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SINGLE UNIT AND POPULATION RESPONSES DURING INHIBITORY GATING OF STRIATAL ACTIVITY IN FREELY MOVING RATS

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Abstract—The striatum is thought to be an essential region for integrating diverse information in the brain. Rapid inhibitory gating (IG) of sensory input is most likely an early factor necessary for appropriate integration to be completed. Gating is currently evaluated in clinical settings and is dramatically altered in a variety of psychiatric illnesses. Basic neuroscience research using animals has revealed specific neural sites involved in IG including the hippocampus, thalamus, brainstem, amygdala and medial prefrontal cortex. The present study investigated local IG in the basal ganglia structure of the striatum using chronic recording microwires. We obtained both single unit activations and local field potentials (LFPs) in awake behaving rats from each wire during the standard two-tone paradigm. Single units responded with different types of activations including a phasic and sustained excitation, an inhibitory response and a combination response that contained both excitatory and inhibitory components. IG was observed in all the response types; however, non-gating was observed in a large proportion of responses as well. Positive wave field potentials at 50–60 ms poststimulus (P60) showed consistent gating across the wire arrays. No significant correlations were found between single unit and LFP measures of gating during the initial baseline session. Gating was strengthened (T_{amp}/C_{amp} ratios approaching 0) following acute stress (saline injection) at both the single unit and LFP level due to the reduction in the response to the second tone. Alterations in sensory responding reflected by changes in the neural response to the initial tone were primarily observed following long-term internal state deviation (food deprivation) and during general locomotion. Overall, our results support local IG by single neurons in striatum but also suggest that rapid inhibition is not the dominant activation profile observed in other brain regions.

Key words: basal ganglia, inhibition, movement, electrophysiology, single unit, local field potential.

The basal ganglia system has been thought of as a brain system involved in inhibitory gating (IG) for many decades (Wilson, 1914; Denny-Brown and Yanagisawa, 1976; Cools, 1980; Schneider and Lidsky, 1987; Kodsi and Swerdlow, 1994). Denny-Brown and Yanagisawa (1976, p. 145) noted that "the basal ganglia have all the aspects of a 'clearing house' that accumulates samples of ongoing cortical projected activity and, on a competitive basis, can facilitate any one and suppress all others." The central location of the basal ganglia and the diverse inputs that locally converge make this system one of the most integrative within the CNS (Levy et al., 1997; Kincaid et al., 1998; Heimer and Van Hoesen, 2006). This high level of diversity of connections most likely contributes to the extraordinary level of complexity in the symptoms observed following basal ganglia dysfunction (Cromwell and King, 2004; Marsden, 1984). Basal ganglia disorders such as Parkinson's disease (PD) and Huntington's disease (HD) have been thought to arise from a breakdown in motor gating, sensorimotor integration and movement sequencing (Georgiou et al., 1995; Agostino et al., 1992; Helmuth et al., 2000).

IG as a neural function has been tested many different ways, but all methods basically evaluate the integrity of internal neural networks that filter information (Eccles et al., 1962; Woodward et al., 1991; Freedman et al., 1987; Swerdlow et al., 2000). In cellular neurophysiology, paradigms that use repetitive stimulation are crucial in revealing membrane dynamics and synaptic processes (Cromwell et al., 1995; Benes and Berretta, 2001; Fitzpatrick et al., 2001). Recently, in clinical neurophysiology a paired pulse or two-tone paradigm has been used to test inhibitory function in clinical disorders such as schizophrenia, post-traumatic stress disorder, obsessive compulsive disorder (OCD) and addiction (Adler et al., 1982, 2001; Boutros et al., 2004; Olincey et al., 2000; Neylan et al., 1999; Jessen et al., 2001; Stojanov et al., 2003; Rossi et al., 2005). It was found that patients with these disorders have defective inhibition of the neural response that follows an identical initial or "conditioned" response. This defect in inhibiting the second or "test" response has been thought to reflect a breakdown in rapid sensory processing and has been shown to be related to the symptoms of schizophrenia such as working memory deficits and negative symptomology (Cullum et al., 1993; Louchart-de la Chapelle et al., 2005). In the clinical setting, patients are recorded using electroencephalographic electrodes placed on different locations on the scalp (Adler et al., 1982; Freedman et al., 1996). Localization of IG is restricted using these procedures and deep brain regions have only recently been examined in human epileptic patients (Grunewald et al., 2003).

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Abbreviations: ANOVA, analysis of variance; C_{tone}, conditioning tone; E-LD, excitatory-long duration response; EP, evoked potential; E-SD, excitatory-short duration response; HD, Huntington's disease; IG, inhibitory gating; InH, inhibitory response; LFP, local field potential; OCD, obsessive compulsive disorder; PD, Parkinson's disease; SP, substance P; T_{tone}, test tone.

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The rodent model has allowed the research on the analysis of specific brain regions and IG to progress rapidly. Previous work used the acute preparation to record from single units in the thalamus (Krause et al., 2003), septum (Miller and Freedman, 1993) or hippocampus (Bickford-Wimer et al., 1990; Miller and Freedman, 1995). These studies found IG in the anesthetized animal and were able to delineate different neuron subtypes that showed different profiles of activity change relative to the sensory input. For example, in the hippocampus a phasic excitatory response was found and attributed to the excitatory pyramidal neurons while a delayed and prolonged increase in activity between stimuli was thought to arise from the local interneuron population (Miller and Freedman, 1995).

More recent investigations have used single unit recording in the awake, behaving rat to examine IG (Moxon et al., 1999; Cromwell et al., 2005a; Mears et al., 2006; Cromwell and Woodward, 2006). These studies have found that IG is a pervasive and long-lasting mechanism in several brain regions including the brainstem, reticular nucleus of the thalamus, hippocampus, amygdala and medial prefrontal cortex. These regions are interconnected and form integrative loops that process diverse sets of information (Alexander et al., 1990; Haber and Fudge, 1997). We have found both excitatory and inhibitory response (InH) types that display gating in the amygdala and medial prefrontal cortex (Cromwell et al., 2005a; Mears et al., 2006). The excitatory responses were either rapid phasic activations or slower long duration responses.

Cognitive and emotional deficits seen in schizophrenia or other psychological disorders could arise from defective gating in these subcortical or prefrontal cortical regions (Berman and Weinberger, 1990). Impairments in basal ganglia function are thought to play a role in the production of psychological disorders such as OCD (Bloch et al., 2005) and drug addiction (Everitt and Robbins, 2005) and gating deficits have been proposed as a major factor in PD and HD (Kaji et al., 2005). The aim of the present study was to investigate auditory IG in the basal ganglia structure of the striatum. This region is the main input structure of the basal ganglia with afferents from the complete cortical mantle including neocortical and allocortical subregions (Webster, 1965; Kemp and Powell, 1970). The structure is composed mainly of GABA containing projection cells that send axons to the globus pallidus or the substantia nigra pars reticulata (Bishop et al., 1982; Gerfen and Young, 1988; Zahm and Heimer, 1990). These neurons also receive input from brain stem catecholamine/indolamine containing neurons including dopamine, noradrenaline and 5-HT containing cells (McGeer et al., 1984). The structure has a minority of intrinsic cells that include GABAergic and cholinergic interneurons (Chang et al., 1982). We used chronic microwires to record from an ensemble of neurons during the standard paired-click paradigm and recorded both single unit and local field potential (LFP) activity from each wire. Portions of the data have been previously presented at the annual Society for Neuroscience Meeting (Klein et al., 2005).

EXPERIMENTAL PROCEDURES

Animals and electrode implantation

Seventeen adult male Sprague–Dawley rats weighing between 240 and 410 g (Harlan Inc., Indianapolis, IN, USA) were recorded from during the course of the investigation. Animals were anesthetized with xylazine (10 mg/kg) and ketamine (100 mg/kg). A stereotaxic apparatus was used for the implantation of recording microwires (NB Laboratories, Denison, TX, USA) into striatum bilaterally (+0.2 mm anterior, ±2.8 mm lateral and −6.2 mm ventral from bregma as measured from the skull) according to the standard rat stereotaxic atlas (Paxinos and Watson, 1998). Anchor screws were affixed to the skull surface to be used in the protective head stage. Rats were bilaterally implanted in striatum with 16 microwires in two bundles of 8 (one bundle in each hemisphere). Grounding wires were implanted bilaterally 2–3 mm caudal to bregma, 2–3 mm lateral and 2–3 mm below dura. The recording electrodes were cemented into permanent placement using dental acrylic. After surgery, rats were allowed 1 week to recover before the beginning of testing. All procedures followed the nationally approved guidelines for the care and use of animals (U.S. Department of Agriculture and Public Health Service) and were approved by the Bowling Green State University Institutional Animal Care and Use Committee. In accordance with these guidelines, all efforts were made to minimize the number of animals used and their suffering.

IG sessions

The testing chamber (20×28×35 cm) was located in a small sound attenuating room. The chamber floor had parallel rods 5 cm above a removable pan. Piezoelectric tone generators were attached to the top of the chamber, and holes were drilled to facilitate sound passing into the chamber. A tone generator produced a distinctive tone pitch of 4.1 kHz. A potentiometer on the tone generator was manually adjusted in order to produce brief tones that were 75 dB in intensity (i.e. measured from a height of 15 cm at two or more points above the chamber floor bars). The tone generator was controlled using Med-PC IV software (Med Associates, Inc., St. Albans, VT, USA) on a computer outside the room. At the beginning of each recording session, the rat's head stage was connected to the preamplifier, and 60 s passed before the beginning of the session in order to allow the rat to acclimate to the chamber. After the acclimation period, 100 stimulus pairs were presented to the rats. Stimuli consisted of 4.1 kHz tones (10 ms, 75 dB) presented at a condition-test interval (CTI) of 500 ms. There was a 10 s interval between pairs of auditory stimuli. We refer to the first tone as the C_{tone} or conditioning tone and the second tone as the T_{tone} or the test tone.

We tested animals for three consecutive sessions using the identical gating paradigm to evaluate variability of gating over short and long time periods. On the fourth day, we examined gating in a subgroup of animals after a saline injection and compared with units from a subgroup receiving no injection. This acute stressor has been shown to cause alterations in gating in other studies (Mears et al., 2006; Mears and Cromwell, 2004; Cromwell et al., 2005a). In another subgroup of animals, we examined gating after 24 h of food deprivation to evaluate the impact of a long-term internal stressor on IG in the striatum.

Data acquisition

Single-units and LFPs were recorded using a digital signal processor and computer with data acquisition software (MAP System, Plexon Inc., Dallas, TX, USA). Using the MAP Sort Client appli-

cation 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 channel used as grounding reference 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 (Rasputin Software Suite, Plexon Inc.). Using the available array of techniques it was possible to discriminate up to four single-units on each channel. Noise levels are reduced or eliminated by using an analog 400 Hz two pole low-cut filter on all recording channels. In addition, programmable reference channels from microelectrodes without units were used to subtract movement and stimulus artifacts from channels with clear, identifiable signals. All channels were monitored continuously during the sessions to ensure integrity of the neural signals and reference channels. Single-units spikes were detected on-line in MAP and imported into Neuroexplorer (NEX, System, Plexon Inc.) for more extensive real-time analyses including: rate-histograms, autocorrelograms, interspike intervals, perievent rasters, and perievent histograms. Off-line fine-tuning and even re-sorting, when necessary, of single-units discrimination was possible using an off-line sorter application (Off-line Sorter, Plexon, Inc.). Field potentials were imported to Matlab (The Mathworks, Nantic, MA, USA) for online averaging and monitoring of LFP responses to tones.

Single-units: data analysis

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 (Plexon Inc.) or Matlab (Mathworks Inc.). Perievent time histograms and raster plots of single-unit firing were generated centering on the times of the stimulus onset. Data were analyzed using several custom-made analyses performed 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.

In the analysis of baseline activity, we used *t*-tests to compare activity from a 3 s control window in order to test the amount of single-unit activity activated or suppressed by each stimulus. The control period was taken from baseline activity beginning 3.5 s and ending 0.5 s before the onset of the C_{tone}. The single-unit activity in the bins 300 ms before C_{tone}, 300 ms after C_{tone}, and 300 ms after T_{tone} was compared with the control period using sliding-window *t*-tests. This analysis indicated activity in response to tone stimuli that was significantly increased or decreased from the baseline level. Only single-units with activations that differed from the control window at the 0.05 level of significance were used for further analysis. For significant differences, the maximum or minimum difference from baseline firing rate within each block was used to represent activation or suppression in firing rate. For each tone-responsive unit, T/C ratios were generated for each session, and ratios were compared between sessions. Repeated-measures ANOVAs were used to compare C_{tone} activation or suppression, T_{tone} activation or suppression, and T/C ratios between sessions for both single unit and LFP activity. Univariate ANOVAs were completed for comparisons between saline-injection and non-saline injection, food-deprived and non-deprived states and between motor and non-motor episodes. Comparisons between cell groups from the non-saline/saline or non-deprived/deprived conditions had significantly different baseline firing rates compelling us to use normalized data in this analyses. We transformed the data by subtracting the mean activity of the single unit from the peak amplitude response and dividing this number by the standard deviation of the activity during the baseline period.

LFPs: data analysis

Within each session, extracellular field potentials corresponding to trials of stimulus pairs were referenced to the onset for each stimulus, and evoked potentials (EPs) were generated through waveform averaging. EPs were analyzed after waveform peaks were quantified through amplitude measurements for certain negative peaks and positive peaks in the average waveform. The peaks were identified according to the local maxima (or minima) in predefined time windows, and the peaks were measured according to the peak's amplitude difference from the baseline amplitude at the time of stimulus onset. With sliding-window *t*-tests, LFP peaks were compared with activity during a 1 s control period that was 3 s 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 C_{amp} or T_{amp}, respectively, for the amplitude of response to C_{tone} or T_{tone}. T/C ratios of T_{amp} divided by C_{amp} served as a crucial comparison for field potential gating. Repeated-measures ANOVAs were used to assess differences between C_{amp}, T_{amp}, and T/C ratios from different sessions.

Additionally, the responses of single-units to C_{tone} and T_{tone} were compared with the responses of LFPs. Relationships between the single-units and the LFP activity were completed using a simple regression procedure and making a correlation matrix between measures from each group. Single-units were grouped into classes based on the pattern of response to the C_{tone}. Finally, the T/C ratios for each single-unit were compared with the T/C ratios for the LFP recorded from the same channel as the single-unit. This comparison of single-unit and LFP ratios gave us a good measure of the degree of correspondence between these two types of neuronal activity.

Videotape scoring

All animals were videotaped during the paired stimulus sessions. Videotapes were scored using a microbehavioral worksheet that allowed the scorer to check whether or not the animal was moving during each stimulus presentation trial (100 trials). The worksheet had categories of movement that included grooming, locomotion, startle and head orienting and a single category for non-movement. Non-movement was defined as a lack of any motor output by the animal during either stimulus presentation. To compare neural activity during motor and non-motor periods we delineated at least seven continuous trials with only movement or non-movement occurring and compared the parameters of firing rate, T_{amp}, C_{amp}, T/C ratio between these trial sets for each animal.

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 transcardially with 0.9% saline solution followed by a 10% solution of phosphate buffered formalin (10%). Just prior to perfusion, 10 mA of current was passed for 15 s through every other microwire of each bundle of recording electrodes to mark their placement. Animals were transcardially perfused with physiological saline (0.9%) followed by 10% formalin in phosphate-buffered saline. Potassium ferrocyanide (0.3%) was added to colorize the electrode locations at the end of the recording wire. After perfusion the brains were removed and stored in the perfusion solution for 1

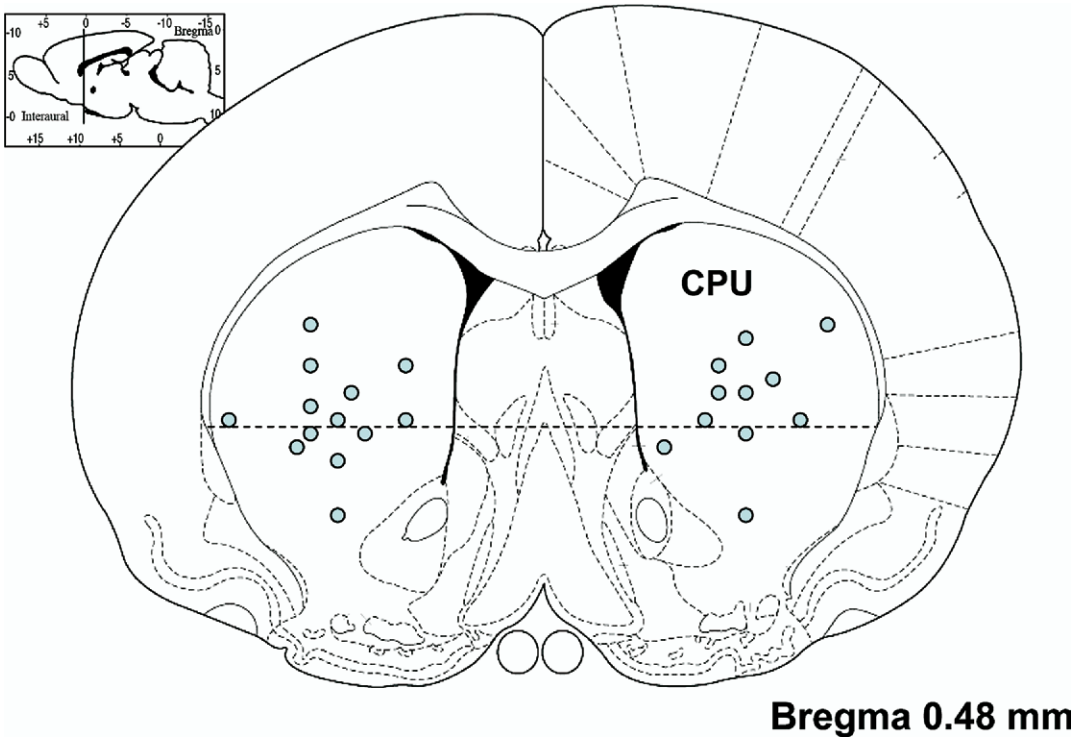

Fig. 1. Map of electrode placements in the anterior and central striatum of the rat. Microelectrode placements overlapped between different animals and only every other electrode was mapped using passage of current to minimize the damage produced by the electrolytic marking lesion.

week. The brains were then transferred to a 30% sucrose/10% formalin solution for 1 day. The brains were then sliced into 40 μm coronal sections on a freezing microtome. The relevant sections were mounted on glass slides and stained with Cresyl Violet. The sections were scanned under digitizing microscope and analyzed to determine the position of each electrode in the striatum. Electrode placements were identified using a rat atlas.

RESULTS

Neuronal database

In the initial session of the paired pulse paradigm, a total of 295 single units were recorded from 17 animals. Neurons were recorded mainly from the anterior and central striatum (see Fig. 1) with a few units located in the lateral caudate putamen or ventral striatum. One hundred eight of 295 units (36.6%) responded to the tone with a significant activity change within 300 ms before or after the tone stimulus. Neural responses prior to the stimulus can be related to the forthcoming stimulus or reward (Cromwell and Schultz, 2003). These anticipatory responses were rare in the present study (n=3) and not further analyzed. This result is similar to the findings from recordings from the amygdala during an identical paired-stimulus procedure (Cromwell and Woodward, 2005). The tone-responsive units had a significantly higher baseline firing rate compared with the non tone-responsive units (tone responsive mean=14.05±2.54 spikes/s versus 5.98±1.02 s/s, $t(293)=3.42$, $P<0.01$). We used a 25% reduction in activity change for the neural response between C_{tone} and T_{tone} obtained from the average T/C ratio for the 100 trial session to denote IG versus non-gating. By this criterion, 70/108 single units displayed IG. There were obvious cases in which gating was not observed (see Fig. 3A–D). The tone responsive and non-tone responsive groups

Table 1. Average statistics for the different response types found in the striatum during auditory stimulation

Response type	Gating	Firing rate	Camp	T_{amp}	T/C ratio
E-SD (n=44)	Yes	17.37±4.56	38.66±8.15*	23.19±5.57	0.53±0.02*
E-LD (n=15)	Yes	8.72±2.42	17.64±4.12*	11.12±2.87	0.65±0.02*
InH (n=10)	Yes	10.06±2.8	3.29±1.69*	5.24±1.97	0.42±0.11*
E-SD (n=23)	No	15.5±6.40	34.73±8.69*	N/A	N/A
E-LD (n=7)	No	14.9±7.82	30.77±12.38*	N/A	N/A
InH (n=8)	No	6.91±4.67	4.27±3.69*	N/A	N/A

Numbers for firing rate, C_{amp}, T T_{amp} (test stimulus amplitude) are in spikes/second (10 ms bin lengths). T/C ratio is the ratio of the test over the conditioned stimulus amplitude response.
* $P<0.05$.

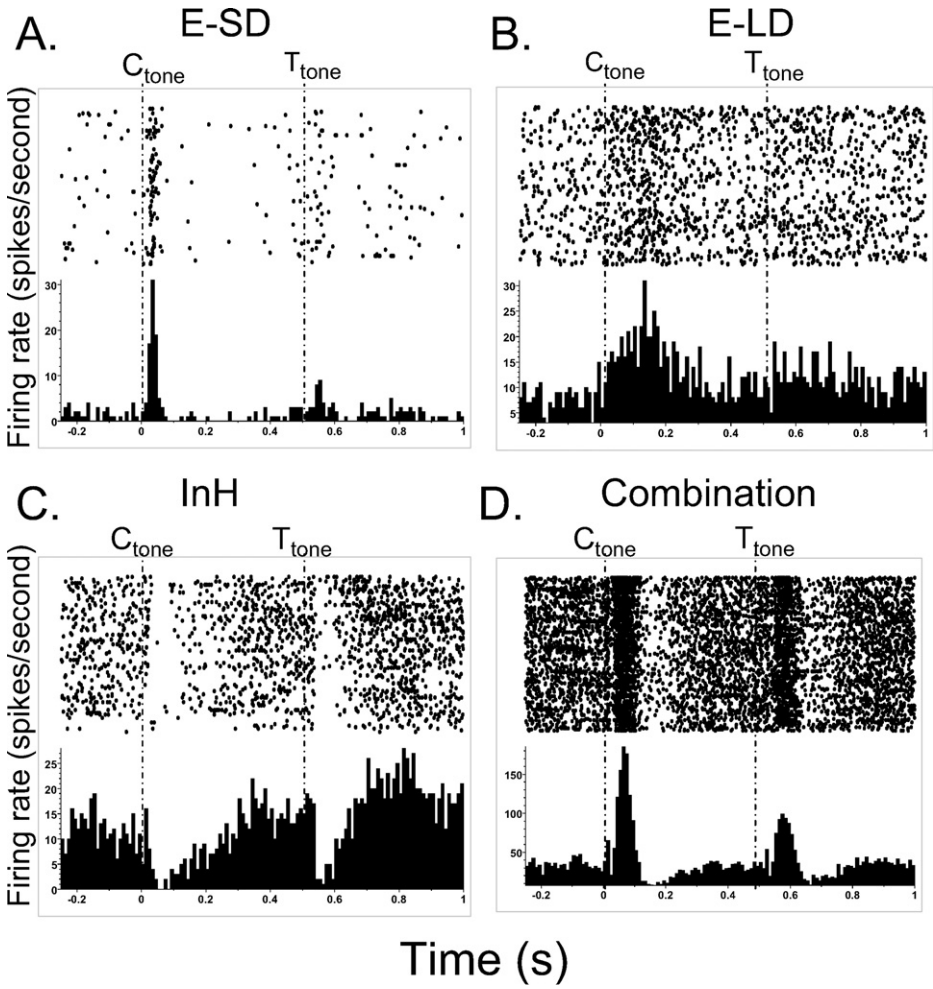

Fig. 2. Examples of single unit responses that display IG from the striatum. (A) E-SD, (B) E-LD and (C) an InH. (D) Displays a combination response that has both excitatory and inhibitory components. Each response displays IG as defined by a T/C ratio of at least 0.75.

could be subdivided into types of responses based on duration and polarity of the activity change (see Table 1 and Fig. 2). Each group was divided into: 1) a phasic excitatory-short duration response group (E-SD with <50 ms duration for excitatory activity change, Fig, 2A), 2) a sustained excitatory activity change (>50 ms duration activity change, Fig. 2B) and 3) an InH (Fig. 2C). The 50 ms cutoff was used because of the fact that the P50 positive wave is used to examine IG during the EEG procedure (P50 suppression), and the overall distribution of tone-responsive units was bimodally distributed with a trough between 50 and 75 ms.

In order to examine heterogeneity of neural responses based on location of the microelectrodes, the striatum was divided into dorsal and ventral halves at the rostro-caudal level of the medial septum at the midline (see Fig. 1). Units above the line were placed in the dorsal subgroup and below the line were placed in the ventral subgroup. We completed an analysis variance on the three dependent measures of C_{amp}, T_{amp} and T/C ratio between these two subgroups. The analysis was completed on the E-SD subtype of responses due to the limited numbers of responses in the subgroups of the other response subtypes (excitatory-long duration response (E-LD) or InH). Results of the analysis found nonsignificant differences for each dependent measure between these two major subregions (P values ranged from 0.39–0.52). The finding does not rule out functional heterogeneity of gating between striatal subregions but suggests that these measures are similar within the rostral and central location investigated in the present work.

LFP database

The positive gating peak at 60 ms was used to evaluate sensory responsivity from the field potential recordings. This P60 was the focus of the analysis due to its consistency across different recording wires and different animals. In addition, the potential is thought to reflect early to mid-latency positive peak recorded from human subjects in clinical neurophysiology. Eighty different wires were examined from five animals. Out of the 80 responses that had a significant positive response at 60 ms, 59 responses (74%) had at least a 25% reduction in the response amplitude from C_{tone} to T_{tone} (see Fig. 4).

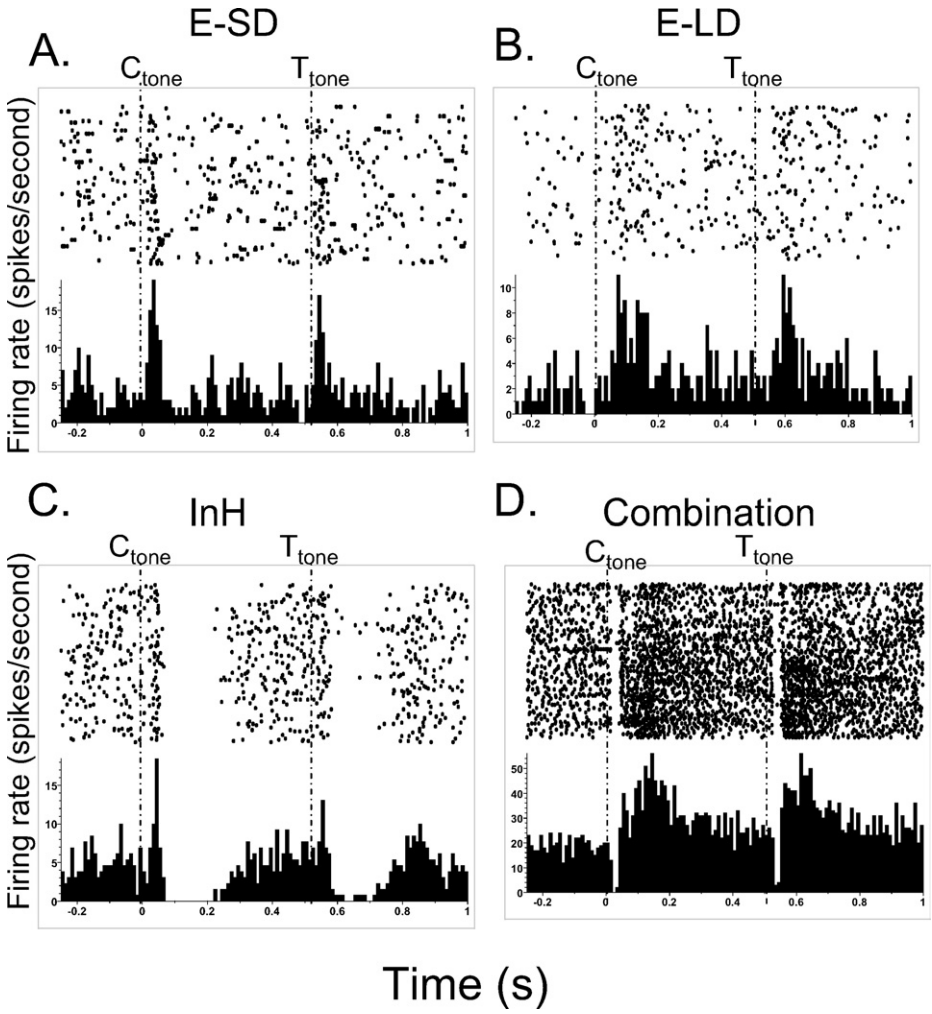

Fig. 3. Examples of non-gated responses in the striatum. The same response types were identified in similar subareas of the striatum that did not display substantial inhibition between the tones. (A) E-SD subtype that shows similar responses to the two tones. (B) An E-LD that is similar between the two tone stimuli and (C) displays an InH that does not show gating. (D) A combination response that persists in responding for the 100 trials in a consistent manner between tones 1 and 2.

We performed a similar analysis between the signals from dorsal and ventral regions on the LFP responses, and obtained a similar result with nonsignificant differences ($P=0.42–0.75$) between the two subareas for all dependent measures ($C_{amp,}$ T_{amp} and T/C ratio).

Comparisons between subtypes of auditory responsiveness

A two-factor analysis of variance (ANOVA) was completed with the gating/non-gating designation and the subtypes of responses (E-SD, E-LD and InH) as the two factors. No significant difference was obtained for either factor for the firing rate (see Table 1). There was a significant difference between the categories for the C_{amp} ($F(2,101)=4.39$, $P<0.01$). This difference reflects the basic difference in direction of activity change between groups (excitatory vs. inhibitory). No significant differences were found for the T_{amp} measure between response subtypes. Most interesting, there was a significant difference between T/C ratios of the different subtypes ($F(2.66)=3.90$, $P<0.05$). The inhibitory activity responses had the greatest inhibition followed by the E-SD subtype and then the E-LD subtype. Differences in C_{amp} reflect an influence in sensory responding more than in IG per se. These primary sensory changes were observed in several of the manipulations completed.

We completed a correlational analysis between the peak amplitudes of the responses and the T/C ratios for each subtype of activity change in the gating group. We did this in order to understand whether the change in gating in each group might rely more upon changes in the amplitude of the first or second auditory response. For the C_{amp} or initial tone response group the results showed a significant positive relationship with the T/C ratio for the InH subtype ($r=0.852$, $P<0.001$) but no significant relationship for the two excitatory subtypes. For the T_{amp}, results indicated a significant positive relationship for both the InH and E-SD subgroups (E-SD, $r=.34$, $P<0.05$ and InH $r=.76$, $P<0.05$). These findings suggest the amplitude of the activity

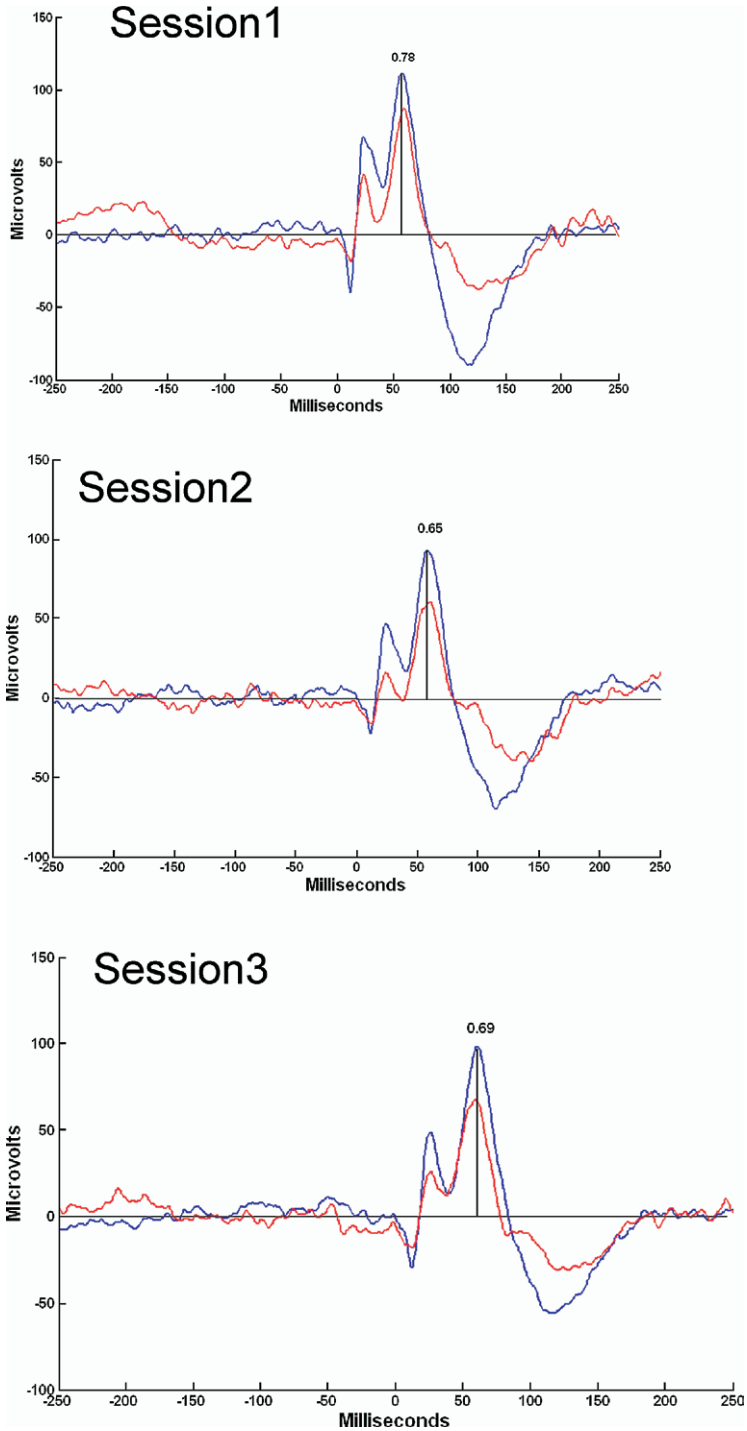

Fig. 4. Examples of LFP responses from the chronic microwires implanted into the central and anterior striatum. Each example is taken from the same microwire over a 3-day testing period (sessions 1–3). The dark line represents the response to the C_{tone} and the lighter line represents the response to the second or T_{tone}. The number at the peak amplitude around 50–70 ms post-stimulus designates the T/C ratio for the set of 100 trials for this specific response.

change would make a poor predictor for gating in the E-LD group but a very good predictor for gating in the InH subgroup. In addition, it appears that within the E-SD subtype, IG is more related to a decrease in T_{amp} more so than shifts at the C_{amp} time period.

Variability of IG: single units

We explored variability of IG at the single unit level by comparing the responses and the T/C ratios between sessions from different test days. The analysis was completed

Table 2. Mean responses and T/C ratios across the three day test period

Response type	Session	C_{amp}	T_{amp}	T/C ratio
Single unit E-SD	Session 1	37.56±12.29	21.77±7.75	0.56±0.05
	Session 2	30.27±9.71	14.31±4.65*	0.46±0.04
	Session 3	28.66±8.38	18.45±6.35	0.64±0.01
Single unit E-LD	Session 1	17.48±2.58	9.86±2.10	0.56±0.07
	Session 2	14.58±1.98	10.31±1.52	0.69±0.02
	Session 3	17.93±4.12	11.25±3.00	0.57±0.06
LFP	Session 1	93.5±5.14	52.33±3.84	0.55±0.01
	Session 2	80.93±5.84	43.17±3.46*	0.54±0.01
	Session 3	75.99±3.86*	44.3±3.13	0.59±0.01

Results show that within the excitatory subtypes gating is stable and amplitudes of single unit responses are not significantly different except for a reduced response to the second tone seen in the E-SD subtype on Day 2. * $P < 0.05$.

on only the excitatory responses due to the instability of the inhibitory single units over chronic periods of recording. We completed repeated measures ANOVAs across these sessions and found few significant changes over this extended period (see Table 2). There was a nonsignificant decrease in C_{amp} between sessions. The high variability of the C_{amp}, especially during the initial session, most likely contributed to the lack of statistical significance for this reduction (see Table 2). There were significant reductions between sessions in the T_{amp} seen in the E-SD subtype of response ($F(30,2)=2.85$, $P<0.05$; see Table 2) but not for the E-LD subtype. For both of these excitatory responses, the T/C ratios remained consistent over time. The persistence in IG arises due to decreases in response amplitudes at both stimulus presentation times despite the decrease at the initial presentation (C_{amp}) time being nonsignificant.

Another way we examined variability was to provide a moderate stressor to the animal. Two different types of stressors were used; 1) an acute stress of receiving an injection immediately prior to the gating session and 2) a long-term stress of being food deprived for 24 h prior to the gating session. We performed an ANOVA on each measure using normalized data for the C_{amp} and T_{amp}. Normalization of spike data was necessary because we did not examine the identical unit populations for this comparison and baseline firing rates were different with a trend toward slower firing rates following saline injection (firing rate averages: no-saline average=9.38 spikes/s versus 4.20 s/s after saline injection) ($t(26)=1.87$, $P=0.07$). There were no significant differences ($P=0.92$) for the C_{amp} between the saline and non-saline conditions but there were significant differences for the response to the T_{amp} and the T/C ratio (see Fig. 5A). The T_{amp} and the T/C ratio were significantly reduced after saline injection (T_{amp}, $F(1,27)=6.39$, $P<0.05$ and T/C ratio, $F(1,27)=6.99$, $P<0.05$). The reduction in the T/C ratio reflects a strengthening of the IG after saline compared with the baseline level (see Fig. 5A). Food deprivation produced a somewhat different profile of alterations in gating and tone responsiveness (see Fig. 6A). Firing rate decreased significantly after 24 h of food deprivation similar to an acute stress of injection (non-food-deprived=14.97±3.42 spikes/s versus food-deprived=5.03±2.38 s/s, $t(25)=2.16$, $P<0.05$). There were no significant differences in the response to the initial tone (C_{amp}; $P=0.27$) or in the T_{amp} levels ($P=0.46$) between the two groups. Most interestingly, the T/C ratio was higher after food deprivation suggesting that IG was weakened following this long-term stressor ($F(1,26)=6.81$, $P<0.05$); see Fig. 6A). This provides another example of nonsignificant differences in the response amplitudes over time yet significant changes in the T/C ratio. In this instance, it arises due to a relatively greater change in the T_{amp} compared with the C_{amp} following food deprivation.

Variability of IG: LFPs

Similar tests were completed on the LFP data. We chose the 59 responses that displayed a T/C ratio of at least 0.75. We found significant alterations in the amplitudes of responses over the 3-day time period (see Table 2 and Fig. 4). There was a significant decrease in the amplitude of the P60 across days (C_{amp} response, $F(2,116)=6.74$, $P<0.01$ and T_{amp} response, $F(2,116)=3.54$, $P<0.05$). Pairwise comparisons showed that there was a significant decline in the C_{amp} from test day 1 to test day 3 ($t(58)=3.6$, $P<0.01$) and a significant decline between days 1 and 2 for the T_{amp} ($t(58)=2.07$, $P<0.05$). T/C ratios did not differ between test days signifying a parallel decrease in both responses having an equal impact on the degree of inhibition over time.

Saline injection preceding the gating sessions led to a reduction in both responses and in a significant change in IG (see Fig. 5B). ANOVA results showed that the reductions were nonsignificant for the C_{amp} ($P=0.10$) and significant for the T_{amp} ($F(1,68)=2.68$, $P<0.01$) and for the T/C ratio ($F(1,68)=32.0$, $P<0.001$). Responses to both stimuli were reduced; however, the greater reduction in the response to the second tone led to the alteration (strengthening) of the IG. Food deprivation altered all three measures (see Fig. 6B). The C_{amp} and T_{amp} were significantly reduced (C_{amp}, $F(1,97)=29.8$, $P<0.001$ and T_{amp}, $F(1,97)=89.2$ $P<0.001$). T/C ratios were dramatically lowered ($F(1,97)=104.6$, $P<0.001$). For tonic food deprivation stress, there was a decrease in the both response amplitudes but the intensity of the decrease was greater for the T_{amp}. This ultimately led to the reduction of the T/C ratio.

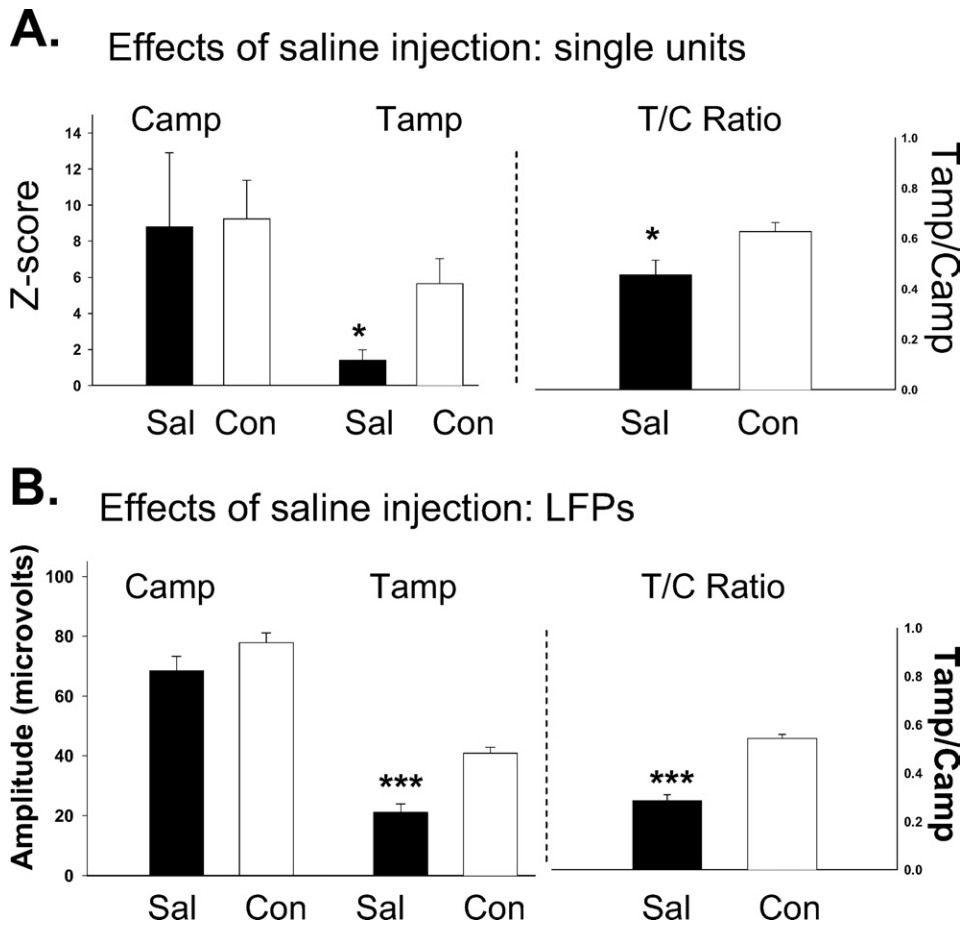

Fig. 5. Effects of saline injection on response amplitudes and IG in the striatum. The top panel (A) is the responses of the single units (E-SD subtype) following saline injection (i.m. isotonic saline 0.9%). Measures of the response amplitude for the first tone (Camp) and second tone (Tamp) are provided as well as the T/C ratio changes between saline and control sessions. The bottom panel (B) provides the same measures for the LFP responses. * $P<0.05$ and *** $P<0.001$.

Movement and IG

An analysis of the effects of movement on IG was completed. We compared the response amplitudes and T/C ratios between sets of movement and non-movement trials. We completed a repeated measure ANOVA for each measure. Thirty-five units were chosen for the analysis with each single unit displaying an E-SD response type. Firing rates did not vary between the movement and non-movement trials. There was a significant difference in the C_{amp} scores between the two periods with greater amplitudes seen for the response to the first tone during movement compared with non-movement trials ($F(1,34)=4.54$, $P<0.05$; see Fig. 7A). T_{amp} did not vary between motor and non-motor periods. T/C ratios did significantly vary ($F(1,34)=7.36$, $P<0.05$) and decreased during the movement period compared with the non-motor period suggesting a strengthening of the IG. The alteration in responsiveness most likely arises from the enhanced sensitivity to the auditory presentation observed to the initial stimulus during movement.

We compared the same measures for the LFP data (see Fig. 7B). There was a significant reduction in the response amplitudes during the non-movement periods compared with the movement periods (C_{amp}, $F(1,32)=14.77$, $P<0.01$ and T_{amp}, $F(1,32)=5.9$, $P<0.05$). There was no difference in the T/C ratios ($P=0.24$) between these two periods meaning that the decreases in the amplitudes between the two response tones were similar and led to similar inhibitory levels.

Correlations between LFP and single unit responses

A correlation matrix was completed for the three measures (C_{amp}, T_{amp} and T/C ratio) between the LFP and single unit responses. Surprisingly, there were no significant relationships between LFPs and single unit responses recorded from the same electrodes in the different animals. These results suggest dissociation between the different levels neural processing. There were few significant correlations within single unit and LFP responses (see Fig. 8). These included a positive relationship between the C_{amp} and T_{amp} for the LFPs ($r=0.50$, $P<0.01$) and for single units ($r=.96$, $P<0.001$). This indicates that the larger responses were observed to both the initial and second stimulus presentation. There was also a positive relationship be-

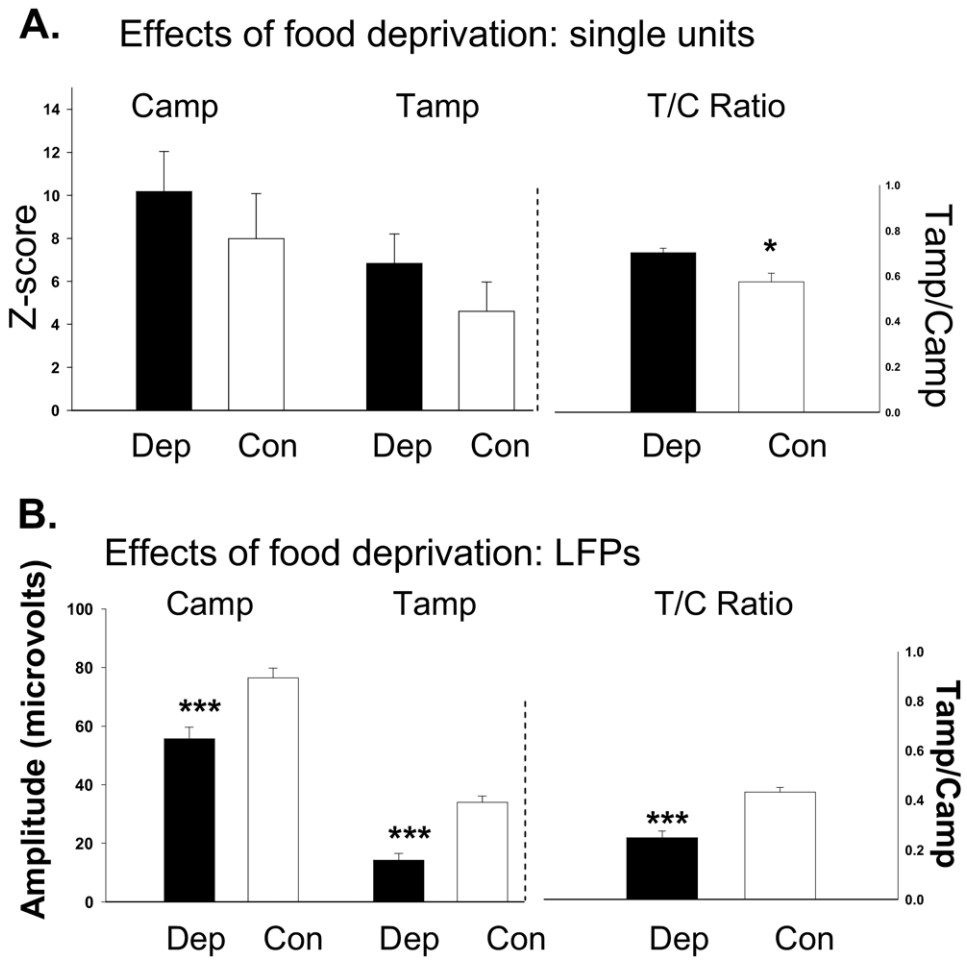

Fig. 6. Effects of chronic stressor of 24 h food deprivation on IG and auditory responses in the striatum. The top panel (A) provides the measures for the single units (E-SD subtype) and shows that gating actually became weakened after food deprivation for this response level. The bottom panel (B) provides the same data for the LFP responses and shows that the opposite response occurred at this neural activity level. *P* value designations the same as Fig. 5.

tween the LFP T_{amp} and the T/C ratio (r=.696, P<0.001). This indicates that as the T_{amp} rose so did the T/C ratio reflecting the lack of inhibition between C_{tone} and T_{tone}.

DISCUSSION

The present data show that striatal cells do respond to auditory information and display IG of this sensory input. IG in this neural subregion is more sparse in terms of the percentage of sensory responsive cells that gate compared with other structures that have been investigated such as the medial prefrontal cortex (Mears et al., 2006) and amygdala (Cromwell et al., 2005a). On balance, the IG observed is persistent and reliable over chronic recording periods at both the single unit and LFP levels. Different subtypes of auditory responsiveness at the single unit level were observed based on duration and polarity of the activity change. These categories of responsiveness have been observed in other brain regions (mPFC; Mears et al., 2006 and amygdala; Cromwell et al., 2005a). The analysis of variability highlighted some interesting similarities and differences between single unit and field potential recordings. Single unit and LFP responses consistently gated over the 3-day test period and responses to the tones decreased at both activity levels across the three sessions. Acute stress led to common strengthening of IG at both activity levels via a significant reduction in the response to the second tone. Chronic stress of food deprivation led to different results with single unit responses displaying an impairment of gating while LFPs actually showed stronger inhibition. Additionally, the different tests led to significant changes in the gating ratio that did not primarily depend upon inhibitory networks per se. These changes were due to alterations in the response to the initial tone stimulus (C_{amp}) and could be categorized as a shift in sensory responding. One example was found when comparing motor and nonmotor episodes during the gating session, an increase of C_{amp} response during movement may signify greater sensitivity to stimuli during exploration. In contrast, we found shifts in both responses at the LFP level during movement suggesting an alteration in sensory processing

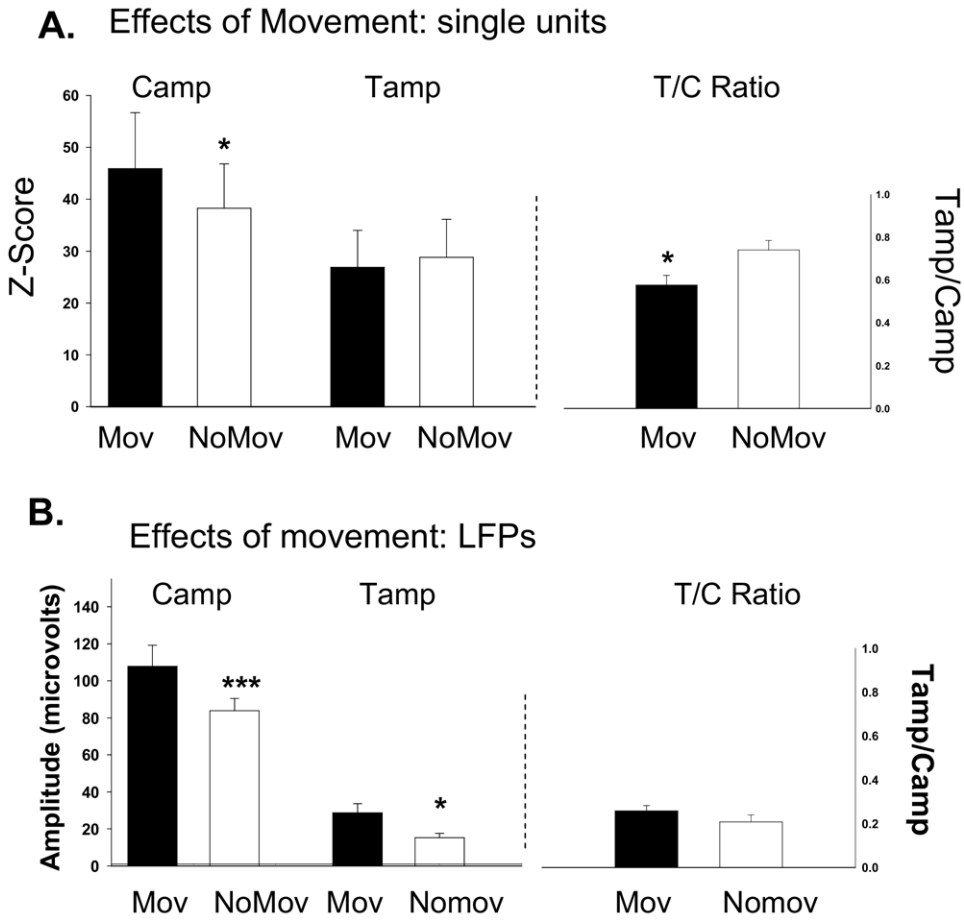

Fig. 7. Effects of movement on IG in the striatum for both single units (A) and field potentials (B). Mov and NoMov episodes were categorized (Mov=movement and NoMov=non-movement). Single units showed improved gating during movement while LFPs showed the opposite effect. *P* value designations similar to Fig. 5.

and inhibitory networks at this more general pool of neural information gathering. Finally we found significant relationships *within* the single unit and LFP groups similar to other work (Mears et al., 2006; Cromwell et al., 2005a; Moxon et al., 1999) but failed to find any significant relationships *between* the single unit and LFP data. This is somewhat surprising given the findings of others for synchrony of activity between the single unit and LFP levels (Kisley and Gerstein, 1999; Berke et al., 2004). One pertinent difference is that the present study reveals phasic single unit and LFP responses to discrete stimuli that other studies have not fully explored. When discrete responses or stimuli are examined dissociations can be found (Fletcher et al., 2005). It is clear the LFP activity is highly dynamic and varies depending upon the brain state experienced and striatal subregion recorded (Magill et al., 2006). Our results suggest that for specific contexts LFP and single unit activity can be significantly different from one another. LFP and single unit responses could reflect information primarily prior to and following intrinsic striatal integration, respectively. The extent of the influence of the integrative process would vary depending upon the quality and intensity of the environmental perturbation (acute or chronic stress) and therefore have varying degrees of impact on the disparity between these measures.

Inhibition and the striatal interneuron

Intrinsic striatal processing depends heavily on both local GABAergic and cholinergic neurotransmission (Windels and Kiyatkin, 2003; Tepper and Bolam, 2004). Both GABAergic and cholinergic transmission have been found to be involved in modulation and inhibition of neurotransmission (Kyriazi et al., 1996; Fendt et al., 2000; Koos et al., 2004; Martin et al., 2004). In the striatum, GABA neurons predominate and either send projections outside the striatum or exist as interneurons that can be dissociated by co-expression with neuropeptide groups (Kita, 1993; Tepper et al., 2004). Feedforward and feedback inhibition has been characterized with feedback networks via collaterals of GABAergic projection cells displaying very faint to completely absent inhibition (Mallet et al., 2005; Tunstall et al., 2002; Jaeger et al., 1994; Nisenbaum et al., 1992). The fast spiking parvalbumin-containing interneurons mediate the feedforward inhibition and seem likely to mediate rapid and potent inhibition throughout striatal subregions (Tep-

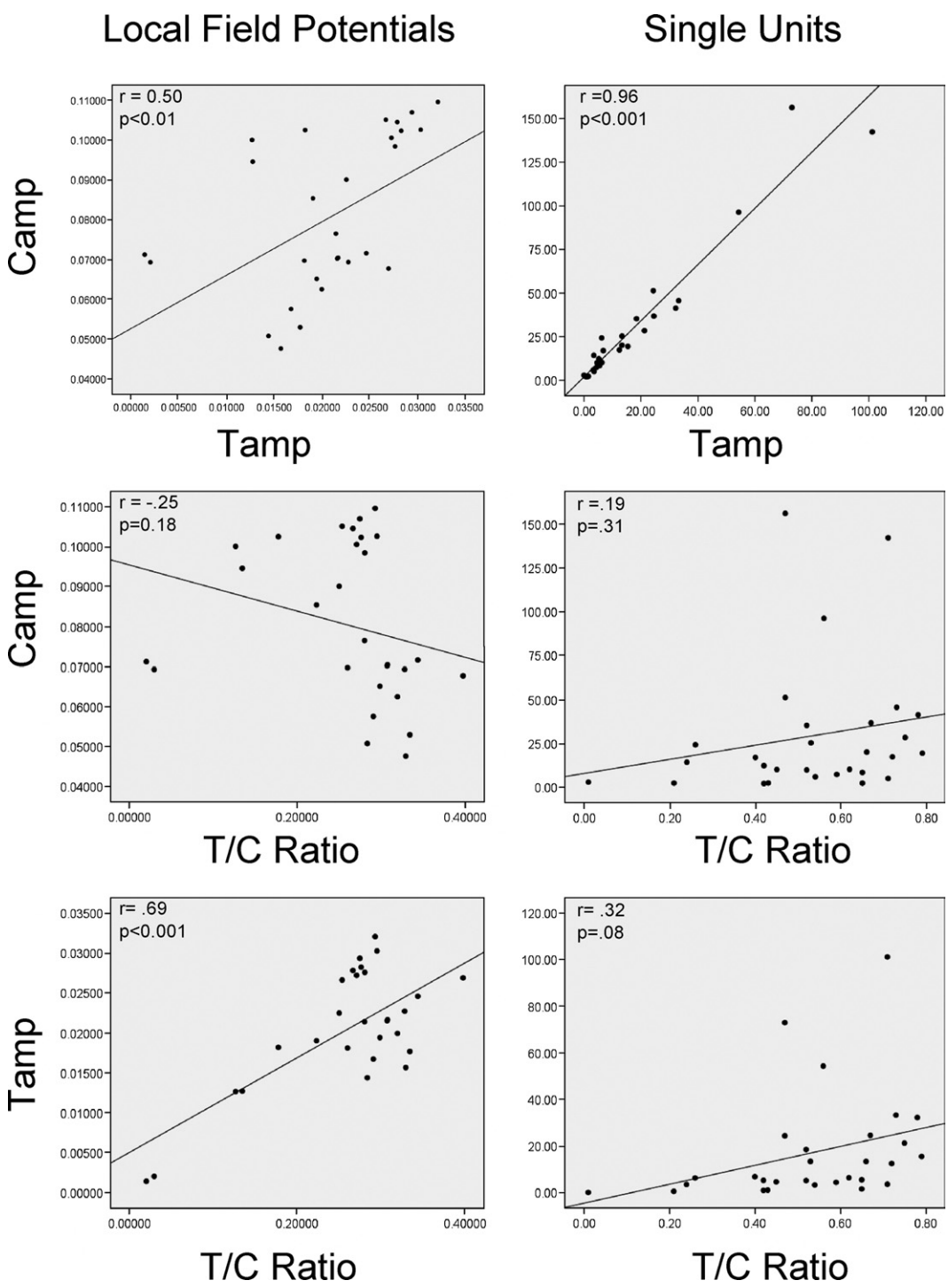

Fig. 8. Correlational analysis between the measures of response amplitudes and T/C ratio for the single units (right-side) and the LFPs (left-side). Correlations between the two measures of neural activity are not shown due to insignificance for these *r* values.

per et al., 2004). These cells have a potentially high level of regulation over the GABAergic projection neural activity (Wickens and Oorschot, 2000) to the degree that even a single spike from the interneuron can alter the dynamics of spiking. These interneurons can be modulated by cortical flow of information and short-term fluctuations of membrane states (Reynolds and Wickens, 2004; Koos and Tepper, 1999; Plenz and Kitai, 1998).

Cholinergic interneurons in the striatum are larger cells with broad-ranging processes (Chang and Kita, 1992; Gerfen, 1992). Recent physiological data reveal that even though these cholinergic cells appear to have potential

wide-ranging influences, they can also have significant local effects on neural activity (Koos and Tepper, 2002; Wilson, 2005). These effects can be mediated via muscarinic or nicotinic mechanisms (Zhou et al., 2002). The cholinergic influences have been shown to be potent modulators of dopaminergic activity (Wang et al., 2006; Zhou et al., 2002; Partridge et al., 2002). Rapid gating of sensory stimulation has been shown to depend on cholinergic mechanisms (Simosky et al., 2002). Nicotine alters gating in human subjects (Adler et al., 1998) and local single unit responses in amygdala (Cromwell and Woodward, 2006).

Altering local inhibitory networks within the striatum can lead to significant changes in neurophysiology and animal behavior. Local administration of substance P (SP) containing saporin destroys striatal interneurons containing SP receptors and leads to impairment in forelimb movements involved in reaching, grasping and retrieving (Chiken and Tokuno, 2005). Intrastriatal injection of SP-PE35 selectively damages cholinergic and somatostatinergic interneurons leading to enhanced excitability in matrix subcompartments and elevated DA-agonist induced rotational behavior (Saka et al., 2002). Acute and chronic drug administration alters transitions between up and down states in medium spiny cells (Brady et al., 2005) and this drug-induced change is thought to arise from loss of internal inhibitory controls. Neural activity related to meaningful events has been shown to be influenced by long-lasting inhibitory mechanisms (Taha and Fields, 2006) and models of basal ganglia function necessarily contain inhibitory networks that order or gate inputs (Gruber et al., 2006; Graybiel et al., 1994; Woodward et al., 1999). Overall, it is clear that normal striatal processing of information depends heavily on local inhibitory networks. Simplified paradigms like IG might be useful in determining the role of these processes. Future work will need to better define the subtypes of cells involved neurochemically and anatomically.

Potential functions for gating in striatum

IG is most likely mediated by the different subpopulations of neurons in the striatum and is possibly expressed for different purposes dependent upon the striatal subregion involved. It is known from previous work that the striatum is functionally heterogeneous (Graybiel, 2004; Pisa and Cyr, 1990; Lidsky and Brown, 1999; Cromwell and Berridge, 1996). In the present work, we did not observe a heterogeneity of IG within the subregion examined, which suggests that the mechanisms of rapid gating may be similar across different subregions of this structure. This finding does not exclude functional heterogeneity of gating within the striatum when tested under different functional contexts nor does it exclude a heterogeneous gating obtained from more spatially disparate regions of the striatum. When the more dorsal and lateral subregions are compared with the most ventral subareas (e.g. nucleus accumbens core or shell) distinct functional properties are more likely to emerge (Buchwald et al., 1979; Mogenson et al., 1983; Schneider, 1984; see Berridge and Cromwell, 1990). Buchwald and colleagues (1979) termed a form of this intermixing "the development of the behavioral sets" that enabled plasticity of action and ability to incorporate flexibility in stimulus-response associations. A piece of supporting evidence includes the response perseveration that ensues after lesioning regions of the striatum (Villablanca et al., 1976; Dunnett et al., 1999). Another function of the striatum potentially reliant on gating of sensory input is the appropriate sequencing of motor acts (Cromwell and Berridge, 1996; Aldridge and Berridge, 1998). This function most likely aids sequencing of complex action patterns by reducing the infiltration of distracting sensations (Berridge and Fentress, 1986, 1987). These types of functions probably rely on rapid inhibition of stimuli and depend upon the appropriate activation of local interneuron populations housed within specific striatal compartments.

It is clear that the striatum contains neurons that respond to sensory input. Visual responses of striatal neurons have been documented in several studies using primates in different behavioral tasks (Aldridge et al., 1980; Hikosaka et al., 1989). Other research groups have revealed topographically organized tactile responses of striatal cells (West et al., 1990; Brown, 1992). Auditory responses have also been found but have not been a major focus of striatal function (Adams et al., 2001; Bordi et al., 1993; Hikosaka et al., 1989). It is known that temporal lobe projects to striatum (Webster et al., 1993; Yeterian and Pandya, 1998) but it is not clear whether rapid responses examined in the present study could arise via primary auditory circuits. Data from others have shown that IG is weak in primary auditory system compared with non-lemniscal pathways involved in audition (Moxon et al., 1999). For each of the sensory modalities examined (visual, tactile, taste, auditory), striatal responsiveness varies depending upon the context (Schneider and Lidsky, 1987), experience (Schultz et al., 2003) and the incentive value of the outcome to be obtained (Cromwell et al., 2005b; Cromwell and Schultz, 2003). This conditional/contextual influence of the sensory response has not been investigated in relation to the rapid mechanism of IG; however, this early detection of stimuli most likely plays a role in the affective responses involved in diverse psychological processes (Smith et al., 2006; Murphy and Zajonc, 1993). Our findings that IG varies depending upon acute or chronic stress or between motor and non-motor episodes support this idea and lead to more questions regarding the functional significance of these types of early forms of inhibition for the production of behavioral flexibility in motivated action (Mogenson et al., 1983) or the formation of habits that effectively proceed without intrusion of sensory input (Barnes et al., 2005).

Gating in the striatum and disease

Clinical science has initiated the use of IG as a tool to reveal endophenotypic markers of disease (Houy et al., 2004; Myles-Worsley et al., 2004; Leonard et al., 1996). Basal ganglia diseases have been proposed to be caused by defective gating (Kaji et al., 2005; Boecker et al., 1999). Symptoms of PD or HD reflect the loss of sensorimotor integration and involve complex motor, emotional and cog-

nitive attributes (Marsden, 1982). Sensory stimulation can dramatically alter performance in PD, HD and Tourette's syndrome (Brown et al., 2006; Nowak and Hermsdorfer, 2006). For example, auditory feedback in a finger tapping task improves performance in PD patients (Lim et al., 2005; del Olmo et al., 2006). In animal models of BG disease, imbalances are observed in the synchronization of activity (Mallet et al., 2006; Courtemanche et al., 2003). Synchrony of the beta band oscillations within striatum have been shown to increase in the PD state (Raz et al., 2001; Williams et al., 2002). This abnormal synchrony appears most similar to the normal resting state of the organisms but can extend into periods of activity when they normally become more infrequent (Hutchison et al., 2004). In the normal brain, oscillatory entrainment most likely involves shifting between states in and out of synchrony and depends upon the unique membrane characteristics and connectivity of striatal neurons (Stern et al., 1997; Kincaid et al., 1998; Hornykiewicz, 2001). IG could be one mechanism of entrainment dependent upon stimulus control. We have tried to mimic the clinical paradigm so that the results can be easily translated to the clinical domain. To make progress on this front, it will be critical to continue to investigate the basic neural processes in more detail and aim toward revealing more precisely the functional properties of this rapid and pervasive neural inhibition.

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