity database was compiled for all local field potentials. Evoked potential maxima and minima were compared to baseline at a 0.01 significance level. For subjects in haloperidol and apomorphine sessions there were respectively 133 and 116 channels that were retained for analysis. For subjects in baclofen and pentobarbital sessions there were respectively 119 and 136 channels that were retained for analysis. For channels that met criterion in the dopamine and GABA manipulations, cAmp, tAmp, and T/C ratios were computed and analyzed.

4.3.2. Dopamine Manipulations

4.3.2.1. Haloperidol. A 3X2 mixed repeated-measures ANOVA was conducted for cAmp. There were three levels of segment: segment 1 (trials 1-120), segment 2 (trials 121-240), and segment3 (trials 241-360). There were two levels of treatment: Saline and Haloperidol injection. The 3X2 repeated measures ANOVA of P60 cAmp revealed a main effect of segment ($F(2, 264) = 106.03$, $p < 0.001$). There was also a significant main effect of P60 cAmp for treatment ($F(1, 132) = 162.69$, $p < 0.01$). There was also a significant interaction of segment X treatment for cAmp ($F(2, 264) = 115.35$, $p < 0.001$).

Post hoc t-tests showed that cAmp was significantly greater for haloperidol compared to saline in each of the three levels of segment (Table 3). Post hoc t-tests for the saline level of cAmp revealed a significant increase in segments 2 and 3 compared to segment 1. Post hoc t-tests for haloperidol showed a significant increase of cAmp in segment 2 compared to segments 1 and 3.

The 3X2 repeated measures ANOVA of P60 tAmp revealed a main effect of segment ($F(2, 264) = 17.60$, $p < 0.001$). There was also a significant main effect of P60 tAmp for treatment ($F(1, 132) = 796.92$, $p < 0.001$). There was also a significant interaction of segment X treatment for tAmp ($F(2, 264) = 82.79$, $p < 0.001$).

Post hoc t-tests showed that tAmp was significantly decreased for haloperidol compared to saline in each of the three levels of segment (Table 4). Post hoc t-tests the saline level of tAmp showed a significant increase for segments 2 and 3 compared to segment 1, and segment 3 was significantly increased compared to segment 2. Post hoc t-tests the haloperidol level of tAmp showed that segment 2 was significantly decreased compared to segments 1 and 3.

A 3X2 mixed repeated-measures ANOVA for P60 T/C ratios revealed a main effect of segment ($F(2, 264) = 26.76$, $p < 0.001$). There was also a main effect of treatment for P60 T/C ratios ($F(1, 132) = 800.21$, $p < 0.001$). There was not a significant interaction of segment X treatment for P60 T/C ratios (Table 5).

4.3.2.2. Apomorphine. A 3X2 mixed repeated-measures ANOVA was conducted for cAmp. There were three levels of segment: segment 1 (trials 1-120), segment 2 (trials 121-240), and segment3 (trials 241-360). There were two levels of treatment: Saline and Apomorphine injection. The 3X2 repeated measures ANOVA of P60 cAmp revealed a main effect of segment ($F(2, 230) = 203.86$, $p < 0.001$). There was also a significant main effect of P60 cAmp for treatment ($F(1, 115) = 1150.13$, $p < 0.001$). There was also a significant interaction of segment X treatment for cAmp ($F(2, 230) = 167.53$, $p < 0.001$).

Post hoc t-tests revealed that cAmp was significantly decreased for apomorphine compared to saline for each of the three levels of segment (Table 6). Post hoc t-tests for the

saline level of cAmp showed a significant increase in segments 2 and 3 compared to segment 1. Post hoc t-tests for the apomorphine level of cAmp showed a significant increase in segment 3 compared to segments 1 and 2.

The 3X2 repeated measures ANOVA of P60 tAmp revealed a main effect of segment ($F(2, 230) = 45.58$, $p < 0.001$). There was also a significant main effect of P60 tAmp for treatment ($F(1, 115) = 273.95$, $p < 0.001$). There was also a significant interaction of segment X treatment for tAmp ($F(2, 230) = 38.08$, $p < 0.001$).

Post hoc t-tests showed that tAmp was significantly decreased for apomorphine compared to saline at each of the three levels of segment (Table 7). Post hoc t-tests for the saline level of tAmp revealed a significant increase in segments 2 and 3 compared to segment 1. There were no significant differences for the apomorphine level of tAmp across the three segments.

A 3X2 mixed repeated-measures ANOVA for P60 T/C ratios revealed a main effect of segment ($F(2, 230) = 11.76$, $p < 0.001$). There was also a main effect of treatment for P60 T/C ratios ($F(1, 115) = 137.56$, $p < 0.001$). There was also a significant interaction of segment X treatment for P60 T/C ratios ($F(1, 230) = 7.79$, $p < 0.001$).

Post hoc t-tests showed that T/C ratio was significantly increased for apomorphine compared to saline for each of the three levels of segment (Table 8). Post hoc t-tests for the saline level of T/C ratio revealed that segments 2 and 3 were significantly decreased compared to segment 1. Post hoc t-tests for the apomorphine level of T/C ratio showed that segment 3 was significantly decreased compared to segments 1 and 2.

4.3.3. GABA Manipulations

4.3.3.1. Baclofen. A 3X2 repeated measures ANOVA was conducted for P60 cAmp. There were three levels of segment. There were two levels of treatment: saline and baclofen. The analysis revealed a main effect of segment ($F(2, 236) = 3.5$, $p < 0.05$).
There was also a significant main effect of treatment ($F(1, 118) = 30.73$, $p < 0.001$). There was a significant interaction of segment X treatment ($F(2, 236) = 24.15$, $p < 0.001$).

Post hoc t-tests showed that cAmp was significantly decreased for baclofen compared to saline in segment levels 2 and 3 (Table 9). Post hoc t-tests for the saline level of cAmp showed segment 3 was significantly increased compared to segments 1 and 2. Post hoc t-tests for the baclofen level of cAmp showed that segment 3 was significantly decreased compared to segments 1 and 2.

A 3X2 repeated measures ANOVA of tAmp revealed a main effect of segment ($F(2, 236) = 17.20$, $p < 0.001$). There was also a main effect of treatment for tAmp ($F(1, 118) = 319.91$, $p < 0.001$). The analysis also demonstrated a significant interaction of segment X treatment for tAmp ($F(2, 236) = 32.65$, $p < 0.001$).

Post hoc t-tests showed that tAmp was significantly decreased for baclofen compared to saline at each of the three levels of segment (Table 10). Post hoc t-tests for the saline level of tAmp showed that segment 2 was significantly decreased compared to segments 1 and 3.Post hoc t-tests for the baclofen level of tAmp revealed that segment 2 was significantly decreased compared to segment 1, and segment 3 was significantly decreased compared to segments 1 and 2.

A 3X2 repeated measures ANOVA of T/C ratios showed a main effect of segment ($F(2, 236) = 14.06$, $p < 0.001$). The analysis revealed a main effect of treatment ($F(1, 118) = 140.27$,

$p < 0.001$). There was also a significant interaction of segment X treatment ($F(2, 236) = 11.08$, $p < 0.001$).

Post hoc t-tests showed that T/C ratio was significantly decreased for baclofen compared to saline at each level of segment (Table 11). Post hoc t-tests showed no significant differences for the saline level of T/C ratio. Post hoc t-tests for the baclofen level of T/C ratio revealed that segments 2 and 3 were significantly decreased compared to segment 1.

4.3.3.2. Pentobarbital. A 3X2 repeated measures ANOVA was conducted for P60 cAmp. There were three levels of segment: pre-conditioning day, post-conditioning day 1, and post-conditioning day 2. There were two levels of treatment: saline and baclofen. The analysis revealed a main effect of segment ($F(2, 270) = 106.17$, $p < 0.001$). There was also a significant main effect of treatment ($F(1, 135) = 77.79$, $p < 0.001$). There was a significant interaction of segment X treatment ($F(2, 270) = 7.15$, $p < 0.01$).

Post hoc t-tests revealed that cAmp was significantly greater for pentobarbital compared to saline at each level of segment (Table 12). Post hoc t-tests for the saline level of cAmp showed a significant increase in segments 2 and 3 compared to segment 1, and there was also a significant increase in segment 3 compared to segment 2. Post hoc t-tests for the pentobarbital level of cAmp revealed a significant increase in segments 2 and 3 compared to segment 1, and there was also a significant increase in segment 3 compared to segment 2.

A 3X2 repeated measures ANOVA of tAmp revealed a main effect of segment ($F(2, 270) = 36.67$, $p < 0.001$). There was also a main effect of treatment for tAmp ($F(1, 135) = 15.13$, $p < 0.001$). The analysis also demonstrated a significant interaction of segment X treatment for tAmp ($F(2, 270) = 8.71$, $p < 0.01$).

Post hoc t-tests showed that tAmp was significantly greater for pentobarbital compared to saline at segment levels 1 and 3 (Table 13). Post hoc t-tests for the saline level of tAmp revealed a significant increase in segments 2 and 3 compared to segment 1. Post hoc t-test for the pentobarbital level of tAmp showed a significant increase in segments 2 and 3 compared to segment 1.

A 3X2 repeated measures ANOVA of T/C ratios showed a main effect of segment ($F(2, 270) = 4.85$, $p < 0.05$). There was not a main effect of treatment for T/C ratios. There was also a significant interaction of segment X treatment ($F(2, 270) = 4.41$, $p < 0.05$).

Post hoc t-tests showed that T/C ratio was significantly decreased for pentobarbital compared to saline only at the level of segment 2 (Table 14). Post hoc t-tests for the saline level of T/C ratio showed that segment 3 was less than segment 2. Post hoc t-tests for the pentobarbital level of T/C ratio showed that segments 2 and 3 were significantly less than segment 1.

4.4. Discussion

4.4.1. Dopamine Manipulations

Manipulations of dopamine neurotransmitter systems produced contrasting effects on inhibitory gating. Administration of haloperidol increased inhibitory gating and administration of apomorphine produced decreases in inhibitory gating. The net effect of haloperidol, a dopamine D_2 receptor antagonist, was an increase in cAmp and a decrease in tAmp, and a decrease in T/C ratio (Figure 9A). The net effect of apomorphine, a dopamine D_1/D_2 receptor agonist, was a dramatic decrease in cAmp and tAmp and an increase in T/C ratio (Figure 9B).

4.4.1.1. Haloperidol Differences between saline and haloperidol for both cAmp and tAmp were utilized to interpret differences between saline and haloperidol for T/C ratios at the level of each section. There were increases in cAmp and, inversely, decreases in tAmp that contributed to reductions in T/C ratios for haloperidol compared to saline at the level of each section. For the level of saline, there were proportionally larger increases in cAmp than tAmp that led to an increase in T/C ratio for section 2 compared to section 1. There was an increase in tAmp that led to a decrease in T/C ratio in section 3 compared to section 2. For the level of haloperidol there were both increases in cAmp and decreases in tAmp that led to a reduction in T/C ratio between section 2 and section 1. There were decreases in cAmp and increases tAmp that led to an increase in T/C ratio from section 2 to section 3.

The response of cAmp following administration of haloperidol is not surprising, for studies of scalp recorded EEG above prefrontal cortex have shown that an identical dose of haloperidol (1 mg / kg), compared to saline, increases spectral power by greater than 150% in the 2-30 Hz range (Sebban et al, 1999a). This reported increase in EEG spectral power along with our observed increase in cAmp makes the decrease in tAmp particularly impressive. The effect of haloperidol over the course of the session was stable, and this effect was predicted by a relatively long half-life of haloperidol compared to the length of the recording session. One estimate of half-life of haloperidol at this concentration (1 mg/kg) was to 1.5 hours (Cheng and Paalzow, 1992). Another estimate of haloperidol administered at this concentration (1 mg/kg) was 2.6 hours (Wurzburger et al, 1981). Reviews of the behavioral effects of haloperidol showed that rats are susceptible to catalepsy (i.e., paucity of movement) at this dose, and catalepsy reflects the extra-pyramidal side effects of D2 antagonists (Kapur et al, 2000). One study of cataleptic side effects of haloperidol (Ezrin-Waters and Seeman, 1977) revealed that catalepsy

was initially low at this dose, but the side effects continued to increase for a while afterwards (2-4 hrs). For a lower dose of haloperidol side effects continued to increase from 1-2 hrs, but the increase leveled off for 3-4 hrs after injection of haloperidol (0.5 mg/kg). Observation of rats in this study revealed that rats became cataleptic during the middle to end of segment 2, and they were immobile for the remainder of the recording session.

4.4.1.2. Apomorphine Differences between saline and apomorphine for both cAmp and tAmp were used to interpret differences in T/C ratio at the level of each section. Comparing apomorphine saline, at the level of each section, there were proportionally larger decreases in cAmp compared to the decreases in tAmp that led to increases in T/C ratios. For the saline level from section 1 to section 2 there was a proportionally greater increase in cAmp than tAmp that contributed to the decrease in T/C ratio. For the saline level from section 2 to section 3 there are no differences in cAmp, tAmp, or T/C ratio. For the apomorphine level from section 1 to section 2 there were no differences in cAmp, tAmp, or T/C ratio. However, for the apomorphine level from section 2 to section 3 there was a cAmp increase that led to a decrease in T/C ratio.

Studies of scalp recorded EEG above prefrontal cortex in rats during administration of a smaller dose of apomorphine (0.5 mg / kg) revealed a 10 percent reduction in spectral power in the range of 4-30 Hz (Sebban et al, 1999b). Despite the higher dose of apomorphine (1 mg/kg) in our study the 80-90% reduction in cAmp would not be explained by a small reduction in background EEG spectral power. From real-time monitoring during our experiment, ongoing EEG activity was observed on an oscilloscope. Another explanation is that the reduction of auditory evoked potentials in our experiment depends on information other than background EEG spectral power. The reduction in T/C ratio from 0.95 to 0.65 in segments 2 and 3 and the slight increase in cAmp in segment 3 might reveal the waning effect of apomorphine. In effect,

the clearance of apomorphine in the rat is quite rapid. Two studies reported a very short blood plasma terminal half-life for apomorphine. For a similar dose of apomorphine (1.25 mg/kg) to our study, half-life of about 10 minutes ($t_{1/2}$ =10.8 minutes) was reported (Bianchi et al., 1986). In another study of a higher dose of apomorphine $t_{1/2}$ = 13.8 minutes was reported (Paalzow and Paalzow, 1986). Reviews of the behavioral effects of apomorphine revealed a host of stereotypical behaviors. In our study, rats began sniffing, chewing, and circling behaviors within sixty seconds after apomorphine injection. The stereotypical behavior continued until a midway in time point in segment 2. One study (Paalzow and Paalzow, 1986) of stereotypy after a dose of apomorphine (1.25 mg/kg) similar to that in our study, revealed that stereotypical behaviors began immediately after injection and sharply declined between 30-45 minutes of after injection. Stereotypical behavior continued through 1 hour for larger doses of apomorphine (2.5 and 5 mg / kg).

4.4.2. GABA Manipulations

Manipulations of GABA neurotransmitter systems revealed effects on inhibitory gating depending on the receptor type involved. Baclofen affected the $GABA_B$ receptor, and pentobarbital involved $GABA_A$ receptor. Manipulations of $GABA_B$ receptors led to reductions in cAmp and tAmp, but there were larger effects on inhibitory gating as measured by T/C ratios (Figure 10A). Manipulations of $GABA_A$ receptors led to increases in cAmp and tAmp, but there were minimal effects on inhibitory gating as measured by T/C ratios (Figure 10B).

4.4.2.1. Baclofen Differences between cAmp and tAmp were used to interpret differences in T/C ratio at the level of the section on the levels of saline and baclofen. For baclofen compared to

saline at the level of each section, there were proportionally greater decreases in tAmp than cAmp that led to decreases in T/C ratio. At the level of saline cAmp and tAmp proportionally increased and decreased from section to section, and there were no differences in T/C ratio to interpret. At the level of baclofen there were proportionally larger decreases in tAmp than cAmp contributing to sequential decreases in T/C ratio in the following relationship: section 1 > section 2 > section 3.

Administration of baclofen produced decreases in cAmp and even larger decreases in tAmp that led to decreases in T/C ratios. Studies of scalp recorded EEG have shown that baclofen produces reductions in background EEG spectral power (Mandema et al, 1992). A lower dose of baclofen (1.25 mg/kg) was administered in the study. The onset of EEG spectral power alterations did not begin until 20 minutes post injection. A 15 percent reduction in background EEG power was observed between 11.5 and 30 Hz. This effect peaked between 20 and 70 minutes post injection. The authors concluded that the slow onset of EEG power reduction reflected a relatively slow blood-brain barrier clearance for baclofen. Similarly, the effects of baclofen in the present study revealed that decreases in cAmp and even larger decreases in tAmp and T/C ratios became more prominent at later time points in the recording session. Another study (Deguchi et al, 1995) has examined this slow rate of blood-brain barrier clearance and has revealed a relatively long half-life for baclofen (pharmacokinetic parameters allow calculation of a $t_{1/2}$ = 176 minutes). The half-life of for a low dose of baclofen (1.25 mg/kg) was $t_{1/2}$ = 120 minutes (Mandema et al, 1992). Overall, baclofen has slow distribution and even slower clearance, so the effects of baclofen would be most prominent at later time points in the recording session. In the present study, animals injected with baclofen tended to

become more sedate in segments 2 and 3. These animals were observed to be inactive for hours after the recording session.

4.4.2.1. Pentobarbital Differences between cAmp and tAmp were used to interpret differences in T/C ratio at the level of each section and at the levels of saline and pentobarbital. For pentobarbital compared to saline at the level of section 2 there was an increase in cAmp contributing to the decrease in T/C ratio. At the level of saline, the difference in T/C ratio from section 2 to section 3 was due to an increase in cAmp. At the level of pentobarbital, there was a decrease in cAmp from section 1 to section 2 that contributed to the decrease in T/C ratio.

Administration of pentobarbital revealed proportional increases in cAmp and tAmp, yet the proportionality of cAmp relative to tAmp led to relatively small differences in T/C ratios. One study by Sato and colleagues (1995) of scalp-recorded EEG background activity revealed 20 percent increases in power spectra almost immediately after injection of pentobarbital (20 mg / kg). Other studies of pentobarbital revealed a range of half-lives depending on the particular dose that was administered: $t_{1/2}$ = 102.9 min for 40 mg/kg injection (Fruncillio and DiGregorio, 1984) and $t_{1/2}$ = 53 min for 27.7 mg/kg injection (Stella and Chu, 1980). Animals in this experiment were sedate for segments 1 and 2, but a few animals struggled in segment 3 with postural equilibrium difficulties. Hatanaka and colleagues (1988) studied the recovery of the righting reflex after doses of pentobarbital. They found that recovery of the righting reflex begins at 30 min post-injection for a 20 mg / kg dose of pentobarbital. They also found that plasma concentrations of pentobarbital are at 50% of their original value at 45 min post-injection at this dose. The recovery of the righting reflex would agree with the postural equilibrium difficulties of rats in this experiment.

4.4.3. Conclusions

As was predicted, apomorphine weakened inhibitory gating, and haloperidol strengthened inhibitory gating. Some further effects of dopamine manipulations included a decrease in cAmp with the D_1/D_2 agonist, apomorphine. The decrease in the amplitude of cAmp was far greater than predicted from suppression of background EEG power alone (Sebban et al, 1999a). The reduction in P60 amplitude was possibly due to a decrease in evoked rather than baseline local field potential activity. The increase in cAmp in the third segment was consistent with a drop in circulating blood levels of apomorphine that could be predicted by pharmacokinetic models of drug distribution. The D_2 antagonist, haloperidol produced an increase in cAmp and strengthening of inhibitory gating, which were the converse of the effects of apomorphine. The decrease in tAmp for haloperidol compared to saline, revealed that the strengthening of IG was due to a combination of tAmp and cAmp effects.

As predicted, the $GABA_B$ agonist, baclofen, produced strengthening of inhibitory gating and a decrease in both tAmp and cAmp. The fact that the statistically significant decrease in T/C ratios did not begin until 20 minutes into the recording session is consistent with slow distribution of baclofen that was predicted by pharmacokinetic models of this drug.

Finally, the effects of the $GABA_A$ agonist, pentobarbital, on inhibitory gating were much weaker than expected, producing only a slight strengthening of inhibitory gating during the middle recording segment. The increase in cAmp and tAmp was consistent with increases in EEG power spectra that have been observed with this dose of pentobarbital.

Chapter 5

GENERAL DISCUSSION

5.1. Comparisons of inhibitory gating: present findings and other studies

The results of the of experiments in chapter 2 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 analysis of inhibitory gating towards investigating the functional significance of IG within the medial prefrontal cortical regions. The 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 one neural structure to another with the basic patterns of inhibition appearing very similar. For example, around 80% of tone responsive neurons in the amygdala display IG, and these neurons can be grouped into similar subtypes observed in the mPFC (Cromwell et al., 2005). These neural responses follow the tone onset with short or long duration responses that are either excitatory or inhibitory, and tone responsive neurons 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.

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 timepoints. 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; Clementz, et al, 1997; Freedman, et al, 1991). 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 15). The first category (I) of inhibitory gating 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 inhibitory gating was designated as a difference in T/C 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.

5.2. Variability of IG in mPFC

5.2.1 Between-sessions analysis

Between-sessions analysis for LFPs showed that there was a decrease in T/C ratio, cAmp, and tAmp in sessions 2 and 3 compared to 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.

5.2.2. Within-session analysis

The within-session analysis of LFPs demonstrated a decrease of the magnitude of cAmp and tAmp over segments 2 and 3 compared to 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 evoked potentials

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).

5.2.3. Conditioned-Test Intervals

The analysis of *Conditioned-test intervals* 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 sec, and 4 sec) 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 Conditioned-Test intervals (Freedman, et al, 1983; Adler, et al, 1986; Nagamoto et al., 1989; Nagamoto,et al 1991; Zouridakis and Boutros, 1992; Dolu, et al, 2001). One study limited the gating of P50 to Conditioned-Test intervals less than 1 second. Two studies of rat evoked potentials have examined the effects of Conditioned-Test intervals (Jongsma et al, 1998; de Bruin, et al 2001). One study limited gating to Conditioned-Test intervals less than 1 to 2.5 seconds (de Bruin, et al 2001).

Thus far, there have been no other studies have examined the effects of Conditioned-Test intervals 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 single-units were classified according to three subgroups, ESD, ELD and Inh, inhibitory gating 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 E-SD 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 E-LD single-units, only the 4 sec 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 sec CTI was entirely due to an increase in tAmp for the 4 sec CTI compared to tAmp at other CTIs. For Inh single-units, there was weakening at both the 150 ms and 4 sec CTIs compared to the 500 ms CTI. The increases in T/C ratios at the 150 ms and 4 sec CTIs was due to an increase in the magnitude of tAmp.

5.2.4. Comparing LFPs and Single-Units

Comparisons of CTI effects between LFPs and single-units reveals that, at the 1sec CTI, LFPs and single-units had different response properties. At the 1sec 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 sec 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 local field potentials 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 would correspondingly be related to information outgoing from a mPFC neuron. The fact that P60 T/C ratios at the 1 sec CTI are significantly different from single-unit T/C ratios at the 1 sec 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 1sec 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.

5.3. 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 (Conde et al., 1995; Reep et al., 1990). 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 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 E-SD single unit activity due to rapid conduction (Shaw, 1995). Subsets of single units had onset of activity increase between 15-20 msec 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 gamma amino butyric acid (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, 1995b) and lesions to this structure significantly reduce the P50 evoked potential (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. 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 ~15msec). 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). An understanding of the fundamental neuropharmacology of IG will enable more effective clinical applications of IG as a neurophysiological tool.

5.4. Fear conditioning

The results of the experiment in chapter 3 provide support that inhibitory gating might be disrupted by fear conditioning. It appears that the comparable pattern of inhibitory gating that was demonstrated in the first set of experiments (i.e., in chapter 2) was also continued for the before conditioning block of paired-tones in chapter 3. The current research presents a novel finding for rat mPFC, as inhibitory gating weakened after aversive footshock conditioning with the tone that was used to test gating. This reduction of inhibitory gating may be characterized as a category I weakening of gating. There was an increase in T/C ratio and an increase in both cAmp and tAmp. Because the T/C ratio increased, the change of ratio was primarily due to an increase of a tAmp, for the increase in cAmp would have decreased the ratio if tAmp had not increased in greater proportion.

In some ways the pattern of our results resembles inhibitory gating effects found in mice that were subjected to restraint stress. Suer (2004) and colleagues recorded hippocampal N40 LFP in mice before and after subjecting the mice to forceful restraint. The aversive experience of forceful restraint produced an increase in T/C ratio that was due to a decrease in cAmp and an increase in tAmp. The decrease in tAmp was interpreted to be caused by a loss of the inhibitory

influence on the conditioning tone. However, the cAmp decrease after stress in the mice (Suer et al, 2004) is different from our results, as we found that both cAmp and tAmp increased (Chapter 3). In some ways, the results of chapter 3 are similar to the effects of psychological stress on inhibitory gating of scalp-recorded human P50. White and Yee (1997) recorded P50 responses in the paired-tone paradigm in three separate conditions. In one condition subjects performed a silent mental arithmetic task, and inhibitory gating was not different from measures of inhibitory gating that were recorded under standard paired-tone conditions of passive listening. In the third condition, subjects performed the mental arithmetic task out-loud in the presence of the researchers. Subjects described this oral arithmetic task as mildly aversive compared to the silent arithmetic task. The oral arithmetic task produced increases in T/C ratios compared to T/C ratios in both the silent arithmetic and standard paired-tone paradigms. Our results differ from the experience of mild psychological stress for humans. For mild psychological stress there was a reduction of cAmp and increase in T/C. After fear conditioning (present results) there was an increase of cAmp while T/C ratios also increased in comparison to before fear conditioning.

In order to further characterize the parallels between these clinical conditions and the pattern of results in the present research, work is necessary to study the neurotransmitter systems and brain areas involved. Results of the present research will likely enhance our understanding of basic patterns of neural dysfunction that may underlie cognitive and emotional impairment in schizophrenia as well as many other human brain disorders. Linking this research with studies of related neurotransmitter effects in mPFC, large increases in dopamine release have been shown to accompany fear conditioning (Feenstra et al, 1999). The relation of amounts of dopamine released in PFC to optimal function has been shown to follow a bell-shaped curve (Murphy et al., 1996). Stress related increases in prefrontal dopamine levels have been shown to alter prefrontal

function (Arnsten, 1998). Therefore, it would not be surprising that other functions of prefrontal cortex should also be affected by stress and excessive release of dopamine (Pezze and Feldon, 2004; Rosenkranz and Grace, 2001).

5.5. Neuropharmacological Manipulations

The results of the third set of experiments from chapter 4 provide support that dopamine and GABA neurotransmitter systems influence inhibitory gating in mPFC. The results of these experiments are novel, in that inhibitory gating in mPFC has never been examined in relation to these pharmacological manipulations. In essence, our manipulations in these experiments test four neurotransmitter receptor types. For dopamine systems, D1 and D2 receptor types were manipulated, and for GABA systems $GABA_A$ and $GABA_B$ receptor types were manipulated. Apomorphine is a dopamine D_1 and D_2 receptor agonist (DiChiara and Gessa, 1978), and the effects of brief but maximal stimulation of D_1 / D_2 receptors together was examined in relation to inhibitory gating. Haloperidol is a selective D_2 antagonist (Cheng and Paalzow, 1992; Kapur et al, 2000), and the effects of D_2 receptor blockade was examined in relation to inhibitory gating. $GABA_B$ receptors are found throughout prefrontal cortex in the human and rat (Ishikawa et al, 2005; Steketee and Beyer, 2005), and baclofen is a selective agonist for this metabotropic receptor (Marshall, 1999; Hammond, 2001). This manipulation of the receptor allowed an examination of $GABA_B$ effects on inhibitory gating. Pentobarbital is a drug that increases the conductance properties of the $GABA_A$ chloride channel through action at the beta-3 subunit, and at lower doses of pentobarbital the drug potentiates the ionotropic effect of endogenous GABA at the $GABA_A$ receptor (Serafini et al, 2000). Administration of pentobarbital allowed an examination of the effect of $GABA_A$ enhancement on inhibitory gating.

5.5.1. Dopamine system manipulations

Differences between saline and haloperidol for both cAmp and tAmp were utilized to interpret differences between saline and haloperidol for T/C ratios at the level of each segment. There were increases in cAmp and, inversely, decreases in tAmp were that contributed to reductions in T/C ratios for haloperidol compared to saline at the level of each segment. This pattern of change was interpreted to be a category III strengthening of gating for haloperidol compared to saline at each segment.

Differences between saline and apomorphine for both cAmp and tAmp were used to interpret differences in T/C ratio at the level of each segment. At the level of each segment, there were proportionally larger decreases in cAmp compared to the decreases in tAmp that led to increases in T/C ratios. This pattern of gating change was interpreted to be category II weakening of gating at each segment for apomorphine compared to saline.

5.5.2. GABA system manipulations

Differences between cAmp and tAmp were used to interpret differences in T/C ratio at the level of the segment on the levels of saline and baclofen. At the level of each segment, there were proportionally greater decreases in tAmp than cAmp that led to decreases in T/C ratio. This pattern of change was interpreted to be category I strengthening of gating at segments 2 and 3 for baclofen compared to saline.

Differences between cAmp and tAmp were used to interpret differences in T/C ratio at the level of each segment and at the levels of saline and pentobarbital. At the level of segment 2

there was an increase in cAmp contributing to the decrease in T/C ratio. This pattern of changes in gating was interpreted as category II strengthening at segment 2.

The magnitude of effects of the drugs and the study range from slight to large, but the effect of each drug varied in numerous ways from the other drugs. Haloperidol produced an increase in cAmp and a decrease in T/C ratio, and apomorphine produced an opposite pattern, with cAmp decrease and T/C ratio increase. Potentially, these two patterns were the result of the contrasting actions of blockade or stimulation of the D2 receptor. However, further research with a D_2 specific agonist, rather D_1/D_2 agonist, is necessary to rule out effects of apomorphine at the D_1 receptor. The effects of the GABA manipulations were opposite. $GABA_B$ agonist, baclofen, decreased cAmp and tAmp, and the $GABA_B$ agonist, pentobarbital, increased cAmp and tAmp. Pentobarbital and baclofen produced strengthening of inhibitory gating to varying degrees. Compared to saline, pentobarbital produced a slight category II strengthening of gating in the middle recording session segment. Baclofen produced category one strengthening of inhibitory gating in the latter two segments of recording sessions.

5.6. Examination of present findings in context of other research

In order to fully understand the relationship of the present research to the broader field of translational neuroscience of inhibitory gating it was necessary to find a suitable means of comparison amidst a variety of measurement and analysis techniques in the animal model and human populations. By comparing across many studies it will be possible to generalize some of the findings according to the new classification scheme for gating changes. Using the three categories of changes in inhibitory gating, it was possible to model the results of a number of important studies in the animal model and in humans.

Sensory gating has classically been defined as inhibition of the neural response to a second identical stimulus (tAmp) due to its repetition following a first stimulus (cAmp) (Adler et al, 1982; Freedman, et al, 1983; Siegel et al, 1984; Freedman, et al, 1991; Freedman, et al, 1996). A computational model of this inhibition has been proposed in order to represent some contributing factors to inhibitory gating in the hippocampus (Moxon et al, 2003a,b).

The loss of inhibition in schizophrenia has been hypothesized to contribute to cognitive dysfunction in schizophrenia. One of the hallmarks of attention problems is the inability to suppress responsiveness to irrelevant stimuli (McGhie and Chapman, 1961; Knight, et al, 1989; Knight et al, 1999; Cullum, et al, 1993). However, there are analytical aspects that complicate the standard description of sensory gating (Clementz et al, 1997; Light and Braff, 1998; Freedman et al, 1998). Furthermore, on a more fine-grained level of analysis, other factors might influence measurement of sensory gating. Evoked potentials such as LFPs in animals and the P50, a mid-latency evoked potential, in humans might be viewed as a measure of neuronal synchrony (Winterer, et al, 2000; Makeig, et al, 2002; Jin, et al, 1997; Patterson et al, 2000; Jensen, et al, 2003; Jensen, et al, 2004). Maximal evoked potential generation relies on consistent synchronization of neural activity with reference to the time-point of the sensory stimulus. One explanation of why individuals with schizophrenia have weak sensory gating suggests that there is poor temporal synchronization of the response to the first stimulus (Ctone) of a pair of stimuli, whereas temporal synchronization of the response to the second stimulus (Ttone) remains less altered in comparison (Jin, et al, 1997; Patterson et al, 2000; Jensen, et al, 2004). It has been observed that there is a decrease in the amplitude of response to the first stimulus in unmedicated schizophrenics (Adler, et al, 1982; Cullum, et al, 1993; Freedman, et al, 1987a,b; Blumenfeld and Clementz, 2001).

5.6.1. Categorizing Gating Changes: A mathematical model

To review, in order to more precisely quantify the factors that produce gating changes in the results of the present research, we have used statistical significance testing to determine differences in cAmp, tAmp, and T/C ratio in many different experimental conditions. The statistically significant differences in cAmp and tAmp were then used to interpret significant differences in T/C ratio across conditions. However, for the majority of research of inhibitory gating, little effort is made to systematically assess how relative differences in cAmp and tAmp contribute to changes in T/C ratios. One problem with utilizing mathematical ratios to represent proportions is that the differences between the resulting products are nonlinear. For example, the proportions 1:5 and 1:7 yield the ratios 0.2 and 0.143, respectively, and the proportions 5:1 and 7:1 yield the ratios of 5.0 and 7.0. The differences between the ratios for 1:7 and 1:5 equals about 0.06, yet the differences between the ratios for 7:1 and 5:1 equals 2. One solution is to make the system numbers linear by using a logarithmic transform. Logarithms were invented in order to simplify complexities of multiplication and division with groups of numbers. Using the natural logarithms, (i.e., log base e) the previous system of proportions becomes linear.

ln(1/5) = -1.61	**ln(1/7) = -1.95**
ln(5/1) = +1.61	**ln(7/1) = +1.95**

The difference between the first two ratios and the difference between the inverse counterparts of these ratios are -0.34 and 0.34, respectively. Using a logarithmic transform of the data, it is possible to compare proportions and ratios in a linear fashion.

The description of categories of gating change depends on using proportional differences. The formalization of categories of change (Table 15) based on proportional differences can also be defined in terms of a logarithmic transform (Table 16). The key advantage of using the

logarithmic transform is that where the ratio is 1:1 the natural logarithm is zero, and proportions greater than 1 or less than 1 are transformed, respectively, to positive or negative numbers. In order to demonstrate utility of a logarithm-transform and with categories of gating changes, four examples will follow: category I weakening, category II strengthening, category III weakening, and category III weakening. A category I weakening of gating is defined as a reduction in T/C ratio from condition A to condition B whereas, the change in T/C ratio is due to a proportionally greater increase of tAmp in condition B.

Example 1: $\mathbf{cAmp_{condition\ A} = 80}$ $\mathbf{tAmp_{condition\ A} = 40}$ $\mathbf{T/C_{condition\ A} = 0.50}$
$\mathbf{cAmp_{condition\ B} = 80}$ $\mathbf{tAmp_{condition\ B} = 60}$ $\mathbf{T/C_{condition\ B} = 0.75}$

$\mathbf{\ln(cAmp_{condition\ B} / cAmp_{condition\ A}) = \ln(80 / 80) = 0}$
$\mathbf{\ln(tAmp_{condition\ B} / tAmp_{condition\ A}) = \ln(60 / 40) = 0.405}$
$\mathbf{\ln(T/C_{condition\ B} / T/C_{condition\ A}) = \ln(0.75 / 0.50) = 0.405}$

A category I strengthening of gating is defined as an increase in T/C ratio from condition A to condition B whereas, the change in T/C ratio is due to a proportionally greater decrease of tAmp in condition B.

Example 2: $\mathbf{cAmp_{condition\ A} = 80}$ $\mathbf{tAmp_{condition\ A} = 60}$ $\mathbf{T/C_{condition\ A} = 0.75}$
$\mathbf{tAmp_{condition\ B} = 80}$ $\mathbf{tAmp_{condition\ B} = 40}$ $\mathbf{T/C_{condition\ B} = 0.50}$

$\mathbf{\ln(cAmp_{condition\ B} / cAmp_{condition\ A}) = \ln(80 / 80) = 0}$
$\mathbf{\ln(tAmp_{condition\ B} / tAmp_{condition\ A}) = \ln(40 / 60) = -0.405}$
$\mathbf{\ln(T/C_{condition\ B} / T/C_{condition\ A}) = \ln(0.50 / 0.75) = -0.405}$

A category II weakening of gating is defined as a proportionally greater change of cAmp than the change of tAmp contributing to an increase in T/C ratio.

Example 3: $\mathbf{cAmp_{condition\ A} = 100}$ $\mathbf{tAmp_{condition\ A} = 50}$ $\mathbf{T/C_{condition\ A} = 0.50}$
$\mathbf{tAmp_{condition\ B} = 60}$ $\mathbf{tAmp_{condition\ B} = 45}$ $\mathbf{T/C_{condition\ B} = 0.75}$

$\mathbf{\ln(cAmp_{condition\ B} / cAmp_{condition\ A}) = \ln(50 / 100) = -0.511}$
$\mathbf{\ln(tAmp_{condition\ B} / tAmp_{condition\ A}) = \ln(45 / 60) = -0.105}$
$\mathbf{\ln(T/C_{condition\ B} / T/C_{condition\ A}) = \ln(0.50 / 0.75) = 0.405}$

In the above example it is important to note that the denominator (i.e., cAmp) of the T/C ratio has changed proportionally more than the numerator (i.e., cAmp), resulting in an overall increase

of T/C ratio. A logarithmic transform makes this difference linear, regardless of whether each proportion is small or large, and a direct comparison of proportional changes for tAmp and cAmp is possible. Finally, in category III weakening of gating, a decrease of cAmp and decrease of tAmp contribute collectively to the increase T/C ratio from condition A to condition B.

Example 4: **$cAmp_{condition\ A} = 100$ $tAmp_{condition\ A} = 50$ $T/C_{condition\ A} = 0.50$**
$cAmp_{condition\ B} = 80$ $tAmp_{condition\ B} = 60$ $T/C_{condition\ B} = 0.75$

$\ln(cAmp_{condition\ B} / cAmp_{condition\ A}) = \ln(80 / 100) = -0.223$
$\ln(tAmp_{condition\ B} / tAmp_{condition\ A}) = \ln(60 / 50) = 0.182$
$\ln(T/C_{condition\ B} / T/C_{condition\ A}) = \ln(0.50 / 0.75) = 0.405$

Another advantage of using a logarithmic transform to analyze proportional differences of gating across experimental conditions is that the relationships can be more easily compared across different inhibitory gating paradigms. For instance, cAmp for single-units and local field potentials are not directly comparable because single units are measured in spikes/sec and local field potentials are measured in tens and hundreds of millivolts. However, the computed proportions are directly comparable, and log-transformation makes these proportions linear. This property is useful in comparing data from rats to data collected on scalp EEG from clinical populations. The scale of scalp EEG measured in humans usually yields measurements of magnitude less than 10 millivolts. Thus, applying the logarithmic transform to analyze proportional differences of gating is useful to compare measurements from the human scalp that are an order of magnitude smaller than measurements of local field potentials in the animal model.

5.6.2. Animal model

5.6.2.1. Category 1 weakening of IG in the animal model

A number of studies in the rat found that inhibitory gating was weakened when certain experimental manipulations were compared with control conditions. There were examples of category I (Table 16) weakening of gating from the present research of CTI effects on gating. In the CTI studies of P60 there was category I weakening of gating comparing the 150 ms to the 500 ms CTI. There was also category I weakening of gating comparing the 1 sec to the 4 sec CTI. This is a perfect example of a weakening of the classical suppression that would be caused by pure inhibition of tAmp. In the study of emotional influences on inhibitory gating was category I weakening of gating comparing the block of tone-pairs before conditioning to the block after fear conditioning. This example is a not the pure effect of suppression of tAmp as was the case with increasing CTI, but this change still classifies as category I weakening. Perhaps stress-induced loss of inhibitory function produced disinhibition of cAmp along with a much larger weakening of the suppression of tAmp.

5.6.2.2. Category II weakening of IG in the animal model

As examples of category II weakening of gating, there was one example from the present research and two examples in other studies. In chapter 4, P60 was measured for blocks of paired-tones following injections of either saline or apomorphine. There was category II weakening of rat P60 gating for apomorphine compared to saline injections. A similar weakening of rat N40 gating was found comparing saline and apomorphine in another study (Swerdlow et al, 2006). Fein and colleagues (1997) found that cocaine produced similar weakening of rat N40 gating. In all three of these studies there was a decrease in both cAmp and tAmp, but there was a proportionally greater decrease in cAmp.

5.6.2.3. Category III weakening of IG in the animal model

The third category of weakening of gating had features of both category I and category II. Reductions in cAmp and, inversely, increases in tAmp had potential to synergistically produce the largest decreases in T/C ratio. Three examples from studies of rat N40 indicated category III weakening of gating. One study compared saline versus amphetamine and saline versus phencyclidine (Adler et al, 1986). Another study replicated the effect of saline versus amphetamine (Stevens et al, 1991). A descriptive account of the effect of these two drugs would be that both reduce the ability of neural pathways to convey a strong neuronal signal following a stimulus event (cAmp), and both drugs neutralized the inhibitory circuitry essential to suppressing tAmp. Amphetamine and phencyclidine are two classic pharmacologic models for psychosis in schizophrenia, respectively representing the dopamine and the NMDA hypotheses of schizophrenia (Javitt and Zukin, 1991; Balla et al, 2003; Abi-Dargham, 2004).

5.6.2.4. Category I strengthening of IG in the animal model

A result in chapter 4 produced category I (Table 17) strengthening of inhibitory gating. When the tone responses of P60 were investigated for blocks of tone pairs following injections of saline and injections of baclofen cAmp and tAmp were reduced. The slight suppression of cAmp could be explained by an increase of inhibitory tone in cortical neuronal networks. The increased inhibitory tone would have been accompanied by additional phasic suppression of tAmp as intrinsic gating circuitry was activated following C_{tone}.

5.6.2.5. Category III strengthening of IG in the animal model

Category III strengthening of inhibitory gating was produced by injections of haloperidol compared to saline (chapter 4). P60 was measured for blocks of paired-tones following injections of either saline or haloperidol, and cAmp increased while tAmp decreased. This result might reflect a strengthening of neuronal signal quality, as indicated by cAmp. Conversely, stronger suppression of tAmp might reflect stronger phasic activation of inhibition resulting from the strong signal (indicated by cAmp) following C_{tone}.

5.6.3. Human research

*5.6.3.1. Category I weakening of IG in clinical r*esearch

Two studies of inhibitory gating have found that there was category I weakening of inhibitory gating (Table 18) in individuals diagnosed with PTSD, compared to control individuals who did not have a history of mental illness (Skinner et al, 1999; Neylan et al, 1999). In one study of PTSD, there was category III weakening of gating, but the magnitude of the decrease in cAmp was marginal compared to the increase in tAmp (Ghisolfi et al, 2004). In one study of patients with migraine there was category I weakening of gating for patients with migraine compared to unaffected individuals (Oranje et al, 2002). In a study of individuals with Bi-polar disorder there was category I weakening of gating for patients during phases of mania (Franks et al, 1983).

5.6.3.2. Category II weakening of IG in clinical research

Two clinical disorders to any number of studies that examined experimental manipulations in non-clinical populations produced results that had category II weakening of inhibitory gating. Chronic cocaine addicts had category II weakening of gating compared to individuals who did

not use cocaine. Patients with hebephrenic (disordered) schizophrenia, had category II weakening of gating compared to normal subjects. Hebephrenic schizophrenia is associated with a class of symptoms that are considered to be clinically distinct from schizophrenia with predominantly positive or predominantly negative symptoms (Grube et al,1998; Andreason, 1995). For most experimental manipulations of gating, analysis of their effects on cAmp and tAmp revealed that experimental manipulations produced category II weakening of inhibitory gating. In two studies, compared to non-stress conditions, subjects who were subjected to mild psychological stress had category II weakening of inhibitory gating (White and Yee, 1997; Yee and White, 2001). A study of the effects of a low dose of L-Dopa (Oranje et al, 2004) and a low dose ketamine (Oranje et al, 2002) found non-significant results for differences in T/C ratios, but in the manipulations statistically significant reductions of cAmp and tAmp were observed. The study reported that the two drugs did not produce alterations in gating, but slight category II weakening of inhibitory gating was produced by the manipulations of L-Dopa and ketamine. The results are more meaningful in the context that the drugs did produce effects on cAmp and tAmp. However, the effects have a slightly different meaning in light of categories of gating change. One study of the effects of caffeine demonstrated category II weakening of inhibitory gating (Ghisolfi et al, 2005). Compared to a placebo, three different doses of caffeine, 100, 200, and 400 milligrams, produce category II weakening of gating. Only the 200 milligrams dose yielded statistically significant effects, yet even for statistically non-significant findings there was category II weakening of gating.

It is clear from the experimental manipulations of inhibitory gating, T/C ratios yield only limited information about the potential effects of inhibitory gating manipulations. In fact, there

were measurable effects on cAmp and tAmp. Alternative analytical strategies, such as categories of gating change, might reveal further gating related effects.

5.6.3.3. Category III weakening of IG in schizophrenia depends on symptoms

A large body of research on for inhibitory gating has focused on schizophrenia (Adler et al, 1982; Siegel et al, 1985; Boutros et al, 1991; Clementz et al, 1997; Ghisolfi et al, 2004). Inhibitory gating is universally weakened in schizophrenia. Only one study has generated results where inhibitory gating was not compromised in schizophrenia (Kathman and Engel, 1990), but the methods of the study were shown to have a critical difference from the majority of other studies of gating (McCallin et al, 1997). However, with the mathematical model described above, categorization of inhibitory gating reveals some differences between the three major symptom groups in schizophrenia, positive, negative and disordered (Andreasen, 1995; Grube et al, 1998). Schizophrenia patients with predominantly positive symptoms, clinical patients with schizotypal personality disorder, and even non-unaffected relatives of schizophrenics have category III weakening of gating.

Four studies that have compared inhibitory gating for normal subjects and schizophrenics have generated findings that can be classified as category III weakening of inhibitory gating (Clementz et al, 1997; Boutros et al, 1999; Adler et al, 2004; Ghisolfi et al, 2004). In a study of the first order relatives of individuals diagnosed with schizophrenia, there was category III weakening of inhibitory gating when the relatives of schizophrenic patients were compared with individuals who did not have a family history of schizophrenia (Clementz et al, 1998; Myles-Worsley et al, 1984). In one study of inhibitory gating for patients with schizotypal personality disorder, there was category III weakening of inhibitory gating in the disordered patients

compared to individuals who did not have the disorder (Cadenhead et al, 2002). There have been two studies of inhibitory gating for schizophrenia with primarily negative symptoms, and there was category I weakening of inhibitory gating in both studies (Adler et al, 1990; Louchart-de la Chapelle et al., 2005). Schizophrenic patients with predominantly disordered symptoms had category II weakening of gating (Ringel et al, 2004). Categorization of gating changes for the results of numerous studies along the entire spectrum of schizophrenia symptoms yields an interesting continuum of effects of inhibitory gating. The ends of the spectrum are defined by disordered and negative symptoms, and the category of gating for rest of the spectrum lies in between those two extremities. Based on the results of one study (Ringel et al, 2004), category II weakening of inhibitory gating in schizophrenia with disordered symptoms might be defined by a weakened P50 response to the Conditioning tone. The category I weakening of inhibitory gating in schizophrenia with negative symptoms appears to be predominantly a result of a loss of inhibition of tAmp (Adler et al, 1990; Louchart-de la Chapelle et al., 2005). Thus, schizophrenia with negative symptoms would meet the classical definition of a singular loss of inhibition. The majority of other schizophrenia-related studies have category III weakening of gating, essentially a combination of the effects of category I and category II weakening of gating.

5.6.4. Strengthening of IG in clinical research: Categories II & III

There are no studies of individuals with clinical disorders that have demonstrated strengthening of inhibitory gating. To knowledge of this author, there are no studies with experimental manipulations in normals that produce category III strengthening of inhibitory gating. Two studies that compare the effects of typical and atypical antipsychotics on patients with schizophrenia reveal category II strengthening of gating after further analysis (Nagamoto et

al, 1996; Becker et al, 2004). Another study comparing the effects of typical and atypical antipsychotics showed category II strengthening of gating (Light et al, 2000). Atypical antipsychotics have been shown to antagonize D4/D2 dopamine receptors, while typical and psychotics antagonize D2 dopamine receptors. Atypical antipsychotics are often prescribed due to their lower levels of extrapyramidal side effects. It is currently unknown why antagonism of both D2 and D4 dopamine receptors will produce category III strengthening of inhibitory gating in humans, whereas antagonism of D2 dopamine receptors produces category III strengthening of inhibitory gating in rats.

5.7. Clinical Implications

Recent data has 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 an excellent model for impairments in schizophrenia based upon genetic and molecular research (Freedman et al., 1994; Freedman et al., 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., 2005). Early hippocampal or

medial prefrontal cortex 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, 2005b). As IG occurs in the hippocampus, mPFC, and amygdala, 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 studies initiate this essential groundwork.

5.8. Conclusions

The first objective of this investigation was to explore the existence and dynamics of inhibitory gating in prelimbic prefrontal cortex of the rat (Chapter 2). As demonstrated by LFPs and single-units, inhibitory gating is an inherent property of mPFC neurons. Auditory stimulus signals reach mPFC either via direct brainstem projections or via projections from thalamus, auditory cortex or amygdala. However, the route to mPFC must be fairly direct for some previously specified single-units with very short response times. This research has demonstrated that inhibitory gating is stable, if not strengthening, over the course of multiple sessions as demonstrated by both single-units and LFPs. Optimal intervals of inhibitory gating exist, but the interval differs between single-units and LFPs. There are optimal intervals of inhibitory gating for150-500 ms between C_{tone} and T_{tone} for LFPs, but gating decreases dramatically when the interval drops to 1 second. For some single-units this optimal CTI range is extended beyond 1 second. The reason for the disparity between optimal CTI for LFPs and single-units might depend on the fact that different neural levels are represented by local potentials and single-units. The second objective of this investigation was to explore the effects of fear conditioning and

stress on inhibitory gating (Chapter 3). The influence of fear conditioning was investigated by manipulating the informational value of tones used in the paired-tone paradigm that was used to assess inhibitory gating. Inhibitory gating was weakened in the paired-tone test after compared to before a session of footshock pairing with the tones. In the mPFC, inhibitory gating is most effective for neutral, uninformative and repetitive stimuli. When stimuli were associated with negative events there was category I weakening of inhibitory gating in the paired-tone paradigm. The category I weakening of inhibitory gating in the fear conditioning experiment was different from the category III weakening of inhibitory gating following restraint stress in mice (Suer et al, 2004) or with the category II weakening of gating following psychological stress in humans (White and Yee, et al, 1997; Yee and White et al, 2001). However, the results in the fear conditioning experiment are similar to the category I weakening of inhibitory gating in the following clinical conditions: PTSD (Neylan et al, 1999; Skinner et al, 1999), migraine (Oranje et al, 2002), schizophrenia with predominately negative symptoms (Adler et al, 1990; Louchart-de la Chapelle et al., 2005), and mania in Bi-polar disorder (Franks et al, 1983).

The third objective in this investigation was to explore the neurotransmitter systems that influence inhibitory gating using systemic neuropharmacological manipulations of dopamine and GABA systems (Chapter 4). To investigate the effect on dopaminergic neurotransmitter systems the drugs haloperidol and apomorphine respectively increased and decreased inhibitory gating. Haloperidol increased gating by increasing the P60 AEP response to the conditioning tone and decreasing the response to the test tone. Apomorphine decreased gating by decreasing the P60 AEP response to the conditioning tone proportionally more than the decrease in response to the test tone. To investigate the effect on GABAergic neurotransmitter systems the drugs baclofen and pentobarbital increased gating, but the drugs had completely opposite effects of respectively

decreasing and increasing cAmp and tAmp. Baclofen increased gating by decreasing the P60 AEP response to the test tone proportionally more than the decrease in response to the conditioning tone. Pentobarbital weakly increased gating for a short time by increasing the P60 AEP response to the conditioning tone proportionally more than the increase in response to the test tone. Converging evidence suggests that these two neurotransmitter systems influence inhibitory gating in humans and the animal model. The present study confirms the effects of dopamine and GABA neurotransmitter systems on inhibitory gating in the mPFC.

Future studies should examine the role of dopamine on the alterations of inhibitory gating observed in the fear conditioning experiment. A simple yet informative experiment would be to administer haloperidol or baclofen after fear conditioning. If the effect of fear conditioning is to produce is to produce elevated levels of dopamine, haloperidol should prevent weakening of inhibitory gating. If the effect of fear conditioning is to reduce the inhibitory suppression of tAmp following the conditioning tone, then baclofen should prevent weakening of inhibitory gating. Another approach to investigate the nature of inhibitory gating weakening following fear conditioning would be to disrupt the reciprocal glutaminergic projection between mPFC and amygdala (Krettek and Price, 1977; McDonald, 1991).

The results of this investigation of inhibitory gating in prelimbic prefrontal cortex provide a basic framework for further investigation, not only in prefrontal cortex, but for a potential functional network of connected structures that display inhibitory gating. The principal brain regions projecting to and receiving projections from prefrontal cortex have also been shown to display inhibitory gating as an inherent property. Brainstem structures, hippocampus, amygdala, reticular thalamus, and striatal structures share extensive connections with prefrontal cortex (McDonald, 1996; Uylings et al, 1990; Groenewegen et al, 2003; Uylings et al, 2003; Vertes,

2004). All of these brain regions have demonstrated positive evidence of inhibitory gating for single-unit and/or local field potentials in the animal model (Moxon et al, 1999; Hoffman et al, 2003; Cromwell et al, 2005; Klein et al, 2005). It inhibitory gating occurs synchronously in all of these connected structures. To the degree that the temporal properties of inhibitory gating match between these structures, there is likely to be coordination of patterns of inhibition in this network of connected structures. The task in the future will be to consider the functional effects and interactions of such coordination.

TABLES

Table 1.

	Session 1			Session 2			Session 3		
	E-SD	**E-LD**	**Inh**	**E-SD**	**E-LD**	**Inh**	**E-SD**	**E-LD**	**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±.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

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

Table 2.

	150 ms Interval			500 ms Interval			1000 ms Interval			4000 ms Interval		
	E-SD	**E-LD**	**Inh**	**E-SD**	**E-LD**	**Inh**	**E-SD**	**E-LD**	**Inh**	**E-SD**	**E-LD**	**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 ±.4	11.1 ±4.6	8.7 ±7.4	1.0 ±.3	10.2 ±3.4	7.7 ±5.9	1.2 ±.2	11.4 ±3.8	3.7 ±1.8	1.1 ±.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	.84 ±.10	0.32 ±0.06	0.44 ±0.07	.51 ±.12	0.55 ±0.08	0.49 ±0.09	.74 ±.05	1.04 ±0.15	0.95 ±0.10	0.91 ±.06

Conditioned-Test Interval neuronal database for three types of single-unit response to paired-stimuli.

Table 3
Mean cAmp values across segments for haloperidol

	Post-Injection Trial Blocks							
	Segment 1		Segment 2		Segment 3		Segments Mean	
	M	SEM	M	SEM	M	SEM	M	SEM
Saline	64.41 [bc]	1.62	92.58 [a]	2.00	89.22 [a]	2.08	82.07	1.62
Haloperidol	113.50 [bc]	2.71	119.58 [ac]	3.35	106.27 [ab]	3.41	113.11	3.06
Treatment Mean	88.95[*]	1.75	106.08[*]	2.43	97.74[*]	2.45		

Note. Significant mean differences between Segments are indicated as follows: [a] Segment 1; [b] Segment 2; [c] Segment 3 Significant mean differences between Saline and Haloperidol are indicated with asterisk ([*]).

Table 4

Mean tAmp values across segments for haloperidol

	Post-Injection Trial Blocks							
	Segment 1		Segment 2		Segment 3		Segments Mean	
	M	SEM	M	SEM	M	SEM	M	SEM
Saline	31.16 [bc]	1.36	37.40 [ac]	1.17	43.12 [ab]	1.40	27.23	1.07
Haloperidol	21.40 [bc]	1.15	15.28 [ac]	2.52	18.67 [ab]	1.28	18.45	1.05
Treatment Mean	26.28[*]	1.21	26.34[*]	0.93	30.90[*]	1.24		

Note. Significant mean differences between Segments are indicated as follows: [a] Segment 1; [b] Segment 2; [c] Segment 3 Significant mean differences between Saline and Haloperidol are indicated with asterisk ([*]).

Table 5

Mean T/C ratios across segments for haloperidol

	Post-Injection Trial Blocks							
	Segment 1		Segment 2		Segment 3		Segments Mean	
	M	SEM	M	SEM	M	SEM	M	SEM
Saline	0.48 [b]	0.01	0.41 [ac]	0.01	0.48 [b]	0.01	0.46	0.01
Haloperidol	0.20 [b]	0.02	0.14 [ac]	0.02	0.18 [b]	0.01	0.17	0.01
Treatment Mean	0.34 [*]	0.01	0.28 [*]	0.01	0.33 [*]	0.01		

Note. Significant mean differences between Segments are indicated as follows: [a] Segment 1; [b] Segment 2; [c] Segment 3 Significant mean differences between Saline and Haloperidol are indicated with asterisk ([*]).

Table 6
Mean cAmp values across segments for apomorphine

	Post-Injection Trial Blocks							
	Segment 1		Segment 2		Segment 3		Segments Mean	
	M	SEM	M	SEM	M	SEM	M	SEM
Saline	52.17 [bc]	1.59	85.97 [a]	2.25	87.89 [a]	2.56	75.34	0.83
Apomorphine	10.49 [c]	0.501	10.61 [c]	0.41	16.59 [ab]	0.69	12.56	0.43
Treatment Mean	31.32 [*]	0.89	48.29 [*]	1.13	52.24 [*]	1.381		

Note. Significant mean differences between Segments are indicated as follows: [a] Segment 1; [b] Segment 2; [c] Segment 3 Significant mean differences between Saline and Apomorphine are indicated with asterisk ([*]).

Table 7

Mean tAmp values across segments for apomorphine

	Post-Injection Trial Blocks							
	Segment 1		Segment 2		Segment 3		Segments Mean	
	M	SEM	M	SEM	M	SEM	M	SEM
Saline	23.12 [bc]	1.05	32.50 [a]	1.42	33.12 [a]	1.52	29.58	1.18
Apomorphine	8.25	0.36	8.67	0.39	8.87	0.42	8.60	0.26
Treatment Mean	15.69 [*]	0.59	20.58 [*]	0.66	21.00 [*]	0.76		

Note. Significant mean differences between Segments are indicated as follows: [a] Segment 1; [b] Segment 2; [c] Segment 3 Significant mean differences between Saline and Apomorphine are indicated with asterisk ([*]).

Table 8

Mean T/C ratios across segments for apomorphine

	Post-Injection Trial Blocks							
	Segment 1		Segment 2		Segment 3		Segments Mean	
	M	SEM	M	SEM	M	SEM	M	SEM
Saline	0.43 [bc]	0.01	0.38 [a]	0.01	0.38 [a]	0.01	0.40	0.01
Apomorphine	1.03 [c]	0.08	0.96 [c]	0.06	0.65 [ab]	0.04	0.88	0.04
Treatment Mean	0.73 [*]	0.04	0.67 [*]	0.03	0.52 [*]	0.02		

Note. Significant mean differences between Segments are indicated as follows: [a] Segment 1; [b] Segment 2; [c] Segment 3 Significant mean differences between Saline and Apomorphine are indicated with asterisk ([*]).

Table 9
Mean cAmp values across segments for baclofen

	Post-Injection Trial Blocks							
	Segment 1		Segment 2		Segment 3		Segments Mean	
	M	SEM	M	SEM	M	SEM	M	SEM
Saline	70.44 [c]	2.45	69.07 [c]	1.89	82.70 [ab]	3.65	74.07	2.34
Baclofen	65.18 [c]	2.50	62.94 [c]	2.53	59.45 [ab]	1.97	61.52	2.12
Treatment Mean	67.81 [*]	1.83	66.01 [*]	1.94	69.57 [*]	2.42		

Note. Significant mean differences between Segments are indicated as follows: [a] Segment 1; [b] Segment 2; [c] Segment 3 Significant mean differences between Saline and Baclofen are indicated with asterisk ([*]).

Table 10

Mean tAmp values across segments for baclofen

	Post-Injection Trial Blocks							
	Segment 1		Segment 2		Segment 3		Segments Mean	
	M	SEM	M	SEM	M	SEM	M	SEM
Saline	33.20 [b]	1.63	30.06 [ac]	1.09	36.44 [b]	1.64	33.23	1.23
Baclofen	22.44 [bc]	1.22	15.56 [ac]	0.80	13.53 [ab]	0.65	17.17	0.79
Treatment Mean	27.82 [*]	1.22	22.81 [*]	0.84	24.99	1.07		

Note. Significant mean differences between Segments are indicated as follows: [a] Segment 1; [b] Segment 2; [c] Segment 3 Significant mean differences between Saline and Baclofen are indicated with asterisk ([*]).

Table 11

Mean T/C ratios across segments for baclofen

	Post-Injection Trial Blocks							
	Segment 1		Segment 2		Segment 3		Segments Mean	
	M	SEM	M	SEM	M	SEM	M	SEM
Saline	0.47	0.01	0.46	0.02	0.46	0.01	0.46	0.01
Baclofen	0.37 [bc]	0.02	0.27 [a]	0.01	0.26 [a]	0.01	0.30	0.01
Treatment Mean	0.42 [*]	0.01	0.36 [*]	0.01	0.36 [*]	0.01		

Note. Significant mean differences between Segments are indicated as follows: [a] Segment 1; [b] Segment 2; [c] Segment 3 Significant mean differences between Saline and Baclofen are indicated with asterisk ([*]).

Table 12
Mean cAmp values across segments for pentobarbital

	Post-Injection Trial Blocks							
	Segment 1		Segment 2		Segment 3		Segments Mean	
	M	SEM	M	SEM	M	SEM	M	SEM
Saline	50.51 [bc]	1.39	71.48 [ac]	2.68	77.08 [ab]	1.68	66.48	1.66
Pentobarbital	87.43 [bc]	4.27	98.40 [ac]	4.07	104.42 [ab]	4.39	96.75	4.01
Treatment Mean	68.97 [*]	2.46	85.12 [*]	2.84	90.75 [*]	2.78		

Note. Significant mean differences between Segments are indicated as follows: [a] Segment 1; [b] Segment 2; [c] Segment 3 Significant mean differences between Saline and Pentobarbital are indicated with asterisk ([*]).

Table 13

Mean tAmp values across segments for pentobarbital

	Post-Injection Trial Blocks							
	Segment 1		Segment 2		Segment 3		Segments Mean	
	M	SEM	M	SEM	M	SEM	M	SEM
Saline	18.44 [bc]	0.72	30.41 [a]	1.46	27.62 [a]	1.08	25.49	0.81
Pentobarbital	28.06 [bc]	1.51	32.23 [a]	2.42	33.76 [a]	1.90	31.35	1.80
Treatment Mean	23.25 [*]	0.90	31.32 [*]	1.74	30.69 [*]	1.18		

Note. Significant mean differences between Segments are indicated as follows: [a] Segment 1; [b] Segment 2; [c] Segment 3 Significant mean differences between Saline and Pentobarbital are indicated with asterisk ([*]).

Table 14

Mean T/C ratios across segments for pentobarbital

	Post-Injection Trial Blocks							
	Segment 1		Segment 2		Segment 3		Segments Mean	
	M	SEM	M	SEM	M	SEM	M	SEM
Saline	0.38	0.01	0.40 [c]	0.01	0.36 [b]	0.01	0.38	0.01
Pentobarbital	0.43 [bc]	0.04	0.34 [a]	0.02	0.34 [a]	0.02	0.37	0.02
Treatment Mean	0.40	0.02	0.37 [*]	0.01	0.35	0.01		

Note. Significant mean differences between Segments are indicated as follows: [a] Segment 1; [b] Segment 2; [c] Segment 3 Significant mean differences between Saline and Pentobarbital are indicated with asterisk ([*]).

Table 15. Categories of gating changes.

Gating Change		Δ T/C ratio	Δ tAmp	Δ cAmp
Category I	Strengthening	↓	↓	
	Weakening	↑	↑	
Category II	Strengthening	↓		↑
	Weakening	↑		↓
Category III	Strengthening	↓	↓	↑
	Weakening	↑	↑	↓

Table 16. Analytic Model for Categories of gating changes.

Gating Change		Δ T/C ratio	Δ tAmp	Δ cAmp
Category I	Strengthening	-	- (- -)	(-)
	Weakening	+	+ (+ +)	(+)
Category II	Strengthening	-	(+)	+ (+ +)
	Weakening	+	(-)	- (- -)
Category III	Strengthening	-	-	+
	Weakening	+	+	-

$$\Delta T/C = \ln\left(T/C_{\text{condition B}} / T/C_{\text{condition A}}\right)$$
$$\Delta tAmp = \ln\left(tAmp_{\text{condition B}} / tAmp_{\text{condition A}}\right)$$
$$\Delta cAmp = \ln\left(cAmp_{\text{condition B}} / cAmp_{\text{condition A}}\right)$$

Table 17. Weakening of Gating In the Animal Model

Gating Change	Condition A	Condition B	Δ T/C	Δ tAmp	Δ cAmp	Reference	Method
Category I	150ms CTI	500 ms CTI	0.7	**0.6**	0.0	Chapter 2 Mears, 2006.	P60
	1 sec CTI	4 sec CTI	0.2	**0.2**	0.0	Chapter 2 Mears, 2006.	P60
	Before Fear Conditioning	After Fear Conditioning	0.2	**0.4**	0.2	Chapter 3 Mears, 2006.	P60
Category II	Saline	Apomorphine (D_1/D_2 agonist)	0.6	-1.2	**-1.8**	Chapter 4 Mears, 2006.	P60
	Vehicle	Apomorphine (D_1/D_2 agonist)	0.8	-0.1	**-0.9**	Swerdlow et al, 2006.	N40
	Saline	Cocaine	0.4	-0.3	**-0.7**	Boutros et al, 1997.	N40
Category III	Unmedicated	Amphetamine: Low Dose	1.8	**1.1**	**-0.7**	Adler et al, 1986.	N40
	Unmedicated	Amphetamine: Medium Dose	1.0	**0.1**	**-0.9**	Stevens et al, 1991	N40
	Unmedicated	Phencyclidine	1.1	**0.4**	**-0.7**	Adler et al, 1986.	N40

Table 18. Strengthening of Gating In the Animal Model

Gating Change	Condition A	Condition B	Δ T/C	Δ tAmp	Δ cAmp	Reference	Method
Category I	Saline	Baclofen	-0.5	**-0.7**	-0.2	Chapter 4 Mears, 2006.	P60
Category III	Saline	Haloperidol	-0.7	**-0.4**	**0.3**	Chapter 4 Mears, 2006.	P60
	Amphetamine (Low Dose)	Haloperidol + Amphetamine	-1.1	**-0.5**	**0.6**	Adler et al, 1986.	N40
	Phencyclidine	Haloperidol + Phencyclidine	-0.8	**-0.2**	**0.6**	Adler et al, 1986.	N40

Table 19. Weakening of Gating in Human Populations

Gating Change	Condition A	Condition B	Δ T/C	Δ tAmp	Δ cAmp	Reference	Method
Category I	No history of disorder	PTSD	1.0	**1.3**	0.3	Skinner et al, 1999	P50
	No history of disorder	Combat experience, no PTSD	0.6	**0.8**	0.1	Skinner et al, 1999	P50
	No history of disorder	PTSD	0.5	**0.8**	0.3	Neylan et al, 1999	P50
	No history of disorder	PTSD	0.6	**0.5**	-0.1	Ghisolfi et al, 2004	P50
	No history of disorder	Migraine	1.1	**1.4**	0.2	Oranje et al, 2002	P50
	No history of disorder	Bipolar (Manic)	1.4	**1.5**	0.1	Franks et al, 1983	P50
	No history of disorder	Bipolar (Euthymic)	0.3	**0.5**	0.2	Franks et al, 1983	P50
	No history of disorder	Schizophrenia (Negative)	1.4	**1.7**	0.3	Adler et al, 1990	P50
	No history of disorder	Schizophrenia (Negative)	0.7	**0.8**	0.1	Louchart delaChappelle et al, 2005	P50
Category II	No history of disorder	Cocaine Addiction	0.9	0.0	**-0.9**	Fein et al, 1996	P50
	Silent Arithmatic	Oral Arithmatic (Stress)	0.7	0.0	**-0.7**	White & Yee, 1997	P50
	Control (no task)	Oral Arithmatic (Stress)	0.4	0.0	**-0.4**	Yee & White, 2001	P50
	Placebo	Caffeine (100 mg)	0.0	0.0	**-0.1**	Ghisolfi et al, 2005	P50
	Placebo	Caffeine (200 mg)	0.2	0.0	**-0.2**	Ghisolfi et al, 2005	P50
	Placebo	Caffeine (400 mg)	0.1	0.0	**-0.1**	Ghisolfi et al, 2005	P50
	Saline	Ketamine	0.1	-0.1	**-0.2**	Oranje et al, 2002	P50
	Saline	L-Dopa	0.3	0.0	**-0.3**	Oranje et al, 2004	P50
	No history of disorder	Disorganized Schizophrenia	0.8	-0.9	**-1.7**	Ringel et al, 2004	P50
Category III	No history of disorder	Schizophrenia	0.7	**0.5**	**-0.3**	Ghisolfi et al, 2004	P50
	No history of disorder	Schizophrenia	1.5	**1.2**	**-0.3**	Boutros et al, 1999	P50
	No history of disorder	Schizophrenia	0.5	**0.3**	**-0.2**	Clementz et al, 1997	P50
	No history of disorder	Schizophrenia	1.4	**1.3**	**-0.1**	Adler et al, 2004	P50
	No history of disorder	Schizotypal Personality	0.6	**0.3**	**-0.2**	Cadenhead et al, 2002	P50
	w/o disorder in family	1° relatives of schizophrenics	0.4	**0.4**	**-0.1**	Clementz et al, 1998	P50
	w/o disorder in family	High risk offspring	0.4	**0.2**	**-0.1**	Myles-Worsley et al,2004	P50

Table 20. Strengthening of Gating in Human Populations

Gating Change	Condition A	Condition B	Δ T/C	Δ tAmp	Δ cAmp	Reference	Method
Category II	Typical Antipsychotic	Atypical Antipsychotic	-0.4	0.1	**0.6**	Nagamoto et al, 1996	P50
	Typical Antipsychotic	Atypical Antipsychotic	-0.1	0.2	**0.4**	Becker et al, 2004	P50
Category III	Typical Antipsychotic	Atypical Antipsychotic	-0.7	**-0.4**	**0.2**	Light et al, 2000	P50

Figures

Figure 1. Example of auditory evoked LFP averaged from a single recording session

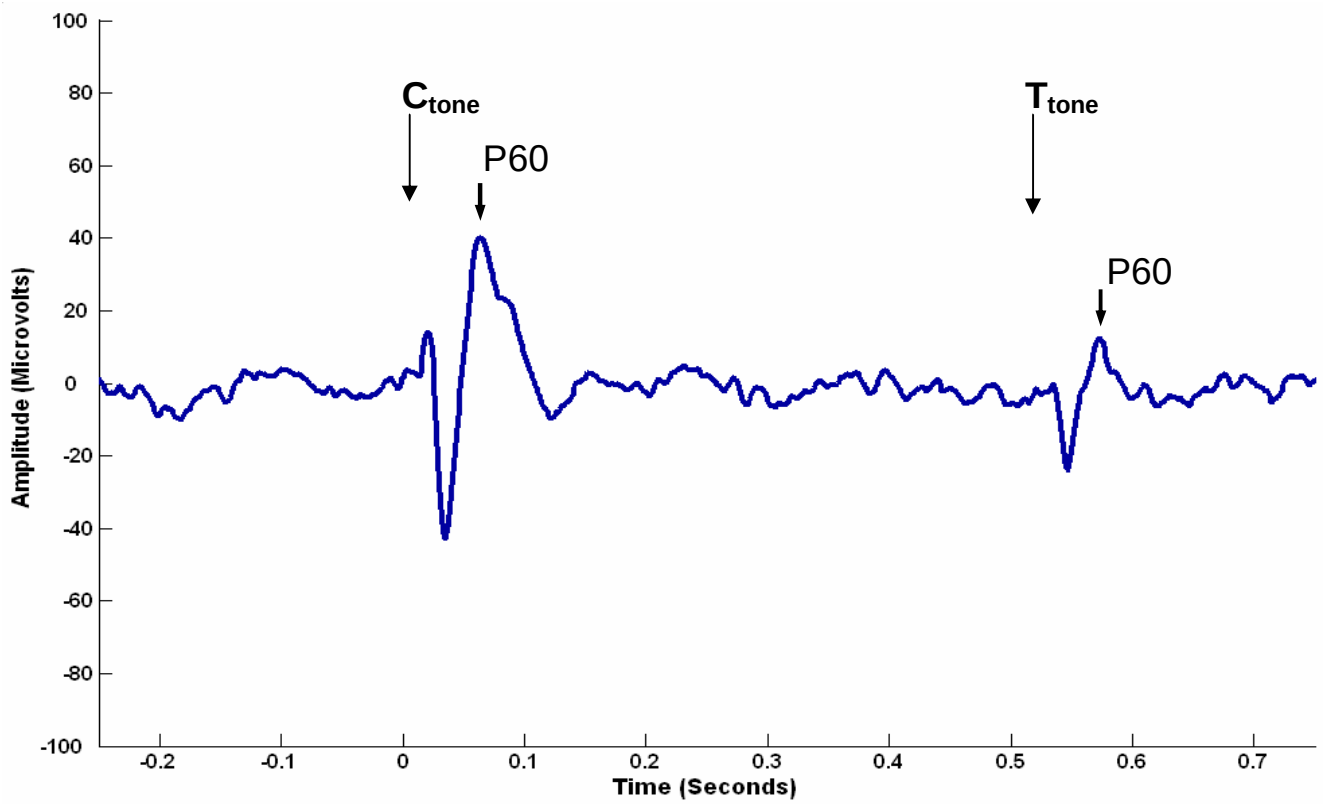


Figure 1. An example of a local field potential recorded from a single microwire yields waveforms for both tones in a block of trials (n=360). A P60 potential occurred as a positive going peak 60 milliseconds after the first tone (C_{tone}) at 0 seconds. Another P60 occurred at 60 milliseconds after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

Figure 2A. Examples of three major classes of single-unit response types

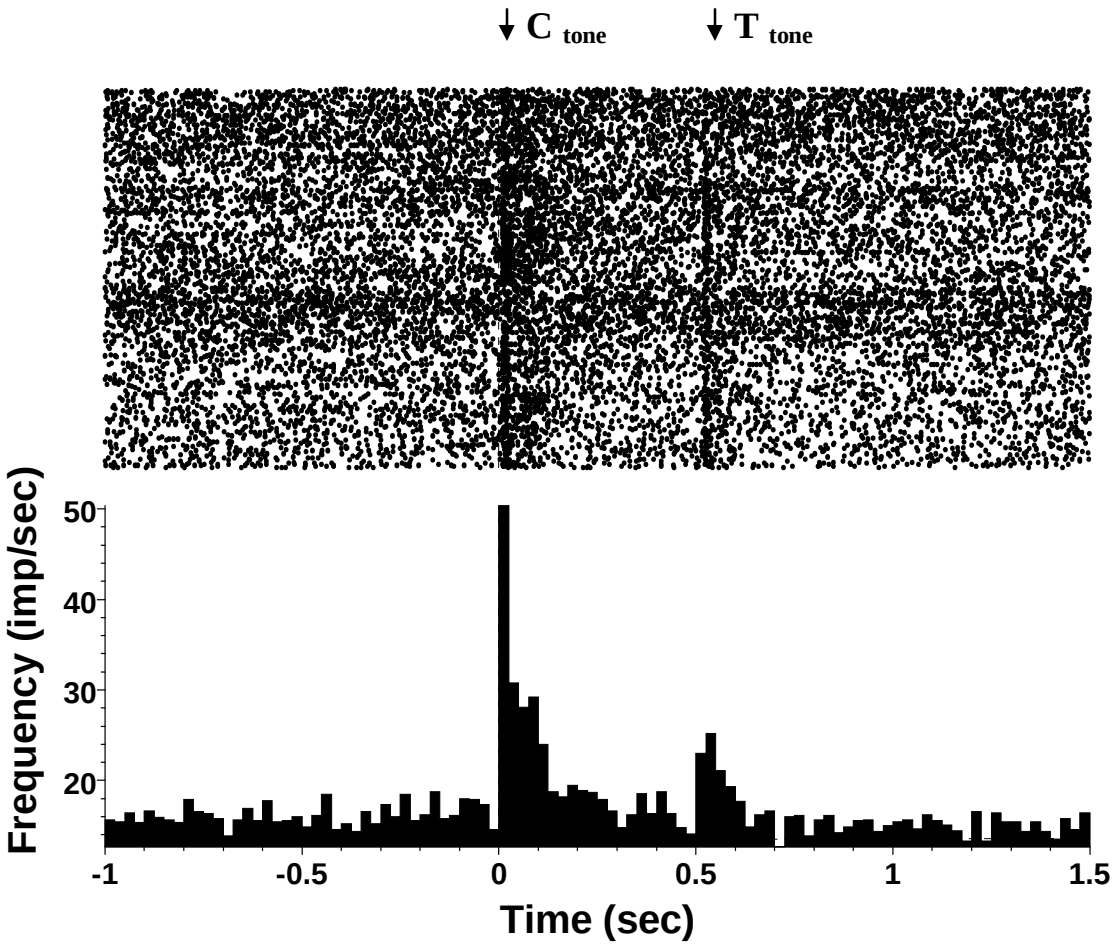


Figure 2A. Single-units that responded significantly to tone stimuli revealed three major classes of tone response. As indicated by raster plots in the top half of each figure, activity to the first tone (C_{tone}) was stronger than activity to second tone (T_{tone}). Excitatory short duration (ESD) single-units responded to tone stimuli with a brief increase in impulses per second above background firing rate.

Figure 2B.

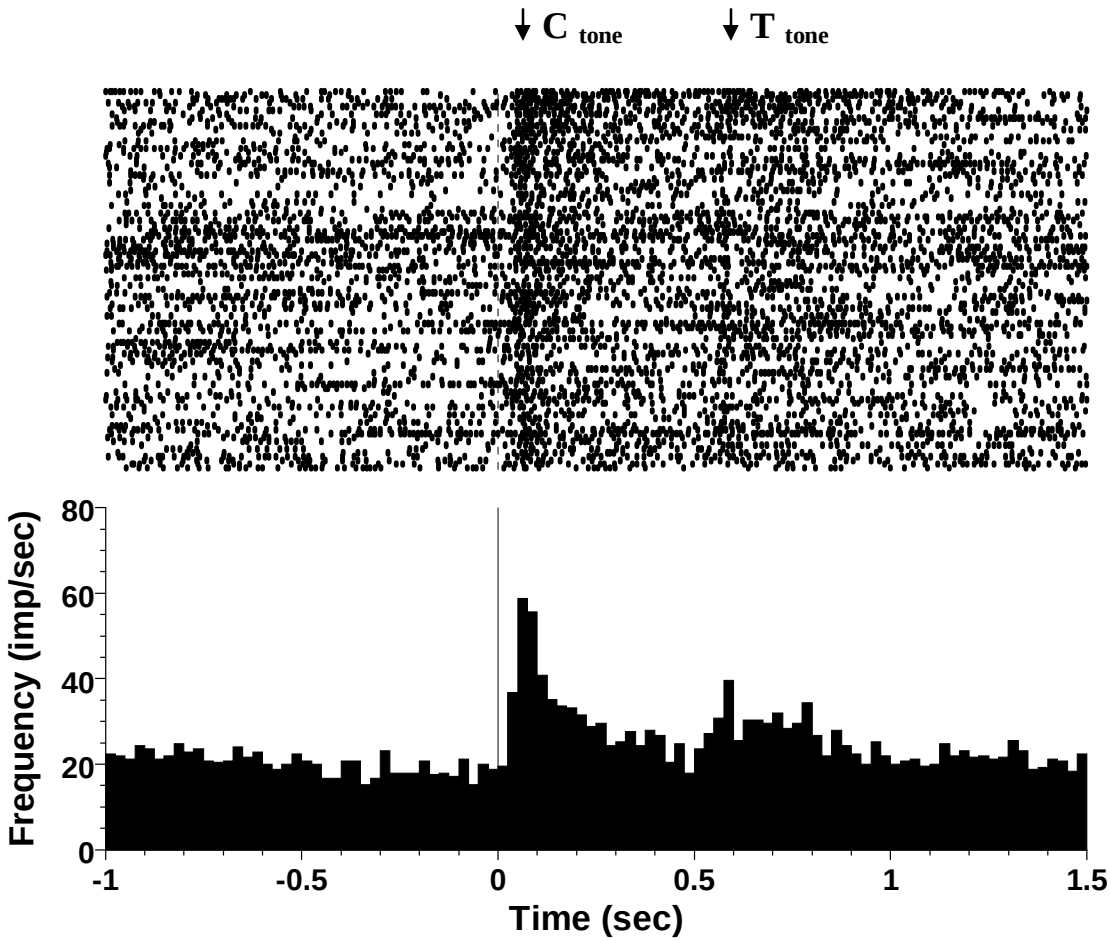


Figure 2B. Excitatory long duration (ELD) single-units often had a sustained response lasting hundreds of milliseconds

Figure 2C.

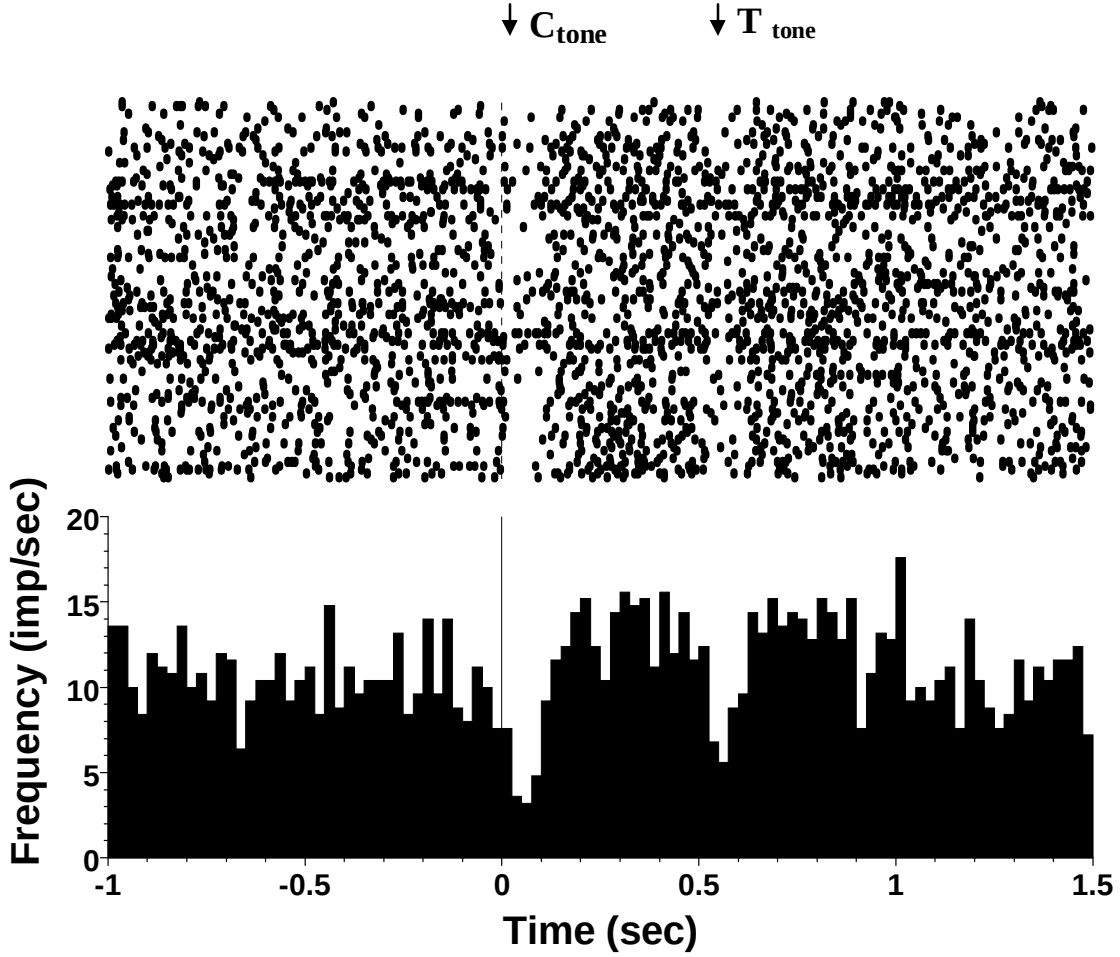


Figure 2C. Inhibitory response (Inh) single-units decreased their firing rate below baseline in response to tone stimuli.

Bin sizes are 50 ms.

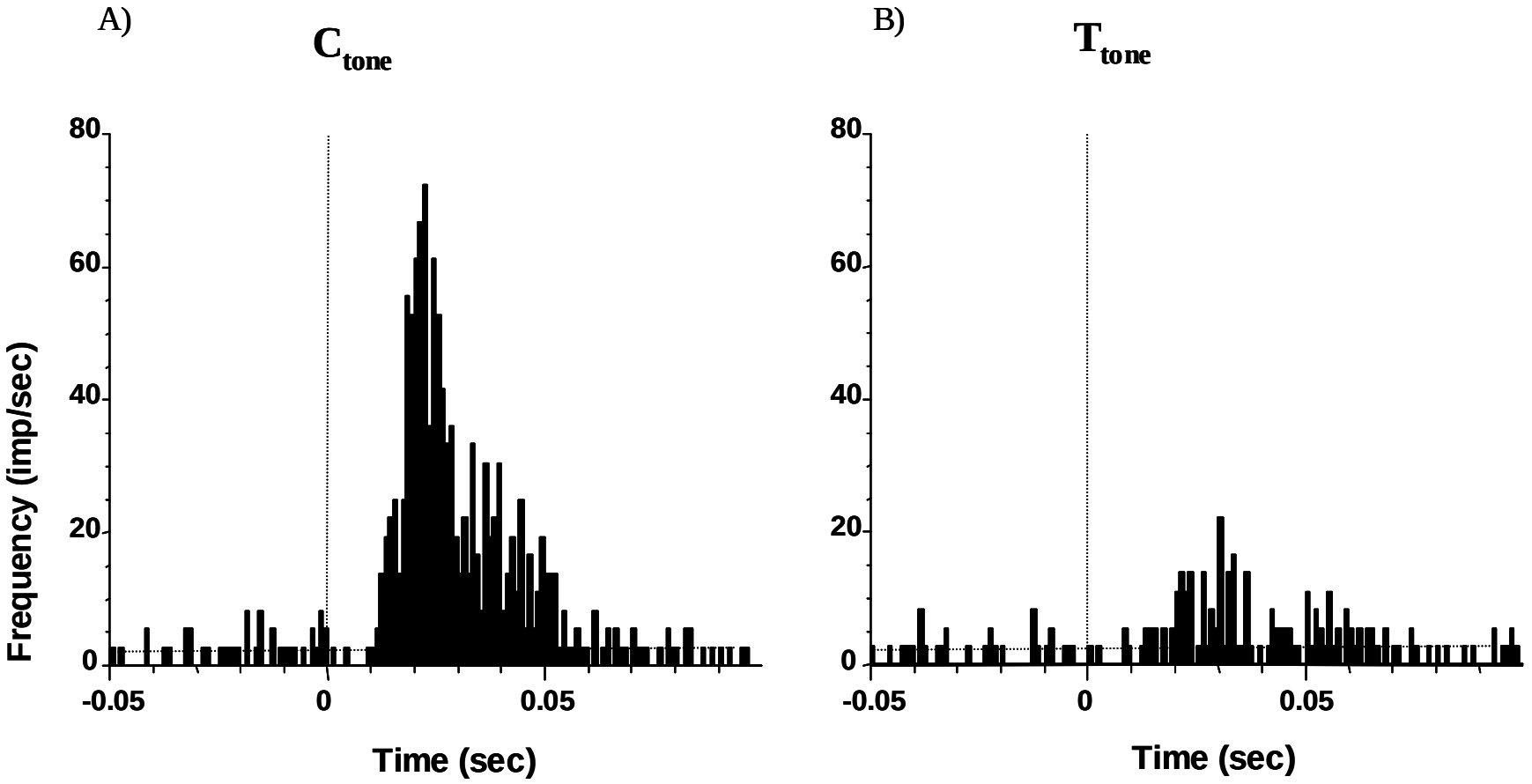


Figure 3. The firing rate increase for one ESD single-unit reveals a very short latency of onset (13-17 ms) for an increase in firing rate following C_{tone}. This increase in firing rate is apparent for a single units response to A) C_{tone}, but the response following B) T_{tone} is less clearly defined.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

Figure 4A. Placement of recording electrodes in mPFC

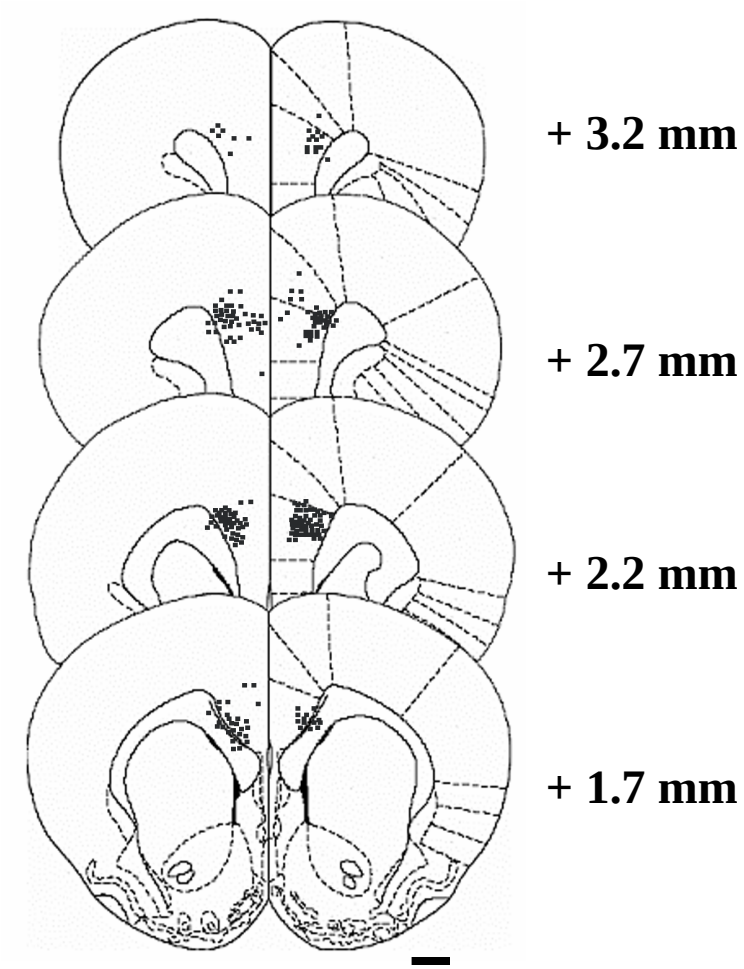


Figure 4. Electrode mapping revealed that A) majority of electrodes were placed in prelimbic mPFC. Diagrams are adapted from Paxon and Watson (1999). Most electrodes were placed between + 2.7 mm and + 2.2 mm anterior to bregma. A measurement bar is calibrated to 1 mm.

Figure 4B.

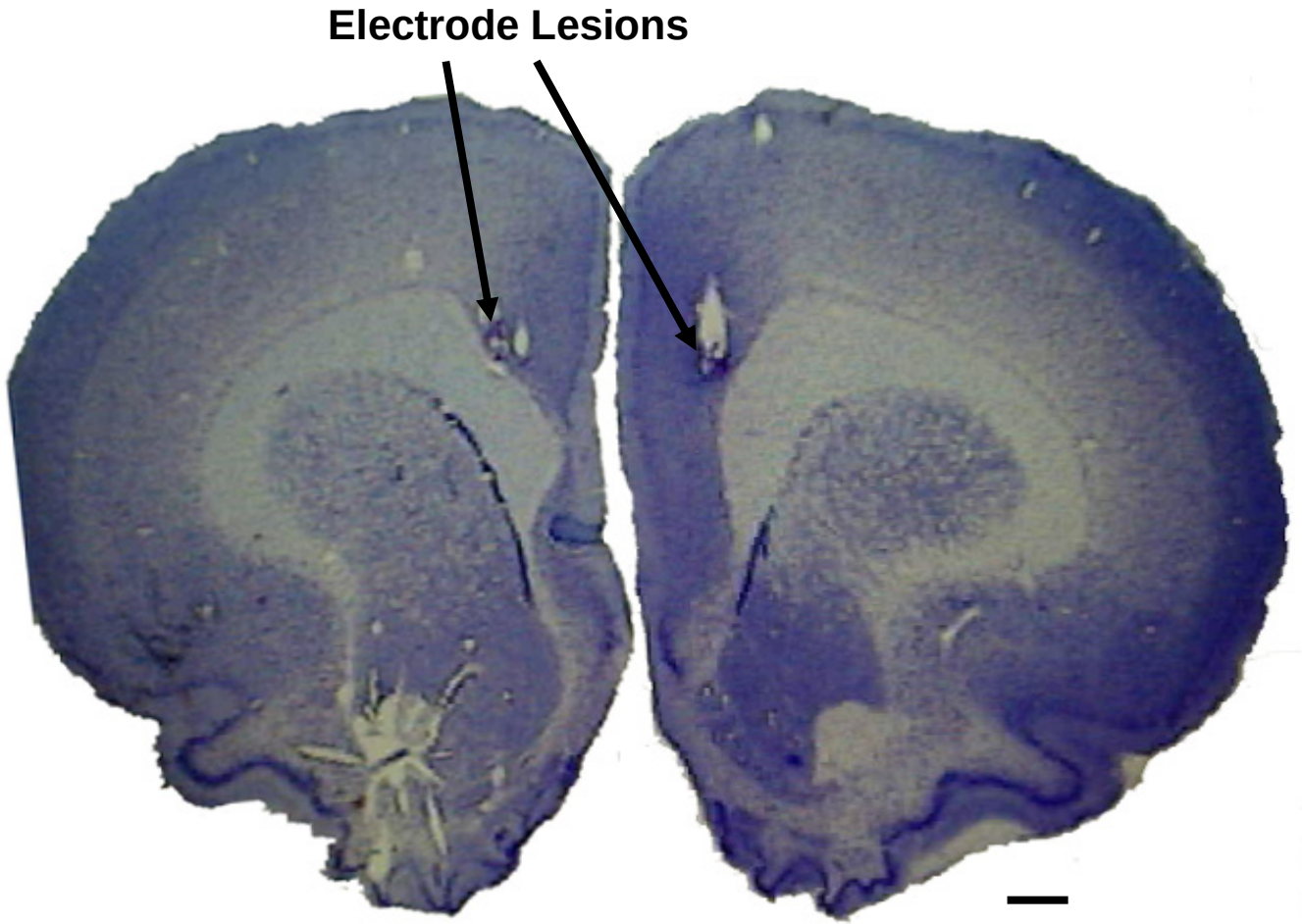


Figure 4B. Electrode lesions are indicated for bilateral pairs of electrodes placed + 2.2 mm anterior to bregma. A measurement bar is calibrated to 1 mm.

Figure 5A. Example of LFP from three recording sessions

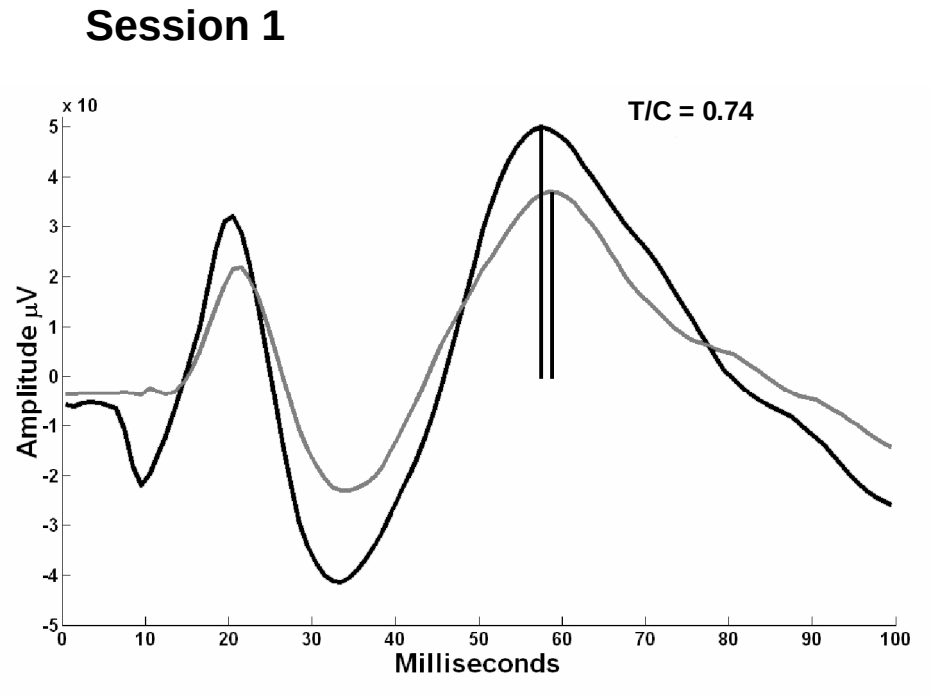


Figure 5A. LFP for C_{tone} (dark line) and T_{tone} (light line) are overlaid in order to compare relative amplitudes. P60 for session 1 reveals a T/C ratio of 0.74, indicating that tAmp is 74% of cAmp.

Figure 5B.

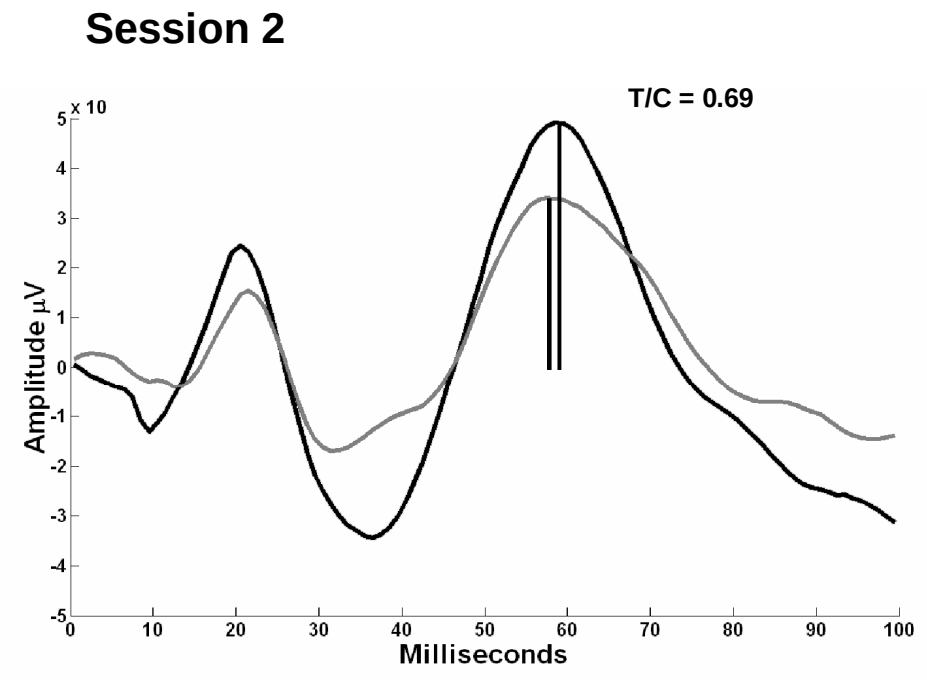


Figure 5B. P60 for session 2 reveals a T/C ratio of 0.69, indicating that tAmp is 69% of cAmp.

Figure 5C.

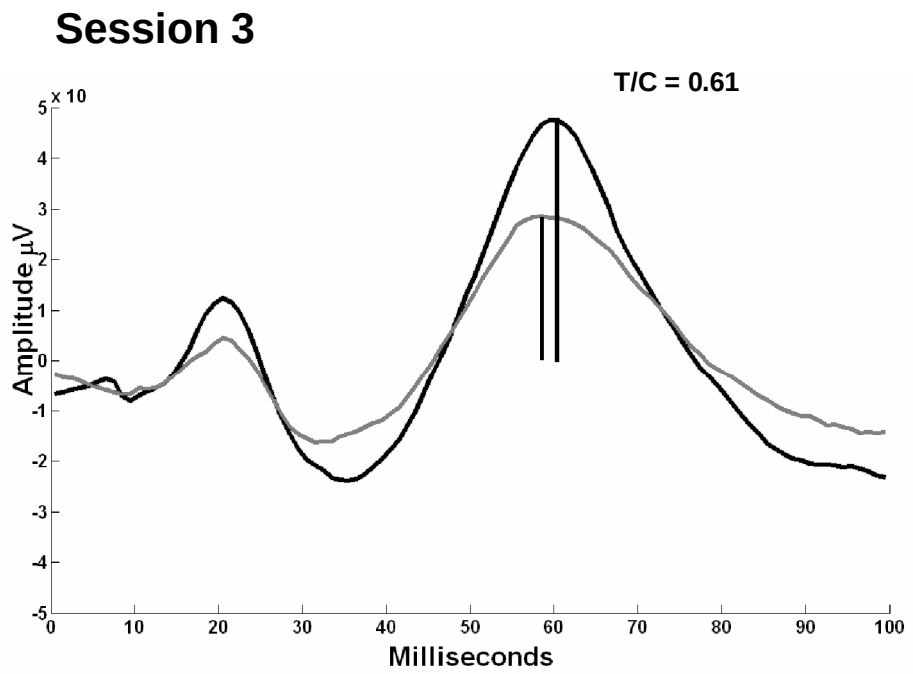


Figure 5C. P60 for session 3 reveals a T/C ratio of 0.61, indicating that tAmp is 61% of cAmp.

Figure 6. Effects for inhibitory gating of LFP from three recording sessions

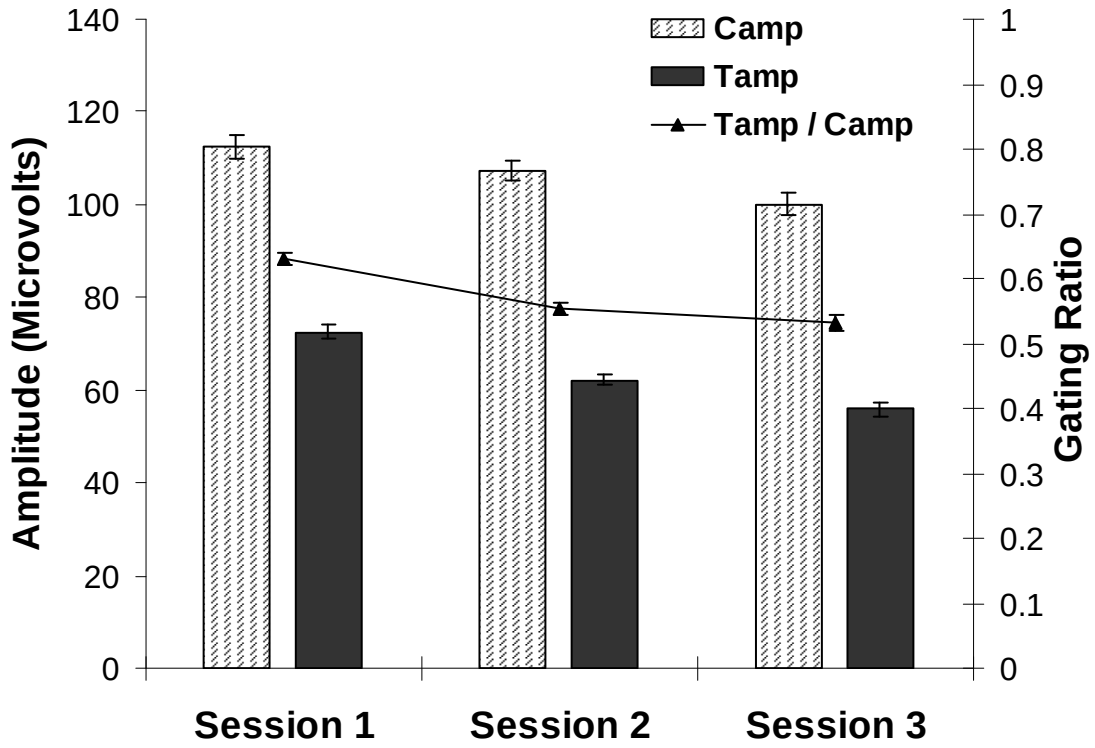


Figure 6. Results of LFP for three sessions are indicated with amplitudes of response for cAmp and tAmp (microvolts) represented on the right-side axis. T/C ratios for each session are represented on the left-side axis. SEM markers are shown for all data.

Figure 7. Group data for inhibitory gating of LFP from four Condition-Test Intervals

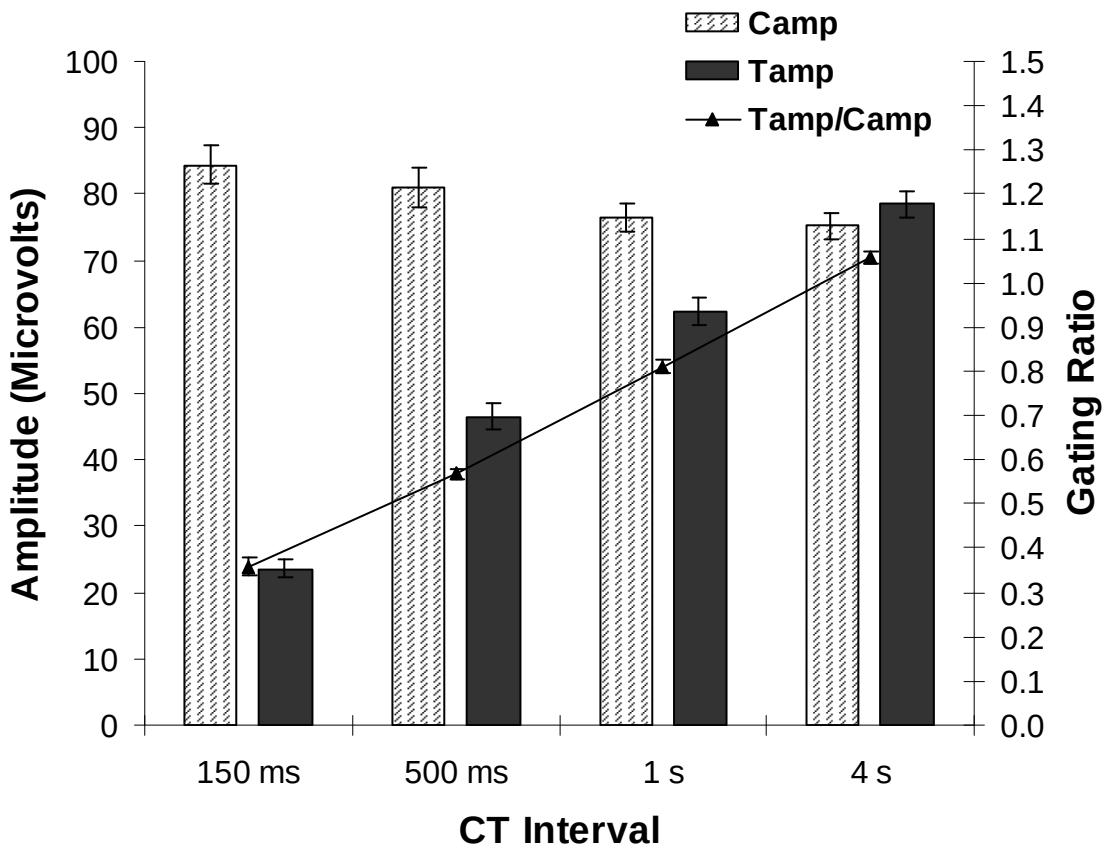


Figure 7. Results for LFP from four CT intervals (CTI) of separation are indicated on the right-side axis for cAmp and tAmp (microvolts). The left-side axis marks T/C ratios for each CTI. SEM markers are shown for all data.

Figure 8A,B. Example of LFP and a single-unit recorded simultaneously from the same wire for paired tones presented at different CTI

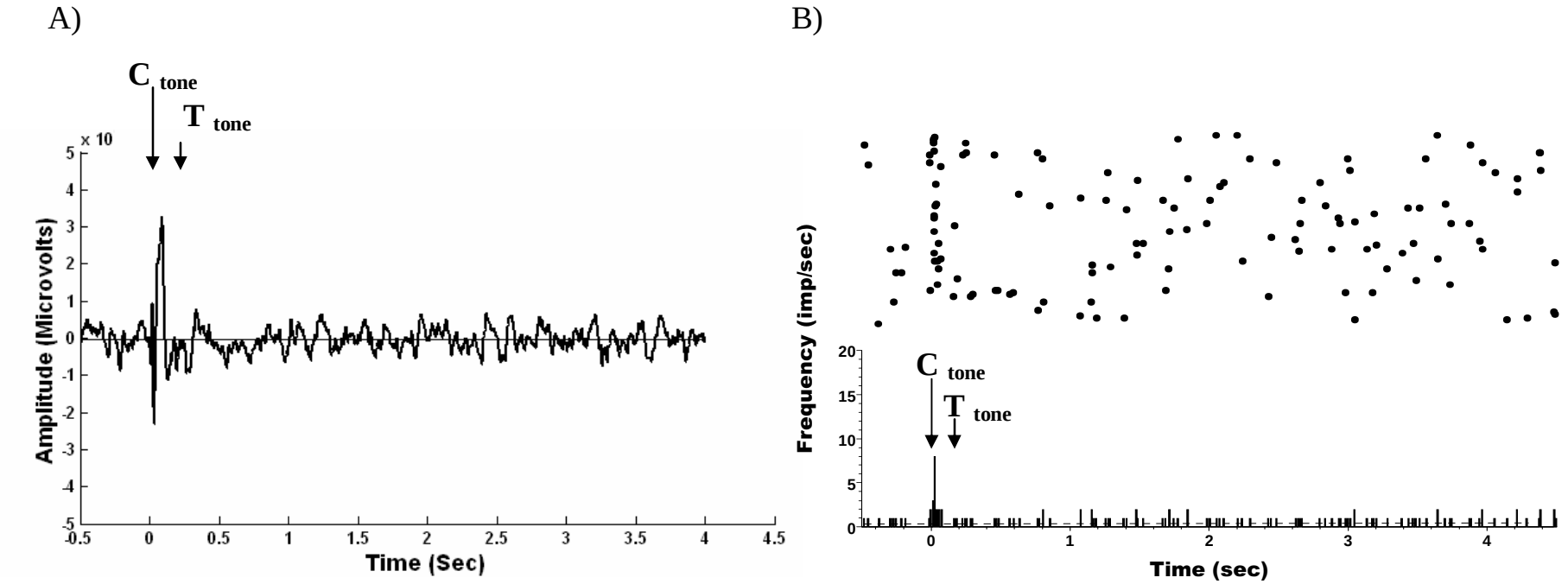


Figure 8 A,B. Examples of LFP and a single-unit recorded simultaneously from the same wire are shown with responses to pairs of tones presented at four different CTI. At a CTI of 150 ms responses of A) LFP and B) single-units are very strongly gated following T_{tone}.

Figure 8C,D.

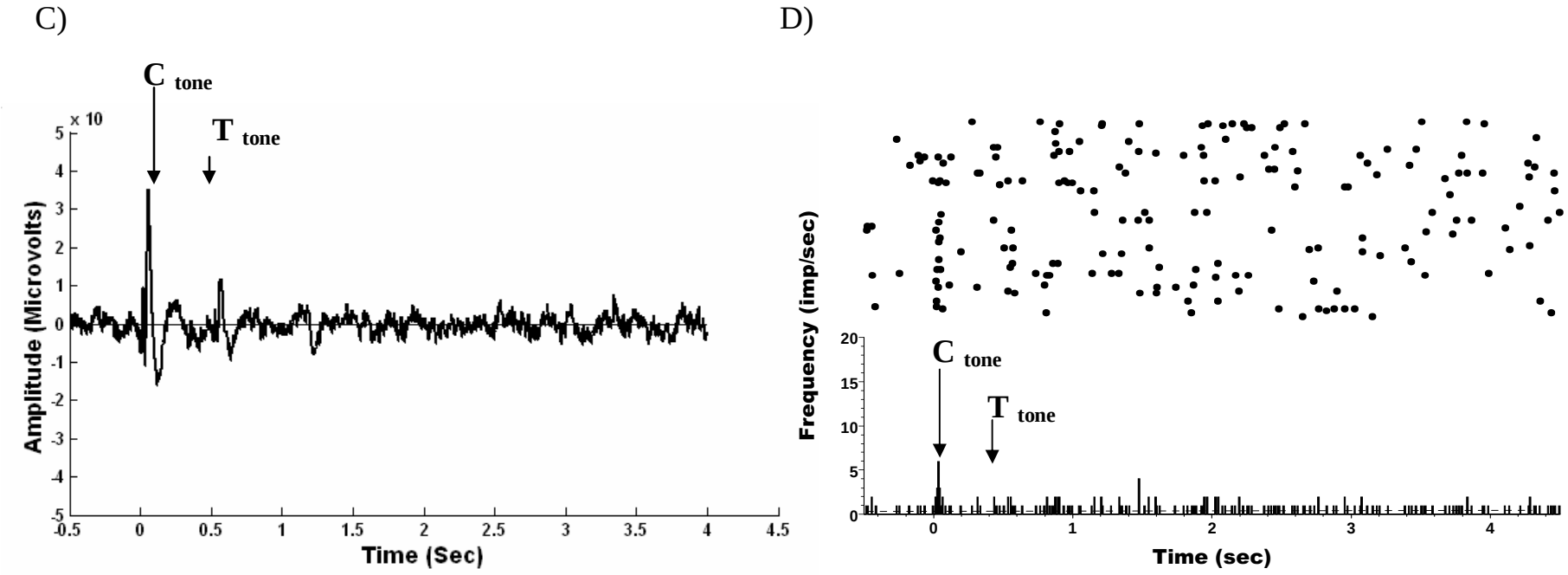
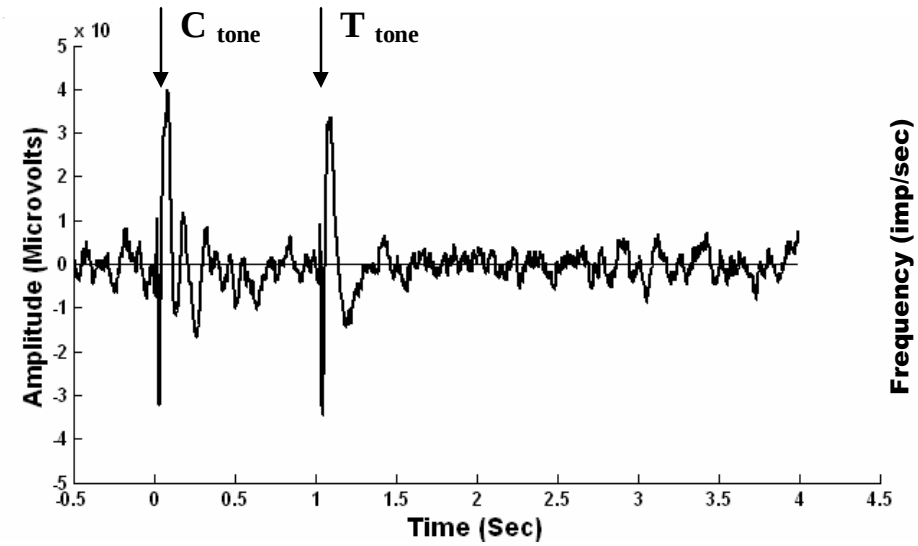


Figure 8 C,D. A CTI of 500 ms responses of C) LFP are strongly gated following T_{tone}, yet responses for D) single-units are very strongly gated following T_{tone}.

Figure 8E,F.

E



F)

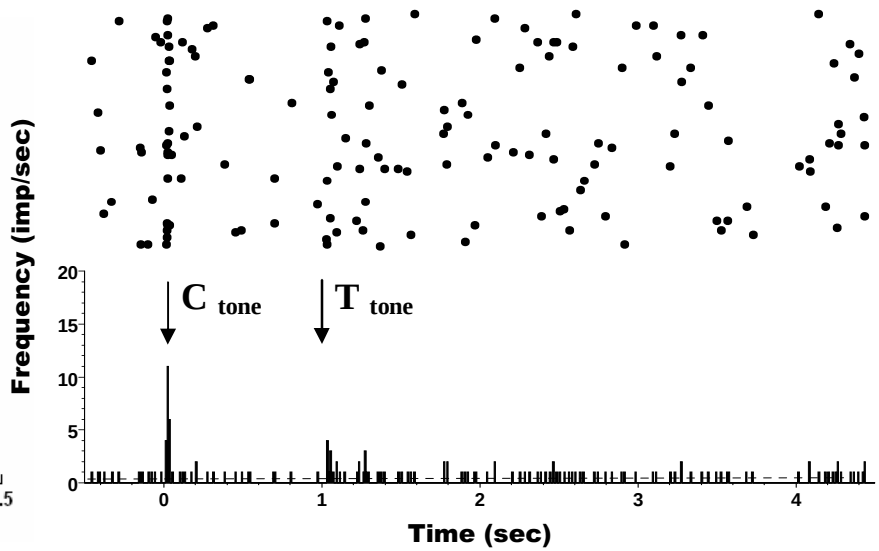
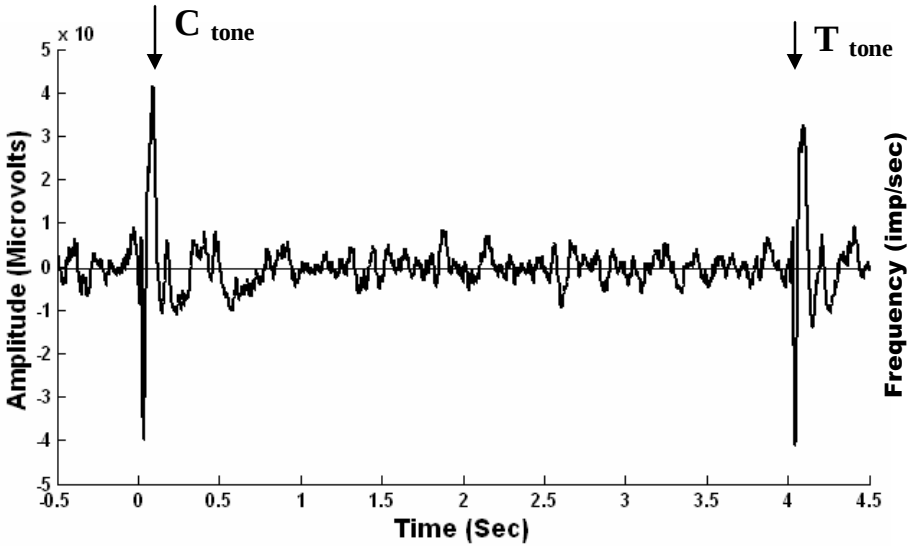


Figure 8 E,F. The CTI of 1 sec E) LFP responses are weakly gated following T_{tone}, indicated by tAmp nearly equal to cAmp. For the F) single-unit responses at 1 sec CTI strong gating is evidenced by much smaller increases in firing rate following T_{tone} than following C_{tone}.

Figure 8 G,H.

G)



H)

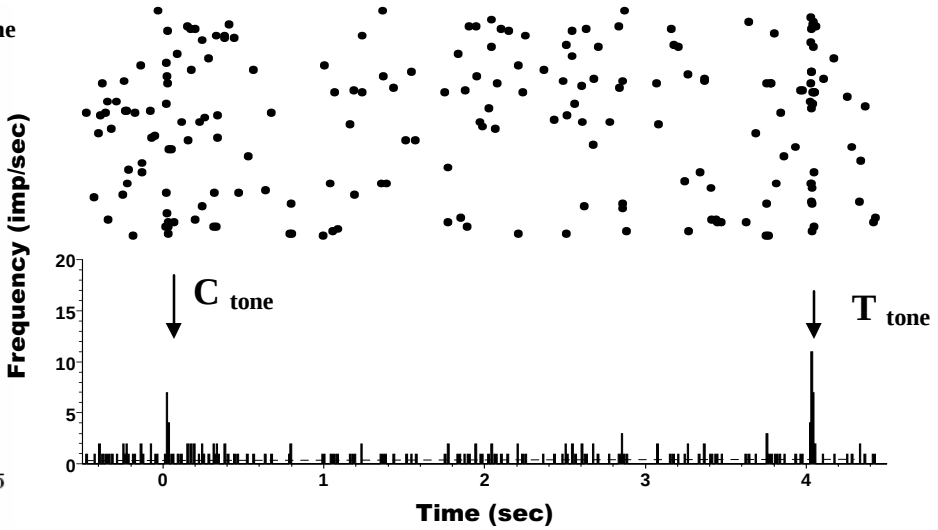


Figure 8 G,H. At a CTI of 4 sec gating is weak for G) LFP. For the H) single-unit at a CTI of 4 sec inhibitory gating is nonexistent, evidenced by a facilitation of firing rate increase following T_{tone}.

Figure 9. Group data for inhibitory gating before and after footshock conditioning

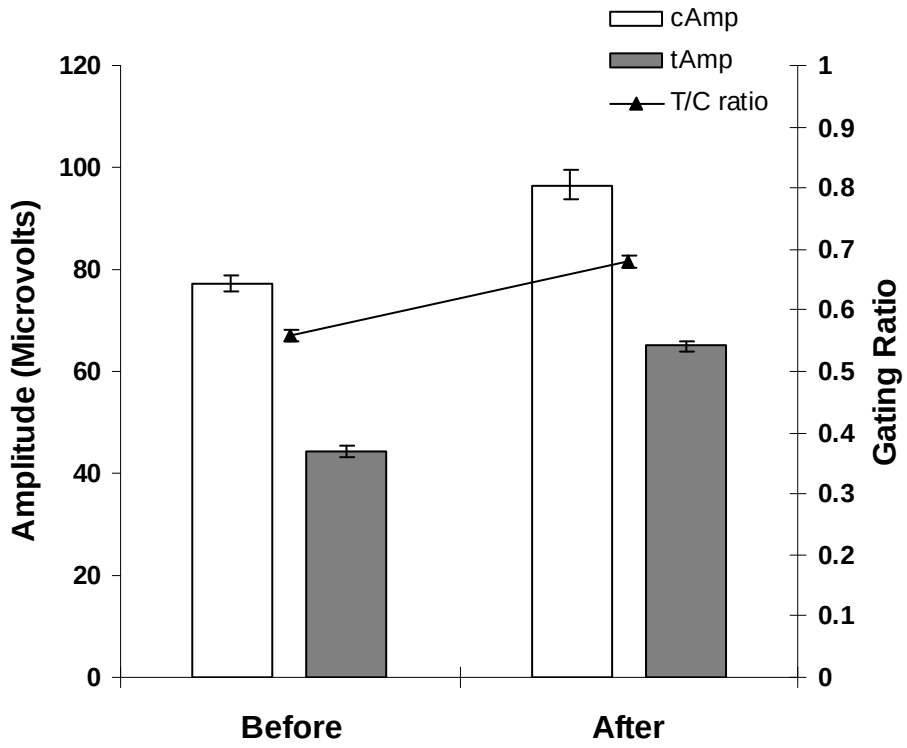


Figure 9. Results of LFP for sessions before and after fear conditioning are indicated with amplitudes of response for cAmp and tAmp (microvolts) represented on the right-side axis. T/C ratios for each session are represented on the left-side axis.

Figure 10. Group data: orienting behavior before and after footshock conditioning

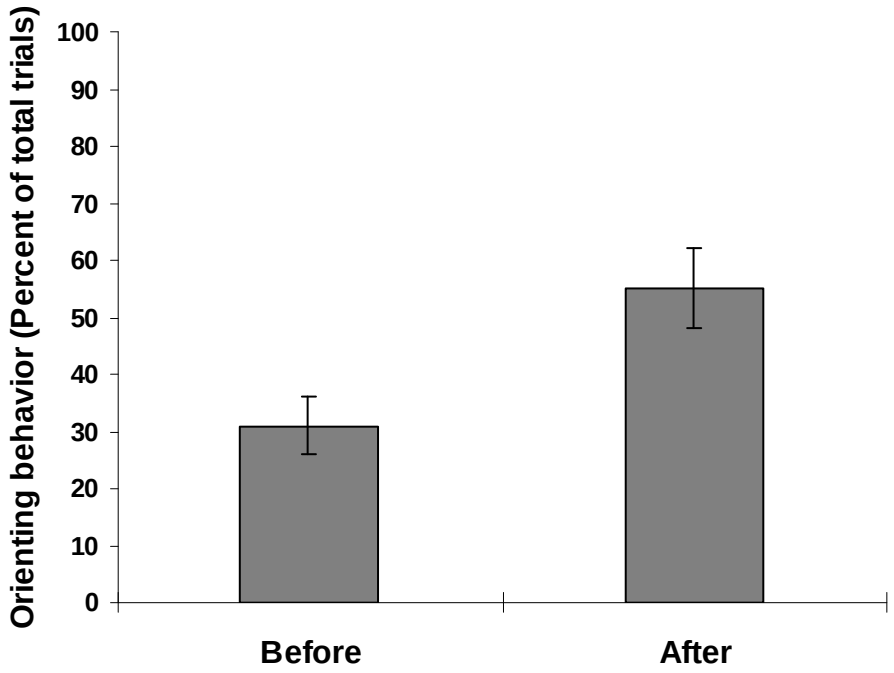


Figure 10. For the entire group of subjects, percentages of total trials with orienting behavior before and after fear conditioning demonstrate that animals were more responsive to the tone-pairs used to test inhibitory gating after fear conditioning.

Figure 11A,B. Group data for dopamine system manipulations on inhibitory gating

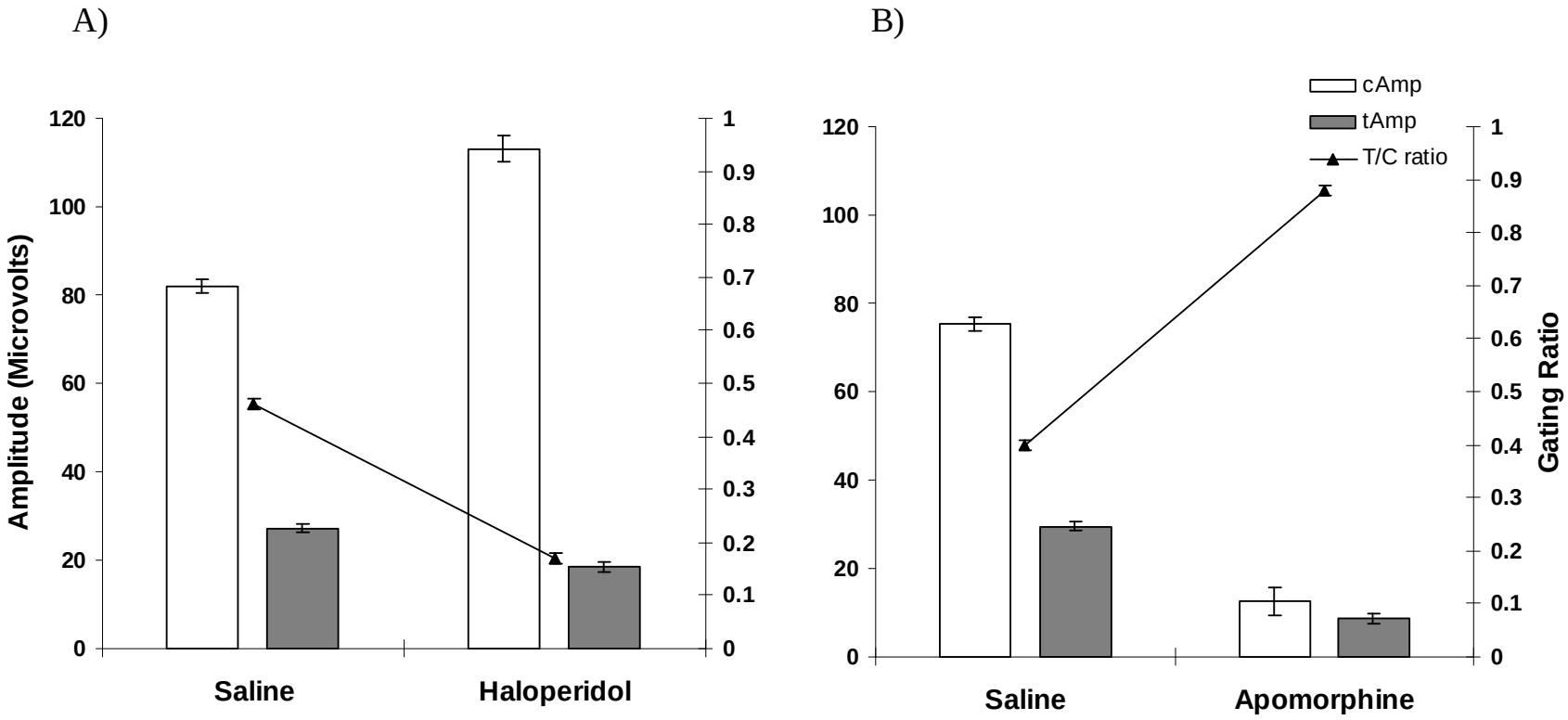


Figure 11. The effects of dopamine system manipulations produced alterations of inhibitory gating when compared over the duration of an entire recording session. A) Compared to saline, injections of haloperidol (1mg/kg) produced increases in cAmp and decreases in tAmp. Inhibitory gating strengthened, as T/C ratios were reduced for haloperidol compared to saline. B) Injections of apomorphine (1 mg/kg), compared to saline, produced reductions of cAmp and tAmp. Decreases in inhibitory gating were indicated by T/C ratios that were much greater for apomorphine than for saline.

Figure 12 A,B. Group data for GABA system manipulations on inhibitory gating

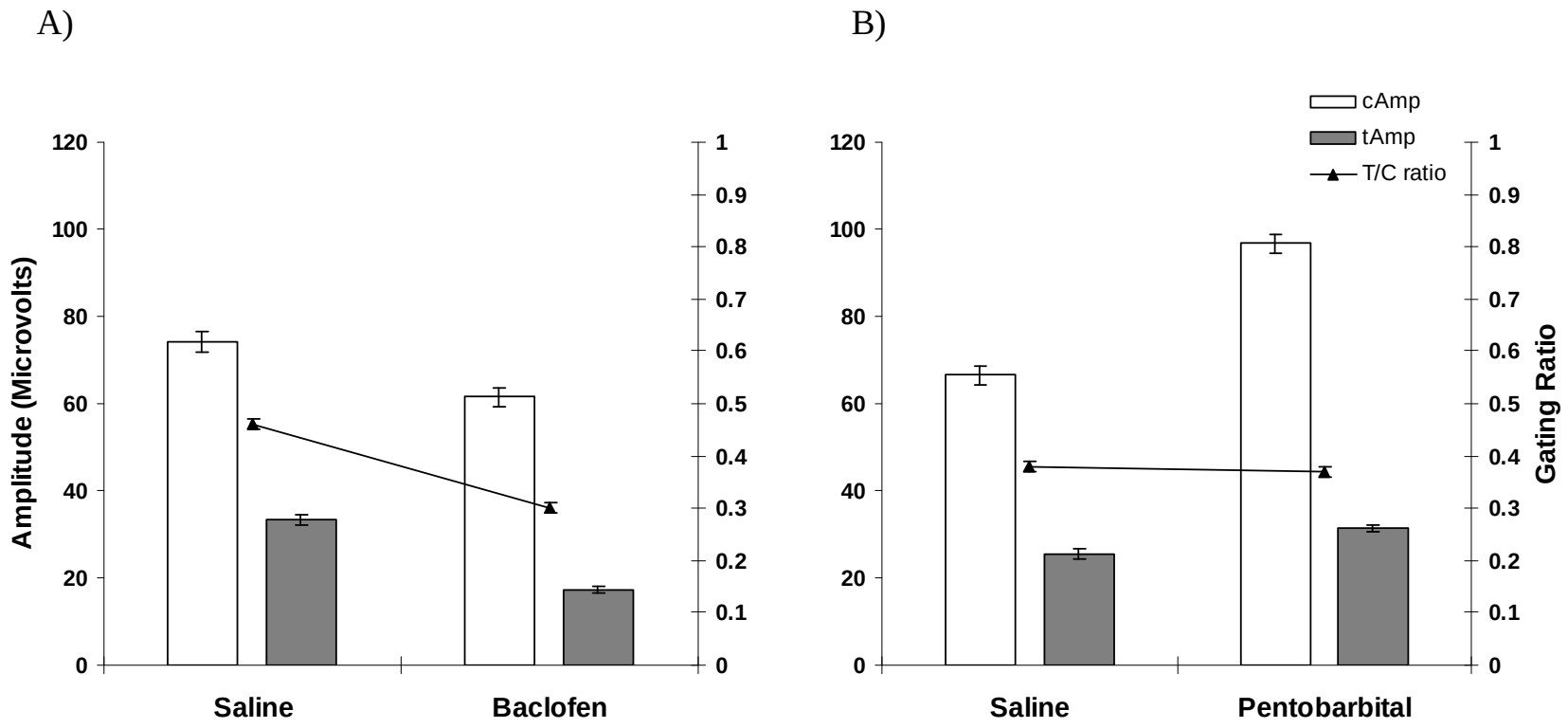


Figure 12. The effects of GABA system manipulations of inhibitory gating when compared over the duration of an entire recording session. A) Injections of baclofen (4 mg/kg) compared to saline produced reductions in cAmp and tAmp, and T/C ratios. The decrease in inhibitory gating was due to a larger decrease in tAmp than cAmp. B) Injections of pentobarbital (20 mg/kg) compared to saline produced increases in cAmp and tAmp. Whole session averages revealed that T/C ratios were not changed for pentobarbital compared to saline because cAmp and tAmp were increased in equal proportion.

REFERENCES

Abi-Dargham, A. (2004). Do we still believe in the dopamine hypothesis? New data bring new evidence. *Int J Neuropsychopharmacol, 7 Suppl 1*, S1-5.

Adler, L. E., Hoffer, L. J., Griffith, J., Waldo, M. C., & Freedman, R. (1992). Normalization by nicotine of deficient auditory sensory gating in the relatives of schizophrenics. *Biol Psychiatry, 32*(7), 607-616.

Adler, L. E., Olincy, A., Cawthra, E., Hoffer, M., Nagamoto, H. T., Amass, L., & Freedman, R. (2001). Reversal of diminished inhibitory sensory gating in cocaine addicts by a nicotinic cholinergic mechanism. *Neuropsychopharmacology, 24*(6), 671-679.

Adler, L. E., Olincy, A., Waldo, M., Harris, J. G., Griffith, J., Stevens, K., Flach, K., Nagamoto, H., Bickford, P., Leonard, S., & Freedman, R. (1998). Schizophrenia, sensory gating, and nicotinic receptors. *Schizophr Bull, 24*, 189-202.

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. *Biol. Psychiatry, 17*(6), 639-654.

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

Adler, L. E., Waldo, M. C., & Freedman, R. (1985). Neurophysiologic studies of sensory gating in schizophrenia: comparison of auditory and visual responses. *Biol Psychiatry, 20*(12), 1284-1296.

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. *Schizophr Res, 3*(2), 131-138.

Alexander, G. E., Crutcher, M. D., & DeLong, M. R. (1990). Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Prog Brain Res, 85*, 119-146.

Andreasen, N. C., Arndt, S., Alliger, R., Miller, D., & Flaum, M. (1995). Symptoms of schizophrenia. Methods, meanings, and mechanisms. *Arch Gen Psychiatry, 52*(5), 341-351.

Arnfred, S. M., Chen, A. C., Glenthoj, B. Y., & Hemmingsen, R. P. (2003). Normal p50 gating in unmedicated schizophrenia outpatients. *Am J Psychiatry, 160*(12), 2236-2238.

Bailey, K. R., & Mair, R. G. (2004). Dissociable effects of frontal cortical lesions on measures of visuospatial attention and spatial working memory in the rat. *Cereb Cortex, 14*(9), 974-985.

Balla, A., Sershen, H., Serra, M., Koneru, R., & Javitt, D. C. (2003). Subchronic continuous phencyclidine administration potentiates amphetamine-induced frontal cortex dopamine release. *Neuropsychopharmacology, 28*(1), 34-44.

Bechara, A., Damasio, H., Tranel, D., & Anderson, S. W. (1998). Dissociation Of working memory from decision making within the human prefrontal cortex. *J Neurosci, 18*(1), 428-437.

Becker, J., Gomes, I., Ghisolfi, E. S., Schuch, A., Ramos, F. L., Ehlers, J. A., Nora, D. B., Lara, D. R., & da Costa, J. C. (2004). Clozapine, but not typical antipsychotics, correct P50 suppression deficit in patients with schizophrenia. *Clin Neurophysiol, 115*(2), 396-401.

Benes, F., & Berretta, S. (2001). GABAergic interneurons: implications for understanding schizophrenia and bipolar disorder. *Neuropsychopharmacology, 25*, 1-27.

Berman, K. F., & Weinberger, D. R. (1990). The prefrontal cortex in schizophrenia and other neuropsychiatric diseases: in vivo physiological correlates of cognitive deficits. *Prog Brain Res, 85*, 521-536.

Bianchi, G., Landi, M., & Garattini, S. (1986). Disposition of apomorphine in rat brain areas: relationship to stereotypy. *Eur J Pharmacol, 131*(2-3), 229-236.

Bickford, P. C., Luntz-Leybman, V., & Freedman, R. (1993). Auditory sensory gating in the rat hippocampus: modulation by brainstem activity. *Brain Res, 607*(1-2), 33-38.

Bickford-Wimer, P. A., Nagamoto, H. T., Johnson, R., Adler, L. E., Egan, M., Rose, G., & Freedman, R. (1990). Auditory sensory gating in hippocampal neurons: a model system in the rat. *Biol. Psychiatry, 27*(2), 183-192.

Birrell, J. M., & Brown, V. J. (2000). Medial frontal cortex mediates perceptual attentional set shifting in the rat. *J Neurosci, 20*(11), 4320-4324.

Blumenfeld, L. D., & Clementz, B. A. (2001). Response to the first stimulus determines reduced auditory evoked response suppression in schizophrenia: single trials analysis using MEG. *Clin Neurophysiol, 112*(9), 1650-1659.

Boutros, N., Uretsky, N. J., Lui, J. J., & Milana, R. B. (1997). Effects of repeated cocaine adminstration on sensory inhibition in rats. *Biol. Psychiatry, 41*, 461-466.

Boutros, N. N. (1998). Dopamine and the P50. *Biol Psychiatry, 44*(9), 936-937.

Boutros NN, B. K., Milanan and Lui J. (1997). A parametric study of the N40 auditory evoked response in rats. *Biol. Psychiatry, 42*, 1051-1059.

Boutros, N. N., Bonnet, K. A., Millana, R., & Liu, J. (1997). A parametric study of the N40 auditory evoked response in rats. *Biol Psychiatry, 42*(11), 1051-1059.

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 Res, 126*(3), 203-215.

Boutros, N. N., & Kwan, S. W. (1998). Test-retest reliability of the rat N40 auditory evoked response: preliminary data. *Psychiatry Res, 81*(2), 269-276.

Boutros, N. N., Overall, J., & Zouridakis, G. (1991). Test-retest reliability of the P50 mid-latency auditory evoked response. *Psychiatry Res, 39*(2), 181-192.

Boutros NN, T. M., Barker BA, Tueting PA, Wu S. and Nasrellah HA. (1995). The P50 evoked potential component and mismatch detection in normal volunteers: implications for the study of sensory gating. *Psychiatry Research, 57*, 83-88.

Boutros, N. N., Zouridakis, G., & Overall, J. (1991). Replication and extension of P50 findings in schizophrenia. *Clin Electroencephalogr, 22*(1), 40-45.

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

Braff, D. L., & Light, G. A. (2004). Preattentional and attentional cognitive deficits as targets for treating schizophrenia. *Psychopharmacology (Berl), 174*(1), 75-85.

Broersen, L. M. (2000). Attentional processes and learning and memory in rats: the prefrontal cortex and hippocampus compared. *Prog Brain Res, 126*, 79-94.

Brown, V. J., & Bowman, E. M. (2002). Rodent models of prefrontal cortical function. *Trends Neurosci, 25*(7), 340-343.

Cacace, A. T., Satya-Murti, S., & Wolpaw, J. R. (1990). Human middle-latency auditory evoked potentials: vertex and temporal components. *Electroencephalogr Clin Neurophysiol, 77*(1), 6-18.

Cadenhead, K. S., Light, G. A., Geyer, M. A., McDowell, J. E., & Braff, D. L. (2002). Neurobiological measures of schizotypal personality disorder: defining an inhibitory endophenotype? *Am J Psychiatry, 159*(5), 869-871.

Cannon, T. D., Hennah, W., van Erp, T. G., Thompson, P. M., Lonnqvist, J., Huttunen, M., Gasperoni, T., Tuulio-Henriksson, A., Pirkola, T., Toga, A. W., Kaprio, J., Mazziotta, J., & Peltonen, L. (2005). Association of DISC1/TRAX Haplotypes With Schizophrenia, Reduced Prefrontal Gray Matter, and Impaired Short- and Long-term Memory. *Arch Gen Psychiatry, 62*(11), 1205-1213.

Cant, N. B., & Benson, C. G. (2003). Parallel auditory pathways: projection patterns of the different neuronal populations in the dorsal and ventral cochlear nuclei. *Brain Res Bull, 60*(5-6), 457-474.

Cardenas, V., Gill, P., & Fein, G. (1997). Human P50 suppression is not affected by variations in wakeful alertness. *Biological Psychiatry, 41*(8), 891-901.

Carli, M., Baviera, M., Invernizzi, R. W., & Balducci, C. (2005). Dissociable Contribution of 5-HT(1A) and 5-HT(2A) Receptors in the Medial Prefrontal Cortex to Different Aspects of Executive Control such as Impulsivity and Compulsive Perseveration in Rats. *Neuropsychopharmacology*.

Carr, D. B., & Sesack, S. R. (1999). Terminals from the rat prefrontal cortex synapse on mesoaccumbens VTA neurons. *Ann N Y Acad Sci, 877*, 676-678.

Carr, D. B., & Sesack, S. R. (2000). GABA-containing neurons in the rat ventral tegmental area project to the prefrontal cortex. *Synapse, 38*(2), 114-123.

Carr, D. B., & Sesack, S. R. (2000). Projections from the rat prefrontal cortex to the ventral tegmental area: target specificity in the synaptic associations with mesoaccumbens and mesocortical neurons. *J Neurosci, 20*(10), 3864-3873.

Chapin, J., & Woodward, D. (1981). Modulation of sensory responsiveness of single somatosensory cortical cells during movement and arousal behaviors. *Exp Neurol, 72*, 164-178.

Chapin, J. K., & Woodward, D. J. (1982). Somatic sensory transmission to the cortex during movement: gating of single cell responses to touch. *Exp Neurol, 78*, 654-669.

Cheng, Y. F., & Paalzow, L. K. (1992). Linear pharmacokinetics of haloperidol in the rat. *Biopharm Drug Dispos, 13*(1), 69-76.

Christakou, A., Robbins, T. W., & Everitt, B. J. (2001). Functional disconnection of a prefrontal cortical-dorsal striatal system disrupts choice reaction time performance: implications for attentional function. *Behav Neurosci, 115*(4), 812-825.

Christakou, A., Robbins, T. W., & Everitt, B. J. (2004). Prefrontal cortical-ventral striatal interactions involved in affective modulation of attentional performance: implications for corticostriatal circuit function. *J Neurosci, 24*(4), 773-780.

Chudasama, Y., Nathwani, F., & Robbins, T. W. (2005). D-Amphetamine remediates attentional performance in rats with dorsal prefrontal lesions. *Behav Brain Res, 158*(1), 97-107.

Clementz, B. A., Geyer, M. A., & Braff, D. L. (1997). P50 suppression among schizophrenia and normal comparison subjects: a methodological analysis. *Biol Psychiatry, 41*(10), 1035-1044.

Clementz, B. A., Geyer, M. A., & Braff, D. L. (1998). Poor P50 suppression among schizophrenia patients and their first-degree biological relatives. *Am J Psychiatry, 155*(12), 1691-1694.

Conde, F., Audinat, E., Maire-Lepoivre, E., & Crepel, F. (1990). Afferent connections of the medial frontal cortex of the rat. A study using retrograde transport of fluorescent dyes. I. Thalamic afferents. *Brain Res Bull, 24*(3), 341-354.

Conde, F., Maire-Lepoivre, E., Audinat, E., & Crepel, F. (1995). Afferent connections of the medial frontal cortex of the rat. II. Cortical and subcortical afferents. *J Comp Neurol, 352*(4), 567-593.

Correll, C. M., Rosenkranz, J. A., & Grace, A. A. (2005). Chronic cold stress alters prefrontal cortical modulation of amygdala neuronal activity in rats. *Biol Psychiatry, 58*(5), 382-391.

Creese, I., Burt, D. R., & Snyder, S. H. (1976). Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science, 192*(4238), 481-483.

Creese, I., Burt, D. R., & Snyder, S. H. (1996). Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *J Neuropsychiatry Clin Neurosci, 8*(2), 223-226.

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 Res, 1043*(1-2), 12-23.

Cullum, C. M., Harris, J. G., Waldo, M. C., Smernoff, E., Madison, A., Nagamoto, H. T., Griffith, J., Adler, L. E., & Freedman, R. (1993). Neurophysiological and

neuropsychological evidence for attentional dysfunction in schizophrenia. *Schizophr Res, 10*(2), 131-141.

Davis, H., Mast, T., Yoshie, N., & Zerlin, S. (1966). The slow response of the human cortex to auditory stimuli: recovery process. *Electroencephalogr Clin Neurophysiol, 21*(2), 105-113.

de Bruin, N. M., Ellenbroek, B. A., van Schaijk, W. J., Cools, A. R., Coenen, A. M., & van Luijtelaar, E. L. (2001). Sensory gating of auditory evoked potentials in rats: effects of repetitive stimulation and the interstimulus interval. *Biol Psychol, 55*(3), 195-213.

de Bruin, N. M., van Luijtelaar, E. L., Cools, A. R., & Ellenbroek, B. A. (2001). Auditory information processing in rat genotypes with different dopaminergic properties. *Psychopharmacology (Berl), 156*(2-3), 352-359.

De Bruin NMWJ, Elenbroek BA, Van Luijtelaar ELJM, Cools AR, & Stevens KE. (2001). Hippocampal and cortical sensory gating in rats: effects of quinpirole microinjections in nucleus accumbens core and shell. *Neuroscience, 105*, 169-180.

Deguchi, Y., Inabe, K., Tomiyasu, K., Nozawa, K., Yamada, S., & Kimura, R. (1995). Study on brain interstitial fluid distribution and blood-brain barrier transport of baclofen in rats by microdialysis. *Pharm Res, 12*(12), 1838-1844.

Delatour, B., & Gisquet-Verrier, P. (2000). Functional role of rat prelimbic-infralimbic cortices in spatial memory: evidence for their involvement in attention and behavioural flexibility. *Behav Brain Res, 109*(1), 113-128.

Di Chiara, G., & Gessa, G. L. (1978). Pharmacology and neurochemistry of apomorphine. *Adv Pharmacol Chemother, 15*, 87-160.

Dias, R., Robbins, T. W., & Roberts, A. C. (1997). Dissociable forms of inhibitory control within prefrontal cortex with an analog of the Wisconsin Card Sort Test: restriction to novel situations and independence from "on-line" processing. *J Neurosci, 17*(23), 9285-9297.

Diergaarde, L., Gerrits, M. A., Brouwers, J. P., & van Ree, J. M. (2005). Early amygdala damage disrupts performance on medial prefrontal cortex-related tasks but spares spatial learning and memory in the rat. *Neuroscience, 130*(3), 581-590.

Diergaarde, L., Spruijt, B. M., Wolterink-Donselaar, I. G., Gerrits, M. A., & van Ree, J. M. (2005). Neonatal amygdala lesions affect appetitive motivational and consummatory aspects of social behavior in the rat. *Behav Neurosci, 119*(3), 814-820.

Doherty, M. D., & Gratton, A. (1999). Effects of medial prefrontal cortical injections of GABA receptor agonists and antagonists on the local and nucleus accumbens dopamine responses to stress. *Synapse, 32*(4), 288-300.

Dolu, N., Suer, C., & Ozesmi, C. (2001). A comparison of the different interpair intervals in the conditioning-testing P50 paradigms. *Int J Psychophysiol, 41*(3), 265-270.

Egner, T., & Hirsch, J. (2005). Where memory meets attention: neural substrates of negative priming. *J Cogn Neurosci, 17*(11), 1774-1784.

Elliott, R., McKenna, P. J., Robbins, T. W., & Sahakian, B. J. (1995). Neuropsychological evidence for frontostriatal dysfunction in schizophrenia. *Psychol Med, 25*(3), 619-630.

Ezrin-Waters, C., & Seeman, P. (1977). Tolerance of haloperidol catalepsy. *Eur J Pharmacol, 41*(3), 321-327.

Feenstra, M. G., Teske, G., Botterblom, M. H., & De Bruin, J. P. (1999). Dopamine and noradrenaline release in the prefrontal cortex of rats during classical aversive and

appetitive conditioning to a contextual stimulus: interference by novelty effects. *Neurosci Lett, 272*(3), 179-182.

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. *Eur J Neurosci, 13*(5), 1051-1054.

Fein, G., Biggins, C., & MacKay, S. (1996). Cocaine abusers have reduced auditory P50 amplitude and suppression compared to both normal controls and alcoholics. *Biol Psychiatry, 39*(11), 955-965.

Ferino, F., Thierry, A. M., & Glowinski, J. (1987). Anatomical and electrophysiological evidence for a direct projection from Ammon's horn to the medial prefrontal cortex in the rat. *Exp Brain Res, 65*(2), 421-426.

Finlay, J. M., & Zigmond, M. J. (1997). The effects of stress on central dopaminergic neurons: possible clinical implications. *Neurochem Res, 22*(11), 1387-1394.

Floresco, S. B., Seamans, J. K., & Phillips, A. G. (1997). Selective roles for hippocampal, prefrontal cortical, and ventral striatal circuits in radial-arm maze tasks with or without a delay. *J Neurosci, 17*(5), 1880-1890.

Franks, R. D., Adler, L. E., Waldo, M. C., Alpert, J., & Freedman, R. (1983). Neurophysiological studies of sensory gating in mania: comparison with schizophrenia. *Biol Psychiatry, 18*(9), 989-1005.

Freedman, R., Adams, C. E., Adler, L. E., Bickford, P. C., Gault, J., Harris, J. G., Nagamoto, H. T., Olincy, A., Ross, R. G., Stevens, K. E., Waldo, M., & Leonard, S. (2000). Inhibitory neurophysiological deficit as a phenotype for genetic investigation of schizophrenia. *Am J Med Genet, 97*(1), 58-64.

Freedman, R., Adler, L. E., Bickford, P., Byerley, W., Coon, H., Cullum, C. M., Griffith, J. M., Harris, J. G., Leonard, S., Miller, C., & et al. (1994). Schizophrenia and nicotinic receptors. *Harv Rev Psychiatry, 2*(4), 179-192.

Freedman, R., Adler, L. E., Gerhardt, G. A., Waldo, M., Baker, N., Rose, G. M., Drebing, C., Nagamoto, H., Bickford-Wimer, P., & Franks, R. (1987). Neurobiological studies of sensory gating in schizophrenia. *Schizophr Bull, 13*(4), 669-678.

Freedman, R., Adler, L. E., Gerhardt, G. A., Waldo, M., Baker, N., Rose, G. M., Drebing, C., Nagamoto, H., Bickford-Wimer, P., & Franks, R. (1987). Neurobiological studies of sensory gating in schizophrenia. *Schizophr Bull, 13*(4), 669-678.

Freedman, R., Adler, L. E., Myles-Worsley, M., Nagamoto, H. T., Miller, C., Kisley, M., McRae, K., Cawthra, E., & Waldo, M. (1996). Inhibitory gating of an evoked response to repeated auditory stimuli in schizophrenic and normal subjects. Human recordings, computer simulation, and an animal model. *Arch Gen Psychiatry, 53*, 1114-1121.

Freedman, R., Adler, L. E., Nagamoto, H. T., & Waldo, M. C. (1998). Selection of digital filtering parameters and P50 amplitude. *Biol Psychiatry, 43*(12), 921-922.

Freedman, R., Adler, L. E., & Waldo, M. (1987). Gating of the auditory evoked potential in children and adults. *Psychophysiology, 24*(2), 223-227.

Freedman, R., Adler, L. E., Waldo, M. C., Pachtman, E., & Franks, R. D. (1983). Neurophysiological evidence for a defect in inhibitory pathways in schizophrenia: comparison of medicated and drug-free patients. *Biol Psychiatry, 18*(5), 537-551.

Freedman, R., Coon, H., Myles-Worsley, M., Orr-Urtreger, A., Olincey, A., Davis, A., Polymeropoulos, M., Holik, J., Hopkins, J., Hoff, M., Rosenthal, J., Waldo, M., Reimherr, F., Wender, P., Yaw, J., Young, D. A., Breese, C. R., Adams, C., Patterson, D.,

Adler, L. E., Kruglyak, L., Leonard, S., & Byerley, W. (1997). Linkage of a neurophysiological deficit in schizophrenia to chromosome 15 locus. *Proc Natl Acad Sci, 94*, 587-592.

Freedman, R., Hoffer, B. J., Puro, D., & Woodward, D. J. (1976). Noradrenaline modulation of the responses of the cerebellar purkinje cell to afferent synaptic activity. *British Journal of Pharmacology, 57*(4), 603-605.

Freedman, R., Leonard, S., Waldo, M., Gault, J., Olincy, A., & Adler, L. E. (2006). Characterization of allelic variants at chromosome 15q14 in schizophrenia. *Genes Brain Behav, 5 Suppl 1*, 14-22.

Freedman, R., Olincy, A., Ross, R. G., Waldo, M. C., Stevens, K. E., Adler, L. E., & Leonard, S. (2003). The genetics of sensory gating deficits in schizophrenia. *Curr Psychiatry Rep, 5*(2), 155-161.

Freedman, R., Waldo, M., Bickford-Wimer, P., & Nagamoto, H. (1991). Elementary neuronal dysfunctions in schizophrenia. *Schizophr Res, 4*(2), 233-243.

Fruncillo, R. J., & DiGregorio, G. J. (1984). Pharmacokinetics of pentobarbital, quinidine, lidocaine, and theophylline in the thermally injured rat. *J Pharm Sci, 73*(8), 1117-1121.

Fuster, J. M. (1990). Prefrontal cortex and the bridging of temporal gaps in the perception-action cycle. *Ann N Y Acad Sci., 608*, 318-329.

Gabbott, P. L., Dickie, B. G., Vaid, R. R., Headlam, A. J., & Bacon, S. J. (1997). Local-circuit neurones in the medial prefrontal cortex (areas 25, 32 and 24b) in the rat: morphology and quantitative distribution. *J Comp Neurol, 377*(4), 465-499.

Garcia, R., Vouimba, R. M., Baudry, M., & Thompson, R. F. (1999). The amygdala modulates prefrontal cortex activity relative to conditioned fear. *Nature, 402*(6759), 294-296.

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. *Int J Psychophysiol, 51*(3), 209-214.

Ghisolfi, E. S., Schuch, A., Strimitzer, I. M., Jr., Luersen, G., Martins, F. F., Ramos, F. L., Becker, J., & Lara, D. R. (2006). Caffeine modulates P50 auditory sensory gating in healthy subjects. *Eur Neuropsychopharmacol, 16*(3), 204-210.

Gisabella, B., Bolshakov, V. Y., & Benes, F. M. (2005). Regulation of synaptic plasticity in a schizophrenia model. *Proc Natl Acad Sci U S A, 102*(37), 13301-13306.

Goldman-Rakic, P. S. (1995). Architecture of the prefrontal cortex and the central executive. *Ann N Y Acad Sci, 769*, 71-83.

Goldman-Rakic, P. S. (1995). Cellular basis of working memory. *Neuron, 14*(3), 477-485.

Goldman-Rakic, P. S. (1996). Regional and cellular fractionation of working memory. *Proc Natl Acad Sci U S A, 93*(24), 13473-13480.

Goldman-Rakic, P. S., & Selemon, L. D. (1997). Functional and anatomical aspects of prefrontal pathology in schizophrenia. *Schizophr Bull, 23*(3), 437-458.

Gonzalez-Burgos, G., Krimer, L. S., Povysheva, N. V., Barrionuevo, G., & Lewis, D. A. (2005). Functional properties of fast spiking interneurons and their synaptic connections with pyramidal cells in primate dorsolateral prefrontal cortex. *J Neurophysiol, 93*(2), 942-953.

Gottesman, II, & Gould, T. D. (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry, 160*(4), 636-645.

Granon, S., & Poucet, B. (1995). Medial prefrontal lesions in the rat and spatial navigation: evidence for impaired planning. *Behav Neurosci, 109*(3), 474-484.

Groenewegen, H. J. (1988). Organization of the afferent connections of the mediodorsal thalamic nucleus in the rat, related to the mediodorsal-prefrontal topography. *Neuroscience, 24*(2), 379-431.

Groenewegen, H. J., Wright, C. I., Beijer, A. V., & Voorn, P. (1999). Convergence and segregation of ventral striatal inputs and outputs. *Ann N Y Acad Sci, 877*, 49-63.

Groenewegen, H. J., Wright, C. I., & Uylings, H. B. (1997). The anatomical relationships of the prefrontal cortex with limbic structures and the basal ganglia. *J Psychopharmacol, 11*(2), 99-106.

Grube, B. S., Bilder, R. M., & Goldman, R. S. (1998). Meta-analysis of symptom factors in schizophrenia. *Schizophr Res, 31*(2-3), 113-120.

Grunewald, T., Boutros, N. N., Pezer, N., von Oertzen, J., Fernandez, G., Schaller, C., & Elger, C. E. (2003). Neuronal substrates of sensory gating in human brain. *Biol. Psychiatry, 53*, 511-519.

Gupta, A., Wang, Y., & Markram, H. (2000). Organizing principles for a diversity of GABAergic interneurons and synapses in the neocortex. *Science, 287*(5451), 273-278.

Hammond, D. L. (2001). GABA(B) receptors: new tricks by an old dog. *Curr Opin Pharmacol, 1*(1), 26-30.

Harris, J. G., Kongs, S., Allensworth, D., Martin, L., Tregellas, J., Sullivan, B., Zerbe, G., & Freedman, R. (2004). Effects of nicotine on cognitive deficits in schizophrenia. *Neuropsychopharmacology, 29*(7), 1378-1385.

Harrison, J. B., Woolf, N. J., & Buchwald, J. S. (1990). Cholinergic neurons of the feline pontomesencephalon. I. Essential role in 'Wave A' generation. *Brain Res, 520*(1-2), 43-54.

Harvey, P. D., Geyer, M. A., Robbins, T. W., & Krystal, J. H. (2003). Cognition in schizophrenia: from basic science to clinical treatment. *Psychopharmacology (Berl), 169*(3-4), 213-214.

Hatanaka, T., Sato, S., Endoh, M., Katayama, K., Kakemi, M., & Koizumi, T. (1988). Effect of chlorpromazine on the pharmacokinetics and pharmacodynamics of pentobarbital in rats. *J Pharmacobiodyn, 11*(1), 18-30.

Hershman, K. M., Freedman, R., & Bickford, P. C. (1995). GABAB antagonists diminish the inhibitory gating of auditory response in the rat hippocampus. *Neurosci Lett, 190*(2), 133-136.

Hsieh, M. H., Liu, K., Liu, S. K., Chiu, M. J., Hwu, H. G., & Chen, A. C. (2004). Memory impairment and auditory evoked potential gating deficit in schizophrenia. *Psychiatry Res, 130*(2), 161-169.

Hur, E. E., & Zaborszky, L. (2005). Vglut2 afferents to the medial prefrontal and primary somatosensory cortices: a combined retrograde tracing in situ hybridization. *J Comp Neurol, 483*(3), 351-373.

Ishikawa, M., Mizukami, K., Iwakiri, M., & Asada, T. (2005). Immunohistochemical and immunoblot analysis of gamma-aminobutyric acid B receptor in the prefrontal cortex of subjects with schizophrenia and bipolar disorder. *Neurosci Lett, 383*(3), 272-277.

Jackson, M. E., Frost, A. S., & Moghaddam, B. (2001). Stimulation of prefrontal cortex at physiologically relevant frequencies inhibits dopamine release in the nucleus accumbens. *J Neurochem, 78*(4), 920-923.

Jansen, B. H., Agarwal, G., Hegde, A., & Boutros, N. N. (2003). Phase synchronization of the ongoing EEG and auditory EP generation. *Clin Neurophysiol, 114*(1), 79-85.

Jansen, B. H., Hegde, A., & Boutros, N. N. (2004). Contribution of different EEG frequencies to auditory evoked potential abnormalities in schizophrenia. *Clin Neurophysiol, 115*(3), 523-533.

Javitt, D. C., & Zukin, S. R. (1991). Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry, 148*(10), 1301-1308.

Jay, T. M., Glowinski, J., & Thierry, A. M. (1989). Selectivity of the hippocampal projection to the prelimbic area of the prefrontal cortex in the rat. *Brain Res, 505*(2), 337-340.

Jerger, K., Biggins, C., & Fein, G. (1992). P50 suppression is not affected by attentional manipulations. *Biol Psychiatry, 31*(4), 365-377.

Jin, Y., Potkin, S. G., Patterson, J. V., Sandman, C. A., Hetrick, W. P., & Bunney, W. E., Jr. (1997). Effects of P50 temporal variability on sensory gating in schizophrenia. *Psychiatry Res, 70*(2), 71-81.

Jodo, E., & Aston-Jones, G. (1997). Activation of locus coeruleus by prefrontal cortex is mediated by excitatory amino acid inputs. *Brain Res, 768*(1-2), 327-332.

Jodo, E., Chiang, C., & Aston-Jones, G. (1998). Potent excitatory influence of prefrontal cortex activity on noradrenergic locus coeruleus neurons. *Neuroscience, 83*(1), 63-79.

Jodo, E., Suzuki, Y., & Kayama, Y. (2000). Selective responsiveness of medial prefrontal cortex neurons to the meaningful stimulus with a low probability of occurrence in rats. *Brain Research, 856*, 68-74.

Johnson, M. R., & Adler, L. E. (1993). Transient impairment in P50 auditory sensory gating induced by a cold-pressor test. *Biol Psychiatry, 33*(5), 380-387.

Jongsma, M., Van Rijn, C., Dirksen, R., & Coenen, A. (1998). Effects of stimulus repetitions with different interstimulus intervals on the rat auditory evoked potential. *Recent Advances in Human Neurophysiology*, 249-255.

Judd, L. L., McAdams, L., Budnick, B., & Braff, D. L. (1992). Sensory gating deficits in schizophrenia: new results. *Am J Psychiatry, 149*(4), 488-493.

Kathmann, N., & Engel, R. R. (1990). Sensory gating in normals and schizophrenics: a failure to find strong P50 suppression in normals. *Biol Psychiatry, 27*(11), 1216-1226.

Kapur, S., Wadenberg, M. L., & Remington, G. (2000). Are animal studies of antipsychotics appropriately dosed? Lessons from the bedside to the bench. *Can J Psychiatry, 45*(3), 241-246.

Kawaguchi, Y., & Kubota, Y. (1997). GABAergic cell subtypes and their synaptic conenctions in rat frontal cortex. *Cerebral Cortex, 7*(6), 476-486.

Kawaguchi, Y., & Kubota, Y. (1998). Neurochemical features and synaptic connections of large physiologically-identified GABAergic cells in the rat frontal cortex. *Neuroscience, 85*(3), 677-701.

Killcross, S., & Coutureau, E. (2003). Coordination of actions and habits in the medial prefrontal cortex of rats. *Cereb Cortex, 13*(4), 400-408.

Kim, Y. B., Jang, J., Chung, Y., Baeg, E. H., Kim, H. T., Mook-Jung, I., Kim, S. U., Jung, M. W., & Chung, Y. K. (2001). Haloperidol and clozapine increase neural activity in the rat prefrontal cortex. *Neurosci Lett, 298*(3), 217-221.

Kisley, M., & Gerstein, G. (1999). Trial-to-trial variability and state-dependenet modulation of auditory-evoked responses in cortex. *The Journal of Neuroscience, 19*, 10451-10460.

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

Kisley, M. A., & Gerstein, G. L. (2001). Daily variation and appetitive conditioning-induced plasticity of auditory cortex receptive fields. *European Journal of Neuroscience, 13,* 1993-2003.

Kisley, M. A., Noecker, T. L., & Guinther, P. M. (2004). Comparison of sensory gating to mismatch negativity and self-reported perceptual phenomena in healthy adults. *Psychophysiology, 41*(4), 604-612.

Kisley, M. A., Olincy, A., & Freedman, R. (2001). The effect of state on sensory gating: comparison of waking, REM and non-REM sleep. *Clin Neurophysiol, 112*(7), 1154-1165.

Knight, R. T. (1984). Decreased response to novel stimuli after prefrontal lesions in man. *Electroencephalogr Clin Neurophysiol, 59*(1), 9-20.

Knight, R. T., Brailowsky, S., Scabini, D., & Simpson, G. V. (1985). Surface auditory evoked potentials in the unrestrained rat: component definition. *Electroencephalogr Clin Neurophysiol, 61*(5), 430-439.

Knight, R. T., Grabowecky, M. F., & Scabini, D. (1995). Role of human prefrontal cortex in attention control. *Adv Neurol, 66,* 21-34; discussion 34-26.

Knight, R. T., Scabini, D., & Woods, D. L. (1989). Prefrontal cortex gating of auditory transmission in humans. *Brain Res, 504*(2), 338-342.

Knight, R. T., Staines, W. R., Swick, D., & Chao, L. L. (1999). Prefrontal cortex regulates inhibition and excitation in distributed neural networks. *Acta Psychol (Amst), 101*(2-3), 159-178.

Krause, M., Hoffmann, W. E., & Hajos, M. (2003). Auditory sensory gating in hippocampus and reticular thalamic neurons in anesthetized rats. *Biol Psychiatry, 53*(3), 244-253.

Krettek, J. E., & Price, J. L. (1977). Projections from the amygdaloid complex to the cerebral cortex and thalamus in the rat and cat. *J Comp Neurol, 172*(4), 687-722.

Lamberti, J., Schwarzkopf, S., Boutros, N., Crilly, J., & Martin, R. (1994). Within-session changes in sensory gating assessed by P50 evoked potentials in normal subjects. *Prog Neuropsychopharmacol Biol Psychiatry., 17*(5), 781-791.

Laroche, S., Davis, S., & Jay, T. M. (2000). Plasticity at hippocampal to prefrontal cortex synapses: dual roles in working memory and consolidation. *Hippocampus, 10*(4), 438-446.

LeDoux, J. (1998). Fear and the brain: where have we been, and where are we going? *Biol Psychiatry, 44*(12), 1229-1238.

Leonard, C. M. (1969). The prefrontal cortex of the rat. I. Cortical projection of the mediodorsal nucleus. II. Efferent connections. *Brain Res, 12*(2), 321-343.

Leonard, S., Adams, C., Breese, C. R., Adler, L. E., Bickford, P., Byerley, W., Coon, H., Griffith, J. M., Miller, C., Myles-Worsley, M., Nagamoto, H. T., Rollins, Y., Stevens, K. E., Waldo, M., & Freedman, R. (1996). Nicotinic receptor function in schizophrenia. *Schizophr Bull, 22*(3), 431-445.

Lewis, D. A., Cruz, D., Eggan, S., & Erickson, S. (2004). Postnatal development of prefrontal inhibitory circuits and the pathophysiology of cognitive dysfunction in schizophrenia. *Ann N Y Acad Sci, 1021*, 64-76.

Liegeois-Chauvel, C., Musolino, A., Badier, J. M., Marquis, P., & Chauvel, P. (1994). Evoked potentials recorded from the auditory cortex in man: evaluation and topography of the middle latency components. *Electroencephalogr Clin Neurophysiol, 92*(3), 204-214.

Light, G. A., & Braff, D. L. (1998). The "incredible shrinking" P50 event-related potential. *Biol Psychiatry, 43*(12), 918-920.

Light, G. A., Geyer, M. A., Clementz, B. A., Cadenhead, K. S., & Braff, D. L. (2000). Normal P50 suppression in schizophrenia patients treated with atypical antipsychotic medications. *Am J Psychiatry, 157*(5), 767-771.

Light, G. A., Malaspina, D., Geyer, M. A., Luber, B. M., Coleman, E. A., Sackeim, H. A., & Braff, D. L. (1999). Amphetamine disrupts P50 suppression in normal subjects. *Biol Psychiatry, 46*(7), 990-996.

Likhtik, E., Pelletier, J. G., Paz, R., & Pare, D. (2005). Prefrontal control of the amygdala. *J Neurosci, 25*(32), 7429-7437.

Lillrank, S. M., Lipska, B. K., & Weinberger, D. R. (1995). Neurodevelopmental animal models of schizophrenia. *Clin Neurosci, 3*(2), 98-104.

Louchart-de la Chapelle, S., Levillain, D., Menard, J. F., Van der Elst, A., Allio, G., Haouzir, S., Dollfus, S., Campion, D., & Thibaut, F. (2005). P50 inhibitory gating deficit is correlated with the negative symptomatology of schizophrenia. *Psychiatry Res, 136*(1), 27-34.

Makeig, S., Westerfield, M., Jung, T. P., Enghoff, S., Townsend, J., Courchesne, E., & Sejnowski, T. J. (2002). Dynamic brain sources of visual evoked responses. *Science, 295*(5555), 690-694.

Mandema, J. W., Heijligers-Feijen, C. D., Tukker, E., De Boer, A. G., & Danhof, M. (1992). Modeling of the effect site equilibration kinetics and pharmacodynamics of racemic

baclofen and its enantiomers using quantitative EEG effect measures. *J Pharmacol Exp Ther, 261*(1), 88-95.

Maren, S., & Quirk, G. J. (2004). Neuronal signalling of fear memory. *Nat Rev Neurosci, 5*(11), 844-852.

Marshall, F. H., Jones, K. A., Kaupmann, K., & Bettler, B. (1999). GABAB receptors - the first 7TM heterodimers. *Trends Pharmacol Sci, 20*(10), 396-399.

Martin, L. F., Kem, W. R., & Freedman, R. (2004). Alpha-7 nicotinic receptor agonists: potential new candidates for the treatment of schizophrenia. *Psychopharmacology (Berl), 174*(1), 54-64.

McCallin, K., Cardenas, V. A., & Fein, G. (1997). P50 event-related brain potential amplitude and suppression measurements recorded with subjects seated versus supine. *Biol Psychiatry, 41*(8), 902-905.

McDonald, A. J. (1991). Organization of amygdaloid projections to the prefrontal cortex and associated striatum in the rat. *Neuroscience, 44*(1), 1-14.

McDonald, A. J. (1998). Cortical pathways to the mammalian amygdala. *Prog Neurobiol, 55*(3), 257-332.

McDonald, A. J., Mascagni, F., & Guo, L. (1996). Projections of the medial and lateral prefrontal cortices to the amygdala: a Phaseolus vulgaris leucoagglutinin study in the rat. *Neuroscience, 71*(1), 55-75.

McGhie, A., & Chapman, J. (1961). Disorders of attention and perception in early schizophrenia. *Br J Med Psychol, 34,* 103-116.

Milad, M. R., Vidal-Gonzalez, I., & Quirk, G. J. (2004). Electrical stimulation of medial prefrontal cortex reduces conditioned fear in a temporally specific manner. *Behav Neurosci, 118*(2), 389-394.

Miller, C. L., & Freedman, R. (1995). The activity of hippocampal interneurons and pyramidal cells during the response of the hippocampus to repeated auditory stimu. *Neuroscience, 69*, 371-381.

Molina, V., Sanz, J., Munoz, F., Casado, P., Hinojosa, J. A., Sarramea, F., & Martin-Loeches, M. (2005). Dorsolateral prefrontal cortex contribution to abnormalities of the P300 component of the event-related potential in schizophrenia. *Psychiatry Res, 140*(1), 17-26.

Morgan, M. A., & LeDoux, J. E. (1995). Differential contribution of dorsal and ventral medial prefrontal cortex to the acquisition and extinction of conditioned fear in rats. *Behav Neurosci, 109*(4), 681-688.

Moxon, K. A., Gerhardt, G. A., & Adler, L. E. (2003). Dopaminergic modulation of the P50 auditory-evoked potential in a computer model of the CA3 region of the hippocampus: its relationship to sensory gating in schizophrenia. *Biol Cybern, 88*(4), 265-275.

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

Moxon, K. A., Gerhardt, G. A., Gulinello, M., & Adler, L. E. (2003). Inhibitory control of sensory gating in a computer model of the CA3 region of the hippocampus. *Biol Cybern, 88*(4), 247-264.

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. *Proc Natl Acad Sci U S A, 93*(3), 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. *J Neurosci, 16*(23), 7768-7775.

Myles-Worsley, M., Ord, L., Blailes, F., Ngiralmau, H., & Freedman, R. (2004). P50 sensory gating in adolescents from a pacific island isolate with elevated risk for schizophrenia. *Biol Psychiatry, 55*(7), 663-667.

Naber, G., Kathmann, N., & Engel, R. (1992). P50 suppression in normal subjects: influence of stimulus intensity, test repetition, and presentation mode. *Journal of Psychophysiology, 6*, 47-53.

Nagamoto, H. T., Adler, L. E., Hea, R. A., Griffith, J. M., McRae, K. A., & Freedman, R. (1996). Gating of auditory P50 in schizophrenics: unique effects of clozapine. *Biol Psychiatry, 40*(3), 181-188.

Nagamoto, H. T., Adler, L. E., Waldo, M. C., & Freedman, R. (1989). Sensory gating in schizophrenics and normal controls: effects of changing stimulation interval. *Biol Psychiatry, 25*(5), 549-561.

Nagamoto, H. T., Adler, L. E., Waldo, M. C., Griffith, J., & Freedman, R. (1991). Gating of auditory response in schizophrenics and normal controls. Effects of recording site and stimulation interval on the P50 wave. *Schizophr Res, 4*(1), 31-40.

Neylan, T. C., Fletcher, D. J., Lenoci, M., McCallin, K., Weiss, D. S., Schoenfeld, F. B., Marmar, C. R., & Fein, G. (1999). Sensory gating in chronic posttraumatic stress

disorder: reduced auditory P50 suppression in combat veterans. *Biol Psychiatry, 46*(12), 1656-1664.

O'Donnell, P., Lavin, A., Enquist, L. W., Grace, A. A., & Card, J. P. (1997). Interconnected parallel circuits between rat nucleus accumbens and thalamus revealed by retrograde transynaptic transport of pseudorabies virus. *J Neurosci, 17*(6), 2143-2167.

Ohara, P. T., Granato, A., Moallem, T. M., Wang, B. R., Tillet, Y., & Jasmin, L. (2003). Dopaminergic input to GABAergic neurons in the rostral agranular insular cortex of the rat. *J Neurocytol, 32*(2), 131-141.

Olincey, A., Ross, R. G., Harris, J. G., Young, D. A., McAndrews, M. A., Cawthra, E., McRae, K. A., Sullivan, B., Adler, L. E., & Freedman, R. (2000). The P50 auditory event-evoked potential in adult attention-deficit disorder: comparison with schizophrenia. *Biol. Psychiatry, 47*(11), 969-977.

Oranje, B., Gispen-de Wied, C. C., Verbaten, M. N., & Kahn, R. S. (2002). Modulating sensory gating in healthy volunteers: the effects of ketamine and haloperidol. *Biol Psychiatry, 52*(9), 887-895.

Oranje, B., Gispen-de Wied, C. C., Westenberg, H. G., Kemner, C., Verbaten, M. N., & Kahn, R. S. (2004). Increasing dopaminergic activity: effects of L-dopa and bromocriptine on human sensory gating. *J Psychopharmacol, 18*(3), 388-394.

Otani, S. (2003). Prefrontal cortex function, quasi-physiological stimuli, and synaptic plasticity. *J Physiol Paris, 97*(4-6), 423-430.

Paalzow, L. K., & Paalzow, G. H. (1986). Concentration-response relations for apomorphine effects on heart rate in conscious rats. *J Pharm Pharmacol, 38*(1), 28-34.

Pantelis, C., Barber, F. Z., Barnes, T. R., Nelson, H. E., Owen, A. M., & Robbins, T. W. (1999). Comparison of set-shifting ability in patients with chronic schizophrenia and frontal lobe damage. *Schizophr Res, 37*(3), 251-270.

Pantelis, C., Barnes, T. R., Nelson, H. E., Tanner, S., Weatherley, L., Owen, A. M., & Robbins, T. W. (1997). Frontal-striatal cognitive deficits in patients with chronic schizophrenia. *Brain, 120 (Pt 10)*, 1823-1843.

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

Petrides, M. (1995). Impairments on nonspatial self-ordered and externally ordered working memory tasks after lesions of the mid-dorsal part of the lateral frontal cortex in the monkey. *J Neurosci, 15*(1 Pt 1), 359-375.

Pezze, M. A., Bast, T., & Feldon, J. (2003). Significance of dopamine transmission in the rat medial prefrontal cortex for conditioned fear. *Cereb Cortex, 13*(4), 371-380.

Pezze, M. A., & Feldon, J. (2004). Mesolimbic dopaminergic pathways in fear conditioning. *Prog Neurobiol, 74*(5), 301-320.

Phan, K. L., Fitzgerald, D. A., Nathan, P. J., Moore, G. J., Uhde, T. W., & Tancer, M. E. (2005). Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. *Biol Psychiatry, 57*(3), 210-219.

Pirch, J. H., & Peterson, S. L. (1981). Event-related slow potentials and activity of singly neurons in rat frontal cortex. *Int J Neurosci, 15*(3), 141-146.

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annu Rev Neurosci, 13*, 25-42.

Powell, D. A., Maxwell, B., & Penney, J. (1996). Neuronal activity in the medial prefrontal cortex during Pavlovian eyeblink and nictitating membrane conditioning. *J Neurosci, 16*(19), 6296-6306.

Powell, K. J., Binder, T. L., Hori, S., Nakabeppu, Y., Weinberger, D. R., Lipska, B. K., & Robertson, G. S. (2005). Neonatal Ventral Hippocampal Lesions Produce an Elevation of DeltaFosB-Like Protein(s) in the Rodent Neocortex. *Neuropsychopharmacology*.

Quirk, G. J., & Gehlert, D. R. (2003). Inhibition of the amygdala: key to pathological states? *Ann N Y Acad Sci, 985*, 263-272.

Quirk, G. J., Likhtik, E., Pelletier, J. G., & Pare, D. (2003). Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdala output neurons. *J Neurosci, 23*(25), 8800-8807.

Quirk, G. J., Repa, C., & LeDoux, J. E. (1995). Fear conditioning enhances short-latency auditory responses of lateral amygdala neurons: parallel recordings in the freely behaving rat. *Neuron, 15*(5), 1029-1039.

Reep, R. L., & Corwin, J. V. (1999). Topographic organization of the striatal and thalamic connections of rat medical agranular cortex. *Brain Res, 841*(1-2), 43-52.

Reep, R. L., Goodwin, G. S., & Corwin, J. V. (1990). Topographic organization in the corticocortical connections of medial agranular cortex in rats. *J Comp Neurol, 294*(2), 262-280.

Reese, N. B., Garcia-Rill, E., & Skinner, R. D. (1995). Auditory input to the pedunculopontine nucleus: I. Evoked potentials. *Brain Res Bull, 37*(3), 257-264.

Reese, N. B., Garcia-Rill, E., & Skinner, R. D. (1995). Auditory input to the pedunculopontine nucleus: II. Unit responses. *Brain Res Bull, 37*(3), 265-273.

Richert, K. A., Carrion, V. G., Karchemskiy, A., & Reiss, A. L. (2005). Regional differences of the prefrontal cortex in pediatric PTSD: an MRI study. *Depress Anxiety*.

Ringel, T. M., Heidrich, A., Jacob, C. P., Pfuhlmann, B., Stoeber, G., & Fallgatter, A. J. (2004). Sensory gating deficit in a subtype of chronic schizophrenic patients. *Psychiatry Res, 125*(3), 237-245.

Roberts, N. A., Beer, J. S., Werner, K. H., Scabini, D., Levens, S. M., Knight, R. T., & Levenson, R. W. (2004). The impact of orbital prefrontal cortex damage on emotional activation to unanticipated and anticipated acoustic startle stimuli. *Cogn Affect Behav Neurosci, 4*(3), 307-316.

Romanski, L. M., & Goldman-Rakic, P. S. (2002). An auditory domain in primate prefrontal cortex. *Nat Neurosci, 5*(1), 15-16.

Romanski, L. M., & Goldman-Rakic, P. S. (2003). An auditory domain in primate prefrontal cortex. *Nat. Neuroscience, 5*(1), 15-20.

Romanski, L. M., Tian, B., Fritz, J., Mishkin, M., & Goldman-Rakic, P. S. (1999). Dual streams of auditory afferents target multiple domains in the primate prefrontal cortex. *Nat. Neuroscience, 2*(12), 1131-1136.

Rose, J. E., & Woolsey, C. N. (1949). The relations of thalamic connections, cellular structure and evocable electrical activity in the auditory region of the cat. *J Comp Neurol, 91*(3), 441-466.

Rosenkrantz, J. A., & Grace, A. A. (2001). Dopamine attenuates prefrontal cortical suppression of sensory inputs to the basolateral amygdala of rats. *J Neurosci, 21*(11), 4090-4103.

Rosenkrantz, J. A., Moore, H., & Grace, A. A. (2003). The prefrontal cortex regulates lateral amygdala activity neuronal plasticity and response to previouslt conditioned stimuli. *J Neurosci, 23*, 11054-11064.

Rosenkranz, J. A., & Grace, A. A. (2002). Cellular mechanisms of infralimbic and prelimbic prefrontal cortical inhibition and dopaminergic modulation of basolateral amygdala neurons in vivo. *J Neurosci, 22*(1), 324-337.

Rossi, S., Bartalini, S., Ulivelli, M., Mantovani, A., Di Muro, A., Goracci, A., Castrogiovanni, P., Battistini, N., & Passero, S. (2005). Hypofunctioning of sensory gating mechanisms in patients with obsessive-compulsive disorder. *Biol Psychiatry, 57*(1), 16-20.

Rule, R. R., Shimamura, A. P., & Knight, R. T. (2002). Orbitofrontal cortex and dynamic filtering of emotional stimuli. *Cogn Affect Behav Neurosci, 2*(3), 264-270.

Runyan, J. D., Moore, A. N., & Dash, P. K. (2004). A role for prefrontal cortex in memory storage for trace fear conditioning. *J Neurosci, 24*(6), 1288-1295.

Salamy, A., Salfi, M., & Fein, G. (1997). Sensory gating deficit following cocaine exposure in the rat. *Neuropsychobiology, 36*(2), 83-86.

Santiago, M., Machado, A., & Cano, J. (1993). Regulation of the prefrontal cortical dopamine release by GABAA and GABAB receptor agonists and antagonists. *Brain Res, 630*(1-2), 28-31.

Saper, C. B. (1982). Reciprocal parabrachial-cortical connections in the rat. *Brain Res, 242*(1), 33-40.

Saper, C. B., & Loewy, A. D. (1982). Projections of the pedunculopontine tegmental nucleus in the rat: evidence for additional extrapyramidal circuitry. *Brain Res, 252*(2), 367-372.

Sato, M. (1992). A lasting vulnerability to psychosis in patients with previous methamphetamine psychosis. *Ann N Y Acad Sci, 654*, 160-170.

Sato, S., Koshiro, A., Kakemi, M., Fukasawa, Y., Katayama, K., & Koizumi, T. (1995). Pharmacokinetic and pharmacodynamic studies of centrally acting drugs in rat: effect of pentobarbital and chlorpromazine on electroencephalogram in rat. *Biol Pharm Bull, 18*(8), 1094-1103.

Schneider, M., & Koch, M. (2005). Behavioral and morphological alterations following neonatal excitotoxic lesions of the medial prefrontal cortex in rats. *Exp Neurol, 195*(1), 185-198.

Seamans, J. K., Floresco, S. B., & Phillips, A. G. (1995). Functional differences between the prelimbic and anterior cingulate regions of the rat prefrontal cortex. *Behav Neurosci, 109*(6), 1063-1073.

Seamans, J. K., Gorelova, N., Durstewitz, D., & Yang, C. R. (2001). Bidirectional dopamine modulation of GABAergic inhibition in prefrontal cortical pyramidal neurons. *J Neurosci, 21*(10), 3628-3638.

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

Sebban, C., Tesolin-Decros, B., Millan, M. J., & Spedding, M. (1999). Contrasting EEG profiles elicited by antipsychotic agents in the prefrontal cortex of the conscious rat: antagonism of the effects of clozapine by modafinil. *Br J Pharmacol, 128*(5), 1055-1063.

Sebban, C., Zhang, X. Q., Tesolin-Decros, B., Millan, M. J., & Spedding, M. (1999). Changes in EEG spectral power in the prefrontal cortex of conscious rats elicited by drugs interacting with dopaminergic and noradrenergic transmission. *Br J Pharmacol, 128*(5), 1045-1054.

Selemon, L. D. (2001). Regionally diverse cortical pathology in schizophrenia: clues to the etiology of the disease. *Schizophr Bull, 27*(3), 349-377.

Selemon, L. D., & Goldman-Rakic, P. S. (1999). The reduced neuropil hypothesis: a circuit based model of schizophrenia. *Biol Psychiatry, 45*(1), 17-25.

Selemon, L. D., Kleinman, J. E., Herman, M. M., & Goldman-Rakic, P. S. (2002). Smaller frontal gray matter volume in postmortem schizophrenic brains. *Am J Psychiatry, 159*(12), 1983-1991.

Selemon, L. D., & Rajkowska, G. (2003). Cellular pathology in the dorsolateral prefrontal cortex distinguishes schizophrenia from bipolar disorder. *Curr Mol Med, 3*(5), 427-436.

Selemon, L. D., Rajkowska, G., & Goldman-Rakic, P. S. (1998). Elevated neuronal density in prefrontal area 46 in brains from schizophrenic patients: application of a three-dimensional, stereologic counting method. *J Comp Neurol, 392*(3), 402-412.

Self, D. W. (1998). Neural substrates of drug craving and relapse in drug addiction. *Ann Med, 30*(4), 379-389.

Semba, K., & Fibiger, H. C. (1992). Afferent connections of the laterodorsal and the pedunculopontine tegmental nuclei in the rat: a retro- and antero-grade transport and immunohistochemical study. *J Comp Neurol, 323*(3), 387-410.

Serafini, R., Bracamontes, J., & Steinbach, J. H. (2000). Structural domains of the human GABAA receptor 3 subunit involved in the actions of pentobarbital. *J Physiol, 524 Pt 3*, 649-676.

Sesack, S. R., & Carr, D. B. (2002). Selective prefrontal cortex inputs to dopamine cells: implications for schizophrenia. *Physiol Behav, 77*(4-5), 513-517.

Shaw, N. A. (1995). The temporal relationship between the brainstem and primary cortical auditory evoked potentials. *Prog Neurobiol, 47*(2), 95-103.

Shin, L. M., Wright, C. I., Cannistraro, P. A., Wedig, M. M., McMullin, K., Martis, B., Macklin, M. L., Lasko, N. B., Cavanagh, S. R., Krangel, T. S., Orr, S. P., Pitman, R. K., Whalen, P. J., & Rauch, S. L. (2005). A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. *Arch Gen Psychiatry, 62*(3), 273-281.

Shinba, T. (1999). Neuronal firing activity in the dorsal hippocampus during the auditory discrimination oddball task in awake rats: relation to event related potential generation. *Brain Res. Cognitive Brain Research, 8*(3), 241-250.

Shinba, T. (2002). Medial agranular cortex activity related to event-related potential generation in the rat. *Brain Res Cogn Brain Res, 14*(2), 264-268.

Shoemaker, J. M., Saint Marie, R. L., Bongiovanni, M. J., Neary, A. C., Tochen, L. S., & Swerdlow, N. R. (2005). Prefrontal D1 and ventral hippocampal N-methyl-d-aspartate regulation of startle gating in rats. *Neuroscience, 135*(2), 385-394.

Siegel, C., Waldo, M., Mizner, G., Adler, L. E., & Freedman, R. (1984). Deficits in sensory gating in schizophrenic patients and their relatives. Evidence obtained with auditory evoked responses. *Arch Gen Psychiatry, 41*(6), 607-612.

Sillar KT, & Roberts A. (1988). A neuronal mechanism for sensory gating during locomotion in a vertebrate. *Nature, 331*, 262-265.

Sinha, R., Catapano, D., & O'Malley, S. (1999). Stress-induced craving and stress response in cocaine dependent individuals. *Psychopharmacology (Berl), 142*(4), 343-351.

Skinner, R. D., Rasco, L. M., Fitzgerald, J., Karson, C. N., Matthew, M., Williams, D. K., & Garcia-Rill, E. (1999). Reduced sensory gating of the P1 potential in rape victims and combat veterans with posttraumatic stress disorder. *Depress Anxiety, 9*(3), 122-130.

Snyder, S. H. (1973). Amphetamine psychosis: a "model" schizophrenia mediated by catecholamines. *Am J Psychiatry, 130*(1), 61-67.

Staines, W., Grahm SJ, Black SE, & McIlroy WE. (2002). Task-relevant modulation of contralateral and ipsilateral primary somatosensory cortex and the role of a prefronatl-cortical sensory gating system. *NeuroImage, 15*, 190-199.

Staines, W. R., Padilla, M., & Knight, R. T. (2002b). Frontal-parietal event-related potential changes assocaited with practicing a novel visuomotor task. *Brain Res.Cognitive Brain Res., 13*(2), 195-202.

Steinbach, J. H., & Akk, G. (2001). Modulation of GABA(A) receptor channel gating by pentobarbital. *J Physiol, 537*(Pt 3), 715-733.

Steketee, J. D., & Beyer, C. E. (2005). Injections of baclofen into the ventral medial prefrontal cortex block the initiation, but not the expression, of cocaine sensitization in rats. *Psychopharmacology (Berl), 180*(2), 352-358.

Stella, V. J., & Chu, C. K. (1980). Effects of short-term dietary exposure to polychlorinated biphenyls on pharmacokinetics of intravenous pentobarbital in rats. *J Pharm Sci, 69*(11), 1274-1278.

Stevens, K. E., Freedman, R., Collins, A. C., Hall, M., Leonard, S., Marks, M. J., & Rose, G. M. (1996). Genetic correlation of inhibitory gating of hippocampal auditory evoked response and alpha-bungarotoxin-binding nicotinic cholinergic receptors in inbred mouse strains. *Neuropsychopharmacology, 15*(2), 152-162.

Stevens, K. E., Kem, W. R., Mahnir, V. M., & Freedman, R. (1998). Selective alpha7-nicotinic agonists normalize inhibition of auditory response in DBA mice. *Psychopharmacology (Berl), 136*(4), 320-327.

Suer, C., Dolu, N., & Ozesmi, C. (2004). The effect of immobilization stress on sensory gating in mice. *Int J Neurosci, 114*(1), 55-65.

Swanson, L. W. (1981). A direct projection from Ammon's horn to prefrontal cortex in the rat. *Brain Res, 217*(1), 150-154.

Swanson, L. W. (1982). The projections of the ventral tegmental area and adjacent regions: a combined fluorescent retrograde tracer and immunofluorescence study in the rat. *Brain Res Bull, 9*(1-6), 321-353.

Swerdlow, N. R., Braff, D. L., & Geyer, M. A. (2000). Animal models of deficient sensorimotor gating: what we know, what we think we know and what we hope to know soon. *Behavioral Pharmacology, 11*(3-4), 185-204.

Swerdlow, N. R., & Geyer, M. A. (1998). Using an animal model of deficient sensorimotor gating to study the pathophysiology and new treatments of schizophrenia. *Schizophr Bull, 24*(2), 285-301.

Swerdlow, N. R., Geyer, M. A., Shoemaker, J. M., Light, G. A., Braff, D. L., Stevens, K. E., Sharp, R., Breier, M., Neary, A., & Auerbach, P. P. (2006). Convergence and divergence in the neurochemical regulation of prepulse inhibition of startle and N40 suppression in rats. *Neuropsychopharmacology, 31*(3), 506-515.

Swerdlow, N. R., Shoemaker, J. M., Bongiovanni, M. J., Neary, A. C., Tochen, L. S., & Saint Marie, R. L. (2005). Reduced startle gating after D1 blockade: Effects of concurrent D2 blockade. *Pharmacol Biochem Behav*.

Tepper, J. M., & Bolam, J. P. (2004). Functional diversity and specificity of neostriatal interneurons. *Curr Opin Neurobiol, 14*(6), 685-692.

Thierry, A. M., Gioanni, Y., Degenetais, E., & Glowinski, J. (2000). Hippocampo-prefrontal cortex pathway: anatomical and electrophysiological characteristics. *Hippocampus, 10*(4), 411-419.

Thompson, S. M., & Robertson, R. T. (1987). Organization of subcortical pathways for sensory projections to the limbic cortex. I. Subcortical projections to the medial limbic cortex in the rat. *J Comp Neurol, 265*(2), 175-188.

Trantham-Davidson, H., Neely, L. C., Lavin, A., & Seamans, J. K. (2004). Mechanisms underlying differential D1 versus D2 dopamine receptor regulation of inhibition in prefrontal cortex. *J Neurosci, 24*(47), 10652-10659.

Tzschentke, T. M. (2001). Pharmacology and behavioral pharmacology of the mesocortical dopamine system. *Prog Neurobiol, 63*(3), 241-320.

Uylings, H. B., Groenewegen, H. J., & Kolb, B. (2003). Do rats have a prefrontal cortex? *Behav Brain Res, 146*(1-2), 3-17.

Uylings, H. B., & van Eden, C. G. (1990). Qualitative and quantitative comparison of the prefrontal cortex in rat and in primates, including humans. *Prog Brain Res, 85*, 31-62.

van den Heuvel, O. A., Veltman, D. J., Groenewegen, H. J., Cath, D. C., van Balkom, A. J., van Hartskamp, J., Barkhof, F., & van Dyck, R. (2005). Frontal-striatal dysfunction during planning in obsessive-compulsive disorder. *Arch Gen Psychiatry, 62*(3), 301-309.

van den Heuvel, O. A., Veltman, D. J., Groenewegen, H. J., Witter, M. P., Merkelbach, J., Cath, D. C., van Balkom, A. J., van Oppen, P., & van Dyck, R. (2005). Disorder-specific

neuroanatomical correlates of attentional bias in obsessive-compulsive disorder, panic disorder, and hypochondriasis. *Arch Gen Psychiatry, 62*(8), 922-933.

van Eden, C. G., Kros, J. M., & Uylings, H. B. (1990). The development of the rat prefrontal cortex. Its size and development of connections with thalamus, spinal cord and other cortical areas. *Prog Brain Res, 85*, 169-183.

Venables, P. H. (1964). Input Dysfunction in Schizophrenia. *Prog Exp Pers Res, 72*, 1-47.

Venables, P. H. (1969). Sensory aspects of psychopathology. *Proc Annu Meet Am Psychopathol Assoc, 58*, 132-143.

Venables, P. H., & Tizard, J. (1956). The effect of stimulus light intensity on reaction time of schizophrenics. *Br J Psychol, 47*(2), 144-147.

Vertes, R. P. (2004). Differential projections of the infralimbic and prelimbic cortex in the rat. *Synapse, 51*(1), 32-58.

Verwer, R. W., Meijer, R. J., Van Uum, H. F., & Witter, M. P. (1997). Collateral projections from the rat hippocampal formation to the lateral and medial prefrontal cortex. *Hippocampus, 7*(4), 397-402.

Waldo, M. C., & Freedman, R. (1986). Gating of auditory evoked responses in normal college students. *Psychiatry Res, 19*(3), 233-239.

Watanabe, M. (1992). Frontal units of the monkey coding the associative significance of visual and auditory stimuli. *Exp Brain Res, 89*(2), 233-247.

Wedzony, K., Fijal, K., & Mackowiak, M. (2005). Alterations in the dendritic morphology of prefrontal pyramidal neurons in adult rats after blockade of NMDA receptors in the postnatal period. *Brain Res*.

Weinberger, D. R., Egan, M. F., Bertolino, A., Callicott, J. H., Mattay, V. S., Lipska, B. K., Berman, K. F., & Goldberg, T. E. (2001). Prefrontal neurons and the genetics of schizophrenia. *Biol Psychiatry, 50*(11), 825-844.

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*(15), 3303-3307.

White, P. M., & Yee, C. M. (1997). Effects of attentional and stressor manipulations on the P50 gating response. *Psychophysiology, 34*(6), 703-711.

Williams, S. M., & Goldman-Rakic, P. S. (1998). Widespread origin of the primate mesofrontal dopamine system. *Cereb Cortex, 8*(4), 321-345.

Winterer, G., & Weinberger, D. R. (2004). Genes, dopamine and cortical signal-to-noise ratio in schizophrenia. *Trends Neurosci, 27*(11), 683-690.

Winterer, G., Ziller, M., Dorn, H., Frick, K., Mulert, C., Wuebben, Y., Herrmann, W. M., & Coppola, R. (2000). Schizophrenia: reduced signal-to-noise ratio and impaired phase-locking during information processing. *Clin Neurophysiol, 111*(5), 837-849.

Wong, A. H., Lipska, B. K., Likhodi, O., Boffa, E., Weinberger, D. R., Kennedy, J. L., & Van Tol, H. H. (2005). Cortical gene expression in the neonatal ventral-hippocampal lesion rat model. *Schizophr Res, 77*(2-3), 261-270.

Woods, D. L., & Knight, R. T. (1986). Electrophysiologic evidence of increased distractibility after dorsolateral prefrontal lesions. *Neurology, 36*(2), 212-216.

Wurzburger, R. J., Miller, R. L., Marcum, E. A., Colburn, W. A., & Spector, S. (1981). A new radioimmunoassay for haloperidol: direct measurement of serum and striatal concentrations. *J Pharmacol Exp Ther, 217*(3), 757-763.

Yago, E., Duarte, A., Wong, T., Barcelo, F., & Knight, R. T. (2004). Temporal kinetics of prefrontal modulation of the extrastriate cortex during visual attention. *Cogn Affect Behav Neurosci, 4*(4), 609-617.

Yamaguchi, S., & Knight, R. T. (1990). Gating of somatosensory input by human prefrontal cortex. *Brain Res, 521*(1-2), 281-288.

Yamashita, H., Okamoto, Y., Morinobu, S., Yamawaki, S., & Kahkonen, S. (2005). Visual emotional stimuli modulation of auditory sensory gating studied by magnetic P50 suppression. *Eur Arch Psychiatry Clin Neurosci, 255*(2), 99-103.

Yee, C. M., & White, P. M. (2001). Experimental modification of P50 suppression. *Psychophysiology, 38*(3), 531-539.

Zouridakis, G., & Boutros, N. N. (1992). Stimulus parameter effects on the P50 evoked response. *Biol Psychiatry, 32*(9), 839-841.