# USING CORTICAL AUDITORY EVOKED POTENTIALS AS A PREDICTOR OF SPEECH PERCEPTION ABILITY IN AUDITORY NEUROPATHY SPECTRUM DISORDER AND CONDITIONS WITH ANSD-LIKE CLINICAL PRESENTATION

A thesis submitted to the University of Manchester for the degree of Master of Philosophy in the Faculty of Medical and Human Sciences

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**SCHOOL OF PSYCHOLOGICAL SCIENCES**

# Contents

## Abbreviations

| | |
|---|---|
| **ABR** | auditory brainstem response |
| **ANSD** | **A**uditory Neuropathy Spectrum Disorder |
| **ART** | acoustic reflex threshold |
| **AS** | active sleep |
| **CAEP** | cortical auditory evoked potential |
| **CM** | cochlear microphonic |
| **EEG** | electroencephalogram |
| **FFT** | fast-Fourier transform |
| **FM** | frequency modulation |
| **IHC** | inner hair cell |
| **IS** | indeterminate sleep state |
| **ISI** | inter-stimulus interval |
| **MMN** | mis-match negativity |
| **NHS** | National Health Service |
| **NHSP** | newborn hearing screening programme |
| **NICU** | neonatal intensive care unit |
| **NREM** | non-rapid eye movement |
| **OAE** | oto-acoustic emissions |
| **PBK** | phonetically balanced kindergarten words test |
| **PCHI** | permanent childhood hearing impairment |
| **QS** | quiet sleep |
| **REM** | rapid eye movement |
| **SCBU** | special care baby unit |
| **SNHL** | sensorineural hearing loss |
| **VRA** | visual reinforcement audiometry |
| **VRISD** | visual reinforcement infant speech discrimination test |

## Tables and figures

# Abstract

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Thesis Title: Using cortical auditory evoked potentials as a predictor of speech perception ability in Auditory Neuropathy Spectrum Disorder and conditions with ANSD-like clinical presentation
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Auditory Neuropathy Spectrum Disorder (ANSD) is diagnosed by the presence of outer hair cell function, and absence or severe abnormality of the auditory brainstem response (ABR). Within the spectrum of ANSD, level of severity varies greatly in two domains: hearing thresholds can range from normal levels to a profound hearing loss, and degree of speech perception impairment also varies. The latter gives a meaningful indication of severity in ANSD. As the ABR does not relate to functional performance in ANSD, there is a lack of clinically useful information after diagnosis in infants until they are developmentally able to perform behavioural assessment. Some neurodegenerative conditions, such a Friedreich's Ataxia (FA) and Charcot-Marie-Tooth disease (CMT) can also present with an ANSD-type perceptual pattern of auditory impairment. There is currently little research into the auditory profile of these conditions. In these neurodegenerative conditions, where physical mobility and test fatigue can be an issue, behavioural testing can be difficult. Thus finding an alternative objective test to the ABR would be useful in both the infant ANSD population, and in adults with neurodegenerative ANSD-type hearing loss. Cortical auditory evoked potentials (CAEPs) are thought to be a promising objective tool in these populations. The aim of this research was to investigate the relationship between CAEPs and speech perception in these participants for whom speech perception does not relate to hearing thresholds or ABR.

The first study of this thesis, a pilot, tested CAEP presence and speech perception ability in FA and CMT. This pilot showed significantly poorer performance amongst those with FA. CAEPs were not present in those with the poorest speech scores, but the sample was too small to identify a relationship. A larger follow-up was carried out in adults with FA, CMT and sensorineural hearing loss (SNHL). This study aimed to assess if CAEPs related to speech perception ability, and to compare the auditory profile of those with FA and CMT to those with the more typical SNHL. This second study did not find a significant correlation between CAEP measures and speech perception, and showed no significant differences in performance between groups. This was likely due to the significantly worse hearing levels of those with SNHL, which was a major limitation of the study. The second study found no significant differences between FA and CMT groups on CAEP measures, hearing levels, speech perception or gap-detection thresholds. The significant differences between groups in the pilot study are likely attributable to differences in global progression, rather than an inherent difference between these neurodegenerative conditions.

Following the adult studies, the relationship between CAEP presence and speech discrimination in three infants with ANSD was assessed. These case studies did not demonstrate a relationship between CAEP presence and degree of ANSD severity, and further research in this area is required with a larger sample. Young infants spend most of the day in sleep, and it can be difficult to maintain a resting state suitable for CAEP testing when awake. The final study revealed that CAEP responses were recordable in infants during sleep, but that it was state dependent. REM sleep was the optimal recording state.

## Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

## Copyright Statement



## Dedication

I dedicate this thesis to Sheila, Alex and Benjamin, in appreciation of the wonderful support and encouragement that they have given.

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# 1. Introduction

The Auditory Brainstem Response (ABR) is used as an objective measure of hearing acuity where behavioural testing is not possible. Amongst infants with a 'typical' sensorineural hearing loss (SNHL), the ABR is used to assess hearing thresholds, which inform management decisions. For those with Auditory Neuropathy Spectrum Disorder (ANSD), the ABR test is used in diagnosis only. ANSD is diagnosed where oto-acoustic emissions (OAEs) and/or a cochlear microphonic (CM) are present, and the auditory brainstem response (ABR) is absent or severely abnormal (Starr et al., 1996; Northern, 2008). Implementation of neonatal hearing screening programmes, using combined OAE and ABR assessment in identified at-risk populations, has led to earlier and more frequent identification of ANSD in infants (Kirkim et al., 2008).

Due to the absence or severe abnormality of ABR in patients with ANSD, it cannot be used to determine hearing thresholds in this population (Pearce et al., 2007). Furthermore, behavioural hearing thresholds are a very poor predictor of speech perception in patients with ANSD (Starr et al., 1996; Rance et al., 2002). Hearing thresholds can range from levels within normal limits to a profound hearing loss (Rance, 2005). Speech perception is also variable, and is a more meaningful measure of severity level in ANSD than hearing thresholds. Because the ABR cannot be used prognostically in this population, until the infant with ANSD is developmentally able to perform behavioural hearing assessment, there is little information available regarding severity of the hearing impairment. The lack of a meaningful prognostic tool can delay the implementation of effective management, with implications for communication development. An objective measure is required to predict severity of hearing impairment in infants diagnosed with ANSD before robust behavioural information is available to the clinician.

An objective tool for the assessment of auditory ability where the ABR is not clinically meaningful is not only relevant for infants with ANSD. Adults with neurodegenerative conditions can present with hearing loss which is more complex than the 'typical' SNHL. Conditions such as Friedreich's Ataxia (FA) and Charcot-Marie-Tooth (CMT) can cause hearing impairment with the perceptual profile of ANSD, in some cases accompanied by the same electrophysiological profile as ANSD (Rance et al, 2008). These groups were considered to be of particular interest as the associated hearing loss is perceptually similar to ANSD. They are under-researched groups, and the underlying cause of hearing loss in these groups, demyelination in CMT type 1a and axonal loss in FA, align with the causes

of difficulty in temporal processing and speech perception in ANSD suggested by Zeng and colleagues (2005). Furthermore, FA and CMT are characterised by physical impairment which can make an audiological test battery difficult to carry out, yet with a hearing loss more complex than SNHL additional testing to pure-tone audiometry (PTA) is recommended in these populations (Lopez-Diaz de Leon et al., 2003). An informative objective method of auditory assessment would facilitate easier testing sessions for these populations.

The demonstration of Cortical Auditory Evoked Potentials (CAEPs) in patients where the ABR is absent (Satya-Murti et al., 1983) has led to a research interest into the use of CAEPs as an objective test in adults with ANSD (Starr et al., 1996; Kraus et al., 2000; Michalewski et al., 2005; 2009). This objective measure is thought to have potential for audiological assessment in hard-to-test populations, such as young infants and those with severe physical disabilities (Michalewski et al., 2005). Initial studies in infants suggest that presence or absence of a CAEP response relates to severity of ANSD and the management strategy required (Pearce et al., 2007), and that the P1 component of the CAEP response is a meaningful biomarker of auditory function, that can be used to measure the effectiveness of amplification (Sharma et al., 2005).

The precise relationship between CAEP measures and speech perception in infants with ANSD, and adults with neurodegenerative conditions presenting with ANSD-like impairment, is as yet unknown. Because speech perception is a more meaningful measure of auditory impairment in ANSD-type impairment than hearing thresholds, if there is a relationship between CAEPs and speech perception, this test could be used as an objective tool to provide clinically useful information that could aid provision of management strategies where behavioural assessment is not possible or is difficult.

One of the benefits of the ABR assessment in paediatric audiology is that it can be recorded from sleeping infants. It can be difficult to keep infants awake and still and quiet enough to record a clean CAEP response in the first few months of life. During these first few months, infants spend the majority of their time in sleep (Sheldon, 1996). Thus, it is important, in assessing the effectiveness of the CAEP tool in early infancy, to see if it is possible to record CAEPs in sleeping infants. It is currently thought that it is not possible to record CAEPs during sleep (Purdy & Kelly, 2001; Rance et al., 2002). However, infant sleep is quantitatively different to that of older children and adults. Some reports suggest

that CAEPs can be used in sleeping infants, and they have been used as a measure of central nervous system maturation during sleep (Peirano et al., 2003). If it is possible to record CAEPs in sleeping infants, this may aid clinical uptake of the test.

This thesis is presented in alternative format. The aim of this research project was to explore the relationship between CAEP presence and speech perception ability in populations for whom the speech perception does not relate to auditory thresholds, and where the ABR may not be able to be used as an objective tool other than in initial diagnosis. Chapter 2 presents a literature review on ANSD, CAEPs in ANSD, maturation of the CAEP response, and CAEPs in sleep. Chapter's 3-6 present studies conducted into the presence of the CAEP and speech perception in those with ANSD or an ANSD-type hearing impairment due to FA and CMT. Chapter 7 gives a summary of the findings of these studies, and discusses the implications of the results.

A pilot study into speech perception in FA and CMT, and the presence of a CAEP response, is described in Chapter 3 of this thesis. This pilot also allowed for CAEP protocol refinement, which was felt to be necessary prior to implementation of testing in infants. A further aim of this study was to further define hearing impairment in FA and CMT, and to explore the differences between these two groups.

Chapter 4 of this thesis presents a study that grew out of the findings of the pilot study reported in Chapter 3. The study in Chapter 4 investigated if CAEPs to speech stimuli would provide a more effective tool for predicting speech perception than the noise stimuli used in Chapter 3, to inform the paradigm used in subsequent studies for infant assessment. A second objective of Chapter 4 was to further explore the auditory profile of neurodegenerative ANSD-like hearing impairment after the results of the pilot, which found a significant difference between participants with Friedreich's Ataxia and Charcot-Marie-Tooth disease on speech perception ability.

In Chapter 5, three case studies are presented. This study explored the relationship between CAEP presence and speech discrimination ability in three infants with ANSD. This study also investigated if the Visual Reinforcement Infant Speech Discrimination (VRISD) test could provide useful information in these infants with ANSD, and compared results to three infants with normal hearing.

The study presented in Chapter 6 aimed to answer the question of whether CAEPs can be recorded during sleep in young infants. This study has a practical application, if CAEPs are to be adopted clinically to provide prognostic information in infants diagnosed with ANSD.

# 2. Literature Review

## 2.1 Identification and management of Auditory Neuropathy Spectrum Disorder

### *2.1.1 Auditory neuropathy*

Auditory neuropathy is a term that has been used to label a spectrum of auditory dysfunctions that are diagnosed by the presence of oto-acoustic emissions (OAEs) and/or cochlear microphonic (CM) in conjunction with an absent or severely abnormal auditory brainstem response (ABR) (Starr et al., 1996; Berlin et al., 1998; Northern, 2008). Auditory neuropathy is also characterised by absent or severely elevated middle ear reflexes (Starr et al., 1996; Berlin et al., 2005) and absence of OAE suppression (Starr et al., 2001). Although this is not a new condition *per se*, the recent routine use of OAEs and ABR in the clinical setting has allowed the diagnostic differentiation of this condition from 'typical' sensorineural hearing loss (SNHL).

There are a number of potential sites of lesion within the auditory system which may contribute to the clinical profile of ANSD. These include the inner hair cells (IHCs), the synapse between IHCs and afferent nerve fibres, auditory neurons in the spiral ganglion, the auditory nerve, the brainstem nuclei, or a combination of more than one of these sites (Starr et al., 1996). The term 'auditory neuropathy' has been argued to be appropriate only where there is evidence of selective involvement of the spiral ganglion cells or their axons, or of the auditory nerve as a whole (Rapin & Gravel, 2006). In cases where the exact site of lesion is unclear, the term 'auditory dys-synchrony' has been suggested (Berlin et al., 2001). A consensus has now been reached by experts in the field to refer to the condition as Auditory Neuropathy Spectrum Disorder (ANSD) (Northern, 2008).

The labelling of ANSD as a 'spectrum disorder' highlights the heterogeneous nature of this condition. Rance (2005) suggests that patients with ANSD may represent a spectrum of the same pathology, or that ANSD may be a group of different disorders of the auditory pathway that present with the same diagnostic profile. In those with ANSD, behavioural pure-tone hearing thresholds range from within normal limits to the level of profound hearing loss (Rance, 2005). Berlin et al. (2010) tested 111 patients with ANSD, and found that 7% of cases were unilateral ANSD. Of those with bilateral ANSD, 77% had symmetrical thresholds. ANSD is typified by poorer speech perception than would be

predicted from the behavioural audiogram (Starr et al., 1996; Kraus et al., 2000; Rance & Barker, 2008). Speech perception ability in children with ANSD varies greatly. Whilst some perform at levels similar to children with a comparable degree of 'typical' SNHL and benefit from amplification, others show little or no speech perception ability even with amplification (Rance et al., 2002). This variation in hearing level and speech perception ability amongst the ANSD population leads to difficulties in providing audiological management strategies, particularly in young infants, for whom reliable behavioural assessment information is not available.

Adults with ANSD demonstrate impaired temporal processing, near normal intensity perception, and severely affected frequency discrimination at low frequencies (Zeng et al., 2005). Two distinct neurophysiological models have been proposed by Zeng and colleagues to explain this perceptual profile. The first is desynchronised discharge at the level of the auditory nerve, due to either dysfunctional synaptic transmission between the IHCs and the auditory nerve (Glowatzki & Fuchs, 2002), or demyelination of the auditory nerve (Waxman, 1977). The second proposed model is reduced discharge from the auditory nerve caused by loss of IHCs (Harrison, 1998; Salvi et al., 1999), or axonal loss (Starr et al., 2003). It is not currently possible to distinguish between these different neurophysiological types clinically.

### *2.1.2 ANSD-like hearing loss in peripheral neuropathies*

Peripheral neurological conditions can have a severe detrimental effect on the auditory system and auditory processing abilities. Two peripheral neuropathies that may present with a hearing impairment perceptually aligned with ANSD are FA and CMT (Satya-Murti et al., 1983; Starr et al., 1996; Rance et al., 2008; 2012a; 2012b).

As is characteristic of ANSD hearing impairment, participants with FA suffer from impaired speech perception (Lopez-Diaz de Leon, 2003; Rance et al, 2008; Rance et al, 2010; Rance et al, 2012a). This has been shown to be the case even when FA patients don't meet the full electrophysiological diagnostic criteria for ANSD (Rance et al, 2008). This challenges the necessity of the diagnostic criteria in patients with clinically diagnosed peripheral neuropathies, if the functional audiological outcome is in line with ANSD. As in other cases of ANSD, the cause of speech perception difficulties are underlying temporal

processing problems in FA (Rance et al., 2010). In FA, the degree of speech perception impairment is related to global disease progression and severity (Rance et al., 2012).

Research into the auditory profile of CMT is very limited. There are a number of variants of CMT. CMT 1a is the most common form. Rance et al (2012b) carried out research into the auditory abilities of children with the demyelinating form (CMT 1 variants) and the axonal form of the condition (CMT 2 variants). Rance and colleagues found that children with both forms of CMT had difficulties in temporal processing and speech perception, and the difficulties were more severe in those with CMT type 2. Knopp et al. (2014) discussed the potential for both optic and auditory nerve involvement in demyelinating forms of CMT. With regards to the management of CMT, very little research is currently available. FM systems have been shown to be more beneficial than traditional amplification in those with FA (Rance et al., 2010), however this work has not yet been replicated in CMT. Both FA and CMT are under-researched, and further attention must be drawn to the need for specialist audiological management in these populations, amongst both the medical and audiological communities.

### *2.1.3 ANSD prevalence and risk factors*

Published prevalence rates of ANSD in infants and children vary widely, ranging from 0.2% (Uus & Bamford, 2006) to 24.1% (Berg et al., 2005) in the neonatal high-risk population. Table 2.1 shows the prevalence rates of ANSD reported in a number of papers. Two of the papers report figures from screening of infants at high risk for hearing loss (Stein et al., 1996; Berg et al., 2005). Madden et al. (2002) provide prevalence figures of ANSD within a population of children with SNHL. Four papers present prevalence figures for both of these populations (Rance et al., 1999; Psarommatis et al., 2006; Uus & Bamford, 2006; Xoinis et al., 2007). Kirkim et al. (2008) present prevalence rates amongst healthy newborns (0.04%) and amongst those with bilateral SNHL (15.38%). The figures in Table 2.1 show that the differences in prevalence rate depend largely on the population that the rate was recorded from. However, some variation cannot be accounted for by population differences alone. Within the high risk infant population, a prevalence rate of 24.1% (Berg et al., 2005) is in stark contrast to those of around 0.2% (Rance et al., 1999; Uus & Bamford, 2006). Some differences may be attributed to sample size. Other variations are due to differing methodologies, including differences in postnatal age of participants at the time of testing. Madden et al. (2002) and Psarommatis et al. (2006) report figures from

retrospective analysis of clinical records. In contrast, Uus & Bamford (2006) report rates observed over one year of hearing screening in England. Prospective studies may allow for more rigorous adherence to diagnostic criteria, whilst this is not guaranteed in retrospective analysis. Differences in infant populations included in targeted screens, and regional differences in patient demographics, may also cause some of the differences observed. Whilst there are large differences between studies, the rates reported by Rance et al. (1999) and Uus & Bamford (2006) are in close agreement. These studies report ANSD prevalence of approximately 0.2% in the high risk infant population, and approximately 10% of infants with SNHL, from large infant screen samples.

A number of risk factors for ANSD have been identified. Infants treated within the neonatal intensive care unit (NICU) for over 48 hours are screened for ANSD in the Newborn Hearing Screening Programme (NHSP) in England (Sutton et al., 2008). Extremely low birth weight infants are ten times more likely to fit the diagnostic pattern of ANSD, and between three and six times more likely to be diagnosed with 'typical' SNHL, than infants from other birth weight groups (Xoinis et al., 2007). Infants with ANSD have a significantly lower gestational age, and spend a significantly longer time in hospital after birth, than their 'typical' SNHL and normally hearing NICU counterparts (Xoinis et al., 2007). Infants with hypoxia, hyperbilirubinaemia, and severe infections have an increased risk of ANSD (Starr, 2008). Hyperbilirubinaemia was reported as a key risk factor by Madden et al. (2002) and Kirkim et al. (2008). In 2014, Can et al. showed no significant difference in ANSD prevalence between pre-term infants treated with phototherapy for severe hyperbilirubinaemia compared to those with non-severe hyperbilirubinaemia, suggesting that in this case severity of the condition was not the key difference. Xoinis et al. (2007) found that peak bilirubin levels were associated with 'typical' SNHL, but not with ANSD. Despite the findings of Xoinis and colleagues, hyperbilirubinaemia is established as a known risk factor for ANSD. Additional factors, associated with NICU treatment, that are significantly higher amongst infants with ANSD than 'typical' SNHL include rates of chronic lung disease, furosemide and vancomycin treatment (Xoinis et al., 2007).

| Author | Year | Population | Sample Size | Prevalence |
|---|---|---|---|---|
| Stein et al. | 1996 | High risk infants | 100 | 4% |
| Rance et al. | 1999 | i. High risk infants<br>ii. Infants with permanent hearing loss | i. 5199<br>ii. 109 | i. 0.23%<br>ii. 11.01% |
| Madden et al. | 2002 | Children with SNHL | 428 | 8% |
| Berg et al. | 2005 | High risk infants | 477 | 24.1% |
| Psarommatis et al. | 2006 | i. High risk infants<br>ii. Infants that did not pass ABR screen | i. 1150<br>ii. 177 | i. 2.17%<br>ii. 14.12% |
| Uus & Bamford | 2006 | i. High risk infants<br>ii. Infants with permanent hearing loss | i. 91,523<br>ii. 169 | i. 0.2%<br>ii. 10.1% |
| Xoinis et al. | 2007 | i. High risk infants<br>ii. Infants with permanent hearing loss | i. 4173<br>ii. 95 | i. 0.58%<br>ii. 25.3% |
| Kirkim et al. | 2008 | i. All newborns<br>ii. Infants with permanent hearing loss | i. 23, 786<br>ii. 65 | i. 0.044%<br>ii. 15.38% |
| Bielecki et al | 2012 | High risk infants with SNHL | 352 | 5.1% |

Table 2.1 Prevalence rates of ANSD in infants and children.

There is a lack of information regarding the prevalence of ANSD amongst the well-baby population (Psarommatis et al., 2006). It is thought that the rate is very low; therefore ANSD screening in England is carried out in high-risk infants only, and not in healthy neonates (Uus, 2011). In healthy infants, ANSD is likely due to an autosomal recessive genetic mutation (Uus, 2011). The encoding of otoferlin (Yasunaga et al., 1999; Varga et al., 2003) and pejvakin (Delmaghani et al., 2006) have been identified as potential causes of recessive ANSD.

*2.1.4 ANSD and prognosis*

Approximately 10% of the 600 neonates born per annum with permanent childhood hearing impairment (PCHI) meet the diagnostic criteria for ANSD (Uus & Bamford, 2006). Implementation of the NHSP in England has reduced the average age of PCHI identification from 18 months to 10 weeks (Uus & Bamford, 2006). Early identification of the ANSD group within this PCHI population is now common.

Whilst very early diagnosis is now possible, the heterogeneity of the clinical profile leads to difficulties in devising a management strategy for the infant with ANSD. Hearing aid amplification can be fitted to infants with 'typical' SNHL using ABR estimates of threshold that are within 15-18 dB of the pure-tone audiogram (Schoonhoven et al., 2000). However, due to the absence or abnormality of the ABR in ANSD, this technique cannot be used (Pearce et al., 2007). Amplification in infants with ANSD should be fitted conservatively based on behavioural observations until reliable behavioural thresholds are available (Sutton et al., 2008; American Academy of Audiology, 2013). Robust and confident intervention is delayed until these thresholds are available, hampering early intervention. Furthermore, as ANSD is a temporal processing deficit (Zeng et al., 1999), amplification is not always of benefit to speech perception (Zeng et al., 1999; Rance et al., 2002). In cases where speech processing difficulties are severe, a cochlear implant is often the intervention of choice (Rance & Barker, 2008). Thus, treatment of ANSD may range from no intervention required, to hearing aid amplification, cochlear implantation, or a visual mode of communication.

Following diagnosis of ANSD in infancy, it is not currently possible to predict where the patient will fall on the spectrums of electrophysiological, speech perception, and behavioural hearing thresholds (Uus, 2011). In addition, it is not possible to predict how stable these dimensions will remain over time. Madden et al. (2002) found that half of the children retrospectively identified as having ANSD showed a spontaneous improvement in audiometric thresholds up to 12 months after diagnosis. A larger improvement was associated with a history of hyperbilirubinaemia. However, the children with hyperbilirubinaemia initially had a more profound degree of hearing loss, and this recovered to a level comparable with other patients. Psarommatis et al. (2006) did not find a link between hyperbilirubinaemia and spontaneous improvement in ANSD. However, low birth weight was shown to be a significant predictor for spontaneous recovery. Low birth weight in these cases was associated with a younger gestational age, which may

support the theory of transient ANSD as a sign of delayed maturation in these newborns. However, the link between hyperbilirubinaemia and spontaneous recovery, as in Madden et al. (2002), suggests that there are factors other than those associated with maturation involved in ANSD recovery (Uus, 2011). Another case study that highlighted the potential for transient ANSD, and the need for close monitoring of children with ANSD, is that of Eom et al. (2013). This case study described a case of ANSD diagnosed at 16 months, and managed with hearing aids, with a subsequent return to normal hearing levels and speech perception three years later.

Thus, with the broad spectrum of functional outcomes that are possible in ANSD, relating to sound awareness, speech perception, and possible recovery, it is hard to provide a reliable prognosis to the parents of infants identified with ANSD. There is, therefore, a great need for the development of a prognostic tool in ANSD.

### 2.1.5 Speech perception and temporal processing in ANSD

#### *2.1.5.1 Speech perception and temporal processing in adults with ANSD*

Speech perception in ANSD is typically worse than would be predicted from behavioural audiometric hearing thresholds (Starr et al., 1996). Zeng et al. (1999) demonstrated impaired gap-detection and reduced sensitivity to temporal modulation functions in adults with ANSD on behavioural testing, compared to a normally hearing control group, which related to level of speech perception impairment. Zeng et al. conclude that speech processing deficits in ANSD are due to problems in temporal processing.

Zeng et al. (2005) suggest that the two possible underlying causes for ANSD are desynchronised neural discharge, or reduced neural conduction. Zeng states that both models of ANSD would lead to impaired gap-detection ability. It is suggested that desynchrony of neural discharge would lead to different levels of delay to the representation of the gap in different nerve fibres, which would smear the central output, leaving the gap imperceptible from the background noise. Reduced conduction is said to impair gap detection ability by way of a reduction in the nerve fibres able to transmit the presence of the gap in the noise. Both models would cause an inability to perceive short

gaps in background noise. An inability to process these rapid changes in input are believed to be the cause of impaired speech perception in ANSD (Zeng et al., 1999).

Michalewski et al. (2005) recorded gap-evoked N1 and P2 CAEP responses in an active and a passive paradigm in adults with ANSD and adults with normal hearing as a measure of temporal processing. The gap-detection threshold was 5ms in the normally hearing group. Within the ANSD group (N=14), in the passive condition, three participants had a gap detection threshold of 10ms, three showed gap detection at 20ms, and one participant had a threshold of 30ms. In these 7 participants for whom a gap-evoked CAEP response could be recorded, 5 of the 7 had N1 latencies that exceeded the upper limit of the normally hearing group. In the normally hearing group, the mean passive N1 latency at gap-threshold was 125 ms (SD 14). The range of N1 latencies to the gap detection threshold was 118-230ms in those with ANSD in the passive condition. In the remaining 7 participants with ANSD, no response was elicited for any of the gap durations in the passive condition. In two of these participants, a profound hearing loss meant that the noise signal could not be made audible for them. Four of the participants, all with mild hearing loss, had gap-evoked potentials in the active, but not passive, condition. Thus, attention was shown to modulate the CAEP response. This worked in two directions. Paying attention and responding to the stimuli abolished the CAEP response in 7 participants, but elicited a response in 4 participants. There was a close agreement between electrophysiological gap detection and behavioural gap detection assessment in the 7 participants for whom passive CAEPs to gaps in noise could be recorded. In the 4 participants for whom gap-evoked potentials could only be elicited in the active condition, there was also close agreement between active CAEP and behavioural gap detection thresholds. The two participants with a profound hearing loss, for whom CAEPs to gaps in noise could not be recorded, were also unable to demonstrate a behavioural gap detection threshold. The remaining participant had no gap-evoked potential, but a behavioural gap detection threshold of 30 ms was recorded. Thus, for the majority of participants, there was some agreement between CAEP and behavioural gap-detection thresholds, but this was paradigm-dependent in an inconsistent manner. This study demonstrates that gap evoked potentials are a useful tool for assessment of those with ANSD.

Zeng and colleagues (1999) reported that some adults with ANSD did not benefit from using conventional hearing aids in the way that those with SNHL would, as they are unable to address difficulties in temporal processing. Kumar and Jayaram (2013) demonstrated

improved speech perception through the modification of temporal cues, with the lengthening of transition times leading to the greatest improvement in speech perception. This was to a greater extent than the combination of increased voice onset time, burst duration and transition duration of speech stimuli. This suggests that enhancing timing cues may be a beneficial strategy to aid speech perception in those with ANSD in the future.

*2.1.5.2 Speech perception in children with ANSD*

Rance et al. (2002) compared speech perception in children with ANSD and a control group with 'typical' SNHL. The Phonetically Balanced Kindergarten (PBK) words test, an open-set monosyllabic assessment, was used as the outcome measure for speech perception ability. Unaided speech perception scores were higher in the SNHL group than the ANSD group. In the aided condition, all children with SNHL demonstrated improved speech perception. Results in the aided condition were divided into two sub-groups for children with ANSD. Seven of the fifteen children demonstrated no benefit on speech perception testing in the aided condition. The remaining eight children with ANSD showed an improvement, to a level similar to that of the SNHL group. PBK scores were significantly correlated to hearing level in children with SNHL, but this was not the case in the children with ANSD. This supports previous findings of speech perception that is disproportionate to degree of hearing loss in adults with ANSD (Starr et al., 1996). Speech perception performance was concluded to be better in children with SNHL than those with ANSD. These differences occurred despite the fact the groups were said to be well matched for audiometric hearing level. Both groups had adequate access to the long-term speech signal at 70 dB SPL, as concluded from Aided Audibility Index scores for the SNHL and ANSD groups (0.93 and 0.87 respectively). However, some issues in matching of groups may have impacted upon the findings. Whilst said to be age-matched, the mean age of the two groups differed by more than 14 months. This has implications for age-appropriate speech perception testing. The presence and types of risk factors in the two groups also varied largely, suggesting that the two groups may represent very different populations. In addition, differences in duration of amplification use between the two groups may affect the assessment of speech perception in the aided condition. The adequacy of hearing aid fit to targets in the ANSD group may also be questionable, given the young age at fitting of some of the participants, and the limited amount of audiological information available at that age in ANSD. However, despite these methodological issues, this paper highlights the

differences that may occur in speech perception in children with ANSD, as compared to those with 'typical' SNHL.

Further research into speech perception in children with ANSD and 'typical' SNHL was carried out by Rance and Barker (2008). This paper compared speech perception in children with ANSD with bilateral hearing aids, children with ANSD fitted with one or two cochlear implants, and a control group of children with 'typical' SNHL who had undergone cochlear implantation. Both groups of children with ANSD performed significantly worse than the children with SNHL. Amongst the children with ANSD, there was not a significant difference in speech perception between those with a cochlear implant and those with bilateral hearing aids. The authors suggest that whilst cochlear implantation may be of benefit in ANSD, expected outcome may be worse than that of children with a 'typical' SNHL. Although mean speech perception scores in children with ANSD fitted with a cochlear implant (59.6%) was significantly worse than children with SNHL with an implant (83.1%), there was a large improvement in scores within the implanted ANSD group. The decision to provide children with ANSD with a cochlear implant was based on poor speech perception in monosyllabic word tests (<40%). As the average score for children with ANSD post-implantation was 59.6%, this represents a large improvement for some children in this group. However, results in both groups with ANSD were much more variable than those of children with SNHL. As poor speech perception was the criterion for implantation in children with ANSD, those with ANSD using hearing aids must have a much higher speech perception baseline score than those requiring an implant. Thus, they may not be a useful comparison group. Pre-implantation speech perception scores and hearing levels are not disclosed for participants with SNHL. Of the participants that have undergone cochlear implantation, it is not stated how many were using bilateral or unilateral implants, or if there was a contralateral hearing aid used in those implanted unilaterally. The effect of bilateral and unilateral implantation on outcome has not been considered in analysis. More research is required into factors that may predict outcome with cochlear implantation or hearing aid amplification in children with ANSD.

Whilst the previous two studies focus on tests of speech perception in quiet, Rance et al. (2007) looked at the effects of background noise upon speech perception in ANSD. This was assessed in children with ANSD, 'typical' SNHL, and normal hearing. Open and closed set speech perception was tested. All children with ANSD were bilateral hearing aid users, and had been aided for at least 4 years. The 'typical' SNHL group was well matched

for age and for average hearing level. Communication method was not specified for the SNHL group. Two children with ANSD were reported to rely entirely on sign language, and another child in this group used total communication. This may have some impact on speech perception scores, as speech is not the main communication mode used by all participants with ANSD. The average age of the normally hearing group was well matched to that of the two groups of children with hearing impairment. However, the youngest child in the normally hearing group was almost 2 years older than the youngest in the hearing impaired groups, which may impact on average score differences.

In contrast to the findings on assessment of speech perception in quiet (Rance et al., 2002; Rance & Barker, 2008), somewhat surprisingly, there were no significant differences between children with ANSD and children with SNHL in assessment of speech perception in noise. Whilst there was a trend for worse performance in the ANSD group, this did not reach significance. This may reflect that children with ANSD perform poorly on speech perception tasks in quiet and in noise, whilst their counterparts with SNHL are affected to a much greater extent in noise than in quiet. The lack of significant difference may also be due in part to the heterogeneity of the ANSD group, in which scores were more varied than the SNHL group. These results may also be influenced by the small sample size in the group of children with ANSD (n=12).

Overall, the results of these three studies into speech perception in children with ANSD indicate that speech perception is worse in children with ANSD than those with 'typical' SNHL. Performance is significantly worse for children with ANSD on speech perception testing in quiet environments. These studies demonstrate the importance of strict criteria for matching of groups in the domains of age, developmental ability, communication mode, duration of amplification, and risk factors when comparing children with ANSD to those with 'typical' SNHL.

Recent work has been carried out into the relationship between CAEP responses to complex stimuli and speech perception in children with ANSD. He et al. (2013) recorded electrically evoked CAEP gap-detection thresholds in children with ANSD with cochlear implants. All participants had a recordable response to the stimuli, and P1 latency and test-retest reliability did not vary with speech perception ability in this group. However, as with adults with ANSD, worse speech perception ability was associated with increased gap-detection threshold in this paradigm.

## 2.2 Cortical auditory evoked potentials in ANSD

### *2.2.3 CAEPs in adults with ANSD*

Satya-Murti et al. (1983) observed recordable CAEP responses in 6 patients for whom an ABR response was absent or abnormal. This was a precursor to investigations into the presence of CAEPs in individuals with ANSD. Starr et al. (1996), in the first paper to clinically define ANSD, recorded N1 and P2 components in 3 out of 5 patients. These responses were reported as abnormal in 2 patients. Latency and amplitude information were not given for these responses; however the CAEP response of one patient was described as being smaller and later than a normal response. The patient with a normal CAEP response also had a recordable wave V on ABR testing. This may suggest a greater degree of neural synchrony in this patient, or a different site of lesion to the other participants.

Table 2.2 gives a summary of CAEP components recorded from 2 studies comparing responses of adults with ANSD to those with normal hearing. Kumar and Jayaram (2005) reported that P2 and N2 components were present for all of the 14 participants with ANSD, whilst P1 and N1 were present for 10 out of these 14 participants. The responses were elicited using an oddball paradigm, and mis-match negativity (MMN) was recorded. MMN was present in 9 of 14 participants with ANSD. Where the P1-N1-P2-N2 complex was elicited, this was not significantly different to the normally hearing group in latency or amplitude.

| Author | Stimulus | P1 | | N1 | | P2 | | N2 | |
|---|---|---|---|---|---|---|---|---|---|
| | | ANSD | NH | ANSD | NH | ANSD | NH | ANSD | NH |
| Kumar & Jayaram (2005) | Natural & synthesised /da/ (Oddball) | 81 (16.2) | 69 (15.2) | 125.4 (23.04) | 120.5 (23.5) | 154.1 (27.1) | 145.3 (25.6) | 205 (23) | 200.2 (26.3) |
| Narne & Vanaja (2008) | Click stimulus | 76 (20) | 50 (8.1) | 124 (31) | 85 (9) | 185 (43) | 142 (12) | 243 (50) | 218 (13) |

Table 2.2 CAEP latencies in adults with ANSD.
Values are in ms, values in parentheses show standard deviation.

Kumar and Jayaram found that behavioural speech identification scores were not associated with latency or amplitude of the P1-N1-P2-N2 complex. This is in contrast to the findings of Narne and Vanaja (2008), who found a correlation between speech identification ability and obligatory CAEP component amplitude. Narne and Vanaja (2008) recorded CAEP responses in 9 of 10 participants with ANSD. There are differences in latency values and spread of data between the two studies (see Table 2.2). Narne and Vanaja (2008) report greater standard deviations from the mean within the group with ANSD than Kumar and Jayaram (2005). This may be influenced by the greater age range of participants within their study, which included two participants aged 12 years and one of 15 years. Kumar and Jayaram (2005) did not find significant differences between responses from participants with normal hearing and those with ANSD. However, the P1 and N1 mean values for normally hearing participants are delayed relative to those of normally hearing participants in Narne and Vanaja (2008). All of the responses within the normally hearing group of Kumar and Jayaram (2005) are more varied than those of Narne and Vanaja (2008). This may represent a more heterogeneous normally hearing group assessed by Kumar and Jayaram (2005). This may also be partially due to the different stimuli and paradigm used. Narne and Vanaja (2008) used a supra-threshold click stimulus, whilst Kumar and Jayaram (2005) used a synthetic /ta/ and a natural /ta/ speech token in an oddball paradigm.

CAEPs, as a recordable objective response in ANSD where ABR information is not available or very limited, are a promising clinical tool. Michalewski et al. (2005) recorded gap evoked CAEP responses in an active and a passive paradigm in adults with ANSD as a measure of temporal processing. Further research, characterising the relationship between CAEPs and functional auditory measures, is required in order to develop the usability of CAEPs in behaviourally difficult-to-test populations with ANSD.

### *2.2.2. Maturation of the CAEP response*

The maturation of the cortical auditory evoked potential (CAEP) in the first year of life reflects the ongoing development of the cortex. The auditory brainstem becomes mature in most aspects between 1 and 3 years of age (Moore & Guan, 2001). The anatomical development of the human auditory cortex, in contrast, continues to mature from the fourth week of gestation to the age of 11-12 years (Moore and Guan, 2001; Illing, 2004; Moore and Linthicum, 2007). The adult form of the CAEP response is developed between 14-16 years of age (Pasman et al., 1999). CAEPs that are recorded during infancy do not bear a resemblance to the mature CAEP response (Kushnerenko et al., 2002). There are maturational differences in amplitude, latency and morphology of the response waveform (Pasman et al., 1999). However, there is some disparity in the current literature with regard to the nature of these maturational changes.

Kurtzberg et al. (1984) demonstrated a change from a dominant negative wave between 250 and 350 ms in pre-term neonates at midline and lateral sites, to a positive peak at around 225 ms at lateral electrode sites by three months corrected age. Full term newborns demonstrated more mature responses at 40 weeks post-menstrual age than pre-term, very low birth weight infants at the same post-menstrual age. (Please refer to the American Academy of Pediatrics policy statement for details of age-terminology, Engle et al., 2004). However, Kurtzberg et al. (1984) recorded CAEPs with the same morphology and topography in pre-term and full term infants by three months corrected age. This suggests a maturational delay that has 'caught-up' within three months corrected age.

Kurtzberg et al. (1984) provide examples of morphological and topographical maturational changes to a single peak CAEP response in the first three months of infancy. Ponton et al. (1996) reported that the immature CAEP waveform is dominated by a single positive peak. Pasman et al. (1999) also found a broad positive peak dominating the CAEP response of newborn infants.

However, there are a number of studies that present a different picture of infant CAEP component morphology. Kushnerenko et al. (2002) recorded CAEP components with a positive-negative-positive-negative peak configuration, a precursor to the P1-N1-P2-N2 adult response, in full-term newborns. However, the nomenclature used by Kushnerenko et al. (2002) was latency based, with components labelled as P150, N250, P350 and N450.

The demonstration of four components differs from the findings of a single component waveform by the authors above. Factors such as the length of interval between stimuli repetitions affect waveform morphology (Ceponiene et al., 2002; Golding et al., 2006). ISI is the interval from stimulus offset to next stimulus onset (Golding et al., 2006). This may have been implicated in the difference in results. Kurtzberg et al. (1984) used a long inter-stimulus interval (ISI) of 2700 ms. Kushnerenko et al. (2002), on the other hand, used a rather shorter ISI of 700 ms. This may explain some of the differences that were found. Kushnerenko states that a short ISI helps to prevent recording attention-related components. These may occur when a stimulus is presented at a slow rate with a silent background.

The effects of interval length on components are complex. Ceponiene et al. (2002) showed, in 9 year old children, that a 700 ms onset-to-onset interval elicited P1 and N2 peaks. However, an onset-to-onset interval of 5 s evoked P1, N1, and P2 components. Golding et al. (2006) showed that changes in P1 latency and amplitude, due to variations in ISI, were inconsistent in infants for speech stimuli /m/ and /t/. Peak latency was not significantly affected by changes to ISI length from 750 ms to 1125 and 1150 ms. Effects on amplitude differed for the two speech stimuli. For the stimulus /t/, there was a significant difference in the amplitude of responses evoked with the shortest and longest ISIs between stimuli. For /m/, there were no significant differences in peak amplitude attributable to ISI. There was a significant interaction between stimulus and ISI for peak amplitude. Thus, it is hard to isolate effects of ISI alone, and the effects of ISI differences on CAEPs are not yet fully understood. Golding et al. (2006) advise that there is no advantage to using ISIs of more than 1125ms in CAEP assessment in infants.

In support of stimulus differences as a contributing factor to CAEP differences in infants, Wunderlich et al. (2006) found that CAEP responses were obtained more frequently to a speech token, /bæd/, compared to pure tones. Like Kushnerenko et al. (2002), Wunderlich et al. (2006) observed a positive-negative-positive-negative peak waveform in the grand-average group waveform of newborns. These peaks were labelled P1-N1-P2-N2. However, whilst a CAEP response was present in all of the infants studied by Wunderlich et al. (2006), they did not all demonstrate all components of the response for each stimuli. There was also great variability between subjects in CAEP component latency and amplitudes.

Despite demonstrating the presence of the same group-average waveform in newborns, Kushnerenko et al. (2002) and Wunderlich et al. (2006) recorded peak responses at very

different latencies, and with differing magnitude (see Table 2.3). The negativities recorded by Wunderlich et al. (2006) were negative values, whereas the N250 response found by Kushnerenko et al. (2002) was negative relative to the positive peaks, but the peak was not below zero. In addition to differences in latency and amplitude of components at birth, the maturation of responses at birth and one year differed. Kushnerenko et al. (2002) demonstrated significant changes in P150 amplitude and latency over the first year of life. N250 amplitude also significantly increased from birth to 12 months. The N450 amplitude increased significantly from birth to 12 months, and the latency decreased significantly over the same time period.

Wunderlich et al. (2006), on the other hand, found inconsistent effects of age upon the amplitudes and latencies of different components. The authors conclude that this reflects the maturation of different component generators at different times. Wunderlich et al. (2006) found that P1 peak latency was significantly shorter in adults than in newborns, toddlers, or children. However, they recorded no significant differences in P1 latency from term-birth to 6 years of age. A systematic and significant increase in N2 amplitude was shown from birth to adulthood. However, latency was only significantly affected by the transition from childhood to adulthood, and there were no significant differences from birth to 6 years of age. Peak P2 amplitude was significantly larger in adults than in term-newborns, and latency was significantly shorter, but there was not a systematic progression to these changes through the toddler and child age groups. N2 amplitude decreased with age, in contrast to Kushnerenko's findings of an amplitude increase in the N450 with age. Wunderlich et al. (2006) showed that N2 latency was shorter in adults than in newborns, toddlers or children, but there were no significant differences amongst the non-adult groups.

The results of Kushnerenko et al. (2002) and Wunderlich et al. (2006) show several differences in the CAEP responses of newborn infants, and their maturational course. Some of these differences may be due to the very different ISIs used, with an ISI of 700 ms used by Kushnerenko et al., in contrast to ISIs of 3100-6050 ms used by Wunderlich et al. However, Wunderlich et al. (2006) and Kurtzberg et al. (1984) both demonstrated very different results using similar ISIs, so this may not be a key contributing factor. Other differences may be due to stimulus differences, such as duration, type (tone burst vs pure tone and speech token), intensity level, and transducer used. Wunderlich et al. (2006) used insert earphones, whilst Kushnerenko et al. (2002) used speakers. With regard to duration

effects, Golding et al. (2006) noted only a small increase in amplitude, and no significant latency changes, to the infant P1 when stimulus duration was varied. There may be an interaction of these different factors, producing the component differences seen in table 2.3.

The shared finding of Kushnerenko et al. (2002) and Wunderlich et al. (2006) was that all 4 components of the CAEP waveform were present from term-birth. Rather than the growth of additional components at a later stage, all components were present in an immature form as a precursor to their adult waveforms. Wunderlich et al. (2006) also reported that the scalp distribution of CAEPS changed from uniform across electrode sites at birth, to more focal distribution in adulthood. However, this conclusion is limited by the fact that in newborns, the authors used only 4 electrode sites, 3 of which were central. Thus, conclusions regarding scalp distribution in the neonatal population could be viewed as overstated.

There is some disagreement in the current literature regarding the maturational changes that occur in the CAEP response of infants with normal hearing. However, there is a consensus that the CAEP response in infants is very different to the mature response recorded in adults. Factors such as ISI, stimulus differences, and recording site may lead to differences in the responses recorded using CAEPs. Thus these issues must be considered carefully when designing CAEP studies in infants, and when comparing results across studies.

| **Kushnerenko et al. (2002).**<br>Age-group: Newborn infants.<br>Stimulus: 100ms, three-partial harmonic tones (500, 625, 750 Hz) at 70 dB SPL.<br>All results from electrode site C3. | | | **Wunderlich et al. (2006)**<br>Age-group: Newborn infants.<br>Stimulus: 200ms, 400 Hz tone, at 75 dB peSPL.<br>All results from electrode site Cz. | | |
|---|---|---|---|---|---|
| **P150** | Amplitude: 2.18 | Latency: 179.6 | **P1** | Amplitude: 1.7 | Latency: 78.0 |
| **N250** | Amplitude: 1.44 | Latency: 226.6 | **N1** | Amplitude: -1.5 | Latency: 185.9 |
| **P350** | Amplitude: 2.32 | Latency: 292.4 | **P2** | Amplitude: 3.1 | Latency: 214.1 |
| **N450** | Amplitude: -0.71 | Latency: 504.0 | **N2** | Amplitude: -3.49 | Latency: 373.1 |

Table 2.3 Comparison of neonatal CAEP components from Kushnerenko et al. (2002) and Wunderlich et al. (2006). Amplitude units: μV, latency units: ms.

*2.2.3 CAEPs in infants and children with ANSD*

The first investigation into the use of CAEPs to assess children with ANSD was carried out by Rance et al. (2002). This study looked at the presence of CAEPs, and the association of CAEP presence with speech perception, as compared to a control group of children with 'typical' SNHL. As discussed in Section 2.1.4, there were some issues regarding the matching of the group of children with ANSD and the control group with SNHL. The factor that may bear the largest impact upon CAEP responses is the difference in age of members of the two groups, due to maturational effects on CAEPs (see section 2.2.1). Nonetheless, this study opened up a new area of research within ANSD.

Rance et al. (2002) recorded the presence/absence, latency, amplitude and morphology of the P1, N1 and P2 CAEP components. These components were recorded for tone-bursts, and for the speech stimuli /bæd/ and /dæd/. These stimuli were presented in an oddball paradigm; however results for the standard condition only were reported. A relationship was demonstrated between speech perception ability and presence or absence of CAEP components in the group of children with ANSD. CAEP responses were present in children with ANSD showing significant speech perception when aided, and often absent in those who showed no benefit from amplification in the PBK test. CAEPs were evoked more frequently in children with 'typical' SNHL than ANSD. For tonal stimuli, 17 of 18 children with SNHL and 11 of 18 children with ANSD had CAEP responses present. When evoked with speech stimulus /dæd/, 15 of 18 children with SNHL had demonstrable CAEPs, compared to 11 of 18 children with SNHL. Where responses were present, latency and amplitude values did not differ significantly between the two groups. These values

were not significantly different to those of a normally hearing sample of children that were included in this paper. This is unexpected, given the lack of temporal synchrony in those with ANSD compared to children with normal hearing. However, though these differences were not significant, the differences between groups appeared large for some components. One example of this is a difference of 41.5 ms for P2 evoked by a 440 Hz stimulus. Level of hearing loss was also said not to be significantly related to CAEP components. However, the study may be underpowered, with 18 participants per group, and large variability in responses, and the lack of statistical significance may be attributable to this. In support of this, the mean hearing threshold in children with ANSD with CAEP present and absent was 65 and 81 dB respectively, and this was said to be not statistically significant.

Rance et al. (2002) highlighted the need for research into the potential use of CAEPs in young infants with ANSD. Sharma et al. (2005) assessed the aided CAEP response of an infant fitting the diagnostic profile of ANSD at 11 months chronological age. P1 was selected as the component of interest. This was used as an indicator of central auditory pathway development in this infant, and two infants with 'typical' SNHL. CAEPs were evoked by the synthesised speech token /ba/, of duration 90ms, with an ISI of 610 ms. The P1 component was significantly delayed in the child with ANSD. The waveform morphology was abnormal, with a large negativity recorded prior to P1. The authors state that this indicates a lack of adequate stimulation provided by the hearing aids. The child with ANSD was fitted with a cochlear implant at 15 months of age. At 6 months after implantation, a normal P1 latency was recorded, and the component continued to mature normally at 18 months after implantation. The transition from an abnormal CAEP response pre-implantation to an increasingly normal response post-implantation suggests that the central auditory system was receiving adequate auditory input post-implantation. The authors suggest that the latency and waveform morphology of the P1 component is an effective tool to assess the development of the central auditory pathway. If the test battery for this child had relied on behavioural assessment alone, which revealed aided thresholds of 45 dB HL at 500 Hz and 65 dB HL at 1 kHz, it may have been assumed that the hearing aids were providing adequate auditory system stimulation. Whilst this is a case study, and thus is not the most robust form of evidence, the use of CAEPs in this case for the verification of hearing aid fit suggests the clinical usefulness of this tool. The participant in this study was 11 months old, and thus CAEPs could be used in this case to support information obtained in behavioural testing. The study does not provide information on the use of CAEPs in younger infants with ANSD, for whom behavioural testing is not possible.

Pearce et al. (2007) addressed the need for investigation into the viability of using CAEPs in younger infants in two case studies of infants with ANSD. Natural speech tokens, /m/, /g/, and /t/, were presented at 65 dB SPL by loudspeaker, with an ISI of 1125 ms. If no response was elicited with a 65 dB SPL signal, the level was increased to 75 dB SPL. Infant 1 was born at 28 weeks at a low birth-weight, and had a history of hyperbilirubinaemia and respiratory distress. Infant 2 was born at full term, and had an unremarkable perinatal history. Infant 2 had a family history of cochlear implant use in two paternal relatives. Infant 1 was tested at 7 weeks (corrected age), where repeatable unaided CAEP responses were recorded at 65 dB SPL. Behavioural testing at 2.5 years revealed that the infant had a mild hearing loss. ABR testing was not carried out again, but it is possible that there may have been ABR recovery. Despite the improved behavioural hearing levels, and the discontinuation of amplification, this infant did display a speech development delay. Assessment of speech perception is not reported, thus it may be the case that despite adequate pure tone hearing levels on audiometric testing, and speech token perception at conversational levels as assessed by CAEPs, there is a residual difficulty with speech perception. CAEP waveforms were provided by Pearce et al. (2007), and different stimuli appear to produce different morphology of waveforms. A broad positive peak could be seen for /m/, whilst a small negative peak preceding the larger positivity is present for /g/ and /t/. This is unlikely to be associated with duration of stimuli, as /m/ and /t/ were both 78 ms, yet elicited different waveforms. The differing component morphologies were not noted by the authors, but it is possible they may indicate different speech processing abilities for different speech segments, which could impact on speech production. Whilst it has been assumed by the authors that this child's speech perception is strong, due to rejection of hearing aids, and parental reports that the child followed instructions well at 2.5 years, this has not been assessed. The infant was reported to follow and understand instructions. However, this could be associated with contextual clues or gestures rather than an indication of strong auditory function.

Infant 2 underwent aided CAEP assessment at approximately 6 months of age. The speech tokens stimuli did not elicit a repeatable response at 65 or 75 dB SPL. However, the infant was said to become restless when tested at 75 dB HL, and testing was stopped. This could indicate the infant is disturbed by the level of the sound, but that due to a lack of neural synchrony or reduced neural conduction (Zeng et al., 2005) it is not possible to record a repeatable response. However, it could be the case that this level was inaudible. The infant

was tested again with a 75 dB SPL presentation level, and an increase to hearing aid maximum gain settings, but it was still not possible to record a response. This child was referred for cochlear implantation at the age of 1 year and 4 months.

Based on these two case studies, Pearce et al. (2007) infer that presence or absence of CAEPs in infants with ANSD can inform management strategy and provide useful clinical information. They suggest that presence of CAEPs at conversational levels, in the unaided condition, allows for assumption of a mild-to-moderate hearing loss when fitting hearing aids. The absence of aided CAEPs may recommend a more aggressive treatment strategy. Whilst these two case studies do suggest that CAEP presence or absence can differentiate between management strategy requirements, further research is required in this population before these conclusions can be generalised and the suggestions implemented in the treatment of ANSD in infancy. The heterogeneity of this population suggests that one should use caution when drawing conclusions from such small samples of infants. In addition, follow up information on infant 2 was not given, and thus it is not known how well CAEP absence predicted future outcome, and whether an implant was fitted after referral. Lack of speech perception assessment in both infants limits the conclusions that can be drawn regarding the association of CAEPS with functional outcome. Behavioural thresholds were given for infant 1, but it is known that this does not correlate to speech perception in those with ANSD. Thus, more research is required in this area before the clinical application of CAEPs in infants with ANSD can be recommended. Rance et al. (2002) highlights the need for further research into the ability of CAEPs to predict speech perception outcome in infants with ANSD. However, the authors suggest that this may be problematic, as sleep in infants can reduce the robustness of CAEP response, and young infants spend much of the day in sleep. Section 2.3 shall examine how sleep may affect CAEP measurement in infants.

## 2.3 Measuring CAEPs in infants: The effects of sleep state

### *2.3.1 Maturation of sleep in early infancy*

Purdy & Kelly (2001) state that the ABR is usually the most suitable form of objective assessment in infants, as it can be recorded during sleep. However, ABR cannot provide useful clinical information in patients with ANSD, and CAEPs may be a more effective clinical tool in this population. Attention level and state of arousal are said to augment the CAEP response (Purdy & Kelly, 2001). Clinicians have been advised to record CAEPs in infants and children during wakefulness (Purdy & Kelly, 2001). However, this is very difficult in young infants as there is increased myogenic activity in the waking state, which can create 'noise' in the CAEP recording. The majority of research into the effects of sleep and attention on the CAEP response has been carried out in adults. Sleep in infants is qualitatively different to that of adults (de Weerd & van den Bossche, 2003). Thus the effects of sleep upon the CAEP response may differ between adults and infants. The maturation of sleep during the first months of life and the effects of sleep on the CAEP response in newborns shall be discussed.

During the first months of life, a number of maturational changes take place in the sleeping pattern of the infant. From birth to 12 months, there is a decrease in the total number of hours spent in sleep each day (de Weerd & van den Bossche, 2003). In early infancy, there is a reduction from approximately 17-18 hours per day at birth, to 14-15 hours per day by 16 weeks (Sheldon, 1996). Adult sleep cycles are divided into rapid eye-movement (REM) and non-REM sleep. Non-REM sleep, is separated into stages from 1-4. Stages 3 and 4 of non-REM sleep are known as 'slow-wave sleep' (Borbely & Achermann, 2000, 377-390). In early infancy, sleep cycles consist of active sleep (AS), quiet sleep (QS) and indeterminate sleep state (IS), which occurs in the transition period between stages (Sheldon, 1996). Between 4 and 6 months of age, slow-wave non-REM sleep becomes more complex, and it is possible to separate non-REM sleep into 3, or in some cases 4, sleep states (Sheldon, 1996). AS is the infant form of REM sleep, and QS corresponds to non-REM sleep (Jenni et al., 2004). It has been suggested that the terms AS and QS should be used in infants under 4 months, and REM and NREM in those older than 4 months (Jenni et al., 2004). The terms REM and NREM will be used throughout this thesis.

Sleep state can be scored using electroencephalography (EEG), and measurement of eye movement, electromyogenic activity, respiration rate, oxygen saturation and behavioural

observations of limb and body movements (Rechtschaffen & Kales, 1968; Sheldon, 1996; de Weerd & van den Bossche, 2003). Whilst the extra information gathered from a combination of these channels is beneficial, EEG recordings and behavioural observation are the key measures in infant sleep assessment (de Weerd & van den Bossche, 2003).

Different sleep states are associated with different patterns of EEG activity (Rechtschaffen & Kales, 1968; Sheldon, 1996). NREM in infants is characterised by the appearance of high-voltage delta waves (3-5 Hz) (Sheldon, 1996). From the age of 2 months onwards, sleep spindles, which are bursts of activity in the sigma frequency region (12-14 Hz), are seen throughout periods of NREM (Sheldon, 1996; Jenni et al., 2004). By 5-6 months of age, large amplitude vertex sharp waves are seen in EEG recordings during NREM sleep (Sheldon, 1996). In early infancy, REM sleep is dominated by EEG pattern activity between 2 and 6 Hz (Sheldon, 1996). As it matures, this develops into a pattern that is spread across frequency regions, and is of relatively low amplitude (Sheldon, 1996).

During the first 12 months of life, the proportion of total sleep time spent in REM sleep reduces (de Weerd & van den Bossche, 2003; Jenni et al., 2004). Jenni et al. (2004) report that in infants aged 2 weeks, 38.7% of sleep is REM, 51.5% is NREM, and the remainder is IS. By 9 months of age, 70% of sleep is NREM; with the other 30% in REM. IS is not a feature of infant sleep beyond 4 months (Jenni et al., 2004). However, one factor that may challenge the validity of the results of Jenni and colleagues is the criterion applied to define the onset of a sleep cycle. Jenni et al. (2004) discarded the first REM stage of all cycles which began in REM rather than NREM sleep. Whilst sleep cycles beginning in REM in adults would be unusual, this is a normal feature of sleep in early infancy (Sheldon, 1996). Thus, for a more accurate picture of the proportion of time spent in REM and NREM sleep, all stages of sleep cycles should be included in analysis.

### *2.3.2 CAEPS in sleeping infants*

Evoked potential measurements in adults during sleep can assess the activity of the central nervous system and its processing abilities (Colrain & Campbell, 2007). Thus, measuring evoked potentials whilst the adult is sleeping may provide different information than that which can be obtained during wakefulness. Evoked potential measurement during sleep in infants serves a different purpose. There may be a clinical benefit to recording potentials during sleep rather than wakefulness, as myogenic activity is reduced. Recording in

wakefulness may cause increased stress levels in the infant, which can affect electrophysiological assessment, and thus recording in sleep may be preferable (Hunter et al., 2008). The limited evidence that is available regarding CAEPS during sleep in infancy has examined the differences in responses during the different sleep states. Differences to CAEPs in different sleep states may necessitate sleep state categorisation before CAEPs can be used clinically in assessing infants with ANSD.

In work published to date, there has been some disparity between the reported effects of sleep state upon the CAEP response. Weitzman et al. (1965) reported that in both REM and NREM sleep, in healthy neonates, clear CAEPs were evoked consistently. N1, P2 and N2 components were prominent in the response, whilst P1 was inconsistent and not included in analysis. Peak latencies for N1, P2 and N2 during REM were significantly shorter than those recorded in NREM sleep, and peak amplitudes were reduced in REM compared to NREM. Kushnerenko et al. (2002), when testing sleeping infants, tested in REM. This methodological decision was informed by the work of Ellingson et al. (1974) and Kurtzberg et al. (1984), who report that there are no significant differences between responses recorded in REM and wakefulness. However, Kurtzberg et al. (1984) report only that this was the case in preliminary work, for which methodology for sleep state categorisation is not reported, nor are the results of testing in REM, NREM and wakefulness given. Kurtzberg does not specify which infant age group this may apply to. Maturational changes that occur during infancy suggest that the effects of sleep would be different for different age groups.

Ellingson et al. (1974) showed that CAEP measures of latency, amplitude and morphology were not significantly different in REM and wakefulness in 6 newborn infants. Significant differences were seen in NREM, in which, in concurrence with Weitzman et al. (1965), larger amplitude responses were seen, of significantly longer latency. However, the authors do not suggest that REM is the most clinically applicable testing state for CAEPs. Ellingson reported that recordings from NREM sleep had the largest number of identifiable components in the CAEP waveform. P2 was evoked in all sleep stages, but N1 and N2, the other most frequently evoked components, were rarely recorded in REM or wakefulness. Comparisons between N1 and N2 latency in REM, NREM and wakefulness were based on the results from fewer than 6 participants over 2 sessions, as N1 and N2 were evoked in less than half of CAEP recordings. Due to the very small sample size, conclusions are limited, and therefore the influence of this report on the work of Kushnerenko et al. (2002)

may not be entirely appropriate. In addition, Ellingson et al. (1974) used an ISI of a minimum of 8 seconds, and therefore responses may be expected to be quite different of those of Kushnerenko et al. (2002) using an ISI of 700 ms.

Duclaux et al. (1991) recorded larger amplitude CAEP responses in NREM than REM in infants aged 6 weeks. N2 latency was significantly shorter in REM than NREM. However, in contrast to the findings of Weitzman et al. (1965) and Ellingson et al. (1974), N1 and P2 latencies were not significantly different in REM and NREM. Duclaux et al. (1991) suggest that these differences may be due to maturational differences from birth to six weeks, or the use of a shorter ISI. Another factor that the authors have not considered may be EEG recording site. Weitzman et al. (1965) and Ellingson et al. (1974) both present responses from central recording sites. However, Duclaux et al. (1991) recorded responses at temporal sites T3 and T4. A combination of these methodological differences may be responsible for the differences that are present in the results. An up-to-date study of the feasibility of using CAEPs in sleeping infants is required in order to assess the clinical viability of this measure.

## 3. The role of aetiology in the manifestation of hearing impairment due to peripheral neuropathy


### Abstract

**Objective:** The aim of this study was to describe the functional auditory profile of Friedreich's Ataxia (FA) and Charcot-Marie-Tooth (CMT) disease, in terms of speech perception, and the presence or absence of Cortical Auditory Evoked Potentials. Differences relating to aetiopathology were explored.

**Methods:** Participants were adults with diagnosed Friedreich's Ataxia (n=4) or Charcot-Marie-Tooth Type 1a (n=4). Participants underwent assessment of speech perception in quiet and background noise with Consonant-Nucleus-Consonant word lists. Cortical Auditory Evoked Potentials (CAEPs) were recorded, to observe how presence of a response related to speech perception ability.

**Results:** Participants with CMT achieved significantly better speech in quiet scores than participants with FA ($p<0.05$). The difference in speech in noise scores was not significant. CAEPs were absent for the two participants with the worst speech in quiet scores (both <30%), and present for the remaining six participants.

**Conclusions:** Hearing function is affected differentially in Friedreich's Ataxia and Charcot-Marie-Tooth. It is important to consider the underlying aetiopathology when planning audiological management. The sample was too small to draw conclusions regarding the relationship between speech perception and CAEPs. Further research into the potential use of CAEPs as a clinical tool for FA and CMT and similar populations is required.

## Introduction

Neurological conditions, such as Friedreich's Ataxia (FA) and Charcot-Marie-Tooth Disease (CMT), can severely affect the auditory system (Starr et al., 1996; Rance et al., 2002). The audiological profile in hearing impaired patients with FA and CMT is reportedly perceptually, if not always electrophysiologically, in line with Auditory Neuropathy Spectrum Disorder (ANSD) (Starr et al., 1996; Lopez-Diaz de Leon 2003; Rance et al, 2010; Rance et al, 2012a; Rance et al, 2012b; Knopp et al, 2014). ANSD patients report considerable difficulty with speech perception, especially in background noise. Unlike 'typical' hearing impairment, for example age-related hearing loss, hearing disability associated with ANSD cannot be predicted by pure-tone audiometry. Devising management strategies for neurological patients with an ANSD-type hearing loss is challenging. Conventional hearing aids tend to offer limited benefit in ANSD (Berlin et al., 2010). Cochlear implantation, which delivers electrical current direct to the auditory nerve, is highly variable and unpredictable in ANSD (Miyamoto et al., 1999). FM systems have proved beneficial amongst adults with FA (Rance et al, 2010), and may also prove to be beneficial for those with CMT, but work in this area is limited. Managing patients with FA and CMT is complex for the audiologist, and there is a clinical need for procedures to guide individualised management plans.

A relationship between speech perception and the presence of cortical auditory evoked potentials (CAEPs) has been reported in patients diagnosed with ANSD (Rance et al., 2002). Rance and colleagues showed that in a sample of children with ANSD, the presence of a CAEP response was associated with better performance on speech perception testing. This suggests that it may be possible to predict functional outcome in ANSD-type impairment, such as that of FA and CMT, using CAEPs. For these patients, for whom a behavioural test battery can be difficult due to physical impairment and test fatigue, the ability to use objective testing would facilitate easier assessment.

The aim of this preliminary study was to describe auditory profiles of patients with two forms of peripheral neuropathy, FA and CMT 1a, with differing aetiologies. The auditory profiles were assessed in terms of speech perception in quiet and background noise, as well as the presence or absence of CAEP. Differences in profile between FA and CMT have not previously been explicitly investigated. It was hypothesised that different aetiopathological entities give rise to distinct audiological manifestations as measured by speech perception

ability. The second hypothesis was that the presence of CAEPs would relate to speech perception abilities.

## Methods

### *Ethical approval*

Ethical approval for research on human subjects was granted by the North West – Lancaster National Health Service Research Ethics Committee (Reference: 08/H1015/102). All participants provided written informed consent for research.

### *Participants*

Eight adults with a confirmed diagnosis of FA (n=4) or CMT type 1a (demyelinating form) (n=4) were recruited. Diagnosed hearing impairment was not a pre-requisite for inclusion. Auditory brainstem response (ABR) testing was attempted, using a GN Otometrics EP200 electrophysiological testing system. However, there was a large amount of background noise present in the recordings, which did not allow for conclusive interpretation. Transient evoked oto-acoustic emission testing was conducted in all participants other than P1 and P3 as a measure of outer hair cell function. An oto-dynamics system was used for testing. OAE presence was defined using the automated pass criteria built-in to the system, used for NHSP infant hearing screening. All participants tested (P2 and P4-P8) had present oto-acoustic emissions, indicating intact outer hair cell function.

### *Procedures*

Pure-tone audiometry was performed, using a Kamplex AC-30 clinical audiometer in a silent test room, to measure hearing threshold levels. Speech perception was assessed using Consonant-Nucleus-Consonant word lists, composed of 50 phonemically-balanced words, such as ‘bean’, ‘lag’, ‘fall’. Speech stimuli were presented monaurally, via an ER-3A insert earphone, from a compact disk player connected to a Kamplex AC-30 clinical audiometer, through which the signal and noise levels were varied. The speech signal was calibrated in dB A. It was presented at 30 dB SPL above the equivalent in dB SPL of the 1 kHz hearing threshold in dB HL, with the dB HL converted to dB SPL using the ANSI S3.6 (1996) RETSPL for speech stimuli. The first word list was presented in quiet. A second word list was presented in the presence of babble noise, at a fixed signal-to-noise ratio (SNR) of +10 dB. Prior to speech perception testing, participants were instructed to repeat the word exactly as they heard it, regardless of whether it appeared to make sense, or if they had

registered the full word or not. They were then scored on the number of correct words and phonemes that they had repeated. Percentage of words correct, rather than phonemic scores, was used for analysis as a more meaningful measure of performance, as real-life speech perception relies on understanding of words. This also allows for comparisons to the results of Berlin et al. (2010), who presented speech recognition scores for words rather than phonemes.

The stimuli presented in CAEP testing were 1 second broadband noise segments, presented using E-Prime v2 presentation software from Psychology Software Tools, Inc. Random Gaussian noise segments, of 1 second duration, were created using Praat software. Ten random noise segments were created, to be presented in random sequence in order to preserve the random nature of the stimuli. The bandwidth of the noise segments was 50-10,000 Hz. The noise was filtered with a pass Hann band, with smoothing of 100 Hz. The ISI selected for these stimuli was 2000 ms, as used by Pratt et al. (2007). Stimuli were presented monaurally, via ER-3A insert earphone, at 30 dB SPL above the 1 kHz hearing threshold (converted from dB HL to dB SPL). Recording took place passively, with no active response from the participant. Participants watched a film with subtitles during CAEP recording. The 1s stimulus was selected as it was initially hoped the same stimulus could be used in future testing, with a silent gap inserted, for gap-detection analysis following the protocol of Pratt et al. (2007). Therefore, a longer stimulus that would allow for 0.5s duration of stimulus before and after the gap in the follow up test was deemed suitable, despite being a longer than usual stimulus duration for CAEP testing without the gap-detection task.

CAEPs were recorded from 64 channels, with the Biosemi Active Electrode system, arranged according to the 10/20 electroencephalogram (EEG) electrode array. An artifact rejection threshold of ± 100 µV was applied, as eye-blinks typically fall within the range of 50-100 µV (Luck, 2005). The ongoing EEG recording was digitised with a resolution of 24 bits, at a sample rate of 256 Hz. The recording was filtered between 0.1-100 Hz online, and subsequently filters of 0.5-15 Hz were applied offline. Data were analysed in the BESA 5.2 analysis software, where an average reference was applied. Data were epoched with a pre-stimulus window of 200ms and a post-stimulus window of 500ms. CAEP waveforms were visually inspected by three experienced researchers, blinded to speech scores, to determine if an N1 response was present. Agreement from the 3 examiners was required to classify a response presence. The N1 criteria used was the presence of a negative peak following a

positive peak, occurring within 250 ms after the onset of the stimulus. Whilst the N1 response typically peaks around 100 ms, a longer time window was given due to the exploratory nature of the testing, as the CAEP morphology of patients with FA and CMT is not clearly defined.

## Results

*Speech perception*

Performance on speech perception in quiet and noise is shown in Table 3.1 and Figure 3.1. Patients with FA showed a wider range of performance for speech in quiet (*M* = 42.5%, *SD* = 33.8%) than patients with CMT (*M* = 87%, *SD* = 4.8%). A Mann-Whitney U test was conducted to compare CMT and FA group performance on speech perception in quiet. A significant between group difference was demonstrated, $U = 1.0$, $p < .05$.

On speech perception in noise assessment, scores of FA participants (*M* = 22.5%, *SD* = 37.1%) were again more variable than those of CMT participants (*M* = 72%, *SD* = 19.0%), though the difference in variability was less extreme than in quiet. A Mann-Whitney U test was conducted, which demonstrated that whilst the group difference was large, this was not significant ($U = 1.5$, $p = .058$).

| **Aetiology** | **Mean pure tone hearing threshold(dB HL)** | | **Speech perception better hearing ear (%)** | | **CAEP in better hearing ear** |
|---|---|---|---|---|---|
| | **RIGHT EAR** | **LEFT EAR** | **QUIET** | **NOISE** | |
| FA1 | 45 | 25 | 4 | 8 | Absent |
| FA2 | 35 | 55 | 28 | 2 | Absent |
| FA3 | 55 | 20 | 56 | 2 | Present |
| CMT1 | 35 | 40 | 80 | 44 | Present |
| FA4 | 5 | 10 | 82 | 78 | Present |
| CMT2 | 5 | 15 | 88 | 78 | Present |
| CMT3 | 15 | 15 | 90 | 80 | Present |
| CMT4 | 5 | 5 | 90 | 86 | Present |

Table 3.1 Mean hearing thresholds across 4 frequencies (0.5, 1, 2, 4 kHz), speech perception in quiet and noise, and CAEP response.

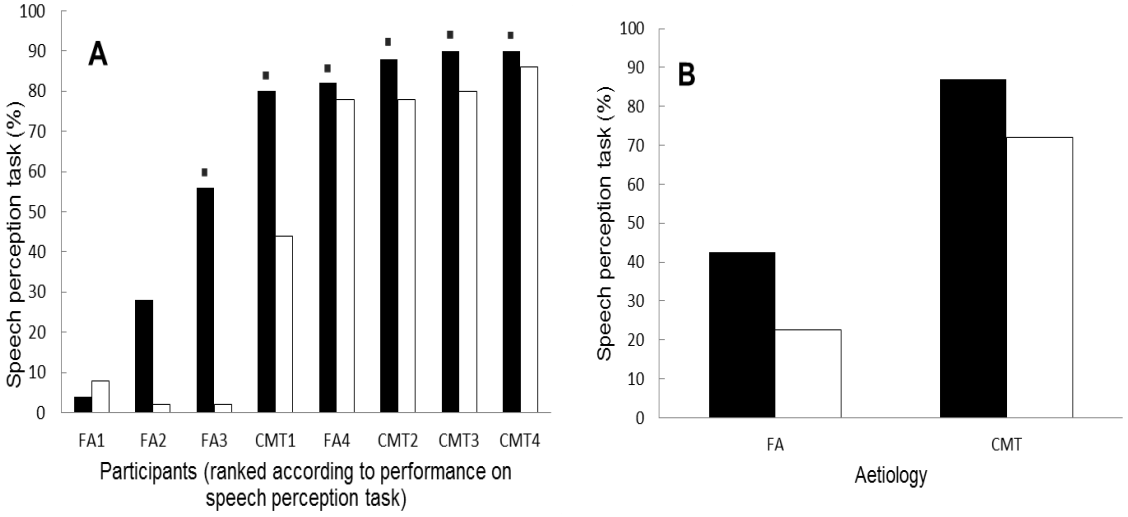

Figure 3.1 Performance on speech perception task (speech perception in quiet, filled columns; speech perception in background noise, open columns). Panel A shows individual participants ranked according to performance in quiet. Square above bar denotes CAEP present. Panel B shows average according to aetiology: Friedreich's ataxia (FA, n= 4), Charcot Marie Tooth (CMT, n= 4).

*CAEP response*

Visual inspection of CAEP waveforms determined that a CAEP response was present in six of the eight participants. For details about presence and absence of CAEP and speech perception performance, see Table 3.1.

The CAEP N1 response was present in 6 of the 8 participants. The response was not present in the 2 worst performers for speech perception in quiet, with scores of <30%, both of whom have FA. A third participant (CMT1) performed very poorly on speech perception testing in noise (2%), but above 50% in quiet, and did have a CAEP response present.

## Discussion

While impaired speech perception has previously been reported in patients with FA and CMT (Waxman, 1977; Rance et al., 2008), the two patient populations have not previously been explicitly compared. The statistically significant difference in performance between FA and CMT type 1a for speech perception in quiet, and the trend towards a difference in speech in noise, supports the hypothesis that different aetiopathologies give rise to distinct audiological manifestations. Difficulties in FA are due to axonal loss, whereas CMT 1a is a demyelinating condition. These known pathologies in FA and CMT type 1a fit with the hypotheses of Zeng et al. (2005) regarding the two possible causes of temporal processing and speech perception impairment in ANSD. In FA patients, the cause is likely to be reduced spike count due to axonal loss (Starr et al., 1996; Zeng et al., 2005) whereas in CMT 1a it is the desynchronised spikes caused by demyelination in the auditory nerve (Zeng et al., 2005). Based on the findings of this preliminary study, we propose that neuropathies resulting in reduced neural spike count may be associated with a poorer outcome, as is demonstrated by worse performance on speech perception in FA than CMT.

The sample size of this study is not sufficient to ascertain if there is a relationship between CAEPs and speech perception performance. The large degree of variability amongst the FA patients also creates difficulty in drawing conclusions. One factor to be considered in the performance of the participants is the duration and the degree of their condition. In this sample of participants, the most severe condition presentation was seen in the FA group. In this group, the two worse performers on speech perception testing, for whom it a CAEP response wasn't present, had the most severe FA progression across motor and sensory systems. The participant in the FA group with the highest speech perception scores (FA4) had an onset of symptoms in adulthood, much later than the other FA sufferers. The significantly shorter duration of the condition may be implicated in his much better performance on auditory testing. In the CMT group, however, duration of symptoms did not appear to relate to performance.

The relationship between CAEPs and speech perception ability is yet to be fully understood. Investigation of how more complex CAEP measures relate to the speech in noise performance, which is clinically and ecologically more meaningful than speech in quiet, may bridge this gap in knowledge. To increase the diagnostic value of the CAEP assessment in future, we propose adopting a paradigm of bifurcation: 1) in the presence of a CAEP response, carry out electrophysiological gap-detection assessment for more

precise assessment of auditory function; 2) in the absence of a CAEP perform jitter correction to assess if a response was present but obscured by latency variation, giving the appearance of an absent CAEP on averaging, where a response was indeed present (Luck, 2005). This may be particularly relevant for these participants for whom there is a lack of neuronal temporal synchrony.

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# 4. Exploring hearing impairment in Friedreich's Ataxia and Charcot-Marie-Tooth: what is the relationship between objective and functional hearing measures in these peripheral neuropathies?


## Abstract

**Objective:** This study investigates the relationship between Cortical Auditory Evoked Potentials (CAEPs) to speech stimuli, and speech perception ability. The relationship between temporal processing capability, assessed by behavioural gap-detection, amongst adults with Friedreich's Ataxia (FA) and Charcot-Marie-Tooth (CMT) (including participants both with and without self-reported hearing difficulties) as compared to a control of people with a 'typical' sensorineural hearing loss (SNHL) is also explored herein.

**Methods:** Three groups of participants were tested with an audiological test battery, these were composed of participants with CMT type 1a (n=8), FA (n=5), and SNHL (n=11). A group of adults with normal hearing (n=7) provided normative data for CAEP assessment only. The test battery for hearing impaired participants included pure-tone audiometry, consonant-vowel-consonant word list speech perception testing in quiet and in noise, gap-detection threshold assessment, and CAEPs to speech stimuli.

**Results:** FA and CMT groups had hearing thresholds at normal or near normal levels, and gap-detection thresholds outside of normal range (FA group $M$ = 12.5ms; CMT group $M$ = 17ms), and poorer speech perception than we would expect (FA group 67% in quiet and in noise; CMT group 73% in quiet, 71% in noise). One-way ANOVA testing revealed no significant differences between groups on CAEP responses, speech perception scores, or gap-detection threshold. Correlational analysis showed a significant correlation between speech in quiet scores and speech in noise scores across the test groups. However, further correlations within test groups, between speech perception scores, gap-detection thresholds, and CAEP responses, were not observed.

**Conclusion:** In this study, measures of CAEP responses to speech stimuli were not related to behavioural measures of auditory function, such as temporal processing and speech perception. This is counter to previous research into ANSD, which the hearing impairment of those with FA and CMT is likened to here. The body of research into hearing loss in FA

and CMT is very limited, and further research with a larger sample would reveal if these results are replicable.

## Introduction

Charcot-Marie-Tooth (CMT) disease and Friedreich's Ataxia (FA) are peripheral neuropathies associated with hearing impairment that does not meet the profile of a 'typical' sensorineural (SNHL) hearing loss. The perceptual profile of hearing impairment in patients with peripheral neuropathies such as CMT and FA is said to be in line with an Auditory Neuropathy Spectrum Disorder (ANSD) hearing loss (Satya-Murti et al., 1983; Starr et al, 1996; Lopez-Diaz de Leon, 2003; Rance et al., 2008; Rance et al., 2010; Rance et al., 2012a; Rance et al., 2012b; Knopp et al., 2014). This is characterised by poorer speech perception ability, particularly in background noise, than would be expected from audiometric thresholds (Starr et al,. 1996; Rance et al, 2002). ANSD is also characterised electrophysiologically by absent or severely abnormal auditory brainstem response (ABR) in the presence of oto-acoustic emissions and/or cochlear microphonic (Starr et al., 1996; Northern, 2008), and absent or severely elevated middle ear acoustic reflexes (Starr et al., 1996; Berlin et al., 2005)

Degraded speech perception in patients with FA was reported as early as 1984 (Quine et al.). More recently, Rance et al. (2008) demonstrated that 9 out of 10 participants with FA had impaired speech perception, due to deficits in temporal processing. Despite fitting the functional auditory characteristics of ANSD, of speech perception that is worse than would be predicted from hearing thresholds and poor temporal processing ability (Zeng et el, 1999), only 3 of the 10 participants met the electrophysiological criteria for ANSD. Following on from this study, Rance et al. (2010) reported auditory processing difficulties in 9 of 14 participants with FA, with the degree of speech perception difficulty related to degree of disruption in temporal processing ability. More recently, Rance and colleagues (2012a) demonstrated near normal sound detection in conjunction with severe temporal processing and speech perception problems in participants with FA. In this study, the degree of auditory processing difficulty was linked to global disease progression. Lopez-Diaz de Leon et al. (2003) also highlighted the presence of ANSD in FA, and called for routine audiological assessment using OAEs and ABR in these patients.

Whilst there is little work published on hearing impairment in FA, yet less research has been carried out into the auditory processing abilities of those with CMT. The authors are not aware of any previous published work into differential auditory profiles in CMT and FA. In 2012(b), Rance et al. investigated auditory function in children with CMT; of which 18 had the demyelinating CMT1 and 8 had the axonal CMT2 form of the condition. In both groups, participants showed evidence of long latency and low amplitude ABR recordings, despite near normal sound detection. In addition, speech perception and temporal processing were outside of the normal range for more than 60% of those with CMT1 and 85% of those with CMT type 2. Knopp et al. (2014) emphasised the potential for auditory, as well as optic, nerve involvement in demyelinating CMT, and highlighted the need for greater awareness of potential auditory issues when working with patients with this condition.

This study follows on from a pilot study that investigated the presence of Cortical Auditory Evoked Potentials (CAEPs) and speech perception ability in patients with demyelinating CMT (type 1a) and the axonal peripheral neuropathy of FA. This pilot study demonstrated differences in speech perception in these two patient populations, and suggested that they should be treated as two distinct clinical entities.

The premise of this study is to further investigate the audiological profile of adults with FA and CMT, and how they differ from the profile of a typical SNHL. This study will investigate the relationship between the presence of a CAEP response to speech stimuli, and the functional measure of speech perception, in these patient groups. It will also explore the temporal processing abilities of participants with FA, CMT and SNHL, using gap-detection assessment, and how this relates to speech perception ability.

## Methods

*Ethical Approval*

Ethical approval for research on human subjects was granted by the North West – Lancaster National Health Service Research Ethics Committee (Reference: 08/H1015/102). All participants provided written informed consent for research.

*Participants*

Three groups of participants were tested for the main body of assessment. These were participants with CMT type 1a (n=8), participants with FA (n=5), and participants with 'typical' SNHL (n=11). The SNHL participants were recruited from an NHS audiology clinic, where they had been diagnosed with a mild-moderate SNHL. Participants with CMT and FA were recruited through regional support groups.

CAEP testing was also carried out in normally hearing participants (n=7), to establish normative values for the study CAEP test stimuli.

*Preliminary Audiological Assessment*

All participants were assessed with pure tone audiometry (PTA) prior to further testing. PTA was carried out using a GSI 61 two-channel audiometer in a sound-proof booth. Normally hearing participants were screened to ensure that audiometric thresholds at test frequencies of 500-8000 Hz were below 20 dB HL, that OAEs were present, and tympanograms normal bilaterally. Tympanometry was carried out using a GSI 38 Tympanometer, and OAE testing performed with a Maico Ero Scan Pro.

*Speech Perception*

Participants were presented with lists of 50 phonemically balanced consonant-nucleus-consonant (CNC) words, in quiet and in the presence of background babble noise at a fixed signal-to-noise ratio of +10 dB. The stimuli were presented monaurally through an ER-3A insert earphone to the better hearing ear, at a presentation level of 20 dB A above the 1 kHz threshold of the test ear, converted to dB SPL. This was the presentation level used for subsequent testing throughout the session. The method of instruction and testing, other than the different stimulus level, was the same as that of the speech perception testing in Chapter 3.

*Speech CAEPs*

CAEPs were recorded using speech stimuli, presented at 20 dB SPL above the SPL equivalent of the 1 kHz hearing threshold. These stimuli were three consonant-nucleus-consonant words, 'dab', 'pick' and 'sun'. These are three words selected from the CNC word lists used for speech perception testing. They were selected because the onset sound of the three words varied, including a voiceless stop in 'pick', a voiced stop in 'dab', and a fricative in 'sun', with the aim of reducing the effects of asymmetric hearing loss which may impair audibility of some speech frequencies and manners of articulation.

For each speech stimulus, two runs of 100 presentations were carried out, at a presentation rate of 0.5/s, giving two averages for each stimulus. This was a passive recording paradigm, with no action required from the participant. During CAEP recording, participants read in a sound-proofed room. Stimuli were presented using a CED 1401 system. Three electrodes were used, connected to a GN Otometrics EP200 Evoked Potential system. An active electrode was placed at Cz, and switching reference and ground electrodes on the ipsilateral and contralateral mastoids to the test ear.

The reduced number of electrodes relative to the pilot study was intended to aid patient comfort during the long assessment session. It was also important to use a small electrode array, as this study was conducted to help refine the protocol for assessment in infants with ANSD, in which 3 electrodes would be used to relate better to clinical testing protocols. A large number of electrodes are not required to identify a CAEP response, particularly when an array with an active Cz and a mastoid reference is used, so that response inversion can be determined (Martin et al, 2008). Responses were analysed offline in the Spike 2 analysis package. Data were filtered between 1 and 15 Hz, and epoched with a pre-stimulus window of 200ms and a post-stimulus window of 750ms. Response presence was assessed visually by two qualified audiologists, using the P2 component for measures of response presence, amplitude, and latency. A response was deemed to be present where both assessors agreed, and where the response was repeatable across the two stimuli runs for each stimuli. The P2 response was defined as a positive peak occurring after a negative peak, approximately 200-350 ms after stimulus onset. A more precise time window was not used as the time delay of the P2 response for those with FA and CMT was not well known at the outset.

*Gap-detection*

The stimuli presented monaurally via an ER-3A insert earphone were noise segments of 1 second duration. A silent gap was inserted between 400 and 600ms after stimulus onset, with onset time varied randomly. Silent gap durations used were 5ms, 10ms, 20ms, 50ms and 100ms. Test trials with a '0ms' gap, i.e. no gap in the signal, were presented to ensure there was not a false-positive response issue. On behavioural assessment, Trehub et al. (1995) demonstrated a 5.2ms gap-detection threshold in normal hearing adults, whilst Samelli & Schochat (2008) recorded average gap detection thresholds of 4.19ms in the adult normal hearing population. An electrophysiological gap-detection threshold of 5ms has been reported in normally hearing participants (Michalewski et al, 2005; Pratt et al, 2007). However, a seminal paper on temporal processing (Moore, 1993) reported gap-detection thresholds as low as 2-3ms. Samelli and Schochat (2008) reported that over 96% of responses were correct for gaps of 5ms or longer. This was taken into consideration, and in order to achieve the balance between overall session testing time and gathering enough data, a minimum gap-duration of 5ms was selected as a potential marker of 'normal' gap-detection.

Participants were instructed to respond with a button press to a perceived silent gap in the noise segment. Participants were trained prior to testing to ensure understanding of the task. The patient response button was connected to a Cambridge Electronic Design (CED) 1401 input port, and registered using Spike 2 software from CED. Responses were scored visually, offline, by 2 audiologists. The criterion used for the identification of a gap was a correct response to at least two-third of the presentations of that particular gap duration.

**Results**

*Preliminary Auditory Assessment*

An independent sample t-test showed that the difference in the 4-frequency average hearing level of the test ear from participants in the neuropathy group, composed of the FA and CMT groups aggregated (n = 12, *M* = 12.50, *SD* = 10.98), and the SNHL group (n = 11, *M* = 22.73, *SD* = 10.34) were statistically significant, t(6) = -3.46, p = .013, 95% CI [-3.41, -0.59], d = -2.45.

On PTA assessment, only 2 of the 8 participants with CMT demonstrated 4-frequency average thresholds (across pure-tone frequencies 0.5, 1, 2, 4 kHz) outside of the normal

hearing range (>20 dB HL), with one additional participant having an 8-frequency average threshold outside of normal limits. However, five out of eight participants report difficulty with hearing, in particular perception of speech in the presence of background noise. See Table 4.1 for hearing levels.

| **Participant** | **4 frequency average** (dB HL) | | **8 frequency average** (dB HL) | |
|---|---|---|---|---|
| | **Left** | **Right** | **Left** | **Right** |
| CMT1 | 25 | 25 | 35 | 35 |
| CMT2 | 15 | 10 | 20 | 20 |
| CMT3 | 5 | 5 | 5 | 5 |
| CMT4 | 5 | 5 | 5 | 5 |
| CMT5 | 10 | 15 | 15 | 15 |
| CMT6 | 40 | 35 | 40 | 40 |
| CMT7 | 0 | -5 | 0 | -5 |
| CMT8 | 30* | NR | 30* | NR |
| FA1 | 15 | 20 | 15 | 20 |
| FA2 | 20 | 20 | 25 | 25 |
| FA3 | 5 | 10 | 5 | 10 |
| FA4 | 15* | NR | 15* | NR |
| FA5 | 20 | 10 | 20 | 15 |
| SNHL1 | 15 | 15 | 15 | 15 |
| SNHL2 | 10 | 10 | 15 | 15 |
| SNHL3 | 30 | 35 | 35 | 35 |
| SNHL4 | 35 | 40 | 40 | 45 |
| SNHL5 | 15 | 10 | 15 | 20*** |
| SNHL6 | 40 | 40 | 40** | 40** |
| SNHL7 | 25 | 25 | 30 | 30 |
| SNHL8 | 25 | 25 | 25 | 20 |
| SNHL9 | 25 | 10 | 15 | 10 |
| SNHL10 | 20 | 15 | 25 | 20 |
| SNHL11 | 15 | 20 | 20 | 20 |
| NH1 | 5 | 5 | 0 | 5 |
| NH2 | 5 | 0 | 5 | 5 |
| NH3 | 5 | 10 | 5 | 5 |
| NH4 | 5 | 0 | 5 | 0 |
| NH5 | 5 | 5 | 5 | 5 |
| NH6 | 5 | 5 | 10 | 5 |
| NH7 | 0 | 0 | 0 | 0 |

Table 4.1 Hearing levels.
4 Frequency PTA average is across test frequencies 0.5,1,2,4 kHz, 8 frequency PTA average is across test frequencies 0.25, 0.5, 1, 2, 3, 4, 6, 8 kHz. * is threshold at 1 KHz, ** is 6 frequency average, *** is 7 frequency average.

In the group of participants with FA, all participants demonstrated 4-frequency average PTA hearing thresholds that were within normal range. Only participant (FA3) exhibited an 8-frequency average threshold just outside of normal hearing range at 25 dB HL. Four out of the five participants that completed testing reported at least moderate difficulty perceiving speech in the presence of background noise.

Though participants with SNHL were all referred from an Audiology clinic, where they had been diagnosed with a mild or moderate hearing loss, in a number of cases the four or eight frequency average threshold was within the normal hearing range. In these cases, participants had a steeply sloping high frequency hearing loss, with very good hearing at low frequencies, which reduced the overall average across test frequencies to a value below 20 dB HL.

*Speech Perception*

The SNHL group had a mean score of 74% (*SD* = 8%) on speech perception assessment in quiet. When background noise was introduced, variability increased (*M* = 76%, *SD* = 13%). SNHL7 was excluded from the results as an extreme outlier. Table 4.2 shows group scores, whilst Table 4.3 shows individual scores, CAEP presence, and the test order of speech perception testing. In the majority of cases, for those with a higher score on testing in background noise this was the second test completed, leading to the questioning of the effect of test order.

The FA and CMT groups together, as a combined neuropathy group, had a mean score of 71% in quiet (*SD* = 15%). In background noise at an SNR of +10 dB, this collective group had a mean score of 69% (*SD* = 14%), giving a decrease in speech perception score of two percentage points in the presence of background noise.

When the aggregated neuropathy group is separated out into the FA and CMT1a sub-groups, the performance of those in the FA group was slightly worse than that of participants with CMT1a. The mean scores for patients with FA in quiet was 67% (*SD* = 10%). In the presence of background noise, the mean score remained flat at 67 (*SD* = 8%). For those with CMT, in quiet there was a mean score of 73% (*SD* 13%). When background noise was introduced, there was a slight decrease in mean perception score to 71% (*SD* = 15%).

| Group | Words in quiet | Words in Noise | Difference |
|---|---|---|---|
| **ANSD** | 71% (SD 15%) | 69% (SD 14%) | -2pp |
| *CMT* | *73% (SD 13%)* | *71% (SD 15%)* | *-2pp* |
| *FA* | *67% (SD 10%)* | *67% (SD 8%)* | *0* |
| **SNHL** | 74% (SD 8%) | 76% (SD 13%) | 2pp |

Table 4.2 Mean group speech perception scores in quiet and in background noise.
PP denotes percentage point difference when mean words in noise score is subtracted from words in quiet score.
SNHL group score excludes SNHL7, an outlier.

One way ANOVA analysis was performed, with speech perception in quiet as the measure, and hearing impairment type as the factor with three levels: CMT, FA and SNHL. A further one way ANOVA test was carried out to investigate if there was a significant difference in speech perception in noise associated with hearing impairment type. Both ANOVA analyses revealed no significant differences, despite the lower scores in the FA group than the CMT and SNHL groups. This may be influenced by the small sample size in the FA group.

| Participant | Speech Perception in Quiet | Speech Perception In Noise | First Test | CAEP responses present (of 3 stimuli) |
|---|---|---|---|---|
| CMT1 | 68% | 42% | No Noise | No CAEPs present |
| CMT2 | 76% | 62% | No noise | Present: 3 |
| CMT3 | 92% | 94% | Noise | Present: 3 |
| CMT4 | 88% | 84% | Noise | Present: 2 |
| CMT5 | 42% | 54% | No noise | Present: 2 |
| CMT6 | 84% | 72% | Noise | Present: 3 |
| CMT7 | 74% | 82% | No noise | No CAEPs present |
| CMT8 | 58% | 76% | No noise | NR |
| FA1 | 62% | 62% | Noise | NR |
| FA2 | 64% | 62% | Noise | No CAEPs present |
| FA3 | 82% | 78% | NR | Present: 3 |
| FA4 | 60% | 64% | No noise | Present: 2 |
| FA5 | 80% | 80% | Noise | NR |
| SNHL1 | 76% | 82% | No noise | Present: 1 |
| SNHL2 | 84% | 90% | Noise | Present: 1 |
| SNHL3 | 64% | 58% | No noise | Present: 3 |
| SNHL4 | 74% | NR | No noise | Present: 3 |
| SNHL5 | 70% | 76% | No noise | No CAEPs present |
| SNHL6 | 72% | 66% | No noise | Present: 3 |
| SNHL8 | 84% | 92% | No noise | Present: 2 |
| SNHL9 | 84% | 88% | No noise | Present: 3 |
| SNHL10 | 73% | 68% | Noise | Present: 1 |
| SNHL11 | 60% | 68% | No noise | Present: 2 |

Table 4.3 Individual Speech Perception scores, Speech perception test order, and CAEP presence.

*Gap-detection*

Participants with FA and CMT, when grouped together, had a mean gap-detection threshold of 15ms (*SD* = 12.14). This mean threshold was slightly lower, but more variable, than that of participants with SNHL (*M* = 17ms, *SD* = 4.83ms).

| Group | Mean gap detection threshold |
|---|---|
| **ANSD** | 15 ms (SD = 12) |
| *CMT* | *17ms (SD = 15))* |
| *FA* | *12.5ms (SD = 5)* |
| **SNHL** | 17 ms (SD = 5) |

Table 4.4 Gap-detection threshold, group results.

When broken down into the two component groups of the aggregated neuropathy group, there was no significant difference between the participants with FA and CMT. The CMT group performed in line with the SNHL group based on mean gap detection threshold, which was 17 ms in both groups. However, the results of the CMT group were highly variable, with a standard deviation of 14.96 (compared to 4.83 in the SNHL group). The scores of the CMT group were skewed by one participant with a threshold of 50 ms. Excluding this score, the CMT score range sits in line with that of the FA and SNHL participants.

A one-way ANOVA test of the means of the three groups (CMT, FA and SNHL) showed that group differences were not significant on gap-detection testing.

*Speech CAEPS*

*CAEP presence*

Gardner-Berry (2011) used presence of a CAEP response to at least two out of three test stimuli as a marker of CAEP presence in ANSD. Using this criterion across the three test stimuli, seven of ten of the participants with ANSD had a definite CAEP response to at least two of the three speech stimuli. The breakdown within the two sub-groups shows that 5 of 7 participants with CMT and 2 of 3 participants with FA have a CAEP response to 2 or more speech stimuli. Of participants with a SNHL, 7 of 11 had a clear CAEP response to 2 or more speech stimuli. Amongst those with NH, all participants demonstrated a clear CAEP response to at least 2 of 3 speech stimuli.

Across the 2 groups (participants with neuropathy and those with SNHL), a Point Biserial correlation test of speech in quiet score and CAEP presence showed no correlation. Within the neuropathy group, there was no correlation between CAEP presence and speech in quiet or noise, or between CAEP presence and 4 frequency average or gap detection

threshold. When looking at correlation for the SNHL group between CAEP presence and speech metrics and gap-detection threshold there was no significant correlation.

*CAEPs: further metrics*

*Pick*

Of the participants with NH, 6 out of 7 had a present response to 'pick'. Of all trials, 67% showed a definite recordable CAEP response to the stimulus 'pick' at 20 dB above their 1 kHz hearing threshold (86% of trials were definite or probable responses). In the participants with CMT, 4 out of the 7 participants tested had at least one trial with a clear response to the 'pick' stimulus. Across all trials, 36% had a clear CAEP response. This presence rate was very similar to that of the FA group, for whom 33% of trials elicited a clear CAEP response, and two out of three FA participants had a response to at least one trial. The SNHL group showed a similar response presence rate to this stimulus, with 36% of trials giving a definite CAEP, and a response present to at least one trial in 5 of 11 participants.

Where a response was present, there was no significant difference across the 4 groups in either amplitude or latency of the P2 CAEP response on ANOVA analysis.

*Dab*

The 'dab' stimulus was more reliable than 'pick' with regards to presence of a clear CAEP response. Amongst normally hearing participants, all 7 participants had a P2 CAEP response to the 'dab' stimulus, with clear responses to 100% of trials. Amongst participants with CMT, 5 out of the 7 tested had at least one CAEP response recorded, with 71% of trials resulting in a clear CAEP response. Two out of the three participants with FA had at least one trial with a clear response to the 'dab' stimulus, with 67% of trials eliciting a CAEP response. Within the group with SNHL, 9 of 11 participants had a CAEP response to at least one trial for the 'dab' stimuli, and overall 77% of trials to this stimulus obtained a CAEP P2 response.

Where a CAEP response was present, there were no significant differences between the four test groups in amplitude or latency of P2 response on one-way ANOVA analysis.

*Sun*

Six out of seven normally hearing participants had at least one trial with a clear response to the 'sun' stimulus, and 79% of trials in this group elicited a P2 response to 'sun'. Of participants with CMT, five of seven tested had a clear response to this stimulus in at least one trial, and overall 50% of trials elicited a P2 response. In the group of participants with FA, two out of three participants had at least one clear response, and overall 67% of trials obtained a clear P2 response. In the SNHL group, 8 of 11 participants had at least one clear P2 response to 'sun', and 64% of trials elicited a response in total.

As for the previous stimuli, where a response was present, there was no significant difference on one-way ANOVA analysis between groups for either latency or amplitude metrics.

*Correlational Analysis*

Pearson product-moment correlation coefficient analysis was carried out to investigate the correlation of a number of measures. Across the three hearing impaired test groups, a significant correlation was noted between speech in quiet and speech in noise scores, $r = 0.72$, $p = 0.01$. Further correlational analysis was carried out to look at the relationship between speech perception scores in quiet and in noise with gap-detection thresholds, but there was no correlation between these metrics. Analyses were then performed on speech perception scores and CAEP metrics of P2 latency and amplitude, but no significant correlation was present. This analysis was then replicated for gap-detection threshold and CAEP metrics, revealing no significant correlations.

## Discussion

The objective of this study was to add to the limited body of research on the auditory profile of patients with FA and CMT, and to look at the relationship between behavioural and objective assessment tools. In this study, in which hearing thresholds were outside of normal limits for only 4 out of 13 participants with these conditions, 9 of the 13 report difficulties with hearing, in particular with speech perception. This highlights the need for robust audiological assessment in patients with peripheral neuropathies such as FA and CMT, for whom PTA alone is not meaningful.

Work by Rance and colleagues in recent years has highlighted the auditory processing problems that are sometimes present in patients with conditions involving peripheral neuropathies, such as FA and CMT, and similarities with Auditory Neuropathy Spectrum Disorder (ANSD). This is an emerging area of research, and little is known at present about the auditory profile of patients with these conditions. In ANSD, the underlying reason for poor speech perception is poor temporal processing ability (Zeng et al, 1999). However, this study did not find a correlation between open-set speech perception scores, in quiet or background noise, and gap-detection threshold in those with FA and CMT.

In ANSD, speech perception is typically worse than would be expected from the pure-tone audiogram, unlike in those with a typical SNHL. Speech-perception scores were not significantly different between the groups of participants with FA, CMT and SNHL in this study. Rance et al. (2007), found no significant difference in speech perception between children with ANSD and SNHL in the presence of background noise. However, on assessment in quiet, significant differences were observed, in line with previous research. Thus, the findings of this study represent a departure from what has been reported previously in the literature on ANSD, despite an aligned perceptual presentation. However, four-frequency average hearing thresholds were significantly worse in the SNHL than the FA and CMT group. Thus, given that the majority of participants with FA and CMT had normal or near normal hearing thresholds, and were compared to a group with diagnosed hearing loss, the lack of significant difference between speech perception scores demonstrated that speech perception is worse than expected for those with CMT and FA.

This highlights the difficulty in using a SNHL group as a control group for comparison with ANSD or ANSD-type hearing impairment, as the audiometric profile is largely very different. Whilst hearing impairment in FA and CMT may not strictly adhere to ANSD

diagnostic criteria in all cases, it is more aligned to ANSD perceptually than SNHL. ANSD itself is a heterogeneous condition, in which hearing levels are highly variable, from normal hearing to profound hearing loss (Rance, 2005). Where hearing levels are elevated in ANSD, this is often to a greater extent in the low frequencies, unlike the 'typical' SNHL typified by a high-frequency loss (Rance, 2005). The difference in severity of hearing loss between SNHL, FA and CMT groups is a major limitation of this study. It must also be noted that a number of participants with SNHL appeared to improve on speech perception testing when background noise was introduced. Table 4.3 shows which test was performed first, either speech in quiet or in background noise. After a number of test sessions, it became clear that some participants appeared to derive benefit from background noise, and the importance of training effects and test order was considered. At this point test order was varied, and the impact of training effects was lessened. Prior to this, all participants underwent testing in quiet before testing in noise. It is thought that because the level of background noise was not very high, some participants improved from the first test to the second due to practice effects. Varying the test order from the outset, or a higher level of background noise (i.e. a more deleterious SNR) would likely have helped to resolve this limitation.

Zeng et al. (2005) demonstrated poor temporal processing ability in participants with ANSD, thought to be due to desynchronised neural discharge, or reduced neural conduction, leading to poor gap-detection. This inability to detect rapid changes in auditory stimuli, for either of these reasons, is posited to be the cause of poor speech perception in ANSD, as speech is a rapidly changing stimulus (Zeng et al., 2005). Gap detection in normally hearing adults has previously been reported to be as low as 2-3 ms (Moore, 1993), and as high as 5.2ms (Trehub et al., 1995). More recently, Samelli and Schochat (2008) reported greater than 96% correct responses for gaps of 5ms or longer, and an average detection threshold of 4.19ms. Thus a 5ms threshold may be taken as a marker of normal gap-detection ability.

The participants with FA and CMT in this study, grouped together, had a mean gap-detection threshold of 15ms, whilst mean gap-detection for those with SNHL was 17ms. Both groups, therefore, are well outside of the normal range. The FA group average gap-detection threshold of 12.5ms was better than that of 17ms in participants with CMT. The minimum gap-detection threshold observed in an individual was 10ms. This demonstrates that gap-detection thresholds were outside of the normal range in all participants.

There was no significant difference in gap-detection thresholds between those with FA, CMT and participants with a typical SNHL, though this is likely impacted by the worse hearing levels in those with SNHL. There was no correlation between gap-detection and speech perception. This was unexpected, and does not align with Zeng's theory that poor speech perception is due to poor gap-detection in those with ANSD. Despite the lack of significant results, it is worth noting again that those with FA and CMT have normal or near normal hearing thresholds in most cases, yet all have gap-detection outside of normal limits and poor speech-perception abilities. Zeng et al. (2005) suggest that limitations in temporal processing in ANSD arise from either desynchronised neural discharge or reduced conduction, both of which would impede gap-detection and speech perception ability. Amongst the general ANSD population, the two are clinically indistinguishable. In FA and CMT, the source of the problem is known. CMT 1a, a demyelinating condition, leads to the desynchronised neural discharge described by Zeng, leading to a delay in the representation of the silent gap in different nerve fibres relative to each other, preventing the gap from being distinguished from the noise signal. FA, a condition in which axonal loss occurs, would fit the second profile identified by Zeng et al. (2005). In this case, a reduction in the nerve fibre resource available to transmit the presence of a gap leads to a reduction in gap-detection ability. Whilst these sources of temporal processing disability are not possible to isolate in ANSD usually, the results of this study suggest that desynchronised neural discharge, as seen in CMT, impacts gap-detection ability more than reduced neural conduction associated with FA. However, this difference in impact is not significant.

CAEP P2 responses were present to at least two of three speech stimuli in 7/10 participants with FA/CMT, and 7/11 participants with SNHL. A normally hearing control group was also assessed with CAEPs to establish laboratory norm values for the test stimuli. All normally hearing participants had a clear CAEP response to at least 2 of the 3 speech stimuli.

The presence of a response in the majority of participants demonstrates that CAEPs may be an effective tool for objective assessment in those with FA and CMT when behavioural testing is not possible or where further objective information is required. Whilst the ABR is not able to provide meaningful information for those with FA and CMT, the presence of a CAEP response in most of the adults studied herein suggests it is an incremental

improvement on the ABR for objective testing, in lieu of an objective test with 100% clinical detection which would represent the gold standard. In this study, amplitudes and latencies of responses to speech stimuli, where present, did not differ significantly to those of participants with SNHL and normal hearing. Whilst the efficacy of the CAEP paradigm used in this study for prediction of auditory function appears to be very limited, with no correlation recorded between CAEP metrics and speech perception and gap-detection measures, the presence of a response in most cases suggests that there is a potential clinical application for CAEP testing in these groups in the future, if optimal parameters can be identified. If this can be achieved, it could provide a very useful tool in cases of ANSD or hearing impairment perceptually similar to ANSD, where behavioural testing is not possible due to physical disability or young age. Further research into the predictive value of CAEPs for functional auditory measures in these populations is required.

In a pilot study that preceded this investigation, significant differences in speech perception were seen between those with FA and CMT, leading to the hypothesis that they represent two forms of auditory impairment, and should be treated as distinct entities. However, in this study no significant differences were found between the two groups on speech perception, gap-detection and CAEP measures. Though the sample size remains small in this study, a limitation for the generalisation of findings, it does suggest that clinicians are able to assess and manage the audiological symptoms of the two groups similarly.

When it comes to management of hearing impairment in FA and CMT, there is a significant clinical challenge, as most of the patients in this study reporting difficulties have hearing thresholds within the normal range. In ANSD, even where hearing thresholds are elevated, hearing aids have a limited benefit (Berlin et al., 2010) as they cannot currently address temporal processing deficits to aid speech perception. Rance et al. (2010) found that FM systems were beneficial for the auditory processing problems of those with FA. Further research into the efficacy of this treatment for those with CMT will help to create recommended treatment guidelines for these groups, which are much needed due to the complex nature of these conditions.

With regards to clinical assessment of those with FA and CMT, the use of OAEs and ABRs to define the electrophysiological profile of the patient is recommended clinically by Lopez-Diaz de Leon et al (2003), to assess if the patient fits the current

electrophysiological criteria for ANSD diagnosis. However, in these conditions in which the cause of the auditory pathology is well defined, where the functional auditory profile, i.e. gap-detection threshold and speech perception are outside of the normal range, this could arguably be considered ANSD even where the diagnostic criteria is not met. Rance et al. (2008) found that only 3/10 participants with FA met the electrophysiological diagnostic criteria for ANSD, whilst 9/10 had the functional profile of ANSD. Thus, further work is required regarding ANSD diagnosis in patients with peripheral neuropathies. The key recommendation arising from this study is that regular audiological testing with speech perception measures, rather than reliance on PTA is recommended, in those with FA and CMT, for whom PTA does not provide a meaningful measure of hearing impairment

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## 5. Three cases of ANSD in infancy: CAEP and speech discrimination assessment


### Abstract

**Objectives:** The Auditory Brainstem Response (ABR) is used routinely in paediatric audiological assessment during early infancy. In later infancy, Visual Reinforcement Audiometry (VRA) is the gold-standard mode of assessment. In children with Auditory Neuropathy Spectrum Disorder (ANSD), both of these methods have poor diagnostic and prognostic abilities. In children with ANSD, the presence or absence of the Cortical Auditory Evoked Potential (CAEP) appears to relate to auditory ability. The three case studies presented herein explore the association between the presence or absence of a CAEP response in ANSD, and speech discrimination on the Visual Reinforcement Infant Speech Discrimination Test (VRISD).

**Methods:** Three infants with ANSD completed VRISD testing, and were assessed for the presence or absence of a supra-threshold CAEP P1 response to a click stimulus. Three infants with normal hearing were screened with VRA, and completed VRISD testing, to establish laboratory norms for this test.

**Results:** A CAEP response was present in 2 of 3 participants with ANSD. VRISD scores in participants with normal hearing were considerably higher than for those with ANSD. This difference was more marked for the phoneme pair /a-i/ where scores were very poor for the ANSD group ($M$ = 7%, $SD$ = 12%) compared to those with normal hearing ($M$ = 89%, $SD$ = 10%). The differences were still large for the phoneme pair /a-u/, despite slightly lower scores for those with normal hearing ($M$ = 80%, $SD$ = 20%) and slightly higher scores for those with ANSD ($M$ = 27%, $SD$ = 46%).

**Conclusion:** The VRISD shows promise as a measure of speech discrimination in infants with ANSD. In these three case studies, there was no demonstration of a clear and consistent relationship between CAEP presence and speech discrimination ability. The sample size was a major limitation, and further research is required before any conclusions on the viability of the CAEP as a prognostic tool in infants with ANSD can be made.

## Introduction

The implementation of Newborn Hearing Screening Programmes (NHSP) facilitates earlier diagnosis of Auditory Neuropathy Spectrum Disorder (ANSD) hearing loss in infants in at-risk populations than was previously possible (Kirkim et al. 2008). In order to optimise early intervention for these infants, robust methods of objective hearing assessment are required as prognostic indicators when it is too early to carry out reliable behavioural audiological assessment. Whilst the Auditory Brainstem Response (ABR) can offer reliable and consistent hearing thresholds in infants with a 'typical' sensorineural (SNHL) hearing loss, absence or severe abnormality of ABR is one of the defining diagnostic features of ANSD (Starr et al., 1996). Furthermore, where audiometric thresholds are available in the ANSD population, they do not relate to the functional audiological measure of speech perception as they do in those with a 'typical' SNHL, and speech perception is typically worse than expected from the pure-tone audiogram (Starr et al., 1996). Management of ANSD in infancy, when subjective information from the patient is not possible, is further complicated by the fact that prescription targets for hearing aids are optimised for the SNHL population, and may not be appropriate in ANSD (Pearce et al., 2007).

Cortical auditory evoked potentials (CAEPs) may provide an effective alternative objective measure of auditory ability in infants diagnosed with ANSD. In the non-ANSD population, for whom CAEP thresholds are typically within 10 dB of behavioural audiometric thresholds (Davis, 1996), normal CAEPs in infancy have been shown to relate to normal receptive language ability at 1 year of age (Kurtzberg et al., 1989). Despite the lack of a clinically useful ABR, CAEPs are present in some individuals with ANSD (Satya-Murti et al., 1983; Starr et al., 1996; Rance et al., 2002; Pearce et al., 2007; Sharma et al., 2011), as it is a long latency response which requires a lesser degree of temporally synchronous neural firing than the ABR. Around half of the ANSD population are thought to have a CAEP response (Rance et al., 2002). Rance et al. (2002) showed that CAEP presence was associated with better speech perception in children with ANSD. The presence or absence of a CAEP response in itself is also informative for prognosis in children with ANSD (Pearce et al., 2007).

In addition to the development of objective measures in early infancy, the clinician would likely benefit from robust behavioural measures of functional auditory ability that can be used from an early stage. This is particularly an issue in the ANSD population, where

hearing level alone is not informative. Poor speech perception ability is the key functional impairment of ANSD, due to difficulties with temporal processing (Zeng et al., 1999). In very young children, there are two key methods for measuring speech perception behaviourally. These methods are a visual fixation paradigm associated with a speech signal, or a conditioned head turn response to detection of a change in speech signal (Johnson & Zamuner, 2010). The latter speech discrimination paradigm uses a visual reward similarly to VRA, and hence has a strong potential for clinical implementation. A pair of speech stimuli is presented in an oddball paradigm, and the ability of the infant to discriminate the stimulus pair is assessed. The pair can consist of vowel-consonant-vowel stimuli, as described in the protocol of the Visual Reinforcement Assessment of the Perception of Speech Pattern Contrasts (Martinez et al., 2008), or phoneme discrimination pairs (Uhler et al., 2011).

The three case studies herein consider the relationship between the CAEP response and the VRISD measure of speech discrimination. This paper is a starting point for further research into the predictive value of the CAEP in infants with ANSD, and its robustness as a prognostic tool. This is also a starting point for evaluation of the VRISD speech discrimination measure in hearing impaired infants, which alongside CAEPs could be adopted by ANSD clinical management protocols in the future, establishing their place in routine clinical practice in this population.

## Methods

### *Ethical Approval*

This study was approved by the National Health Service North West 10 REC - Greater Manchester North (Reference number: 10/H1011/26).

### *Normally hearing participants*

Three infants with normal hearing, aged 9 months, were assessed using the VRISD assessment tool in order to gather normative data for test stimuli. All three infants were born at full-term with no significant pre- or post-natal history, with no family history of hearing loss. All participants had displayed clear responses on NHSP screening at birth, and demonstrated healthy age-typical development at the time of assessment.

Participants were screened at 30 dB HL in the sound-field, at test frequencies of 500, 1000, 2000 and 4000 Hz. All demonstrated a consistent response at this level, with the exception of participant NH1, who had a hearing threshold of 35 dB HL at 2000 Hz, and for whom testing at 4000 Hz could not be completed due to restlessness.

*ANSD participants*

Three infants with a clinical diagnosis of ANSD underwent CAEP, VRA and VRISD assessment.

*Patient 1*

Patient 1 (AN1) was born at 39 weeks of gestation, following an uncomplicated pregnancy and delivery. AN1 was screened for ANSD due to immediate family history of ANSD. AN1 was diagnosed with bilateral ANSD following screening and further assessment.

AN1 attended for CAEP testing at 3 months of age, and returned for VRA and VRISD testing at the age of 9 months. In the intervening period, AN1 was fitted with bilateral hearing aids. These were initially fitted conservatively, with gain increased incrementally due to a lack of response to aiding at lower gain levels. AN1 was to be fitted with a cochlear implant soon after the second assessment session.

*Patient 2*

Patient 2 (AN2) was diagnosed with unilateral ANSD in the left ear, following an uncomplicated pregnancy and full-term labour. She attended for assessment at 17 months of age, and underwent CAEP, VRA and VRISD testing in a single session. CAEPs were recorded in her left ear with ANSD, VRA and VRISD testing was carried out on both ears individually using ER-3A insert earphones.

AN2's language was developing relatively well for her age, with only minor delays, and she had been assessed by a Speech and Language Therapist without significant findings. AN2 had not been fitted with a hearing aid, due to the unilateral nature of the condition.

*Patient 3*

Patient 3 (AN3) was born very prematurely at 26 weeks, at an extremely low birth weight (545g). She was the only survivor of twins. During the neonatal period, at 36 weeks post-menstrual age, AN3 suffered from chronic lung disease and bacterial septicaemia. She was discharged from the neonatal unit after 5 months with hyperbilirubinaemia and metabolic bone disease.

AN3 attended for audiological assessment at 36 months of corrected age, during which she completed CAEP, VRA and VRISD testing. AN3 was a good bilateral hearing aid user, and appeared to manage well with her amplification.

*CAEP assessment*

CAEP recording took place whilst participants watched a silent cartoon (AN2 and AN3), or sat quietly in their parent's lap (AN1). Participants were assessed for CAEP presence with the GN Otometrics EP200 clinical evoked potential system. This system was selected for this study as it is an evoked potential system that is used, or similar to those used, clinically. This was felt to be a benefit, as the results of this project are intended to have a clinical application. The electrode array used was an active electrode at Fz, with ground and reference electrodes at mastoid sites (ipsilateral reference, contralateral ground). As the study in Chapter 4 did not show a benefit to using speech stimuli over broadband noise, a simple click stimulus was selected for use here. Two repeats of twenty-five click stimuli, of 100 μs duration, were presented at varying intensity levels, commencing at 70 dBnHL in the test ear. If a response was not present, the intensity level was increased by 10 dBnHL to a maximum presentation level of 90 dBnHL.

During recording sessions, the ongoing electroencephalogram signal was low-pass filtered at 15 Hz, and high-pass filtered at 1 Hz. Click stimuli were presented at a rate of 0.7 per second, with an alternating polarity. The response recording window had a pre-stimulus period of 120 ms, and a period of 600 ms post-stimulus. A positive amplitude peak (P1), peaking within approximately 225ms of stimulus onset, characteristic of a mature infant CAEP response (Kurtzberg et al., 1984) was a marker of a present CAEP response. The P1 response has been identified as an effective marker of auditory cortical pathway development in infancy (Campbell et al, 2011). A response was only considered present if it was repeatable across the 2 runs of stimuli. Response presence was evaluated by the two

assessors carrying out the test sessions (an audiologist and an audiological paediatrician), and agreement between the two examiners was required to deem a true response.

*VRA and VRISD assessment*

VRA testing was carried out in order to screen normally hearing participants, and to establish VRA thresholds to inform VRISD presentation level in participants with ANSD. VRA assessment was carried out in a sound-proof test room with a one-way glass window. Warble tones were presented from a Kamplex AC-30 Clinical Audiometer at test frequencies of 500, 1000, 2000 and 4000 Hz. The signal was conducted through loudspeakers for sound-field testing in those with normal hearing. Speakers were placed at 90 degree angles, 1 metre on either side of the participant's head. For VRA assessment in participants with ANSD, the transducer used was an ER-3A insert earphone. Visual reinforcement was presented using videos shown on a screen next to the loud speaker on the side of stimulus presentation. The videos were presented by the Intelligent Hearing Systems Visual Reinforcement Audiometry software system. Conditioning to the VRA test paradigm was carried out with a 2000 Hz warble tone stimulus. Normally hearing participants were then screened for a response to 500, 1000, 2000 and 4000 Hz stimuli at a level of 30 dB HL. Participants with ANSD completed VRA threshold assessment at test frequencies of 500, 1000, 2000 and 4000 Hz.

VRISD testing was conducted using the Intelligent Hearing Systems Visual Reinforcement Audiometry software system. Stimuli were presented at 65 dB SPL to infants with normal hearing. Participants with ANSD were tested at a supra-threshold level, based on their VRA results. The three normally hearing infants performed VRISD in the sound-field, with phonemes presented through a speaker on their left hand side, at a distance of 1 metre, at a 90 degree angle. Two of the infants with ANSD (AN1 and AN2) received stimuli through ER-3A insert earphones, in order to present stimuli to each ear individually. AN3 was first tested using ER-3A insert earphones unaided, followed by testing in the sound-field with hearing aids in situ. The room setup was similar to that of conventional Visual Reinforcement Audiometry, and complied with the setup instructions of the Intelligent Hearing Systems Visual Reinforcement Audiometry software system.

VRISD assessment commenced with a training discrimination pair in order to establish conditioning to the test protocol. The pair of speech segments used for discrimination

training was /sa-ma/. This pair was used successfully as a training and fatigue assessment tool in VRISD assessment by Uhler et al. (2011). An oddball paradigm was used for stimulus presentation. Test procedure for VRISD commenced with presentation of a phonemic stimuli repeatedly, for example ‘sa’ in the training exercise, followed by an acoustic change to a second phoneme at random intervals, in this example ‘ma’, followed by the repetitive first phoneme again, with an inter-stimulus interval of 1200ms. Five acoustic changes to the second phoneme were presented for each discrimination pair in the testing phase. During the training section of the assessment, the infant was encouraged to turn to the side from which the stimulus was presented when the stimulus changed to the second phoneme, and a short animated video was presented as a ‘reward’. Participants were conditioned to respond to a visual video reinforcement by a clinician present in the testing room with the infant and their parent. During testing, the clinician carried out low-level distraction of the participant. A second clinician was outside of the sound booth, behind a one-way glass window, to present stimuli and reinforcement videos. A response was said to be present when observed and verified by both clinicians. At the point at which both clinicians felt that the infant was conditioned to turn their head to a stimulus change, the testing phase commenced. The discrimination pairs used in testing were the vowel phonemes /a-i/ and /a-u/, two of the pairs of the vowel triangle (/u-i/ was the remaining pair, not used in this protocol) used by Uhler et al. (2011). During the testing phase the clinician did not respond to the stimulus change, in order to ensure that any response was a true response from the participant.

**Results**

*Normally hearing participants*

Speech discrimination scores for the two test discrimination pairs (/a-i/ and /a-u/) from three normally hearing participants are displayed in Table 5.1. The discrimination index of the phoneme pair /a-i/ had a higher mean score, and was less variable, (*M* = 89%, *SD* = 10%) than the /a-u/ discrimination pair (*M* = 80%, *SD* = 20%).

| **Participant** | **Age at assessment** | **/a-i/ Discrimination Index** | **/a-u/ Discrimination Index** |
|---|---|---|---|
| NH1 | 9 months | 86% | 80% |
| NH2 | 9 months | 80% | 60% |
| NH3 | 9 months | 100% | 80% |
| | | *M* = 89% (*SD* = 10%) | *M* = 80% (*SD* = 20%) |

Table 5.1 VRISD performance in infants with normal hearing.

*AN1*

AN1 underwent CAEP and VRISD testing in the right ear, with stimuli presented via ER-3A insert earphone for both tests. On CAEP testing at 3 months of age, AN1 did not display a clear or consistent response when tested with intensity levels up to 90 dBnHL. At the second assessment session, VRISD testing was performed unaided at a level of 105 dB HL. Results are displayed in Table 5.2. After training and conditioning had been completed, AN1 scored 20% for the contrast pair /a-i/ and 0% for the /a-u/ contrast pair.

*AN2*

AN2, tested at 17 months of age in the left (ANSD) ear did not have a recordable CAEP response at levels of 70 and 80 dBnHL. A CAEP response was present however at the maximum test presentation level of 90 dBnHL.

VRISD assessment was performed in both the left and right ears. In the right, normally hearing, ear she demonstrated a discrimination index of 80% for the discrimination pair /a-i/, and 60% for the pair /a-u/. These scores are consistent with those of her normally hearing peers at the age of 9 months (Table 5.1). However, in the left ear with unilateral ANSD she scored 0% on the speech discrimination index for both test discrimination pairs (Table 5.2).

*AN3*

On CAEP testing in the right ear, consistent cortical responses were recorded at a stimulus presentation level of 80 dBnHL.

Unaided VRISD assessment in the right ear only was conducted, followed by aided assessment in the sound-field. AN3 scored 0% on the discrimination index for the /a-i/ discrimination pair unaided, 80% for the /a-u/ phoneme pair. On sound-field testing with hearing aids in-situ, AN3 showed an increase in speech discrimination score from 0% to 20% for the /a-i/ discrimination pair. However, for the /a-u/ discrimination pair, performance dropped from 80% unaided to 40% when aided.

| **Participant** | **Age at assessment** | **/a-i/ Discrimination Index** | **/a-u/ Discrimination Index** | **CAEP response present?** |
|---|---|---|---|---|
| AN1 | 9 months | 20% | 0% | No |
| AN2 | 17 months | 0% | 0% | Yes (90 dBnHL) |
| AN3 | 36 months | 0% | 80% | Yes (80 dBnHL) |
| | | *M* = 7% (*SD* = 12%) | *M* =27 % (*SD* = 46%) | |

Table 5.2 VRISD performance and CAEP presence in infants with ANSD.

**Discussion**

In these three case studies, the presence or absence of a CAEP response was not related to speech discrimination ability in a clear or consistent manner. The three cases showed three very different result patterns, and did not allow for any conclusions to be drawn.

Where a CAEP response was absent in early infancy (AN1), speech discrimination was poor and hearing aid amplification not sufficient, and the audiological management strategy required in this case was cochlear implantation. For participant AN3, a CAEP response was present at 80 dBnHL, functional auditory performance on speech discrimination testing was stronger than that of AN1, and the participant manages well with bilateral hearing aid amplification. Performance decreased on assessment with the /a-u/ stimulus pair on aided testing in AN3, which is an unexpected result. However, this was thought to be influenced by AN3 becoming distracted at the end of the assessment session,

rather than a true reflection of speech discrimination ability, and is not considered an accurate measurement. On consideration of these two cases, where a CAEP response was present it was associated with stronger functional auditory performance than where a response was absent. This is in agreement with the finding of Pearce et al. (2007). Pearce presented two cases of ANSD in infancy, in which the presence or absence of a CAEP response was associated with functional auditory outcome and aggressiveness of management strategy required.

Participant AN2 presented an interesting combination of results. In the ear with unilateral ANSD, a CAEP response was present at the maximum protocol intensity level used (90 dBnHL). However, on speech discrimination testing, AN2 scored 0% for both test phoneme pairs presented to the ANSD ear. AN2 performed well, and in line with the normally hearing participants, when tested in her normally hearing ear, hence she was well conditioned to the assessment. AN2 was the only participant to score 0% for both test discrimination pairs, despite the presence of a CAEP response. This may be attributable to the fact that she is not a user of amplification, due to the unilateral nature of her ANSD, and likely relies heavily on the contribution of the normally hearing contralateral ear. From around 6 months of age, infants begin to attend to the fine-grained aspects of speech and language (Panneton & Newman, 2012). Whilst there is some degree of auditory detection in the ANSD ear, as evidenced by the presence of the CAEP, it is likely that the ANSD auditory pathway has not developed to the extent where it can attend to these fine-grained aspects, such as phonemic discrimination. However, the presence of a CAEP response along with no speech discrimination ability in the test ear does not support the hypothesis that a CAEP response is associated with stronger speech discrimination ability, and confuses the emerging picture presented from the results of participants A1 and A3.

More research is required into the use of CAEPs in early infancy as a prognostic indicator in ANSD. This preliminary work is underpowered, and unable to conclude that the CAEP is an effective tool in predicting the level of intervention required by infants with ANSD. The VRISD does appear to be a useful tool for early assessment of auditory function, as it can be used from the age at which a head turn response can be elicited to an auditory stimulus (usually from 6 months upwards). However, many children with ANSD have co-morbidity of additional health conditions. Global developmental issues, which preclude the ability to perform a head-turn response, would prevent use of this tool in some cases. Whilst at this initial stage the VRISD appears promising as a method to provide early

information regarding speech discrimination ability, further research into test optimisation is very important. The low sensitivity shown here in normal hearing children would limit the ability to use this test clinically, and this must be resolved prior to clinical uptake. From this limited sample, the presence of a CAEP response does not relate to speech discrimination ability.

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## 6. Can CAEPs be recorded from sleeping infants?


### Abstract

**Objective:** Auditory Brainstem Response (ABR) is the most frequently used mode of objective audiological assessment in young infants. One of the benefits of ABR assessment is that it can be carried out during sleep as well as in wakefulness. Current audiological convention is that sleep obliterates the cortical auditory evoked potential (CAEP) response. This pilot study tests the hypothesis that in very young infants, maturational phenomena allow for CAEP recording during sleep.

**Methods:** Six healthy infants, aged 2-4 months, underwent CAEP testing during sleep and wake states. Sleep state was assessed with electroencephalographic and behavioural measures.

**Results:** All participants recorded in sleep and whilst awake (n=4) demonstrated a recordable CAEP during sleep, whilst 3 of 5 of those assessed whilst awake had a present CAEP. All 4 participants recorded during REM sleep had a CAEP response, versus one out of four recorded during non-REM sleep.

**Conclusion:** CAEPs were present in a greater proportion of REM sleep state recordings than in wakefulness or NREM sleep. Whilst more successful CAEP recordings in wake would be expected, in line with previous research, the increase in CAEP presence in REM sleep compared to NREM sleep is likely to be due to the active role that REM sleep plays in central nervous system maturation. These maturational phenomena may allow for sensory stimulation to continue in the dominant REM sleep state during the first months of life.

## Introduction

For the clinician wishing to record a Cortical Auditory Evoked Potential (CAEP) response in young infants, the ability to record during sleep would be greatly advantageous, due to the frequent presence of electromyogenic activity during wakefulness. Electrophysiological recordings in awake infants can be stressful, thus recordings during sleep are desirable (Hunter, 2008). However, in the audiological community, the feasibility of recording CAEPS in sleep has long been debated. Cody et al. (1967) demonstrated that CAEPs were not reliably present during sleep in adults. This finding has been extrapolated into paediatric clinical practice; to this end, clinicians are advised to record CAEPs in infants whilst awake (Purdy & Kelly, 2001; Purdy & Gardner-Berry, 2009). However, in the area of sleep medicine, event related potentials are often recorded during sleep as a measure of central nervous system (CNS) integrity (Colrain & Campbell, 2007), suggesting that CAEPs can be used effectively during sleep in some circumstances.

The Auditory Brainstem Response (ABR) is often the most suitable method of objective audiological assessment in the infant population, due to the fact it can be recorded during sleep (Purdy & Kelly, 2001). The infant spends the majority of each day in sleep, with approximately 17-18 hours of sleep per day at birth, decreasing to 14-15 hours of sleep per day by 16 weeks (Sheldon, 1996), and continuing to decrease until the age of 12 months (de Weerd and van den Bossche, 2003). In infants diagnosed with Auditory Neuropathy Spectrum Disorder (ANSD), the ABR cannot be used to provide either diagnostic or prognostic information regarding hearing ability (Pearce et al., 2007). Evidence suggests that cortical auditory evoked potentials (CAEPs) may provide a favourable electrophysiological assessment method in this patient group (Rance et al., 2002; Pearce et al., 2007; Sharma et al., 2011). Thus, the question of whether CAEP recordings are present in sleeping infants is particularly prescient for the ANSD population. This preliminary study aims to carry out an initial investigation into the feasibility of cortical evoked potential recordings in sleeping infants within the audiological context.

Infant sleep is qualitatively different to that of adults and children (de Weerd and van den Bossche, 2003). Furthermore, infant sleep changes remarkably over the first months of life, and maturation and development of sleep may play a role in the feasibility of recording CAEPs in sleeping infants. Sleep is composed of different states, which take place in a regular cyclical pattern throughout the time spent in sleep. There are two sleep stages in the neonate, which occur in a cycle of 50-60 minutes duration (Weitzman, 1965). By 35 weeks

conceptional age, all of the electroencephalographic and behavioural features of the two infant sleep states are distinguishable, but additionally a large component of sleep cannot be classified as one of those two states, and is labelled as indeterminate sleep state (Grigg-Damberger et al., 2007). The two definable sleep states of the neonate are active sleep (AS) and quiet sleep (QS). AS and QS are thought to be the immature precursors of REM and NREM sleep respectively (Anders et al., 1971; Frank & Heller, 1997; Peirano et al., 2003). However there is some dispute, and Grigg-Damberger et al. (2007) challenges the notion as there is no evidence categorically demonstrating that QS is the precursor to NREM slow wave sleep. The two key infant sleep states display well regulated activity patterns, reflective of underlying neural functions, thus they have a clear role and are more than the absence of wakefulness (Peirano et al., 2003). Sleep state in infants can be differentiated using a variety of physiological measurements and behavioural observations. For a comprehensive review, see de Weerd and van den Bossche (2003) and Grigg-Damberger et al. (2007). Different strategies for differentiation have been employed in different studies, ranging from analysis of behavioural observations only (Anders & Chalemain, 1974; Prechtl, 1974), to full electrophysiological polysomnography (Crowell et al., 1997). The key features of sleep state classification are said to be behavioural observations and features of the continuous EEG (de Weerd and van den Bossche, 2003).

With regard to the terminology of infant sleep states, Jenni et al. (2004) suggest that sleep states in infants should be labelled AS and QS until 4 months of age, and as REM and NREM thereafter. However, the 2007 position paper of the Paediatric Task Force of the American Academy of Sleep Medicine (Grigg-Damberger et al., 2007) state that 2 months of age is a more appropriate cut-off point, with the terms REM and NREM being adopted in place of AS and QS at this point. Hence the terms REM and NREM shall be used for the participant sample of this study.

Due to the potential clinical value of being able to record CAEPs in sleeping infants, a pilot study was conducted to investigate the feasibility of this methodology.The aim of this pilot is to attempt the recording of CAEPs in sleeping healthy normally hearing infants, aged 3-4 months. The study addresses the following research questions: is it possible to record a CAEP response in sleeping infants? Does the ability to record a response vary depending on sleep state? The authors hypothesise that it will be possible to record a response in sleep, and that the response will be morphologically distinct depending upon the sleep state.

## Methods

*Ethics*

This study was approved by the National Health Service North West 10 REC - Greater Manchester North (Reference number: 10/H1011/26). Participants were recruited through posters advertising at parent and baby groups, posters within The University of Manchester, and leaflets distributed at the Wellcome Trust Clinical Research Facility, Manchester.

*Participants*

Six infants were tested (male n= 3) at 2-4 months (*M* = 3.6 months) postnatal age. All infants were recruited from the well-baby population, with no history of illness pre- or post-term, and were delivered without any perinatal adverse events. All infants had passed their newborn hearing screen at birth, and had no risk factors for hearing loss. P1, P2 and P3 performed follow-up behavioural testing at 9 months of age, at which point they demonstrated visual reinforcement audiometric thresholds within normal limits (see chapter 5).

*Sleep state assessment: behavioural sleep features*

Presence of the behavioural features described in the REM features column of Table 6.1 were scored with 1 point for each feature that was observed within a 60 second epoch. For example, presence of more than 1 eye movement in a 60 second epoch was scored with 1 point. No eye movements or one eye movement in the epoch was scored with 0 points. Respiration regularity was monitored by a paediatric nurse, based on respiration rate and oxygen saturation levels measured using a Nonin paediatric pulse oximeter. Small movements included head and limb movements. Behavioural features were noted during each 60 second epoch of recording, during the presentation of CAEP stimuli.

| **REM (Active sleep) features** | **NREM (Quiet Sleep) features** |
|---|---|
| Facial movements: ≥1 eye movement, facial grimace or smile | Face relaxed |
| Body movements: limb/head movements | Absence of movement |
| Irregular respiration | Regular respiration |
| Vocalisations | Absence of vocalisations |

Table 6.1 Behavioural sleep features used in sleep state classification

*Sleep state assessment: EEG sleep features*

Recordings were obtained using the 32 channel Biosemi Active EEG system. A large electrode array was selected as this was an exploratory study, in which it was not known if response sites would vary during different sleep states. It was considered beneficial to have a large number of electrodes, to increase the chance of finding a response if present. A large electrode array was also required for sleep-state analysis. The 32 electrodes were attached to a soft cap, arranged according to the 10/20 EEG array. The use of active electrodes ensured that there was no need for scalp abrasion prior to testing, which was of benefit when trying to record from sleeping infants. The scalp was washed with a soft flannel prior to electrode placement with Signagel electrode gel (Parker Laboratories).

During stimulus presentation, the continuous background EEG trace was monitored. High voltage, slow wave EEG patterns were indicative of NREM sleep, whilst low amplitude, mixed frequency EEG indicated REM sleep. Background patterns were noted, and served as a first indicator of sleep state.

After the session, offline analysis of the continuous EEG data was used to verify sleep state. BESA Research 5.3 was used for analysis. The EEG recording was split into 60 second epochs. A fast-Fourier transform (FFT) was used to determine the frequency spectrum of the ongoing EEG, and the amplitude of the peak EEG frequencies. Mixed frequency EEG epochs denote REM sleep (Sheldon, 1996). Epochs dominated by high amplitude delta-band activity (<4 Hz) was an indicator of NREM sleep (Sheldon, 1996). The presence of sleep spindles, seen as sigma bursts, was also a characteristic indicative of NREM sleep (Jenni et al., 2004).

| **REM (Active sleep) EEG features** | **NREM (Quiet Sleep) EEG features** |
|---|---|
| Low amplitude, mixed frequency | High amplitude, slow wave, delta dominant |
| No sleep spindles present | Sleep spindles present |

Table 6.2 EEG sleep features used in sleep state classification

Behavioural sleep features were scored with one point each for features in the REM sleep column of table 6.1, with a total possible score of 4.The presence of low amplitude, mixed frequency EEG gave a score of 2 points, and an absence of high amplitude, slow wave, delta dominant EEG scored 1 point. The absence of sleep spindles scored 1 point. Thus the

possible score of features was 8 points, with ≥4 points scored as REM and <4 points scored as an NREM sleep epoch. There were 3 epochs within a stimulus block. If 2 of the 3 epochs was judged to have the physiological characteristics of a certain state (REM, or NREM) then the stimulus block was said to be in that state. This is based on Crowell et al (1997), in whose study an epoch was rated as a certain sleep state if more than half of it displayed the characteristics of that state.

*Cortical auditory evoked potentials*

Stimuli were presented using E-Prime application suite (Psychology Software Tools). The stimuli were transmitted from the presentation PC to a GSI 38 audiometer, from which they were presented monaurally via an ER-3A earphone at a level of 65 dB SPL. Stimuli were 1 second segments of broadband noise, Butterworth filtered between 50 and 10000 Hz, with an inter-stimulus interval of 2 seconds. CAEP analysis of EEG data was performed using BESA Research 5.3.

During recording, an artifact rejection threshold of ± 100 μV was applied. The digitised EEG signal had a resolution of 24 bits and a sample rate of 256 Hz. During recording, the EEG signal was filtered between 0.1 and 100 Hz. Data were then epoched offline, using the BESA analysis software, with a pre-stimulus window of 100 ms and a post-stimulus period of 600 ms. The EEG signal was filtered between 1 and 15 Hz for CAEP analysis, with an average reference applied. Results from frontal and central channels were used for CAEP detection, and with amplitude and latencies reported from Fz. Exceptionally, F3 was used to define the characteristics of the CAEP response in the waking blocks of P2, due to poor quality Fz recording.

The presence of a response was based on stimulus blocks in which 100 stimuli were presented. Infant CAEP morphological features differ from those of the adult response, and are more variable. It was also unknown what morphological differences may exist between sleep states, or how consistent this would be between subjects. A response was considered present if it occurred at Fz and surrounding sites, showed polarity inversion at posterior sites, and was repeatable in at least two testing blocks within the same sleep state. For the purposes of this study, response presence was not dependent upon polarity of response. Kurtzberg et al. (1984) demonstrated that the polarity of the infant CAEP inverts in the first months of life, from a primarily negative to positive response, thus polarity may differ between infants depending on stage of maturation. Response presence was assessed by two

experienced examiners. Where there wasn't agreement on a response presence it was deemed not a true response. Where a response was present, the runs from each sleep state for each participant were then averaged across the minimum of two runs, amplitude and latency information is presented from the averaged waveform (see Table 6.3.).

## Results

*Sleep vs. Wake*

Where trials were present in sleep and wakefulness, a CAEP response was observed in 100% (4/4) of recordings carried out during sleep, and in 60% (3/5) of wake recordings. Two participants (P3, P5) did not sleep during their session, and thus a sleep versus wake comparison could not be made for these patients.

| | **REM amp.** | **REM latency** | **NREM amp.** | **NREM latency** | **Wake amp.** | **Wake latency** |
|---|---|---|---|---|---|---|
| **P1** | 2.84 µV | 201 ms | -8.14 µV | 105 ms | -2.65 µV | 123 ms |
| **P2** | 2.66 µV | 215 ms | *NR* | *NR* | *NT* | *NT* |
| **P3** | *NT* | *NT* | *NT* | *NT* | -3.37 µV | 98 ms |
| **P4** | 3.4 µV | 156 ms | *NR* | *NR* | 0.54 µV | 164 ms |
| **P5** | *NT* | *NT* | *NT* | *NT* | *NR* | *NR* |
| **P6** | 3 µV | 295 ms | *NR* | *NR* | *NR* | *NR* |
| | | | | | | |
| **Mean** | **2.98 µV** | **216.75 ms** | **-** | **-** | **1.96 µV** | **128.33 ms** |
| **SD** | **0.32** | **57.92** | **-** | **-** | **2.08** | **33.32** |

Table 6.3 Average amplitude and latencies of CAEP responses according to sleep state.
NR= No CAEP response present; NT = No trials in this sleep state as did not enter this stage of sleep cycle / did not sleep /could not tolerate wake recording

*CAEPs in wake, REM and NREM*

In the REM sleep state, all 4 infants with trials recorded in this state had a CAEP response. During the NREM state, only 1/4 infants had a recordable CAEP response (Table 6.3). The mean response amplitude in REM sleep was 2.98 µV (*SD* 0.32), which was slightly larger in magnitude, and much less variable than that of the wake recordings (1.96 µV, *SD* 2.08). Amplitude and latency of CAEP responses in REM sleep and when awake are shown in Figures 6.1 and 6.2. Differences in mean amplitude are skewed by polarity difference in wake responses. When polarity is corrected for, and amplitude magnitude rather than polarity is the variable tested, mean waking CAEP amplitude was 2.19 µV (*SD* 1.47. The mean latency of responses recorded in REM sleep was 216.75 ms (*SD* 57.92), and whilst

awake was 128.33 ms (*SD* 33.32). The latency of the wake response, therefore, is less variable than in REM sleep, and is a much shorter latency response. Example raw CAEP responses from different sleep states (from one run, not averaged across two or more runs) are shown in Figure 6.3.

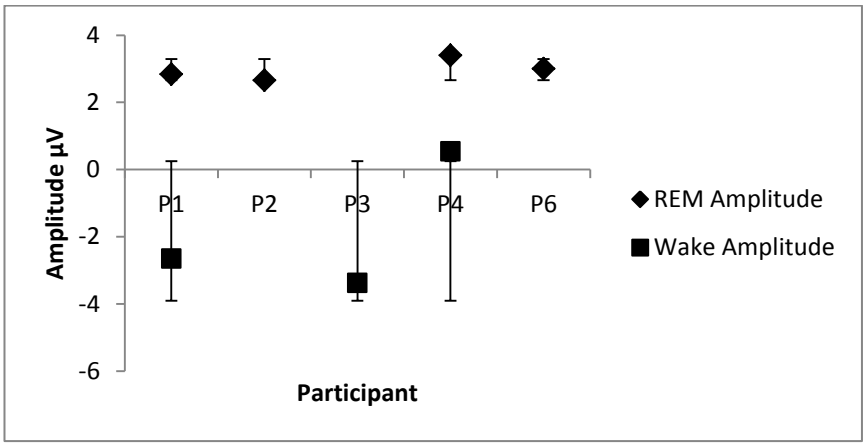



Figure 6.1 Amplitude of dominant CAEP peak during wake and REM testing

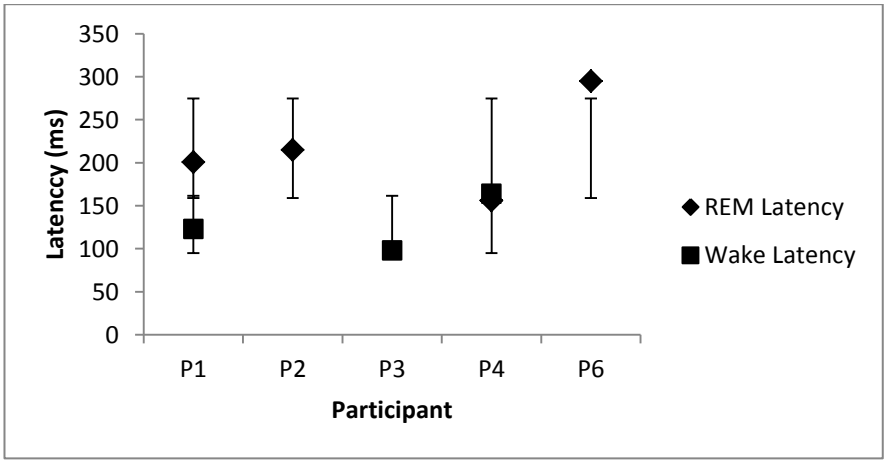
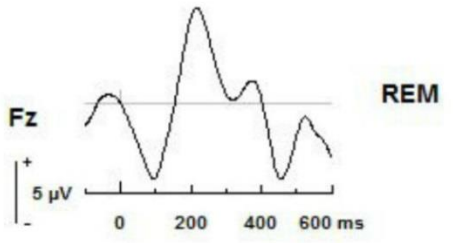
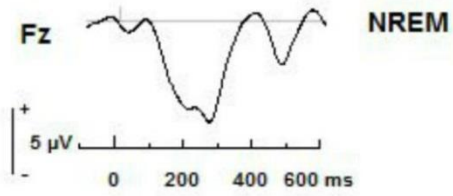
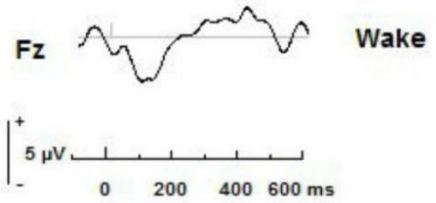


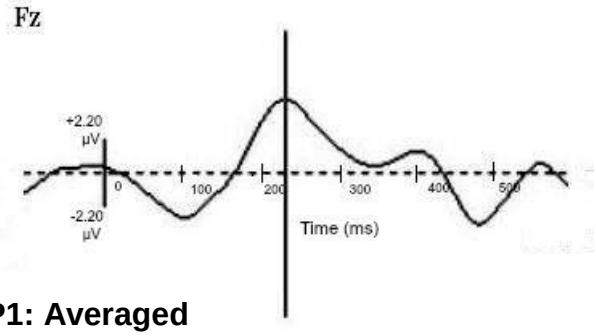

Figure 6.2 Latency of dominant CAEP peak during wake and REM testing




P1




**P1: Averaged waveform, REM**

Figure 6.3 Example waveforms from each sleep state. N.B. amplitudes and latencies in Table 6.3 give results averaged over 2 or more runs where a response was present. Waveforms in this figure are from one run only, other than P1: Averaged waveform, REM as an example.

**Discussion**

This preliminary investigation into the feasibility of recording CAEPs in sleeping infants demonstrated that CAEPs were indeed recordable during sleep, but that the presence was highly influenced by sleep stage. All four infants that were tested in the REM sleep state

demonstrated a repeatable CAEP response, as opposed to one out of four in NREM sleep. In addition, responses were present in a higher proportion of REM recordings than wake recordings, due largely to the presence of electromyogenic activity in wakefulness, caused by crying and movement, which reduced the CAEP signal-to-noise ratio. This finding adds weight to the argument that recording CAEPs from sleeping infants is clinically beneficial, allowing for an improved signal to noise ratio compared to waking responses. The findings of this study suggest that it may be possible for clinicians to optimise recordings of CAEPs in infants in the future, using simple behavioural observations to characterise sleep state in order to record during REM sleep.

During the first months of life, the majority of each day is spent in sleep, leaving little waking time for CNS stimulation. REM sleep is the prevailing state in these first months. It is thought that this dominant state is involved in providing sensory stimulation to the infant during sleep, inducing the neuronal activity required for neuro-maturation to take place (Peirano et al., 2003). This is largely based on the proposition of Roffwarg et al. (1966) that the primary purpose of REM sleep in infants, therefore the reason for the REM dominance in infancy, is that REM sleep induces CNS maturation. This theory has been supported by animal studies. Namely, stimulation of the central visual system occurs during REM in the infant rat brain in a way that replicates waking activity (Shafferey et al., 2002; Peirano et al., 2003). Peirano et al. (2003) suggest that this is likely to extend to the other sensory systems, and thus it is plausible that the auditory system receives stimulation during REM sleep in early infancy. If this is correct, and these findings are translatable to human neuro-maturation, this could explain why it was possible to record CAEP responses during the dominant REM sleep state in this study.

CAEP responses have been demonstrated in sleeping infants in previous studies. Ellingson et al. (1974), Kurtzberg et al. (1984) and Duclaux et al. (1991) also report findings of a CAEP response during REM sleep in a small sample of infants. In this pilot study, morphological differences were noted between CAEP responses in different states. However, there was no significant difference in response amplitude between REM sleep and wake when polarity was corrected for. This gives some support to the suggestion of Ellingson et al. (1974) and Kurtzberg et al. (1984) that responses in REM and wakefulness are not significantly different. This is also in line with the findings of Shafferey et al., 2002, who showed great similarities between CNS activation in wake and REM sleep in the infant rat, suggesting that in the time period in which REM sleep is dominant there may

not be a difference between neural resources available for sensory perception during REM sleep compared to wakefulness. However, significant differences in response latency between REM sleep and wakefulness in this study suggest that though the same amount of resources may be available, the time course for perception is slower in REM than during sleep. The results of this study, with regard to latency differences between REM and wake, differ from the findings of Ellingson et al. (1974) and Kurtzberg et al. (1984). The parameters of sleep state characterisation in Kurtzberg's 1984 paper are not published; hence it is not possible to say if these differences are attributable to methodological factors. The six infants tested by Ellingson et al. (1974) were newborn, therefore maturational factors may play a role. The age of participants for whom sleep state categorisation was carried out on in Kurtzberg's work is not given, so differences may also be influenced by maturational factors. Contrary to the results of these studies, and in contrast to the findings of this pilot study, Duclaux et al. (1991) recorded CAEP responses in both REM and NREM sleep in infants aged 6 weeks, with a significantly higher magnitude response in NREM sleep. Responses were reported from T3 and T4 sites, and this methodological difference could be thought to contribute to a difference in response. However, this pilot study used multi-site recordings (though results were reported from central sites), and responses at temporal sites were not seen during NREM sleep.

Polarity differences between sleep states were seen in P1 (see Table 6.3). This may be reflective of morphological differences associated with underlying neuronal differences between sleep wake states. Colrain & Campbell (2003) discuss morphological differences and additional event related potential components that can be seen when recording in sleeping adults compared to the waking response, and this may hold true for infant recordings too. Polarity differences also occurred between, as well as within, participants. These polarity differences may be linked to maturational factors, given that even a small difference in age in the first months of life can represent a large difference in function. Kurtzberg et al. (1984) showed that the maturational course of the CAEP during the first months of life showed a change in polarity from a primarily negative to positive response in infancy, thought to be due to changes in intra-cortical synaptic organisation. Therefore, infants may have differed in their stage of CAEP response maturation, leading to morphological differences in their response.

The potential clinical applications for recording CAEPs in sleeping infants are vast, especially in the context of newborn hearing screening. Infants undergo diagnostic

assessments at a very early age, and 10% of those diagnosed with hearing loss have audiological test results consistent with Auditory Neuropathy Spectrum Disorder (Uus & Bamford, 2006). These infants do not have the recordable ABR that is routinely used for audiological threshold estimation in infants with sensorineural hearing loss, hence other electrophysiological measures are needed to support clinical decision making. Rance et al. (2002) demonstrate the effectiveness of CAEP recording in delivering prognostic information in children with ANSD. Rance also highlights the potential benefit of using CAEPs in young infants diagnosed with ANSD, before other audiological information is available, if it was possible to reliably record the response at such an early stage. The option of testing a young infant in their sleep is a desirable one, to minimise distress to the infant and to optimise SNR, as with ABR. In order for CAEP testing in sleeping infants to be accepted in clinical practice it is vital to validate behavioural sleep state categorisation against the gold-standard electrophysiological measures, as well as establish the age range at which CAEPs in sleep are no longer recordable regardless of the sleep state. A large scale longitudinal study is now needed to explore the clinical feasibility of recording CAEPs in sleeping infants, and to see if the findings of this pilot hold on a larger scale.

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# 7. General Discussion

The research described in this thesis investigated the relationship between cortical auditory evoked potentials (CAEPs) and speech perception ability in populations for whom speech perception ability does not relate to hearing thresholds. The main aim of the project was to assess the potential value of CAEPs as an objective method of assessment in these populations. This discussion chapter will summarise the objectives and key findings of the research, and discuss the potential implications for future research.

**Aims of the research:**

The overarching aim of this thesis was to better understand the relationship between objective CAEP assessment and functional measures of hearing ability, in order to inform objective assessment of infants with ANSD following diagnosis, and to facilitate auditory assessment in those with neurodegenerative conditions. The aim of the two studies with adult participants was to investigate overall auditory function and understand the relationship between CAEPs and speech perception in FA and CMT, and to refine the CAEP protocol used for testing in infants. The first of two studies with infant participants aimed to explore the relationship between CAEPs and speech discrimination in infants with ANSD. A second aim of testing in infants with ANSD was to investigate the potential application of the VRISD speech discrimination paradigm in ANSD as a functional outcome measure. Finally, the project aimed to investigate the possibility of recording CAEPs in young infants during sleep, in the hope of extending the potential time available for recording CAEPs in young infants who spend the majority of the day asleep during the first months of life.

**Summary of findings:**

*Chapter 3: The role of aetiology in the manifestation of hearing impairment due to peripheral neuropathy*

CMT and FA are neurological conditions, affecting the peripheral nerves, which have previously been shown to manifest in the auditory system in a hearing impairment fitting the perceptual profile of ANSD loss (Starr et al., 1996; Rance et al., 2008; Rance et al., 2010; Rance et al., 2012a; Rance et al., 2012b). The audiological profile of these conditions is not well documented, in particular the profile of those with CMT. Previously, the two populations have not been tested comparatively, to the knowledge of the author. This pilot study was conducted to look at the presence of CAEP responses and speech perception ability in these two clinical groups, prior to testing in infants.

This pilot study revealed that participants with CMT had significantly stronger speech perception in quiet than those with FA. This indicates that the different underlying aetiopathological causes of hearing impairment in these groups manifests in a difference in functional performance. This finding suggests that the two populations should be treated as distinct sub-groups.

The sample in the pilot study was too small to define a relationship between CAEP presence and speech perception ability. However, the two participants with the poorest speech perception did not have a CAEP response, unlike the other participants. The results of the pilot study indicated that it is worth investigating the relationship between CAEPs and functional measures further in these complex and under-researched groups, where behavioural assessment may be difficult in some cases due to impaired dexterity.

*Chapter 4: Exploring hearing impairment in Friedreich's Ataxia and Charcot-Marie-Tooth: what is the relationship between objective and functional hearing measures in these peripheral neuropathies?*

Following the pilot study described in Chapter 3, further assessment was carried out into the auditory profile of those with the peripheral neuropathies of FA and CMT. A control group of adults with sensorineural hearing loss (SNHL) was also assessed. This study assessed the presence of CAEPs to speech stimuli in these test groups, along with speech perception ability and gap-detection thresholds. Zeng et al. (1999) demonstrated that the difficulties in speech perception in those with ANSD are due to deficits in temporal processing abilities. In order to decipher a rapidly fluctuating auditory signal, such as speech, the listener must be able to perceive changes in signal to the degree of milliseconds. The gap-detection threshold test assesses the ability to perceive these rapid fluctuations in auditory signal, by measuring the minimum silent gap that can be distinguished from a signal, for example a broadband noise segment. Zeng (1999) showed that speech perception ability is correlated with degree of temporal processing ability in ANSD. Rance et al. (2010) also demonstrated a correlation between temporal processing and speech perception ability in FA. This study compared the differences between the FA, CMT and SNHL groups on gap-detection and speech perception testing. It also investigated the correlation between these measures and the presence or absence of a CAEP response to speech stimuli.

Participants with FA and CMT were not audiogram-matched to the SNHL control group. Low frequency audiometric configuration is a reasonably common finding in ANSD (Rance, 2005). There are inherent difficulties in matching the more 'typical' SNHL, in which high frequencies are usually impacted more than low-frequencies, to hearing impairment that is closer to ANSD in presentation. Sininger & Oba (2001) and Starr et al. (2000), found around 30% of cases of ANSD to have a low-frequency hearing loss, with a high-frequency hearing loss observed in only around 10% of patients (cited in Rance, 2005). This data is not available, to the knowledge of the author, for the CMT and FA populations. A further difficulty arises due to the heterogeneity of hearing levels in ANSD-type hearing impairment, where hearing levels can range from normal hearing to a profound hearing loss (Rance, 2005), and do not necessarily relate to functional hearing such as speech perception (Starr et al., 1996; Kraus et al., 2000; Rance & Barker, 2008). In this study, most participants with ANSD had hearing levels near normal limits (7 of 12

had thresholds within normal limits). Despite this, nine of twelve participants report difficulties with hearing, exacerbated in the presence of background noise. In this study, participants with SNHL had 4-frequency average audiometric thresholds significantly higher than those with FA/CMT. In spite of the discrepancy in hearing levels, there was no significant difference in functional performance between the groups, suggesting the FA and CMT groups performed worse than expected for their auditory levels.

Gap-detection thresholds amongst all participants were outside of the normal range. Normal thresholds have previously been reported from 2-3ms (Moore, 1993) to 5.2ms (Trehub et al., 1995). On assessment in this study, the mean gap-detection threshold amongst those with FA/CMT was 15ms. Within the SNHL group, average gap-detection was at 17ms. This is the same threshold as that recorded within the CMT group. Participants with FA performed better than the two other groups, with an average gap-detection threshold of 12.5ms. On ANOVA analysis, this mean threshold was not significantly different to the 17ms threshold of the CMT and SNHL groups. However, this is almost certainly due to the very small sample size within the FA group (n=5), which was a major limitation in the interpretation of results.

On speech perception assessment, there was no statistically significant difference amongst groups in quiet or in the presence of background noise at a signal-to-noise ratio (SNR) of +10 dB, despite the significantly worse audiometric thresholds of the SNHL group. Participants with FA had a mean speech perception score of 67% in both quiet and noise. This was not significantly different to those with CMT, who scored on average 73% in quiet and 71% in noise. Amongst participants with SNHL, speech perception mean scores were 74% in quiet and 76% in noise. An interesting phenomenon was seen amongst those with SNHL in particular, whereby in some cases speech scores in noise were higher than in the absence of noise. This was attributed to the effects of test order, and the order was alternated between participants on discovery of the problem.

Contrary to the pilot study, these experiments revealed no significant differences between FA and CMT groups, suggesting they can be treated as one sub-group of the peripheral neuropathy spectrum in terms of audiological assessment. Though it was not significantly different, speech perception was stronger in FA participants than those with CMT. This is a reversal of the findings of the pilot study in Chapter 3. Rance et al. (2012a) reported that severity of auditory difficulties in FA is related to severity of global disease progression.

Overall progression of participants with FA in the pilot study was more severe than in the participants tested in Chapter 4 (though one participant was tested in both studies). Progression of hearing impairment and disease severity is yet to be explored in CMT. However, on future investigation into differences between CMT and FA it would be prudent to consider disease progression when matching groups.

On CAEP assessment, a group of adults with normal hearing were tested as an additional control. P2 responses were present in 7/10 participants with FA/CMT to at least two of three speech stimuli. Comparatively, each of the 7 participants with normal hearing and 7/11 of those with SNHL had a P2 response to at least two of the three stimuli. Where responses were present, there was no significant difference between groups on presence of response, latency or amplitude on ANOVA analysis.

Correlational analysis was carried out, to investigate the relationship between CAEP response measures and the functional speech perception and gap-detection threshold assessment. Using correlational analysis, no significant relationship was identified between these measures.

*Chapter 5: Three cases of ANSD in infancy: CAEP and speech discrimination assessment*

Three case-studies investigated the presence of a CAEP response, and speech discrimination ability, in infants diagnosed with ANSD. Chapters 3 and 4 demonstrated that a CAEP response was recordable in many of the adult participants with the peripheral neuropathy form of ANSD. This was then tested in infants with ANSD, for whom an objective mode of assessment is particularly important.

Rance et al. (2002) demonstrated a link between CAEP presence and speech perception ability in older children with ANSD. In early infancy, Pearce et al. (2007) presented two case studies looking at CAEPs in infants with ANSD. In the first case, a CAEP response was present in an infant that went on to manage well with hearing aid amplification. A second case was presented, in which the infant went on to have a cochlear implant fitted, and did not have a CAEP present on earlier testing. These studies suggest that the presence or absence of a CAEP response in infants with ANSD may be informative for prognosis. The case-studies in Chapter 5 aimed to build on these previous studies, by looking at CAEP presence and speech discrimination in infancy. A secondary objective was to

investigate the potential value of the Visual Reinforcement Speech Discrimination (VRISD) test as a method of assessing functional hearing in infants with ANSD, earlier than other clinical measures of speech perception may be used currently.

Three infants with ANSD were assessed, one of whom had unilateral ANSD. Of the three infants, a CAEP response was present in two, elicited by a click stimulus. The participant for whom no CAEP response was present at presentation levels between 70 and 90 dBnHL went on to have a cochlear implant fitted. He also performed poorly on speech discrimination assessment, scoring 0% for the /a-u/ stimulus pair, and 20% for /a-i/. This is in contrast to the average scores of three normally hearing controls on the VRISD test, who scored 89% and 80% for the /a-u/ and /a-i/ stimulus pairs respectively. Audibility may have played a role in the lack of CAEP response for this participant, as the maximum test stimuli was set at 90 dBnHL, to prevent the risk of damage to any residual hearing. A CAEP response may have been present if tested at a more elevated presentation level.

A second case study, of unilateral ANSD, presented an interesting picture on assessment. In the ANSD ear, the participant had a CAEP response at 90 dBnHL. On VRISD assessment in the ANSD ear, the participant scored 0% for both sets of test stimuli. This picture suggests that sounds may be audible to the participant at elevated presentation levels, but that the ability to perform the fine-grained analysis required for speech discrimination (Panneton & Newman, 2012) is not present in the ANSD ear. On the contralateral side, the participant performed in line with levels of the normally hearing control group on VRISD assessment. The lack of speech discrimination ability in the ANSD ear is potentially compounded by a lack of input to the auditory pathway on this side, and contralateral dominance of the normally hearing ear.

A third participant with ANSD was assessed, and had a CAEP response present at 80 dBnHL. This participant is managing well with hearing aid amplification, and speech and language is developing well. On VRISD assessment, the participant scored 0% for the /a-i/ stimulus pair, and 80% for the /a-u/ stimuli.

Whilst these three case-studies do not show a clear pattern, and the study is limited due to the very small sample size, there are consistencies with the work of Pearce et al. (2007) when looking at the performance of the first two participants. The results of the third

participant represent a point of divergence, and make it impossible to define a clear relationship.

More recently, Cardon & Sharma (2013) showed a relationship between CAEP P1 measures and speech perception ability, assessed with the IT-MAIS measure, in children with ANSD fitted with cochlear implants. The growing body of literature suggests that CAEPs have prognostic value, in the prediction of functional hearing, which is more meaningful than auditory thresholds in the ANSD population. CAEPs may have the potential to be used as part of the clinical protocol for ANSD assessment in the future, as a predictor of outcome in ANSD in early infancy. However, this study was inconclusive, and more research is required into the relationship between CAEP presence and functional outcome in infants with ANSD.

*Chapter 6: Can CAEPs be recorded reliably in sleeping infants?*

If CAEPs are to form part of the audiological clinical test battery for infants diagnosed with ANSD in the future, it is important to optimise the recording protocol. ANSD can be diagnosed within the first weeks of life due to the implementation of NHSP (Kirkim et al., 2008). In infants with SNHL, the ABR is used to assess hearing levels, and can be recorded in sleeping infants. This is of real benefit, as in the first months of life, infants sleep up to 18 hours per day (Sheldon, 1996). However, the ABR is of little prognostic value in infants diagnosed with ANSD, as an absent or severely abnormal ABR is part of the diagnostic criteria for the condition (Northern, 2008). Thus, following diagnosis, there is little prognostic information available to the clinician treating the infant with ANSD.

Previous research has found CAEPs to be a promising tool for patients with ANSD, though this hasn't been replicated in the studies of this thesis, which may be due to the small sample sizes. In order to increase ease of assessment, it would be beneficial to the clinician to be able to record CAEPs in infants whilst sleeping or awake, as with the ABR. However, amongst the audiological community, there is a general consensus that CAEPs are not recordable in sleep (Purdy & Kelly, 2001; Rance et al., 2002).

Five infants, aged 2-4 months, underwent CAEP assessment whilst awake. These infants had passed neonatal hearing screening examination, and had no risk factors for ANSD. Four of the five also had CAEPs recorded in both rapid-eye movement (REM) and non-

rapid eye movement (NREM) states of sleep. Three of the five infants recorded whilst awake had a demonstrable CAEP response. Where a response was not recordable, this was due to high levels of noise in the EEG recording, caused by movement of the infants who could not be settled. During NREM sleep, only one of the four infants had a recordable CAEP response, suggesting that recording in this sleep state would not be a useful clinical measure in the future. However, in REM sleep, all four of the infants had a present CAEP response. This suggests that it may be clinically viable to record during REM sleep. As the REM sleep state is identifiable behaviourally by eye movement, facial movement and grimaces, and body movement, this had the potential to be built into a clinical protocol for CAEP assessment in early infancy, if subsequent research confirms the findings.

**Discussion:**

*Peripheral neuropathy and ANSD-type hearing impairment*

Patients with FA and CMT were amongst those presented in the paper which first defined ANSD (Starr et al., 1996). However, little subsequent research has been carried out to characterise the audiological profile of patients with these peripheral neuropathies. To ensure that management strategies are appropriate for these patients, a well-defined auditory profile is essential. In these patients, audiological problems, when present, sit within a range of other severe health conditions. Facilitating good communication becomes very important. Sadly, it is often overshadowed by other health problems and hence overlooked.

The pilot study described in Chapter 3 found that speech perception in quiet was worse in participants with FA than those with CMT. It was concluded that the underlying axonal cause of auditory impairment, as opposed to demyelination in the participants with CMT 1a, was a more severe form of disruption to the signal in the auditory pathway. Zeng et al. (2005) reported that reduced neural conduction, as in the axonal condition of FA, and desynchronised neural discharge, as in the demyelinating form of CMT, both lead to impairment in gap-detection, and related to this, impairment in speech perception. These two forms of impairment cannot be clinically distinguished in the more typical forms of ANSD. However, in FA and CMT, where the source of the auditory problem is known, it is possible to assess the differential impact of these factors on temporal processing and

speech perception. This led to the investigation of gap-detection thresholds and speech perception in Chapter 4.

However, Chapter 4 contradicted the conclusion of Chapter 3 that FA and CMT groups have a different manifestation of audiological impairment due to different underlying causes. In this study, there were no statistically significant differences between those with CMT 1a and FA. There are two major limitations of the sample used in Chapter 3. The first of these is the small sample size, which reduces the potential of finding a significant result if present. Secondly, and key to explaining the difference in findings between Chapters 3 and 4, is the difference in hearing impairment related to disease progression and severity of disability in FA and CMT. Rance et al. (2010) report a correlation between speech perception and gap-detection impairment, and progression of the global condition in FA. Participants tested, particularly in the FA group, in Chapter 3 had a more severe progression in most cases than those tested in the study reported in Chapter 4. Thus, even within populations with the same condition, it is difficult to compare results between those with differing degrees of condition severity. It is therefore difficult to conclude if there is a significant difference between FA and CMT, as reported in Chapter 3, or if there isn't a significant difference, as reported in Chapter 4.

A key objective of the studies described in Chapters 3 and 4 was to investigate the relationship between CAEPs and speech perception. Previous findings of Rance et al. (2002), Narne & Vanaja (2008), and Cardon & Sharma (2013) showed that CAEPs relate to speech perception ability in ANSD. The sample in Chapter 3 was too small to draw conclusions, but suggested that the CAEP holds promise as an objective tool in FA and CMT. The study in Chapter 4 followed up, with a larger sample. Correlational analysis revealed no significant relationship between CAEP measures of presence, latency and amplitude and speech perception in quiet and in noise. The lack of relationship between speech perception scores and CAEP presence in the second study, contrary to previous research in ANSD which is perceptually close to the hearing impairment of FA and CMT, is a challenge for interpretation. However, Kumar & Jayaram (2005) also found no relationship between speech identification scores and CAEP measures in ANSD. Within the second study, the sample size was larger for the aggregated FA/CMT group than in the pilot, thus the chance of finding a relationship if it exists was higher. The potential promise of the CAEP in the pilot study which was not repeated with the larger sample in Chapter 4 may be attributable to the different participants tested in the two studies, with

differing degrees of condition severity. It may also be due to the different recording paradigms. Michalewski et al. (2005) found that some participants with ANSD had a CAEP response in an active paradigm, where they were required to perform a task, whilst they had no response in the passive paradigm. In a higher number of cases the converse was shown, and a CAEP response was seen in the passive and not the active recording paradigm. The studies in Chapters 3 and 4 both used a passive recording paradigm, so this is not a factor. However, it does demonstrate how susceptible to changes in paradigm the CAEP response is. The limitations caused by not alternating the test order initially in Chapter 4 may have contributed to a less accurate picture of real speech perception ability, reflected in the lack of significant relationship to CAEP metrics. The presentation level of speech stimuli in these two studies may also have played a role in the differing findings. Presentation level in Chapter 4 was lower, relative to PTA threshold, than in Chapter 3. This may have led to initially poorer performance as the participants adjusted to the task, followed by an improvement with training effects as participants adapted. In order to conduct a meaningful comparison of the two studies, test parameters would need to be the same.

Though gap-detection thresholds were not found to be significantly different between those with FA/CMT, and the worse-hearing SNHL group, all groups exhibited a mean threshold which far exceeded normal limits. Zeng et al. (1999) found that those with ANSD had gap-detection thresholds that were elevated beyond those of normally hearing listeners. Rance et al. (2010) also demonstrated elevated gap-detection thresholds amongst those with FA. However, these studies also demonstrated a relationship between degree of gap-detection impairment and impairment in speech perception ability. This relationship was not replicated here. One potential reason for this is that the groups were too small to see a significant relationship. This relationship may also be impacted by speech perception results if there are test order effects. The lack of a significant difference between the FA/CMT and SNHL groups is very likely caused by the significantly worse hearing of the SNHL group, skewing the comparison. This is a major limitation in the interpretation of findings of this study.

When defining auditory impairment amongst those with FA and CMT, the research presented in this thesis demonstrates that speech perception is frequently impaired, and is perceived to be a problem by the participants, despite normal or near-normal hearing

thresholds. This highlights the need for speech perception to be tested routinely in these populations, for whom PTA is not informative.

Where carrying out a behavioural test battery is difficult, where manual dexterity or fatigue are problems, the work of Rance and colleagues suggests CAEP assessment may hold promise as a tool for objective assessment in these populations, though this was not replicated in the studies of this thesis. Further research is required to optimise the testing protocol, and further explore the relationship between this objective test and functional hearing measures if it is to inform clinical management strategies. Areas that may be tested for optimisation include testing further stimulus types to find the strongest predictor of functional hearing, optimisation of electrode array, finding an objective method for CAEP response recognition, using jitter-analysis with CAEPs in these populations, and assessment of the predictive value of electrophysiological gap-detection assessment for speech perception. Whilst the pilot study suggested that FA and CMT should be treated as two distinct entities of audiological impairment, further study suggested that this isn't the case, as significant differences were not observed. Overall disease progression may be a more significant factor than underlying aetiopathology when differentiating between peripheral neuropathy sub-groups. However, caution when generalising between the two groups is encouraged until further research, with groups matched for disease progression and severity, has been carried out to explore group differences.

*Objective and functional assessment of infants with ANSD*

An objective protocol, to provide prognostic information regarding infants diagnosed with ANSD, is a needed to inform early management strategies. The most important potential clinical implication to come out of this thesis is that CAEPs can be recorded during sleep in very young infants. Furthermore, the VRISD assessment appears to be a useful behavioural assessment tool in ANSD. This test may be particularly useful, as it can be tested on the same time-course as the VRA (and using the same clinical test set-up), thus it can provide information on speech discrimination earlier than previously possible clinically. This is of real potential value for those with ANSD, whether as a measure of how the participant is functioning with amplification, or assessing severity of hearing impairment.

Given that CAEPs have been shown to be a promising clinical prognostic tool in infants with ANSD elsewhere in the literature (Rance et al., 2002; Pearce et al., 2007; Cardon & Sharma, 2013), though not in this thesis, the ability to record in both sleep and wake states in early infancy is of clinical benefit. Recording in sleep may help to reduce electromyogenic activity, and prevent an increase in stress levels which can affect the electrophysiological recording (Hunter et al., 2008). It is also of practical value, in that during a testing session, assessment does not have to be halted if the infant is to fall asleep. Based on assessment experience for the study presented in Chapter 6, under 3 months it is difficult to keep an infant awake and quiet. Chapter 6 showed that CAEP assessment was possible during REM sleep state. In the first weeks of life, infants spend as much as 39% of sleep in the REM state, falling to around 30% by 9 months of age (Jenni et al., 2004). REM sleep is easy to identify, associated as it is with increased movement of body and face, vocalisations, and increased respiration rate (Sheldon, 1996).

Roffwarg et al. (1966) showed that REM sleep plays an active role in the maturation of the central nervous system. This may be the reason why it is possible to record CAEPs during REM sleep in very young infants, where it is not possible in children and adults. Shafferey et al. (2002) showed that CNS activation whilst awake and in REM sleep were very similar in the infant rat during stimulation of the visual system. Peirano et al. (2003) suggest that this is likely to extend to other sensory systems, such as the auditory pathway. Thus, the clinician may be able to record CAEPs during REM sleep in the first months of life, whilst the CNS continues to be activated during sleep in a manner very similar to waking activation.

## Directions for future research

### *Peripheral neuropathies*

Auditory impairment in those with peripheral neuropathies is not well defined, thus there are a multitude of directions of research that could be proposed. There are three key areas for further research in participants with FA and CMT. The first of these follows from the discrepancy between the findings reported in Chapters 3 and 4, regarding the distinctness of the two groups. Further research to characterise hearing impairment in FA and CMT would be informative, particularly to identify whether or not there are any differences on functional testing when groups are matched for disease progression and duration. A well

powered study, investigating conclusively whether the aetiopathological differences underpinning auditory impairment in FA and CMT lead to significant differences in auditory profile, would be a key next step to developing clinical protocols in these groups. In particular, investigation into differences in speech perception ability would impact meaningfully upon management strategies employed with these groups.

It is also important to continue to develop effective methods of objective assessment in those with FA and CMT, where physical disabilities can make assessment on an audiological test battery difficult and more tiring for the patient, A good starting point for this would be to assess gap-detection thresholds electrophysiologically using CAEPs, and to look at the relationship to behavioural gap-detection thresholds, and to speech perception, in these populations. Michalewski et al. (2005) showed agreement between CAEP gap-detection thresholds and behavioural gap-detection thresholds in ANSD. Investigation into the effectiveness of this as a predictive measure of impairment severity in those with FA and CMT may prove beneficial for a future objective clinical testing paradigm.

Finally, if clinical recommendations regarding assessment and management tailored to those with FA and CMT are to be made, further research is required into effective management strategies in these populations. Due to the deficits in temporal synchrony in ANSD, traditional hearing aid amplification is usually not effective (Zeng et al., 1999; Rance et al., 2002). Kumar and Jayaram have shown that speech perception in ANSD is improved when timing cues are enhanced (2013), which shows promise as a potential hearing aid signal processing strategy in the future. Rance et al. (2010) found that FM systems were an effective tool in improving SNR of speech and overall speech perception ability in those with FA. Assessment of FM systems in those with CMT would be beneficial, along with clinical recommendations for fitting FM systems for those with FA and CMT in the future if they prove to be the best tool available currently for those with ANSD with good audition alongside poor speech perception.

*Infants*

Further research into CAEPs and speech in early infancy would allow definitive clinical protocols to be written. A larger-scale, longitudinal study into the ability of CAEPs in early infancy to predict degree of hearing impairment, along with optimisation of CAEP

recording parameters, and clarity in interpretation would give the paediatric audiology team and families vital information to use in the management of infants with ANSD. This would have a strong impact on the potential for effective early intervention, key to speech and language and educational development.

An extended study into the effectiveness of the VRISD testing protocol in infants with ANSD, and a comparison to a control group with SNHL, in a clinical setting would determine the efficacy of this assessment method with the complex population of those with ANSD. Again, the opportunity to test on a large sample size and optimise study stimuli would be beneficial and suggest the potential to use this tool clinically to provide much needed information on functional auditory ability in infants with ANSD.

Further to the results presented in chapter 6, an extension of the study into recording CAEPs in different sleep-wake states in infants is required to confirm findings prior to potential clinical adoption. Carrying out this research using a clinical auditory evoked potential system would add value and replicability for the clinician. In addition, use of just the behavioural section of the sleep-state checklist used in this study (see Table 6.1) would allow the researchers to verify that the REM sleep state can be easily identified from behavioural observation alone. Furthermore, assessment of infants of a variety of age groups, to find the point at which CAEPs can no longer be reliably recorded in sleeping infants, would be a key part of the information required prior to creation of clinical protocol recommendations.

**Conclusions**

CAEPs have previously been shown to be a promising method of objective assessment in ANSD, but this was not replicated here amongst adults with the ANSD-like hearing impairment of FA and CMT, or in infants with ANSD. CAEP response presence looked promising in terms of a potential relationship to speech perception in a pilot study, but a relationship was not shown in a second, larger study. Speech perception and gap detection are not significantly different in those with FA and CMT, despite the differing underlying aetiopathologies. Both groups have impaired speech perception, in quiet and in the presence of background noise, and have impaired temporal processing abilities as measured with gap-detection thresholds despite normal hearing thresholds. Where PTA

thresholds are within normal limits, this is not an indication of auditory ability, as auditory thresholds are not correlated with speech perception and temporal processing ability in these populations.

In infants with ANSD, there was no clear or consistent relationship between CAEP presence and speech discrimination. The behavioural VRISD, however, holds promise as a useful assessment of speech discrimination in infancy, providing information on ANSD severity, which the VRA does not provide. A robust objective prognostic tool for infants diagnosed with ANSD is still required. If an optimised CAEP protocol is shown to relate to speech discrimination in the future, the finding that CAEP assessment can be conducted during REM sleep in very young infants (<4 months) should aid clinical uptake, although this finding should be treated with caution as the sample size was low. Further research with larger samples is required to find an ANSD testing protocol in order to provide information during the first year of life where current prognostic ability is very limited.

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