Effects of Stimulus Rate on Auditory Brain Response in Auditory Neuropathy Spectrum Disorder

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EFFECTS OF STIMULUS RATE ON AUDITORY BRAIN RESPONSE IN
AUDITORY NEUROPATHY SPECTRUM DISORDER

by

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M.B., Ch.B., University of Edinburgh, 1988

A thesis submitted to the
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of the requirement for the degree of Master of Arts
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Department of Speech, Language,
and Hearing Sciences

2017
EFFECTS OF STIMULUS RATE ON ABR IN ANSD

This thesis entitled:

Effects of Stimulus Rate on Auditory Brain Response in

Auditory Neuropathy Spectrum Disorder

written by Rosemary J McKnight

has been approved for the Department of Speech, Language, and Hearing Sciences

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The final copy of this thesis has been examined by the signatories and we find that both the content and the form meet acceptable presentation standards of scholarly work in the above-mentioned discipline.

IRB protocol #0906.16
Auditory Neuropathy Spectrum Disorder (ANSD) affects approximately 5 – 15% of children with sensorineural hearing loss. ANSD is characterized by the presence of otoacoustic emissions (OAE) and an absent or abnormal auditory brainstem response (ABR). The purpose of this study was to investigate the potential utility of slow stimulus rate ABR in patients with a diagnosis of ANSD and to investigate whether ABR morphology at a slow stimulus rate might exhibit features which could indicate the prognosis for central auditory pathway maturation, auditory skills development and speech-language outcomes. This retrospective case review included 4 children with a diagnosis of ANSD, for whom auditory brainstem responses had been collected at the Brain and Behavior Laboratory at the University of Colorado - Boulder. ABRs were recorded using a slow rate stimulus (5.1 clicks per second) and a faster rate (> 11.1 – 31.1 clicks per second). ABR waveform characteristics were compared between slow rate and faster rates, and were assessed for recognizable morphology. Results indicated that there was no recognizable ABR waveform morphology in the slow click rate ABR when compared to the faster click rate ABR. These findings suggest that even when stimulus rates are greatly slowed, neural dys-synchrony persists at the level of the brainstem. Additionally, neither the slow nor faster click rate ABR had morphological features which could predict central auditory pathway maturation or cortical auditory evoked potentials.
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Dedication

- to my family and friends in Colorado and Scotland -

The SLHS Class Of 2017 embraced me as a peer and friend, and the support of the SLHS faculty allowed me to explore my passions in the field of Speech-Language Pathology. My mum, Kamala (who pursued a Master’s degree whilst working as a high school English teacher), my dad, John (who encouraged students from all over the planet to pursue further education), and my mother-in-law, Sheena (a retired English teacher who has tireless energy and patience), visited Colorado on frequent occasions to lend a hand, and consistently had confidence in my abilities to get things done! Their lives and achievements have motivated me to work hard for what I want to achieve. I also appreciate the encouragement from my brother, John, and from my good friends Ian and June Underwood in Edinburgh.

I dedicate this thesis to my best friend and husband, Doug, and to our amazing children, Stuart and Kate. Doug’s work ethic, inquisitive mind and passion for knowledge are truly inspiring. His unrelenting support of my academic and professional goals made this master’s degree possible and enjoyable. Stuart & Kate’s encouragement, sense of fun, willingness to eat take-out and cook lots of quick pasta meals, and their never-ending belief in their mum has meant the world to me. With the support of family and friends, I have not only survived, but also thrived throughout three years of graduate school, and for that I will always feel grateful.
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I am immensely grateful to my thesis advisor, Anu Sharma, Ph.D., for her expertise and engagement throughout this study. Dr. Sharma’s enthusiasm for research is both infectious and inspiring. Additionally, I would like to thank my thesis committee members, Kathy Hardin, M.A., CCC-SLP, and Neeraja Sadagopan, Ph.D., CCC-SLP, for their encouragement, flexibility and insightful comments. Finally, I am also grateful to Garrett Cardon, Ph. D., and Hannah Glick, B.A., for their support throughout my thesis.
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Chapter 1

INTRODUCTION

Auditory Neuropathy Spectrum Disorder (ANSD) is a diagnostic classification of hearing loss with a variable clinical presentation, which is present in 5 – 15% of children with sensorineural hearing loss (SNHL) (Berlin et al., 2010; Kirkim, Serbetcioglu, Erdag, & Ceryan, 2008; Talaat, Kabel, Samy, & Elbadry, 2009; Vignesh, Jaya, & Muraleedharan, 2016). Initially, Auditory Neuropathy was described in 1996 by Starr and colleagues who identified hearing impairment in ten patients which was attributed to a disorder of the auditory portion of the eighth cranial nerve (CN VIII) and was characterized by normal outer hair cell (OHC) function, as indicated by preservation of otoacoustic emissions and cochlear microphonics (CM), but abnormal auditory pathway function, as evidenced by abnormal or absent auditory brainstem responses (Starr, Picton, Sininger, Hood, & Berlin, 1996). Subsequently, to reflect the lack of neural synchrony of the auditory brainstem response, the descriptor Auditory Dys-synchrony was added to the Auditory Neuropathy diagnostic term, leading to the creation of a further diagnostic label, Auditory Neuropathy/Auditory Dys-synchrony (Berlin, Hood, Morlet, Rose, & Brashears, 2003; Berlin, Hood, & Rose, 2001; Berlin, Jeanfreau, Hood, Morlet, & Keats, 2001). Since then, it has been widely recognized that the terms auditory neuropathy and auditory dys-synchrony do not reflect the multiple etiologies and sites of lesion that result in this category of hearing loss, which has an inconsistent clinical presentation with permanent or fluctuating hearing loss and a variable impact on hearing and communication. Therefore, the term Auditory Neuropathy Spectrum Disorder has been adopted to ‘unify the concept of an auditory disorder with a range of presentations secondary to a variety of etiologies’ (Sininger et al., 2008).
Clinically, ANSD is diagnosed by the presence of otoacoustic emissions (OAE), absent or elevated acoustic reflex (ART) responses, and an absent or abnormal auditory brainstem response (ABR) (Berlin et al., 2010; Rance & Barker, 2009; Starr et al., 1996). The purpose of this study was to investigate the potential value of slow rate ABR as a prognostic indicator of central auditory pathway maturation and speech and language outcomes in ANSD. This retrospective case series reviewed behavioral audiometric and electrophysiological data from research participants for whom auditory brainstem responses were collected at the Brain and Behavior Laboratory at the University of Colorado - Boulder. ABRs were recorded using 2 different stimulus rates. ABR waveform characteristics were compared between the slow click rate (5.1 clicks per second) and a faster click rate (> 11 – 31.1 clicks per second) typically used clinically for eliciting ABR responses in infants and children with hearing loss. Morphology of the responses at each stimulation rate was compared within and across participants.

In the following section, literature which reviews the etiology and pathophysiology, diagnostic and prognostic biomarkers, characteristics, and management of ANSD is presented. The goal of the review is to provide an understanding of ANSD and the rationale for searching for improved identification of biomarkers which may inform intervention and predict prognosis in this heterogeneous population.
Chapter 2

LITERATURE REVIEW

Etiology and Pathophysiology of Auditory Neuropathy Spectrum Disorder

Auditory Neuropathy Spectrum Disorder (ANSD) is a diagnostic classification of hearing loss, which is present in 5 – 15% of children with sensorineural hearing loss (SNHL), in which pre-neural, cochlear function appears normal, but the afferent neural function of the auditory pathway is disrupted. (Berlin et al., 2010; Kirkim et al., 2008; Rance, 2014; Talaat et al., 2009; Vignesh et al., 2016). Three main sites of lesion have been proposed – the inner hair cells (IHC), the synapse between the IHC and the auditory nerve (CN VIII), and the auditory nerve itself with the underlying mechanism leading to ANSD being the dys-synchronous firing of the auditory neurons (Starr et al., 1996).

ANSD may be congenital or acquired (Norrix & Velenovsky, 2014). Considering acquired ANSD, prematurity and its associated complications (e.g., hyperbilirubinemia, hypoxia, low birth weight and infection) represent one of the greatest predisposing risk factors, since premature infants appear to have inner hair cells which are vulnerable to damage from co-morbid conditions (Beutner, Foerst, Lang-Roth, Von Wedel, & Walger, 2007). The complication of hyperbilirubinemia is noted in the past medical history of up to 70% of neonates diagnosed with ANSD (Bielecki, Horbulewicz, & Wolan, 2012; Kirkim et al., 2008). Hypoxia has been noted to cause damage to vulnerable inner hair cells, resulting in abnormal ABRs in animal populations (Mazurek, Winter, Fuchs, Haupt, & Gross, 2003) which could explain the mechanism of injury in infants (Sawada, Mori, Mount, & Harrison, 2001). Low birth weight (Manchaiah, Zhao, Danesh, & Duprey, 2011; Xoinis, Weirather, Mavoori, Shaha, & Iwamoto, 2007), perinatal infection with exposure to ototoxic drugs (Bielecki et al., 2012; Madden, Rutter, Hilbert,
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Greinwald, & Choo, 2002) and prolonged mechanical ventilation have all been suggested as risk factors for ANSD (Bielecki et al., 2012); however, analysis of these risk factors has failed to find a factor or combination of factors which is predictive of ANSD (Beutner et al., 2007).

At least 40% of cases are due to a genetic cause, whether syndromic or non-syndromic. (Manchaiah et al., 2011; Sninger, 2002; Uhler, Heringer, Thompson, & Yoshinaga-Itano, 2012). Manchaiah (2011) notes that a significant proportion of non-syndromic causes are due to mutations in the otoferlin gene (OTOF) while syndromic examples of ANSD may include Charcot-Marie-Tooth Disease or Fredreich’s Ataxia. A more unusual genetic cause of ANSD has been described, in which hearing impairment deteriorated with an increase in body temperature (Marlin et al., 2010; Starr, Sninger, Winter, Oba, & Michaelewski, 1998), leading Berlin and colleagues to suggest that changes in body core temperature may contribute to the fluctuating hearing loss noted in some individuals (Berlin et al., 2010). An even more unusual case was reported by Gorga and colleagues who described a case of intermittent and reversible ANSD that was thought to be vasospastic in nature (Gorga, Stelmachowicz, Barlow, & Brookhouser, 1995).

Although less common, acquired ANSD may be attributed to demyelinating diseases such as multiple sclerosis, Guillain Barre syndrome and AIDS/HIV infection (Rapin & Gravel, 2003; Starr, 2001; Talaat et al., 2009).

In summary, ANSD can be associated with a wide variety of underlying causes – infectious, immunological, secondary to perinatal insults, genetic, syndromic – or there may be no identifiable medical cause.
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Diagnostic and Prognostic Markers of ANSD

The diagnostic hallmarks of ANSD include functioning outer hair cells (OHC), evidenced by the presence (currently, or at one time) of otoacoustic emissions (OAE) and/or a cochlear microphonic (CM), absent or elevated acoustic reflex (ART) responses, and an absent or grossly abnormal ABR (Berlin et al., 2010).

The absent or grossly abnormal ABR is crucial in the diagnosis of ANSD (Starr et al., 1996). The ABR indicates the electrophysiological response of the auditory nerve and brainstem pathway to an auditory stimulus. As first described by Jewett and Williston, in normal-hearing individuals, the ABR consists of a characteristic waveform (see Figure 1) comprising 5 identifiable peaks, labelled with a Roman numeral system (Waves I – V) (Jewett & Williston, 1971). The waveform components occur within a predictable timeframe (latency) in response to an auditory stimulus, with Wave I appearing approximately 1.5 ms after the stimulus, and subsequent waves occurring at approximately 1ms intervals thereafter (Hall, 2015c). Per Hall, each peak in the ABR waveform, reflects neural activity along the auditory pathway, with function at the level of the auditory nerve indicated by Waves I and II, and with multiple generators in the brainstem, including the cochlear nucleus, the superior olivary complex and lateral lemniscus/inferior colliculus contributing to Waves III, IV and V respectively.
Figure 1. Sample ABR in a normal individual (the author), showing the cochlear microphonic (CM) and Waves I – V.

As summarized by Hall, a range of etiologies of hearing loss can result in an absent or abnormal ABR, and the characteristics of the abnormal ABR may be changed by altering the rate of the auditory stimulus (Hall, 2015a). For example, when secondary to certain pathologies, such as multiple sclerosis (MS), by increasing the stimulus rate, there may be deterioration of the ABR and consequently improvement in the diagnostic sensitivity of the ABR (Antonelli et al., 1988; Elidan, Sohmer, Gafni, & Kahana, 1982; Paludetti, Maurizi, & Ottaviani, 1983). Furthermore, it is well documented that in certain demyelinating pathologies, decreasing the click stimulation rate improves neural synchrony and hence the morphology of the ABR improves, resulting in higher amplitudes and earlier latencies (Paludetti et al., 1983; Parthasarathy, Borgsmiller, & Cohlan, 1998).

In addition to assessing brainstem auditory evoked responses, there is value in assessing the electrophysiology of the central auditory pathway in ANSD by using cortical auditory evoked potentials (CAEP) (Cardon & Sharma, 2011; Kraus et al., 2000; Pearce, Golding, & Dillon, 2007; Sharma & Cardon, 2015). Specifically, the P1 CAEP is an objective biomarker of
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auditory cortical development (Campbell, Cardon, & Sharma, 2011). Studies of the P1 CAEP have revealed that the P1 latency varies as a function of age, with latency decreasing with increasing age (Ponton, Eggermont, Kwong, & Don, 2000; Sharma, Kraus, McGee, & Nicol, 1997) and therefore, P1 latency can be used to infer the maturational status of the central auditory pathway (Sharma et al., 2005). Furthermore, auditory cortical responses (in particular the P1 biomarker) are considered a reliable indicator of auditory skill development and speech and language outcomes in children with ANSD (Alvarenga et al., 2012; Cardon & Sharma, 2013; Sharma, Cardon, Henion, & Roland, 2011).

Characteristics of ANSD

As might be expected with such a diverse etiology, the presenting features of ANSD vary greatly between cases. Individuals with ANSD may have temporary, fluctuating or permanent mild to profound hearing loss, including greater difficulty with speech perception, especially in noise (Kraus et al., 2000; Michalewski, Starr, Zeng, & Dimitrijevic, 2009; Rance, 2005; Rance et al., 2007; Starr et al., 1996; Zeng & Liu, 2006). Thresholds obtained through pure tone audiometry may not reflect the degree of impairment that the individual has in perceiving speech, and audiograms are a poor predictor of language acquisition trajectories in ANSD (Berlin et al., 2010; Deltenre et al., 1999; Rance, Cone-Wesson, Wunderlich, & Dowell, 2002). In some children, ANSD may be unilateral. Unfortunately, the characteristics of children with unilateral ANSD are less well documented largely due to the fact that unilateral deafness does not qualify for early intervention, unless there is significant developmental delay; therefore, some of these children are not followed-up resulting in incomplete data (Uhler et al., 2012). Due to the high incidence of genetic etiologies, it is not uncommon for other disabilities to co-exist with ANSD. Uhler describes that in a cohort of Colorado children with bilateral ANSD, 32% had
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significant cognitive delays, which was 3 times more prevalent than in children with SNHL. However, despite this high percentage of children with additional disabilities, it is expected that two thirds will develop language skills within the low average to normal range during their first 3 years of life (Uhler et al., 2012).

Patients with ANSD vary in their ability to perceive speech because auditory neuropathy results in degraded processing of the temporal cues in speech (Berlin et al., 2010; Rapin & Gravel, 2003; Talaat et al., 2009). The speech signal is highly complex compared to a pure tone, and is determined not only by the spectral information, but also the temporal information. While spectral information relates to vowel formants and place of articulation, temporal processing yields critical information about manner and voice (Young, 2008). In other words, decoding the speech signal is reliant on processing both frequency and precise timing. Therefore, it is logical that a disorder which affects neural synchrony and causes temporal distortion will impact speech perception (Zeng & Liu, 2006; Zeng, Oba, Garde, Sininger, & Starr, 1999).

Management of ANSD

The diverse etiology, variable presentation and difficulties in accurately assessing deficits in infants and children, lead to different approaches to treatment and intervention. Starr and Rance describe two principal approaches to management; namely modifying the listening environment to improve the clarity of the speech signal, and amplifying or modifying the signal reaching the ear using hearing aids or cochlear implants (Starr & Rance, 2015). Hearing aids have been reported as successful modes of treatment (Ching et al., 2013; Deltenre et al., 1999; Rance & Barker, 2009), but due to the variability of auditory thresholds obtained via routine pure tone audiometry in some patients with ANSD, some researchers have questioned the value of pure tone audiometry in clinical decision-making (Cardon & Sharma, 2013; Rance et al., 1999;
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Rapin & Gravel, 2003; Sharma et al., 2011; Zeng et al., 1999), and concerns persist that hearing aid fitting may be based on an unreliable or fluctuating audiogram (Berlin et al., 2010). Cochlear implants (CI) have been effective in patients with ANSD, due to their ability to impose a stronger synchronized signal on the neural elements (Berlin et al., 2010). In a systematic review of the literature conducted by ASHA’s National Centre for Evidence-Based Practice, Roush noted that 80% of studies reported that cochlear implantation was implemented following unsuccessful trials of amplification, and 85% of the children who received CI had severe-profound hearing loss (Roush, Frymark, Venediktov, & Wang, 2011). Roush additionally recommended that more research with children who have less severe hearing loss is required, as well as studies of the developmental outcomes of children with ANSD.

A multidisciplinary approach is required to ensure optimal developmental outcomes for children with ANSD, frequently involving audiologists, speech-language pathologists (SLP) and physicians such as pediatricians and otolaryngologists. The ultimate treatment outcome is the development of language (Stredler-Brown, 2002) and a communication method supported by the child’s family must be established. As discussed by Uhler, auditory skills development and language acquisition can be monitored by early interventionists and SLPs specialized in aural (re)habilitation through administration of parent questionnaires such as the Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS) (Zimmerman-Phillips, Amy, & Osberger, 2000), Rossetti Infant Communication Scale (Rossetti, 1990) and the MacArthur-Bates Communicative Development Inventories (Fenson et al., 2007). Additionally, since many children with ANSD have co-morbid disabilities, overall development should be monitored with a tool such as the Minnesota Child Development Inventory (Ireton & Thwing, 1974) so that language outcomes can be appropriately interpreted. In addition to monitoring progress, SLPs
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need to ensure that parents and teachers are aware of the importance of improving the listening environment and of daily checks of hearing aids, CIs or FM systems. Parent education and counseling is a key component of the management of ANSD as communicative needs and intervention change over time (Uhler et al., 2012).

Clearly, patients with ANSD constitute a highly heterogeneous population. In a review of ANSD, Norrix and Velenovsky highlight the need for more precise tools to diagnose and describe this disorder to aid in clinical decision making and to provide better prognostic indicators (Norrix & Velenovsky, 2014). This study addresses the need to look for a more precise prognostic tool through investigating the effect of slowing the click stimulus rate of the ABR in patients with ANSD to determine whether an improved ABR will be present at the slower rate and whether in children with ANSD, the slow-rate ABR along with a cortical development biomarker and behavioural results, can be a reliable prognostic indicator of speech and language development.
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Chapter 3
METHODS

Procedures

A retrospective case review of medical histories, parent/patient interviews, including all available behavioral audiometric data (including pure tone thresholds, speech awareness thresholds and speech recognition thresholds) and available results of electrophysiological testing (including OAEs, ABRs and P1 CAEPs), was performed. Results from diagnostic electrophysiological procedures carried out by hospital audiologists were available in some cases. In addition, behavioral audiometric data were gathered by audiology doctoral candidates at the Brain and Behavior Laboratory at the University of Colorado, Boulder.

Participants

The target population in the study was patients over the age of 18 months with an established diagnosis of ANSD. The cases were all research subjects at the Brain and Behavior Laboratory on the Boulder campus of the University of Colorado. A series consisting of four research participants, each with a confirmed diagnosis of ANSD, was available for the study. All subjects had received prior behavioral and electrophysiological testing. Although this series had a wide age range (ranging from 19 months to 10 years), it was appropriate to use this heterogeneous sample, which reflected the spectrum of ANSD in the community, since the subjects all had mature ABRs which were available for analysis. Prior research has indicated that the ABR is adult-like from around the age of 18 – 24 months (Gorga, Kaminski, Beauchaine, Jesteadt, & Neely, 1989; Spitzer, White-Schwoch, Carr, Skoe, & Kraus, 2015).
Further reflecting the diverse clinical spectrum, the etiology, degree of hearing loss and treatment varied between participants. Pertinent participant information including hearing thresholds are detailed in the results section and are summarized in Table 1.

Table 1. Summary of participants’ case history information

<table>
<thead>
<tr>
<th>Case</th>
<th>Age y; m</th>
<th>Risk Factors</th>
<th>Diagnosis: newborn</th>
<th>PTA unaided R / L (dB HL)</th>
<th>SAT R / L (dB HL)</th>
<th>SRT R / L (dB HL)</th>
<th>Hearing aid use</th>
<th>IT-MAIS at age y;m</th>
<th>P1 CAEP latency at age y;m</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10;7</td>
<td>Genetic</td>
<td>Passed NBHS OAE + CM + ABR Abn</td>
<td>70 / 80</td>
<td>65 / 70</td>
<td>no</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>2</td>
<td>3;7</td>
<td>NICU</td>
<td>OAE + CM + ABR Abn</td>
<td>60 / 65</td>
<td>30 / 40</td>
<td>yes</td>
<td>19/40 at 2;1</td>
<td>0/36 at 0;6</td>
<td>0/10 &amp; 2;1</td>
</tr>
<tr>
<td>3</td>
<td>6;2</td>
<td>NICU</td>
<td>CM + OAE - ABR - ABR Abn</td>
<td>65 / 70</td>
<td>65 / 70</td>
<td>yes</td>
<td>20/40 at 3;4</td>
<td>No P1 identifiable at age 3;5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1;7</td>
<td>NICU</td>
<td>OAE + ABR - ABR Abn</td>
<td>20 / 20</td>
<td>18 / 20</td>
<td>no</td>
<td>31/36 at 1;3</td>
<td>18/36 at 1;1</td>
<td>Delayed latency at 1;7</td>
</tr>
</tbody>
</table>

*Note that due to the age of participant 4, pure tone threshold and SAT were assessed using sound field testing & visual reinforcement audiometry (VRA). Abn = abnormal; PTA = pure tone audiometry; SAT = speech awareness threshold; SRT = speech recognition threshold; IT-MAIS = Infant-Toddler Meaningful Auditory Integration Scale; P1 CAEP = P1 cortical auditory evoked potential.

**ABR recordings**

ABRs were measured in the 4 participants. ABRs were recorded with the Bio-Logic Navigator Pro AEP System (Natus Medical Inc.) using standard clinical procedures in a soundproof booth at the Brain and Behavior Laboratory at the University of Colorado, Boulder.

Click stimuli, of duration 0.1 ms, were presented mono-aurally using insert earphones (ER3-14A or ER3-14B, depending on the age of the child) to each ear separately. At least one ABR
recording run with a minimum of 500 acceptable, artifact-free data points, was collected for each patient during a single clinic visit, using rarefaction and condensation clicks at suprathreshold intensities ranging from 75 dB HL to 90 dB HL. Where possible, at least one run for each participant was recorded at a “fast rate” (ranging from 11.1 to 31.1 clicks per second, or CPS) and at least one run was recorded at a "slow rate" (5.1 CPS). Three participants received an ABR with one or more sets of slow and fast click rates. The youngest participant (Case 4), could only tolerate one slow rate ABR due to difficulties sitting still for testing. Therefore, Case 4 received an ABR test using an alternating condensation-rarefaction stimulus rather than separate condensation and rarefaction runs to maximize the chances of obtaining a successful recording in a shorter time.

**ABR analysis**

The slow click rate and fast click rate ABRs were analyzed as a group to look for any trends in replicable morphological changes associated with slowing the stimulus rate. All the slow and fast rate ABRs recorded from the four participants were rated. The ABR stimulus rates, intensity levels, and the subjects’ identifying information were hidden, and the sequence of the graphed waveforms was then randomized for subsequent viewing and rating. This allowed for blind rating of ABR morphology using a metric for classifying ABRs created by the raters. Four raters independently judged and assigned values to two pre-determined intervals within each waveform. Three of the raters were graduate students who were novices in judging the integrity of ABR waveforms, and the fourth rater was an audiologist and PhD candidate experienced in interpreting ABR waveforms of patients with ANSD.
Table 2. Rating Index Specifications for slow rate and fast rate ABRs

<table>
<thead>
<tr>
<th>Early interval rating (0-3 ms)</th>
<th>Late interval rating (3-10 ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1: Inverse pattern present with minimal distortion in &gt;50% of the early stage</td>
<td>Category 1: Replicable pattern is present with minimal distortion, and a definitive characteristic of an ABR waveform, e.g. Wave V</td>
</tr>
<tr>
<td>Category 2: Inverse pattern present with moderate distortion</td>
<td>Category 2: Moderately replicable pattern is present with some degree of ABR waveform characteristics</td>
</tr>
<tr>
<td>Category 3: No definable inverse pattern</td>
<td>Category 3: No definable characteristic of an ABR waveform</td>
</tr>
</tbody>
</table>

Because of a lack of existing ABR waveform descriptive metrics in the literature, a Ratings Specifications Index for the waveforms for both intervals was developed, as shown in Table 2. Each ABR was subdivided to create an early interval (0-3ms) and a late interval (>3ms). The 3ms cutoff was chosen based on findings that prominent cochlear microphonics (CM) may occur and may persist within this time period (Starr et al., 2001, 1996). A rating of category 1, category 2 or category 3 was assigned to each early and late interval per features of the waveform. Thus, the early interval rating mostly focused on the presence or absence of features of a CM, which was suggested by an inverse pattern when the rarefaction and condensation waveforms were overlaid (see Fig 1). The late stage ABR interval was aimed at determining the integrity or absence of later ABR waveform components, specifically Wave V.

After the de-identified ABRs had been analyzed as a group, identities were re-assigned to the waveforms to allow for review on an individual case basis, and linked with the appropriate clinical information. The recordings were assigned to either a “fast rate” group (rates > 10 CPS) or to a “slow rate” group (rates < 10 CPS).
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*Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS)*

The Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS) (Zimmerman-Phillips et al., 2000) is an infant- and toddler-appropriate modified Meaningful Auditory Integration Scale (Robbins, Renshaw, & Berry, 1991). Scores for the IT-MAIS were available for 3 of the subjects.

The IT-MAIS consists of a structured 10-probe interview with the infant’s parents which is designed to assess functional auditory skills by rating the infant’s response to sounds in their everyday environment. The 10 probes assess three main areas: vocalization behavior, alerting to sounds, and deriving meaning from sound. One of the probes assumes use of a hearing aid or cochlear implant; therefore, in patients for whom this was not appropriate, a 9-item scale was used. The target behaviors which were probed, such as searching for the source of the sound, discriminating speech from non-speech sounds, or responding to the cessation of a sound, are developmentally appropriate for infants and toddlers. Auditory skills development, and hence severity and impact of hearing loss, may be suggested by the IT-MAIS score. Expected values for the IT-MAIS related to the child’s age and degree of hearing loss have been identified (Liang, Soli, Zheng, Li, & Meng, 2016; Zheng et al., 2009).

*P1 Cortical Auditory Evoked Potential*

Multiple P1 CAEP recordings over several research visits to the Brain and Behavior Laboratory were available for review for Case 2, Case 3 and Case 4. CAEPs were obtained in response to the synthesized speech syllable /ba/ according to a well-documented procedure developed and described by Sharma and colleagues (Sharma et al., 2005, 2011). Expected P1 CAEP latencies for normal-hearing children and young adults aged 1 month – 20 years have been identified (Sharma, Dorman, & Spahr, 2002). As discussed by Sharma (2002), P1 latency
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values which fall within the 95% confidence interval predict normal auditory cortical maturation resulting from adequate auditory stimulation. Conversely, values which fall outside the 95% confidence interval indicate delayed maturation of the auditory cortex due to insufficient auditory stimulation. The P1 CAEP latencies for the research cases were plotted by patient age against the 95% confidence intervals for typical P1 latency development in normal-hearing children.
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Chapter 4

RESULTS

Case 1

Patient 1 is a 10-year 3-month old male child who had an uneventful birth and neonatal history. His mother has a moderately severe hearing loss and a confirmed diagnosis of ANSD. He passed his newborn hearing screening, per parent report, but was noted by his mother to have a hearing loss in childhood. He was reported to have “good and bad hearing days”, had never used hearing aids, and relied heavily on reading lips. Per chart review, he had a moderate-severe to severe hearing loss confirmed by pure tone audiometry (Figure 2.1), his speech recognition thresholds (SRT) were 65 dB HL (R) and 70 dB HL (L), and it was noted that he struggled to recognise speech for the SRT testing when he was unable to see lips. Word recognition thresholds were not possible to obtain due to the loudness level required. Both slow rate and fast rate ABRs were recorded. In the slow rate ABR, a more prominent CM was evident when compared to the fast rate ABR; however, the late interval beyond 3 ms did not show improved morphology with the slower stimulus rate (Figures 2.2 & 2.3). A P1 CAEP was not collected on this patient.
Figure 2. Case 1 behavioral and electrophysiological data
1. Pure tone audiogram
2. ABR at slow click rate
3. ABR at fast click rate
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Case 2

Patient 2 is a 3-year 7-month old male child who was born prematurely at 28 weeks’ gestation, following an intrauterine infection. Per chart review, he had a complicated birth and neonatal history, which included apnea of prematurity, mechanical ventilation, pulmonary insufficiency, hyperbilirubinemia, periventricular leukomalacia and chronic lung disease. He did not pass several newborn hearing screenings prior to discharge from the Neonatal Intensive Care Unit (NICU). Testing at age 3 months confirmed a diagnosis of ANSD, with OAEs and CMs present and an abnormal ABR with a delayed Wave V. He received early intervention services from a speech language pathologist from the age of 6 months, and was fitted with hearing aids at age 3 years.

Pure tone audiometry revealed a moderate – moderately severe hearing loss unaided, which improved to normal – mild hearing loss with hearing aids (Figure 3.1). P1 CAEPs were obtained when the child was 6 months, 10 months, and 25 months old. P1 responses were clearly present at all ages. The P1 latencies fell within the 95% confidence interval for normal development of the P1 response (Sharma et al., 2002), suggesting that Patient 2 was receiving adequate auditory input for the development of the central auditory pathways (Figure 3.2). The IT-MAIS was administered at age 25 months, at which time the child scored 34/36 (94%). Overall the IT-MAIS results indicated only mild delay in early prelingual auditory development which was consistent with the parent report of delayed language acquisition. Slow and fast rate ABRs were obtained when the child was 3 years, 7 months old. Slowing the stimulus rate of the ABR increased the clarity of the CM pattern in the early interval, but did not improve the overall morphology of the ABR waveform (Figure 3.3 & 3.4).
Figure 3. Case 2 behavioral and electrophysiological data

1. Pure tone audiogram: unaided right and left ear; aided (A)
2. P1 latency over 3 visits (IT-MAIS at final visit was 94% which is mildly delayed for his age)
3. ABR at slow click rate
4. ABR at fast click rate
Case 3

Patient 3 is a 6-year 2-month old male child who was born prematurely at 24 weeks’ gestation. He was an inpatient in the NICU for 5 months, during which time he received prolonged mechanical ventilation, potentially ototoxic medications, and was diagnosed with an intraventricular hemorrhage and seizures. Per chart review, investigations at age 5 months revealed absent OAEs, a robust cochlear microphonic at 85 dB HL, but no neural response on ABR testing leading to a clinical diagnosis of ANSD. He received early intervention services from a speech language pathologist and an occupational therapist from the age of 6 months. He was fitted with hearing aids at age 2, improving from a moderately severe-severe hearing loss unaided, to a normal-mild hearing loss aided.

At ages 3;4 and 3;5, Patient 3 was referred for CAEP testing. At that time, per parent report, Patient 3’s speech was “very delayed” and he was learning American Sign Language at preschool. Pure tone audiometry confirmed a moderately-severe to severe hearing loss unaided (Figure 4.1). At both 3;4 and 3;5, a cortical auditory evoked potential was observed; however, a clear P1 CAEP response could not be identified suggesting that development of the central auditory pathways delayed (Figure 4.2). His IT-MAIS at that time scored 20/40 (50%) which was consistent with delayed auditory development due to severe hearing loss (Liang et al., 2016). At age 6;2 this patient received slow and fast rate ABR testing (Figure 4.3 & 4.4). Reducing the rate of the click stimulus did not improve the morphology of the ABR waveform.
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Figure 4. Case 3 behavioral and electrophysiological data
1. Pure tone audiogram
2. P1 Latency – no P1 identified (IT-MAIS at time of P1 was 50% which is very low for his age)
3. ABR at slow click rate
4. ABR at fast click rate
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Case 4

Patient 4 is a 1-year 7-month old female child who was born prematurely at 33 weeks’ gestation. She had a complex history including twin-to-twin transfusion syndrome (as the donor) with resulting hypoxia, hyperbilirubinemia, necrotizing enterocolitis requiring colectomy, sepsis, exposure to potentially ototoxic medications, and extended mechanical ventilation. She was identified with ANSD at age 3 months.

Results from several hearing evaluations indicated a fluctuating hearing loss; however, her most recent hearing evaluation, at 16 months, using visual reinforcement audiometry (VRA) indicated normal hearing in a sound field (500 Hz – 2000 Hz) and bilaterally at 4000 Hz – 8000 Hz (Figure 5.1). The IT-MAIS was administered on multiple occasions: at ages 4 months (7/36 19%), 11 months (11/36 31%), 13 months (18/36 50%), and 15 months (31/36 86%). Although initially lower than for typically hearing infants (Zheng et al., 2009), the increase in IT-MAIS scores over time indicated gradual improvement in functional auditory skills. By 15 months of age, the IT-MAIS was consistent with age-appropriate early prelingual auditory development (Figure 5.4). P1 CAEP responses were recorded at 4, 11, 13, 19 and 37 months. At age 4 months, the P1 CAEP latency was borderline normal for expected age. However, the latency did not decrease with age as expected, occurring outside the 95% confidence interval for normal development when tested at 11 months and 19 months (Figure 5.2). This coincided with fluctuating auditory thresholds. At age 19 months, a slow rate ABR had a recognizable CM, but did not have any recognizable later morphological features (Figure 5.3). Due to young age, this toddler could not tolerate the full evaluation, and so received only one slow stimulus rate ABR and no fast stimulus rate ABR. Patient 4 was referred for a repeat measure of the P1 CAEP at age 3;1. At that time, a replicable and robust P1 occurred within a normal latency range for the patient’s age, indicating age appropriate maturation of the central auditory pathways (Figure
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5.3). This coincided with substantial growth in receptive and expressive language, per parent report. The growth in language acquisition paralleled the improved latency of the P1 CAEP response.

Figure 5. Case 4 behavioral and electrophysiological data
1. Visually reinforced audiometry (VRA) at 11 months and 16 months, showing fluctuating thresholds
2. Series of P1 latencies showing improvement as this patient matured
3. ABR at a slow click rate only: unable to tolerate the procedure due to young age
4. IT-MAIS scores over time showing auditory development with increasing age. Final IT-MAIS score is within expected range for age.
**Integrated Results Cases 1 – 4**

The slow rate and fast rate ABRs from cases 1 – 4 were analyzed as a group to look for any trends in replicable morphological changes associated with slowing the stimulus rate. The de-identified waveforms were rated, and then the category assigned by each rater was compared. Raters were consistent in their judgment: there was either complete agreement in the waveform rating (14 of 22 occasions), or the reviewers differed by one category only (8 of 22 occasions). There were no waveforms in which raters differed by two categories in their rating.

An average reviewer rating was calculated for each interval (early and late) in each rate group (slow and fast), and then the mean values for slow rate early interval, slow rate late interval, fast rate early interval and fast rate late interval, were calculated (Table 3).

### Table 3. ABR early and late interval values for slow and fast rate ABRs

<table>
<thead>
<tr>
<th></th>
<th>Slow Stimulus Rate</th>
<th></th>
<th>Fast Stimulus Rate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early Interval</td>
<td>Late Interval</td>
<td>Early Interval</td>
<td>Late Interval</td>
</tr>
<tr>
<td></td>
<td>Mean Category Rating</td>
<td>Mean Category Rating</td>
<td>Mean Category Rating</td>
<td>Mean Category Rating</td>
</tr>
<tr>
<td>Case 1</td>
<td>1</td>
<td>3</td>
<td>1.75</td>
<td>2.92</td>
</tr>
<tr>
<td>Case 2</td>
<td>1</td>
<td>2</td>
<td>1.25</td>
<td>2.38</td>
</tr>
<tr>
<td>Case 3</td>
<td>1.5</td>
<td>3</td>
<td>2.25</td>
<td>3</td>
</tr>
<tr>
<td>Case 4*</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>1.125</td>
<td>2.75</td>
<td>1.75</td>
<td>2.77</td>
</tr>
</tbody>
</table>

The waveform ratings for each participant were averaged across raters and across each participant’s waveforms for the early and late stage of both slow and fast rates. 14 of 22 individual stages had complete concordance between raters.

*Slow rate set of data only: inability to tolerate the procedure due to patient age.

For the slow rate ABRs, the mean early interval rating value was 1.125 and for the fast rate ABRs, the mean early interval rating value was 1.75, indicating that there was a mildly or moderately distorted inverse pattern noted in the initial 3ms of the slow and fast rate ABRs which represented a CM. Examples of a slow stimulus rate ABR and fast stimulus rate ABRs are shown in Figure 6. Overall, the inverse pattern was more likely to be mildly distorted with the
slow stimulus rate (Fig 6.1) and moderately distorted with the fast rate (Fig 6.2). However, since there is variability of the ABR within the same participant with ANSD, it was also possible to observe a range of distortions within the early interval when several fast rate ABRs were recorded (Figures 6.2 – 6.4). Considering the late interval, in the slow rate ABR the mean rating value was 2.75, and in the fast rate ABR the mean rating value was 2.77, indicating that any later waveform characteristics were consistently moderately distorted to undefinable (Fig 6.1 – 6.4).

When slow and fast rate waveforms across all subjects were considered, these results suggested that when slowing the click stimulus, there was a greater likelihood of observing a mildly distorted inverse pattern relating to a prominent cochlear microphonic. However, for the interval of the ABR occurring after 3ms, slowing the stimulus rate did not alter the ABR, and the late interval of the waveforms remained grossly abnormal.
Figure 6. Case 1: ABR waveforms over several runs. Early Interval and Late Interval Mean Category Ratings for Case 1 are provided.

1. Slow rate: Early Interval Mean = 1, Late Interval Mean = 3;
2. Fast rate: Early Interval Mean = 1.25, Late Interval Mean = 2.75;
3. Fast rate: Early Interval Mean = 1, Late Interval Mean = 3;
4. Fast rate: Early Interval Mean = 3, Late Interval Mean = 3.

- Condensation
- Rarefaction
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Considering Cases 2 - 4, overall the scores obtained on the IT-MAIS reflected the degree of central auditory pathway maturity indicated by the P1 CAEP latency. Those scores which fell close to or within the normal range described by Zheng (2009) had a P1 latency within the expected latency range for the child’s age. On the other hand, Case 2 had severely delayed prelingual auditory development as suggested by the very low IT-MAIS score, and did not have an identifiable P1 response. The differing IT-MAIS scores were not in any way reflected in the ABR waveform (Table 4).

Finally, for those patients for whom a P1 CAEP had been collected, central auditory pathway maturity – as indicated by P1 CAEP latency – was independent of the slow and fast stimulus rate ABR morphology. Cases 2, 3 and 4 all had grossly abnormal ABRs, with a complete lack of recognizable Wave I - V morphology, but they each differed in their prior P1 CAEP results. Case 2 had no identifiable P1 in prior testing; Case 3 had a P1 response which fell within the normal range for expected latency; and Case 4, at the time of the ABR, had a delayed P1 response (Table 4).

Table 4. Cases 2 – 4: ABR, P1 CAEP latency and IT-MAIS result

<table>
<thead>
<tr>
<th>Case</th>
<th>ABR (slow &amp; fast rate)</th>
<th>P1 CAEP Latency</th>
<th>IT-MAIS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>#2</td>
<td>Absent</td>
<td>Absent</td>
<td>Very Low</td>
</tr>
<tr>
<td>#3</td>
<td>Absent</td>
<td>Normal</td>
<td>Mild delay</td>
</tr>
<tr>
<td>#4</td>
<td>Absent</td>
<td>Delayed, but normalized</td>
<td>Average</td>
</tr>
</tbody>
</table>

ABR = auditory brainstem response; P1 CAEP = P1 cortical auditory evoked potential; IT-MAIS = Infant-Toddler Meaningful Auditory Integration Scale
Effects of Stimulus Rate on ABR in ANSD

Chapter 5

Discussion

Ever since Jewett and colleagues first described auditory evoked potentials (Jewett, Romano, & Williston, 1970; Jewett & Williston, 1971), numerous researchers have investigated the effect of the click stimulus rate on the latency, morphology, and threshold of the auditory brainstem response in humans with normal hearing (For example, Paludetti et al. 1983; Burkard & Sims 2001; Sininger & Don 1989; Yagi & Kaga 1979). It is widely recognized that increasing click rates above 20 CPS leads to an increase in ABR latency and a decrease in amplitude in normal-hearing adults (Hall, 2015b), and that decreasing the stimulus rate in patients with either normal hearing or a sensorineural hearing loss leads in particular to a decrease in the latency of Wave V (Debruyne, 1986; Parthasarathy et al., 1998; Stockard, Stockard, Westmoreland, & Corfits, 1979). Furthermore, in certain pathologies, such as multiple sclerosis, increasing the click rate causes progressive desynchronization with characteristic and diagnostic loss of waveform morphology (Paludetti et al., 1983).

The body of research indicates that the ABR is sensitive to the effect of stimulus rate on neural synchrony. Despite this, there is a lack of published research on slow stimulus rates in patients with ANSD. At the time the data were being collected and analyzed, there was no published research addressing the question of whether a profoundly slowed stimulus rate would distinguish the ABR of patients with ANSD. Since increasing the rate of stimulus in ABRs taxes the neural system and affects the synchronous firing of the auditory nerve especially in those with demyelinating pathology, it was reasonable to investigate whether profoundly slowing the rate of stimulus might improve neural synchrony, resulting in a replicable waveform in the ABR.
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of those with ANSD. If an ABR were apparent at a slow stimulus rate, it would also provide an objective measure of hearing thresholds in children with ANSD, aiding in clinical decision making such as amplification fitting.

The results from this case series were not consistent with the prediction that there would be replicable and robust ABR patterns at a slower stimulus rate. Evidence from this study found that considering the entire ABR, there were no reliable differences in ABR waveform characteristics between the stimulus rates, and no evidence of recognizable Wave I-V shapes when using the slowed rate.

Analyzing the early and late intervals of the ABR separately yielded some differences with manipulation of stimulus rate. There was a difference noted between the early intervals of the slow versus fast rate ABRs. A more replicable inverse pattern was recognized in the early interval waveforms obtained from the slow rate ABRs compared to the fast rate ABRs, reflecting more prominent cochlear microphonics (CM). This is not surprising since the morphology (and hence clarity) of all waveform components, including the CM which reflects outer hair cell function, was expected to improve at a slower rate. Since outer hair cell function is not disrupted in ANSD, the diagnostic and prognostic relevance of this finding is unclear, and further research with a larger sample size is warranted to assess its significance.

The lack of difference in the waveforms of the late interval of the slow click rate versus fast click rate ABRs suggested that a slower click rate does not promote neural synchrony. Again, due to the small size of this case series, it is not possible to say if this negative result would persist in a larger sample size. However, our results are consistent with a previous study which showed no differences in ABRs with stimulus rates ranging from 12 CPS – 30 CPS (Rance et al., 1999). Kraus et al. (2000) suggest that the absent ABR is the result of the
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desynchronized high frequency biphasic action potentials, that are separated by fractions of a millisecond, being canceled out during averaging. The present results align with Kraus, and further suggest that synchronized firing of the brainstem neurons does not improve even at very slow click rates.

The three youngest participants in this case series had also received P1 CAEP testing in conjunction with assessment of auditory skill development using the IT-MAIS. In each case, the P1 CAEP latency was related to the degree of auditory skill development, with normal P1 latency predicting typical development of auditory skills, which is consistent with previous research in this area (Alvarenga et al., 2012; Cardon & Sharma, 2013; Sharma et al., 2011).

Finally, in this case series, the absent, normal and delayed latency of the P1 CAEP was not reflected in any way in the ABR waveform. That is, Case 2, Case 3 and Case 4 all showed absent ABRs at slow and fast click rates, but had vastly differing patterns of central auditory maturation and speech and language development. Case 2 had P1 latencies within the normal range and a mildly delayed IT-MAIS score; Case 3 did not have an identifiable P1 and had a very low IT-MAIS score; and Case 4 initially had a borderline normal latency at 4 months of age, which became delayed by 11 months and then normalized by age 3 years and had an IT-MAIS score which increased with age and was within the expected range. Despite these differing P1 CAEP responses, none of the cases had any element other than a CM in the ABR that was discernable even when a slow rate of stimulus theoretically improved the likelihood of neural synchrony. This aligns with previous research which indicates that cortical potentials are not as sensitive to neural synchrony as the ABR (Kraus et al., 2000).

Overall the results of this case series suggest that the grossly abnormal or absent ABR is a useful tool in the diagnosis of ANSD and that using traditional ABR stimulation rates
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continues to be clinically appropriate for diagnosis. Considering prognosis, manipulating ABR click rate did not provide prognostic information; however, P1 CAEP latency predicted auditory skill development, as shown by the IT-MAIS scores. This is consistent with previous studies that the P1 CAEP is a reliable predictor of behavioral outcomes and is a reliable tool in clinical decision making (Alvarenga et al., 2012; Cardon & Sharma, 2013; Sharma et al., 2011).

Limitations of the study

This retrospective study had the limitations inherent in a retrospective case series and further research is warranted. Caution is required in extrapolating from a small sample of an uncommon condition in a heterogeneous population. Since this study involved a retrospective review of cases, there was variation in the frequency and type of prior investigations for which results were available. Further, due to the fluctuating nature of ANSD pathology, ABR characteristics varied within and between the research participants. There was a lack of consistency in click stimulus rates since the ABRs were administered by different clinicians, with the stimulus for the “fast rate” ranging from 11.1 to 31.1 clicks per second. Additionally, participants differed in the numbers of slow and fast click rate ABRs that were collected. Research has failed to find significant differences in the ABRs of normal-hearing adults and children with ANSD with changes in the click rate from 12 - 30 CPS (Rance et al., 1999); however, consistency in the faster rate would be preferable, and a future study would ideally specify the number of ABR runs and restrict stimulus rates to predetermined values.

This case series had only four research participants due to ANSD being a relatively rare disorder with an annual incidence of 1 – 3 new cases per 10,000 live births (Sinninger, 2002). In a study of children whose neonatal or family histories put them at increased risk of hearing loss, Rance and colleagues determined the prevalence of ANSD to be 0.23%. (Rance et al., 1999).
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Given the low prevalence of ANSD, many findings in the literature are reported in the form of case studies. The age range of the case studies in this series (1 year, 7 months – 10 years, 7 months) was not considered to be a limitation since each had an abnormal, but mature, ABR which was diagnostic of ANSD. In this respect, it was the waveform which was of interest rather than the specific clinical cases, in what is known to be a heterogeneous population. In future research, ideally more participants with ANSD would be recruited to participate in a prospective study and a larger sample size may yield more pronounced differences between cases.

Conclusion

This study produced a “negative” result and did not lend support to the original hypothesis that slowing the stimulus rate of the ABR would improve neural synchrony and result in a reproducible and replicable pattern within the ABR. Although the size of this study was small, it is essential to document such negative findings and further explore the auditory stimulus used to elicit diagnostic information. Through modification of the auditory stimulus, the reliable finding of any replicable component of the ABR waveform could be valuable in refining the diagnosis, pinpointing the type or site of lesion, and informing subsequent treatment. As understanding and use of electrophysiological biomarkers evolves in this heterogeneous population with ANSD, it will become possible to further individualize intervention to maximize communication function, and to predict speech and language outcomes.
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