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Sensory Experience in Development Balances Excitation and Inhibition to Stabilize Frequency Tuning in Central Auditory Neurons

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Abstract: The balance between excitation and inhibition is critical in shaping receptive field tuning properties in sensory neurons and, ultimately, in determining how sensory cues are extracted, transformed and interpreted by brain circuits. New findings suggest that developmentally-regulated, experience-dependent changes in intracortical inhibitory networks are key to defining receptive field tuning properties of auditory cortical neurons.

Keywords: inhibition, auditory cortex, critical period, development, excitatory-inhibitory balance, tuning curve

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At central auditory neurons, a cell's frequency tuning is synonymous with its functional signature in auditory processing. Tuning at auditory neurons is generally understood as a cell's dominant frequency, a characteristic that is ultimately determined in a labeled line fashion that connects a cortical neuron with an encoding region on the basilar membrane in the cochlea. Given that the primary auditory cortex (A1) is tonotopically organized, the response and receptive field properties of an isolated neuron in A1 largely reflect the integration of neighboring active thalamic inputs that convey the dominant excitatory drive, along with influences from local cortical processing—whether excitatory or inhibitory. The relative timings and strengths of these converging signals give rise to neuronal tuning that is dynamic and often not the textbook, concentric center-surround, static receptive field.

The route by which a relationship between sensory transduction and firing patterns in cortical neurons is established and stabilized is of considerable interest to sensory neuroscientists. It is known that important developmentally-driven changes occur in the structural and functional organization of receptive fields; however, the specific forces acting at A1 neurons to refine these response properties and ultimately to achieve response stability remain elusive. For decades it has been known that excitatory responses alone cannot explain all aspects of receptive field tuning in its final and stable form in sensory neurons, including those in the central auditory pathways. It is now clear that the functional receptive field is a product of excitatory and inhibitory synaptic inputs that overlap in the temporal domain, or that by virtue of memory in the cellular membrane, influence a neuron's response properties to ensuing, incoming signals.[1–8] Evidence also exists to suggest that even from relatively early development, the interplay between cortical inhibition and excitation is central in shaping tonal receptive field properties within the auditory cortex. The specific neuronal mechanisms underlying such processes, however, remain largely unknown.

In a highly challenging set of in-vivo, whole-cell voltage-clamp studies, Dorrn and colleagues[9] were able to resolve sub-threshold synaptic activity occurring at A1 neurons during auditory stimulation. The tuning of A1 neurons was identified by presenting animals with pure tones while holding the cell membrane at different potentials. Comparisons of the tone-driven changes in either inhibitory or excitatory conductances were used to reconstruct the qualities of sensory input that most effectively drive or suppress firing for that central auditory neuron. These data, therefore, provided direct indicators for the inhibitory versus excitatory sub-domains of a neuron's receptive field. More specifically, the experiments of Dorrn and co-workers involved monitoring response profiles in whole-cell mode for rat A1 neurons from neonatal and adult in-vivo preparations (postnatal day 12 [p12] to p30). In the young animals, the authors demonstrated sensory-evoked excitatory and inhibitory receptive field responses that were initially mismatched immediately after the onset of hearing. The results also showed that refinement of excitatory and inhibitory fields may be on different developmental schedules. Whereas excitatory fields reached adult-like states around p15, inhibitory tuning did not reach adult-like configuration until p25. During the postnatal development of the auditory cortex, differences between tone-evoked excitatory and inhibitory responses lessened and became highly correlated, with clear improvements in correlated activity occurring by p21. In animals older than p21, patterned sensory stimulation prevented additional exposure-induced modification in tuning curves for either excitatory or inhibitory sub-domains. The authors suggested that their data show that early in life, inhibitory and excitatory responses at the same neuron are functionally separated, and that either domain can be engaged by external sensory drive; however, the optimal inputs for either sub-domain differ. They attributed this mismatch to broad and poorly resolved tuning for the inhibitory domain. Any incongruence between inhibitory or excitatory sub-domains is dramatically altered with post-natal development and has, as its end result, the overlapping of excitatory and inhibitory elements of the receptive field.

The findings of Dorrn and colleagues suggest that central auditory neurons may exploit coincidence in sensory drive during development to align the dominant opposing forces in neural processing—excitation and inhibition. The byproduct of this juxtaposition is the enhanced central representation for one final set of frequencies. According to the authors, the observation of excitatory-inhibitory (E-I) balance as a function of sensory experience during post-natal development impacts neurons in at least two ways. First, when E-I ratios are balanced, neurons move into electrical states that confer functional stability such that cells can respond to the same inputs in roughly similar ways. The functional importance of E-I balance can be best understood at the two extremes of imbalance where all “E” leads to epileptogenic activity and all “I” leads to failures to respond at all. Second, either stabilization or equalization of the E-I relationship appears to be important in suppressing access to mechanisms of neural plasticity, a neuron’s repertoire to adapt itself physically and/or functionally to recent sensory experience, thereby promoting a greater operational rigidity (stability) over time.

In this work the authors provide evidence for the idea that developing auditory circuits are likely to be activity-driven, self-assembling networks that move towards stability—a configuration that indeed would be useful to hold encoded response patterns for frequently encountered statistically-related sensory experiences. In summary, using whole-cell patch-clamp on A1 neurons in rat cortex, the authors showed remarkable changes in synaptic inhibitory and excitatory drive as a function of post-natal development. Implicitly, testing animals at advancing developmental stages offers insights on the impact of sensory experience in receptive field tuning. The authors found that that early adjustments in the E-I balance could be attributed mainly to a constriction and realignment of the inhibitory sub-domain towards the tuning parameters of the excitatory field. The improved correlation in timing and tuning of inhibitory and excitatory conductances found in later development and approaching adulthood, manifests functionally as more highly resolved tuning curves. These findings suggest that refinements in the E-I balance may become increasingly combinatorial as auditory networks approach a mature and stable state.

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