Overview: Development and Plasticity of the Central Auditory System

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1. Some Good Reasons for Studying CNS Auditory Development and Plasticity

Basic science studies of the auditory system have provided neuroscience with some of its most instructive examples of highly-specialized functions arising from unique structures (e.g., reviews by Carr and Soares 2002; Fettiplace and Ricci2003; Fuchs et al. 2003; Pollak et al. 2003; Ryugo and Parks 2003)]. Working out the developmental mechanisms by which these structures and functions arise continues to provide information of great value to general developmental biology (Riley and Phillips 2003) as well as understanding of how the many complex elements coalesce during normal development to form a functional auditory system (Rubel et al. 1998).

Two facts add additional importance to studies of auditory system development and plasticity. First, very large numbers of people experience significant hearing loss and the often-profound disruptions of personal development and social life that follow. Because the human auditory system matures over at least the first decade of life, understanding how early hearing loss affects the development of the central auditory system and auditory processing is of great importance for optimizing the treatment of hearing loss in children (Moore 2002).

Second, because sensorineural hearing loss was the first neural sensory disorder to be treated successfully with a prosthesis, the neurobiological and psychophysical knowledge of human patients' and animal subjects' adaptation to use of cochlear implants forms the intellectual basis for future developments in brain-machine interfaces (Mussa-Ivaldi and Miller 2003). The continuing hope that induced hair-cell regeneration will someday be able to reverse sensorineural hearing loss in people (Bermingham-McDonogh and Rubel 2003; Kawamoto et al. 2003) adds to the importance of understanding how variations in input to the central auditory system can affect its function at all stages of life.

1.1 The Many Meanings of "Plasticity"

Although there is no controversy about the meaning of "development," it may indeed be true that, as one prominent scientist was recently quoted as saying, "'plasticity' is the most abused word in neuroscience" (Holloway 2003, p. 80). The term has been applied to such a broad range of phenomena (recovery of function after injury, adult neurogenesis, synaptic changes associated with learning, experience-dependent reorganization of cortical sensory maps, etc.) that it sometimes seems to mean little more than a capacity to change. Since the ability to change or adapt--over millennia, decades, months and milliseconds-- is a well-recognized feature of nervous systems, it is questionable if the term "plasticity" any longer has value as an aid to learning,

discovery, or experimental problem-solving. Perhaps it has become an example of what Holmes (1921) described as "inadequate catch words...phrases which originally were contributions, but which, by their very felicity, delay further analysis for fifty years... [and indicate] a slackening in the eternal pursuit of the more exact." Although the editors of this volume maintain some reservations about the excessively plastic meaning of "neural plasticity," they also acknowledge that there is no other commonly-used term that describes the same range of changes in the nervous system. And, in its broadest sense, the term really does apply aptly to the contents of the present volume, whose expert authors variously define "plasticity" as alterations in structure, connections or function that occur in response to experimental manipulations such as hearing loss, injury or overstimulation—but not use-dependent changes during normal development (Friauf, Chapter 3); any change in the structure or function of the binaural auditory system induced by altered inputs, occurring either naturally as a consequence of head growth or as a result of the introduction of abnormal inputs (Moore and King, Chapter 4); or as systematic long-term changes in the response of neurons to sound as a result of experience (Weinberger, Chapter 5). Clearly, with respect to the definition of "plasticity," the editors and authors of this volume have embraced the masterful approach to word meaning presented by Carroll (1872): "When I use a word," Humpty Dumpty said, in rather a scornful tone, "it means just what I choose it to mean—neither more nor less." "The question is," said Alice, "whether you *can* make words mean so many different things." "The question is," said Humpty Dumpty, "which is to be master—that's all."

1.2 Accomplishments and Challenges

The ultimate goal of developmental neurobiology is to understand, at a predictive causal level, the biological mechanisms that produce mature function in the auditory system. En route to that destination investigators have labored to establish the normal developmental sequences of behavioral, anatomical, physiological and molecular events that define the process of maturation (Rubel et al. 1998). When the basic timetable of ontogeny is known, experimental manipulations can be used to determine which of many identified mechanisms are necessary and sufficient to permit normal development of particular features of normal hearing. The six review chapters in this book cover a spectrum of issues in the development of audition but all also describe experimental manipulations that illuminate ontogenetic mechanisms responsible for the development of particular aspects of central auditory system development.

Rubel, Parks and Zirpel (Chapter 2) focus on development of the cochlear nucleus (CN), among the best understood of the CNS auditory centers. These authors first review the molecular

mechanisms responsible for specification, selective aggregation and migration of CN neurons and find that relatively little is known about these critical steps in development of the central auditory system. Although there is some normal correlative data suggesting that cadherins and ephrins-Eph receptor signaling are important in selective aggregation of the CN, Rubel et al. conclude that further progress will require considerably more experimental study of the molecular mechanisms by which the CN cell groups are specified as auditory neurons in the early rhombencephalon, how these neurons migrate selectively to the lateral brainstem, and how they aggregate in the appropriate pattern to form the striking mosaic pattern of the mature CN. In their review of the innervation of the CN by cochlear nerve axons, Rubel et al. note the substantial amount of normative data on spatio-temporal patterns of innervation and the surprisingly precise nature of these processes at the earliest stages of development. These authors also emphasize the relative paucity of evidence concerning the molecular mechanisms responsible for the bifurcation of ingrowing cochlear nerve axons, their topographic arrangement in the subdivisions of the CN, the formation of highly-specialized axon terminals on appropriate target neurons, and the establishment of tonotopic axes that are not aligned with any of the basic embryonic axes. Recent data relating the complex and transient expression patterns of certain ephrins and Eph receptors to the organization of afferent axons in the CN and higher auditory centers are described. Because the deafferented CN was the best early example of the essential role of afferent synaptic input in survival of some CNS neurons, there is a relatively rich literature describing the mechanisms by which cochlear nerve synapses and activity preserve CN neurons. Rubel, Parks and Zirpel (Chapter 2) review the detailed evidence concerning 1) the natural history of age-dependent deafferentation-induced death and atrophy of CN neurons, 2) presynaptically-released glutamate's role as the trophic agent responsible for mediating afferent-dependent survival of CN neurons, 3) the role of excessive intracellular calcium concentrations produced via calcium-permeable AMPA receptors in causing CN neuron death, and 3) the ability of calcium-dependent phosphorylation of the CREB transcription factor to prevent death in those CN neurons that survive deafferentation. These authors emphasize the unusual calcium challenges presented to CN neurons, the special calcium-homeostatic mechanisms these neurons employ to survive, and the involvement of anti-apoptotic genes in the sharply age-dependent effects of deafferentation on CN neuron survival.

In reviewing the extensive research literature on normal development of the mammalian superior olivary complex (SOC), Friauf (Chapter 3) notes how many key events occur prior to the onset of hearing: neurogenesis, cell migration, axon and dendrite outgrowth, target selection, and synaptogenesis. The fact that these events do not proceed sequentially from periphery to center

but rather in parallel is also noted, as is the relatively precise topography of initial axonal projections, which are then subjected to activity-dependent refinement. One particularly interesting aspect of SOC development is the presence of excitatory and inhibitory synaptic inputs during development of many SOC neurons and Friauf reviews the evidence for competitive interactions among these developing neurotransmitter systems. The SOC provide dramatic examples of aberrant functional projections induced by deafferentation of immature auditory neurons. Although the capacity of the auditory pathway to make these major structural changes is restricted to the period before the onset of hearing, the size and structural complexity of SOC neurons remain dependent upon normal auditory input well past hearing onset.

In their review of plasticity in binaural hearing, Moore and King (Chapter 4) note that adjustments in binaural processing are probably involved in the natural response to growth-related changes in head size and other natural changes in interaural cues, as well as disease- and injury-induced hearing asymmetries. The deleterious effect of early otitis media on development of binaural hearing in children can be persistent, which has important implications for education, pediatrics, and otolaryngology. The persistence of binaural plasticity into later life also suggests that balancing spectra between the two ears should be an important goal in treatment of adult hearing loss. This life-long plasticity prompts Moore and King to conclude that individual variations in CNS structure and behavioral performance, including use-dependent changes within an experiment, should be seen not as evidence of poor experimental control but rather of the malleable response of a living system. Research on binaural plasticity in the computational map of auditory space in the midbrain has created one of the most successful experimental systems for investigating the role of sensory experience in shaping the developing brain. As Moore and King note, some progress has been made in understanding the cellular mechanisms of these phenomena but much remains unclear. These authors also emphasize the importance of extending cellular studies of binaural plasticity to the thalamus and auditory cortex.

Although studying plasticity in the auditory cortex is important, it is particularly difficult, for reasons Weinberger explains in Chapter 5. He focuses on the challenges of designing the most informative experiments, challenges which arise in large part from the differing perspectives of sensory physiologists, who have mainly been interested in isolating sensory processes from experience-dependent effects during experiments, and of learning and memory specialists, who have not directed much attention to the capacity for learning in structures outside the medial temporal lobe. Weinberger notes that there are two disparate views of how learning is involved in the functions of the auditory cortex. One view is that experience-dependent plasticity is just another parameter, along with stimulus parameters like frequency and sound level, that has to be

taken into account during experiments. In this approach, there is often an implicit assumption that auditory function can be understood adequately without regard to behavior, so that learning is regarded merely as a modulator of normal auditory cortical neuron function rather than an embedded influence in all auditory processing. An opposing view holds that an adequate account of the auditory system requires investigation within the context of awake and behaving organisms, a position which makes many interesting experiments impossible or exceptionally difficult. Weinberger argues for a broadly integrative approach to studies of learning in auditory cortex, using all the available techniques (and inventing new ones) while evaluating the extent to which auditory function studied in the anesthetized state or reduced preparation reflects the reality of the behaving organism.

Analysis of auditory neuron function in awake behaving organisms has yielded some of its most impressive results in the study of bird song. As Brenowitz and Woolley (Chapter 6) discuss, the study of neural plasticity in bird song has also led neuroscience to recognize the existence of ongoing generation and replacement of projection neurons in the endotherm brain and hormonally-induced seasonal changes in the morphology, pharmacology and physiology of CNS neurons. Since both birdsong and human speech are learned early in life, young birds and children must hear adult vocalizations in order to imitate them accurately and each species shows an innate predisposition to learn conspecific vocalizations. Both song and speech acquisition have an early perceptual phase in which models of the sounds are listened to and memorized. These sensory templates then guide vocal production, with auditory feedback being necessary for both the development and maintenance of normal song and speech. After reviewing the considerable body of evidence concerning the neural mechanisms involved in each stage of vocal learning, Brenowitz and Woolley describe the most important open questions for research in this field: these include the basis of innate auditory preferences for conspecific song; the factors determining the opening and closing of the sensitive period for memorization of song models; the interaction of steroid hormones, neurotrophins, neurotransmitters and their receptors during development and adult plasticity; the functional significance of ongoing neuronal replacement in the song system; and the molecular determinants of song system plasticity at different stages of life.

The realization that many, if not most, Drosophila genes have homologues with similar functions in mammals has underscored the value of studying nervous system functions in the most advantageous subjects, which in a number of cases are insects. Lakes-Harlan (Chapter 7) approaches plasticity in the insect auditory system by considering four contexts in which it occurs Plasticity during development provides several interesting examples. Because many insects add

sensory receptor cells throughout life, central circuits must be continuously modified to accommodate them. Similarly, there is epigenetically-mediated variation in auditory cell number and connections in individual animals of even isogenetic lineages. Activity-dependent modifications of the auditory system during development or in mature animals include habituation, experience-dependent changes in sound-mediated behaviors, and deprivation-sensitive growth of auditory neurons. Lakes-Harlan also discusses several examples of modulatory effects of hormones or behavioral status on auditory system function and reviews the extensive literature on post-injury compensatory plasticity in insects.

1.3 Conclusions

This volume includes representative contributions from most of the areas of current research on plasticity in the developing auditory system. As is perhaps clear from the summaries of the chapters given above, the field embraces investigations ranging from cellular studies of normal development to experimentally- or pathologically-induced reorganizations in connectivity and function to the effects of normal sound-related context-dependent learning. Because of the wide range of biological mechanisms encompassed, the field necessarily relies on the full range of neuroscience methods, from molecular genetics to pharmacology to psychophysics and functional brain imaging. The peculiarities of the auditory system differentiate the study of its plasticity from comparable efforts in other neural systems. While the complexity of subcortical auditory pathways and the incompletely defined organization of auditory cortex present unique difficulties for experimenters, the richness of behaviorally-relevant information conveyed by acoustic stimuli offers many unique opportunities. Due to the relatively high prevalence of hearing loss in neonates and children, the clinical relevance of understanding CNS consequences of early deafness will likely continue to engender support for basic science studies of auditory system plasticity. If researchers in this field continue to apply to the auditory CNS the full range of technical and conceptual approaches available for investigating neural development, the study of auditory CNS plasticity should continue to advance general understanding of CNS development as well as better treatment of early hearing loss.

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