Editorial

Deficient brainstem encoding in autism

Beginning students of human neuroanatomy are invariably frustrated by the brainstem, the relatively small but exceedingly complex region of the central nervous system (CNS) that is first understood mainly as the communicating link between cortex and spinal cord. Confusion about the complex structure and function of the brainstem is no doubt exaggerated by the contrasting ease with which major landmarks of the cerebral hemispheres, along with obvious neuroanatomical structures subjacent to the cortex, can be discerned and whose general functions seem easy to describe (and memorize).

And while the student quickly comes to understand that the brainstem is vitally important as a center of vegetative control and arousal, in addition to being the necessary thoroughfare for ascending and descending sensory-motor fibers, it is the cortex that seems far more interesting. After all, the cortex occupies a position of rostral supremacy and overarching size, and is universally acclaimed to be the seat of "higher" cognitive functions. Thus, while lesions in the brainstem can result in death or pervasive vegetative state, lesions of comparable size in the cortex result in specific and focal neurological and/or cognitive deficits. The detection and definition of such deficits are not only theoretically interesting, but have become the stock in trade of clinical neurology and neuropsychology.

In the field of human sensory electrophysiology the cortex has also reigned supreme, with an extensive literature spanning more than 50 years concerning long-latency (approximately 100 ms and beyond) "cortical" evoked potentials. Moreover, the importance of higher cortical processing has been reinforced by event-related potential (ERP) studies, in which the "event" can be far more interesting than merely a physical sensory stimulus. This includes, for example, stimuli with discriminative or cognitive meaning (Näätänen, 1992), or even affective valence (Ofek and Pratt, 2005). Thus, not only for beginning students of neuroanatomy, but also for researchers in the field of human electrophysiology, there is a basis for thinking that most of what is interesting and important takes place mainly within higher regions of the CNS.

This thinking was not undone even when it was shown that short-latency (less than approximately 10 ms) auditory brainstem responses (ABR) to brief acoustic stimuli could be extracted from the human electroencephalogram (EEG) by widening amplifier bandpass and delivering greater numbers of computer-averaged trials (Jewett et al., 1970). Thus, the ABR became important in the assessment of hearing, including infants (Klein, 1985), as well as in the detection of neuropathology such as acoustic neuroma (Selters and Brackmann, 1977), and mental retardation syndromes (Squires et al., 1980). However, the ABR failed to capture the interest of most researchers studying higher cognitive functions such as attention and learning. After all, the ABR components only originate in the brainstem, not in the "higher" cortex.

Yet there was always reason to believe that the brainstem had much to reveal when it came to the processing of auditory signals. This expectation was obvious considering the complex anatomy of multiple nuclei and crossed and uncrossed pathways which are marvelously unique to the auditory brainstem. Indeed, not only is there the obligatory system of afferent fibers carrying sensory information to the auditory cortex, but there is also an extensive system of descending efferent fibers that synapse all along the auditory pathway, extending even to the outer hair cells of the basilar membrane (Guinan, 1996; Suga et al., 2000). Interestingly, the efferent fiber count may actually exceed the number of afferent fibers, which is counterintuitive if the principal purpose of the auditory system is to passively convey acoustic information from receptor to auditory cortex for final and more complex processing.

Animal studies also reinforced the expectation that the human auditory brainstem might be more actively and dynamically involved in processing sensory information. This expectation began with early studies like that of Hernandez-Peon et al. (1956) who showed that altered states of

visual attention modified evoked-response amplitudes in the cochlear nucleus of unanesthetized cats. Yet, while many early human studies did demonstrate selective attention effects on long-latency cortical ERPs (Näätänen, 1992), attempts to show similar influences on the ABR were largely unsuccessful (e.g., Collet and Duclaux, 1986; Connolly et al., 1989; Hackley, 1993; Hilliard and Picton, 1979; Picton and Hilliard, 1974; Woods and Hilliard, 1978), leading to the conclusion, once again, that important auditory processing in humans takes place mainly, if not exclusively, in the cortex. (However, see Perrot et al., 2006, for recent convincing evidence of corticofugal modulation of peripheral auditory activity in humans.)

1. Brainstem transcription of speech

In order to record the ABR it is necessary to deliver very brief (e.g., 100 μs) acoustic clicks or sine pulses that do not overlap the sequence of evoked ABR waves. Such brief stimuli may have ecological significance for many animals, such as the snap of a twig in predator/prey scenarios. But for humans a much stronger case can be made for the ecological significance of the most human of all activities, namely, the processing of language. And, consistent with the complexities of the auditory brainstem in humans, it seemed reasonable to assume that the effects of attention, learning, and even subtle forms of neuropathology might be uniquely detected in the brainstem coding of language.

To detect such coding, however, an electrophysiological measure of acoustic signal processing in the brainstem is required that yields reliable information about important aspects of language, such as the fundamental voicing frequency ($f0$), which codes obvious distinctions between male and female voices; slower patterns of $f0$ pitch change (prosody), which convey supra-segmental information about intention and emotion; faster pitch changes that code essential linguistic information such as the tonal inflections of Mandarin Chinese; and still faster pitch changes that code consonants and consonant–vowel transitions.

Such a measure of brainstem activity exists in the form of the frequency-following response (FFR), which reliably reproduces many of the periodic frequency properties of ongoing acoustic stimuli (Smith et al., 1975). This response periodicity is attributed to phase-locking neurons synchronized to each stimulus cycle, but with ensemble latencies similar to that of ABR wave V, thereby assuring a brainstem origin of the response. Thus, the FFR provides direct evidence concerning brainstem coding of speech and music sounds whose elements consist of "pitch" and "harmonics" (timbre/formants) and "timing" (ranging from consonants to rhythm in music) (Banai and Kraus, in press).

2. Reciprocal cortical–subcortical interactions: the dynamic brainstem

When the dependent measure of neural activity is the FFR, the effects of selective attention at the level of the hu-

man brainstem become more tractable (e.g., Hoormann et al., 2000, 2004; Galbraith and Arroyo, 1993; Galbraith et al., 2003). Moreover, the effect appears more robust when the stimuli are speech sounds (Galbraith et al., 1995, 1998). And in exciting recent results, it is apparent that auditory brainstem function is malleable as a result of lifelong language (Krishnan et al., 2004, 2005; Xu et al., 2006) and music (Musacchia et al., 2007; Wong et al., 2007) experience, as well as short-term training (Russo et al., 2005; Song et al., in press). Consequently, it appears that in the normal system, cortical functions such as language, music, memory, and attentional focus act to shape subcortical sensory circuitry. Such top-down control is necessarily mediated via the extensive corticofugal efferent system.

3. Abnormal brainstem processing in autism

In this issue of *Clinical Neurophysiology* we are introduced to a quite remarkable study (Russo et al., 2008) coming from the laboratory of Nina Kraus, reporting abnormal brainstem processing in children with autism spectrum disorder (ASD). They observed the subcortical representations of prosodic speech in children with ASD as compared with typically developing (TD) children. By recording FFRs evoked by speech syllables with descending and ascending pitch contours they were able to isolate a subgroup of ASD children with deficient pitch tracking, as evidenced by increased frequency and slope errors (both measures of pitch-coding accuracy over the duration of the stimulus) and reduced phase locking (quantified by a running/lagged autocorrelation function over the course of the response).

Russo et al. (2008) note that while "only a subset of our population showed abnormalities in the auditory brainstem it is consistent with the findings of other investigators and also consistent with the known heterogeneity within and between diagnostic categories of the autism spectrum" (p. 1720). Thus, it should not be surprising that only a subset of the ASD population showed brainstem abnormalities. It is surely asking too much for any single measure of brain activity to uniformly discriminate all forms of ASD; after all, it must be remembered that the "S" stands for *spectrum*. Even so, a remarkable finding of the Russo et al. study is that the different subgroups of ASD children did not differ in behavioral tests of receptive and expressive language, but did differ significantly in FFR measures. This is an impressive result suggesting that the FFR paradigm "could conceivably be utilized to screen for severe deficits in pragmatic language in infants or young children, which may be indicative of early symptoms of ASD" (p. 1720). This would seem to be especially significant in the testing of infants, since brainstem auditory pathways are myelinated and functional even before birth (Moore et al., 1995; Yakovlev and Lecours, 1967). Moreover, there is reason for optimism in the possible treatment of autism, since it appears that children with poor brainstem function are

particularly likely to benefit from auditory training (Hayes et al., 2003; King et al., 2002; Warrier et al., 2004).

What is impressive, beyond the significance of the factual results presented by Russo et al. (2008), is the logical and experimental pathway, based on extensive research, which led to their study of ASD. The Kraus lab had previously noted that children with reading disorders have problems with brainstem representation of timing and harmonics, but not pitch (Banai et al., 2005; Cunningham et al., 2002; Johnson et al., 2005, 2007; King et al., 2002; Wible et al., 2004), which they have attributed, at least in part, to faulty corticofugal shaping of subcortical sensory function (Kraus and Banai, 2007). Timing and harmonic cues of speech are mainly responsible for perceiving "what" is said (the verbal message), consistent with the phonological processing inherent in reading disorders. But some children with autism have a disordered representation of pitch, and are notorious for incorrectly perceiving the "intention" of what is said. To better assess these distinctions in terms of brainstem processing, Kraus and Nicol (2005) developed a conceptual framework whereby acoustic aspects important for pitch, timing and timbre can be disambiguated and possibly related to the functionally segregated cortical streams known as "what", "where" pathways (Kaas and Hackett, 1999; Rauschecker and Tian, 2000; Romanski et al., 1999). This conceptual advance and its implementation in the expert system (e.g., musicians) and clinical populations (e.g., autism, poor readers) have allowed the Kraus Lab to make fundamental advances in how we think about the shared biological resources underlying the neural processing of the signals important for language and music.

All of this now returns full-circle to the developmental role and ongoing influence of the cortex, and whether or not, or how, it fulfills its role of rostral importance. One obvious scenario is that brainstem dysfunction in disordered populations occurs because deficient development of language at cortical levels does not trickle down to allow normal shaping of the subcortical sensory infrastructure. There is evidence for this in brainstem–cortical interactions with respect to hemispheric dominance (Abrams et al., 2006), speech in background noise (Wible et al., 2004) and the representation of fine-grained stimulus differences (Banai et al., 2005). However, it is also possible that the auditory system is shaped in precisely the reverse, with inherently abnormal brainstem anatomy and physiology being the primary source of distorted inputs to the cortex, which subsequently "learns" abnormal processing patterns. Such questions can only be answered by prospective and longitudinal studies in which some infants are found to manifest deficient brainstem encoding prior to the development of abnormal patterns at the cortical level; and, most significantly, prior to the appearance of abnormal behavioral phenotypes. Whatever the case, the importance of brainstem encoding in both normal and abnormal language processing is now confirmed.

The powerful sensory-cognitive perspective and analytic techniques demonstrated in this issue of *Clinical Neurophysiology* by the Kraus Lab will be most helpful in providing definitive answers to many vital questions concerning dynamical brainstem function. Indeed, the unique and rigorous analyses of FFR waveforms employed by these authors have set a very high standard for future researchers.

References

Abrams DA, Nicol T, Zecker SG, Kraus N. Auditory brainstem timing predicts cerebral asymmetry for speech. J Neurosci 2006;26:11131–7.

Banai K, Kraus N. The dynamic brainstem: implications for CAPD. In: McFarland D, Cacace A, editors. Current controversies in central auditory processing disorder. San Diego, CA: Plural Publishing Inc.; in press.

Banai K, Nicol T, Zecker SG, Kraus N. Brainstem timing: implications for cortical processing and literacy. J Neurosci 2005;25:9850–7.

Collet L, Duclaux R. Auditory brainstem evoked response and attention. Acta Otolaryngol 1986;101:439–41.

Connolly JF, Aubry K, McGillivary N, Scott DW. Human brainstem auditory evoked response fails to provide evidence of efferent modulation of auditory input during attentional tasks. Psychophysiology 1989;58:333–42.

Cunningham J, Nicol T, King C, Zecker SG, Kraus N. Effects of noise and cue enhancement on neural responses to speech in auditory midbrain, thalamus and cortex. Hear Res 2002;169:97–111.

Galbraith GC, Arbagey P, Branski R, Comerci N, Rector P. Intelligible speech encoded in the human brainstem frequency-following response. NeuroReport 1995;6:2363–7.

Galbraith GC, Arroyo C. Selective attention and brainstem frequency-following responses. Biol Psychol 1993;37:3–22.

Galbraith GC, Bhuta SM, Choate AK, Kitahara JM, Mullen Jr TA. Human brainstem frequency-following responses to dichotic vowel stimuli during attention. NeuroReport 1998;9:1889–93.

Galbraith GC, Olfman DM, Huffman TM. Selective attention affects human brain stem frequency-following response. NeuroReport 2003;14:735–8.

Guinan JC. Physiology of olivocochlear efferents. In: Dallos P, Popper AN, Fay RR, editors. The cochlea. New York: Springer; 1996. p. 435–502.

Hackley SA. An evaluation of the automaticity of sensory processing using event-related potentials and brain-stem reflexes. Psychophysiology 1993;30:415–28.

Hayes EA, Warrier CM, Nicol TG, Zecker SG, Kraus N. Neural plasticity following auditory training in children with learning problems. Clin Neurophysiol 2003;114:673–84.

Hernandez-Peon R, Scherrer H, Jouvet M. Modification of electric activity in cochlear nucleus during attention in unanesthetized cats. Science 1956;123:331–2.

Hilliard SA, Picton TW. Event-related brain potentials and selective information processing in man. In: Desmedt JE, editor. Cognitive components in cerebral event-related potentials and selective attention. Progress in clinical neurophysiology, vol. 6. Basel: Karger; 1979. p. 1–51.

Hoormann J, Falkenstein M, Hohnsbein J. Early attention effects in human auditory-evoked potentials. Psychophysiology 2000;37:29–42.

Hoormann J, Falkenstein M, Hohnsbein J. Effects of spatial attention on the brain stem frequency-following potential. NeuroReport 2004;15:1539–42.

Jewett DL, Romano NM, Williston JS. Human auditory evoked potentials: possible brain stem components detected on the scalp. Science 1970;167:1517–8.

Johnson KL, Nicol TG, Kraus N. Brain stem response to speech: a biological marker of auditory processing. Ear Hear 2005;26:424–34.

Johnson KL, Nicol TG, Zecker SG, Kraus N. Auditory brainstem correlates of perceptual timing deficits. J Cogn Neurosci 2007;19:376–85.

Kaas JH, Hackett TA. 'What' and 'where' processing in auditory cortex. Nat Neurosci 1999;2:1045–7.

King C, Warrier CM, Hayes E, Kraus N. Deficits in auditory brainstem pathway encoding of speech sounds in children with learning problems. Neurosci Lett 2002;319:111–5.

Klein AJ. Frequency and age-dependent auditory evoked potential thresholds in infants. Hear Res 1985;16:291–7.

Kraus N, Banai K. Auditory processing malleability: focus on language and music. Curr Dir Psychol Sci 2007;16:105–9.

Kraus N, Nicol T. Brainstem origins for cortical 'what' and 'where' pathways in the auditory system. Trends Neurosci 2005;28:176–81.

Krishnan A, Xu Y, Gandour J, Cariani P. Encoding of pitch in the human brainstem is sensitive to language experience. Cogn Brain Res 2005;25:161–8.

Krishnan A, Xu Y, Gandour JT, Cariani PA. Human frequency-following response: representation of pitch contours in Chinese tones. Hear Res 2004;189:1–12.

Moore JK, Perazzo LM, Braun A. Time course of axonal myelination in the human brainstem auditory pathway. Hear Res 1995;87:21–31.

Musacchia G, Sams M, Skoe E, Kraus N. Musicians have enhanced subcortical auditory and audiovisual processing of speech and music. Proc Natl Acad Sci USA 2007;104:15894–8.

Näätänen R. Attention and brain function. Hillsdale, NJ: Erlbaum; 1992, 494 p.

Ofek E, Pratt H. Neurophysiological correlates of subjective significance. Clin Neurophysiol 2005;116:2354–62.

Perrot X, Ryvlin P, Isnard J, Guénot M, Catenoix H, Fischer C, et al. Evidence for corticofugal modulation of peripheral auditory activity in humans. Cereb Cortex 2006;16:941–8.

Picton TW, Hilliard SA. Human auditory evoked potentials. II. Effects of attention. Electroencephalogr Clin Neurophysiol 1974;36:191–200.

Rauschecker JP, Tian B. Mechanisms and streams for processing of "what" and "where" in auditory cortex. Proc Natl Acad Sci USA 2000;97:11800–6.

Romanski LM, Tian B, Fritz J, Mishkin M, Goldman-Rakic PS, Rauschecker JP. Dual streams of auditory afferents target multiple domains in the primate prefrontal cortex. Nat Neurosci 1999;2:1131–6.

Russo NM, Skoe E, Trommer B, Nicol T, Zecker S, Bradlow A, et al. Deficient brainstem encoding of pitch in children with autism spectrum disorders. Clin Neurophysiol 2008;119:1720–31.

Russo NM, Nicol TG, Zecker SG, Hayes EA, Kraus N. Auditory training improves neural timing in the human brainstem. Behav Brain Res 2005;156:95–103.

Selters WA, Brackmann DE. Acoustic tumor detection with brain stem electric response audiometry. Arch Otolaryngol 1977;103:181–7.

Smith JC, Marsh JT, Brown WS. Far-field recorded frequency-following responses: evidence for the locus of brainstem sources. Electroencephalogr Clin Neurophysiol 1975;39:465–72.

Song JH, Skoe E, Wong PCM, Kraus N. Plasticity in the adult human auditory brainstem following short-term linguistic training. J Cogn Neurosci, in press.

Squires N, Aine C, Buchwald J, Norman R, Galbraith G. Auditory brainstem responses abnormalities in severely and profoundly retarded adults. Electroencephalogr Clin Neurophysiol 1980;50:172–85.

Suga N, Gao E, Zhang Y, Ma X, Olsen JF. The corticofugal system for hearing: recent progress. Proc Natl Acad Sci USA 2000;97:11807–14.

Warrier CM, Johnson KL, Hayes EA, Nicol T, Kraus N. Learning impaired children exhibit timing deficits and training-related improvements in auditory cortical responses to speech in noise. Exp Brain Res 2004;157:431–41.

Wible B, Nicol T, Kraus N. Atypical brainstem representation of onset and formant structure of speech sounds in children with language-based learning problems. Biol Psychol 2004;37:299–317.

Wong P, Skoe E, Russo N, Dees T, Kraus N. Musical experience shapes human brainstem encoding of linguistic pitch patterns. Nat Neurosci 2007;10:420–2.

Woods DL, Hilliard SA. Attention at the cocktail party: brainstem evoked responses reveal no peripheral gating. In: Otto D, editor. New perspectives in event-related potential research. Washington, DC: United States Government Printing Office; 1978. p. 230–3.

Xu Y, Krishnan A, Gandour J. Specificity of experience-dependent pitch representation in the brainstem. NeuroReport 2006;17:1601–5.

Yakovlev PI, Lecours A. The myelogenetic cycles of regional maturation of the brain. In: A. Minkowski, editor. Regional development of the brain in early life. Oxford: Blackwell Scientific Publication; 1967. p. 3–70.

Gary Cloyd Galbraith
*Mental Retardation Research Center,
Department of Psychiatry and Biobehavioral Sciences,
David Geffen School of Medicine,
University of California at Los Angeles,
Los Angeles, CA 90024, USA*
Tel.: +1 909 444 7442; fax: +1 909 444 2832
E-mail address: garyg@ucla.edu