Neural circuits for selective auditory filtering

Aims and key research questions

To facilitate sensory processing in complex environments, the brain can selectively filter auditory input to enhance neural responses to relevant sounds and suppress responses to background distractors. Because different sounds may be relevant at different times, this filtering must be dynamic such that the brain’s internal representation of the same auditory scene can vary depending on behavioral demands. Neural correlates of selective filtering have been observed in auditory cortex (AC), but the underlying circuitry has not yet been identified.

A synthesis of existing results and our preliminary data suggests that selective auditory filtering arises through interactions between AC and two thalamic structures: the medial geniculate body (MGB), which sends direct excitatory input to AC and receives direct excitatory feedback from AC, and the thalamic reticular nucleus (TRN), which relays indirect inhibitory feedback from AC to MGB (figure 1). Based on this hypothesis, we propose a program of research to answer three key questions:

Q1: Are selective spectral and temporal filtering evident in the auditory thalamus?
We predict that selective filtering similar to that observed in AC will also be evident in MGB and TRN, with both spectral filtering that alters frequency tuning and temporal filtering that aligns ongoing fluctuations in excitability with the expected timing of sound onsets (figure 2).

Q2: How do thalamocortical interactions contribute to spectral and temporal filtering?
We hypothesize that filtering arises through thalamocortical interactions; MGB responses to relevant sounds are enhanced by direct excitatory feedback from AC, while MGB responses to distractors are suppressed by indirect inhibitory feedback from AC via TRN.

Q3: How does attention modulate spectral and temporal filtering?
We expect that spectral and temporal filtering can enhance responses to an isolated sound source even during passive listening, while selective enhancement of responses to one of several sound sources requires attention to specific acoustic features.

To answer these key questions, we will carry out experiments to record and manipulate thalamic and cortical activity during passive listening and the performance an auditory task. We will use mice as an animal model to take advantage of tools for selective manipulation of thalamocortical interactions that are not available for other species.

Motivation

While several studies have reported neural correlates of selective auditory filtering, little is known about how this filtering is implemented by the circuitry of the auditory pathway. This lack of knowledge limits our ability to understand the higher level functions that underlie perception and cognition, and also makes it difficult to improve the ability of hearing assistance technologies to operate in complex listening conditions. The function of TRN, in particular, is an open question. While the basic properties of AC and, to a lesser extent, MGB have been well characterized, there have been very few studies of TRN. Our preliminary data demonstrate that TRN can strongly modulate MGB and, thus, AC, which suggests that elucidating the role of TRN could lead to major advances in our understanding of auditory processing.

While our research questions are focused on audition, it is likely that our results will also provide insight into the mechanisms that facilitate selective filtering in other modalities. In fact, the
contribution of thalamocortical interactions to selective filtering in other modalities has already been established at a phenomenological level\textsuperscript{1,2}, but a detailed understanding of the underlying circuitry has not yet been achieved. It is also clear that the importance of thalamocortical interactions goes far beyond sensory processing; there is strong evidence implicating thalamocortical dysfunction in a number of pathologies including neurogenic pain, tinnitus, Parkinson’s disease, depression, autism, and schizophrenia\textsuperscript{3–6}. By characterizing the mechanisms that govern healthy thalamocortical interactions, the results of our proposed research may also provide insight into the nature of these pathologies and facilitate the development of improved therapies.

Background

Numerous psychophysical studies have shown that attention to specific acoustic features can aid in the processing of complex auditory scenes\textsuperscript{7}, and neural correlates of selective auditory filtering have been observed in AC\textsuperscript{8} with both spectral and temporal components. Spectral filtering alters frequency tuning such that AC responses to frequencies near that of a target sound are enhanced, while responses to other frequencies are suppressed\textsuperscript{9–11}. Temporal filtering enhances AC responses to sounds that occur at predictable times and suppresses responses to distractors at other times\textsuperscript{12}. This temporal filtering improves perception in a number of contexts\textsuperscript{13–17} and appears to arise from the entrainment of ongoing fluctuations in excitability such that periods of high excitability coincide with the expected onset of each target sound\textsuperscript{18}.

While spectral and temporal filtering can operate independently of one another, they also have the potential to interact. For example, the presentation of a rhythmic tone can sharpen frequency tuning by eliciting counterphase entrainment across different cortical columns such that the onset of each tone coincides with the high excitability phase of neurons that are tuned to the tone frequency and the low excitability phase of neurons tuned to other frequencies\textsuperscript{12}. Many forms of selective filtering do not appear to require attention; even during passive listening, spectral and temporal filtering can be activated by an isolated sound source to enhance the neural representation of that source. Previous studies have observed selective filtering in passively listening primates\textsuperscript{19}, and our preliminary data demonstrate that similar phenomena are also observable in mice (figure 3). Attention is, of course, required to direct the focus of selective filtering in a complex scene with multiple salient sound sources. Because the circuitry that underlies selective filtering has not yet been identified, the precise nature of the interactions between passive filtering and attention is not yet known.

We hypothesize that selective spectral and temporal filtering are controlled by interactions between AC, MGB, and TRN that shape frequency tuning and synchronize ongoing fluctuations in excitability. The potential of the thalamus to control the flow of sensory information has long been recognized\textsuperscript{20}, but experimental studies have only recently begun to explore the role of the thalamus, and TRN in particular, during active sensory processing\textsuperscript{21–26}. Although there have been few studies of thalamic activity during active listening, there is clear evidence that thalamic responses are modulated by attention, and that this modulation impacts perception\textsuperscript{27–30}.

The circuitry that connects AC, MGB and TRN provides a natural substrate for selective filtering\textsuperscript{31–38}. The ventral division of MGB receives extensive feedback from layer 6 (L6) of primary AC, both directly and via TRN. The direct excitatory feedback from a given L6 corticothalamic (CT) neuron targets only a small number of MGB neurons with similar preferred frequencies, while the indirect inhibitory feedback is much less specific. Thus, an AC neuron can manipulate its MGB input in a manner that promotes its own excitation, with ‘egocentric’ feedback that excites similarly-tuned MGB neurons and suppresses others, increasing the excitatory drive to its own cortical column, while
decreasing the drive to other columns (and, thus, the strength of the lateral inhibition it receives from those columns). While the role of corticothalamic feedback in spectral filtering during active listening has not yet been investigated, experiments in anesthetized animals have shown that activation\textsuperscript{39} or inactivation\textsuperscript{40,41} of AC can change the frequency tuning of MGB neurons. Our preliminary data further demonstrate that manipulation of activity in AC can shape frequency tuning in TRN, and that manipulation of activity in TRN can shape frequency tuning in MGB (figures 4B,D).

The direct and indirect pathways from AC to MGB also have different temporal dynamics\textsuperscript{42,43}; the activation of direct cortical feedback results in transient excitation in MGB, while the activation of indirect feedback via TRN results in prolonged inhibition. The combination of these dynamics and the intrinsic properties of thalamic neurons can facilitate the filtering of sensory information\textsuperscript{44,45} and the synchronization of ongoing fluctuations in excitability in AC and MGB\textsuperscript{46–48}. Because these fluctuations can be entrained by rhythmic sounds\textsuperscript{49}, this synchronization could serve to maximize both MGB and AC responses to expected sound onsets. Our preliminary data demonstrate that manipulation of activity in AC or TRN can indeed strongly modulate temporal filtering (figure 5).

Research approaches

Our proposed research is centered on recording and manipulating thalamic and cortical neural activity in mice that are passively listening or performing an auditory task. This section provides an overview of our methodology followed by detailed descriptions of several representative example experiments.

Sounds and task

We have designed sounds to probe selective filtering during both passive listening and during the performance of an auditory task (figure 6). The task will be performed in a three-port arena and all trials will have a standard two-alternative forced choice (2AFC) structure\textsuperscript{21,28,50,51}. The animal will initiate a trial by poking in the central port and will remain there during the presentation of cue sounds and a target sound before making a decision to go left or right to receive a reward. The cue sounds will be either tones or noise with different spectral and temporal properties, and the target sound will be either an upward-sweeping or downward-sweeping frequency-modulated (FM) tone, the starting frequency or onset time of which may or may not be predictable from the cue sounds. During some sessions, ongoing distractor tones will also be presented. The nature of the task will depend on the cues contained in the cue sounds and the presence or absence of ongoing distractor tones.

Neural recordings

We will make extracellular recordings in AC, MGB and/or TRN of awake mice using chronically implanted multi-tetrode arrays. The position and geometry of the arrays will allow us to record from neurons with different preferred frequencies, and from L4 and L6 in AC. We will record wideband signals and extract local field potentials (LFPs), multi-unit activity (MUA), and single-unit spiking. Animals will be head-fixed during passive listening sessions to ensure that sounds are presented from the same location as during task performance.

Data analysis

Our proposed experiments involve a number of specific comparisons across different conditions, but many of the measures that we will use in our analysis will be the same for all experiments.

Spectral filtering: We will measure frequency tuning from neural responses (MUA and single-unit spiking) to the last tones in each cue sound (where applicable) and/or the target tone, and we will
assess the dependence of frequency tuning on the frequency content of the cue sounds and distractor tones (where applicable).

Temporal filtering: We will measure the strength of neural responses (MUA and single-unit spiking) to the target tone, and we will assess its dependence on the rhythmicity of the cue sounds. To relate any observed temporal filtering to ongoing fluctuations in excitability, we will measure the phase of the LFP at the frequency of the cue sound rhythm, quantify entrainment (phase consistency across trials) and alignment (phase consistency between AC, MGB and/or TRN, or between recording sites within the same structure that have different preferred frequencies), and we will assess the dependence of the target response strength on these quantities.

Neural performance: We will train a decoder to classify neural responses (MUA and spiking from populations of single units) as elicited by either an upward-sweeping or a downward-sweeping target tone and measure the percentage of correct classifications.

Psychophysical performance: In all experiments involving the performance of a task, we will measure the percentage of correct choices and reaction time.

Optogenetic manipulation of corticothalamic interactions

Decoupling direct and indirect feedback from AC to MGB is complicated by the fact that the two pathways may include collaterals from the same L6 CT neurons. However, the indirect pathway from AC to MGB can be manipulated at the level of the TRN.

To activate or suppress all corticothalamic feedback: We will use Ntsr1-Cre mice in which Cre is expressed selectively in L6 CT neurons (figure 4A). This mouse line has already been widely used in studies of corticothalamic interactions in other modalities. To manipulate L6 CT activity on a trial-by-trial basis, we will inject a Cre-dependent virus containing a light-driven neural activator (Chronos) or silencer (Jaws) into L6 of AC and deliver light through an optical fiber mounted over the injection site. The precise location and timing of the natural, sound-driven activation within L6 will depend on the properties of the sounds presented; the neural silencer will allow us to eliminate this activity altogether, while the neural activator will allow us to eliminate its specificity by activating L6 CT neurons across most of AC.

To activate or suppress feedback from TRN to MGB: We will use VGAT-Cre mice in which Cre is expressed specifically in GABAergic neurons (figure 4C). Since the rodent MGB contains only excitatory thalamocortical relay cells, the only GABAergic auditory neurons in the thalamus are those in the TRN. This mouse line has already been used successfully to manipulate TRN activity in other modalities. To manipulate TRN activity on a trial-by-trial basis, we will use the same optogenetic approaches as described above.

Detailed descriptions of example experiments

Space limitations prevent us from describing all of our planned experiments in detail, but we provide representative example experiments related to each of our specific research questions below.

Q1: Are selective spectral and temporal filtering evident in the auditory thalamus?

To answer this question, we will compare thalamic and cortical activity during the presentation of different sounds in passively listening animals.
**Example spectral filtering experiment:** Compare spectral filtering in AC and MGB elicited by arrhythmic tones with either random or fixed frequency (sound 1 vs. sound 3).

**Expected results:** We expect to observe spectral filtering in MGB that is comparable to that in AC. We predict that frequency tuning in MGB will be selectively altered by tones with fixed frequency due to a buildup of egocentric corticothalamic feedback such that responses to targets that are similar in frequency to the cue tones will be enhanced and responses to targets that differ in frequency from the cue tones will be suppressed. As a result of this selective filtering, decoding of responses to the target tone will be enhanced.

**Example spectrotemporal filtering experiment:** Compare spectral filtering in AC and MGB elicited by arrhythmic or rhythmic tones with fixed frequency (sound 3 vs. sound 5).

**Expected results:** We expect to observe that spectral filtering is enhanced by the temporal cues in the rhythmic tones. We predict that the rhythmic tones will promote counterphase entrainment of oscillations across regions with different preferred frequencies that serve to reinforce the egocentric feedback elicited by the arrhythmic tones. The enhanced spectral filtering driven by the rhythmic tones will be strongest at the times of expected target onsets, and weaker, or even reversed, at times in between.

**Q2: How do thalamocortical interactions contribute to selective spectral and temporal filtering?**

To answer this question, we will compare thalamic and cortical activity in passively listening animals while using optogenetic techniques to manipulate the activity in specific pathways.

**Example temporal filtering experiment:** Compare temporal filtering elicited by either arrhythmic or rhythmic noise (sound 2 vs. sound 4) during passive listening with and without suppression or sustained activation of thalamocortical feedback.

**Expected results:** We expect that target responses and oscillatory entrainment will be stronger during the presentation of rhythmic noise. We predict that both suppression and sustained activation of corticothalamic feedback will reduce the degree of entrainment, as well as the alignment of oscillations across MGB and L4 of AC, and, thus, also reduce target response strength and decoding accuracy. The reduction in response strength will be strongest in MGB, but also evident in L4 of AC due to the reduced thalamocortical input.

**Q3: How does attention modulate spectral and temporal filtering?**

To answer this question, we will compare thalamic and cortical activity in animals that are passively listening or performing an auditory task. We will also use optogenetic techniques to identify contribution of specific pathways to attentional modulation.

**Example spectral filtering experiment:** Compare spectral filtering elicited by arrhythmic tones with fixed frequency with and without ongoing distractor tones (sound 3) during passive listening and task performance.

**Expected results:** We expect that frequency tuning will be similar during passive listening and task performance in the absence of distractor tones, as the isolated sound source will activate egocentric feedback even in the absence of attention. In the presence of distractor tones, however, we expect that there will be large differences in tuning during passive listening and task performance, with selective spectral filtering evident only during task performance (passive mechanisms will be engaged by both the cue sounds at the target frequency and the distractors, so sharpened tuning will only be evident once attention is focused toward the relevant sounds and away from the distractors).
Outlook

At the end of the proposed study, we will have made several major advances in our understanding of how the brain processes complex auditory scenes, including (1) characterizing selective filtering in the auditory thalamus and its contribution to selective filtering in cortex, (2) identifying the contributions of direct and indirect corticothalamic feedback to selective filtering, and (3) differentiating the aspects of selective filtering that require attention from those which are already present during passive listening. These results will provide the basis for a number of subsequent studies to investigate (1) how thalamocortical interactions contribute to spatial filtering and attention, (2) how the neural circuits for selective filtering are altered in conditions in which the processing of complex auditory scenes is compromised (i.e. age-related hearing loss), and (3) how thalamocortical interactions contribute to cross-modal filtering and attention.
References


The ventral division of MGB (MGBv) relays ascending input from the central nucleus of the inferior colliculus (ICc) to the primary auditory cortical fields A1 and AAF. MGBv receives extensive feedback from AC, both directly and via the thalamic reticular nucleus (TRN). The direct excitatory feedback from a given cortical neuron targets only a small number of MGBv neurons with similar preferred frequencies, while the indirect inhibitory feedback is much less specific, providing a substrate for spectral filtering via center-surround antagonism. The direct and indirect pathways also have different temporal dynamics which promote oscillation and entrainment of fluctuations in excitability.

Selective filtering can facilitate auditory processing by enhancing the representation of a target sound relative to background distractors. A periodic target sound embedded in background noise is represented as a spectrogram showing the power as a function of frequency over time. We hypothesize that spectral filtering, which increases power at the target frequency and decreases power at other frequencies, is implemented via egocentric excitatory and inhibitory feedback from cortex to thalamus. We hypothesize that temporal filtering, which increases power at expected target onset times and decreases power at other times, also arises through corticothalamic feedback via synchronous entrainment of ongoing fluctuations in excitability. After spectral and temporal filtering, the representation of the target relative to the background is enhanced.

(A) We implanted a multi-tetrode array into AC and recorded neural activity while mice moved freely on a small platform. We first presented 50 ms noise bursts to determine the sound intensity that evoked a weak response. We then presented periodic sounds at this intensity to examine the entrainment on ongoing slow fluctuations in excitability. (B) The LFP in the delta range (1-4 Hz) was similar during the presentation of periodic noise or tones at best frequency (BF), with the falling phase (indicating increasing excitability) beginning before sound onset. During the presentation of a non-BF tone, however, sound onset coincided with the rising phase of the LFP (indicating decreasing excitability). This suggests that the same counterphase entrainment of fluctuations in excitability that underlie selective spectral and temporal filtering in primates is also evident in mice.

(A) To manipulate corticothalamic feedback, we will inject viruses containing neural activators or silencers into AC of Ntsr1-Cre mice, which express Cre selectively in L6 CT cells. (B) We activated Jaws in AC via red light to suppress corticothalamic feedback while recording evoked responses to sound in TRN. During suppression of AC, TRN responses to tones were suppressed and had sharper frequency tuning (reflecting the remaining direct excitation of TRN by MGB, see figure 1). TRN spiking reflected intrinsic properties similar to those that have been well described in MGB, such as burst spiking. (C) To manipulate activity in TRN, we will inject viruses containing neural activators or silencers into the thalamus of VGAT-Cre mice. Because mice do not have interneurons in MGB, the only GABAergic auditory neurons in the thalamus are those in TRN. (D) We activated ChR2 in TRN via blue light to increase inhibition in MGB while recording evoked responses to sound. During activation of TRN, MGB responses to tones were suppressed, but this effect was limited to the sustained portion of the response.
We have designed sounds to probe selective filtering during both passive listening and during the performance of an auditory task. The task will be performed in a three-port arena and all trials will have a standard 2AFC structure. The animal will initiate a trial by poking in the central port and will remain there during the presentation of cue sounds and a target sound before making a decision to go left or right to receive a reward. The cue sounds will be either tones or noise with different spectral and temporal properties, and the target sound will be either an upward-sweeping or downward-sweeping frequency-modulated (FM) tone, the starting frequency or onset time of which may or may not be predictable from the cue sounds. During some sessions, ongoing distractor tones will also be presented. The speed of the FM will be chosen such that the task is relatively difficult with cue sounds 1 and 2 (which contain no spectral or temporal cues), and fixed at the same value for cue sounds 3, 4, and 5 (which contain spectral and/or temporal cues), allowing us to observe the degree to which selective filtering improves performance.