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Research report

Auditory inhibitory gating in the amygdala: Single-unit analysis in the behaving rat

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Abstract

Inhibitory sensory gating has been proposed to be a fundamental physiological process that filters neural input. Its temporal properties could allow for a rapid influence on vigilance and attention processes. Inhibitory mechanisms are reflected by reductions in neural responsiveness to repeated and well-predicted stimuli; for auditory gating, this translates into an inhibition of the neural activation to subsequent tone stimuli embedded within sequential and identical tone presentations. Here we expand previous neurophysiological data on inhibitory gating by examining gating in the amygdala using single-unit recording in freely moving animals. Previous data have shown the amygdala to be important in mediating rapid auditory sensory processing involved in emotional conditioning. We measured inhibitory gating with two matching auditory tones presented in a repetitive fashion (10 ms tones, ISI = 500 ms and 10 s between pairs) for 1 h (360 pairs). The majority of the tone responsive units showed inhibitory gating (78/95 units) located in both the medial and lateral subnuclei of the amygdala. Different types of tone responses were gated, including both shorter- and longer-duration excitatory tone responses as well as inhibitory tone responses. Different degrees of gating were found ranging from 100% inhibition (complete gating category) to 25% inhibition (graded gating category). The degree of gating varied over short-term and long-term time intervals. These findings demonstrate the existence of inhibitory gating in the amygdala and provide a detailed description of the basic properties of this rapid neural inhibition that could play an important role in filtering stimulus input.

Theme: Other systems of the CNS
Topic: Limbic system and hypothalamus

Keywords: Auditory processing; Gamma amino butyric acid; Neural inhibition; Aversion; In vivo electrophysiology; Schizophrenia; Autism

1. Introduction

Inhibitory sensory gating has been a useful term for the primary neural filter thought to play a critical role in the selection of incoming sensory information. Traditional definitions for inhibitory gating have emphasized 'gating out' or the blockage of sensory information [21]. More recent definitions have extended the functional role of gating to involve both 'gating out' and 'gating in' as distinct processes. These opponent processes could function interactively to both disable and enable central access for incoming information [10,33,44,73]. A neurophysiological assay to explore gating involves repeated presentations of identical stimuli to gauge the strength of intrinsic inhibitory processes. Physiologists have used this well-established paradigm to examine the role of inhibition in basic neural communication [14,15,21,63,75]. Over the last several decades, clinical neurophysiologists and psychologists have adopted the paradigm and have offered it as a potential neurophysiological indicator of attentional and arousal deficits in patients with cognitive disorders [3,11,23,24]. In the clinical paradigm, the experimenter places the subject in a relaxed setting and presents

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identical auditory stimuli at very short intervals (0.5 s) for an extended session (1-h session). The tones are well predicted and presented at a constant interval (10 s interpair interval) [18,24,50,60]. In the control subject with no attentional deficits, the second auditory evoked potential is dramatically reduced, while in certain patients with cognitive impairment, this inhibition is compromised [2,18,23,39].

Little is known about the basic underlying neurophysiological mechanisms of this clinical observation. Several recent studies have focused on the role of the hippocampus in inhibitory gating [9,20,35,56]. Freedman and colleagues have suggested that inhibitory networks within the hippocampus play a central role in filtering information and that inhibitory gating in this structure influences sensory processing as a dynamic event in several other brain regions [2,23,25,26]. In a recent study recording brain activity from freely moving rats, inhibitory gating was found to be robust in hippocampus, medial septal area, and brain stem regions [57]. Inhibitory gating of the hippocampal response was well correlated with gating in the medial septal nucleus and brainstem reticular nucleus [57]. In contrast, sensory gating in hippocampus was not well correlated with reductions in tone responses seen in auditory cortex, suggesting that the inhibitory gating of an auditory-evoked response depends upon multiple brain circuits including subcortical non-lemniscal pathways which include structures outside of the typical, primary auditory receiving pathway [31].

The amygdala has strong connections with the hippocampus [4,5,64] and has been suggested to be a critical brain structure in the rapid processing of meaningful auditory information [28,48]. Interestingly, the amygdala has been thought to receive auditory information through both a cortical route and a non-cortical, thalamic pathway [37,48]. A growing amount of data has supported the idea that the amygdala plays a key role in basic mechanisms of vigilance related to adaptive responses [27,59,80]. Lesions to the amygdala reduce the rapid, reflexive responses of startle or freezing that are observed to conditioned stimuli following fear conditioning [48]. Recordings of amygdala single units before and after conditioning have shown that neuronal activity can selectively be recruited to auditory stimuli paired with an aversive stimulus [66].

Our aim was to initially characterize the inhibitory gating at the single-unit level in the amygdala and begin to describe the basic temporal and functional properties of the neural inhibition. The functional role of rapid inhibitory gating could substantially vary in different brain regions and depend upon a host of specific properties inherent to the individual brain region. In order to pinpoint these potential unique structure-dependent contributions of inhibitory gating, it is imperative that a detailed characterization of the mechanism be completed at a reduced level of physiological analysis within these different yet interconnected brain regions. If inhibitory gating is important for attentional and motivational processing, then it should play a significant role in amygdala physiology and the processing of sensory input. The results of this work have been presented previously in abstract form [81].

2. Materials and methods

2.1. Animals and surgery

Eighteen male Sprague–Dawley rats weighing 250–350 g were used in these experiments. Animals were singly housed under a reverse light–dark cycle (lights off from 7:00 to 19:00 h). Animals were housed at least 7 days in the reverse light–dark cycle prior to neurosurgery. Recording microwires were implanted following administration of ketamine (100 mg/kg, im) and xylazine (10 mg/kg, im). Two splayed bundles of eight stainless steel Teflon-insulated microwires (50 μm diameter, NB Labs, Denison Texas), soldered onto connecting pins on a headstage, were stereotaxically lowered bilaterally into the amygdala (8 wires per hemisphere). Coordinates for the amygdala from the atlas of Paxinos and Watson [61] were −2.8 mm posterior to bregma, ±4.7 mm lateral to longitudinal suture, and −8.2 mm ventral to the brain surface. Four screws were embedded in the skull for anchoring the implant and for acting as reference grounds. Electrode connectors were secured onto the cranium using dental cement. Rats were allowed 7 days post-surgery to recover before recording was initiated. All procedures were approved by the Wake Forest University School of Medicine Animal Care Committee and all animals were treated in accordance with the U.S. Public Health Service *Guide for the Care and Use of Laboratory Animals*.

2.2. Two-tone paradigm

During the final 4 days of post-surgical recovery, the animals were handled daily to acclimate them to the experimental procedure. Following the 1-week recovery period, animals were taken to the recording chamber and connected to a FET headstage plug with lightweight cabling between a commutator and the implanted microwire assembly. The commutator was free to rotate as needed and this permits unrestrained ambulation of the subject during the recording session. Neuroelectric signals were sent from the headset assembly to programmable amplifiers, filters (0.5 and 5 kHz cutoffs) and a multichannel spike-sorting device (Biographics Inc., Winston-Salem, N.C.). Spike activity and tone presentations were monitored and controlled with custom data acquisition software operating at a time resolution of 1 ms (Magnet Software, Biographics Inc., Winston-Salem, N.C.).

The recording chamber (40 cm × 20 cm × 20 cm) was made of Plexiglas and equipped with a small fan to provide air circulation and background noise and a speaker mounted at the top of the chamber to deliver the tones. The chamber was housed in a sound-attenuating cubicle. All sessions were monitored with an infrared camera placed at the side of the cage and a video signal sent to a monitor for viewing. After a 200-s control period, the two-tone paradigm was initiated. Two identical tones (75 dB SPL, 2.5 kHz) were presented every 10 s with an intrapair interval of 500 ms. Rats were exposed to 360 tone pairs over a 1-h session each day. We labeled the initial tone, conditioning tone, and the subsequent tone, test tone to follow standard terms used in other electrophysiological work both at the single-unit [57] and EEG levels [3,43].

We examined temporal and emotional influences on inhibitory gating using two tests: (1) *A repeated sessions test* and (2) *An aversive stimulus test*. The repeated stimulus test included repeated exposure of the animals to the auditory tone paradigm. Animals were exposed for three consecutive days to the two-tone paradigm. Rats were tested in the same order and time on the different days. For the aversive stimulus test (Day 4), rats were administered an aversive saline injection (0.9%, im, 2 cc) immediately prior to the inhibitory gating recording session. It has been shown that an initial single saline injection has aversive and novel properties to the rat [29] and produces alterations in prepulse startle inhibition [65,74]. This initial isotonic saline injection combines aversive aspects of pain and novelty that lead to higher arousal of the animal for at least 1 h post-injection. We chose this method of mild stress because we did not want to use methods of stress-induction that produced changes in global movement (restraint or cold) or pharmacological changes (formalin or hypertonic saline injection) that could significantly influence neural activity.

2.3. Data analysis

Single neuron recording from the microwires was distinguished over time by using auto-correlograms, interspike intervals, and analysis of the peri-event rasters and histograms computed around the time of the tone stimuli. Neurons that exhibited a lack of firing within 1–5 ms of a reference spike in the auto-correlalogram and the interspike interval histogram and had similar waveform shapes across different sessions were labeled as identical cells from the same recording wire. Each waveform template is retained between daily sessions for each single unit. Only those waveforms that matched the template were counted as spike events and subsequently analyzed. Waveforms for the single units remained consistent throughout the short-term period of recording. Peri-event histograms (0.01 s bins, ±1 s total time period) surrounding the 2 tone presentations were produced for each neuron (Stranger Analysis Program, Biographics Inc., Winston-Salem, N.C.). To compare neural activity to tone presentations, firing rates ±500 ms surrounding the tone were compared with a 500-ms control period 2.5 s prior to tone onset. The neural activity within the 1-s period around the tone was compared using a sliding window technique executed via a Matlab script. The 1-s window was moved in 0.01-s steps and differences between these periods and the baseline were detected using the Student's t test at a significance level of $P < 0.01$ at each step with three consecutive steps required to achieve significance. This analysis allowed us to determine response latencies with a time resolution of 10 ms (1 bin length). Latencies of response activations were determined as the initial bin showing a significant increase in activity compared to the control period. A second Matlab script was used to compare activity differences in the amplitudes of the responses between the conditioning and test tones. Amplitudes of the conditioning tone (cAMP) and test tone (tAMP) were calculated as the percent increase from baseline at the peak of the response. Test/conditioning ratios (T/C ratios) were calculated from these amplitudes.

A similar sliding window technique was used over the 1-s period surrounding both tones to compare tone-related neural activity between different sessions. Conditioning tones from the different sessions were compared to each other to determine if any significant alterations in the basic tone response might have occurred over time. Similar analysis was completed comparing neural responses to test tones between sessions. T/C ratios were determined for each session for each single unit from the amygdala. Repeated measures analysis of variance was used to compare the firing rates, latencies, and durations of the neural activities between sessions ($P < 0.01$).

2.4. Histology and electrode localization

At completion of the gating sessions, the animals were deeply anesthetized with pentobarbitol (100 mg/kg, ip) and the electrode placements marked by passing 10–20 μA for 10–20 s through 4 microwires in each bundle of eight wires in an alternating fashion (e.g., wires 1, 3, 5, and 7 could be used for current passage). This allows us to distinguish sites in between the marked placements by estimating electrode placement based on bundle configuration. The wire configuration is fixed for each electrode bundle (e.g., wires 1 through 8 are located rostrocaudally in the left amygdala), and by regulating the current intensities between recording sites (10 μA for 10 s vs. 20 μA for 20 s), we can more accurately determine the individual wire number (Fig. 1B). After electrode marking, the animals were perfused with saline (0.9%) followed by 10% formalin with 5% potassium ferrocyanide (in PBS). Potassium ferrocyanide is used because it reacts with the iron deposits left after electrode marking in the form of visible blue dots. Brains were stored in 10% formalin until 24 h prior to sectioning. At this time, they were transferred to a formalin–sucrose solution (20%), and after another 24

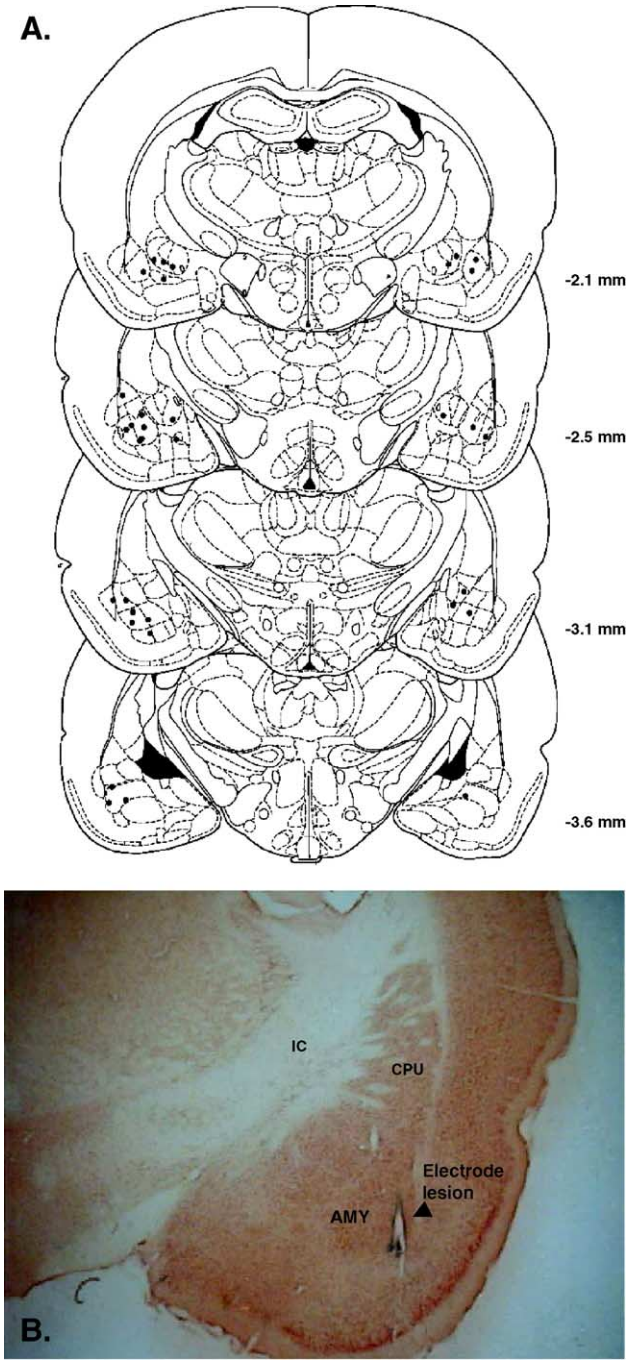

Fig. 1. (A) Histological reconstruction of recording sites within the amygdalar complex. Selected microwires (1st, 3rd, 5th, and 7th) were labeled with potassium ferricyanide staining. The locations of wires were concentrated within the lateral subnuclei but many sites were also found in the central and medial nuclei. Number of sites does not equal the number of units due to the fact that not all wires were marked with current and more than one unit could be obtained from each recording wire. (B) Photomicrograph of an electrode marking lesion in the amygdala (AMY, amygdala; CPU, caudate nucleus and putamen; IC, internal capsule).

h, they were sectioned (40 μm) and mounted on slides. Sections were stained with cresyl violet and electrode placements mapped using the rat brain atlas of Paxinos and Watson [61] as a reference.

3. Results

3.1. Neuronal database

A total of 121 amygdala neurons was recorded from both the lateral (n = 71) and more medial and central nuclei (n = 50; see Fig. 1). There were no significant differences between the lateral and medial regions for basic neurophysiological parameters or for gating characteristics so these data were pooled. A total of 95 (79%) amygdala neurons had a significant activity alteration within 100 ms of the conditioning tone onset. This included both anticipatory activity before the tone onset (8/95, 6%) and post-stimulus activity following the tone (87/95, 94%). Average latency for onset of activity change was 20 ms post-stimulus and average duration equaled 50 ms for all responses.

A substantial majority of the neurons that demonstrated a tone response exhibited inhibitory gating of at least a 25% reduction in the activity change [78/95 cells (82%), T/C ratio of at least 0.75]. Firing rate for the overall group of neurons displaying inhibitory gating was 3.4 spikes/s within the baseline period. These 78 neurons were located both in the medial and lateral subregions of the amygdala (Fig. 1).

3.2. Types of inhibitory gating

Four different types of tone responses were observed in these amygdala subregions. Each of the four response types was found in the medial and lateral subareas of the amygdala. We labeled these 4 types as (1) Excitatory-short duration (E-SD; Fig. 2A), (2) Excitatory-long duration (E-LD; Fig. 2B), (3) Excitatory-Anticipatory (E-Ant; Fig. 2C), and (4) Inhibitory (Inh; Fig. 2D). A one-way ANOVA was completed on the measures of baseline firing rate, cAMP, tAMP, and T/C ratio. Significant differences were found for each of these measures [Table 1; baseline firing rate, $F(3,74) = 35.5$, $P < 0.001$; cAMP, $F(3,74) = 67.25$, $P < 0.001$; tAMP, $F(3,74) = 48.9$, $P < 0.001$; T/C ratio, $F(3,74) = 10.9$, $P < 0.001$]. Post hoc analysis of pairwise comparisons using Tukey's HSD revealed significant differences between the E-LD response type and all the other response types for baseline firing rate, cAMP, and tAMP ($P < 0.001$). E-LD responses had significantly higher baseline firing rates and greater amplitude responses for both tone presentations (Table 1). Significant differences were obtained for the T/C ratio between the E-SD group and the E-LD/Inh groups ($P < 0.001$). The E-SD group clearly had the most robust neural inhibition compared to these other groups reflected by the lowest T/C ratio (Table 1). Even though the groups showed substantial diversity in the degree of inhibitory gating, a subset of single units within each category showed complete gating with no response at the time of the 2nd tone presentation (T/C ratio = 0).

We completed correlational analyses between the peak amplitude tone response levels and the T/C ratios. Results

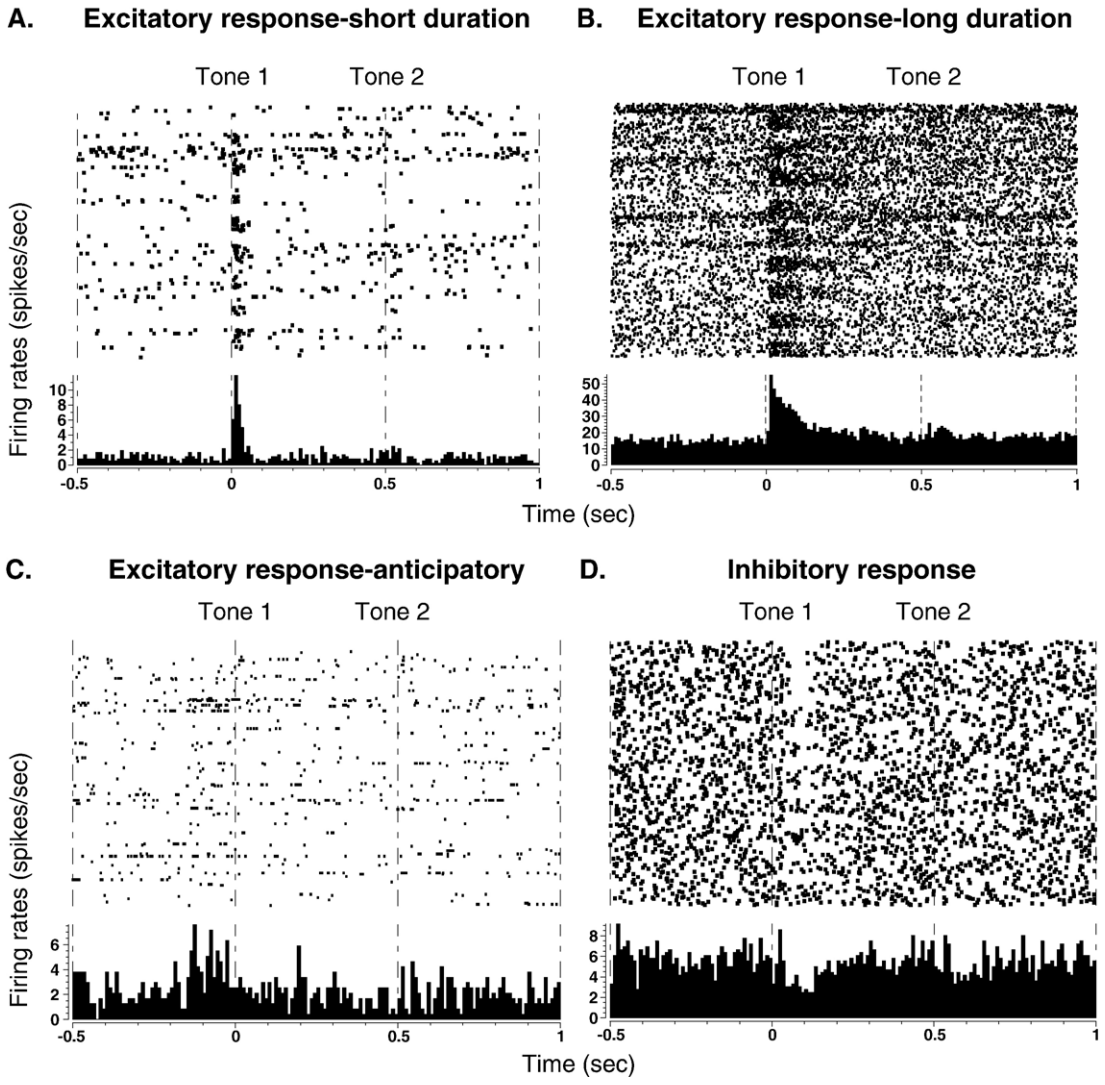

Fig. 2. (A) Excitatory response-short duration gating (E-SD). This response is a very brief increase in activity following the initial, conditioning tone. The increase in activity related to the tone response is completely absent from the test tone 2. (B) Excitatory response-long duration (E-LD). This response was a sustained increase in activity following the test stimulus. In some cases, the increase in activity was prolonged through the onset of the conditioning stimulus 500 ms later. (C) An example of anticipatory gating. A select set of cells showed this gradual increase in activity prior to the test tone that was absent prior to the conditioning tone. (D) An example of inverse gating (Inh). Some neurons showed an inhibition following the test stimulus that was significantly reduced at the time of the conditioning stimulus.

showed a significant relationship between the tone activation amplitudes (cAMP and tAMP) and the *T*/*C* ratio for the three excitatory responses and a lack of a significant relationship between these measures for the inhibitory post-stimulus response (Fig. 3). For both post-stimulus excitatory responses, the tAMP had a significant positive correlation with the *T*/*C* ratio. For the E-LD response type, an additional positive correlation was found between the cAMP and *T*/*C* ratio (see Fig. 4B). The pre-stimulus response (E-Ant) had a weak negative relationship between

Table 1
Amplitudes of the single-unit responses and their test/condition ratios

Response	Baseline firing rate	cAMP (▩)	cAMP (range)	tAMP (▩)	tAMP (range)	*T*/*C* ratio (▩)	*T*/*C* ratio (range)
E-SD (n = 43)	1.3 s/s	2.2	0.4–5.6	0.56	0–3.3	0.25*	0–0.66
E-LD (n = 15)	10.8*** s/s	7.3***	2–10.6	4.0***	0–7	0.50	0–0.75
Inhibit (n = 12)	5.8 s/s	0.50	0.2–1	0.28	0.1–0.5	0.56	0.2–0.75
Anticipate (n = 8)	1.5 s/s	0.61	0.3–1	0.16	0–0.3	0.31	0–0.6

The amplitudes are calculated as percent increase over baseline levels. cAMP is the conditioning amplitude and tAMP is the test amplitude. *T*/*C* ratio is the ratio of these two amplitudes and a measure of the intensity of inhibitory gating. *P < 0.05 and ***P < 0.001.

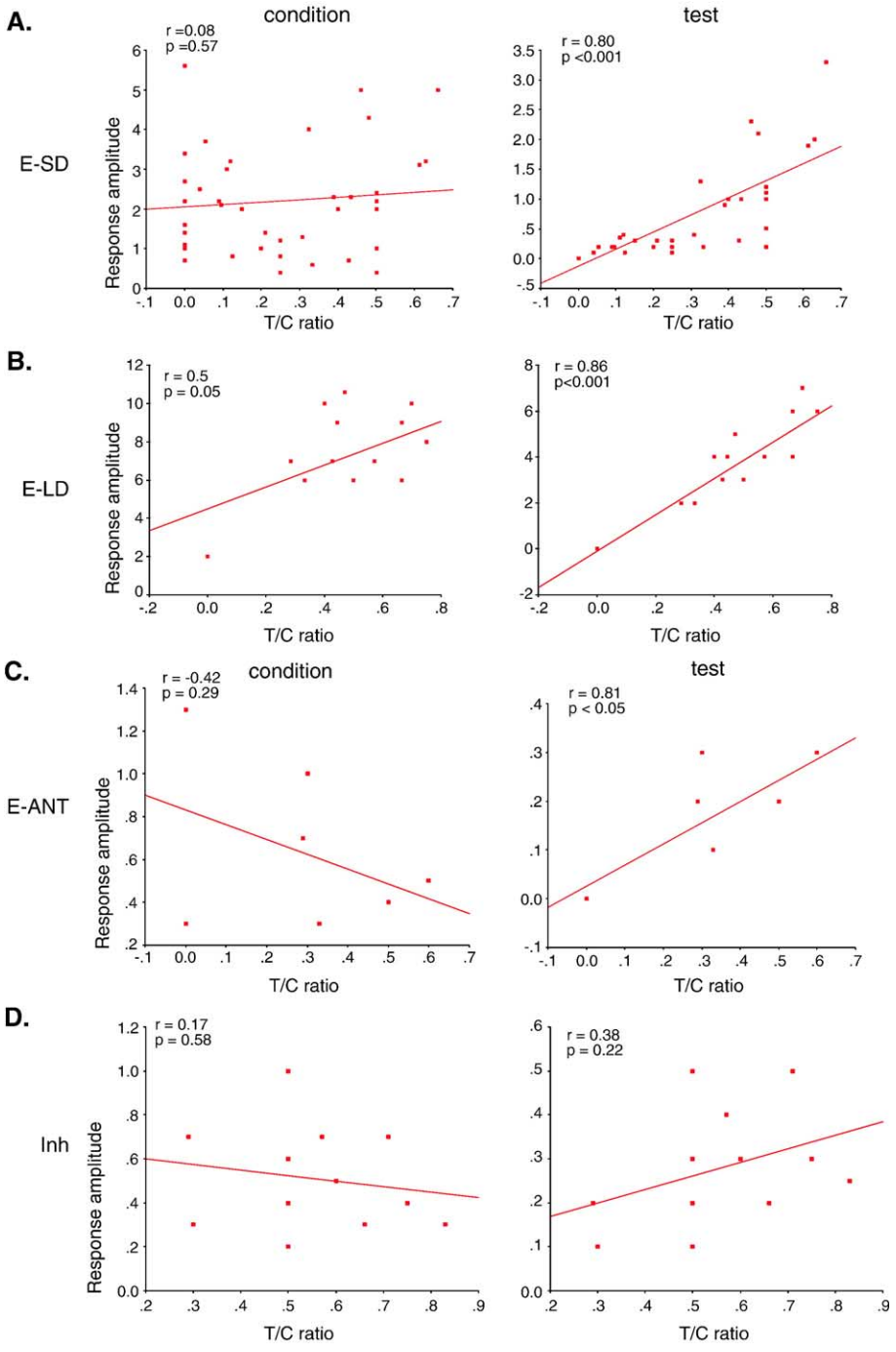

Fig. 3. Correlational analysis of the relationship between the tone response amplitudes and the *T*/*C* ratios. (A) Correlations between the cAMP/tAMP and *T*/*C* ratio for the E-SD response type. A significant positive correlation coefficient was obtained between the tAMP and *T*/*C* ratio. (B) Similar analysis for the E-LD group. Both the cAMP and tAMP responses were positively correlated with *T*/*C* ratios. (C) E-Ant response had a significant positive correlation between tAMP and *T*/*C* ratio. (D) No significant relationships were found for the inverse gating response.

the cAMP and *T*/*C* ratio while displaying a strong positive relationship between the tAMP and the *T*/*C* ratio (Fig. 3). These results demonstrate that alterations in inhibitory gating can occur via differing routes as changes in the cAMP, tAMP, or both responses together. Another way to examine how the individual neural activations vary over time is to examine the activity between short- and long-term time periods.

3.3. Within- and between-session variability

We explored the variability of inhibitory gating within and between individual sessions by completing a two-factor ANOVA with session and time segment as the two repeated factors. The session factor was the comparison between the 24-h intervals between daily sessions. The time segment factor was derived from dividing the total session into equal

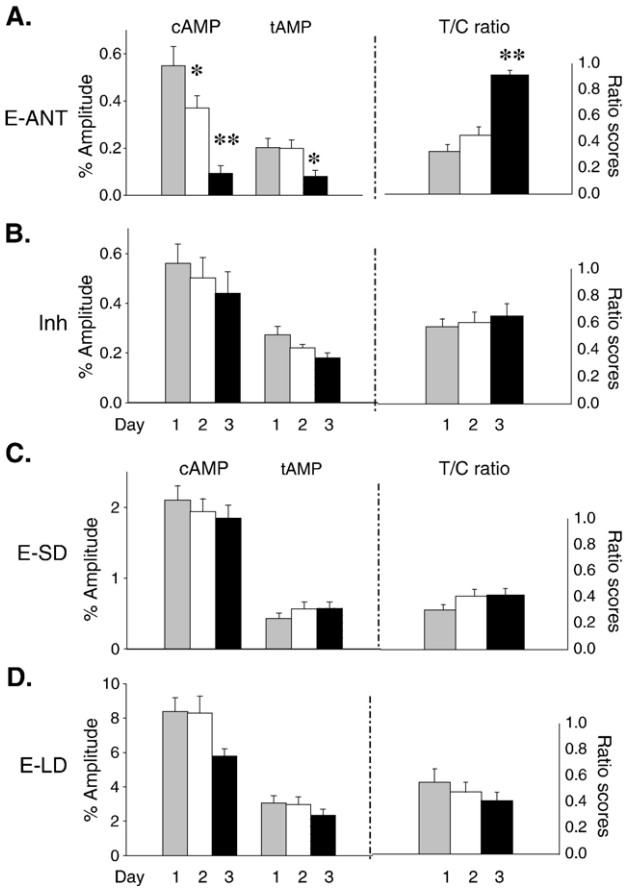

Fig. 4. Bar graphs depicting the cAMP, tAMP, and *T*/*C* ratios between sessions. Panel (A) shows the three measures for the E-Ant group in which significant differences were seen between sessions for each. Panel (B) provides the results for the inverse gating responses. Panel (C) shows these data for the E-SD response. No significant differences were found. Panel (D) shows the results for the E-LD group. **P* < 0.05; ***P* < 0.01.

early, middle, and late segments, each with 120 trials. A significant decrease in the neural activity to both the conditioning and test tones was found for the E-Ant response type between sessions (Fig. 4). This decrease was observed for both the cAMP [$F(2,8) = 13.7$, $P < 0.01$] and tAMP [$F(2,8) = 6.4$, $P < 0.05$]. Due to the significant decrease in the neural response to the tone at both time points, the *T*/*C* ratio was dramatically elevated [*T*/*C* ratio mean = 0.83; $F(2,8) = 11.5$, $P < 0.01$]. These results suggest that the anticipatory response found in the amygdala diminishes between sessions over a 3-day period. Conversely, the other response types that occur following the tone presentation persisted across the 3-day test interval and showed little variability between sessions (Fig. 4).

When short-term variability was analyzed by examining alterations within the different sessions, significant differences were found for the excitatory post-stimulus neural activations (Fig. 5). The E-SD response displayed a significant reduction in the cAMP [$F(2,34) = 5.0$, $P < 0.05$] with a concomitant increase in the tAMP [$F(2,34) = 7.3$, $P < 0.01$] within the single 1-h session. This led to a significant increase in the *T*/*C* ratio for this rapid response group [$F(2,34) = 12.3$, $P < 0.001$]. The E-LD response had fewer significant alterations. These neurons had significant variability within single sessions with a reduction in the amplitude of the response to the initial tone stimulus [$F(2,26) = 3.9$, $P < 0.05$] and no significant alterations in the neural response to the second tone (tAMP). There was a nonsignificant reduction in the *T*/*C* ratio in the response group.

3.4. Effects of saline injection on inhibitory gating

To analyze the effects of a novel/aversive stimulus upon gating responses, we administered an intramuscular injection of saline (0.2 cc) immediately prior to initiating a recording session with the two-tone paradigm. A series of paired sample *t* tests were completed between the control and saline injection conditions. The comparison control condition was the last session (3rd session) from the overall initial series. Following saline injection, the cAMP was found to be significantly increased for E-SD, E-LD, and E-

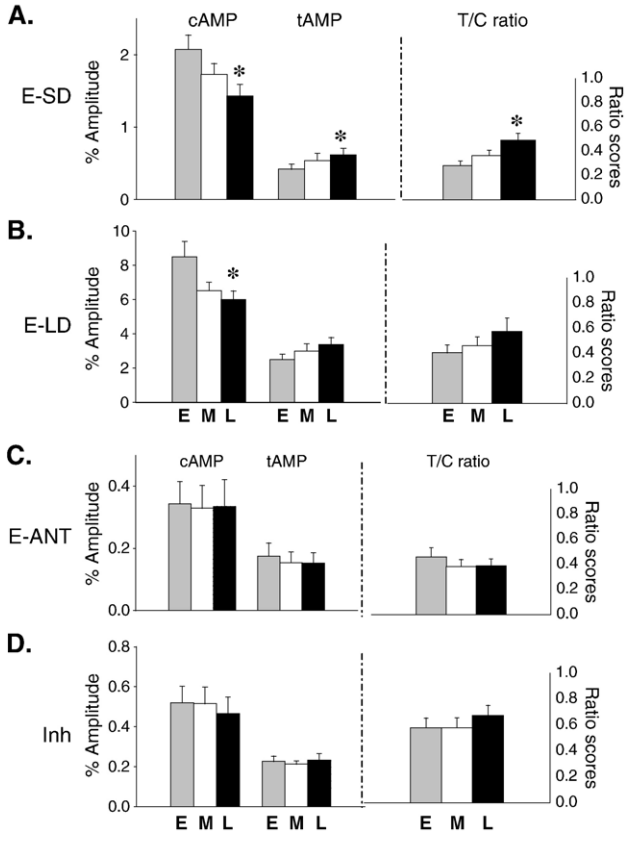

Fig. 5. Bar graphs depicting within-session variability for the tAMP, cAMP, and *T*/*C* ratios for the different neural responses. (A) The three measures for the E-SD group. Significant differences were found for all three measures in this response type. (B) Results for the E-LD subgroup. Significant variability was seen only for the neural response to the initial conditioning tone. (C and D) Amplitude measures and *T*/*C* ratios for the anticipatory and inhibitory responses. **P* < 0.05.

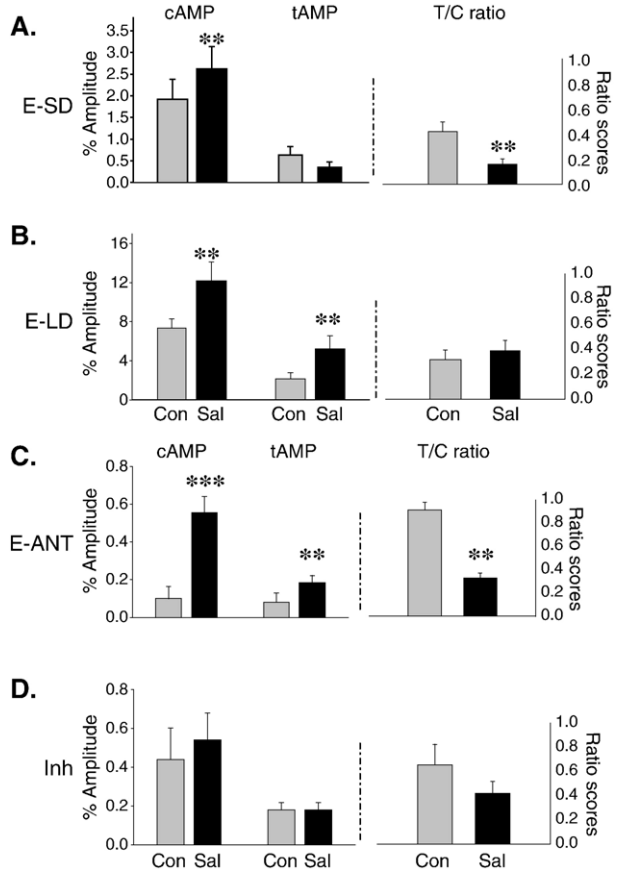

Fig. 6. Bar graphs showing the changes in cAMP, tAMP, and *T*/*C* ratio after aversive saline injection. (A) The results for the E-SD group. cAMP and *T*/*C* ratio were significantly altered after saline. (B) In the E-LD group, significant increases in both cAMP and tAMP were seen without a concurrent change in the *T*/*C* ratio. (C and D) Data for the anticipatory and inhibitory cell groups. Significant differences for the E-Ant group were noted for all measures (top panel) while no significant changes were recorded in the inhibitory cell group (bottom panel). $^{**}P < 0.01$; $^{***}P < 0.001$.

Ant tone responses (see Fig. 6; E-SD, $t = -4.4$, $df = 4$, $P < 0.01$; E-LD, $t = 4.0$, $df = 12$, $P < 0.01$; Anti, $t = 11.6$, $df = 4$, $P < 0.001$). The tAMP was significantly increased for the E-LD and E-Ant (E-LD, $t = 6.0$, $df = 12$, $P < 0.001$; Anti, $t = -3.2$, $df = 4$, $P < 0.05$). The *T*/*C* ratio was significantly decreased for both the excitatory responses of E-SD and E-Ant (E-SD, $t = 4.5$, $df = 10$, $P < 0.01$; E-Ant, $t = 9.2$, $df = 4$, $P < 0.01$). We found no changes in the amplitude changes or the measure of inhibitory gating for the inhibitory tone response.

4. Discussion

4.1. Neurophysiological mechanisms of gating

Our findings are the initial neurophysiological analysis of inhibitory gating to describe a diverse set of single-unit tone responses that exhibit neural inhibition. We have demonstrated that there are several different types of pre- and post-stimulus auditory responses and that each of these shows inhibitory gating to a certain degree. Additionally, our contribution includes a detailed description of the variability of inhibitory gating across different time periods and different emotional contexts. Inhibitory gating was found to vary between 24-h periods in the same single unit and to vary within a single session from the early segments to the later segments. Finally, we found a strong modulation of inhibitory gating by an arousing stimulus. In every case, the inhibitory gating was actually increased (lower *T*/*C* ratios), demonstrating that the greater gating of stimuli occurs at the level of the amygdala after the animal has experienced a stressful stimulus. The increased inhibitory gating could be due to the fact that the stimulus in this series of trials holds no meaning and does not predict the occurrence of a potential rewarding or aversive stimulus. Future work will be needed to decipher whether inhibitory gating is reduced to stimuli that have acquired meaning through a learning process like classical conditioning.

The neural mechanisms related to inhibition of information flow are not well known but are thought to include interactions between glutamatergic projection neurons with local GABAergic inhibitory networks [8,21,32]. Inhibitory GABAergic feed-forward and feedback circuits are likely to control firing patterns of glutamatergic projection cells within many brain regions including pyramidal neurons within the cortex and hippocampus [12,70,79]. Here, they are hypothesized to supply the background context so the information content may be processed by the excitatory projection cells. Evidence is growing to show that intrinsic GABAergic networks influence internal firing rhythms and frequency oscillations [82] as well as play a role in sensory filtering (vision: [76], somatosensory: [45]) and spatial working memory within the dorsolateral prefrontal cortex [68].

4.2. Amygdala and gating

Based upon the present results, the amygdala can be added to the list of brain regions to show inhibitory sensory gating functions. Inhibition was found to be robust (100% reduction) within both the medial and lateral nuclei. The amygdala has been thought to be a key structure in the integration of sensory information between the cortex and subcortical circuits including the striatopallidal loops, hippocampal circuits, and brainstem networks. These also involve pontine reticular formation nuclei that mediate prepulse startle inhibition [80]. Intrinsic GABAergic neurons within the amygdala have been proposed to regulate activity between amygdala subnuclei [59,70] and to modulate incoming sensory information [37,46]. The amygdala receives multi-modal sensory input from several sensory cortical and subcortical areas including primary auditory and olfactory cortex, somatosensory cortex, inferior temporal cortex involved in visual processing, and thalamic subregions [53,77]. Related to the present findings,

the different neural activations that display inhibitory gating most likely represent distinct neurochemical cell types housed in the amygdala. Based on other electrophysiological evidence, the excitatory responses observed in the present work could represent excitatory projection neurons of the amygdala [71] while the higher firing rate cells with inhibitory responses could be intrinsic GABAergic neurons [51,69]. Both medial and lateral subnuclei contain these cell populations [59,64]. The differential variability observed in these cell types in their inhibitory gating over time and in response to stress may reflect differential incoming input information and functional significance for the distinct groups. One possible functional role would be in emotional learning. The amygdala has been hypothesized to be involved in the forming of associations between stimuli and primary aversive or rewarding events in the environment [28,48]. These types of complex, highly prevalent learning processes could depend upon inhibitory gating mechanisms both intrinsic and external to orient attentional resources and disregard irrelevant stimuli [47].

4.3. Plasticity of gating within and between sessions

In our previous work, we have found neural activations between stimuli that persist over long periods of time in well-trained animals [17]. The environmental contexts for these typical delayed response tasks utilize predictable situations similar to the standard gating procedure. The persistence in the inhibitory gating may be related to the consistency in neural responsiveness over time for other types of more sustained activity thought to be involved in memorial or expectancy functions [17,32]. Inhibitory gating was abolished in only the anticipatory response group over the 3-day testing period signifying potential functional specialty for this type of response compared to the others. It could be that the anticipatory responses require variety or meaning to remain over extended time periods. It does seem to be the case that these cells were injured or lost, because during the 4th testing day, they were observed after the aversive saline injection.

Within the 1-h session, variability was noted for both of the excitatory response types. This was characterized by a decline in the amplitude of the response to the initial tone stimulus with either no change in the response to the second or an actual increase in response to the second tone. The second effect led to an increase in the T/C ratio in the E-SD type responses that reflects the reduction in inhibitory gating. After the 3 days of testing, the gating was still below 0.75 for the group and was characterized by a substantial reduction in tone responsiveness.

Other groups have found variability in evoked responses or inhibitory gating across different contexts and states [1,14,41–43,60,63]. Since no specific state change was varied systematically in the present study, it is difficult to speculate on the functional nature of the variability. One important point is that the between- and within-session variability significantly differed for the diverse response types suggesting that the responses may play different roles in the rapid type of stimulus information processing involved.

4.4. Clinical considerations

Inhibitory gating is thought to be altered in many disorders of attentional processing including schizophrenia, Alzheimer's disease, and Tourette's syndrome [13,23,38,59,78]. Deficits in gating functions may take different forms in different syndromes. To tease apart the different functional abnormalities, it will be worthwhile to develop basic gating tests that can reveal particular gating abnormalities. Dysfunctions including a failure to gate have been statistically linked to neurobiological and genetic abnormalities in schizophrenia [25,26]. This neurophysiological assay has been used as a diagnostic indicator for perceptual defects seen in schizophreniform disorders, and most recently, it has been used as the phenotypic assay to pinpoint genotypic profiles of schizophrenic patients and their relatives [25]. The combination of genotypic and phenotypic analysis using inhibitory sensory gating has led to a novel theory in terms of the neuropathological mechanisms contributing in part to schizophrenic phenotypes that is centered on linkage disequilibrium at the chromosome 15 of the α7-nicotinic acetylcholine receptor subunit gene [25,26]. The findings have suggested that factors contributing to schizophrenia include an interaction between a heritable deficit in nicotinic cholinergic receptors and the circuit mechanisms of inhibitory gating including the dysfunction of several brain regions, especially the hippocampus [2,23,33,52].

It is highly reasonable to suspect that different sorts of gating defects will be observed in patients with different mental or emotional disorders [39,40,49,58]. An alteration within the internal gating system could include excessive inhibition to stimuli that would lead to under-reactivity to stimuli or obsessive focus upon particular stimuli or acts [7]. If we examined the gating functions closer, we might reveal an exaggerated gating that over-filters information and leads to a deficit in responding, persistence in habitual or ritual behavior, and a loss of emotional or social interactiveness. Disorders such as autism may appear to gate stimuli normally [39] but are unable to locally regulate the intrinsic inhibitory mechanisms that are dependent upon contextual and experiential feedback.

Our clinically relevant and unique finding is that gating actually increases for certain neural responses following exposure to stress. This finding is related to inhibitory gating defects found in post-traumatic stress disorder and other anxiety disorders [30,34,58,72]. It will be very important to examine inhibitory gating in these populations following a stressful challenge as we would predict a significant increase in gating in the amygdala region. Other regions of the brain may be reacting to the stress in other

fashions [16,54,55]. The functional nature of inhibitory gating must be analyzed in greater detail using psychological challenges at the cognitive and affective level. Until these tests are undertaken in animal models, the meaning of alterations in inhibitory gating will be unclear.

The amygdala has been postulated to be dysfunctional in a number of attentional and perceptual disorders including schizophrenia [27,52,67], Tourette's syndrome [38,62], and autism [6,7,19,22,36], making it a potential region within the forebrain where gating mechanisms involved in complex attentional functions could reside. If we can determine the details underlying these basic neurophysiological mechanisms, we can then formulate better uses for this classic paradigm for testing patients and diagnosing complex disorders more accurately and quickly.

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