

Learning to Encode Timing: Mechanisms of Plasticity in the Auditory Brainstem

Thanos Tzounopoulos^{1,2,3,*} and Nina Kraus^{4,5,6}

¹Department of Otolaryngology

²Department of Neurobiology

³Center for the Neural Basis of Cognition

University of Pittsburgh, Pittsburgh, PA 15260, USA

⁴Auditory Neuroscience Laboratory, Department of Communication Sciences

⁵WCAS Neurobiology and Physiology

⁶Department of Otolaryngology, Feinberg School of Medicine

Northwestern University, Evanston, IL 60208, USA

*Correspondence: thanos@pitt.edu

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Mechanisms of plasticity have traditionally been ascribed to higher-order sensory processing areas such as the cortex, whereas early sensory processing centers have been considered largely hard-wired. In agreement with this view, the auditory brainstem has been viewed as a nonplastic site, important for preserving temporal information and minimizing transmission delays. However, recent groundbreaking results from animal models and human studies have revealed remarkable evidence for cellular and behavioral mechanisms for learning and memory in the auditory brainstem.

Introduction

During the last 10 years, the auditory brainstem has provided neuroscientists with the unique opportunity for studying cellular adaptations that contribute to the preservation of temporal information and the minimization of transmission delays observed in neuronal pathways. While some computational tasks performed by the auditory brainstem are not understood in detail for all its nuclei, there is no doubt that (1) timing of firing of neurons carries information that is used both to localize and to interpret sound and that (2) neurons in the auditory brainstem nuclei are highly specialized for precisely timed electrical signaling (Oertel, 1999).

The auditory brainstem is an area of great refinement in terms of detecting and preserving temporal information. Among the more dramatic specializations are those in the auditory brainstem neurons that participate in localizing low-frequency sounds (<4000 Hz in mammals). For this task, the auditory brainstem circuitry utilizes differences between the phases of each cycle of the sound waves received by each ear, differences that are in the microsecond range (von Gersdorff and Borst, 2002). Detection of pitch in humans has also been shown to depend on a timing code of lower frequencies. On the other hand, the timing of transient complex sounds is better resolved in the higher frequencies. For example, the features that distinguish consonants in human speech are rapid, broadband transients. Resolution of these features becomes especially difficult with presbycusis, the most common pattern of hearing loss in humans (Oertel, 1999).

For the last 10 years, research in auditory brainstem nuclei has focused on how neurons, whose action potentials alone are often many times longer than the timing differences that they detect, preserve and reliably transmit this information. Detailed anatomical, physiological, and biophysical work has largely answered this question. Cellular adaptations involve large somatic synapses, fast release time course, fast AMPA receptor

kinetics, and low-voltage-activated potassium currents that produce fast membrane time constants (Trussell, 1999; von Gersdorff and Borst, 2002). These cellular adaptations lead to brief synaptic responses that promote minimal temporal summation, one-to-one signaling, short-latency spikes, and a short refractory period. The surety and consistent timing of the response are essential in transmitting the onset and time-varying frequency of an acoustic stimulus and in promoting entrainment.

Studies related to long-term plasticity and learning-related phenomena have focused on higher processing stages of the auditory system, such as the auditory cortex (Schreiner and Winer, 2007; Fritz et al., 2007; Weinberger, 2007; Atiani et al., 2009). Knowing that neurons in the auditory brainstem are specialized for generating fast, reliable, and consistent electrical signals, it has been assumed that the synaptic relays of auditory brainstem nuclei are ill-suited to plasticity.

Two series of observations have led to reevaluation of these views. The first is that long-term synaptic and intrinsic plasticity do occur in some auditory brainstem nuclei. Second, electrophysiological studies in humans have uncovered new forms of learning and behavioral plasticity that are mediated by auditory brainstem structures. These findings establish a new role for the auditory brainstem and its modification by experience and pathology.

Evoked Auditory Brainstem Responses in Humans: Evidence for Plastic Auditory Brainstem

Synchronized neural activity in response to sounds can be measured in humans by means of auditory evoked potentials. Simple (brief nonspeech) stimuli evoke an orderly pattern of responses from the auditory brainstem nuclei. The auditory brainstem response (ABR) is a noninvasive measure of far-field representation of stimulus-locked, synchronous electrical

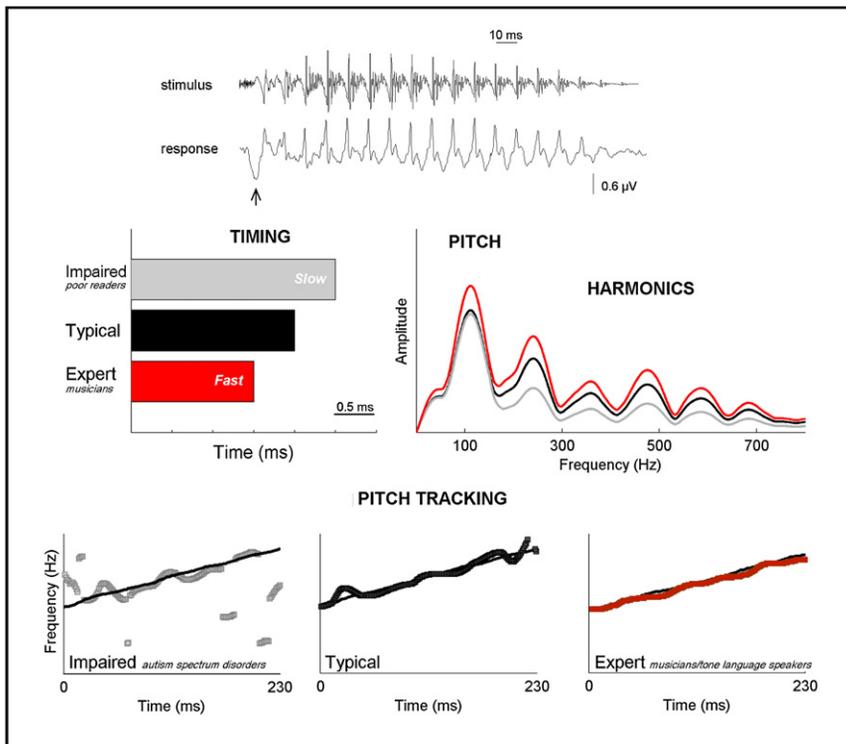


Figure 1. Schematic Representation of Brainstem Processing in Impaired (Gray), Typical (Black), and Expert/Specialized (Red) Systems

This figure provides a schematization of the findings that have emerged from nearly a decade of research on impaired (poor readers, autism spectrum disorders [ASD]), typical, and expert (musicians, tonal language speakers) systems. (Top) Time-amplitude stimulus “da” and brainstem response waveform. The stimulus has been shifted by ~ 8 ms (approximate neural travel time) to increase visual coherence with the response. Following a sharp onset response (demarcated with an arrow), the primary periodicity of the syllable—the fundamental frequency (F_0)—is clearly preserved in the response via phase locking. (Middle left) A significant subset of children with reading problems (8–12 years old) have atypical subcortical timing resulting in later (i.e., slower) responses. In contrast, musicians have more precise subcortical timing leading to earlier (i.e., faster) responses than nonmusicians. These temporal disruptions and enhancements occur on the order of tenths of milliseconds (x axis tick marks = 0.5 ms) to selective components of the response. (Middle right) A fast Fourier transform illustrates the frequency content of the response (the F_0 and its harmonics). Musicians represent the pitch and harmonics of the stimulus more robustly and efficiently than their nonmusician counterparts. A different pattern is seen in a subgroup of children with reading impairments who demonstrate reduced neural encoding of the harmonics, despite normal pitch representa-

tion. (Bottom) By analyzing the brainstem response over small time bins, we can measure the precision with which brainstem nuclei phase-lock to the time-varying pitch of the stimulus, a phenomenon known as pitch tracking. In the three bottom panels, the thicker lines (gray, red) represent the pitch contour extracted from the brainstem response, and the thin black line, which is most apparent in the left panel, represents the pitch contour of the stimulus. Pitch contours were calculated using a running-window short-term Fourier analysis (40 ms time bins, 1 ms interval between the start of each consecutive bin). In these time-frequency graphs, the frequency with the largest magnitude for each given time bin is plotted. A subset of children with ASD showed poor pitch tracking relative to typically developing children, paralleling the prosodic deficit frequently occurring in autism. Musicians, on the other hand, show more accurate brainstem pitch tracking than nonmusicians.

events. In response to an acoustic signal, a series of potential fluctuations measured at the scalp provides information about the functional integrity of brainstem nuclei along the ascending auditory pathway, making it a widely used clinical measure of auditory function. The frequency following response (FFR), a component of the ABR that occurs in response to a periodic stimulus, is well suited for examining how speech elements are encoded subcortically (Figure 1). There is a vast literature demonstrating the existence of a temporal code of pitch encoding at the level of the auditory nerve and the brainstem (Langner, 1997). In the neuronal representation of speech, neural phase locking via the FFR reflects the period of the fundamental frequency (F_0) and its harmonics (Figure 1, top, middle right, bottom panels).

Auditory evoked responses originating at the brainstem reflect the temporal and spectral characteristics of complex stimuli with remarkable precision (Kraus and Nicol, 2005; Krishnan et al., 2005; Akhoun et al., 2008). Temporal fidelity of the evoked ABR makes it useful in a wide array of studies and clinical applications. Thus, not only are the major morphologic features of the response stable over time within an individual (Russo et al., 2005), but the peaks are also highly replicable between individuals (Akhoun et al., 2008), hence making deviations from the normal range easily identifiable (Figure 1, middle left).

The remarkable fidelity of subcortical encoding of speech sounds, as measured using auditory evoked potentials, could be interpreted as reflecting automatic detection of the acoustic features of sound in the absence of activity-dependent changes usually associated with higher processing structures, such as the cortex. However, recent studies suggest that this is not the case, and that the auditory brainstem is a site where experience-dependent plasticity does occur. Galbraith recognized the dynamic nature of the human brainstem response over a decade ago, finding that responses were affected by attention (Galbraith et al., 1998) and were larger to a speech syllable than to its time-reversed version (Galbraith et al., 2004). Krishnan and colleagues were the first to demonstrate that language experience affects brainstem activity by showing that speakers of tonal languages have enhanced neural representation of pitch (Krishnan et al., 2005). Conversely, distinct aspects of brainstem encoding are disrupted in a subset of children with language impairment (e.g., poor readers, children with autism) (Figure 1, middle and bottom panels, Cunningham et al., 2001; Banai et al., 2009; Russo et al., 2008).

Musical experience can also result in more robust brainstem encoding of speech sounds, linguistic pitch-patterns, and processing of vocal expressions of emotion (Figure 1, middle and

bottom panels, Musacchia et al., 2007; Wong et al., 2007). Musicians also show greater “processing efficiency” of the fundamental frequency of vocal expressions of emotion, selectively in response to complex portions of the stimulus (Strait et al., 2009). Modification of auditory brainstem processing by language and musical experience does not result in a stimulus-independent, generalized gain effect. Instead, distinctive aspects of stimulus processing (e.g., high-frequency phase locking, onset synchrony) are impaired or enhanced depending on the behavioral relevance and relative complexity of the stimulus, likely influencing how the sensory system responds (Figure 1). While language, musical training, and subcortical impairments represent lifelong experiences, brainstem processing can also be modified by shorter-term auditory training (e.g., over the course of weeks) (Russo et al., 2005; Song et al., 2008; de Boer and Thornton, 2008).

Taken together, these results suggest that sound processing in the human brainstem is dynamic and that experience-dependent plasticity results in specific alteration of receptive field properties.

Plasticity in the Auditory Brainstem

A key question is whether the auditory brainstem in mammals expresses the mechanisms that allow activity-dependent modulation of neural circuits and that could support the learning phenomena observed in human studies. Activity-dependent changes in synaptic strength represent the leading experimental model for the cellular changes that may underlie and support learning behavior (Malenka and Bear, 2004). More specifically activity-dependent, long-lasting increases (long-term potentiation: LTP) and decreases (long-term depression: LTD) in synaptic strength represent the most popular “neural” model of memory formation and learning. In addition to these synaptic changes, recent data provide evidence that many learning tasks and artificial patterns of activation in brain slices produce long-lasting changes in intrinsic neuronal excitability by changing the function of voltage-gated ion channels, a process called intrinsic plasticity (Zhang and Linden, 2003). Therefore, all neural circuits supporting experience-dependent plasticity display synaptic or intrinsic plasticity or both. In agreement with activity-dependent changes in human auditory brainstem evoked responses and contrary to the traditional views that early sensory processing is largely hard-wired, recent studies have revealed that the auditory brainstem is a site where robust synaptic and intrinsic plasticity take place.

Synaptic Plasticity

Recent studies of the dorsal cochlear nucleus (DCN), an auditory brainstem nucleus bearing significant resemblance to the cerebellum (Figure 2), have revealed synaptic plasticity at synapses between parallel fibers and their targets: the principal cells (fusiform) and feedforward inhibitory interneurons (cartwheel cells) located in the molecular layer (Fujino and Oertel, 2003; Tzounopoulos et al., 2004, 2007). Both cell types receive glutamatergic input from parallel fibers through synapses that can undergo LTP and LTD, measured with classical pairing of presynaptic activation and postsynaptic depolarization (Fujino and Oertel, 2003). Over the last decade, studies in spike-timing-dependent plasticity (STDP), a more physiological form of synaptic plasticity

where the size and sign of plasticity depends on the relative timing of presynaptic and postsynaptic action potentials, have revealed physiologically relevant differences in synaptic plasticity timing rules in many brain areas (Bell et al., 1997; Magee and Johnston, 1997; Markram et al., 1997). In the DCN, synapses in the molecular layer show cell-specific STDP timing rules (Tzounopoulos et al., 2004). STDP observed at parallel fiber-fusiform cell synapses is Hebbian (Figure 3) and resembles STDP timing rules observed in the cortex and hippocampus (Caporale and Dan, 2008). At these synapses, presynaptic inputs that are successful in driving postsynaptic spikes are strengthened; therefore, LTP is observed when postsynaptic spikes follow excitatory postsynaptic potentials (EPSPs). In contrast, parallel fiber-cartwheel cell synapses are characterized by an anti-Hebbian timing rule. Presynaptic inputs that reliably cause, or predict, a postsynaptic spike are weakened and therefore LTD is observed when postsynaptic spikes follow EPSPs (Figure 3) (Bell et al., 1997).

The DCN is involved in sound localization on the vertical plane (Figure 2). Cerebellum-like structures act as adaptive sensory processors in which the signals conveyed by parallel fibers in the molecular layer predict the patterns of sensory input to the deep layers through a process of associative anti-Hebbian synaptic plasticity (Bell et al., 2008). In the cerebellum-like electrosensory lobe of mormyrid fish, *in vivo*, *in vitro*, and modeling efforts have linked anti-Hebbian STDP at parallel fiber synapses onto Purkinje cell-like interneurons with the systems level cancellation of the expected sensory consequences of the animal’s own motor actions (Bell et al., 2008). In this system, parallel fibers convey information related to movements of the fish, including corollary discharge inputs associated with the motor command that drives the electric organ. Parallel fiber inputs that consistently predict incoming sensory inputs are weakened according to the anti-Hebbian learning rule and uncorrelated inputs are strengthened. In this way, anti-Hebbian STDP adjusts parallel fiber synaptic weights in order to sculpt a “negative image” of the neural response caused by the fish’s own movements.

A key question is whether anti-Hebbian plasticity observed in the DCN can serve a similar function. Electric fish are faced with the challenge of differentiating external sensory signals (predator or prey) from self-generated “noise.” The auditory system faces a similar task in that it must differentiate spectral changes in a sound introduced by the animal’s own movements from spectral changes introduced by the movement of an external sound source relative to the animal. Proprioceptive input from the pinna has particularly strong effects on DCN granule cells in the cat (Kanold and Young, 2001). In addition, DCN granule cells receive input from brainstem nuclei associated with vocalization and respiration that may convey corollary discharge signals (Shore and Zhou, 2006). Movements of the animal’s pinna, head, or body have predictable effects on how the cochlea responds to an external sound source; therefore the animal’s own vocalization and respiration will have predictable consequences on auditory input. Thus, the DCN may act as an adaptive sensory processor in which the signals conveyed by parallel fibers in the molecular layer predict the patterns of sensory input to the deep layers through a process of associative synaptic plasticity.

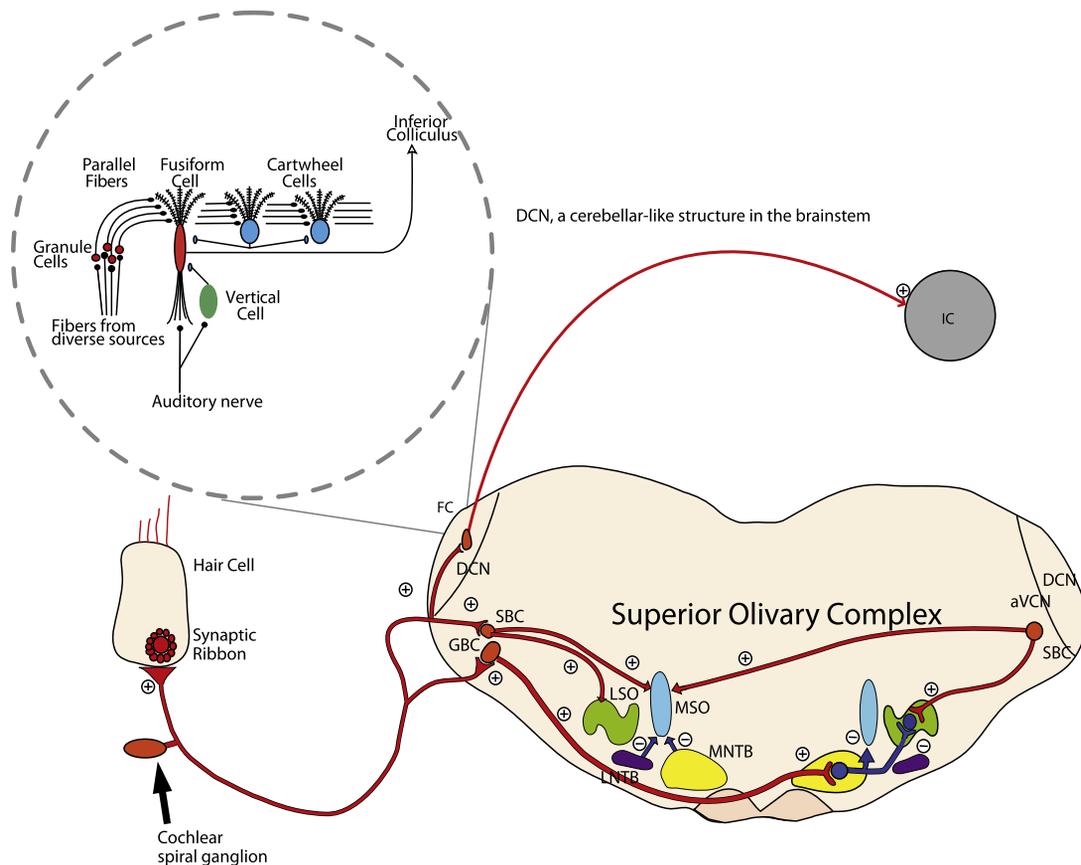


Figure 2. Auditory Brainstem Circuitry and Function

Sound coming from a lateral direction reaches one cochlea first, and then, with a short delay, the other cochlea, at a slightly attenuated intensity because the head acts as a sound barrier. The microsecond interaural time differences (ITDs) in the arrival of sound are used to determine the spatial location of low-frequency sounds, whereas differences in the intensity of sound arriving at each cochlea are used to locate high-frequency sounds. The superior olivary complex (SOC) of the mammalian brainstem is involved in computing sound localization from these two binaural cues, and the precise timing of action potential (AP) firing is thought to be crucial for this task. Auditory signals arriving at the cochlea are transmitted to the ipsilateral anterior ventral cochlear nucleus (aVCN) by excitatory synapses onto globular and spherical bushy cells (GBCs and SBCs). The synapse onto the SBC is the so-called endbulb of Held. The axons of the GBCs then cross the brainstem midline and synapse onto the principal cells of the contralateral medial nucleus of the trapezoid body (MNTB). These myelinated axons have a large diameter (4–12 μm), allowing a fast conduction velocity, and give rise to the calyx of Held, a glutamatergic synaptic terminal. The principal cells of the MNTB are glycinergic and project to the lateral superior olive (LSO). The LSO also receives excitatory input from SBCs of the ipsilateral aVCN. Discharge trains evoked by sound at the two cochleas therefore converge on LSO neurons as ipsilateral excitation (through the aVCN) and contralateral inhibition (through the MNTB). So, relative to the cochlear nuclei, excitation in the LSO is monosynaptic, whereas inhibition is disynaptic. However, the inhibitory input in the cat arrives in the LSO with a delay of only 200 μs after the excitatory input, and in the bat, inhibition can arrive even earlier than excitation. The precise timing of the two inputs is crucial in determining the response of the LSO to interaural intensity differences. It is at the level of the LSO that discharges evoked by interaural intensity differences are first represented as differences in the timing of excitatory and inhibitory inputs. So, the LSO is thought to function as a coincidence detector of binaural signals, whereas the main role of the MNTB is simply to act as a fast, sign-inverting relay station. Medial superior olive (MSO) neurons of low-frequency-hearing mammals compute the horizontal location of low-frequency sounds using the difference in the time required for a sound to propagate to each ear. These ITDs are submillisecond cues, the physiological range of which is dependent on the diameter of the animal's head. The principal neurons of the MSO are able to extract these brief ITDs from converging binaural inputs that include an excitatory component from the ipsilateral and contralateral VCN and an inhibitory component from both the medial nucleus (MNTB) and lateral nucleus (LNTB) of the trapezoid body. Although the mechanism for extracting ITDs from these excitatory and inhibitory inputs has yet to be fully elucidated, ITD information is conveyed to higher auditory centers through a rate code. Brainstem nuclei are also important for sound localization on the vertical plane. In contrast to previous sound localization schemes that require binaural inputs, sound localization on the vertical plane is monaural. The shapes of the heads and ears of mammals are asymmetrical top-to-bottom and front-to-back. Reflections of sounds from these structures differ with the angle of incidence, producing cues for monaural sound localization in the vertical plane. Neurons in the dorsal cochlear nucleus (DCN) respond specifically to these spectral cues and integrate them with somatosensory, vestibular, and higher-level auditory information through parallel fiber inputs. The circuitry of the DCN has cerebellar-like features and differs significantly from other brainstem nuclei. DCN principal neurons project to the contralateral inferior colliculus (IC).

Most studies of synaptic plasticity in the auditory brainstem have been performed in brain slices. This experimental approach has substantial differences from studying intact brains *in vivo*. For example, high spontaneous spike rates occur for some auditory nerve fibers under *in vivo* conditions, which have not been taken into account in brain slice recordings. Introduction of

high spontaneous, *in-vivo*-like activity in brain slices prepared from the medial nucleus of the trapezoid body (MNTB) revealed synaptic failures during high-frequency activity (Hermann et al., 2007) not seen in previous studies. This is an important finding suggesting that the MNTB is not a simple and faithful relay nucleus, and while it encodes precisely the onset of sound-like

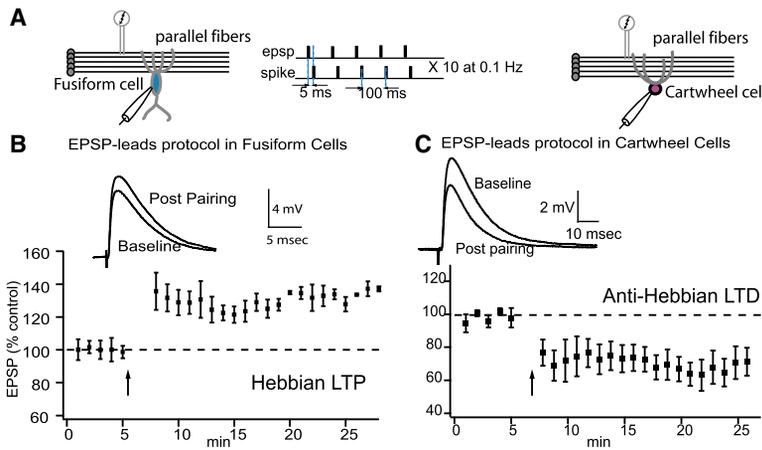


Figure 3. Cell-Specific Synaptic Plasticity in the DCN
Long-term, cell-specific synaptic plasticity by time-dependent pairing of presynaptic and postsynaptic activity. (A) Plasticity was induced by a protocol of excitatory postsynaptic potential (EPSP)-spike pairs. (B) Representative traces of averaged EPSPs before and 15–20 min after pairing and time course of induced synaptic plasticity for fusiform cells. (C) Representative traces and time course of induced synaptic plasticity for cartwheel cells. The same protocol induces LTP in fusiform cells and LTD at cartwheel cells. These studies have demonstrated unique, opposing forms of spike-timing-dependent plasticity (STDP) at parallel fiber synapses onto fusiform and cartwheel cells. Error bars report \pm SEM. Reproduced with permission from Tzounopoulos (2008).

stimuli (as bursts of discharges), it may not reliably entrain to high-frequency stimuli for prolonged periods, due to short-term plasticity. In addition these results highlight that several plasticity protocols may be modified by in-vivo-like conditions.

Intrinsic Plasticity

Recent findings have revealed that neurons in the MNTB and anterior ventral cochlear nucleus (aVCN) change their firing pattern in an activity-dependent manner (Song et al., 2005; Steinert et al., 2008). The presence of rapidly activating and deactivating Kv3.1b potassium channels in these neurons allows for action potentials to be repolarized very rapidly without compromising the initiation or amplitude of a second action potential triggered by a stimulus closely following the first one (Rudy and McBain, 2001). Recent studies indicate that changes in the acoustic environment alter the ability of auditory neurons to fire at high frequencies. At low levels of sound intensity (quiet environment), phosphorylation of Kv3.1b by protein kinase C (PKC) reduces potassium current, thus allowing low-frequency firing. Conversely, in response to high-frequency auditory or synaptic stimulation, channel dephosphorylation and increased Kv3.1b channel promote the ability of neurons to fire at high frequency (Song et al., 2005). Future studies are expected to reveal whether the expression and the distribution of Kv3.1b channels along the tonotopic axis may change as a result of auditory activity.

More recent studies have shown that nitric oxide (NO) is another activity-dependent modulator of Kv3 channels in MNTB neurons. Diffusion of NO from MNTB principal neurons provides modulatory control of excitability via direct suppression of postsynaptic Kv3 channels (Steinert et al., 2008). In these studies activity in one MNTB neuron can modulate the excitability of adjacent neurons, suggesting that this modulation can serve as a homeostatic function for gain reduction during loud noise conditions.

In the auditory brainstem it is possible to directly relate synaptic and intrinsic plasticity with function. Responses of auditory brainstem nuclei to sound have been well characterized and therefore can be manipulated in predictable ways by manipulating the auditory environment. For example, recent studies in the lateral superior olive (LSO) indicate that retrograde GABA signaling adjusts sound localization by balancing excitation

and inhibition in the brainstem (Magnusson et al., 2008). Modulation of the strength of synaptic input by the release of a retrograde neurotransmitter allows LSO neurons to adjust the balance between excitation and inhibition over short periods, possibly helping animals adapt to variable listening situations. This study illustrates the power of the auditory brainstem for identifying the system and behavioral effects of retrograde neurotransmitter release. We expect that similar studies in other auditory brainstem nuclei in the future will provide critical insight into the role of activity-dependent synaptic and intrinsic plasticity in sensory processing. For example, similar mechanisms may mediate sensitivity to ensuing stimuli observed in the auditory brainstem (Park et al., 2008). Finally and most importantly, the possibility of assessing the function of auditory brainstem nuclei noninvasively in humans makes it possible to relate auditory processing in these nuclei to the performance of sensory tasks.

Brainstem Plasticity-Induced Diseases Due to Adaptations to Sensory Inputs

While synaptic and intrinsic plasticity can lead to the formation of memory or learning, compensation for loss of function, and adaptation to changing demands, recent studies suggest that plasticity-induced changes in the auditory brainstem may also cause signs and symptoms of disease. Tinnitus—commonly referred to as ringing in the ears or “brain”—is the persistent perception of sound in the absence of an environmental acoustic stimulus and most often is the result of extreme sound exposure. Despite the wide prevalence of tinnitus, the pathophysiology of the disorder is poorly understood. Although damage to the cochlea causes hearing loss and often initiates tinnitus, recent studies have established that it is the central nervous system that plays a key role in the maintenance of chronic tinnitus. Numerous studies in animal models of tinnitus have shown that DCN fusiform cells exhibit elevated levels of spontaneous electrical activity and hypersensitivity to sound (Kaltenbach and Godfrey, 2008).

Activity-dependent mechanisms that change the balance of excitation and inhibition on fusiform cells could lead to hyperactivity of fusiform cells, via plasticity-like mechanisms discovered in the parallel fibers of the DCN (Tzounopoulos, 2008).

Synapse-specific synaptic plasticity, by decreasing the activity of inhibitory interneurons (disinhibition) and simultaneously increasing excitatory input to fusiform cells, can lead to hyperactivity in fusiform cells, similar to the kind observed in animals with behavioral evidence of tinnitus. While it is obvious that electrical stimulation of parallel fibers can induce synaptic plasticity that could change the balance of excitation and inhibition in fusiform cells, it is not entirely clear how stimulation caused by noise exposure could produce similar plasticity effects. Fusiform cells are contacted by synaptically plastic parallel fibers and by nonplastic auditory nerve fibers (Figure 2) (Fujino and Oertel, 2003). However, auditory nerve fiber activity can serve to induce/modulate synaptic plasticity of the parallel fiber by analogy with the climbing fiber and parallel fiber in the cerebellum. Spikes initiated by intense auditory activity (e.g., during noise exposure) could provide the trigger to induce the types of synaptic plasticity observed in the parallel fiber inputs of fusiform cells (Figure 2).

Therefore, further understanding and potential manipulation of plasticity mechanisms observed in the DCN could perhaps be used to treat or manage tinnitus. Consistent with this view, signaling molecules involved in synaptic plasticity in the DCN, such as cannabinoid receptors (Tzounopoulos et al., 2007), are downregulated in the cochlear nucleus in rats showing behavioral evidence of tinnitus (Zheng et al., 2007).

Cognitive Modulation of Brainstem Sensory Processing

Language and musical experience affect auditory timing of transient and harmonic acoustic events (reviewed above). This finding suggests that higher-order processing levels should have efficient feedback pathways to brainstem lower-order processing levels. Consistent with this view, several studies have revealed that there is a straightforward anatomical-physiological mechanism for these cognitive-sensory interactions in the auditory system. The downward-projecting auditory efferent system is massive and synapses all along the auditory pathway (Suga, 2008). A theory to account for the interactions between sensory input and top-down processes (e.g., attention, language, and memory) is the Reverse Hierarchy Theory (RHT) (Ahissar and Hochstein, 2004). The RHT postulates that the performance of a perceptual task is first based on the highest available level of sensory representation. If the task cannot be accomplished at that level (because of poor sensory resolution), it proceeds down the representational hierarchy to obtain more detailed, lower-level cues that participate in generating the percept. Because the top-down mechanism was originally proposed for the impact of higher-order visual cortical areas to lower-order cortical areas, the focus has been primarily on the intracortical feedback pathway. Recent studies have extended the RHT to auditory perception (Nahum et al., 2008; Gutschalk et al., 2008), and top-down corticofugal enhancement of brainstem representation of selective features of sound provides evidence for the expansion of the RHT theory outside the cortical areas (Suga, 2008; Luo et al., 2008; Perrot et al., 2006). Recent findings indicate that cortical activation shapes the tuning properties of neurons in the cochlear nucleus (Luo et al., 2008) similar to intracortical, experience-dependent shaping of receptive fields observed in primary auditory cortex (Schreiner and Winer, 2007; Fritz et al., 2007; Atiani et al., 2009).

Therefore, it is our view that RHT may apply to subcortical sensory processing and that the application of its principles may initiate or modulate plasticity at the auditory brainstem. The auditory brainstem expresses all the mechanisms that allow activity-dependent modulation of neural circuits. Whether activity-dependent changes are initiated/modulated in a top-down fashion, as predicted by the RHT through the efferent, corticofugal system linking the cortex and the auditory brainstem; through local mechanisms of adaptation to the acoustic properties of the input (Dean et al., 2005); or through an interaction of afferent and efferent mechanisms is a challenge for future research to resolve.

Summary

Contrary to traditional views that early stages of sensory processing are not plastic, new studies discussed in this article have established that the auditory brainstem is dynamic. The plethora of intrinsic and synaptic plasticity mechanisms observed in the auditory brainstem in combination with the noninvasive methods of assessing auditory brainstem function in humans provides a platform for relating subcortical auditory processing to higher-order sensory and cognitive tasks involving speech and music. Therefore, we suggest that the auditory brainstem offers an ideal model to study the mechanisms and functions of nontraditional aspects of sensory processing, such as synaptic and intrinsic plasticity and recurrent feedback from higher levels of processing.

The past 10 years of research have revealed how timing information is fed through auditory brainstem pathways. This research has provided insight into how sounds are localized by vertebrates, but much less is known about how these pathways adapt to ongoing sensory activity and how they contribute to the perception and interpretation of environmental sounds, including speech, under normal and pathological conditions. Therein lies the exciting future of revealing the role of plasticity observed in the auditory brainstem.

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REFERENCES

- Ahissar, M., and Hochstein, S. (2004). The reverse hierarchy theory of visual perceptual learning. *Trends Cogn. Sci.* 8, 457–464.
- Akhoun, I., Gallego, S., Moulin, A., Menard, M., Vuillet, E., Berger-Vachon, C., Collet, L., and Thai-Van, H. (2008). The temporal relationship between speech auditory brainstem responses and the acoustic pattern of the phoneme /ba/ in normal-hearing adults. *Clin. Neurophysiol.* 119, 922–933.
- Atiani, S., Elhilali, M., David, S.V., Fritz, J.B., and Shamma, S.A. (2009). Task difficulty and performance induce diverse adaptive patterns in gain and shape of primary auditory cortical receptive fields. *Neuron* 61, 467–480.
- Banai, K., Hornickel, J.M., Skoe, E., Nicol, T., Zecker, S., and Kraus, N. (2009). Reading and Subcortical Auditory Function. *Cereb. Cortex*, in press. Published online March 17, 2009. 10.1093/cercor/bhp024.

- Bell, C.C., Han, V.Z., Sugawara, Y., and Grant, K. (1997). Synaptic plasticity in a cerebellum-like structure depends on temporal order. *Nature* 387, 278–281.
- Bell, C.C., Han, V., and Sawtell, N.B. (2008). Cerebellum-like structures and their implications for cerebellar function. *Annu. Rev. Neurosci.* 31, 1–24.
- Caporale, N., and Dan, Y. (2008). Spike timing-dependent plasticity: a Hebbian learning rule. *Annu. Rev. Neurosci.* 31, 25–46.
- Cunningham, J., Nicol, T., Zecker, S.G., Bradlow, A., and Kraus, N. (2001). Neurobiologic responses to speech in noise in children with learning problems: deficits and strategies for improvement. *Clin. Neurophysiol.* 112, 758–767.
- de Boer, J., and Thornton, A.R. (2008). Neural correlates of perceptual learning in the auditory brainstem: efferent activity predicts and reflects improvement at a speech-in-noise discrimination task. *J. Neurosci.* 28, 4929–4937.
- Dean, I., Harper, N.S., and McAlpine, D. (2005). Neural population coding of sound level adapts to stimulus statistics. *Nat. Neurosci.* 8, 1684–1689.
- Fritz, J.B., Elhilali, M., David, S.V., and Shamma, S.A. (2007). Auditory attention—focusing the searchlight on sound. *Curr. Opin. Neurobiol.* 17, 437–455.
- Fujino, K., and Oertel, D. (2003). Bidirectional synaptic plasticity in the cerebellum-like mammalian dorsal cochlear nucleus. *Proc. Natl. Acad. Sci. USA* 100, 265–270.
- Galbraith, G.C., Bhuta, S.M., Choate, A.K., Kitahara, J.M., and Mullen, T.A., Jr. (1998). Brain stem frequency-following response to dichotic vowels during attention. *Neuroreport* 9, 1889–1893.
- Galbraith, G.C., Amaya, E.M., de Rivera, J.M., Donan, N.M., Duong, M.T., Hsu, J.N., Tran, K., and Tsang, L.P. (2004). Brain stem evoked response to forward and reversed speech in humans. *Neuroreport* 15, 2057–2060.
- Gutschalk, A., Micheyl, C., and Oxenham, A.J. (2008). Neural correlates of auditory perceptual awareness under informational masking. *PLoS Biol.* 6, e138.
- Hermann, J., Pecka, M., von Gersdorff, H., Grothe, B., and Klug, A. (2007). Synaptic transmission at the calyx of Held under in vivo like activity levels. *J. Neurophysiol.* 98, 807–820.
- Kaltenbach, J.A., and Godfrey, D.A. (2008). Dorsal cochlear nucleus hyperactivity and tinnitus: are they related? *Am. J. Audiol.* 17, S148–S161.
- Kanold, P.O., and Young, E.D. (2001). Proprioceptive information from the pinna provides somatosensory input to cat dorsal cochlear nucleus. *J. Neurosci.* 21, 7848–7858.
- Kraus, N., and Nicol, T. (2005). Brainstem origins for cortical ‘what’ and ‘where’ pathways in the auditory system. *Trends Neurosci.* 28, 176–181.
- Krishnan, A., Xu, Y., Gandour, J., and Cariani, P. (2005). Encoding of pitch in the human brainstem is sensitive to language experience. *Brain Res. Cogn. Brain Res.* 25, 161–168.
- Langner, G. (1997). Neural processing and representation of periodicity pitch. *Acta Otolaryngol. Suppl.* 532, 68–76.
- Luo, F., Wang, Q., Kashani, A., and Yan, J. (2008). Corticofugal modulation of initial sound processing in the brain. *J. Neurosci.* 28, 11615–11621.
- Magee, J.C., and Johnston, D. (1997). A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. *Science* 275, 209–213.
- Magnusson, A.K., Park, T.J., Pecka, M., Grothe, B., and Koch, U. (2008). Retrograde GABA signaling adjusts sound localization by balancing excitation and inhibition in the brainstem. *Neuron* 59, 125–137.
- Malenka, R.C., and Bear, M.F. (2004). LTP and LTD: an embarrassment of riches. *Neuron* 44, 5–21.
- Markram, H., Lubke, J., Frotscher, M., and Sakmann, B. (1997). Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* 275, 213–215.
- Musacchia, G., Sams, M., Skoe, E., and Kraus, N. (2007). Musicians have enhanced subcortical auditory and audiovisual processing of speech and music. *Proc. Natl. Acad. Sci. USA* 104, 15894–15898.
- Nahum, M., Nelken, I., and Ahissar, M. (2008). Low-level information and high-level perception: the case of speech in noise. *PLoS Biol.* 6, e126.
- Oertel, D. (1999). The role of timing in the brain stem auditory nuclei of vertebrates. *Annu. Rev. Physiol.* 61, 497–519.
- Park, T.J., Brand, A., Koch, U., Ikebuchi, M., and Grothe, B. (2008). Dynamic changes in level influence spatial coding in the lateral superior olive. *Hear. Res.* 238, 58–67.
- Perrot, X., Ryvlin, P., Isnard, J., Guenot, M., Catenoix, H., Fischer, C., Mauguire, F., and Collet, L. (2006). Evidence for corticofugal modulation of peripheral auditory activity in humans. *Cereb. Cortex* 16, 941–948.
- Rudy, B., and McBain, C.J. (2001). Kv3 channels: voltage-gated K⁺ channels designed for high-frequency repetitive firing. *Trends Neurosci.* 24, 517–526.
- Russo, N.M., Nicol, T.G., Zecker, S.G., Hayes, E.A., and Kraus, N. (2005). Auditory training improves neural timing in the human brainstem. *Behav. Brain Res.* 156, 95–103.
- Russo, N.M., Skoe, E., Trommer, B., Nicol, T., Zecker, S., Bradlow, A., and Kraus, N. (2008). Deficient brainstem encoding of pitch in children with Autism Spectrum Disorders. *Clin. Neurophysiol.* 119, 1720–1731.
- Schreiner, C.E., and Winer, J.A. (2007). Auditory cortex mapmaking: principles, projections, and plasticity. *Neuron* 56, 356–365.
- Shore, S.E., and Zhou, J. (2006). Somatosensory influence on the cochlear nucleus and beyond. *Hear. Res.* 216–217, 90–99.
- Song, P., Yang, Y., Barnes-Davies, M., Bhattacharjee, A., Hamann, M., Forsythe, I.D., Oliver, D.L., and Kaczmarek, L.K. (2005). Acoustic environment determines phosphorylation state of the Kv3.1 potassium channel in auditory neurons. *Nat. Neurosci.* 8, 1335–1342.
- Song, J.H., Skoe, E., Wong, P.C., and Kraus, N. (2008). Plasticity in the adult human auditory brainstem following short-term linguistic training. *J. Cogn. Neurosci.* 20, 1892–1902.
- Steinert, J.R., Kopp-Scheinflug, C., Baker, C., Challiss, R.A., Mistry, R., Hausteil, M.D., Griffin, S.J., Tong, H., Graham, B.P., and Forsythe, I.D. (2008). Nitric oxide is a volume transmitter regulating postsynaptic excitability at a glutamatergic synapse. *Neuron* 60, 642–656.
- Strait, D.L., Skoe, E., Kraus, N., and Ashley, R. (2009). Musical experience and neural efficiency: effects of training on subcortical processing of vocal expressions of emotion. *Eur. J. Neurosci.* 29, 661–668.
- Suga, N. (2008). Role of corticofugal feedback in hearing. *J. Comp. Physiol. A. Neuroethol. Sens. Neural. Behav. Physiol.* 194, 169–183.
- Trussell, L.O. (1999). Synaptic mechanisms for coding timing in auditory neurons. *Annu. Rev. Physiol.* 61, 477–496.
- Tzounopoulos, T. (2008). Mechanisms of synaptic plasticity in the dorsal cochlear nucleus: plasticity-induced changes that could underlie tinnitus. *Am. J. Audiol.* 17, S170–S175.
- Tzounopoulos, T., Kim, Y., Oertel, D., and Trussell, L.O. (2004). Cell-specific, spike timing-dependent plasticities in the dorsal cochlear nucleus. *Nat. Neurosci.* 7, 719–725.
- Tzounopoulos, T., Rubio, M.E., Keen, J.E., and Trussell, L.O. (2007). Coactivation of pre- and postsynaptic signaling mechanisms determines cell-specific spike-timing-dependent plasticity. *Neuron* 54, 291–301.
- von Gersdorff, H., and Borst, J.G. (2002). Short-term plasticity at the calyx of held. *Nat. Rev. Neurosci.* 3, 53–64.
- Weinberger, N.M. (2007). Associative representational plasticity in the auditory cortex: A synthesis of two disciplines. *Learn. Mem.* 14, 1–16.
- Wong, P.C., Skoe, E., Russo, N.M., Dees, T., and Kraus, N. (2007). Musical experience shapes human brainstem encoding of linguistic pitch patterns. *Nat. Neurosci.* 10, 420–422.
- Zhang, W., and Linden, D.J. (2003). The other side of the engram: experience-driven changes in neuronal intrinsic excitability. *Nat. Rev. Neurosci.* 4, 885–900.
- Zheng, Y., Baek, J.H., Smith, P.F., and Darlington, C.L. (2007). Cannabinoid receptor down-regulation in the ventral cochlear nucleus in a sailcylate model of tinnitus. *Hear. Res.* 228, 105–111.