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Cortical Maturation and Behavioral Outcomes in Children with Auditory Neuropathy Spectrum Disorder

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Abstract

Objective—Auditory Neuropathy Spectrum Disorder (ANSD) affects nearly 10% of patients with sensorineural hearing loss. While many studies report abnormalities at the level of the cochlea, auditory nerve and brainstem in children with ANSD, much less is known about their cortical development. We examined central auditory maturation in 21 children with ANSD.

Design—Morphology, latency and amplitude of the P1 Cortical Auditory Evoked Potential (CAEP) were used to assess auditory cortical maturation. Children's scores on a measure of auditory skill development (IT-MAIS) were correlated with CAEPs.

Study Sample—Participants were 21 children with ANSD. All were hearing aid users.

Results—Children with ANSD exhibited differences in central auditory maturation. Overall, two-thirds of children revealed present P1 CAEP responses. Of these, approximately one third (38%) showed normal P1 response morphology, latency and amplitude, while another third (33%) showed delayed P1 response latencies and significantly smaller amplitudes. The remaining children (29%) revealed abnormal or absent P1 responses. Overall, P1 responses were significantly correlated with auditory skill development.

Conclusions—Our results suggest that P1 CAEP responses may be: (i) a useful indicator of the extent to which neural dys-synchrony disrupts cortical development, (ii) a good predictor of behavioral outcome in children with ANSD.

Keywords

P1 Cortical auditory evoked potential; central auditory maturation; Auditory Neuropathy Spectrum Disorder (ANSD); Auditory Neuropathy/Dys-synchrony (AN/AD); children

INTRODUCTION

Auditory Neuropathy/Spectrum Disorder (ANSD), also referred to as Auditory Neuropathy/Dys-synchrony (AN/AD) is a recently described form of hearing impairment (Starr et al., 1996). However, it is not a rare form of hearing loss, with estimates suggesting that approximately 10%–15% of patients with congenital sensorineural hearing loss (SNHL) present with this disorder (Berlin et al., 2010; Kirkim et al., 2008; Talaat et al., 2009). For nearly two decades, researchers and clinicians have produced reports of patients presenting with symptoms that include the presence of otoacoustic emissions (OAE), absent or grossly abnormal auditory brainstem responses (ABR) and stapedial reflexes, and, speech

perception and behavioral outcomes which are disproportionate to pure tone auditory thresholds. Unlike more traditional forms of SNHL which result mainly from abnormalities in cochlear (outer) hair cells (OHC), in ANSD, the outer hair cells appear to be functioning in many or most cases. Starr and colleagues (1996) proposed that the site of lesion in ANSD could be the cochlear receptors or inner hair cells (IHC), the synapse between the IHC and the VIII nerve, or the VIII nerve itself (e.g., demyelination).

ANSD can occur in the absence of any apparent medical problem, or it can be associated with a variety of other symptoms and conditions such as infectious diseases (e.g., mumps), genetic conditions (e.g., Freidreich's ataxia, Charcot Marie Tooth syndrome), neonatal insults such as anoxia, hyperbilirubinemia, acidosis and transiently with fever (See Kraus 2001 for a review). More recent studies have explored the genetic bases of abnormalities in patients with ANSD. For example, disruption of the DFNB9 gene, which encodes otoferlin, precedes problems with neurotransmitter release from the IHC to the VIII nerve (Yasunaga et al., 1999). Also, the DFNB59 gene, which encodes the protein Pejvakin, has been identified in many of the major nuclei along the auditory nerve in mice. Though the exact function of this protein is currently unknown, mutations of it seem to cause problems with neural conduction and have been proposed to be associated with ANSD (Schwander et al., 2007).

Unlike typical SNHL where the behavioral outcome is largely dependent on the severity of the hearing loss (Yellin, Jerger, & Fifer, 1989), in children with ANSD, speech and language skills do not appear to correspond with the behavioral audiometric findings (Deltenre et al 1999; Rance et al., 1999; Rance et al., 2002; Rapin & Gravel, 2003). The heterogeneity underlying this population and the lack of predictability regarding behavioral outcome make it difficult for clinicians to diagnose, understand and treat patients with ANSD, particularly young children.

After Starr and colleagues' (1996) initial characterization of patients with auditory neuropathy, the descriptor *auditory dys-synchrony* was added to the disorder (Berlin et al., 1998) to reflect the common defining characteristic that regardless of the site of lesion, patients show clear abnormalities in subcortical afferent conduction demonstrated by a lack of synchrony in the ABR. In order to produce a normal ABR, VIII nerve and brainstem neural populations have to be synchronously active (Kraus et al., 2000). This does not occur in patients with ANSD, but rather, these populations of neurons are activated in a dys-synchronous manner or with atypical patterns of neural synchrony resulting from a possible loss of fibers, constant or variable slowing of fibers, or demyelination (Starr, Picton & Kim, 2001).

It is commonly held that the brain requires both normal intrinsic and extrinsic factors for typical development. Cortical specification begins with molecular and genetic factors and then is further driven by sensory input (see Pallas, 2001 for a review). Many studies have shown that changing the pattern of afferent input to the cortex significantly affects cortical organization. For example, Sur, Garraghty, and Roe (1988) showed that re-routing visual thalamic inputs through the auditory thalamus caused auditory cortex to exhibit visual cortex-like properties. These and other studies suggest that cortical structure and function are modulated to a large extent by the pattern of the incoming signal. Therefore, it stands to reason that abnormal, or dys-synchronous, patterns of subcortical transmission, which occur in children with ANSD, have the potential to disrupt normal cortical development. Given that normal maturation and functioning of auditory cortical areas is a precondition for normal development of speech and oral language skills, it is reasonable to assume that a disruption of normal cortical maturational processes will result in diminished capacity for

speech/language acquisition in children with ANSD (Rance et al., 2002). However, very little is known about cortical neuromaturation and plasticity in children with ANSD.

One way to objectively measure the developmental status and limits of plasticity of the auditory cortical pathways is to examine the morphology, latency, amplitude and topography of cortical auditory evoked potentials (CAEPs). CAEPs have been successfully recorded in children and adults with ANSD (Starr et al, 1996; Kraus, et al., 2000; Rance et al, 2002; Cone, 2008; Narne, & Vanaja, 2008; Pearce, Golding, & Dillon, 2008; Michalewski et al., 2009). The latency of the first positive peak (P1) of the CAEP in children is considered a biomarker for maturation of the auditory cortical areas (Sharma, Dorman, & Spahr, 2002a; 2002b; Sharma et al., 2005). Evidence from intracranial recordings in humans, as well from animal models, suggests that the neural generators of the P1 CAEP originate from the thalamo-cortical projections to the auditory cortex and may represent the first recurrent activity in the auditory cortex (Eggermont & Ponton, 2003). P1 latencies are also believed to be modulated by second order processing in the auditory cortex, including input from feedback and recurrent loops between primary auditory and association areas (Kral & Eggermont, 2007). The P1 is a robust positivity occurring at around 100 – 300 milliseconds in children. Latency of the P1 reflects the sum of synaptic delays throughout the peripheral and central auditory pathways. The P1 peak latency varies as a function of age, and is therefore considered an index of cortical auditory maturation (Ponton et al., 2000; Sharma et al., 1997).

In this study, we examined the development of the P1 CAEP in 21 children with ANSD. Our aims were to 1) To document patterns of cortical maturation in ANSD; 2) To better understand the link between central auditory development and behavioral outcome in children with ANSD.

MATERIALS & METHODS

Subjects

The current study involved retrospective review of audiological records for 21 children clinically diagnosed with ANSD. Subjects' ages at the time of P1 CAEP testing ranged from 9 months to 11.5 years. However, the majority of participants were at or under three years of age. There were 13 males and 8 females. Case history information is provided in Table 1. All participants were fit with hearing aids. There was no single strategy used for fitting participants with hearing aids. Some were fit to the degree of loss and others were fit more conservatively based on whether the OAEs were present, depending on audiologist professional preference.

The 21 subjects were chosen based on the availability of complete electrophysiologic and behavioral results for each of them. Because many of these individuals had several CAEP test dates, the P1 result from the same or closest date to the time of behavioral testing was chosen to be included in the analysis.

Measures

Several physiologic and behavioral test results were taken into account in the current study. Clinical audiological tests included pure tone average (PTA; 500 Hz, 1kHz, 2kHz), otoacoustic emissions (TEOAE, DPOAE, or both), and click evoked auditory brainstem response (ABR). These measures are part of the standard clinical audiological battery and therefore are not described here. In addition, the P1 component of the cortical auditory evoked potential (CAEP) was recorded, and the Infant Toddler Meaningful Auditory Integration Scale (IT-MAIS) (Zimmerman-Phillips, Robbins, & Osberger, 2000) was administered. We provide methodological details on these two procedures below.

IT-MAIS

In 2000, Zimmerman-Phillips and colleagues introduced the Infant Toddler Meaningful Auditory Integration Scale (IT-MAIS) as an adaptation of the Meaningful Auditory Integration Scale (MAIS) (Robbins, Renshaw, & Berry, 1991) for young children. The IT-MAIS measures auditory skill development through a structured parent interview that is completed by a clinician. Questions focus on three main areas of auditory development. These include: 1) vocalization behavior; 2) alerting to sounds; 3) deriving meaning from sounds. The interviewer asks a total of ten open-ended questions to elicit responses from the parent. Each of the ten questions is scored from one (lowest) to four (highest) for a total of 40 points, at the most. Since its introduction, the IT-MAIS has been used consistently for studies of auditory skill development in children with hearing loss (e.g., McConkey Robbins et al., 2004), including ANSD (Peterson et al., 2003). Data have also been reported for the IT-MAIS in children with normal hearing (Kishon-Rabin et al., 2001). The IT-MAIS affords several advantages as a clinical measure. For instance, the evaluation can be completed for infants and young children who have short attention spans and/or who could not perform other measures of auditory skill development or speech perception because of developmental delay or other physical restriction. In addition, the measure is not language-biased.

P1 CAEP Recordings

Stimuli—CAEPs were recorded in response to a synthesized speech syllable /ba/. The duration of the speech sound was 90 ms. The stimulus was identical to the one used in Sharma et al. (1997, 2002a, 2002b). The five formant CV stimulus was generated using the Klatt speech synthesizer. The starting frequencies of F1 and F2 were 234 and 616 Hz, respectively. The center frequencies for the formants of the vowel/a/were 769, 2862, 3600 and 4500 Hz for F1, F2, F3, F4, and F5, respectively. F3, F4, and F5 were steady-state formants. The amplitude of voicing was constant for 80 ms and fell linearly to 0 in the last 10 ms of the stimuli. The fundamental frequency began at 103 Hz, increased linearly to 125 Hz over 35 ms and then decreased to 80 Hz over 55 ms.

The stimulus was presented at an offset-to-onset interstimulus interval of 610 ms. Stimuli were presented to the participants at suprathreshold levels via loudspeakers placed in a sound attenuating booth. Typically stimuli were presented at 75dB HL and all participants were tested with their hearing aids on. As needed, stimulus presentation levels were increased. Audibility was determined by reviewing audiological records and by patient observation during testing.

Electrophysiologic Recording Process

Subjects were seated comfortably in a reclining chair or on their parent's lap in a sound attenuating booth during testing. They watched a movie on a flatscreen monitor placed approximately four feet in front of them in the sound booth. The audio levels of the movie were muted during recording of the CAEPs. This has been shown to be an effective way of engaging youngsters (Kraus et al., 1995). Evoked potentials were collected using a Compumedics Neuroscan evoked potentials system. Silver/silver chloride cup electrodes were used for the recordings. The active electrode was placed at Cz. The reference electrode was placed on either one of the mastoids of the subject. The ground electrode was placed on the subject's forehead. Eye movements were monitored using a bipolar electrode montage (lateral outer canthus-superior orbital). P1 responses have been collected using an identical setup and stimuli in studies examining central auditory development in children with normal hearing and SNHL (e.g., Sharma et al., 2002a, 2002b)

Averaging was automatically suspended by the recording computer when eye blinks were detected. The recording window included a 100 ms pre-stimulus and 600 ms post-stimulus time. Responses were sampled at 1.0 kHz. Incoming evoked responses were analog filtered from 1.0 to 100 Hz. At least two runs of 300 response sweeps were collected for each subject. The typical test session including electrode application and evoked response recording lasted about 30 minutes.

Data Analysis for Electrophysiological Recordings

Sweeps greater than $\pm 100\mu\text{V}$ were rejected offline, after that the remaining sweeps were averaged to compute an averaged waveform. Individual subjects had at least two averaged CAEP waveforms of 300 sweeps each. If the waveforms were judged replicable based on visual inspection, then the waveforms were averaged together to create a grand average waveform for individual subjects. The P1 peak was defined as the first robust positivity in the waveform. Peak latencies were measured in milliseconds (ms). For subjects in whom P1 latencies were computed, the latencies were compared to the 95% confidence intervals for normal P1 latency development (Sharma et al, 2002a, 2002b). Absolute peak amplitudes were also observed. These were defined as the magnitude of positive deflection from zero, measured in microvolts (μV). Cross correlations and intra-class correlations were performed on the waveforms in the time window between 50 and 350 milliseconds (i.e., in the latency range of the P1 response) in order to quantify replicability of waveforms across two different recordings within a subject. While cross-correlations report the correlation of the waveforms according to their amplitude, the intra-class correlation takes into account wave shape, in addition to amplitude. We used values at zero milliseconds of the cross-correlation (i.e., no temporal shift of either waveform).

RESULTS

P1 morphology and latency

P1 morphology for individual subjects was independently rated by 2 experienced clinicians as typical or abnormal (Authors AS and GC). Waveforms that were judged as having normal or typical morphology were generally replicable across two runs and had an identifiable P1 peak for which a latency could be computed (comparable to our previous studies, e.g., Sharma et al., 2002; 2005). P1 latencies for children with normal morphology were compared to the 95% confidence interval for normal development of P1 latencies from Sharma et al. (2002a, 2002b). Waveforms were judged as abnormal based on the fact that the waves did not replicate across two or more runs (subject 18), showed no observable peak in the characteristic P1 time frame or flat and low amplitude morphology (subjects 17, 20, 21), or showed atypical morphology (subject 16, 19). In only one case the waveform was clearly non-replicable (subject 18). As described above, based on morphology, and latency, the subjects fell into three distinct groups: Children with normal P1 latency and morphology ($n = 8$), children with normal morphology but delayed P1 latency ($n = 7$), and children with abnormal or absent P1 responses ($n = 6$). P1 responses for all children relative to the 95% confidence intervals for normal P1 development (Sharma et al., 2002a, 2002b) are seen in Figure 1.

A one-way ANOVA revealed no significant differences between the three groups (i.e., children with normal, delayed or abnormal P1 responses) in either the cross-correlation ($p = 0.758$) or the intra-class correlation analyses ($p = 0.779$). These results suggest that there was not a difference in the overall replicability of the waveforms across the three groups as measured by the waveform correlation analyses. That is, regardless of whether there was an identifiable P1 peak, waveforms from each of the groups were replicable to a similar degree. For instance, though several of the children who had abnormal P1s had essentially flat

responses (e.g., participants 17, 20, and 21), the two waveforms that made up the grand average waveform had a similar (flat) wave shape, and thus received high scores on both cross correlations and intra-class correlations.

Grand averaged waveforms for each participant are presented below in Figure 2. Because these are stacked from oldest (top) to youngest (bottom), the expected decreases in waveform latencies and amplitudes with increasing age are generally seen for the group with normal P1 latencies, consistent with Sharma et al. (1997) and Ponton et al. (1996). We do not see this normal pattern of CAEP development for the group with delayed and abnormal or absent P1 responses.

P1 CAEP amplitude

Absolute (or baseline to peak) P1 peak amplitude (μV) was computed for each subject who presented with a replicable and recognizable P1 response (i.e., for children who had normal and delayed latency P1 responses). A one-way ANOVA performed between the groups with normal and delayed P1 responses showed a significant difference between the two groups' mean P1 amplitudes ($F=8.708$; $p = 0.011$). This suggests that the children with ANSD who showed delayed P1 latencies also significantly showed reduced amplitudes for the P1 responses (see Figure 3).

Planned comparisons of key variables

We performed planned comparisons for two key variables between the three groups of children (i.e., children with normal, delayed and abnormal P1's). These variables included pure-tone average and hearing aid fit age:

Pure-tone average—A one-way ANOVA did not yield a significant result when the unaided pure tone average (PTA) was compared across the three groups ($p = 0.425$). These results demonstrate that children with normal, delayed, and abnormal cortical responses could not be separated based on their hearing thresholds.

Age at which hearing aids were fitted—We compared the age at which hearing aids were fitted for children with ANSD across the three groups. The mean hearing aid fit ages for the normal, delayed and abnormal groups are shown in Figure 4. Overall, one-way ANOVA results revealed that mean fit age between groups was significantly different ($F = 5.377$; $p = .015$). Post-hoc Sheffe analysis revealed that mean hearing aid fit age for groups with normal and abnormal P1 responses were significantly different ($p = .018$).

IT-MAIS score

One-way ANOVA comparing the mean IT-MAIS scores between the three groups of children yielded a statistically significant main effect ($F = 10.441$; $p = .001$). Post-hoc Sheffe analysis showed a significant difference between the group with normal P1 responses and the groups with delayed ($p<0.013$) and abnormal ($p<0.002$) P1 responses. IT-MAIS scores were not significantly different ($p = .596$) between children who had delayed and abnormal P1 responses (Figure 5A). In addition, linear regression analysis revealed that P1 latency was a strong predictor of IT-MAIS results ($r = -0.86$; $r^2 = 0.74$) for children with normal and delayed P1 latencies (Figure 5B).

DISCUSSION

The goals of the current study were to examine central auditory development in children with ANSD and to examine the relationship between an electrophysiological measure of central auditory maturation (i.e., P1 CAEP) and a measure of behavioral auditory

development (i.e., IT-MAIS). Overall, the results of this study demonstrate that: (i) children with ANSD show distinct patterns of central auditory maturation as reflected by morphology, latency and amplitude of the P1 CAEP, and, (ii) P1 CAEP latencies are strong predictors of behavioral outcome (as measured by the IT-MAIS) in children with ANSD.

Children with ANSD fell into three distinct groups based on their P1 CAEP results. These were: 1) children with normal P1 waveform morphology, latency, and amplitude; 2) children with normal waveform morphology, but delayed P1 latency and decreased amplitude; 3) children with grossly abnormal waveform morphology, for whom P1 latency and amplitude could not be computed. That is, the majority, but not all, subjects demonstrated recordable cortical potentials. This finding is consistent with reports of previous studies that have measured CAEPs in pediatric patients with ANSD (Starr et al, 1996; Kraus, et al., 2000; Rance et al, 2002; Cone, 2008; Narne et al., 2008; Pearce et al., 2008; Michalewski et al., 2009). For example, Rance et al., (2002) reported that in a sample of 15 children with AN/AD, 50% showed absent CAEP responses, while 50% had present CAEP responses, of these 40% had normal P1 latencies, while 10% had delayed P1 latencies. Those figures are generally consistent with the present study, which found that 71% of participants presented with present CAEP (of whom 38% had normal P1 latencies and 33% had delayed P1 latencies) and 29% of participants had absent CAEP responses.

In the present study, while the majority of children showed replicable CAEP responses, all children showed absent auditory brainstem responses (ABR). Kraus et al (2000) have noted that the ABR measures spike discharges, or action potentials, in the axons of the auditory nerve, while CAEPs are thought to measure the summation of excitatory postsynaptic potentials (EPSPs) arising from dendritic zones in the cortex. Because the action potentials measured by the ABR are biphasic and high in frequency, they are cancelled when separated by mere fractions of a millisecond when averaged. On the other hand, CAEP components are low in frequency and broad in shape relative to the ABR. So, dys-synchronous firing, which could cause waves from subsequent CAEP sweeps to be separated by several milliseconds, can still result in a meaningful aggregate waveform (Kraus et al., 2000). However, as the level of underlying jitter increases, the aggregate CAEP response will be degraded to a higher degree due to fewer time-locked peaks contributing to the averaged CAEP waveform, and/or fewer than normal active nerve fibers responding (Starr, et al., 2001). This can result in lower than normal amplitudes and delayed latencies in the aggregate waveform (e.g., responses in Fig. 2b) and very low amplitude CAEP responses where no peak could be discerned (several responses shown in Fig. 2c).

Patterns of firing of subcortical inputs influence both neuronal connections and specificity of cortical areas (Pallas, 2001, Sur et al., 1988). In typical brain development, the extent to which neurons connect is also highly dependent on their pattern of firing. In early stages of cortical development, a surplus of neuronal connections is formed (synaptogenesis). As the cortex matures, appropriate sensory experience causes many of these neuronal connections to be eliminated (pruned). Neuronal patterns of firing which are most robust and consistent are the ones whose connections persist (see Goodman & Shatz, 1993 for a review). As this competition for connection goes on, stronger connections are made between pre- and post-synaptic neurons who fire most often and whose patterns are typical to that cortical area. In this scenario, dys-synchronous neuronal firing patterns in individuals with congenital ANSD could plausibly lead to abnormalities in synaptic pruning and/or result in strengthening abnormal neuronal connections leading to deficits in cortical development and organization. Given that the P1 CAEP is a reliable index of central auditory maturation, we can conclude that absent or delayed P1 responses in our study reflect the underlying delays and/or abnormalities in auditory cortical development, most likely resulting from highly dys-synchronous input patterns to the cortex.

On the other hand, typical P1 CAEP morphology, latency and amplitudes in children with ANSD (Fig. 2a) suggest a normal level of maturation of central auditory pathways, implying that the underlying neural dys-synchrony is mild enough to allow for normal cortical organization to occur. We are presently conducting longitudinal studies that examine whether these children continue to show a normal developmental trajectory for the CAEP over their lifespan (e.g., the emergence of the P1/N1/P2 complex described in normal adolescents, Gilley et al., 2006, Ponton et al., 2000; Sharma et al, 1997). Future studies should employ high density EEG and other brain imaging methods to examine in greater detail the cortical organization in children who exhibit normal and abnormal P1 responses. It should be noted that our study elicited P1 responses using a passive paradigm. Michalewski et al. (2005) have recently shown that attention may have a powerful effect on CAEPs in children with AN/AD. They reported that adults with AN/AD had absent CAEPs when elicited using a passive paradigm (similar to the present study), however, when subjects were asked to attend to the task, their CAEPs were present, albeit delayed. In future studies, we will examine the use of attentive paradigms for eliciting CAEPs in pediatric ANSD patients.

Previous studies have suggested a link between the severity of the underlying neural dys-synchrony, using standard clinical measures and CAEPs, in ANSD patients and their perceptual capabilities (Zeng et al., 1999; Kraus et al., 2000, Rance et al., 2002, Michalewski et al., 2005). The present results support this interpretation, in that, children with ANSD who had robust neural responses (i.e., CAEPs with normal morphology, latency and amplitude) showed the highest level of behavioral auditory skill development (as reflected by IT-MAIS scores), while those that had abnormal or delayed CAEP responses were associated with lower levels of perceptual auditory development. Since the majority of children in our study were infants or toddlers, the IT-MAIS provided a useful measure of their auditory skill development. However, as these children grow older, it would be useful to correlate their CAEP data against more definitive clinical tests of speech perception in quiet and in noise (Berlin et al., 2010). Furthermore, the present results were obtained using a stop consonant with a short formant transition. Recent studies have suggested that stop consonants are particularly difficult for patients with Friedrich ataxia, which has been associated with ANSD in adults, to perceive (Rance et al., 2008). Future studies should examine temporal processing using stimuli such as stop consonant or gap thresholds in children with ANSD.

Management of young children with AN/AD presents a significant clinical challenge. Typical habilitation strategies include amplification, cochlear implants or a manual approach such as cued speech or sign language. In particular, reports of success of intervention with amplification have been mixed (Berlin et al., 1998, 2002, 2003, Rance et al., 2002, Pearce et al., 2007). Given that all the children in the present study were fitted with amplification at the time of testing, we are able to comment on the efficacy of this intervention for this group of children. We found that approximately 38% of the children showed demonstrable benefit from amplification, in that, these children showed evidence of normal central auditory maturation and progress in auditory skill development. These results are consistent with Rance et al., (2002) and Pearce et al., (2007). However, also consistent with other investigators (Berlin et al., 1998, 2002, 2003) we found that the majority of subjects (62%) appeared not to benefit from amplification, in that they showed delayed/abnormal P1 responses and significantly lower scores on the IT-MAIS. For these children cochlear implantation may be a useful alternative (Trautwein et al., 2001) and several of these children have received an implant since we collected our data.

It is interesting to note that children who showed normal central auditory development (and high IT-MAIS scores) were fit with hearing aids at a significantly earlier mean age (10

months) relative to children fit, on average, at age 3.3 years who showed abnormal central auditory development. While difficult to interpret at this point due to the small numbers of subjects, this finding may point towards the existence of a sensitive period for intervention in children with ANSD. Animal studies have demonstrated the existence of sensitive periods in development for animals reared in degraded listening environments that were different from those reared in normal listening environments (Chang and Merzenich, 2003; Villers-Sidani et al., 2007), which may have some parallels to the patients with congenital ANSD.

Finally, results of the present study did not show a significant correlation between unaided pure tone averages (PTA) and either the IT-MAIS score or P1 CAEP latencies. It is interesting to note that, in the present study, there were three subjects with unaided PTA thresholds greater than 80 dB HL (i.e., subject numbers 1, 3, & 7) that had normal P1 latencies and high IT-MAIS scores. This finding is consistent with previous studies (e.g., Rance et al., 2002; Zeng et al., 1999), which have shown that unlike in children with SNHL, unaided PTA is not a good predictor of behavioral performance in children with AN/AD. Given that ABR and behavioral audiometric thresholds are unreliable indicators of behavioral outcome in children with ANSD, CAEPs may provide a useful alternative. The present findings are consistent with recent reports which suggest that CAEPs can be recorded reliably in children with AN/AD and that they are useful predictors of behavioral outcome in this population (Rance et al., 2002, Pearce et al., 2007).

Conclusion

We find that ANSD can have significant effects on cortical development and functioning. The results of our study demonstrate that children with ANSD exhibit different degrees of central auditory maturation as indicated by morphology, latency and amplitude of the P1 CAEP. Approximately one third of children (38%) showed normal P1 responses, while another third (33%) showed delayed P1 response latencies and significantly smaller amplitudes, and the remaining third of children (29%) showed absent P1 responses. Consistent with previous studies, P1 responses appear to be a good predictor of behavioral outcome (as measured by the IT-MAIS score) in ANSD patients, suggesting that P1 CAEP might provide a clinical tool for guiding intervention choices and assessing their efficacy in this population.

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DECLARATION OF INTEREST

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Acronyms and Abbreviations

ANSD	Auditory Neuropathy Spectrum Disorder
CAEP	Cortical auditory evoked potentials
AN/AD	Auditory Neuropathy/Dys-synchrony
IT-MAIS	Infant Toddler Meaningful Auditory Integration Scale
SNHL	Sensorineural Hearing Loss
OAE	Otoacoustic Emissions

ABR	Auditory Brainstem Response
OHC	Outer Hair Cell
IHC	Inner Hair Cell
TEOAE	Transient Evoked Otoacoustic Emission
DPOAE	Distortion Product Otoacoustic Emission
PTA	Pure Tone Average
ANOVA	Analysis of Variance
EPSP	Excitatory Post-synaptic Potential

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Figure 1. P1 Latencies by Age of Children with ANSD

P1 latencies for children with ANSD plotted against the 95% confidence interval for normal development of the P1 response (adapted from Sharma et al., 2002).

Figure 2. Participant Waveforms

A, B, & C: P1 waveforms for each participant with normal (A), delayed (B), and abnormal (C) P1 responses respectively. Waveforms are listed from oldest (top) to youngest (bottom) in each figure.

Figure 3. P1 Amplitude

Mean P1 response amplitudes for children with normal P1 latency and delayed P1 latencies.

Figure 4. Hearing Aid Fit Age

Mean ages of hearing aid fittings for children with normal, delayed and abnormal P1 responses.

Figure 5. IT-MAIS Scores

A: Mean IT-MAIS scores for children with normal, delayed and abnormal P1 responses.

B: IT-MAIS scores vs. P1 latency for children with normal (filled circles) and delayed (unfilled circles) and delayed P1 responses.

Table 1

Summary of participants' case history information

Subject	Etiology	ABR	OAE	PTA unaided R (dB HL)	PTA unaided L (dB HL)	HA Fit Age (years)
1	Jaundiced	Polarity reversal of CM	DPOAE absent	118	108	1.08
2	No risk factors	Polarity reversal of CM	TEOAE present	63	31	1.19
3	Hypoxia	Polarity reversal of CM	DPOAE absent	Unavailable	95	1.68
4	Premature, low birth weight, jaundiced, ototoxic medication	Polarity reversal of CM	TEOAE absent	62	70	0.77
5	Premature, mechanical ventilation, ototoxic medication	Polarity reversal of CM	TE- and DPOAE present	72	75	0.27
6	Premature, jaundiced, blood transfusion, mechanical ventilation	Polarity reversal of CM	TE- and DPOAE present	38	70	0.36
7	Premature	Polarity reversal of CM	TE- and DPOAE absent	82	78	0.33
8	Mechanical ventilation	Polarity reversal of CM	DPOAE absent	85	85	0.68
9	No risk factors	Polarity reversal of CM	DPOAE absent	102	95	1.74
10	Premature, blood transfusion	Polarity reversal of CM	Unavailable	95	Unavailable	0.63
11	No risk factors	Polarity reversal of CM	DPOAE absent	90	80	0.16
12	Premature, low birth weight, jaundiced, blood transfusion	Polarity reversal of CM	TE- and DPOAE absent	60	Unavailable	1.29
13	Premature, ototoxic medication, mechanical ventilation	Polarity reversal of CM	TEOAE absent	70	67	2.62
14	No risk factors	Polarity reversal of CM	TEOAE absent, DPOAE present	82	85	2.38
15	Premature, jaundiced, mechanical ventilation	Polarity reversal of CM	TEOAE absent	80	82	0.59
16	No risk factors	Polarity reversal of CM	TE- and DPOAE present	93	68	6.72
17	Jaundiced	Polarity reversal of CM	TE- and DPOAE present	98	93	2.4
18	Premature, blood transfusion, ototoxic medication	Polarity reversal of CM	DPOAE absent	83	85	2
19	Family history of hearing loss	Polarity reversal of CM	TEOAE absent, DPOAE present	93	98	6.12
20	Epilepsy	Polarity reversal of CM	TEOAE absent	111	80	1.82
21	Premature, mechanical ventilation, blood transfusion, ototoxic medication	Polarity reversal of CM	TE- and DPOAE absent	62	93	0.72