Timing is everything: corticothalamic mechanisms for active listening

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ABSTRACT:
In this issue of *Neuron*, Guo et al. (2017) describe a layer 6 corticothalamic circuit that alternately drives cortical states favoring either sensory detection or discrimination. They also identify a neural mechanism that resets the phase of low-frequency cortical oscillations.

MAIN TEXT:

A muffled, barely audible sound in the quiet concert hall catches your attention. Uh oh is that your mobile phone? You listen again as the faint ring tone recurs, and then you relax; moments later, another audience member three rows away fumbles urgently with her bag. What happened in your brain when you perceived the first ring, and then when you differentiated the second ring from your own remembered ring tone? Measured at your ear, the two sounds may have been identical, but in one case your feat was detecting that the sound had occurred at all, while in the second your task was discriminating it from another familiar sound. Detection and discrimination are both fundamental aspects of active listening, but place different demands on sensory processing. Strategies that might be optimal for sensory detection might not be optimal for discrimination, and vice versa. Understanding the brain mechanisms that optimize sensory processing for detection versus discrimination is a key challenge in sensory neuroscience.

Layer 6 corticothalamic (L6 CT) neurons appear well-positioned to play an important role in enabling sensory systems to switch between detection and discrimination modes of sensory processing. L6 CTs send a feedback projection to the thalamus but also have dense local connections with both excitatory and inhibitory neurons throughout the cortical column; therefore, activity of L6 CT neurons could modulate both thalamocortical input and intracortical processing. Previous studies in the visual and somatosensory systems have reported that optogenetic activation of L6 CTs produces mixed facilitatory and suppressive effects in the thalamus, but primarily suppressive effects within the cortical column, mediated by connections from L6 CTs to fast-spiking (FS) inhibitory neurons (Denham and Contreras, 2015; Bortone et al., 2014; Temereanca and Simons, 2004). Importantly, a recent study in the somatosensory thalamocortical slice preparation demonstrated that corticothalamic feedback can either suppress or enhance sensory thalamic excitability depending on the rate and time course of L6 CT activation (Crandell et al., 2015). This *in vitro* work suggested that L6 CT circuits could act as a bidirectional switch enabling modulation of sensory processing by behavioural demands.

In this issue of *Neuron*, Guo et al. (2017) not only validate this idea in awake, behaving animals, but also report the discovery of temporally multiplexed corticothalamic and intracortical mechanisms that help to optimize sensory cortical processing for either detection or discrimination. They begin with experiments demonstrating that L6 CT neurons can either suppress or enhance auditory cortical responses to sound in awake animals, depending on the time interval between L6 CT spiking and sensory stimulation. After targeting expression of channelrhodopsin (ChR2) to L6 CT cells, they manipulated the activity of L6 CT neurons optogenetically in awake mice while recording spontaneous and sound-evoked neuronal activity throughout the layers of the primary auditory cortex (A1). In contrast to the suppressive effects

of L6 CT activation observed previously in visual cortex (Bortone et al., 2014), Guo et al. (2017) found that spontaneous and sound-evoked firing rates in A1 were elevated during laser activation of L6 CT neurons. However, they also observed robust suppression of A1 spiking at short delays following offset of L6 CT activation (50-100 ms after laser offset), and enhancement of spiking at longer delays (150-200 ms after laser offset). This distinctive alternating pattern of cortical suppression and enhancement following offset of L6 CT activation has not been reported previously in any sensory system.

To examine the impact of these temporal variations in cortical excitability on sensory processing, Guo et al. (2017) analyzed laser-induced changes in evoked responses to tone pips presented in three different periods: (1) during laser activation of L6 CT neurons, (2) at short (50-100 ms) delays following laser offset, or (3) at long (150-200 ms) delays following laser offset. Neurons in cortical layers 2/3, 4 and 5 all showed an alternating pattern of response modulation across the three periods: a large additive shift in tone-evoked response magnitude during L6 CT activation; divisive scaling of tuning curves combined with a small subtractive magnitude shift at short delays following laser offset; and multiplicative scaling combined with a small additive shift at long delays following laser offset. A caveat must be mentioned here: given that cortical neurons are embedded in highly nonlinear networks, it is unclear how much can be inferred about changes in sensory representation based on this linear analysis of response modulation (Seybold et al., 2015), except that cortical activity was generally suppressed in the short-delay period and enhanced in the long-delay period. However, Guo et al. (2017) also directly tested tuning precision, and found that the half-width of frequency tuning curves narrowed significantly during the short-delay period, and broadened during the long-delay period.

Thus, at short delays following offset of L6 CT activation, tone-evoked responses in L2/3-5 of the auditory cortex were weaker but more precisely tuned, while at long delays, responses were stronger but less precisely tuned. Guo et al. (2017) therefore postulated that in the short-delay period, behavioural performance on tone discrimination tasks might be improved while performance on tone detection tasks was impaired; conversely, in the long-delay period, detection performance might be improved and discrimination performance impaired. These strong, specific and opposing predictions for the two time periods were confirmed in behavioural studies. When L6 CT activation was concurrent with tone presentation, there was no change from baseline in the behavioural performance of mice on either tone detection or discrimination tasks. However, when tones were presented in the short-delay period following offset of L6 CT activation, mice showed improved ability to discriminate small differences in sound frequency but impaired ability to detect quiet tones. Conversely, when tones were presented in the long-delay period, detection performance was improved and discrimination performance impaired. The results provide a compelling demonstration that L6 CT neurons can enhance either detection or discrimination, depending on the delay between the offset of their activity and the sensory stimulus.

What are the neural mechanisms underlying this bidirectional switch? To find out, Guo et al. (2017) recorded simultaneously from all layers of A1 and from tonotopically matched regions of the thalamic reticular nucleus (TRN) and primary subdivision of the auditory thalamus (the ventral division of the medial geniculate body, or MGBv). The TRN contains GABAergic neurons that project to the MGBv, and the MGBv contains glutamatergic neurons that project to TRN and to A1. Both components of this excitatory-inhibitory intrathalamic circuit are targeted by L6 CT projections, which send axon collaterals to the TRN and then terminate in MGBv. In the short-delay period 50-100 ms following offset of L6 CT activation, Guo et al. (2017) found no change in tone-evoked responses in either MGBv or TRN (relative to the tone-alone, no-laser condition), suggesting that intrathalamic mechanisms do not drive cortical suppression and improved behavioural discrimination performance in this period. However, in the long-delay period 150-200 ms following offset of L6 CT activation, tone-evoked responses were increased in the MGBv and reduced in the TRN, and the MGBv response enhancement was similar to that

observed in A1. These results led the authors to conclude that enhancement of cortical responses and improved behavioural detection performance at long delays following offset of L6 CT activation arise from an intrathalamic shift in excitatory-inhibitory balance between the MGBv and the TRN.

Thus, the cortical and behavioural changes observed in the long-delay period could be the consequence of intrathalamic changes alone. In contrast, the suppression of cortical responses and improved behavioural discrimination performance observed at short delays following offset of L6 CT activation had no thalamic correlate, suggesting an intracortical mechanism. Therefore, Guo et al. (2017) analyzed the intracortical impact of L6 CT activation and de-activation, using a linear multi-electrode array to record the local field potential and the spiking activity of single units across cortical layers in A1. Previous work has demonstrated that spike probability and tuning of neurons in the auditory cortex vary with the amplitude, frequency and phase of the oscillations in the cortical electric field (Kayser et al., 2015). To determine whether the observed suppression in spiking of cortical single units at short delays following offset of L6 CT activation was associated with changes in cortical oscillations, Guo et al. (2017) analyzed changes over time in the translaminar current-source density (CSD), the second spatial derivative of the local field potential. CSD analysis provides a means of tracking low-frequency oscillations in cortical electric fields at high spatial resolution.

This analysis revealed a distinctive impact of L6 CT activation on cortical electric field oscillations, which was not observed following activation of other populations of cortical projection neurons, interneurons, or afferents. Laser activation of L6 CT neurons drove high-frequency gamma oscillations throughout the cortical column, and the abrupt termination of L6 CT spiking at laser offset was followed by a strong cycle of low-frequency delta-theta rhythm (2-6 Hz). This one reliable cycle of delta-theta oscillation was elicited regardless of the preceding duration of L6 CT activation, and was associated with a L2/3 current source 50-100 ms after laser offset and a current sink 100-200 ms later. To determine whether this robust delta-theta cycle following laser offset might account for the suppression and enhancement of cortical responses observed in the short-delay and long-delay periods, Guo et al. (2017) analyzed spontaneous and sound-evoked activity at different phases of naturally occurring L2/3 delta-theta rhythms. In agreement with previous work (Lakatos et al., 2008; Lakatos et al., 2013), they found that the upstroke of the L2/3 current sink (phase 0) in naturally occurring delta-theta oscillations was associated with suppression of cortical spike probability and divisive/subtractive modulation of sensory responses. This finding suggests that cortical suppression and improved behavioural discrimination in the short-delay period following offset of L6 CT activation could arise from intracortical induction of the early, low-excitability phase of a delta-theta cycle. However, there was no change in cortical spike probability or frequency tuning at the downstroke of the L2/3 current source (phase π) in naturally occurring delta-theta oscillations, suggesting that cortical enhancement and improved behavioural detection observed in the long-delay period does not arise from the late, high-excitability phase of the cortical delta-theta cycle.

The ~~findings~~data therefore support the conclusion that cortical suppression and improved tone discrimination observed in the short-delay period following offset of L6 CT activation arise from induction of the early, low-excitability phase of an intracortical delta-theta rhythm, while cortical enhancement and improved tone detection in the long-delay period arise primarily from intrathalamic disinhibition of the MGBv. But what is the neural circuit that resets the cortical delta-theta rhythm in the short-delay period? To find out, Guo et al. (2017) analyzed spike-triggered changes in CSD phase and amplitude for neurons recorded in A1, MGB and TRN, seeking to identify single units for which spontaneously occurring spikes were clearly associated with L2/3 CSD phase resets and reliably evoked a complete cycle of delta-theta rhythm. Among the many “resetter” units they identified in this way, only two subpopulations produced spikes that significantly led (rather than lagged) resets in the spontaneous L2/3 CSD rhythm: resetter units in the MGBv (MGBvr), and cortical fast-spiking resetter units (CtxFSr). Cross-correlation

of spike trains revealed no relationship between L6 CT spiking and MGBvr spiking, but a significant correlation between L6 CT spiking and CtxFSr spiking, with CtxFSr spikes lagging L6 CT spikes by approximately 13 ms. Importantly, following cessation of L6 CT firing at laser offset, CtxFSr units continued to fire for at least 10 ms. Reset of the cortical delta-theta rhythm following offset of L6 activation therefore appears to be triggered by CtxFSr units in the brief moment when these neurons fire unopposed.

Overall, the most novel contributions of this elegant study are to demonstrate that: (1) offset of L6 CT activation reliably induces suppression of auditory cortical responses at short delays followed by enhancement at long delays, (2) tone discrimination behaviour is improved and detection impaired in the short-delay period, but conversely detection is improved and discrimination impaired in the long-delay period, and (3) a subpopulation of FS interneurons resets the phase of low-frequency cortical oscillations in the short-delay period, while intrathalamic mechanisms alone can account for cortical changes in the long-delay period.

These findings suggest many further questions for future research. First and foremost, are the identified corticothalamic mechanisms actually deployed during active listening? Previous work has demonstrated that active listening involves resetting the phase of cortical oscillations to increase the neurophysiological and perceptual salience of attended stimulus features (Lakatos et al., 2008; Lakatos et al., 2013; Zion Golumbic et al. 2013). Is this process driven by the intracortical mechanism of delta-theta phase reset described here, or by other intracortical, intrathalamic or corticothalamic mechanisms? More generally, are the short-delay and long-delay periods following L6 CT spiking differentially engaged during active listening, or is one of them essentially an epiphenomenon of the other? Does the brain exploit the stereotyped changes in cortical gain and tuning precision following offset of L6 CT activation by altering anticipatory timing of L6 CT spiking to optimize sensory processing for either discrimination or detection? Alternatively, on the timescale of most natural sounds, could the temporal multiplexing of different processing states enable formation of sensory representations optimized for *both* discrimination and detection? The answers to these questions may reveal that for neural mechanisms of detection and discrimination, timing is everything.

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