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Inhibitory mechanisms shaping delay-tuned combination-sensitivity in the auditory cortex and thalamus of the mustached bat

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Abstract

Delay-tuned auditory neurons of the mustached bat show facilitative responses to a combination of signal elements of a biosonar pulse-echo pair with a specific echo delay. The subcollicular nuclei produce latency-constant phasic on-responding neurons, and the inferior colliculus produces delay-tuned combination-sensitive neurons, designated “FM-FM” neurons. The combination-sensitivity is a facilitated response to the coincidence of the excitatory rebound following glycinergic inhibition to the pulse (1st harmonic) and the short-latency response to the echo (2nd–4th harmonics). The facilitative response of thalamic FM-FM neurons is mediated by glutamate receptors (NMDA and non-NMDA receptors). Different from collicular FM-FM neurons, thalamic ones respond more selectively to pulse-echo pairs than individual signal elements. A number of differences in response properties between collicular and thalamic or cortical FM-FM neurons have been reported. However, differences between thalamic and cortical FM-FM neurons have remained to be studied. Here, we report that GABAergic inhibition controls the duration of burst of spikes of facilitative responses of thalamic FM-FM neurons and sharpens the delay tuning of cortical ones. That is, intra-cortical inhibition sharpens the delay tuning of cortical FM-FM neurons that is potentially broad because of divergent/convergent thalamo-cortical projections. Compared with thalamic neurons, cortical ones tend to show sharper delay tuning, longer response duration, and larger facilitation index. However, those differences are statistically insignificant.

Keywords

Distance information; Echolocation; FM-FM neurons; GABAergic inhibition; Hierarchical processing

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1. Introduction

The orientation sound (bio-sonar pulse or pulse) of the mustached bat, *Pteronotus parnellii*, is composed of four harmonics, each consisting of a constant frequency (CF) and a frequency modulated (FM) component. Therefore, each pulse consists of eight components: CF₁₋₄ and FM₁₋₄. The central auditory system of the mustached bat contains “delay-tuned combination-sensitive” neurons which show facilitative responses to pulse-echo pairs with specific echo delays and a maximal response at the “best delay” (BD). Of the 16 components in a biosonar pulse-echo pair, only the pulse FM₁ and echo FM_n (n=2, 3 or 4) are essential to generate the facilitative response. Therefore, these combination sensitive neurons are named FM-FM neurons, more specifically, FM₁-FM_n neurons (Suga et al. 1978; O’Neill and Suga 1979).

The basic response properties of FM-FM neurons are theoretically created by four components: “constant-latency-phasic” on-responders, delay lines, coincidence detectors and amplifiers (Suga 1990). Constant-latency-phasic on-responders are ideal for coding a stimulus time by discharging just one action potential with a constant latency regardless of stimulus levels (Suga 1970; Bodenhamer and Pollak 1981). Neurons with this property are created in the subcollicular auditory brainstem nuclei, such as the ventral nucleus of the lateral lemniscus (Covey and Casseday 1991; Haplea et al. 1994). Delay lines for delaying the response to an emitted bio-sonar pulse are created in the subcollicular and collicular nuclei. Rebound excitation following glycinergic inhibition in the inferior colliculus acts as a delay line longer than 6 ms (Nataraj and Wenstrup 2005). Collicular FM-FM neurons showing delay-dependent facilitation act as coincidence detectors and amplifiers (Mittmann and Wenstrup 1995; Yan and Suga 1996a). The rebound excitation plays the major role in this delay-dependent facilitation. Glutamate receptors are not involved in it (Nataraj and Wenstrup 2005; Sanchez et al. 2008). The collicular FM-FM neurons relay the responses to pulse alone, echo alone and pulse-echo pair to thalamic FM-FM neurons.

Unlike collicular neurons, thalamic FM-FM neurons show glutamate-dependent facilitation mediated by N-methyl-D-aspartate (NMDA) receptors that make the thalamic FM-FM neurons respond more specifically and for a longer duration to a paired FM-FM stimulus than to either pulse or echo presented separately. The duration of the NMDA-mediated facilitation is limited by GABAergic inhibition (Butman and Suga 2016).

Thalamic FM-FM neurons project to the auditory cortex. Cortical FM-FM neurons are clustered in three separate cortical areas: FF (previously, FM-FM), DF (dorsal fringe) and VF (ventral fringe) areas. Among those three areas, the FF area is the largest and represents echo delays from 0.4 to 24 ms. The three areas are different from each other in the length of delay axis (Suga and O’Neill 1979; Suga and Horikawa 1986; Edamatsu et al. 1989), neural response properties (Edamatsu and Suga 1993), and connectivity (Fitzpatrick et al. 1998). They interact each other for the adjustment and improvement of delay tuned responses (Xiao and Suga 2004; Tang et al. 2007; Tang and Suga 2008, 2009).

The response properties of thalamic (Olsen and Suga 1991; Wenstrup 1999) and cortical (O’Neill and Suga 1979, 1982; Suga and O’Neill 1979; Suga et al. 1983; Hagemann et al.

2011) FM-FM neurons have been studied and theoretical acuities based on facilitative responses of cortical FM-FM neurons have been computed (Suzuki and Suga 2017). However, the differences in response properties between thalamic and cortical FM-FM neurons have remained to be explored. The aim of our current paper is to report our findings that although response properties of both thalamic and cortical FM-FM neurons are relatively similar, these neurons exhibit dramatically different alterations in delay tuned response properties when exposed to an antagonist of gamma-aminobutyric acid (GABA) receptors, bicuculline methiodide (BMI). Different from thalamic neurons, delay tuning of cortical neurons are potentially broad because of divergent/convergent thalamo-cortical projections, but it is sharpened by intra-cortical inhibition.

2. Methods

2.1. Experimental preparation

The experimental subjects were 12 Jamaican mustached bats, *Pteronotus parnellii parnellii*, weighing from 10 to 14 g. The animals were anesthetized by intramuscular injection of the neuroleptanalgesic Innovar-vet (0.08 mg fentanyl and 4.0 mg droperidol per kg b.w.), the temporal muscles were laterally reflected, and a 15 mm-long steel post was affixed to the skull with cyanoacrylate glue. At least two days of recovery were allowed prior to the first experimental session. For recording, the animal was placed in a styrofoam body mold suspended by elastic bands at the center of an echo-attenuating soundproof room maintained at 29-31°C. To stabilize the bat's head, the steel post was securely attached to the experimental apparatus with setscrews. The head was directed at a pair of 5-cm-diameter condenser loudspeakers (one directly above the other) placed 82 cm away. Pulse and echo stimuli were delivered from the different loudspeakers. Vascular landmarks on the cortex (visible through the skull) were sketched with the aid of a 40X Jena dissection microscope with a grid reticule for reference. Multibarreled electrodes were inserted through small holes (50-200 μ m), drilled in the skull with a wire needle, and the exposure was sealed with mineral oil-petroleum jelly mix. A tungsten-wire grounding electrode (20-50 μ m tip) was placed on the surface of non-auditory cortex. The animal was awake during the recording session, and was provided water every 1-2 hours. Recording sessions occasionally lasted up to 10 h and took place no more frequently than once every other day. The protocol of our research was approved by the animal study committee of Washington University, St. Louis, Missouri, U.S.A. (Approval No: 890486).

2.2. Acoustic stimuli

Since FM-FM neurons found by Suga et al. (1978), it has been well established that the essential components of a pulse-echo pair for evoking their facilitative responses are pulse FM₁ and echo FM_n (n=2, 3 or 4) (O'Neill and Suga 1979, 1982; Suga et al. 1983; Kawasaki et al. 1988). Therefore, FM₁ and FM_n stimuli in the current paper respectively represent pulse and echo stimuli. For a FM₁-FM₂ neuron, for example, FM₁ and FM₂ stimuli were pulse and echo stimuli.

FM sounds (3-ms duration, 0.5-ms rise/fall) swept downward by 6, 12, 18, or 24 kHz according to the particular harmonic. They were generated by shaping the output of a

voltage-controlled function generator (Wavetek 130) with a custom-built electronic switch. Frequency modulation was introduced by applying linear voltage ramps, synchronized with the electronic switch, to the voltage controlled function generator. Sound amplitude was controlled by a decade attenuator (Hewlett-Packard 350D) or by a computer-controlled digital attenuator. Delay-response functions were obtained by delivering FM stimuli at the best amplitudes for facilitation of individual neurons.

The FM sound stimuli were presented as a train called a delay scan which consisted of 13 time blocks to deliver a pulse alone, 10 pulse-echo pairs, an echo alone, and a no stimulus (N) block, as in our previous paper (Butman and Suga 2016). Echo delay systematically varied in the 10 pulse-echo pairs and was adjusted so that the BD of a given neuron occurred near the middle of the train. The duration of each time block was set at 100 or 150 ms, so that the duration of the delay scan was 1300 or 1950 ms. The delay scan was repeatedly presented once every 1400 or 2000 ms.

2.3. Electrodes

For recording action potentials during the iontophoretic application of a neurotransmitter-receptor agonist and its antagonist, 5-multibarreled carbon-fiber microelectrodes were assembled according to the procedure of Armstrong-James et al. (1979) and Armstrong-James and Miller (1979). Five 2.0 mm capillary tubes (barrels) were placed around a 1.2 mm capillary tube through which a 50- μ m carbon fiber was inserted. Electrodes were pulled in two stages with a vertical puller (Narishige PE-2) to obtain an electrode with a shank diameter less than 50 μ m along a 1.5-3.0 mm length. Electrical contact to the carbon fiber was made with a tungsten wire whose end was coated with colloidal silver. The carbon fiber was etched with chromic acid to a pencil-shaped point extending about 50 μ m (25 μ m point, 25 μ m shank) from the end of the glass pipette.

2.4. Drug iontophoresis

Two kinds of drugs were iontophoretically applied to thalamic and cortical FM-FM neurons. They were GABA and its antagonist, BMI. Iontophoretic currents were controlled by a Neurophore BH-2 iontophoresis apparatus. The timing of ejection currents was usually controlled manually while single-unit responses were monitored continuously, allowing time for drug effects to stabilize. Automatic current balancing was performed through a saline filled barrel or an indifferent tungsten-wire electrode placed on the cortex. Retention currents were typically set at 5 to 10 nA with negative polarity.

Means and standard errors of response magnitude (spike number/stimulus) and response probability (response/stimulus) were used to generate delay response curves (e.g. Figs. 2 and 5). Delay-width was computed as the width of the curve at half of the maximal response, determined by linear interpolation.

2.5. Recording sites

The FF (previously, FM-FM) area is easily located using the skull and vascular landmarks based on the physiologic map (O'Neill and Suga 1982; Suga et al. 1983). Cortical FM-FM neurons were isolated at depths up to 750 μ m below the cortical surface. Thalamic FM-FM

neurons were located from 1600-3500 μm below the cortical surface in electrode penetrations oriented in an approximately coronal plane, 30° from vertical, through posterior FF, dorsal Doppler-shifted CF, and dorsomedial regions of the auditory cortex (Olsen and Suga 1991; Butman and Suga 2016). Characteristic rhythmic field potentials at ~ 30 Hz were usually noted as the electrode penetrated through the hippocampal formation to reach the underlying medial geniculate body (MGB). Penetrating the MGB was clearly marked by the appearance of an evoked auditory response.

2.6. Data acquisition

Action potentials were "accepted" when they exceeded a threshold level and then filtered through a window discriminator (BAK electronics), thereby marking the time of occurrence of an action potential with a logic pulse. Both the filtered and unfiltered spike waveforms were monitored on a digital storage oscilloscope (Tektronix 2211). A high speed clock (Modular Instruments) was used to record arrival times relative to the onset of the stimulus train with a bin width of 0.2 or 0.4 ms. Times of spike occurrence were stored on a computer hard drive and displayed as raster dots and histograms. Thalamic data that were mostly reported by Butman and Suga (2016) were utilized for the comparison with our current cortical data.

2.7. Response magnitude and response probability

The mean and standard error of the response (spikes/stimulus) was computed by averaging spike counts over a 50-100 ms window following stimulus onset. Background discharges in the "no stimulus" block were computed over a similar window and were subtracted from the response. Since there was pronounced post-excitatory suppression in most cases, the window was adjusted to include only the excitatory response. After adjusting the window based on the PST histogram, the fraction of stimuli to which activity was counted in the window gives us the unadjusted response probability, $P(R \text{ OR } B)$ in which R represents stimulus evoked activity occurring in the window, and B represents background activity occurring in the same window, as either may be counted. To estimate the probability of a stimulus evoked response, $P(R)$, an adjustment for background activity was made by assuming that background and stimulus-driven activity were independent. Under this assumption, probability of recording any activity, either stimulus evoked (R) or background (B), is given by $P(R \text{ OR } B) = 1 - P(\text{NOT } R \text{ AND NOT } B) = 1 - P(\text{NOT } R)P(\text{NOT } B)$. Since $P(B)$ can be determined from the background in the no stimulus block, $P(R)$ may then be calculated according to $P(R) = [P(R \text{ OR } B) - P(B)]/[1 - P(B)]$, using $P(\text{NOT } X) = 1 - P(X)$ and re-arranging terms. (Here, OR, NOT and AND are used formally as Boolean logical operators.)

2.8. Statistics

The specific statistical procedures used for determining significant differences are indicated where "P" values are reported in the data. Non-parametric tests were used (e.g. the Wilcoxon matched-pairs signed ranks test for paired data, and the Mann-Whitney U-test for unpaired data) except in situations where only means, standard deviations, and the number of samples were available (in which case paired or unpaired t-tests were used). Mean values are reported along with the standard deviation of the population or, if indicated by "SE", with standard error.

3. Results

In 33 cortical and 29 thalamic FM-FM neurons, stable recordings were made in which neurons remained well isolated throughout an iontophoretic application of BMI or GABA, and in which the responses recovered to 80%-100% of a control level within 20 min after the cessation of a drug injection. These FM-FM neurons showed strong facilitative responses to FM₁-FM_n pairs (pulse-echo stimuli), as previously reported (Suga et al. 1978, 1983; O'Neill and Suga 1979, 1982; Olsen and Suga 1991). Electrode penetrations were varied along the delay axis (Suga and O'Neill 1979; Olsen and Suga 1991), so that the BDs of sampled neurons ranged between 0.5 and 17 ms. No more than two neurons were studied per penetration.

3.1. General effects of BMI and GABA on delay-dependent facilitative responses

The delay scan evoked facilitative responses of cortical FM-FM neurons, i.e., no response or very poor responses to pulse alone and echo alone, but a facilitative response (burst of several spikes) to pulse-echo pairs (Fig. 1, A1 and B1). The cortical neuron in Fig. 1 responded to pulse-echo pairs with echo delays of 1.50 through 5.25 ms. Its BD was 3.0 ms. An iontophoretic application of BMI (20 nA) revealed facilitative responses to pulse-echo pairs with echo delays ranging from 0.75 to 6.75 ms (Fig. 1, A2 and B2), in addition to an increase in response at the BD. That is, BMI broadened the delay tuning of the neuron. It was clear that the response to the 6.75-ms echo delay was a facilitative response, although a weak response to pulse alone was present with BMI. It was also noted that post-excitatory suppression was pronounced in the presence of BMI. GABA uniformly suppressed background and evoked activity (Fig. 1, A4 and B4).

Thalamic FM-FM neurons exhibited delay-tuned responses similar to those of cortical ones. However, BMI iontophoretically applied to them changed their responses quite differently from those observed in the auditory cortex. In Fig. 1, a thalamic FM-FM neuron was tuned to 3.5 ms echo delay (Fig. 1, C1 and D1). BMI (20 nA) dramatically increased the response magnitude at its BD nearly 8-fold and extended the response duration to over 75 ms, although the duration of the paired stimulus (including pulse and echo) was only 6.0 ms. Despite these dramatic changes, facilitative responses were still confined to the same echo delays (2.5 to 4.5 ms) as those in the control situation (Fig. 1, C2 and D2). Combination specificity was maintained, as no response was elicited to either pulse alone or echo alone in both control and BMI conditions. As in the auditory cortex, GABA application in the MGB had suppressive effects on both background activity and auditory responses (Fig. 1, C4 and D4).

3.2. Effects of BMI on delay tuning and BD

BMI effects on the delay-response curves of cortical FM-FM neurons tuned to echo delays of 3.0 ms and of 5.0 ms echo delay are shown in Fig. 2. For the 3.0-ms-tuned neuron, BMI resulted in an ~8-fold increase in the facilitative response (Fig. 2A) and symmetrical broadening of the delay-response curve. The width of the response curve at half-maximal response (DW) increased from 2.2 ms to 3.8 ms, a 72% increase with no change in BD (Fig. 2B).

In Fig. 2, C and D, BMI increased the facilitative response of the 5.0-ms-tuned cortical neuron ~3 fold and broadened its delay-tuning curve: DW increased from 4.0 to 6.8 ms, a 70% increase. This broadening was asymmetrical, with a release of delay-dependent responses from inhibition exclusively for stimuli with echo delays longer than the BD. The BD did not change, despite these changes.

BMI affected the delay tuning of thalamic FM-FM neurons to a lesser extent than that of cortical ones, although it increased their facilitative responses 3-4 fold. Fig. 3 shows BMI effects on the delay-response curves of two thalamic FM-FM neurons with BDs of 0.75 ms and of 7.0 ms. For the 0.75-ms tuned neuron (Fig. 3, A and B), BMI increased response 2.5 fold with virtually no effect on BD and on DW. Similarly, the delay tuning of the 7.0-ms tuned neuron (Fig. 3, C and D) was little changed by BMI.

3.2.1. Effects of BMI on delay-tuning width—Changes in delay tuning for 33 cortical and 29 thalamic FM-FM neurons induced by 20-60 nA BMI are summarized in Fig. 4, in which the fractional change in DW is plotted against the commensurate change in facilitative response at the BD and best amplitude of a given neuron. For FM-FM neurons in the AC, BMI increased the response at in all but one case. BMI increased response magnitude at BD by a factor of 2.2 ± 1.1 ($n=33$). BMI significantly broadened the delay response curve of AC FM-FM neurons by 26% (Fig. 4A). ($\text{BMI DW} / \text{Control DW} = 1.26 \pm 0.07$, $\text{mean} \pm \text{SEM}$, $n=33$, $p<0.02$, Wilcoxon test). DW recovered with the cessation of the BMI application to 97% of the control value (Fig. 4, small dots).

In 17 of 33 cortical neurons (52%), the DW increased by over 20% with a mean 54% increase in DW, whereas it reduced (sharpened) greater than 20% in two neurons. In 13 of the 17 neurons showing significant broadening, the expansion was asymmetrical toward longer echo delays as in Fig. 2, C and D, whereas it was symmetrical in the remaining four neurons as in Fig. 2, A and B. No neurons showed expansions exclusively toward echo delays shorter than the BD. In several neurons, DW was measured at least four times in both control and BMI conditions (from 50 stimuli). In these neurons, paired t-tests which were able to detect significant changes at the $p<0.05$ level corresponded to changes of at least 20%, suggesting that changes of this magnitude may be considered significant.

The DW of FM-FM neurons in the MGB was little affected by BMI (Fig. 4B). The average DW in the MGB decreased by 9% ($\text{BMI DW} / \text{Control DW} = 0.91 \pm 0.03$, $\text{mean} \pm \text{SEM}$, $n=29$, $p<0.01$, Wilcoxon test). Response magnitude increased 3.54-fold, a greater change than that observed in the AC. Although this change in DW was statistically significant with respect to the control measurement, it was not significantly different from recovery, where DW remained at 92%.

3.2.2. Effects of BMI on BD—The BDs of FM-FM neurons were relatively unaffected by the removal of inhibition by BMI in both AC (Fig. 4C) and MGB (Fig. 4D). As shown in Fig. 4C, the BD of cortical neurons was not affected by the application of BMI, as the changes in BD for this population were essentially randomly scattered about the line $y=x$, for an overall increase of 4% in BD ($P=0.7$, Wilcoxon test, $n=32$). Considering only long BDs (>4 ms), there was virtually no change as well ($\text{BMI BD} / \text{Control BD} = 0.98$ $P=0.4$,

n=22). This scatter may reflect a greater variability in the measurement of BD after expansion of the delay-tuning width.

In the MGB, removal of GABAergic inhibition by BMI had little effect on the BDs of both short (<4 ms) and long (>4ms) delay-tuned neurons. Overall, BD decreased by 4% ($P<0.01$, $n=27$) for the group as a whole. However, 16 neurons with long BDs exhibited a 7% decrease in BD ($P<0.01$). Their changes were significantly different than the measurements from the recovery data. In a few neurons greater shifts in BD were observed in the presence of BMI, but these shifts were not maintained despite a continuous application of BMI. Control records also showed spontaneous shifts of BD to shorter delays of comparable magnitude in the absence of any exogenously applied neuroactive agents in these cases. Because of this phenomenon, BMI application was not terminated in the midst of a possible change in BD. Only sustained changes were further evaluated.

3.2.3. Dependence of BMI induced changes in delay width on BD and delay tuning—FM-FM neurons in the AC and MGB were subclassified by BD and by delay-width (DW) in order to examine whether BMI-induced expansions were specific to a particular subpopulation of neurons. Since DW in delay-tuned neurons measured at best amplitude is linearly related to the BD of neurons, neurons with short BDs are sharply tuned, and those with long BDs are broadly tuned (Suga and Horikawa 1986, Olsen and Suga 1991).

In the current sample of neurons, DW was correlated well to BD with regression slopes of 0.82 (SEM=0.11, $r=0.81$, $P<0.0005$, $n=30$) in the AC and 0.85 (SEM=0.12, $r=.81$, $P<0.0005$, $n=20$) in the MGB, as has been demonstrated in previous studies of both the AC (slope=1.0, Suga and Horikawa 1986) and MGB (slope=0.85, Olsen and Suga 1991). Neurons were subdivided into short-BD (<4 ms) and long-BD (>4 ms) categories. Of the 20 long-BD neurons, DW increases by 20% on the average in 7 (35%), whereas DW increased in 10 of the 13 short-BD neurons (77%). This difference between the short- and long-BD groups was significant ($P<0.05$, Fisher's exact test), suggesting that inhibition sharpens delay tuning to a greater extent in short-BD neurons than in long-BD neurons.

Because of this linear relationship between DW and BD, we classified neurons as "relatively broadly" tuned if $DW > BD$, and "relatively sharply" tuned otherwise (if $DW < BD$). According to this scheme, 36% (12/33) of cortical neurons were classified as "broad" and the remaining 64% (21/33) as "sharp". Since BMI induced broadening in 50% of the sample, we expected that inhibition might create relatively "sharp" neurons, and to be absent in relatively "broad" neurons. However, this was not the case. BMI increased DW by more than 20% in 7 of the 12 broadly tuned neurons (58%), and in 10 (48%) of the 21 sharply tuned neurons. These proportions were not significantly different ($P=0.32$, Fisher's exact test), suggesting that relatively sharply tuned neurons do not uniquely depend on GABAergic inhibition for the sharpness of their delay tuning.

3.2.4. Effects of BMI on response probability—Echo delays close to a neuron's BD evoke strong and more reliable responses (Fig. 1, raster dots). That is, there is a higher response probability as well as larger response magnitude (number of spikes per stimulus).

Because of the stochastic nature of the response, a delay-tuning curve can be generated from response probability as well as response magnitude. Fig. 5C shows the delay-probability and delay-response curves of a single cortical FM-FM neuron. The former is broader than the latter. BMI broadened both the curves without changing the BF (Fig. 5, A and B). The amount of broadening of the delay-probability curve was larger than that of the delay-response curve.

Half-widths of the curves were calculated so that a delay “probability” width (DWp) was measured in addition to the traditional delay width, which is properly a delay “response” width (DWr) taking into account the magnitude of the response. Low background discharge rates allowed calculation of DWp in 27 cortical and 24 thalamic neurons. In Fig. 6, DWr is plotted against DWp for 27 cortical (A) and 24 thalamic (C) FM-FM neurons. Virtually all data points lie below the $y=x$ line, indicating that the response magnitude results in further sharpening of delay tuning, although DW is primarily determined by response probability. This sharpening was slightly greater in the AC, as indicated by the regression lines with the slopes of 0.70 ($r=0.92$) in the AC and 0.77 ($r=0.97$) in the MGB. (Both slopes were significantly different from a slope of 1.0 ($p<0.0001$)).

To measure the effects of BMI across the population of FM-FM neurons, DWr and DWp were measured with and without BMI. And recovery conditions were normalized to the control values of DWp. The effects of BMI on the DWr and DWp are summarized in Fig. 6, B and D. Both DWr and DWp increase with the application of BMI in the cortical neurons by 30% and 49% for DWr and DWp, respectively ($P<0.001$ and $P<0.0005$, Wilcoxon test), but are essentially unchanged in the thalamic neurons, -7% for DWr and $+14\%$ for DWp ($P=0.13$, $P=0.68$ Wilcoxon test). However, it is clear that the sharpening imparted by the magnitude of the burst response is not eliminated. In fact, its relative contribution is enhanced, since the ratio of DWr to DWp is reduced from 77% to 66% with an application of BMI. Increase of DWp indicate that BMI induced broadening of delay tuning was not simply due to saturation of the peak response, but represented a true increase in the delays which were effective stimuli.

3.2.5. Effects of BMI on response duration and magnitude—Response duration at BD and best amplitude was measured from peri-stimulus time cumulative (PSTC) histograms as the difference between the minimum latency and the time at which the histogram reached 90% of the cumulative response, corrected for background discharges. Facilitative responses of both cortical and thalamic neurons consisted of a burst that varied in duration and in the number of action potentials. This burst started at a relatively fixed latency from the echo, so that the PSTC histogram rises rapidly at the onset of the response, and attained its maximal level in an approximately exponential manner (Fig. 7, A and C). The PSTC histograms of thalamic FM-FM neurons were distinct from those of cortical ones, having a steep vertical onset, followed by a shallow tail. Cortical and thalamic FM-FM neurons showed a comparable response duration (32.8 ± 9.8 ms, $n=33$ vs. 27.2 ± 18.9 ms, $n=27$). The difference was not significant ($P=0.07$, Mann-Whitney U test). Whereas cortical neurons were relatively tightly and normally distributed about the mean, ranging from 11.6 to 32.8 ms ($SD=9.8$), thalamic neurons had durations ranging from as short as 3 ms to as long as 78 ms ($SD=18.9$), nearly uniformly distributed from 3 to 50 ms.

Unexpectedly, BMI had opposite effects on the response durations of cortical and thalamic FM-FM neurons, despite the fact that BMI increased the response magnitude for neurons at both anatomical locations. In cortical FM-FM neurons, the response magnitude became larger in the presence of BMI, as expected. However, unexpectedly, the response duration became shorter and response latency became slightly longer and variable. Fig. 7A shows the typical changes in the response of a cortical FM-FM neuron evoked by BMI. The PSTC histogram converts from a decaying exponential (control) to a sigmoid with a steep linear rise upon the application of BMI. For the population as a whole, the response duration decreased from 33 to 22 ms ($P < 0.0001$, Wilcoxon test). The largest individual decrease was 31 ms. The scatter plot in Fig. 7B shows that in about one-half (17/33), the response duration in the presence of BMI was in the range of 10-20 ms, irrespective of the control response duration (mean $\pm$ SEM: 14.41 ± 2.61 , $n=17$). Some neurons in which BMI greatly enhanced the response magnitude showed little reduction in response duration, whereas others showed a marked reduction in response duration with little change in response magnitude. Thus, the extent of this reduction was not correlated with the increase in response magnitude generated by BMI. Furthermore, response duration and response magnitude were not correlated in either control ($r=0.05$) or BMI ($r=0.35$) conditions ($P > 0.05$ in both cases).

In thalamic FM-FM neurons, BMI dramatically increased the duration of the facilitative response (burst of spikes) as much as 75 ms. Fig. 7C shows that BMI had little effect on the initial rise of a PSTC histogram but enhanced the tail portion, due to a "burst" of spikes, which far outlasted the duration of the stimulus (Fig. 7C, solid bars at the bottom left; Butman and Suga 2016). For the population, the duration increased by about 20 ms from 27 to 47 ms ($P < 0.0001$, Wilcoxon test). While only 2 thalamic and 1 cortical neuron had response durations longer than 50 ms prior to a BMI application, over one-third (11/27, 39%) of the thalamic neurons showed such long response duration in the presence of BMI. The scatter plot in Fig. 7D suggests that the BMI-enhanced bursts have a maximum duration of 60-70 ms. Unlike cortical FM-FM neurons, thalamic ones showed a clear correlation between the change in response duration and the change in response magnitude: $r=0.49$ ($P < 0.05$) for control and $r=0.45$ ($P < 0.05$) for BMI. BMI had much less effect on background activity than on the stimulus-driven activity, as can be seen in the first 10 ms of the PSTC histograms and raster plots in Fig. 7, A and C.

3.2.6. Effects of BMI on facilitation index—The facilitation indices (FIs) of individual neurons ranged from about close to 0 to 1. The mean FI across cortical and thalamic FM-FM neurons was similar, 0.63 ± 0.26 (SEM 0.05, $n=32$) in the cortex, and 0.58 ± 0.34 (SEM 0.06, $n=29$) in the thalamus (Fig. 8, bar graphs at left), corresponding to approximately 4-fold increases in the response to the paired stimulus relative to the single components. Although the mean FI across neurons at the two sites is similar, note that FI is more-or-less uniformly distributed between 0.1 and 1.0 in the thalamus, but is mostly larger than 0.5 in the cortex (Fig. 8, bar graphs at center).

BMI had no consistent effect on the FI of individual neurons in either the AC or the MGB (Fig. 8, scatter plots). Although individual neurons showed large changes, these were essentially randomly distributed so that there was no difference in the population means

(Fig. 8, bar graphs at right). In both locations, almost all the points lie in the upper right quadrant of the scatter plot, indicating facilitation in both the control and BMI conditions.

4. DISCUSSION

We found that cortical FM-FM neurons tend to show sharper delay-tuning, longer response duration, and stronger facilitative responses to P-E pairs than do thalamic ones, and that BMI lengthens the response duration of thalamic FM-FM neurons without changing delay-tuning, whereas it shortens the response duration and broadens the delay tuning of cortical ones. We will discuss (1) control of response duration, (2) the functional significance of divergent/convergent thalamo-cortical projections for sculpturing cortical delay tuning by inhibition, and (3) then the hierarchical processing of distance information carried by echo delays.

4.1. Control of response duration

We identified dramatic changes in response magnitude and response duration with an application of BMI to FM-FM neurons. It seems that these response parameters are tightly regulated by GABAergic inhibition. The sustained response of thalamic FM-FM neurons is NMDA receptor-dependent (Butman and Suga 2016). Regulation of response duration is presumably important in determining the persistence of the sensory trace as a neural representation. The response duration of both cortical and thalamic FM-FM neurons far exceeds the stimulus duration. The response duration of cortical neurons is similar to that of thalamic ones. But this similarity breaks down when the inhibitory mechanism is disrupted as cortical response shortens and thalamic one lengthens.

BMI has non-GABAergic effects such as blocking a calcium-dependent potassium current setting the resting membrane potential (Johansson et al. 2001). So the changes in the responses of cortical FM-FM neurons evoked by BMI must depend on its GABAergic and non-GABAergic effects on them. We may speculate the neural mechanism for shortening the response duration of cortical FM-FM neurons evoked by BMI, as follows. BMI's GABAergic effect increases the discharge rate and response duration of a cortical FM-FM neuron. BMI's non-GABAergic effects somehow increase the threshold for spike (action potential) discharges. The cortical neuron has multiple inputs. Its threshold for spike discharges is higher than single EPSPs, so that multiple EPSPs must overlap each other for spike discharges. A spike discharge rate is usually high within the initial 10-15 ms of facilitative response. It gradually reduces thereafter. If BMI increases the threshold, the trailing portion of the response would be eliminated. That is, the response duration would be shortened, as observed in the responses of the BMI-applied cortical FM-FM neurons.

4.2. Thalamo-cortical divergent/convergent projections and cortical delay tuning

As a results of divergent/convergent projections, multiple thalamic FM-FM neurons with slightly different delay tuning curves overlapping each other project to a single cortical FM-FM neuron. Therefore, without inhibition, the cortical neuron responds strongly to a P-E pair and broadly delay-tuned, as shown by BMI-applied cortical neurons*. By inhibition, however, the delay-tuning curve is sharpened and the response is reduced. The divergent/

convergent thalamo-cortical projection and cortical inhibition must play an essential role in plasticity for the adjustment and improvement of information processing according to behaviorally meaningful sounds. [*BMI has non-GABAergic side-effects such as an effect on calcium-dependent potassium channels (Johansson et al. 2001), whereas gabazine is highly specific for GABAergic receptors (Michaud et al. 1986). In the auditory cortex of Mongolian gerbils, BMI increases the response magnitude and duration and often broadens frequency tuning, whereas gabazine has little effects on the response duration and frequency tuning, although it increases response magnitude (Kurt et al. 2006). The effects of BMI observed in Mongolian gerbils show similarity and dissimilarity to those observed in the FF area of mustached bats. The effects of gabazine on FM-FM neurons remain to be studied.]

In the mustached bat, delay- and frequency-tuning curves systematically change for the reorganization of the delay or frequency map according to the specific relationship in BD (Xiao and Suga 2004; Tang et al. 2007; Tang and Suga 2008, 2009) or in best frequency (Xiao and Suga 2005; Suga et al. 2010) between recorded and electrically stimulated cortical neurons. In the auditory cortex of the big brown bat (*Eptesicus fuscus*) and rodents, frequency-tuning curves systematically change for the reorganization of the frequency map according to the relationship in best frequency between recorded and electrically stimulated neurons (Chowdhury and Suga 2000; Ma and Suga 2001, 2004; Suga et al. 2010; Yan and Zhang 2005; Sakai and Suga 2001, 2002) or between the best frequencies of recorded neurons and the frequency of a conditioning tone for auditory fear conditioning (Gao and Suga 2000; Ji et al. 2001, 2005; Ji and Suga 2003; Weinberg 1998, 2007, 2011). The changes in tuning curves are based on focused positive feedback associated with lateral inhibition (Yan and Suga 1996b; Suga et al. 2002, 2010). The divergent/convergent thalamo-cortical projections and inhibition for the selection of tuning must be part of the mechanisms for the cortical reorganization for optimizing the processing of behaviorally relevant sounds.

In the auditory cortices of pallid bats or rats, it has been demonstrated that intracortical inhibition sharpens neural tuning in different auditory dimensions: auditory space (Razak and Fuzessary 2010), intensity (Wu et al. 2006; Tang et al. 2007), direction of frequency sweep (Zhang et al. 2003) and Phasic responses* to temporal patterns (Wehr and Zador 2003). [*Constant-latency-phasic on-responding neurons in the inferior colliculus of little brown bats are produced by balanced inhibition (Suga 1971).] The mammalian auditory cortex contains different types of inhibitory inter-neurons that play different roles in modulating cortical activities (Wu et al. 2011; Li et al. 2015). So, the role of intra-cortical inhibition in auditory information processing and plasticity remains to be further studied.

4.3. Hierarchical processing of distance information

The processing of distance information by delay-tuned (FM-FM) neurons is hierarchical, as briefly described in the introduction. Different from collicular FM-FM neurons (Portfors and Wenstrup 1999, 2001; Macias et al. 2012), thalamic and cortical FM-FM neurons show: (1) weak or no responses to individual FM sounds, but strong responses to paired FM sounds (Taniguchi et al. 1986; Olsen and Suga 1991; Hagemann 2011); (2) larger facilitation indexes when calculated with the data obtained “at the best amplitudes for facilitation” (Yan and Suga 1996a); (3) dramatically lower thresholds of facilitative responses to FM-FM

stimuli than those of responses to single FM stimuli (Suga et al. 1983; Olsen and Suga 1991); (4) the NMDA-receptor-dependent burst of discharges which functions not only to increase the selectivity to pulse-echo stimuli, but also to produce a short sustained image rather than a brief stroboscopic one (Butman and Suga 2016); (5) poor level-tolerance (Macias et al. 2012) and sharper tuning to a specific combination of echo delay and echo amplitude (O'Neill and Suga 1982; Suga et al. 1983); (6) delay tuning curves tilted toward long echo delays, suited for target tracking (Hagemann et al. 2011; Hechavarria et al. 2013). The amount of the tilt may be more prominent in the cortex than in the thalamus (Olsen and Suga 1991); and (7) Cortical FM-FM neurons are clustered in the three areas: FF, DF and VF. FM-FM neurons in the FF area tend to show sharper delay-tuning, longer response duration, and stronger response to paired sounds than do thalamic ones. Thalamic and cortical FM-FM neurons are dramatically different from each other in terms of the effect of BMI (our current paper).

The FF, DF and VF areas mutually interact through cortico-cortical projections consisting of positive feedback associated with lateral inhibition for improvement and adjustment of delay tuning of cortical FM-FM neurons (Xiao and Suga 2004; Tang et al. 2007; Tang and Suga 2008, 2009). Such interactions may not present in the inferior colliculus and thalamus. There have been the multiple findings indicating that cortical FM-FM neurons are different from collicular ones. (1) The cortex contains tracking (O'Neill and Suga 1979, 1982) and multi-combination-sensitive neurons (Suga et al. 1983; Misawa and Suga 2001). (2) Cortical FM₁ and FM_n responses both are inhibited by FM₁-FM_n paired stimuli, if FM_n delay from FM₁ is shorter than a BD (Suga et al. 1983; Edamatsu and Suga 1993). (3) Most of cortical FM-FM neurons have a facilitative delay-tuning curve sandwiched between inhibitory regions (Edamatsu and Suga 1993). (4) Delay-widths measured with double echoes are narrower than those measured with a single echo, and the amount of narrowing is larger in the VF area than in the FF area (Edamatsu and Suga 1993). (5) The facilitative responses of neurons in the VF area adapt quickly for repetitive stimuli with a FM₁-FM_n pair (Edamatsu and Suga 1993). The differences in response properties among the inferior colliculus, thalamus and cortex indicate the hierarchical processing of distance information.

Portfors and Wenstrup (1999, 2004) found that the facilitation index based on the response “at 10 dB above minimum threshold (MT)*” is not different between collicular and thalamic FM-FM neurons, unlike the data obtained by Yan and Suga (1996a) and Olsen and Suga (1991). Wenstrup and Portfors (2011) concluded that the response properties of collicular FM-FM neurons are similar to those of thalamic and cortical ones, indicating no hierarchical signal processing. Yan and Suga (1996a), Olsen and Suga (1991), and Suga and Horikawa (1986) measured the delay-widths of the delay tuning curves “at the best amplitudes” of given neurons to express the sharpness of the curves and calculated the facilitation indexes with the responses at the best amplitudes, because most FM-FM neurons are tuned to a specific echo amplitude as well as a specific echo delay. Facilitative response is a non-linear phenomenon, so that the different measures would result the different conclusions.

Wenstrup and Portfors (2011) hypothesized that a hierarchical change from the inferior colliculus through the auditory cortex is the development of a delay map or axis: no map in the inferior colliculus (Portfors and Wenstrup 2001), emergence of the map in the thalamus

(Wenstrup 1999), and establishment of the map in the auditory cortex (Suga and O'Neill 1979). However, an alternative hypothesis should be considered. That is, the delay map exists in the inferior colliculus (Yan and Suga 1996a; Suga 2015).

*[The sharpness of the tuning curve of an auditory neuron expressed by the tuning-width at 10 dB above MT or $Q_{10\text{dB}}$ originates from Kiang et al (1965) who studied frequency-tuning curves of cat's primary auditory neurons. They chose a tuning-width at 10 dB above MT "for convenience" without any consideration of whether it is the best stimulus level to characterize the sharpness of neural tuning curves. In the central auditory system, frequency-tuning curves as well as delay-tuning curves are not a simple triangular shape. Therefore, the measure at 10 dB above MT is not necessarily adequate to express the sharpness of neural tuning curves (Suga 1995).]

Summary

(1) The functional role of inhibition in delay tuning of "delay-tuned combination-sensitive (FM-FM)" neurons in both the auditory cortex and thalamus was studied with multi-barreled carbon-fiber microelectrodes, enabling the iontophoretic applications of inhibitory transmitter gamma-aminobutyric acid (GABA) and its antagonist at the GABA-A receptor, bicuculline methiodide (BMI).

(2) Delay tuning, response duration, and facilitation index respectively tend to be sharper, longer, and larger for cortical FM-FM neurons than for thalamic ones. However, those differences are statistically insignificant. Cortical and thalamic FM-FM neurons show remarkable differences from each other in the changes in facilitative response evoked by BMI that eliminates inhibition mediated by GABA-A receptors.

(3) In thalamic FM-FM neurons, BMI does not substantially change both the BD and the width of a delay-tuning curve, despite two to twelve fold increases in response magnitude. Inhibitory delay lines responsible for delay tuning are apparently located peripheral to the thalamus. In cortical FM-FM neurons, BMI also does not change the BD, but noticeably widens the delay-tuning curve. The widening is more than 20% in one-half of the cortical neurons, with the largest widening of 2-fold (100%).

(4) Delay-dependent facilitative responses were examined in terms of both response magnitude (number of spikes/stimulus) and response probability (response/stimulus). In both thalamic and cortical FM-FM neurons, the majority of delay tuning can be accounted for by the delay-dependent response probability, with a further 20-30% sharpening resulting from a delay-dependent burst response. In thalamic FM-FM neurons, BMI little affects response probability, despite prominent increase in response magnitude. In cortical FM-FM neurons, BMI broadens delay tuning by increasing the response probability to non-optimal stimuli, but the response magnitude (burst of discharges) is still responsible for sharpening the tuning.

(5) For BMI, thalamic FM-FM neurons greatly increase response magnitude with an increase of the response duration to as long as 100 ms. On the other hand, cortical ones increase response magnitude with a slight decrease in response duration. This BMI-

shortened response duration is slightly shorter than the thalamic response duration in the control condition.

(6) BMI increases not only the response to a pulse-echo pair, but also pulse alone and echo alone, so that it does not consistently alter the facilitation index in both thalamic and cortical FM-FM neurons.

(7) We conclude that in the thalamus, GABAergic inhibition operates as a feedback system to regulate the gain of the response, but it has little role in modulating delay tuning, and that in the cortex, GABAergic inhibition modulates delay tuning by regulating divergent/convergent thalamo-cortical inputs to FM-FM neurons by intra-cortical inhibition.

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Abbreviations

AC	auditory cortex
BMI	bicuculline methiodide
CF₁₋₄	1 st - 4 th harmonics of a constant frequency component
DF	dorsal fringe
DW_{r p}	width at half-maximum of a delay-response magnitude or probability curve, respectively
FF	frequency modulation-frequency modulation
FI	facilitation index
FM₁₋₄	1 st - 4 th harmonics of the frequency modulated component of a bio-sonar pulse
FM_n	2 nd - 4 th harmonics of the FM component of an echo
FM-FM	a pair of FM sounds to which delay-tuned neurons show a facilitative response
GABA	gamma-aminobutyric acid
MGB	medial geniculate body
MT	minimum threshold
NMDA	N-methyl-D-aspartate
PSTC histogram	post-stimulus-time cumulative histogram
VF	ventral fringe

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Highlights:

The facilitative responses of thalamic FM-FM neurons are glutamate-dependent.

The fast and slow components of those responses are non-NMDA- and NMDA-dependent.

The slow component (burst of discharges) produces sharp delay tuning in the thalamus.

Inhibition modulates the duration of the slow component in thalamic FM-FM neurons.

Inhibition modulates the sharpness of delay tuning in cortical FM-FM neurons.

Fig. 1. Effects of bicuculline methiodide (BMI) and gamma-aminobutyric acid (GABA) on the delay-tuned facilitative responses of a cortical and a thalamic FM-FM neuron to delay scans. Raster dot (A,C) and post-stimulus time (PST) histograms (B,D) demonstrating the facilitative responses of a cortical (AC) and a thalamic (MGB) FM₁-FM₄ neuron with BDs of 3.0 ms and 3.5 ms respectively. 1: Neither neuron responded to pulse (P) or echo (E) alone, but exhibited facilitative responses consisting of fast and slow components. 2: BMI increased the response magnitude and broadened cortical delay tuning, but did not change thalamic delay tuning. The slow component of the facilitative response was relatively reduced in the cortical neuron, but increased in the thalamic neuron. 4: GABA reduced the responses of the cortical and thalamic neurons to P-E pairs. 3 and 5: Recovery after a BMI or a GABA application. P and E were the best amplitudes of the neurons for evoking their facilitative responses: FM₁ at 80 dB SPL and FM₄ at 65 dB SPL for A and FM₁ at 65 dB SPL and FM₄ at 65 dB SPL for C. Raster resolution: 0.4 ms. Histogram bin width: 2 ms. Y-scale: 25 spikes/bin. X-tics: 100 ms.

Fig. 2.

Changes in facilitative response and delay tuning of two cortical FM-FM neurons evoked by BMI.

(A) and (C) BMI (25 nA in A and 20 nA in C) increased facilitative response and broadened delay tuning of cortical FM-FM neurons without changing their BD: 3.0 ms for A and 5.5 ms for C. (B) and (D) The peak normalized delay response curves in A and C demonstrate the reversible broadening of the curves by BMI. Pulse (P) and echo (E) stimuli at best amplitudes for facilitation were respectively FM₁ at 70 dB SPL and FM₂ at 60 dB SPL in A; and FM₁ at 55 dB SPL and FM₄ at 40 dB SPL in C. Data points for control, BMI and recovery indicate means and standard errors for 200, 150 and 200 stimuli in A; and 60, 50 and 100 stimuli in C. BMI: bicuculline methiodide; Con.: control; Rec.: recovery.

Fig. 3.

Effects of BMI on the facilitative response and delay tuning of two thalamic FM-FM neurons.

(A) and (C) BMI (10 nA in A and 40 nA in C) increased the facilitative responses of thalamic FM-FM neurons without changing delay tuning. For these neurons BDs were either 0.8 or 7.5 ms. (B) and (D) The peak normalized response curves in A and B demonstrate no broadening of tuning in response to BMI. The pulse and echo stimuli at best amplitudes for facilitation were respectively FM₁ at 70 dB SPL and FM₂ at 55 dB SPL for A; and FM₁ at 70 dB SPL and FM₂ at 45 dB SPL for C, respectively. Data points for control, BMI and recovery indicate means and standard errors for 200, 150 and 200 stimuli in A; and 100, 75 and 75 stimuli in C.

Fig. 4.

Effects of BMI on the widths of delay tuning curves, the response magnitudes, and BDs of cortical and thalamic FM-FM neurons.

(A) and (B) The fractional change in delay response width (DWr) relative to control values is plotted against the fractional change in response magnitude (number of spikes/stimulus) at the BDs and best amplitudes of individual neurons. Data points are normalized values for BMI (BMI/control, filled circles) and recovery (recovery/control, small dots). The horizontal dashed lines indicate $\pm 20\%$ changes from control values of DWr. BMI increased the response magnitude for virtually all cortical (A) and thalamic (B) FM-FM neurons. The DWr increased by over 20% in many cortical, but few thalamic neurons. Large and small ellipses indicate the 95% confidence limits for the population means for BMI and recovery, respectively. Data was computed from 30-200 consecutive stimuli for control, BMI and

recovery periods. **(C)** and **(D)** BMI did not significantly alter the BDs of cortical and thalamic FM-FM neurons (B and D: Butman and Suga 2016).

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Fig. 5.

Effects of BMI on two different measures of the neural responses of a single cortical FM-FM neuron to pulse-echo pairs: probability of response (i.e., response/stimulus) and peak normalized response magnitude (i.e., number of spikes/stimulus).

(A) and (B) Probability of response (A) and response magnitude (B) are plotted as a function of echo delays for control (dashed lines with open symbols) and BMI (undashed lines with filled symbols) conditions. (C) Delay tuning of the response magnitude is sharper than that of the probability of response. (D) This sharpening becomes more prominent in the BMI applied condition. Responses were defined as at least 1 action potential within a 50 ms window following the stimulus, and probability was calculated from 100 consecutive stimuli. Pulse and echo stimuli were respectively FM₁ at 75 dB SPL and FM₃ at 60 dB SPL, best amplitudes for facilitation. Mag.: magnitude of response; Pro.: probability of response.

Fig. 6.

Relationship between the widths of delay-response magnitude curve (DWr) and the delay-response probability curves (DWp) of cortical and thalamic FM-FM neurons, and the effects of BMI on DWr and DWp.

(A) and (C) The DWr and DWp were measured at 50% of the maximum response at the best amplitudes and BDs of 27 cortical and 24 thalamic FM-FM neurons. DWr were narrower than DWp in both the cortex and thalamus. (B) and (D) To facilitate comparisons across neurons with different response widths, DWr and DWp in each condition (control, BMI and recovery) were normalized by dividing by the control DWp for each neuron (hence, the absence of error bars for control DWp). BMI resulted in significant increases in both nDWr and nDWp in the cortex ("n" stands for "normalized". B: nDWr $P<0.002$, nDWp $P<0.001$ Wilcoxon matched-pairs signed ranks test), but not in the thalamus (D: nDWr $P>0.05$, nDWp $P>0.5$ Wilcoxon matched-pairs signed ranks test). Note that BMI increased nDWp to a relatively greater extent (+49%) than nDWr (+30%), (C and D: Butman and Suga 2016).

Fig. 7.

Effects of BMI on the durations of facilitative responses to pulse-echo stimuli at the BDs and best amplitudes of cortical and thalamic FM-FM neurons.

(A) and (C) Response of a cortical and a thalamic FM-FM neuron to a P-E pair at its BD (3.0 or 6.0 ms) was differently affected by BMI (40 or 60 nA). The response of the cortical neuron was more vigorous and terminated more abruptly than normal, whereas that of the thalamic one was lengthened in duration (2). The PSTC histograms in “3” are based on the raster dots in “1” and “2”. The vertical lines in “3” indicate 90% of the PSTC histograms. P and E were respectively FM₁ at 70 dB SPL and FM₄ at 60 dB SPL for A; and FM₁ at 65 dB SPL and FM₂ at 60 dB SPL for C. P and E stimuli are expressed by the white and black rectangles, respectively. E-delay from P is 3.0 ms in A and 6.0 ms in C.” (B) and (D) Effects of BMI on the durations of facilitative responses of 33 cortical and 27 thalamic FM-FM neurons. The bar graph indicates the means and standard errors of the response durations prior to, during and after a BMI application (C and D: Butman and Suga 2016).

Fig. 8.

No effect of BMI on the facilitation indices of cortical and thalamic FM-FM neurons. Facilitation index (FI) was defined by $FI = (F - S) / (F + S)$, where F is the response to P-E pair at BD and best amplitude; and S is the sum of the responses to P alone and E alone (corrected for background discharges). Points in the upper right quadrant indicate facilitation (response to P-E pair greater than the sum of pulse alone and echo alone responses). The distributions of FIs in the control and BMI conditions are also shown by the white (center) and black (right) bar graphs. The population of neurons in both the cortex (A) and thalamus (B) showed little net change with the application of BMI (bar graphs at left, population distributions), despite large individual changes (scatter plots at center).