Plasticity in the Developing Auditory Cortex: Evidence from Children with Sensorineural Hearing Loss and Auditory Neuropathy Spectrum Disorder

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Abstract

The developing auditory cortex is highly plastic. As such, the cortex is both primed to mature normally and at risk for reorganizing abnormally, depending upon numerous factors that determine central maturation. From a clinical perspective, at least two major components of development can be manipulated: (1) input to the cortex and (2) the timing of cortical input. Children with sensorineural hearing loss (SNHL) and auditory neuropathy spectrum disorder (ANSD) have provided a model of early deprivation of sensory input to the cortex and demonstrated the resulting plasticity and development that can occur upon introduction of stimulation. In this article, we review several fundamental principles of cortical development and plasticity and discuss the clinical applications in children with SNHL and ANSD who receive intervention with hearing aids and/or cochlear implants.

Key Words: Auditory neuropathy spectrum disorder, central auditory maturation, cochlear implants, cochlear nerve deficiency, cortical auditory evoked potential, experience-dependent plasticity, hearing aids

Abbreviations: ABR = auditory brainstem response; ANSD = auditory neuropathy spectrum disorder; ASSR = auditory steady state response; CAEP = cortical auditory evoked potential; CM = cochlear microphonic; CND = cochlear nerve deficiency; CNS = central nervous system; DPOAE = distortion product otoacoustic emission; IHC = inner hair cells; IT-MAIS = Infant Toddler Meaningful Auditory Integration Scale; OAE = otoacoustic emission; PTA = pure tone average; REEL-3 = Receptive-Expressive Emergent Language Test Third Edition; SNHL = sensorineural hearing loss; TEOAE = transient evoked otoacoustic emission

The central auditory system is highly plastic in early childhood. During periods of increased cortical plasticity, sensory deprivation (e.g., hearing loss) can lead to developmental abnormalities. However, the fact that the cortex is highly plastic also means that intervention can produce positive effects. Because the time during which the cortex is most responsive to intervention is finite, proper timing of intervention is vital. Thus, at least two factors may be important for taking advantage of the brain’s plasticity for management of a sensory disorder such as hearing loss: (1) input or stimulation and (2) timing. These two factors have proven to be critical to the plasticity of the auditory cortex in children with sensorineural hearing loss (SNHL). On the other hand, relatively little is known about cortical development and plasticity in children with auditory neuropathy spectrum disorder (ANSD). In this review, we summarize principles of cortical plasticity in SNHL and more recent work aimed at characterizing central auditory maturation and plasticity in children with ANSD.

GENERAL PRINCIPLES OF CENTRAL MATURATION AND PLASTICITY

Neuroplasticity, or the ability of neuronal groups to adjust function based upon input, is present throughout a human’s lifetime. The potential for neuroplasticity appears to be greatest at the level of the cortex, with development being more dependent upon

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environmental input rather than innate mechanisms (see Buonomano and Merzenich, 1998, for a review; Hartmann et al, 1997; Kral, 2007). At the cortical level, various sensory and cognitive systems interact and adjust functional properties based upon experience and learning. At no time is human cortical neuroplasticity greater than during the first years of life. During this developmental period, cortical neurons cultivate in abundance, creating a framework upon which various cortical systems build and begin to mature. Thus, input to the cortex provided by experience and environment is key during early development when neuroplasticity is at peak levels (Sur et al, 1988, Pallas, 2001, Eggermont, 2008).

In early development, neuroplasticity reaches its highest levels due to developmental physiologic changes. Neurons at the level of the cortex proliferate rapidly in the first 3.5 yr of life, in areas including visual, auditory, and prefrontal cortices (Huttenlocher and de Courten, 1987; Huttenlocher and Dabholkar, 1997). This growth results in an overabundance of synapses, or connections between neurons. Rapid myelination of axons occurs as well during this time. By 1 yr of age, the cortex demonstrates the presence of all six layers (Moore and Guan, 2001). After approximately 4 yr of age, cortical neurons in the visual, auditory, and prefrontal cortices undergo a pruning phase, during which extraneous neurons and their synapses are eliminated from the respective sensory system if not functionally necessary (Huttenlocher and de Courten, 1987; Huttenlocher and Dabholkar, 1997).

The mechanisms that drive pruning and refinement of cortical neural circuits are still largely under debate. However, several components of the process have been identified. For example, as early as 1947, Hebb introduced the principle of coincidental activity. That is, neural circuits that exhibit both the requisite levels and patterns of concurrent activity are stabilized throughout development, while the brain eliminates those with insufficient levels or abnormal patterns of synchronized activity (i.e., “neurons that fire together, wire together”) (Goodman and Shatz, 1993; Katz and Shatz, 1996). More recent findings have supported these notions and expanded upon them. For instance, it appears that neurotrophins, a category of proteins found in both the peripheral and central nervous system (CNS), are instrumental in plasticity (see McAllister et al, 1999, for a review). That is, these activity-dependent molecular factors may be responsible, to a large degree, for both molecular changes within neurons (i.e., modulation of levels of membrane excitability) and neuronal morphology and connectivity, such as axonal branching, dendritic modification, and mediation of number of synapses. It also seems that there is a limited amount of neurotrophins available in the cortex, especially in layer 4, the target layer of thalamo-cortical projections (Riddle et al, 1997). Coincident activity appears to alter the function and structure of connected neurons, at least in part by triggering release of restricted neurotrophins. These constraints set up a true competition between neurons for establishing and maintaining activity-dependent and neurotrophin-mediated connections.

Where excitatory activity (i.e., long-term potentiation and depression; LTP and LTD, respectively) was once thought to be the primary mediator of development and plasticity, it now appears that inhibitory activity in the CNS may be instrumental in the opening and closing of critical periods, or finite periods of time during which the brain is most plastic. Strong evidence has been provided for the notion that sensory experience initiates systematically increasing inhibitory activity in the cortex (Foeller and Feldman, 2004). Variations in the levels of inhibitory activity appear to mark both the beginning and end of critical periods (Fagiolini and Hensch, 2000; Hensch, 2005). In all, it seems that a proper balance of excitatory and inhibitory activity is requisite for typical cortical maturation, especially in terms of critical period regulation. This has been specifically shown to be the case in the auditory cortex (Kral et al, 2001; Takesian et al, 2009).

While activity-dependent circuits are a major focus of cortical maturation, both intrinsic and extrinsic factors drive cortical development. Intrinsic factors include genetic encoding, maturation specific to designated regions of the cortex, and ongoing specific cortical developmental patterns occurring without external influence. Extrinsic factors include molecular input arising from afferent pathways and external input to the cortex from the environment (Pallas, 2001). Central development at lower levels of the brain tends to be driven intrinsically. For example, animal data have shown that basic auditory inputs into auditory cortex are present in congenitally deaf cats (Hartmann et al, 1997; see Kral and Eggermont, 2007, for a review). Such development is clearly intrinsic, as the primary central auditory development was not dependent upon successful auditory stimulation. Similar maturation has been identified for the central visual pathways in animals (Moore and Linthicum, 2007).

The mere existence of intrinsically developed pathways does not guarantee normal function or transmission of sensory information in auditory deprivation, even if stimulation such as auditory input is later introduced (Kral et al, 2000). This discrepancy is likely due to the significance of extrinsic factors in cortical development. Sur and colleagues (1988) demonstrated the importance of extrinsic stimulation. These investigators changed the pattern of stimulation to the auditory cortex, without changing the anatomy of the thalamo-cortical projections, by surgically inserting visual inputs to the thalamus into auditory thalamic areas in animals. Results from this study revealed that auditory cortex began to exhibit similarities to visual cortex (i.e., in
their structure and function). Thus, it seems that the pattern, in addition to the presence, of extrinsic stimulation is a key factor in cortical development.

Auditory input, specifically, has been shown to drive the development of both lower- and higher-level cortical connections. For instance, both reduced and delayed activity in superficial cortical layers has been observed in adult congenitally deaf cats stimulated via cochlear implants. Additionally, even less activation was present in deep cortical layers due to a lack of maturation in top-down projections from the superficial layers (Kral et al., 2000; Kral and Eggermont, 2007). Thus, though intrinsic factors contribute to anatomical development of the central auditory pathways, the absence of auditory stimulation is reflected in the lack of maturation of cortical layers.

**CENTRAL AUDITORY MATURATION AND PLASTICITY IN CHILDREN WITH SENSORINEURAL HEARING LOSS**

SNHL in children has allowed for a naturally occurring model of deprivation of cortical input and plasticity resulting from appropriate intervention. As such, the general principles of cortical maturation and plasticity described above can be applied in children with SNHL.

From investigations performed in both humans and animals, one can see that auditory neuroplasticity flourishes in the first few years of life, decreasing thereafter. It appears that intrinsic factors set up the cortical framework upon which extrinsic factors inform further development, such as the formation and strengthening of synapses (Holtmaat et al., 2006; Fu and Zuo, 2011). If the extrinsic auditory input is not delivered to the auditory cortex normally during optimal levels of plasticity, deficits are observed upon introduction of auditory stimulation (Ponton and Eggermont, 2001; Gordon et al., 2003, 2005; Sharma and Dorman, 2006). These assertions are based on large-scale studies of auditory cortical maturation in both congenitally deaf animals and human children who receive cochlear implants at various ages. For instance, Kral and colleagues (2005) reported several differences in cortical development between congenitally deaf cats and controls. One example of these differences is generation of functional synapses in the auditory cortices of congenitally deaf cats was delayed, as compared to young control cats, even after the introduction of hearing via a cochlear implant. Thus, while cortical neurons may have been in place, important connections were not formed in a normal manner in congenitally deaf cats. This synaptic deficit highlights one of the consequences of sensory deprivation and the significance of extrinsic stimulation to cortical development.

Evidence that insufficient stimulation of the cortex during optimal periods of plasticity can cause abnormalities has also been shown in humans. Using the P1 cortical auditory evoked potential (CAEP) which is considered a biomarker of auditory cortical maturation, research by Sharma and colleagues (Sharma et al., 1997; Sharma, Dorman, Spahr, 2002a, 2002b; Sharma, Dorman, Spahr, Todd, 2002; Sharma, Dorman, et al. 2005; Sharma, Martin, et al., 2005; Sharma and Dorman, 2006; Sharma et al., 2007, 2009) has demonstrated a sensitive period, or timeframe of optimal neuroplasticity, during which sound may be introduced to auditory cortex and promote normal, age-appropriate development. It should be noted that the term “sensitive period” significantly differs from “critical period” in that a critical period of neuroplasticity denotes a sudden cutoff after which a neural system is unable to adapt. In other words, neuroplasticity is absent outside of the critical period. In contrast, neuroplasticity reaches its height during a sensitive period, with reduced levels of plasticity still present as the period ends (Harrison et al., 2005; Tomblin et al., 2007). For instance, Sharma and colleagues (Sharma, Dorman, Spahr, 2002a, 2002b; Sharma, Dorman, Spahr, Todd, 2002; Sharma and Dorman, 2006) studied 245 children with congenital deafness, and showed that the latency of the P1 CAEP biomarker response decreases to within normal limits in children who receive a cochlear implant by 3.5 yr, while children implanted after the age of 7 yr demonstrate abnormal P1 CAEP responses. These abnormal responses persist even after years of experience with implant use. Children implanted between the ages of 3.5 and 7 yr show mixed auditory cortical development, with some children demonstrating P1 CAEP responses within normal limits, and others never reaching normal central auditory maturational status. These findings are consistent with both positron emission tomography (PET) imaging studies performed pre- and postimplantation in children, as well as intracortical studies in congenitally deaf cats (Hartmann et al., 1997; Kral et al., 2000, 2001; Lee et al., 2001; Kral et al., 2002; Oh et al., 2003; Kral et al., 2005; Kral and Tillein, 2006; Lee et al., 2007). Thus, 3.5 yr of age has been described as the terminus of the sensitive period for cochlear implantation in congenitally deaf children; approximately the same period of time during which exponential increases in synaptic density are observed and thereafter decrease (Huttenlocher and Dabholkar, 1997). After 7 yr of age, neuroplasticity in the central auditory system is significantly reduced, resulting in an inability of auditory cortex to process auditory information normally if sound is introduced at this time (Sharma, Dorman, et al., 2005). Furthermore, studies describing developmental outcomes of speech and language skills in children implanted at various ages indicate significantly improved outcomes with younger implantation age (Oh et al., 2003; Geers, 2006; Geers et al., 2009), especially for development of oral spoken language (Holt and Svirsky, 2008).
Clearly, it is crucial to determine candidacy for cochlear implantation in a timely manner, due to a sensitive period of neuroplasticity in the auditory cortex and resulting speech and language development. Because the P1 CAEP is a biomarker for central auditory maturation, measurement of this electrophysiological response provides a noninvasive means of direct assessment of the developmental status of auditory cortex in individual patients. The human CAEP contains several peak components that evolve across the lifespan, providing information indicative of various stages of cortical auditory maturation (Nääätänen and Picton, 1987; Gilley et al, 2005; Wunderlich et al, 2006; Sussman et al, 2008). For example, in normal-hearing children under the age of 7 yr, the P1 peak (occurring between 150–250 msec post-stimulus) decreases exponentially in latency values as the central auditory system forms efficient cortico-cortical circuits and as normal neuronal development increases processing speed of auditory information (Liégeois-Chauvel et al, 1994; Ceponiene et al, 1998). The P1 is generated in primary auditory cortex and secondary auditory cortices, arising from thalamo-cortical and cortico-cortical connections, or a “flow” of information between thalamus, and primary and secondary auditory cortices (Erwin and Buchwald, 1987; Liégeois-Chauvel et al, 1994; McGee and Kraus, 1996; Eggermont and Ponton, 2002). Because of the decrease in P1 peak latency with increases in age, measurement of this component can provide valuable information concerning central auditory development in children with hearing loss, including cochlear implant candidates and recipients (Sharma, Dorman, Spahr, 2002a, 2002b; Sharma, Dorman, Spahr, Todd, 2002). Between the ages of 7 and 11 yr, the N1 component (occurring around 100 msec poststimulus) begins to reliably appear, separating the P1 and P2 peak components (Ponton et al, 2000; Gilley et al, 2005). This component arises from several cortical generators and may be indicative of normal development for higher-level auditory processing (Nääätänen and Picton, 1987; Eggermont and Ponton, 2003). The P2 and N2 peak components of the CAEP response are not as well understood in terms of generator site or as neurophysiologic correlates of language processing though research is ongoing in examining the underlying neurophysiology of these components in relation to speech and language (Vidal et al, 2005; Gomot et al, 2007; Tong et al, 2009).

Analysis of the CAEP components allows for observation of the state and organization of the cortex as a result of appropriate intervention being provided within or outside of the sensitive period. For instance, if auditory deprivation is not ameliorated within the sensitive period, animal studies suggest that cortical “decoupling” may take place. Decoupling occurs when cortico-cortical loops between primary and secondary auditory cortices fail to develop properly because of the lack of auditory input. A lack of these connections results in higher-order auditory cortex decoupling from primary auditory cortex, prohibiting the top-down modulatory input from higher-order auditory cortex to primary auditory cortex, necessary for speech and oral language development (Kral et al, 2005; Kral, 2007; Kral and Eggermont, 2007). In humans, the absence of the N1 component (which reflects activity of cortico-cortical loops between higher-order auditory cortex and primary auditory cortex) in late-implanted children suggests that some degree of partial or complete decoupling may occur in long-term congenital deafness (Eggermont and Ponton, 2003; Kral, 2007; Kral and Eggermont, 2007; Sharma et al, 2007). Such decoupling likely leaves higher auditory cortices available for possible recruitment by other sensory modalities, such as somatosensory, visual, or multimodal input (cross modal re-organization) (Finney et al, 2001, 2003; Sharma et al, 2007; Gilley et al, 2008).

CROSS MODAL RECRUITMENT IN AUDITORY DEPRIVATION

Evidence for cross modal reorganization due to auditory deprivation has been demonstrated in several studies. Sharma et al (2007) showed evidence of somatosensory activation of auditory cortex in long-term congenital deafness, while Finney et al (2001, 2003) demonstrated auditory cortical activation by visual motion stimuli in congenitally deaf adults. Thus, cross modal plasticity appears to be a compensatory plasticity that, at the same time, may negatively affect auditory processing capability upon introduction of sound (e.g., a cochlear implant). Such recruitment also appears to be correlated with poor speech perception skills in cochlear-implanted adults and children (Doucet et al, 2006; Giraud and Lee 2007; Buckley and Tobey, 2011). For example, Doucet and colleagues (2006) presented visual motion stimuli to normal-hearing adults, adult cochlear implant users with good speech perception, and adult cochlear implant users with poor speech perception. Upon analysis, these researchers found a correlation between visual activation of temporal cortices (auditory cortical area) and speech perception scores. In other words, adult cochlear implant users who demonstrated less cortical activation in temporal cortices in response to visual stimuli also tended to show better speech performance, and adult cochlear implant users with greater cortical activation in temporal cortices in response to visual stimuli showed poorer speech performance. These results have been corroborated by Buckley and Tobey (2010), who found a correlation between the strength of cortical activation in response to visual stimuli in the right temporal cortex and poor speech perception scores in adult cochlear implant users. Similarly, Giraud and Lee (2007) reported that congenitally deaf children who showed greater than normal
activation in visual areas on PET scans showed poor outcomes after cochlear implantation.

In addition to cross modal recruitment of auditory areas by somatosensory and visual systems, there exists evidence of “rerouting” of introduced auditory information outside of auditory cortex to multimodal cortical areas in children implanted over 7 yr of age. Gilley et al (2008) recorded cortical responses to auditory stimulation for children who received cochlear implants under 3.5 yr of age and over 3.5 yr of age. Children implanted under 3.5 yr of age demonstrated auditory cortical activation relegated to the temporal cortex (auditory cortical area), whereas children implanted after 3.5 yr showed the greatest cortical response in the parietal region, an area involved in multisensory or multimodal processing. This finding suggests that cross modal re-organization appears to render higher-order auditory cortex unavailable for auditory processing, likely affecting oral language acquisition in late-implanted children.

Functionally, cross modal reorganization appears to result in enhanced processing of the recruiting modality. For example, visual processing abilities such as enhanced visual localization, visual attention, and motion detection have been reported to be enhanced in congenital deafness (Neville et al, 1983; Neville and Lawson, 1987; Bavelier et al, 2000, 2001; Dye and Bavelier, 2010; Lomber et al, 2010). As visual performance becomes enhanced, it is likely that auditory performance suffers. Such results have been observed in studies measuring auditory-visual integration. Children implanted after 3.5 to 4 yr of age show deficits in auditory-visual integration performance (Bergeson et al, 2005; Gilley et al, 2010). When visual and auditory information conflict, many implanted children tend to rely on visual information in comparison to normal-hearing children but show greater capability and success in the blending of auditory-visual information if implanted at a younger age (Schorr et al, 2005).

Overall, the results of auditory deprivation at the level of the cortex beyond the sensitive period may be seen as a sequence of events. First, due to a lack of auditory input there are deficits in the development of top-down modulatory connections between higher-order auditory cortex and primary auditory cortex; therefore, higher-order auditory cortex may decouple either partially or totally from primary auditory cortex, becoming available for recruitment by other sensory modalities (Kral and Eggermont, 2007). Second, recruitment of higher-order auditory cortex by visual and somatosensory systems may take place (Finney et al, 2001, 2003; Sharma et al, 2007). Third, if auditory input is introduced after the sensitive period and cross modal reorganization has occurred, it appears to be rerouted to multisensory cortices for higher-order processing (Gilley et al, 2008). Finally, functional consequences of this reorganization appear as increases in performance of the recruiter modality (e.g., increases in visual performance) and deficits in auditory performance, including sensory integration (e.g., auditory-visual fusion) (Bergeson et al, 2005; Schorr et al, 2005; Gilley et al, 2010). However, auditory cortical organization may be maintained if extrinsic auditory input is introduced in a timely fashion, resulting in normal maturation of the central auditory pathways and optimal outcomes in speech and language performance, as well as multisensory processing (Sharma, Dorman, Spahr, Todd, 2002; Holt and Svirsky, 2008; Gilley et al, 2010).

To summarize this portion of the review, we find that studies of animals and children with cochlear implants have provided a reasonable model of neuroplasticity in deafness with clear clinical implications for early intervention with appropriate auditory prostheses.
nerve itself, or any combination thereof (Starr et al., 1996; Harrison, 1998; Yasunaga et al., 1999; Varga et al., 2003; Schwander et al., 2007; Shapiro and Popelka, 2011). A disorder at any of these sites of lesion, or an amalgamation of them, leads to dys-synchrony of the auditory nerve and brainstem (Berlin et al., 1998; Kraus et al., 2000; Starr et al., 2001). Dys-synchrony, in turn, has been shown to cause primarily temporal processing deficits in patients with ANSD (e.g., Zeng et al., 1999, 2004, 2005; Rance et al., 2004; Rance, 2005; Michalewski et al., 2005; Zeng and Liu, 2006; Rance et al., 2004; Hassan, 2011), as opposed to spectral deficits that are the hallmark of SNHL. In other words, in order for the peripheral and central pathways to encode the fine-grained temporal acoustic information from the environment, these structures must be able to first transduce acoustic signals into neural impulses and then convey the rapid acoustic changes that are characteristic of these signals (e.g., formant transition, rate of speech) along the neural pathways in a precisely synchronous manner. Unfortunately, synchrony is degraded to differing degrees in patients with ANSD, leading to varying behavioral outcomes for speech understanding, especially in the presence of background noise (Kraus et al., 2000; Sininger and Oba, 2001).

While diagnosis of ANSD is relatively established, clinical decision making beyond diagnosis can be challenging. That is, many of the widely accepted clinical procedures for children with SNHL are not as effective for children with ANSD. For instance, for a child with SNHL who is diagnosed early, ABR and auditory steady state response (ASSR) thresholds can be used to provide early intervention in the form of amplification and/or cochlear implantation allowing relatively little time during which the child’s auditory system is deprived of stimulation. In contrast, an infant diagnosed with ANSD does not often follow the same time course for treatment, mainly because clinicians do not have ABR or ASSR results to guide intervention. Though stable behavioral thresholds may be obtained later in life for some patients, in other patients behavioral results may be variable or inconsistent. Given these and other clinical hurdles, which have the potential to compromise central auditory maturation in the ANSD population, innovative solutions that address cortical plasticity and development must be pursued.

The dys-synchronous activity of the auditory pathway in ANSD represents an abnormal pattern of extrinsically driven subcortical input to the cortex. Since the level and pattern of extrinsic stimulation coming into the cortex dictates, to a large degree, the developmental course of the latter (Sur et al., 1988; Pallas, 2001; Foeller and Feldman, 2004), one might make at least two conjectures as these principles are applied to ANSD. First, given a reduced level of input (resulting from the hearing loss that is often coexistent with ANSD) cortical development might be affected negatively (Starr et al., 2001). Second, it is reasonable to believe that a dys-synchronous or abnormal pattern of extrinsic input would cause cortical developmental abnormalities (Kraus et al., 2000; Rance et al., 2002; Sharma et al., 2011). In this scenario, important experience-dependent synaptic connections may not be made, or may be altered, in the developing brains of children with ANSD.

As previously mentioned, CAEPs have proven effective in the measurement of the developmental status of the auditory cortex. Until relatively recently, most investigations using CAEPs to measure cortical maturation focused on children with normal hearing and SNHL. However, several reports in the literature now illustrate the effective use of CAEP measures in children with ANSD (Rance et al., 2002; Campbell et al., 2011; Cardon and Sharma, 2011; Sharma et al., 2011). This may seem counterintuitive given that other evoked potentials from lower centers of the central auditory system are typically absent or unreliable in children with ANSD (e.g., ABR, ASSR; Rance et al., 2005). Kraus and colleagues (2000) assert that CAEPs may be measured despite absent ABR responses due to the fact that while the ABR measures action potentials in the auditory nerve and brainstem, CAEPs measure dendritic activity in the cortex. Thus, ABRs are much higher in frequency and more biphasic than CAEPs, which tend to be broader in shape and low frequency in comparison. Given these characteristics, when ABR sweeps that are out of synchrony by even a small degree (i.e., out of phase) are averaged, they are most often cancelled out. In contrast, because CAEP components typically comprise several tens of milliseconds (i.e., from the beginning to the end of a peak), some jitter in the timing of the evoked potential sweeps can still lead to an averaged waveform with observable, even normal, CAEP components. The fact that CAEPs can be measured in patients with ANSD, when traditional clinical tests provide limited information, positions this measure as a promising clinical tool to assess cortical development, plasticity, and function in patients with ANSD.

Recently, several studies have focused on central auditory maturation in children with ANSD using CAEPs. For example, Rance et al (2002) reported being able to reliably measure CAEPs in approximately 50% of children with ANSD. The children that presented with robust responses were also those who benefitted from amplification and performed well on measures of speech perception. These findings seem at first to suggest that children with ANSD differ in the level of cortical development, with some progressing relatively well and others not maturing typically. The former group also appears to receive some benefit from hearing aids. In addition, Rance et al (2002) suggest that the extent to which a given child’s auditory cortex has developed is important in predicting behavioral outcome.
The findings of Rance and colleagues were corroborated by recent findings from our laboratory (Sharma et al., 2011). Differences in cortical maturation were found in 21 children with ANSD who were fitted with hearing aids. CAEP measures of cortical maturation divided the 21 subjects into three discrete groups: (1) those with robust and replicable P1 responses of normal latency and amplitude; (2) children with replicable P1 responses of delayed latency and decreased amplitude; and (3) participants with absent or abnormal P1 responses. Additionally, a significant difference was found between the groups on a measure of auditory skill development (Infant Toddler Meaningful Auditory Integration Scale [IT-MAIS]; Zimmerman-Phillips et al., 2000), such that the children with normal P1 responses performed considerably better than the other two groups. Interestingly, the children with normal P1 responses were also fitted with hearing aids significantly earlier than the other two groups (i.e., on average at less than 1 yr of age). Finally, it is significant that behavioral auditory threshold was not significantly different between any of the groups, suggesting that, unlike SNHL, in ANSD pure tone hearing thresholds may not be correlated with cortical development or behavioral outcome. In all, results showed that there were distinct differences in cortical maturation throughout the group of children with ANSD, which may be attributable to differing degrees of dys-synchrony, but not auditory threshold. In addition, these data suggest that the developmental status of the cortex is highly correlated with behavioral outcome. Findings surrounding hearing aid fit age also seem to support the idea that timing of normal or improved input is important for typical cortical maturation. These conclusions may be of interest clinically as they provide a means to offer prognoses and have the potential to help guide management decisions.

**Cochlear Nerve Deficiency**

A particularly challenging form of ANSD is found in children diagnosed with cochlear nerve deficiency (CND). CND reflects hypoplasia (abnormally small VIII nerve, absence of many neural fibers) or aplasia (absence of VIII nerve), identified via magnetic resonance imaging (MRI) (Buchman et al., 2006; McClay et al., 2008; Huang et al., 2010; Roche et al., 2010; Maris et al., 2011). These children commonly present with a comorbid diagnosis of CND and ANSD, likely due to the poor conductivity of neural firing as a result of few functional neural fibers (Buchman et al., 2006; Walton et al., 2008). Recent results from our laboratory (Roland et al., 2012) report that CAEP measurements in these children were useful in verification of the presence or absence of the VIII nerve. For instance, we reported that three out of four children diagnosed with CND demonstrated robust P1 peak responses, indicating at least partial stimulation of the central auditory pathways via the VIII nerve. In two of these three patients, the CAEP was present despite abnormal ABR responses. Children with robust P1 responses who met all other candidacy criteria were fit with cochlear implants. Thus, the P1 peak response was useful in determining cochlear implant candidacy, including VIII nerve viability, for children diagnosed with CND.

While these and other studies provide initial evidence that cortical maturation is adversely affected by neural dys-synchrony and/or dys-function in ANSD (and coexisting CND), more work needs to be done to elucidate the details of central auditory maturation and plasticity in pediatric ANSD and to develop cortical biomarkers for assisting in clinical decisions. To this end, we discuss four cases of children with ANSD. Each of these cases illustrates different principles of cortical development and plasticity in the ANSD population.

**CASE REPORTS**

**Case 1**

SC (participant #8 in Sharma et al., 2011) was born at full term and relatively healthy. While he required supplemental oxygen for approximately 1 min at the time of birth, he quickly gained the ability to breathe and was found to be healthy otherwise. SC failed initial newborn hearing screening, though his parents reported no family history of hearing loss. Further diagnostic testing revealed abnormal ABR responses (i.e., absent wave V) with present and robust CMs bilaterally. In addition, SC’s distortion product otoacoustic emissions (DPOAEs) were absent bilaterally. When SC was a little older, behavioral pure tone audiometry yielded pure tone averages (PTAs) in the severe hearing loss range bilaterally (i.e., 85 dB HL). At this point, SC’s audiologists suggested a trial with binaural hearing aids. SC’s parents agreed to the trial but noted that they had observed SC hearing and responding to environmental sounds on many occasions prior to hearing aid fitting. SC was first fit with hearing aids at 0.68 yr. He also began to receive weekly speech and language therapy at this time. SC received a score of 39/40 on IT-MAIS testing performed following significant experience with hearing aids, indicating promising auditory skill development.

As a means to monitor the progress of SC’s central auditory maturation, P1 testing was performed both pre- and posthearing aid fitting at 0.43 and 0.75 yr, respectively. The prehearing aid fitting results showed replicable, albeit delayed, P1 responses, suggesting delayed maturation of the central auditory pathways. That is, the latency of the P1 peak was outside of the normal limits (i.e., 95% confidence intervals) for normal P1 latency development for SC’s age (Sharma, Dorman, Spahr, 2002b). In contrast, after some experience with amplification, replicable P1 responses of normal latency for his age were elicited.
These findings suggest normal development of the auditory cortex. Both waveform and latency trajectory results can be seen in Figure 1A and B.

SC’s case illustrates several points related to plasticity and maturation of the central auditory pathways in ANSD. For instance, prior to amplification, SC’s central auditory maturation was delayed. This suggests that the input provided to SC’s auditory system without the aid of amplification was insufficient to drive normal cortical development. In contrast, the addition of hearing aids to the system allowed SC’s auditory cortex to mature in a more typical manner.

Several researchers have argued that hearing aids likely do not provide adequate benefit for children with ANSD (e.g., Hood, 1999; Berlin et al, 1998). While it is probably true that many do not profit sufficiently from such devices, it appears that some do, at least in terms of cortical maturation. The latter point is supported by the current case, the studies previously discussed, and others (Rance et al, 2002; Pearce et al, 2007; Berlin et al, 2010; Cardon and Sharma, 2011; Sharma et al, 2011). Rance et al (2002) asserted that hearing aids might provide benefit for children with ANSD for several reasons. First, hearing aids serve to make speech elements more salient to their user, whether the patient has SNHL or ANSD. In addition, others (e.g., Javel, 1986) have noted that increasing the intensity of input to the cochlea, in turn, may cause at least two phenomena: (1) increased phase locking and synchronous discharge of IHCs and (2) an overall increase of IHCs and VIII nerve fiber activity. Because ANSD may arise from disordered phase locking (i.e., dys-synchrony) and/or fewer than normal functional IHCs or VIII nerve fibers, it is reasonable to believe that traditional amplification might help certain patients with ANSD, albeit a minority. Sharma et al (2011) conjectured that the children who exhibited normal CAEP responses with hearing aids likely had a milder form of ANSD (i.e., less severe dys-synchrony) than those who either had delayed or abnormal/absent P1 responses. If this is true, then merely amplifying incoming stimuli may prove to provide adequate benefit for those children with the mildest forms of ANSD, at least in terms of allowing normal central auditory maturation to progress.

It is also interesting to note that SC received his hearing aids at a relatively early age (0.68 yr). His hearing aid fit age was certainly within the sensitive period that appears to be important for treatment of children with SNHL (i.e., 3.5 yr; see Sharma, Dorman, Spahr, Todd, 2002; Sharma, Dorman, Spahr, 2002a; Sharma, Martin, et al, 2005), which may also be critical in the optimal treatment of children with ANSD. The concept of a sensitive period for treatment in ANSD is further supported by recent findings (Sharma et al, 2011), in which children with ANSD who were fit under approximately 1 yr of age had normal P1 responses and good behavioral outcome compared with children who were fit at later ages. These results are in keeping with animal studies that have demonstrated the existence of sensitive periods in development for animals reared in degraded listening environments (Chang and Merzenich, 2003; de Villers-Sidani et al, 2007), which may have some parallels with congenital ANSD. Overall, this case corroborates the critical nature of the timing aspect of plasticity in clinical intervention.

Case 2

JF (participant #6 in Sharma et al, 2011) was born at 31 wk gestation after a complicated pregnancy and delivery via cesarean section. Following birth, JF stayed in the NICU for 7 wk, during which he was...
treated for jaundice with a blood transfusion and required mechanical ventilation. In addition, JF presented with early feeding problems, which later resolved. JF failed his newborn hearing screening. Subsequently, diagnostic ABR testing performed at approximately 3 mo of age revealed present CM bilaterally. During the same testing session, present transient evoked otoacoustic emissions (TEOAEs) and DPOAEs were observed bilaterally. JF was fitted with binaural hearing aids at a very early age (0.36 yr). Later, it was determined via behavioral audiometric testing that JF had unaided PTAs of 38 and 70 dB HL in the right and left ears, respectively. In addition, aided testing yielded PTAs of 38 dB HL in the right ear and 41 dB HL in JF's left ear.

The Receptive-Expressive Emergent Language Test Third Edition (REEL-3; Bzoeh et al, 2003) was performed with JF's mother by his speech/language pathologist when JF was 3 mo old. The REEL-3 is a parent interview regarding receptive and expressive language that is commonly used in children up to 3 yr of age. This measure indicated that while JF scored in the normal range for his corrected age in the expressive language category, his scores for receptive language were delayed for his age. At 1.67 yr of age, JF's speech/language therapist performed a MacArthur Communicative Developmental Inventory (Fenson et al, 1993) with his mother. This assessment focuses on a child's developmental status on several categories of development by polling a parent or guardian as to the child's behavioral developmental performance. In the developmental category of Words and Gestures, JF scored severely below age-level expectations. Furthermore, JF showed a severe delay in use of vocabulary for his age on the Words and Sentences developmental category (<5th percentile). These findings lead JF's family to pursue cochlear implantation for him. A pre-implant MRI revealed normal VIII nerves. At 1.76 yr of age, JF received a cochlear implant in the left ear.

P1 testing was performed several times throughout JF's life and progression through his various treatments (Fig. 2A). Initially, even with significant experience with his hearing aids (from 0.67 up to 1.36 yr), no replicable P1 response could be identified. In contrast, replicable, but delayed, P1 responses were observed during testing that was done when JF had recently received his cochlear implant. Later results, however, revealed that JF's P1 latency systematically decreased until it finally entered the normal limits for P1 latency development when JF was 2.18 yr of age (0.44 yr of experience with the device) (see Fig. 2B).

Given that JF's precochlear implant P1 responses were absent and that hearing aids did not provide adequate stimulation to drive normal central auditory maturation, it is reasonable to argue that he had a more severe case of dys-synchrony than SC (Case 1). Since cochlear implantation caused a systematic decrease in P1 latency, such that by the latest recorded data point, JF's P1 results were normal, we might conclude that electric stimulation improved input sufficiently to promote normal cortical development. It should also be noted here that JF received his cochlear implant before the end of the sensitive period for treatment of children with SNHL (i.e., 3.5 yr). Thus, not only was the input to his auditory system improved, the timing also seemed optimal. CAEPs were instrumental in both determining candidacy and verifying treatment decisions in JF's case.

Several investigators have produced reports supporting the use of cochlear implants for treatment of children with ANSD (Miyamoto et al, 1999; Shallop et al, 2001; Trautwein et al, 2001; Rance and Barker, 2008, 2009; Berlin et al, 2010; Teagle et al, 2010; Fulmer et al, 2011). However, several of these reports caution
that while cochlear implantation seems to produce positive results in many children with ANSD, it is not optimal for all (see Case 3 below). That is, children with ANSD represent a heterogeneous group. As such, very few clinical decisions regarding the management and treatment of children with ANSD should be automatic. For example, Walton et al (2008) found that children with ANSD who had associated CND did not benefit as much from having received cochlear implants as those without CND. In fact, it is possible that the site of lesion of a given child’s ANSD may be correlated with his or her success with the device. That is, if the site of lesion is cochlear or synaptic, a cochlear implant is likely to bypass the problem areas and stimulate the VIII nerve directly, thereby restoring synchrony and resulting in good outcome. On the other hand, if the site of lesion is postsynaptic, in some cases a cochlear implant may not be able to overcome the anatomical and physiologic phenomena that lead to dys-synchrony, such as demyelination. Several investigators are attempting to devise methods of determining the site of lesion and the characteristics of pre- and postsynaptic forms of ANSD (e.g., Santarelli and Arslan, 2002; Varga et al, 2003; Santarelli et al, 2008, 2009; Dimitrijevic et al, 2011; Santarelli, 2011). In addition, ongoing investigations in our laboratory are focusing on determining the characteristics of successful cochlear implant use in children with ANSD.

Case 3

RB was born full term without complications. The family reports no family history of hearing loss. RB initially failed his newborn hearing screening in only the left ear. Upon diagnostic follow-up testing, his audiologist found absent TEOAEs bilaterally and limited presence of DPOAEs, despite normal middle ear function. In addition, RB presented with abnormal ABR morphology (i.e., no wave V), with present CMs bilaterally. These findings, taken together, ultimately lead to a diagnosis of ANSD.

Following several behavioral audiometry sessions, which consistently revealed profound rising to severe bilateral hearing loss, RB was fit with binaural hearing aids (approximately 1 yr of age). Subsequently, aided audiometry showed a mild sloping to severe hearing loss in the 0.5–4 kHz frequency range. Though at some frequencies RB’s functional gain with the devices had improved significantly, the managing team ultimately decided that traditional amplification was insufficient for RB. An MRI confirmed the presence of normal anatomy including VIII nerves bilaterally, cochlear, and internal auditory meatuses. Subsequently, RB received a cochlear implant in the right ear at 1.64 yr of age. Additional treatment included weekly home intervention for hearing, oral speech and language, and sign language from the age of 3 mo until RB was 3 yr old. RB now attends a center-based school that specializes in serving children with hearing loss.

Initial audiography and parent reports conveyed that RB was doing well with his implant. For instance, his parents mentioned on many occasions that RB did not like when the implant was off and would ask for it upon waking in the morning or after naps. However, as time passed, it became clear to the managing team (i.e., home intervention provider, speech/language therapist, audiologist) and family that RB had limited interest in sound and had very inconsistent responses of questionable reliability during behavioral audiometry testing. Parents and therapists also reported, on several occasions, significant variability in RB’s everyday performance (i.e., “good and bad hearing days”). Behavioral audiometry with the cochlear implant in place was inconsistent at best. However, the best thresholds that were obtained showed moderate hearing loss rising to normal auditory thresholds and speech awareness thresholds (SAT) between 20 and 30 dB HL.

Serial P1 testing was performed with RB to monitor progress with his cochlear implant (2.53, 3.61, and 4.19 yr of age; see Fig. 3A). Initial testing revealed a replicable P1 of normal latency for RB’s age. In contrast, the second testing session yielded P1 waveforms that were not replicable, despite several CAEP recording runs. Finally, during the most recent P1 appointment, RB produced P1 waveforms that exhibited a delayed P1 response that was only marginally replicable (Fig. 3B). IT-MAIS testing performed with RB at 3.61 and 4.19 yr of age yielded scores of 14/40 and 20/40, respectively. These seem to correlate well with RB’s P1 results suggesting that CAEP morphology and latency are correlated with behavioral outcome in ANSD (Rance et al, 2002; Sharma et al, 2011). It should be noted that the IT-MAIS is specifically designed to be administered to infants and toddlers. The fact that this measure has been used in other children with ANSD may be indicative of the severity of their auditory impairment.

Case 3 illustrates that even with optimal timing and input, the negative effects of a neural dys-synchrony cannot always be ameliorated by a cochlear implant. Though RB’s case is a difficult one, several assertions and conclusions can be made from studying it. For example, ANSD is a disorder that likely cannot be fully explained in every case with means and averages. While some patterns have been established in patients with ANSD (e.g., diagnostic criteria), it seems that there are many exceptions to proposed clinical rules in this population. For example, classically, OAEs are found to be present in patients with ANSD; however, this is not always the case (e.g., Berlin et al, 2010). Variability in patients with ANSD may be due to various factors such as the genetic, anatomical, and physiological heterogeneity of those with the diagnosis of ANSD, diversity of etiology, and differences in site of lesion (Rapin and Gravel, 2003; Hood, 2011). In addition, it appears...
that there is a wide spectrum of the severity of dysynchrony between patients with ANSD (Sharma et al., 2011). As such, care must be taken to consider each patient as an individual (Hood, 2011).

Furthermore, it is interesting to note that both RB’s parents and the professionals with whom he works have reported variability in RB’s listening capability from day to day. A number of accounts from the literature surrounding several neurologic disorders other than ANSD have reported similar intra-individual variability in performance (see MacDonald et al., 2006, for a review). For example, this phenomenon appears to be a hallmark of age-related cognitive decline, schizophrenia, attention deficit hyperactivity disorder (ADHD), dementia, and head injury. It seems, as well, that intra-individual variability can be a sign of various neural problems, such as degeneration and disconnectivity. Thus, it is not surprising that a variable pattern might be found in some with ANSD. In fact, some investigators have found variation in performance on various measures driven by changes in body temperature in children with ANSD (Starr et al., 1998; Varga et al., 2006). This case illustrates that CAEPs may provide an objective means to assess intra-individual variability in children with ANSD. We have noted that while some cases of children with ANSD benefit from cochlear implantation, others, such as RB, do not appear to share these results. Additional research is needed to elucidate the details of important factors in cochlear implantation in children with ANSD.

**Case 4**

KG was born at 26 wk gestation after a complicated pregnancy. She spent the following 116 days in the NICU, where she received several blood transfusions, underwent heart surgery, and remained on mechanical ventilation until she went home. While in the NICU, KG failed newborn hearing screening three times. Hearing loss was confirmed at approximately 5 mo of age, at which point a diagnosis of ANSD was made. Since diagnosis, behavioral auditory testing has revealed thresholds that have fluctuated between the moderate and severe hearing loss ranges bilaterally. KG was fitted with binaural amplification at approximately 8 mo of age. Aided behavioral audiometry confirmed aided auditory thresholds between 20 and 30 dBHL. In addition, from the time of hearing loss diagnosis to the present time, KG’s family has received weekly visits from two home interventionists: one who focuses on oral speech and language development and another who teaches American Sign Language (ASL) to the family.

We performed P1 testing with KG at 1.48 yr of age to evaluate the status of her central auditory maturation with the use of her hearing aids. Five CAEP recording runs—comprised of approximately 250 sweeps each (1251 sweeps total)—were executed with KG on the day of testing. When averaged together we saw a P1 of normal latency (see Fig. 4, bottom trace). On the surface, this normal P1 response appeared to be inconsistent with KG’s lower-than-expected score of 28/40 on the IT-MAIS. However, upon closer inspection of each of the five recording runs, we noted that while two of the CAEP runs yielded waveforms that were replicable (runs 3 and 4), the remaining runs’ waveforms had atypical morphology and did not replicate (Fig. 4, upper traces).
Case 4 further demonstrates the intra-individual variability inherent in some people with ANSD (Nash et al, in preparation; Starr et al, 1998; Uus, 2011). CAEP testing with KG showed neural inconsistency during an hour-long testing session. At times, the P1 response was normal in morphology and latency, indicating an appropriate and synchronous neural response for KG’s age. In contrast, during the other recording runs, the morphology of the CAEP was abnormal, such that no P1 could be identified, likely due to underlying neural dys-synchrony. In our experience, while possible in children with ANSD, this type of variability does not occur in CAEP recording in most children with normal hearing or children with SNHL, who presumably have appropriate and stable neural synchrony. Furthermore, it is interesting to note that the variability in CAEP recordings occurred after an early hearing aid fitting and more than 9 mo of hearing aid use. That is, despite appropriate aided auditory thresholds, timing, and use of the devices, a portion of KG’s cortical responses was still atypical. Ultimately, KG’s highly variable cortical responses were consistent with her lower-than-expected behavioral performance on the IT-MAIS. Thus, this case exhibits at least two important points: (1) hearing aids may not adequately improve neural synchrony in some patients with ANSD (consistent with Berlin et al, 1998, 2002, 2003; Rance, et al, 2002; Hood, 2011; Sharma et al, 2011); (2) even with a high degree of intra-individual variability, the auditory brain may be plastic enough to develop some degree of normal function, as indicated by the two runs exhibiting P1 responses of normal latency. In light of the results from Case 4, we suggest that multiple CAEP recordings of large sweep counts be performed in a given testing session to appropriately estimate the intra-individual variability in some patients with ANSD.

As reviewed in Cases 1–4, some of the commonly held principles of plasticity hold true in the ANSD population. However, much work remains to be done to fully characterize central auditory maturation and plasticity in children with ANSD. Both previously published data and two of the above cases suggest that providing appropriate input to the cortex and doing so early in life play an important role in the development of many children with ANSD. These reports also highlight CAEPs as a potentially useful tool that might be employed to determine candidacy for a given treatment and the efficacy of such intervention. However, it has also been shown that even treatment provided at a young age may not always ameliorate the negative effects of neural dys-synchrony on cortical maturation. Thus, the degree of severity of a given patient’s dys-synchrony may be predictive of outcome. In all, children with ANSD must be considered individually, although assessments of cortical maturation may provide clinicians and families with information that may positively guide management decisions.

**SUMMARY**

The principles that govern cortical maturation and plasticity are numerous and complex. However, as we have discussed in this review, two major principles of neuroplasticity direct clinical outcomes: (1) adequate stimulation provided to the cortex and (2) appropriate timing of this stimulation. Early intervention with appropriate auditory prostheses (such as cochlear implants) results in high likelihood of normal auditory cortical development in children with congenital deafness. In addition, recent work regarding central auditory maturation and plasticity in children with ANSD suggests that plasticity can often be harnessed via amplification and/or electrical stimulation for positive clinical outcomes in this patient population. The initial reports of CAEP measures of central auditory maturation in children with SNHL and ANSD appear promising in their ability to help determine a given patient’s candidacy for treatment and in verifying the effectiveness of the audiological intervention. A better understanding...
of the deleterious effects of absent, abnormal, and/or late auditory stimulation and the potential for plasticity via auditory prostheses in individual patients will allow us to better customize clinical management and rehabilitation for pediatric patients.

REFERENCES


