AUDITORY EVOKED ELECTROPHYSIOLOGICAL MEASURES AS BIOMARKERS FOR NEURODEVELOPMENTAL COMMUNICATION DISORDERS

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<tr>
<td>ABR</td>
<td>Auditory Brainstem Response</td>
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<tr>
<td>ADHD</td>
<td>Attention-Deficit Hyperactivity Disorder</td>
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<td>ASD</td>
<td>Autism Spectrum Disorder</td>
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<tr>
<td>AM</td>
<td>Amplitude-Modulated</td>
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<td>ANSD</td>
<td>Auditory Neuropathy Spectrum Disorder</td>
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<td>CCT</td>
<td>Central Conduction Time</td>
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<td>CCC</td>
<td>Children’s Communication Checklist</td>
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<tr>
<td>DFT</td>
<td>Discrete Fourier Transform</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<tr>
<td>eSP</td>
<td>eScreener Plus</td>
</tr>
<tr>
<td>FFR</td>
<td>Frequency Following Response</td>
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<tr>
<td>$f_0$</td>
<td>Fundamental Frequency</td>
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<tr>
<td>OAE</td>
<td>Otoacoustic Emissions</td>
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<td>SLI</td>
<td>Specific Language Impairment</td>
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<td>TFS</td>
<td>Temporal Fine Structure</td>
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<td>MS</td>
<td>Multiple Sclerosis</td>
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<td>NHSP</td>
<td>Newborn Hearing Screening Programme</td>
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<tr>
<td>NICU</td>
<td>Neonatal Intensive Care Unit</td>
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<tr>
<td>PCHI</td>
<td>Permanent Congenital Hearing Impairment</td>
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<tr>
<td>SNRs</td>
<td>Signal-to-Noise Ratios</td>
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Abstract
The University of Manchester
Anna May Emily Terry
Doctor of Philosophy
Auditory Evoked Electrophysiological Measures as Biomarkers for Neurodevelopmental Communication Disorders
June 2016

Three studies were conducted to address gaps in knowledge pertaining to the use of auditory evoked electrophysiological measures as potential biomarkers for neurodevelopmental communication disorders. Some subjects with these disorders demonstrate auditory temporal processing deficits, which may have a basis in impaired myelin within the auditory brainstem. Given their sensitivity to such deficits and their feasibility for use with very young infants, electrophysiological measures make feasible candidates as biomarkers for these disorders. In particular, a subset of neonatal Intensive Care Unit graduates show a transient failure of the auditory brainstem response (ABR) at newborn hearing screening that may indicate an onset of impaired myelin. The study in Chapter Three was conducted to investigate the hypothesis that this transient failure may be associated with communication difficulties in later childhood. No association was found between this transient failure and communication ability. However, parental concern over general development of a child was found to be a potentially useful marker for children who demonstrated communication difficulties. Some subjects with neurodevelopmental communication disorders also show atypical frequency following responses (FFRs). The FFR is not currently used in a clinical setting, despite evidence that it may be more sensitive to auditory temporal processing deficits than the ABR. The results of the study in Chapter Four showed that group delay latency of the FFR, which represents where in the auditory brainstem the response is likely to be generated, occurs significantly later than latency of the click-evoked ABR wave V, which signals the offset of this response. These results indicate that the FFR may reflect auditory processing efficiency in separate structures of the auditory brainstem and therefore, provide more insight into temporal synchronicity than the ABR alone. However, the study in Chapter Five found that the FFR could not distinguish adults with a neurodevelopmental communication disorder from a control group. In contrast, adults with Autism Spectrum Disorder (ASD) could be distinguished from a control group by the wave III-V inter-peak latency of the click-evoked ABR. Prolongation of this inter-peak latency was also found in adults with a demyelinating disorder. These results suggest that the auditory temporal processing deficits in ASD may have a basis in impaired myelination that can be measured by inter-peak interval latency of the click-evoked ABR. However, a behavioural measure of speech-in-noise ability was found to be a more important predictor of the presence of a communication disorder than the wave III-V inter-peak latency. Overall, the findings of the studies in this thesis shed new light on the potential usefulness of auditory evoked electrophysiological measures as potential biomarkers for neurodevelopmental communication disorders.
Declaration

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Dedicated to my parents.

“Happiness is being the reason behind your parents’ smiles.”
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I must thank my most amazing circle of friends. They have always believed in me, pushed me and bolstered my self-belief. I want to thank my sister for always being there for me when things got really tough and for believing in me.

Most importantly, I want to thank my parents, without whom I would not have made it through the last four years. I want to thank my Dad for teaching me the meaning of hard work and perseverance and my Mum for always reminding me of my strengths and capabilities. Thank you.
Preface

The author of this thesis graduated from The University of Birmingham with a first class degree in Psychology in July 2009. After graduating, the author spent some time in Italy before taking up a part-time research assistant role at The University of Birmingham, analysing data for a study that explored visual extinction in stroke patients. This work resulted in a published paper for the author (Chechlacz *et al*., 2013 “Common and distinct neural mechanisms of visual and tactile extinction: A large scale VBM study in sub-acute stroke”) and presentation of the abstract at the 13th International Multi-Sensory Research Forum, Oxford University, in June 2012. The author has a keen interest in brain injury and rehabilitation and recently undertook a role as a volunteer assistant psychologist for the Salford Community Neuro-Rehabilitation Team. The author was attracted to pursuing a PhD at the University of Manchester by the opportunity to learn electrophysiology and deepen her knowledge of brain anatomy and functioning.
Chapter 1. Introduction

The screening of newborn babies for permanent congenital hearing impairment (PCHI) is currently implemented across the UK, with current prevalence in the general population reported at 1.64 per 1000 cases (Wood, Davis and Sutton, 2013). Newborn hearing screening was initially only targeted at neonates demonstrating at least one of the following three risk factors: a family history of PCHI, craniofacial abnormalities or having spent more than 48 hours in a neonatal Intensive Care Unit (NICU, Fortnum and Davis, 1997). However, from 2001 onwards, several hospitals began trialing the screening of all newborns and from 2006, the Newborn Hearing Screening Programme (NHSP) was implemented nationwide and now advocates the screening of all newborn infants for PCHI. In the well-baby ward, the screening protocol comprises only a transient-evoked otoacoustic emissions (OAE) test, used to assess outer hair cell integrity (Kemp, 1978). Protocol in the NICU requires measurement of the click-evoked auditory brainstem response (ABR) in addition to the transient-evoked OAE assessment.\(^1\) The ABR is an auditory evoked potential originating from the distal portion of the cochlear nerve and extending up to the inferior colliculus of the auditory brainstem (Jewett, 1970; Jewett and Williston, 1971). It produces a set of five distinct and clinically useful waveforms that can be recorded far-field using scalp electrodes. Automated ABR equipment is now used in most UK hospitals for screening purposes and provides one of three results: clear response, no clear response or inconclusive. If there is an inconclusive or no clear response in one or both ears then a referral for early audiological assessment is recommended. The addition of the automated ABR assessment to the NICU protocol is due to a higher risk of auditory neuropathy spectrum disorder (ANSD) amongst this population (Berg et al., 2005; Xoinis et al., 2007). ANSD is characterised by present OAEs but an abnormal or completely absent ABR, and

sites of lesion are believed to lie along the auditory pathway Starr et al., 1996; Berlin et al., 1998). Although individuals with ANSD can have profound hearing loss, others may have hearing thresholds within normal limits (Kraus, 2001). Despite this, they may still demonstrate little or even no understanding of speech especially in noisy environments (Starr et al., 1996; Doyle, Sininger and Starr, 1998; Rance et al., 2002, 2007) highlighting a relationship between efficiency of the ABR and communication ability.

There is a subset of infants screened in the NICU who show a transient form of ANSD by exhibiting a normal response on their OAE assessment but a no clear response or inconclusive result on their automated ABR assessment. These infants then go on to produce a normal response at their follow up appointment and in most cases are discharged from hospital and monitored only if risk factors for PCHI are present. In an evaluation of the data produced by the NHSP, it was found that 24% of newborns exhibiting normal OAEs but abnormal ABRs went on to demonstrate a normal ABR at their first diagnostic follow up appointment (Uus, 2004). Similar patterns have been found internationally. For example, Clemens, Davis and Bailey (2000) followed up infants in the first year of a hearing screening program in a women’s hospital in North Carolina and found that 80% who had failed an initial automated ABR assessment showed a normal ABR the following day. Psarommatis et al. (2006) retrospectively identified 25 infants from a cohort of 1,150 NICU graduates who demonstrated present OAEs but an absent ABR at initial screening. At a follow up around 6 months later, 60% of these infants who were re-examined showed a completely healthy ABR. In a later study, Psarommatis et al. (2011) replicated these findings reporting that 64% of 178 infants showed a similar pattern to those in their 2006 study, with 15% showing partial improvement. The question remains as to what pathology, if any, is behind this transient failure of the ABR. It has been reported in children after the raising of body temperature (Starr et al., 1998; Marlin et al., 2010) and in infants diagnosed with perinatal hypoxia-ischaemia (Jiang et al., 2007). Nevertheless, the pa-
thology behind this transient failure in the absence of such conditions remains little understood.

Starr et al. (1996) has suggested that failure of the ABR in ANSD is due to suppression of the response as a result of poor temporal synchronicity. In particular, a lack of temporal precision by auditory nerve fibres results in a poor signal-to-noise ratio as the short duration components of a response are cancelled in the averaging process, and cannot be distinguished from background noise.

They further suggest that the source of this poor synchronicity may be impaired myelin within the auditory nerve. Given that transient failure of the ABR could be looked upon as a transient form of ANSD, it too may be the result of a temporary poor signal-to-noise ratio. Myelination of the peripheral portion of the brainstem (waves I-III) by Schwann cells is believed to occur prior to myelination of the central portion (waves III-V) by oligodendrocytes (Moore, Perazzo and Braun, 1995, Moore and Linthicum, 2001). Therefore, a transient failure of the ABR could reflect the impact of delayed myelination that temporarily blocks conduction and generation of the later waves of this response. In support of this hypothesis, deficiency of myelin has been found to result in decreased or even blocked conduction of electrical impulses (Waxman, 1977; Inagaki et al., 1987; Rance, 2005). The ABR would then show recovery at diagnostic follow up due to adequate time for myelination to ‘catch up.’ Uus (2011) has suggested that this transient form of ANSD is not simply due to normal maturational delay. Rather, it is the result of a pathological neuromaturational delay that may include atypical myelination. Jiang (1995) has argued that because of the centripetal direction of the myelination process, a delay in myelination is more likely to affect central components of the ABR (waves III to V) than peripheral components (waves I to III). However, a delay in this timeline of myelination would still temporarily affect production of the ABR. Temporary poor signal-to-noise ratio in the auditory brainstem could result in degraded auditory stimulation during very early infancy. Tanguay and Edwards (1982) have postulated that early distortions in acoustic input could
act as a neuropathological agent and impact upon the development of neural connections within the auditory brainstem (see also Moore, 2002). Furthermore, there is evidence to suggest that electrical activity in neurons can mediate myelination of the central nervous system (Demerens et al., 1996) and that a lack of sensory input can reduce myelination (Li et al., 2011; Barrera et al., 2013). Therefore, if a transient failure of the ABR results in reduced neural activity, this may impact further myelination of the auditory brainstem and temporal synchronicity, the development of which is dependent on healthy myelination (Waxman, 1977; Rance, 2005; Kim, Renden and Gersdorff, 2013). This would mean that a transient failure of the ABR at newborn screening could potentially act as an early warning sign for poor temporal synchronicity within the auditory brainstem. Figure 1.1 summarises the proposed pathology that may result from a transient failure of the auditory brainstem.

The five waves produced by the click-evoked ABR are highly replicable to the point that timing delays of only a fraction of millisecond long can be clinically meaningful (Hood, 1998), and measurement of ABR latencies can provide insight into the temporal synchronicity of neural populations in the auditory brainstem. Indeed, the ability of the auditory system to encode temporal information accurately has been described as the hallmark of normal auditory perception (Sninger and Starr, 2001), and the proficient encoding of temporal information contained within an auditory stimulus is believed to be essential for both processing and understanding speech (Anderson et al., 2010; Golumbic, Poeppel and Schroeder, 2012). With this in mind, it is perhaps unsurprising that some studies have demonstrated that the temporal stretching of speech improves language ability in children with language disorders (Merzenich et al., 1996; Tallal et al., 1996). Temporal stretching involves prolonging the duration of a speech signal, whilst preserving its spectral content. In addition, enhancement of the fast transitional elements of the speech signal are thought to result in more reliable temporal integration and limit the impact of forward or backward masking (Tallal, 1996).
A subset of NICU infants show transient failure of the ABR at newborn hearing screening.

This transient failure may be the result of poor signal-to-noise ratio due to delayed myelination of the peripheral portion of the auditory brainstem.

Transient suppression of electrical activity may impact on further myelination and temporal synchronicity within the auditory brainstem.

Poor temporal synchronicity has been found in a subset of children and young adults with neurodevelopmental communication disorders.

Therefore, transient failure of ABR at newborn hearing screening may act as a useful biomarker for neurodevelopmental communication disorders.

**Figure 1.1:** Flowchart to illustrate the possible link between transient failure of the ABR at newborn hearing screening and neurodevelopmental communication disorders.

Atypical functionality of the auditory brainstem in the form of prolonged ABR central conduction time (CCT), absolute wave latencies and inter-peak intervals have all been previously reported in cases of Autism Spectrum Disorder (ASD, Rosenhall *et al.*, 2003; Fujikawa-Brooks *et al.*, 2010; Roth *et al.* 2011), Attention-Deficit Hyperactivity Disorder (ADHD, Puente *et al.*, 2002; Azzam and Hassan, 2010; Jafari, Malayeri and Rostami, 2015), dyslexia (Vandermoten *et al.*, 2010, 2011) and specific language impairment (SLI, Basu, Krishnan and Weber-Fox, 2009). According to the latest Diagnostic and Statistical Manual of Mental Disorders (DSM-V, American Psychiatric Association, 2013), these disorders are all classed under the same umbrella.
term of neurodevelopmental communication disorders, which also encompass other language disorders, including expressive and receptive language impairments and social pragmatic communication disorders. Given this link between auditory temporal processing deficits and neurodevelopmental communication disorders, transient failure of the ABR may act as a useful biomarker for such disorders. In keeping with this speculation, a study by Cohen et al. (2013) reported that 28% of a sample of 74 NICU graduates who showed this transient failure of the ABR had a diagnosis of ASD, in comparison to just 4% (one case) of NICU graduates who did not show this transient failure. The authors postulate that even though the ABR normalised in all cases, this transient failure could still reflect atypical brainstem development that impacts upon more rostral brainstem structures and projections, with variable severity. The results of this study suggest that functionality of the auditory brainstem, and transient failure of the ABR in particular, could act as a potentially useful biomarker for ASD. Infants in the Cohen et al. (2013) study who showed the transient failure of the ABR and were diagnosed with ASD, also showed an atypical preference for high rates of visual stimulation, meaning that a preference for stronger rates of visual stimulation were significantly associated with poorer scores on measures of social communication competence. This atypical preference was presumed to be the result of deficient brainstem functioning (Gardner and Karmel, 1995). In contrast, there was a subset of the sample who showed the transient failure of the ABR in addition to problems with both behavioural and mental development, but did not show the visual stimulation preference. The authors suggest that this subtle difference in developmental trajectory may result in these children being diagnosed with ADHD, which shares many characteristics of ASD. Therefore, if transient failure of the ABR indicates risk of poor temporal synchronicity which is found in a subset of children and young adults with a range of neurodevelopmental communication disorders, then it may prove useful as a biomarker for this subset in particular. Given that this transient failure is detectable through the NHSP, it makes sense to at least explore whether the NHSP could provide an opportunity to flag infants at risk
of developing neurodevelopmental communication disorders in later childhood.

If the detection of early auditory temporal processing deficits presents an opportunity to flag infants at risk of neurodevelopmental communication disorders, then another auditory-evoked electrophysiological measure that may present as a potentially useful biomarker is the frequency following response (FFR). The FFR is also a measure of auditory brainstem processing, which reflects the activity of phase-locked neurons and represents temporal encoding of complex stimuli (Rose et al., 1967; Gardi, Merzenich and McKean, 1979). The FFR is believed to originate around the auditory midbrain lateral lemniscus (Galbraith, 1994) and inferior colliculus (Stillman, Moushegian and Rupert, 1976; Glaser et al., 1976; Daly, Roeser and Moushegian, 1976), although its neural correlates are still not as established as those of the click-evoked ABR. FFR deficits have been reported in neurodevelopmental communication disorders such as ASD (Russo et al., 2008, 2009), dyslexia (McAnally and Stein, 1996), ADHD (Jafari, Malayeri and Rostami, 2015) and SLI (Basu, Krishnan, Weber-Fox, 2009). Furthermore, a number of studies have found FFR deficits in children with neurodevelopmental communication disorders, despite the same sample of children having normal click-evoked ABRs (King et al. 2002; Song et al., 2006; Russo et al., 2008, 2009). If the auditory temporal processing deficits found in a subset of children and young adults with neurodevelopmental communication disorders have a biological basis in impaired myelination, then the click-evoked ABR may not be sensitive enough to problems in separate structures of the auditory brainstem or separate neural populations that respond to more complex stimuli. This suggests that the FFR may be a potentially useful biomarker for neurodevelopmental communication disorders in addition to the click-evoked ABR.

Use of auditory-evoked electrophysiological measures to identify infants at risk of developing a neurodevelopmental communication disorder would have numerous clinical applications and benefits. Firstly, electrophysiological measures can be carried out on much
younger infants than behavioural measures and may therefore facilitate much earlier identification. Early identification is essential to minimise the impact of these disorders, such as poor academic performance (Aram, Ekelman and Nation, 1984; Beitchman et al., 1996; Johnson, Beitchman and Brownlie, 2010). In turn, earlier identification should facilitate earlier intervention. Early intervention has been found to be effective in minimising the impact of temporal processing deficiencies (Hayes et al., 2003), and behavioural training has proven beneficial in the case of neurodevelopmental communication disorders such as ASD (Birnbrauer and Leach, 1993; Smith, Groen and Wynne, 2002; Green, Brennan and Fein, 2002). The click-evoked ABR is already collected through the NHSP and therefore presents a simple and cost-effective opportunity to assess temporal resolution in the auditory brainstem of infants. Amin et al. (2014) have highlighted that although the click-evoked ABR gives insight into the progress of myelination, links with global neurodevelopment are not well studied. In light of the above, the first aim of this thesis was to explore whether transient failure of the click-evoked ABR is associated with communication difficulties in later childhood. Given that the FFR could be more sensitive to auditory temporal processing deficits in subjects with neurodevelopmental communication disorders than the click-evoked ABR (King et al. 2002; Song et al., 2006; Russo et al., 2008, 2009), the second aim of this thesis was to address gaps in knowledge pertaining to the clinical feasibility of the FFR as a potential biomarker for neurodevelopmental communication disorders.
Chapter 2. Literature Review

2.1 The Newborn Hearing Screening Programme

Since being launched and implemented in the UK, the Newborn Hearing Screening Programme (NHSP) has more than doubled the number of cases of permanent congenital hearing impairment (PCHI) that are identified before a child reaches 9 months of age (Kennedy et al., 2005) and has improved outcomes for these children in a number of areas (Newton, 2013; Pimperton et al., 2014). The NHSP has also vastly improved on the health visitor distraction test that was administered at around 7-8 months of age, by considerably reducing the average age of identification of PCHI from 22 months (Fortnum and Davis, 1997) to 10 weeks (Uus and Bamford, 2006). The Wessex Trial (1998) was conducted on the benefits of the NHSP over behavioural screening. The trial monitored all infants born in four participating hospitals between October 1993 and 1996 who underwent neonatal screening or behavioural screening only, depending on their birth date. It was found that neonatal screening was able to yield significantly more confirmed cases of PCHI than the health visitor distraction test. In particular, the number of infants able to receive referral before the age of 6 months was 19 times higher for those receiving screening than those who underwent behavioural health visitor testing only. Bamford, Ankjell and Crockett (2004) concluded that the first phase of the NHSP was a success, with high coverage and uptake rates, good cost effectiveness and a positive impact on interagency relations. A more recent study by Wood et al. (2015) assessed performance of the NSHP using a large cohort of children screened between April 2004 and March 2013. The study concluded that the NHSP has continued to improve over time including improvements in coverage and an overall reduction in referral times for hearing aid fitting.

It has been claimed that the ability of the NHSP to facilitate earlier identification of PCHI has had a positive impact on speech and language outcomes for this population of children. Yoshinaga-Itano, Coulter and Thomson (2000) found that hospital based newborn hear-
ing screening was positively correlated with speech and language performance in children due to the ability of the screen to identify hearing problems at an earlier stage. A recent review by Pimperton and Kennedy (2012) concluded that newborn hearing screening and early identification of PCHI consistently led to beneficial effects on speech and language development. However, this claim is not conclusive. For example, Kennedy et al. (2006) evaluated the language outcomes of 120 children at age eight, finding that although receptive language scores were higher for those children identified using newborn screening, there was no significant difference between these children and children identified using traditional methods on measures of expressive language ability and speech production. Furthermore, studies by Wake et al. (2005) and Korver et al. (2010) failed to find any significant difference between children diagnosed with PCHI either through the screen or the health visitor distraction test, on several measures of communication development.

At first glance, these studies may suggest that the early identification provided by the NHSP is not advantageous for future language outcomes. However, on closer inspection it can be found that although the children who underwent neonatal screening were identified earlier, they did not necessarily benefit from earlier intervention than children identified through traditional behavioural assessment. If not treated early enough, PCHI can have detrimental effects on a wide range of areas including language development, family functioning, literacy, academic achievement, social–emotional well-being and employment (Moeller, 2000; Yoshinaga-Itano, 2003; Kennedy et al., 2006). In the Wake et al. (2005) study, the average age of hearing aid fitting was 23.2 months and in the Korver et al. (2010) study it was 15.7 months. This highlights that early identification may be fruitless without the addition of early intervention. It is therefore promising that the review by Wood et al. (2015) found that in the majority of cases both identification of PCHI and management occurred within the 6 month period, although it was noted that there was room for improvement.
However, an Australian study by Ching et al. (2013a) found that children who were fitted with a hearing aid at a median age of 3.3 months had global language performance just one standard deviation below the mean of normally hearing children. This result suggests that this early management had a positive impact upon future speech and language development. In contrast, Ching et al. (2013b) found that the effect of age of hearing aid fitting had a small impact on language outcomes. Furthermore, the study identified five factors that were associated with better global language outcomes for children including better maternal education, less severe hearing loss, an absence of additional disabilities, earlier cochlear implant switch on and being female. This suggests that there may be many variables that influence language outcomes for children with PCHI rather than just age of hearing aid fitting.

Despite the many merits of the NHSP, it is not without its limitations. Paradise (1999) has warned that false-positive results that may be caused by transient conductive problems on the day of testing could have a negative effect on parent-child relationships. Paradise (1999) has claimed that rates of false-positive results in well-baby populations can exceed 90% and has highlighted the issue as a key clinical limitation that can create unwanted outcomes such as unnecessary parental anxiety and the false labelling of normally hearing infants as hearing impaired. Clemens, Davis and Bailey (2000) reported a particularly high false-positive rate in their study following infants in the first year of a hearing screening program in a women’s hospital in North Carolina. They found that 80% of infants who had failed an initial automated auditory brainstem response (ABR) went on to pass the following day. In the neonatal Intensive Care Unit (NICU), babies receive assessment of both their otoacoustic emissions (OAE) and ABR due to a higher incidence of Auditory Neuropathy Spectrum Disorder (ANSD). However Clemens, Davis and Bailey (2000) also found that although around 80% of mothers reported feeling anxious that their child had been asked to attend a follow up appointment, 91% claimed to have not treated their child any differently until hearing
impairment was actually confirmed. Furthermore, 94% of respondents regardless of whether they had felt anxiety or not, had been thankful that such a test was available.

New techniques and two-stage screening procedures appear to have lowered the number of false-positive results. For example, Mason and Herrmann (1998) found a 3.5% false-positive rate after initial automated ABR testing that was reduced to 0.2% after a second round of testing. In a follow up study by Clemens and Davis (2001), it was found that systematic re-testing of the ABR 12 to 24 hours after initial testing reduced the false positive rate from 3.9% to 0.8%. The Wessex Trial (1998) found that neonatal screening yielded a lower rate of false-positive results than the previously used health visitor distraction test. This suggests that although it is still an issue within hearing screening, false-positive levels have at the very least been improved upon with the introduction of the NHSP.

Overall, the evidence suggests that the potentially negative effects of false-positive results and parental anxiety during the referral process may be outweighed by the peace of mind a hearing screening provides for parents and guardians. However, as touched upon in Chapter One, one alternative explanation for false-positive results in the NICU is a transient failure of the ABR caused by a delay in myelination. Research has shown that the central pathway of the auditory brainstem matures later than the peripheral pathway (Moore, Perazzo and Braun, 1995, Moore and Linthicum, 2001). Therefore, an onset delay in myelination would affect transmission of neural signals from peripheral through to central generators of the ABR. Once the ABR is retested, myelination may have had time to ‘catch up’ and reach structures such as the inferior colliculus, which is thought to generate the offset wave of the click-evoked ABR (Starr, 1976).

There are explanations for a transient failure of the ABR that are completely unrelated to myelination of the auditory brainstem. For example, it could also be argued that this particular pattern of screening results may be due to poor testing conditions. The environment may have been noisy during testing or the infant may have been rest-
less, causing myogenic interference (Suppiej et al., 2007). The NICU can be a noisy and frantic environment. Indeed, Mason and Hermann (1998) found that when neonates were assessed in a quiet nursery rather than the NICU, there was a reduction in the number of referral cases. However, a study into the ease of use of three different automated ABR machines found that time needed for use ranged from just 4-8 minutes (Meier et al., 2004). Given that newborn babies tend to sleep the majority of the time, it is unlikely that restlessness will be a common issue, especially when testing time is so low.

Another potential cause of a transitory failure of the ABR is hyperbilirubinemia (Jiang and Chen, 2014). Hyperbilirubinemia is an elevation of serum bilirubin concentration and causes a yellow discolouration of the skin and eyes. Perlman et al. (1983) reported prolonged ABR latencies in neonates with hyperbilirubinemia that rapidly reversed in the majority of cases. Impairment of the ABR that shows recovery has been reported in neonates with anoxia (Jiang et al., 2004) and iron deficiency (Roncagliolo et al., 1998). As most ABRs are assessed using a pre-designated template on an automated machine, latency prolongations may result in a no clear response outcome. Once the neonate recovers from the medical condition, the ABR may return to normal. However, Berg et al. (2005) found that neonates that demonstrated a transitory failure of the ABR could not be differentiated from babies who passed both OAE and ABR assessments on such factors as gestational age, presence of hyperbilirubinemia, low birth weight or anoxia. Although the researchers did not follow up on these infants, it is possible that a myelination delay within the auditory brainstem could have accounted for the difference between groups. de Hoog et al. (2003) found that serum concentrations of vancomycin, tobramycin and furosemide that were above the therapeutic range could not account for failure of the ABR at newborn screening, suggesting that high doses of antibiotic cannot account for why these infants are failing initially and then recovering at a later date. Furthermore, Roncagliolo et al. (1998) suggest altered myelination as an underlying causal factor in their results.
Another alternative explanation for an initial ABR fail could be middle ear problems. Maruthy and Mannarukrishnaiah (2008) found that early-onset otitis media significantly increased wave I-V latency of the ABR, with the effect disappearing after a maximum of 3 months. However, Doyle et al. (2000) found that neither decreased tympanic membrane mobility nor occlusion of the ear canal had an effect on the pass rate of the automated ABR assessment at newborn hearing screening, suggesting that these variables may not be to blame and that in fact the issue may be neurological. Indeed, Roberts et al. (1982) found that from their cohort of 75 NICU infants who failed their ABR screen, only one went on to be diagnosed with a severe hearing loss. They concluded that the initial ABR failure resulted from delayed myelination of the auditory brainstem. Harbord et al. (1990) found that failure of ABR components after wave I was associated with abnormal myelination in developmentally delayed children, although there was no control for hearing loss.

Starr et al. (1996) have suggested that failure of the ABR in ANSD results from a lack of temporal precision by auditory nerve fibres. In turn this causes a poor signal-to-noise ratio as the response is cancelled in the averaging process and cannot be distinguished from background noise. ANSD is characterised by present OAE but an absent or disordered ABR. Furthermore, they suggest that this poor temporal synchronicity is the result of impaired myelination of the auditory nerve, which impacts upon afferent nerve impulses. Given that transient failure of the ABR could be looked upon as a transient from of ANSD, this phenomenon may also reflect temporary suppression of the response and provide an early warning sign for atypical neurodevelopment of the auditory brainstem. Whilst it is important to note that other factors in neurodevelopment such as axonal and synaptic pathologies may impact upon neural transmission through the auditory brainstem (Starr et al., 1996), transmission velocity tends to be more affected by impaired myelin than axonal impairment (Rapin and Gravel, 2013).
Cohen et al. (2013) followed the outcomes of 74 children who had demonstrated a transient failure of their screening ABR during their time in the NICU. The ABR was collected as an indicator of neural conduction within the auditory brainstem. At an average age of 3.5 years, the child’s mother completed a Pervasive Developmental Disorders Behavior Inventory (Cohen and Sudhalter, 2005) to assess for the presence of Autism Spectrum Disorder (ASD). During follow up of the 74 infants, 14 were found to have a diagnosis of ASD and 93% of these cases were found to have had abnormal ABRs at initial screening. In particular, all but one infant who showed an abnormal ABR demonstrated a normal response before discharge from the hospital. The authors concluded that being in the abnormal ABR group increased risk of developing ASD in later childhood. Moreover, infants who showed this transient failure of the ABR tended to have mild to no evidence of structural insult within the brainstem. Children with ASD also showed poor regulation of attention, leading the authors to suggest that multiple markers of disorder within the brainstem are likely to detect ASD. Furthermore, gestational age was not an influencing factor, with full-term infants showing temporary failure of the ABR in addition to premature infants. This suggests that the transient failure was not a maturational issue, rather, it may indicate atypical auditory brainstem development. This supports the suggestion of Uus (2011). Cohen et al. (2013) speculate that such atypical development is likely to vary in severity and its impact on development of the auditory brainstem. In keeping with this speculation, some researchers have suggested that the auditory temporal processing deficits seen in children with neurodevelopmental communication disorders may have a basis in delayed myelination (McClelland et al., 1992; Fujikawa-Brooks et al., 2010; Basu, Krishnan and Weber-Fox, 2009). This draws a link between myelination of the auditory brainstem and subsequent communication development. Therefore, electrophysiological data collected through the NHSP may offer a new opportunity to enhance its clinical contribution to the early identification and intervention of children at risk of neurodevelopmental communication disorders.
The myelination hypothesis is discussed in more detail in the following section.

2.2 Myelination of the Auditory Brainstem

Maturation of the click-evoked ABR is relatively well understood. Inter-peak intervals and overall central conduction time (CCT) shorten, and waveform definition becomes clearer as childhood progresses (Salamy and McKean, 1976; Starr et al., 1977). Basic structures of the auditory brainstem pathway are identifiable from 8 weeks gestational age (Cooper, 1948). Between the third trimester of pregnancy and 6 months postnatal age there is a rapid increase in myelin density to the point that it is adult-like by 12 months postnatal age (Inagaki et al., 1987; Moore, Perazzo and Braun, 1995). The myelination of neurons allows for rapid transmission and synchronisation of neural impulses, and has been shown to be an essential component for the onset of a recordable ABR (Inagaki et al., 1987). In keeping with this physiological timeline, the maturity of basic auditory functions such as the perceptual detection of temporal, frequency and intensity elements is reached by around 6-12 months of age (Trehub, Schneider and Henderson, 1995; Werner, 1996), with more complex functions continuing to develop well into late childhood. The peripheral auditory system, responsible for generating waves I-II of the click-evoked ABR, is myelinated by Schwann cells, whilst the central auditory system responsible for generating waves III-V, is myelinated by oligodendrocytes (Rapin and Gravel, 2003). Figure 2.1 illustrates the anatomy of the ascending auditory pathway.

It has been postulated that the auditory temporal processing deficits found in children with neurodevelopmental communication disorders may be the result of delayed myelination within the brainstem. For example, in a study by McClelland et al. (1992), it was found that autistic children did not show the normal shortening of the ABR CCT with increasing age that typically developing children demonstrate, leading the authors to suggest that this may be due to a defect in
myelination of the brainstem. Fujikawa-Brooks et al. (2010) concluded that as all children with ASD in their study had normal hearing, prolongation was likely due to abnormalities in brainstem myelination, axon diameter or synaptic efficiency. Basu, Krishnan and Weber-Fox (2009) have suggested that a delay in myelination could be used to explain their findings of poor phase locking and prolongation of absolute latency of ABR waves III and V with increased click repetition rate in children with Specific Language Impairment (SLI). In particular, they postulate that such results reflect a neural conduction delay as a consequence of impaired myelination, drawing on evidence that the same exaggerated prolongation has been found in patients with a confirmed demyelinating disorder (Jacobsen, Murray and Deppe, 1987).

Figure 2.1: The ascending auditory pathway in humans (Cope, Baguley and Griffiths, 2015).
As touched upon in Chapter One, a delay in the onset of myelination of the auditory brainstem may result in a period of degraded auditory input and poor signal-to-noise ratio. There is now a growing body of evidence suggesting that early auditory deprivation can have a negative impact upon development of auditory cortical pathways (Ponton et al., 2000; Ponton and Eggermont, 2001).

Animal studies have found that auditory deprivation can have a profound effect on neural development, with the deprived brainstem showing irregularities in processing external acoustic stimuli, disordered connectivity and poor frequency and temporal processing (Clopton and Winfield, 1976; Silverman and Clopton, 1977; Knudsen, 1998; Yu et al., 2007). Although these are animal studies, it still raises the possibility that similar processes are at work in the human developing brain. Demerens et al. (1996) have reported evidence to suggest that electrical activity in neurons can mediate myelination of the central nervous system. In the visual system of animals raised in the dark, myelination may not even occur due to a lack of electrical activity from neurons. Therefore, an early delay in myelination may have a detrimental impact on further myelination and subsequently, temporal synchronicity. Unmyelinated neurons have been found to have reduced transmission velocity covering as little as 1 meter per second as opposed to between 25-120 meters per second seen in myelinated neurons (Hess, 1997). This is thought to be the result of increased internodal conduction times (Raminsky and Sears, 1972) and conduction velocity has been found to be dependent on myelin thickness (Waxman, 1980). Indeed, impaired myelination is thought to affect production of the ABR. For example, faster presentation rates (> 30/sec) have consistently been shown to result in a prolongation of waves III and V of the ABR and it has been hypothesised that this is likely due to delayed neural transmission caused by impaired myelination (Jiang, Brozi and Wilkinson, 1998; Basu, Krishnan and Weber-Fox, 2010). This same effect of presentation rate has also been found in subjects with demyelinating disorders (Jacobsen, Murray and Deppe 1987).
The myelination hypothesis may even account for the finding that only a subset of children and young adults with neurodevelopmental communication disorders are found to have auditory temporal processing deficits. In particular, Steinbrink et al. (2013) suggest that although recordable deficits in temporal processing may minimise over time, the effect of these early deficits will leave its mark outwardly expressed as dyslexia. Therefore, the degree to which delayed myelination impacts upon neurodevelopment of the auditory brainstem may account for why auditory temporal processing deficits are still present in some subjects but not others. Roncagliolo et al. (1998) found delayed myelination within the auditory brainstem of infants with iron deficiency anemia. Although these infants began to show a decrease in CCT after receiving iron therapy, this decrease did not keep up or catch up with the decrease seen in a control group. These results suggest that early delays in myelination may have a lasting and irreversible effect on the development of temporal synchronicity within the auditory brainstem. Therefore, it is possible then that these early auditory temporal processing deficits as a result of delayed myelination could have a permanent effect on the development of the auditory system of a child.

Galbraith et al. (2004) have postulated that exposure to the phonemes and prosody of speech, which can begin even before birth, may evoke a preferential processing of familiar sounds. Furthermore, Hornickel and Kraus (2013) have hypothesised that stable neural representation of the physical properties of our acoustic environment is essential in being able to map sounds to meaning and in the development of communication. Therefore, poor temporal synchronicity during very early infancy may impact upon these neural representation processes and subsequently impact communication development. Children who are born prematurely have been found to be at greater risk of developing a neurodevelopmental communication disorder (Luoma et al., 2008; Barre et al. 2011). As the auditory system of premature babies is unlikely to have fully developed at the point of their early exposure to the outside environment, they may be less like-
ly to appropriately process incoming acoustic stimuli. Zeng et al. (2005) have suggested that impaired myelination may in part contribute to the problems those patients with ANSD experience in understanding speech. Although some subjects diagnosed with ANSD have hearing thresholds within normal limits (Kraus, 2001), they may still demonstrate little or even no understanding of speech, especially in noisy environments (Starr et al., 1996; Doyle, Sininger and Starr, 1998; Rance et al., 2002; Rance et al., 2007). It has been found that the development of the ability to accurately perceive speech-in-noise continues to develop up until around 11 years of age (Stuart, 2005). Therefore, early auditory temporal processing deficits could result in poor speech-in-noise detection abilities. Indeed, many subjects with neurodevelopmental communication disorders demonstrate a speech-in-noise difficulty, which is highlighted in Section 2.3.5 of this chapter.

Amin et al. (2014) carried out a prospective and longitudinal study, gathering evidence from 80 premature infants on the relationship between auditory brainstem myelination at 35 weeks premenstrual age and language ability at the later developmental stage of 3 years corrected age. The authors focused on the click-evoked ABR CCT as a measurement of myelination functionality. Potential confounds such as middle ear disease and outer-hair cell damage were controlled for. When the children were of 3 years corrected age, the Preschool Language Scale 4 (Zimmerman, Steiner and Pond, 2002) was used to assess both expressive and receptive language. The results showed that CCT was significantly associated with later language ability. In particular, a one unit increase in the click-evoked ABR CCT was associated with a 5.4-5.5 score decrease on receptive language scales and a 5.6-6.4 decrease on expressive language scales. One weakness to note within the study is that the Preschool Language Scale 4 represents only a limited snapshot of a child’s language ability. Nevertheless, the study can demonstrate that delayed myelination along the auditory pathway (as measured by a prolonged CCT) is associated with a higher incidence of expressive and receptive language that are known to be
deficient in neurodevelopmental communication disorders such as ASD (Kwok et al., 2015), dyslexia (Torppa et al., 2010) and Attention-Deficit Hyperactivity Disorder (ADHD) (Humphries et al., 1994). Taken together, the evidence discussed in this section suggests that impaired myelination may impact upon temporal processing ability and may subsequently lay a foundation for the development of neurodevelopmental communication disorders. Transient failure of the ABR may provide insight into atypical development of temporal synchronicity and provide an opportunity to monitor the development of at risk infants. Indeed, auditory temporal processing deficits have been repeatedly found in subjects with neurodevelopmental communication disorders.

2.3 Auditory Processing Deficits in Neurodevelopmental Communication Disorders

The following section will focus on the role of accurate temporal processing in communication ability in addition to evidence of auditory temporal processing deficits in subjects with neurodevelopmental communication disorders. There have been two auditory evoked electrophysiological measures that have commonly been used to explore auditory temporal processing in subjects with neurodevelopmental communication disorders: the click-evoked auditory ABR and the frequency following response (FFR). The click-evoked ABR is widely used in both clinical and research settings to assess temporal synchronicity within the auditory brainstem. Click stimuli evoke five transient yet highly replicable wave peaks across a 10 ms time window and even the minutest of timing delays can be of clinical significance (Hood, 1998). Wave I is believed to originate from the cochlear nerve, wave II from the cochlear nucleus, wave III from the superior olivary complex, wave IV from the lateral lemniscus and wave V from the inferior colliculus (Lev and Sohmer, 1972; Starr, 1976). The FFR is a sustained auditory-evoked potential elicited by more complex acoustic stimuli and reflects the activity of phase-locked neurons
(Gardi, Merzenich and McKean, 1979), which are believed to represent temporal encoding at the brainstem level (Levi, Folsom and Dobie, 1995). When evoked by complex stimuli the FFR accurately mimics a stimulus’ temporal characteristics to the point that when presented to naïve listeners, it is perceived as intelligible speech (Galbraith et al. 1995). For complex sounds such as speech, the FFR is strongly driven by the envelope of the stimulus waveform, reflecting the fundamental frequency ($f_0$) of the stimulus. The FFR also reflects phase locking to the temporal fine structure (TFS) of a stimulus (Ai-ken and Picton, 2008; Chandrasekaran and Kraus, 2010). These two components convey important temporal information, with the envelope reflecting the slow variations in amplitude over time and the TFS reflecting the fast variations.

Our ability to perceive and efficiently process these rapidly changing temporal cues of a speech signal is essential for successful communication development (Johnson, Nicol and Kraus, 2005; Russo et al., 2008; Rocha-Muniz, Befi-Lopes and Schochat, 2012). Speech sounds contain both linguistic and paralinguistic information that must be processed by a listener with exquisite accuracy (Johnson, Nicol and Kraus, 2005). Linguistic information refers to the phonetic message of a signal, whereas paralinguistic information is the emotional element of speech, for example, is the speaker happy or angry. The auditory system must have high temporal resolution to process the temporal elements of a speech signal meaning that both linguistic and paralinguistic information could be disrupted by poor temporal processing at the brainstem level. It remains unclear as to whether envelope and TFS cues play a separate or complimentary role in the processing and comprehension of speech. Both envelope cues (Shannon et al., 1995; Loizou, Dorman and Tu, 1999; Smith, Delgutte and Oxenham, 2002) and TFS cues (Gilbert and Lorenzi, 2006; Lorenzi et al., 2006) have been found to result in good speech identification scores when presented alone. An impaired ability to process the envelope cue of a speech signal has been linked to a difficulty in understanding speech in noisy environments (Houtgast and Steenhen, 1985), although this
link is controversial (Narne and Vanaja, 2009). More recent evidence suggests that TFS cues may be essential for understanding speech-in-noise (Hopkins and Moore, 2009), and it appears as though the processing of TFS and envelope cues may serve different real-life purposes. However, efficient and accurate processing of both these cues appears essential for understanding speech and effective communication (Rosen, 1992).

Evidence that temporal processing in the auditory brainstem is important for communication also comes from subjects diagnosed with auditory neuropathy spectrum disorder (ANSD). These subjects demonstrate a disordered or absent ABR, believed to reflect damaged temporal processing mechanisms, which has a detrimental effect on speech comprehension in this patient group (Zeng et al., 1999). Both Zeng et al. (1999) and Rance, McKay and Grayden (2004) studied patients with ANSD and observed a strong correlation between speech perception and an individual’s ability to detect temporal modulations in a signal. Narne and Vanaja (2009) found that the temporal smearing of stimuli could mimic the perceptual deficits of individuals with ANSD in a normally hearing sample. Furthermore, enhancing the envelope of a speech signal significantly improved speech identification scores amongst a sample of individuals with mild to moderate ANSD. These results support the argument that accurate encoding of the temporal cues of a signal is important for understanding speech (Kraus et al., 2000). Given that accurate temporal processing is important for understanding speech, it is perhaps unsurprising that auditory temporal processing deficits have been found in subjects diagnosed with neurodevelopmental communication disorders.

2.3.1 Auditory Processing Deficits in ASD

The majority of research into potential links between auditory temporal processing deficits and neurodevelopmental communication disorders has focused on children with ASD, which is characterised by difficulties communicating and stereotypical behaviour patterns (Kanner, 1943; Kanner and Eisenberg, 1956; Wing and Gould, 1979). Re-
cent global prevalence estimates report 62 cases per 10,000 (Elsabbagh et al., 2012), a rise from just a few years previously that stood at around 20 cases in every 10,000 (Fombonne, 2009). ASD is a spectrum disorder meaning that there is variation in both severity and the degree to which the disorder affects a person’s everyday life. Some cases of ASD may be coupled with severe learning difficulties and result in the need for lifelong support. At the other end of the spectrum are cases of Asperger’s syndrome (Wing, 1981), where people are able to function at a high level during everyday life. Atypical reactions to auditory stimuli in subjects on the autistic spectrum are well documented and include both hyperacusis (Bonnel et al., 2003; Khalfa et al., 2004) and under-sensitivity, especially to speech sounds (Klin, 1991; Dawson et al., 1998). Indeed, Wing (1996) has commented that many children who are eventually diagnosed with ASD are often thought to be deaf because of their lack of appropriate reactivity to sounds. Such is the abundance of evidence that points to atypical responses to auditory stimuli in ASD, that the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V, American Psychiatric Association, 2013) now includes atypical responses to auditory stimuli as a mandatory component in its diagnostic criteria. It has been proposed that the failure of subjects with ASD to attach importance to certain sounds is sensory in nature and in fact reflects difficulty processing auditory stimuli (Tecchio et al., 2003; Kern et al., 2006; Tomchek and Dunn, 2007), which could be the result of distorted neural firing in the auditory brainstem. Student and Sohmer (1978) have suggested that such abnormal firing may cause a distorted view of the world, which may subsequently present itself clinically as autism.

Early studies began to indicate some degree of temporal processing deficit within the auditory brainstem of subjects diagnosed with ASD in the form of latency prolongation. Absolute and interpeak intervals provide a useful reflection of temporal processing within the auditory brainstem by reflecting the synchronous activity of neurons in response to acoustic stimuli. Using click stimuli presented at a rate of 10 clicks per second, Rosenblum et al. (1980) reported a
significantly increased wave I-V inter-peak interval in their autistic participants compared to a control group, in addition to significantly longer absolute latencies of waves III and V. This indicated that the delay was likely the result of poor synchrony in the central portion of the auditory brainstem. Their findings were later replicated by Gillberg, Rosenhall and Johansson (1983) and McClelland et al. (1992) who also found that their autistic participants had a significantly longer CCT than normal controls in response to click stimuli.

However, there were a number of key methodological issues with these early studies. To begin with, there was a failure to control for hearing impairment. Both conductive and sensorineural hearing loss have been found to affect absolute wave latencies of the ABR (Fria and Sabo, 1980), although inter-peak intervals appear to be unaffected by sensorineural hearing loss (Fabiani et al., 1979; Rosenhamer, Lindstrom and Lundberg, 1981). Incidence of hearing impairment in autistic subjects has been found to be higher than in normal populations (Rosenhall et al., 1999). Therefore, any prolongation in absolute wave latencies found in autistic participants in these earlier studies may in fact have been due to sensorineural hearing loss rather than neurological abnormality within the auditory brainstem. Secondly, there does not seem to have been enough control over neurological comorbidities. For example, Gillberg, Rosenhall and Johansson (1983) included three participants with epilepsy, one of whom had also been diagnosed with neurofibromatosis. It would therefore be extremely difficult to determine if atypical ABRs were associated with the participants’ autism or other neurological problems.

More recent studies have been able to improve somewhat on some of the earlier methodological issues. Maziade et al. (2000) used a larger sample size, assessing the click-evoked ABR in 73 autistic children, their relatives and matched controls. In comparison to controls the autistic sample had a significantly prolonged wave I-III inter-peak interval. However, this increase in latency was also found in their first degree, non-autistic relatives. As an abnormal ABR appears not to be unique to the autistic participants, the authors suggest that the results are perhaps indicative of an environmental or genetic inter-
action with a neurological abnormality that may or may not then be expressed outwardly as autism. However, this study also failed to provide details about the hearing status of participants and although they excluded those with a completely absent ABR, this does not control for the effects of a milder peripheral hearing loss, which may have accounted for prolongation of the wave I-III inter-peak interval. Rosenhall et al. (2003) were able to study a large sample of autistic subjects with a span of intellectual abilities ranging from severe learning difficulties to average intelligence. Furthermore, the authors controlled for any effect of hearing loss by excluding those with a loss from their measurement of absolute wave latencies. Autistic children with normal hearing showed significantly prolonged absolute latencies of both wave I and wave V in response to click stimuli when compared to matched controls. Across all autistic children, the wave III-V inter-peak interval was also significantly prolonged. The inter-peak interval for waves I-III and I-V were within normal limits.

Kwon et al. (2006) assessed click-evoked ABRs in 71 children diagnosed with ASD and found that in comparison to a control group, the ASD group had significantly prolonged absolute wave V latencies in addition to significantly prolonged wave I-V and III-V inter-peak intervals. Wave I was found to be of normal latency, suggesting that both inter-peak interval prolongations were a result of a prolongation of transmission between the neural generators of waves III and V, believed to be the superior olivary complex and inferior colliculus respectively (Lev and Sohmer, 1972; Starr, 1976). However, only 8.5% of the ASD sample showed prolonged ABR latencies and when the group was split into those children with ‘pure’ autism and those on the spectrum, it was found that the pure autism group did not differ significantly from the control group. Fujikawa-Brooks et al. (2010) investigated the ABR in 20 autistic children in comparison to 20 age-matched typically developing children aged between 7 and 13 years. They used both a slow and fast presentation rate of click stimuli in both ears. In keeping with previous research, it was found that some but not all children with ASD showed prolongation of the ABR. In particular, prolongation of waves I and III showed a trend toward sig-
nificance yet only wave V of the left ear was found to be significantly prolonged between the two groups. In general, the left ear showed more prolongation than the right ear, which was far more varied in its results. Roth et al. (2011) found significantly prolonged inter-peak intervals and absolute latencies in response to click stimuli, in a sample of 26 children with ASD and a mean age of 32.5 months. These children were compared to an age and sex matched group of children with language delay and clinical norm data. It was found that in both the ASD and language delay groups, wave I had an absolute latency within the normal range (1.54 ms and 1.49 ms respectively). However, waves III and V were significantly prolonged in the ASD group and the language delay group, although the prolongation was more prolific in the ASD group. The same profile was found for the wave I to III inter-peak interval. Although, a significantly prolonged I-V and III-V inter-peak interval was found only in the ASD group.

Some studies have failed to find prolongation in the waves of the click-evoked ABR in subjects with ASD. Courchesne et al. (1985) found no click-evoked ABR abnormalities in a group of high functioning autistic subjects, a finding replicated by Grillon, Courchesne and Akshoomoff (1989) with a subset of the same sample. The authors argued that these findings are the result of their participants being unaffected by other neurological disorders and demonstrate that ABR abnormality is not a prerequisite of ASD. However, whereas Courchesne et al. (1985) and Grillon, Courchesne and Akshoomoff (1989) used high functioning autistic participants, many of the other early studies appear to have used low-functioning participants. For example, Rosenblum et al. (1980) only recruited autistic children who demonstrated extreme autistic behaviours. Both Gillberg, Rosenhall and Johansson (1983) and McClelland et al. (1992) used a specific diagnostic criteria (Rutter and Schopler, 1978) when recruiting participants, potentially under-representing autistic subjects who may have had milder forms of the disorder or who would not strictly fit their diagnostic criteria. Therefore, the difference in results across these studies could be due to an effect of participants’ level of functioning and a lack of uniformity in sample selection. Overall sample sizes were also
very small, the average size being less than 17, which reduces the
generalisability and reliability of the findings. Further methodological
differences that may also account for the variability in findings across
studies include differences in diagnostic criteria over time for ASD.

ASD is notoriously challenging to diagnose and over the years the la-
bel has often been applied to a wide clinical population. Klin (1993)
has suggested that a more exact and standardised recruitment of autis-
tic participants may go a long way in reducing the inconsistency
across findings. It is also possible that differences in stimulus presenta-
tion rates used by different studies had an impact on the findings.

However, on closer inspection, these methodological differences
do not always provide a satisfactory explanation for the variability
across results. Courchesne et al. (1985) used a range of fast and slow
click presentation rates but did not find any ABR prolongations, nor
did Grillon, Courchesne and Akshoomoff (1989) who used a slow
presentation rate of 7 clicks per second. Faster presentation rates may
be more likely to ‘stress’ the auditory system and reveal auditory pro-
cessing deficits. However, even studies using very slow presentation
rates of around 10 clicks per second found latency prolongations
(Wong and Wong, 1991; Maziade et al. 2000; Kwon et al., 2006). There-
fore, both fast and slow presentation rates have been found to
evoke prolongation of the click-evoked ABR waves. In terms of dif-
erent diagnostic criteria, studies using the identical DSM-III qualify-
ing criteria still produced a mixture of results. It would seem that these
particular methodological differences cannot wholly account for vari-
ability across studies. Roth et al. (2011) have proposed that variances
in the age of children tested could account for variances in the results.

Indeed, the studies that failed to find differences in ABRs between
autistic subjects and controls (Courchesne et al. 1985; Grillon,
Courchesne and Akshoomoff, 1989) used much older subjects with an
age range of 14-28 years, whereas the studies that did find a difference
all used children under 11 years.

Although a number of studies have found prolonged ABR wave
latencies and inter-peak intervals in children and young adults with
ASD, no specific pattern of prolongation has yet been identified. Despite the variability in findings, one particularly interesting theme does emerge. Gillberg, Rosenhall and Johansson (1983) found that 50% of their autistic participants showing an abnormal ABR had no language ability compared to only 19% of autistic participants who showed a normal ABR. This was later supported by McClelland et al. (1992) who found that their autistic participants showing an abnormal CCT also had an almost complete absence of speech. In very severe cases of ASD subjects may have no speech at all and when it is present it is often slow, emotionless and overly literal (Kanner, 1946; Bartak, Rutter and Cox, 1975). This finding that autistic subjects with more severe speech problems have a higher incidence of an atypical ABR suggests that although an atypical ABR may not be a necessary characteristic of ASD in general, it may well be a key characteristic in ASD subjects for whom communication difficulties are a prominent symptom. Although more recent studies have improved on many previous methodological issues there is still a discrepancy in findings, highlighting a continuing gap in knowledge when it comes to understanding the relation between abnormal ABRs and ASD. Even though neurophysiological abnormalities have been found in autistic children, failure of other studies to find any abnormalities in the autistic auditory brainstem suggests that it is not a necessary condition for autism (Klin, 1993).

Individual differences in the impact of delayed myelination could be a possible explanation for the variability across studies examining abnormal ABRs in children and young adults with neurodevelopmental communication disorders. In the case of ASD, Maziade et al. (2000) found a prolonged wave I-III inter-peak interval in both autistic and control participants, yet Rosenhall et al. (2003) found a prolonged wave III-V in autistic participants only. This could reflect differences between the neural structures of the brainstem that were damaged by delays in early myelination. For example, the subjects in Rosenhall et al.’s (2003) sample may have experienced delayed myelination from the superior olivary complex onwards. This would fit
well with findings of morphological abnormality within this area in autistic participants (Kulesza and Mangunay, 2008; Kulesza, Lukose and Stevens, 2011) as not only is this area believed to be the origin of wave III but it is also involved in interpreting sound sources and temporal features. Nevertheless, there is clear evidence that auditory temporal processing deficits are present in some cases of ASD. ASD is a hugely heterogenous disorder and so it would be extremely challenging to pinpoint exactly how atypical auditory temporal processing may map on to both the language and communication difficulties exhibited by individuals with the disorder. Indeed, this issue is something that is often not addressed in studies reporting auditory temporal processing deficits in this patient group. However, in addition to click-evoked ABR deficits, subjects with ASD have also been found to have disordered FFRs, and it has been suggested that FFR deficiencies could partly account for the prosody deficits in understanding speech found amongst subjects with ASD (Shriberg et al., 2001; Boucher, 2003). It is the prosodic elements of speech, such as emphasis on particular words or a speaker’s emotional state, that convey pragmatic information and allow us to make appropriate social responses. Accurate encoding of the $f_0$ in the auditory brainstem is believed to be essential for understanding these elements (Schon, Magne and Besson, 2004; Russo et al., 2008). Russo et al. (2008) manipulated the $f_0$ of a naturally spoken /ya/ syllable so that it was perceivable as either a statement or a question and presented it to 21 children with ASD and 21 typically developing controls all aged 7-13 years. The FFRs of each group were analysed for frequency error (the accuracy of pitch encoding over the duration of the stimulus), pitch strength (the robustness of phase locking to the stimulus $f_0$ contour) and slope error (preservation of the pitch contour). A lower frequency error score and significantly higher pitch strength value led the authors to conclude that the speech signal was more robustly preserved and processed in typically developing children than in children with ASD. However, this effect was the result of five children with ASD identified as being deficient pitch trackers, whereas the remaining 16 were found to have pitch tracking abilities that were within normal limits. Russo et al. (2009) found that
children with ASD had reduced neuronal synchrony and phase locking at the brainstem level to speech cues in both quiet and noisy conditions. This in turn reflected a reduced ability to accurately process speech filter cues, which aid distinction between consonants and vowels, and source cues, which help to identify speakers and their intent (Johnson, Nicol and Kraus, 2005). Combined with findings that processing of the $f_0$ and its harmonics within speech signals is important for understanding the prosodic elements of speech, these results further add to the argument that an aberrant FFR in some autistic children may account for their difficulties in understanding prosody in speech.

A key characteristic of the communication difficulties that individuals with ASD demonstrate is unusual attentional behaviour during social situations. For example, Klin (1991) found that infants with autism preferred to attend to nonsense sound rather than their mother’s voice. If accurate auditory temporal processing is essential for learning and distinguishing speech sounds then atypical processing may impact upon an autistic child’s ability to attach meaning to speech stimuli. Ceponiene et al. (2003) have suggested that if social stimuli are not meaningful, then autistic infants may lack motivation to attend to such stimuli, or may even feel frustrated in situations when speech stimuli are used. In the same vein, individuals with autism have been found to have reduced use of temporal dips when listening to speech in noisy environments (Alcantara et al., 2004). Difficulties in extracting speech from competing noise due to poor temporal processing may also contribute to the lack of orientation to speech stimuli that some individuals with ASD demonstrate during social situations.

Some individuals with autism produce no speech whatsoever or have a delayed onset of language. Given that the ability to process accurate temporal processing of rapid auditory cues is essential in both speech comprehension and subsequent speech production, atypical temporal processing at the brainstem level may also map on to these communication difficulties.
In summary, studies investigating a potential role for aberrant auditory temporal processing in the auditory brainstem in ASD have reported prolongation of absolute wave latencies, inter-peak intervals latencies and CCT of the click-evoked ABR as well as no prolongation at all. The variability in findings is likely to be down to the heterogeneous nature of the disorder, as well as methodological variations. However, the data do suggest that any abnormality is likely to reside in the central and not the peripheral portion of the auditory brainstem (Rosenhall et al., 2003; Kwon et al., 2006, Roth et al., 2011). Those studies finding prolongation of absolute latencies or inter-peak intervals involving waves I to III either found these same prolongations in non-autistic relatives or controls (Maziade et al., 2000), or in children with general language delay (Roth et al., 2011). Only the Rosenhall et al. (2003) study found that a prolonged absolute wave I latency was unique to their ASD group. In contrast, prolonged absolute latencies or inter-peak intervals involving waves III to V were almost always unique to subjects with ASD (Rosenblum et al., 1980; Rosenhall et al., 2003; Roth et al., 2011). Furthermore, aberrant ABRs appear to be only present in a subset of subjects with ASD rather than being a prerequisite of the entire ASD spectrum. It remains unclear as to what defines this subset, although as discussed in Chapter One, it could have some relationship with the severity to which the development of temporal processing ability is affected by impaired myelination of the brainstem at infancy. Unfortunately, there are limited studies investigating auditory temporal processing in ASD using the FFR and most studies that have used this measurement come from the same lab, which somewhat limits generalisability.

2.3.2 Auditory Processing Deficits in ADHD

ADHD usually has a childhood-onset and is characterised by a persistent pattern of inattention and/or hyperactivity-impulsivity (American Psychiatric Association, 2013). Prevalence estimates in children are high at around 5-8% (Polanczyk et al., 2007) and around 2.5% for adults (Simon et al., 2009). Children with ADHD have been
found to have communication difficulties when compared to normal controls (Geurts et al., 2004) and they have been reported to have autistic-like symptoms particularly in the areas of social interaction and communication with others (Clark et al., 1999). Like ASD, ADHD is extremely heterogeneous and the underlying mechanisms behind the disorder remain unclear. There are arguments for a genetic causation (Khan and Faraone, 2006) and neurobiological deficits in both the dopaminergic system and the prefrontal cortex (Levy, 1991; Faraone and Biederman, 1998). However, the attempt to discover a more refined pathogenesis for ADHD continues and this exploration has extended to a small number of studies examining auditory temporal processing in ADHD.

Lahat et al. (1995) compared 114 children who had been referred to hospital with attention deficit disorder or ADHD, against 41 controls. CCT was significantly longer in the ADHD group, as was the absolute latency of wave V. Absolute latencies of wave I were reported to be identical in both groups and the authors suggest that this indicates that abnormalities in the experimental group cannot be explained by inner ear problems and indicate a central auditory processing problem (Picton et al., 1977). Porras et al. (1999) also reported ABR abnormality in two children with attention disorders and postulate that response desynchronisation within the auditory pathway could exist in other such attention disorders. However, the extremely small sample makes these findings hard to generalise. Puente et al. (2002) also found a significantly prolonged CCT in 18 children diagnosed with attention-deficit disorder compared with 18 matched controls. Unfortunately, in both studies there was a sample bias in that all the children in the experimental group had been initially referred due to parental concern. ADHD is plagued by similar diagnostic challenges to ASD and it has been found that too much reliance on parental concern about unusual behaviour can lead to over eager and potentially inaccurate diagnoses (Sleator and Ullman, 1981). A more recent study by Azzam and Hassan (2010) found that 33% of a sample of 15 children with ADHD had significant prolongation of absolute wave III
latency and inter-peak intervals for waves I to III and waves III to V when compared to age matched controls.

As is the case for ASD, there are studies that have found no evidence of aberrant auditory processing in ADHD. Ismail and Amin (1999) used click stimuli to assess the ABR of 30 children diagnosed with ADHD in comparison to a control group. No significant differences were found between the two groups for absolute or inter-peak intervals. A more recent study by Vaney, Anjana and Khalilq (2011) was also unable to find any differences in click-evoked absolute ABR latencies or inter-peak intervals between a group of male children diagnosed with ADHD (mean age 10 years) and a control group. Overall, there are a limited number of studies that have investigated auditory temporal processing in ADHD using the click-evoked ABR, leaving an incomplete picture. In addition, findings are variable as they are for studies that used subjects with ASD.

Knowledge on the FFR in subjects with ADHD is even more limited. A search of the literature generated just one study. Jafari, Malayeri and Rostami (2015) recorded both click-evoked ABRs and speech-evoked FFR in 50 children diagnosed with ADHD (age range 8-12 years). They found that in comparison to controls, the ADHD group had significantly prolonged wave III and V absolute latencies, although inter-peak intervals were within normal limits. Researchers from Northwestern University have identified a set of reliable FFR waves evoked by the /da/ syllable (Johnson, Nicol and Kraus, 2005). These positive and negative waves include the positive waves I to V of the conventional click-evoked ABR, which are followed by a negative peak labelled as ‘A.’ What follows is the sustained FFR composed of five additional negative peaks ‘C,’ ‘D,’ ‘E,’ ‘F,’ and negative peak ‘O,’ which signals the offset of the response. Figure 2.2 shows the formation of these waves in normally hearing subjects. Waves A, C and O are thought to be generated by neural mechanisms that reflect the filter cues of speech, namely information about specific vowels
Figure 2.2: FFR to the synthetic speech syllable /da/ averaged across 24 normally hearing subjects. Top box: Frequency spectrum of the FFR (waves D-F) for 23-44 ms time window (Johnson, Nicol and Kraus, 2005).

and consonants. Whereas waves D, E and F are thought to be generated by neural mechanisms that reflect source cues, including speaker identity and prosody (Johnson, Nicol and Kraus, 2005; Kraus and Nicol, 2005). Jafari, Malayeri and Rostami (2015) found that their ADHD group showed significant prolongation of both the onset and offset waves of the FFR evoked by the /da/ syllable, as well as prolongation of waves D, E and F, which represent the sustained phase locking part of the response. A gap in knowledge remains as to whether FFR deficits are present in a wider population with ADHD.

2.3.3 Auditory Processing Deficits in Developmental Dyslexia

Developmental dyslexia affects around 10-15% of the population (O’Hare, 2010) and is characterised by problems with reading, writing, or both, that are not in keeping with age or general cognitive ability (Lyon, 1995). Under new diagnostic criteria of the DSM-V dyslexia is now defined as a specific learning disorder. A central cause of the reading and writing difficulties displayed by dyslexic subjects is thought to be poor phonological awareness in the form of
poor phonemic coding and segmentation (Vellutino, 1987; Vellutino et al, 2004). Research suggests that these phonemic difficulties may have an auditory basis.

In particular, it has been suggested that dyslexic subjects may have a general temporal processing deficit within the auditory domain (Tallal, 1980). This hypothesis postulates that dyslexic subjects have a deficit in processing rapidly presented acoustic stimuli in the form of both speech and pure tones. Phonemes can be segmented based on the rapid changes in frequency bands (formants) within speech and as a result, the slow processing of such rapid frequency changes could lead to less precise phonemic representations (Steinbrink et al., 2013). A proportion of studies into the theory of a temporal processing deficit in developmental dyslexia focused on behavioural measures. In particular, temporal order judgement tasks (Mody, Studdert-Kennedy, and Brady, 1997; de Martino et al., 2001) and the gap detection test (Van Ingelghem et al., 2001; Cohen-Mimran and Sapir, 2007). The gap detection test is designed to challenge subjects to identify when a temporal gap appears between two stimuli, with the subject indicating the threshold at which they can hear the stimuli as one sound or two distinct sounds. However, there have also been studies that have failed to replicate the finding that subjects with developmental dyslexia perform more poorly than controls on temporal order judgement tasks (Griffiths et al., 2003; Bretherton and Holmes, 2003). Vandermosten et al. (2010, 2011) have more recently re-ignited the case for a general temporal processing deficit within the auditory domain of dyslexic subjects. These two studies found that when compared to normal readers, both adults and children with dyslexia demonstrate a much poorer ability to categorise both speech and non-speech stimuli based on their rapidly changing temporal cues. The finding that this inability to accurately categorise sounds based on their temporal cues is present in both young dyslexic readers aged 11 years and in adults suggests that the deficit could be causal in nature and not the result of a long period of reading difficulties.
Some studies have used electrophysiological measures to further pursue the theory of poor temporal processing in developmental dyslexia. McAnally and Stein (1996) found that dyslexic adults were impaired on tasks that required accurate phase locking to the TFS of a stimulus. Furthermore, FFR amplitudes were significantly smaller in dyslexics than in control participants, indicating a weaker phase-locking response. The authors concluded by suggesting the presence of impairment in auditory brainstem neural populations of dyslexic adults. Participants in the study by McAnally and Stein (1996) were also found to have normal ABRs, suggesting that the FFR was able to detect auditory processing deficits that the click-evoked ABR was not able to. Menell, McAnally and Stein (1999) found that adults with dyslexia were poorer than a control group at detecting amplitude modulation within white noise and had a smaller electrophysiological response. The authors concluded that these results could reflect an impaired perception of amplitude modulation within speech. However, the same research failed to find a difference between groups on a gap detection test, which is a behavioural measure of temporal processing. This could suggest that behavioural measures are not sensitive enough to detect subtle temporal processing problems. A poor ability to detect amplitude modulation was also found in dyslexic subjects by Goswami et al. (2002). In particular, they performed worse in a test designed to assess sensitivity to amplitude envelope onsets, which are believed to represent the acoustic structure of a syllable and are perceived as unique rhythms. The dyslexic group were also found to perform significantly worse than controls on two measures of rapid spectro-temporal integration. Together, these results indicate an auditory temporal processing problem that span both the successful integration of rapidly occurring stimuli but also the accurate processing of the onset of signals. As is the case for other neurodevelopmental communication disorders, the evidence for a general auditory temporal processing deficit is not conclusive. Several studies have failed to find a temporal processing deficit in subjects with dyslexia (Bishop et al., 1999a; 1999b; Marshall, Snowling and Bailey, 2001; Waber et al., 2001). A review study by Ramus (2003) found that only 40% of the
dyslexic population included in the 10 studies that were analysed were found to have auditory deficits, suggesting that the majority of dyslexic subjects do not appear to have auditory deficits. Based on the evidence, it appears as though if auditory deficits are a pre-requisite of dyslexia then these deficits may be temporal in nature, such as an impaired ability to follow amplitude modulations within an auditory signal. More recently, difficulties in the subcortical encoding of temporal features has been earmarked as a risk factor in the development of dyslexia (Plakas et al., 2013). However, in keeping with the research on auditory processing in other neurodevelopmental communication disorders, knowledge on these deficits in developmental dyslexia remains incomplete.

2.3.4 Auditory Processing Deficits in Language Disorders

The DSM-V has recently made diagnostic changes that define SLI as a language disorder. It is now included under the same umbrella term as expressive language disorders, mixed expressive-receptive language disorders and speech-sound (phonological) disorders. SLI affects around 7% of children (Tomblin et al., 1997) and is diagnosed when a child’s oral language production and/or comprehension appear to lag behind all other areas of development without a clear clinical reason for doing so (Leonard, 1998). The underlying mechanisms of language disorders are still currently debated, although it has been speculated that phonological processing deficits may be a causal factor as they are thought to be in dyslexia (Gathercole and Baddeley, 1990, Sussman, 1993). Indeed, the rapid temporal processing hypothesis has been applied to children with language disorders (Tallal et al., 1996). However, in another behavioural study, Corriveau, Pasquini and Goswami (2007) found that language disordered children were significantly worse than age matched controls at detecting amplitude rise times and the duration of pure tones, and that this ability predicted a fair amount of variance in phonological awareness. The authors concluded that the temporal processing problem for those with language
disorders lies in the processing of long duration temporal cues and not the processing of rapid cues.

Basu, Krishnan and Weber-Fox (2010) tested the temporal processing deficit hypothesis of SLI using 10 children diagnosed with the disorder and 10 controls aged 4-11 years. The authors measured both the FFR using tonal sweep stimuli and the ABR using 100-μs clicks. Tonal sweeps are believed to mimic time varying speech stimuli such as some consonant-vowel syllables. In particular, the tonal sweeps used in this study were designed to represent the /ba/ and /be/ syllables. The children with a language disorder were found to have dramatically poorer phase locking to the tonal sweep stimuli, especially as the rate of frequency change increased. Furthermore, they also showed greater prolongation of latency for waves III and V of the ABR with increasing stimulus presentation rate. FFR amplitude was also significantly smaller amongst the language disordered group, possibly reflecting degradation within a particular neural generator of the response or reduced phase locking coherence across multiple neural generators. Johnson et al. (2007) studied a group of children with a language disorder and found them to demonstrate poor backward masking thresholds, which are indicative of difficulties in the perception of rapidly occurring auditory stimuli. When compared to language disordered children with normal backward masking thresholds and a control group without a language disorder, the children with poor backward masking thresholds showed prolonged FFR latencies. These latency prolongations were significantly different from the two other groups for waves A, C and O, indicating delayed onset and offset responses to a synthesised /da/ syllable. A prolonged latency for the onset wave A for a subset of language disordered children was also reported by King et al. (2002) when evoked by the /da/ syllable. If deficits are temporal in nature then it makes sense that the language disordered children have prolonged onset and offset responses because these are the points within the speech signal where changes occur extremely rapidly (King et al. 2002). Johnson et al. (2007) postulate that delayed latency of the onset (A) and offset (O) waves of the
FFR account for the poor backward masking performance seen in children with a language disorder, which may manifest as poor consonant and vowel recognition (filter cues). The onset of any given consonant contains unique spectral information (Stevens and Blumstein, 1978) and the transition from the sudden onset to the more periodic vowel sound that follows is an essential cue for a listener to determine information about the preceding consonant. Therefore, if these language disordered children show a delay in the processing of this transition (delayed waves A and C) then this may translate to poor consonant and vowel recognition. However, as is the case for the neurodevelopmental communication disorders already discussed, evidence that a temporal processing deficit at the brainstem level is present in subjects with language disorders is not unequivocal (for a review see Rosen, 2003).

2.3.5 Speech-in-Noise

Another indication of an auditory temporal processing deficit across neurodevelopmental communication disorders are findings regarding speech-in-noise abilities. Cunningham et al. (2001) suggest that temporal processing deficits such as imprecise phase locking in the auditory brainstem could cause a ‘blurred’ neural representation of speech sounds, especially in the presence of noise. In support of this, many subjects with neurodevelopmental communication disorders show difficulties with speech-in-noise. Alcántara et al. (2004) found that children with ASD were poorer than controls at listening to and understanding speech in noise. In particular, it was found that participants with ASD fared significantly worse in temporally modulated background noise than control participants. The authors concluded that this deficit may be due to an inability of the ASD subjects to take advantage of the phenomenon of “masking release” in which a temporally modulated background should yield better speech reception thresholds than un-modulated backgrounds, which are far more effective at masking speech. The authors go on to postulate that such deficits may account for the difficulties that some ASD subjects have
shown in classroom environments (Ashburner, Rodger and Ziviani, 2008). Ashburner, Rodger and Ziviani (2008) found that the ability to comprehend and maintain attention to speech in the presence of background noise was the most significant predictor of academic performance for children diagnosed with ASD.

Expanding on this theory, Alcántara et al. (2012) suggest that masking release deficits may be explained by a deficiency in dip listening ability, which allows a listener to take advantage of the momentary decreases in background noise. In turn, Alcántara et al. (2012) believe this deficit to be caused by a reduced ability of subjects with ASD to process temporal envelope cues of acoustic signals, after discovering that a small sample (n=6) of children with Asperger’s syndrome had reduced temporal-envelope processing ability when compared to a control group. Nevertheless, the generalisability of the results are weakened by the small sample size of just six young Asperger’s sufferers. Cunningham et al. (2001) manipulated the acoustic features of an /ada/ to /aga/ continuum so as to mimic ‘clear’ or ‘conversationalist’ speech (Picheny, Durlach and Braida, 1986). It was found that children with general language disorders, some of whom were also diagnosed with attention-deficit disorder, were significantly poorer than controls using the just noticeable difference test when the conversational continuum was presented in noise. When the continuum was presented in quiet, the language disordered group performed as well as a control group. It was also found that performance on the just noticeable difference test for the continuum presented in the noise condition was significantly correlated with wave V latency of the ABR in response to a /da/ syllable. This suggests that a subject’s ability to distinguish speech sounds in noisy conditions is associated with delayed onset responses to speech. In other words, temporal processing deficits in the form of a delayed synchronised electrophysiological response to a speech signal are related to increased difficulty in distinguishing speech sounds in noisy environments. However, it should be noted that the sample size was also very small in this study (n=9) and that the significance level of the correlation between just noticeable test performance and wave V latency was just about signif-
icant \( p = 0.05 \). Speech in noise difficulties have also been found in dyslexia (Ziegler et al., 2009) and ADHD (Schafer et al., 2013).

### 2.4 Early Identification of Neurodevelopmental Communication Disorders

Auditory encoding deficits at the brainstem level have been found to cut across diagnostic criteria for a range of different neurodevelopmental communication disorders (Kraus et al., 1996). Indeed, such is the breadth of studies that have reported auditory processing deficits in individuals with neurodevelopmental communication disorders, that it has been suggested that these disorders may lay on a spectrum of communication ability as opposed to representing unique disorders (Miller, 2011). Disorders such as ASD and ADHD may represent one end of the scale, where communication difficulties extend into the social domain. More sub-clinical language disorders may represent the other end of the scale. Indeed, subjects with SLI have been shown to have both poor (Fujiki, Brinton and Todd, 1995) and normal (van de Lely, Rosen and McClelland, 1998) social skills, suggesting that the disorder is spectrum-like. Children diagnosed with auditory processing disorder have often been reported as having communication difficulties (Dawes et al., 2008), and Miller and Wagstaff (2011) have suggested that SLI and auditory processing disorder may be ‘indistinguishable’ disorders. Auditory processing disorder has been defined by Moore (2006) as any aspect of hearing that is affected by the abnormal processing of acoustic signals, whilst the British Society of Audiology (2005) characterises it by poor auditory perception of both non-speech and speech sounds.

The theory that neurodevelopmental communication disorders may indeed lie on a spectrum of language and communication development can be seen throughout the literature. There is both genetic and behavioural evidence that the communication impairments found in ASD have features in common with other neurodevelopmental communication disorders such as dyslexia and SLI (Herbert and Kenet, 2007; Smith, 2007). These similarities include delayed and ab-
normal development of language and deficits in the understanding and use of the pragmatics of language. To further highlight the similarity between many of the disorders for which communication difficulties are a common characteristic, Moore (2006) has commented that the referral route that a child is subjected to can have an astonishing impact on the subsequent diagnosis. For example, the same child may be diagnosed with SLI by a speech and language therapist, ASD by a psychiatrist, or auditory processing disorder by an audiologist. There is also frequent comorbidity between ADHD and dyslexia (Germano, Gagliano and Curatolo, 2010) and the DSM-V now recognises the high level of comorbidity between ADHD and ASD.

Arguments have been made that the degree of overlap between neurodevelopmental communication disorders is not as wide as many researchers have reported. For example, Chermak, Tucker and Seikel (2002) found that audiologists and paediatricians identified separate key behaviours as most common to auditory processing disorder and predominantly in-attentive ADHD. However, audiologists were asked to rate the most characteristic behaviours of auditory processing disorder exclusively, and paediatricians were asked to do the same for ADHD. This means that each type of professional was likely to have focused only on behaviours that they particularly look for when making a diagnosis, behaviours that may be the same but interpreted differently depending on a professional’s outlook. Indeed, Dawes and Bishop (2009) have suggested that a diagnosis of auditory processing disorder may simply be an alternative diagnosis of ADHD seen from the perspective of an audiologist. Miller (2011) has suggested that research into auditory temporal processing deficits could be combined to reveal more about the role of auditory processing in disorders such as SLI and dyslexia. Given evidence to show that auditory temporal processing deficits can be characteristic across a range of neurodevelopmental communication disorders, auditory-evoked electrophysiological measures may prove useful in detecting those infants at risk of developing such disorders. Cortical responses to acoustic stimuli have been explored as potential biomarkers for ASD (Roberts et al., 2010,
2011), yet despite the wealth of studies that have found auditory temporal processing deficits in subjects with neurodevelopmental communication disorders, little work has been done on exploring potential auditory evoked electrophysiological biomarkers at the subcortical level.

The early identification of neurodevelopmental communication disorders is highly encouraged. Children with these disorders are known to show less educational attainment than those without (Nathan et al., 2004) and in adulthood, such disorders are associated with poorer social adaptation (Clegg et al., 2005) and the perception of a lower quality of life (Cottenceau et al., 2012). Howard et al. (2005) compared the outcomes of 61 children diagnosed with ASD or pervasive developmental disorder before the age of 48 months. The children were split into three intervention groups and received intensive behaviour analytic treatment, autism educational planning or general educational planning. Intensive behaviour analytic treatment provided the most intensive intervention whereas the generic educational planning provided the least. Children were assessed on their skills in the following areas both before and after 14 months of intervention: cognitive skills, non-verbal skills, receptive and expressive skills, and adaptive skills. It was found that children receiving the intensive behaviour analytic treatment scored significantly higher than the other two groups of children put together on each outcome measure. Although these children did not reach the level of their typically developing peers, the authors claimed that continued intervention would put them on a developmental trajectory that would have seen them close the gap over the next 1-2 years and ready them for the normal classroom environment. There is also evidence to suggest that early identification for a range of neurodevelopmental communication disorders, not just ASD, is highly advantageous and desirable (McGoey, Eckert and Dupaul, 2002; Woods and Wetherby, 2003; Schatschneider and Torgesen, 2004).

There is also growing evidence that auditory training can improve temporal processing ability over time. Hayes et al. (2003)
trained 27 children diagnosed with either attention-deficit disorder or language disorders using the Earobics (Houghton Mifflin Harcourt) software. This programme focuses on using fun and interactive games to encourage improvement in phonological awareness, as well as auditory and language processing skills. Children who received this training were found to have improved cortical responses to speech stimuli post-training, in addition to improved scores on measures of auditory processing on the Woodcock-Johnson-Revised test battery (Woodcock and Johnson, 1989). In particular, it was found that children with a delayed ABR to the speech syllable /da/ had a much greater improvement in terms of the cortical representation of speech stimuli, indicating that poor subcortical processing of speech stimuli may be a pre-requisite condition to a more beneficial outcome when using auditory training programmes. Similar results had been reported previously by King et al. (2002). However, it should be noted that despite apparent improved cortical processing due to training, Hayes et al. (2003) found no difference in academic achievement between the experimental and control group. Therefore, such changes may be superfluous if they do not result in any academic or educational benefit. This is especially important as children with neurodevelopmental communication disorders have continuously been found to under-achieve academically (Aram, Ekelman and Nation, 1984; Beitchman et al., 1996; Johnson, Beitchman and Brownlie, 2010). Furthermore, all three studies used the exact same training programme, which limits the generalisability of the findings to other auditory training programmes.

The effectiveness of early interventions ties into evidence showing that there is a sensitive period for neurobiological development and a time limit on our ability to harness neuroplasticity for clinical applications. In particular, before the age of 42 months seems to be when the central auditory pathway shows the most plasticity (Sharma, Nash and Dorman, 2009). Although behavioural tools are available for clinicians to identify disorders such as ASD in infants as young as two years old, in reality the diagnosis is closer to 4 years of age (Mandell,
Novak and Zubritsky, 2005), which is beyond the sensitive period identified by Sharma and colleagues. In this respect, auditory-evoked electrophysiological measures would have an enormous advantage over behavioural methods of identification.

There is evidence to suggest that interventions based on improving temporal processing within the auditory brainstem are ineffective. McArthur et al. (2008) have suggested an alternative explanation as to why some previous studies found that auditory training programmes improved linguistic skills in children with a neurodevelopmental communication disorder. Namely, these studies delivered training on complex linguistic skills in addition to training designed to improve auditory temporal processing. McArthur et al. (2008) have argued that it is this additional training that could account for reported improvements rather than changes in auditory temporal processing ability. In their study, McArthur et al. (2008) found that whilst children with both SLI and specific reading disability scored higher on measurements of spoken language and spelling after a targeted training programme designed to improve their specific auditory processing deficit, a untrained control group also showed the same improvements. This result led them to conclude that although auditory temporal processing deficits can be improved in a subset of children with a neurodevelopmental communication disorder, there is no evidence in this study that this improvement has a direct link to improvements in written and spoken language.

In a meta-analysis, Strong et al. (2011) assessed the effectiveness of the Fast ForWord program (Merzenich et al., 1996, Tallal et al., 2006) and found little evidence across studies to suggest that it improved either auditory processing or language outcomes for children. The program aims to improve auditory temporal processing by slowing down or ‘stretching’ speech within a series of audiovisual games. Strong et al. (2011) highlight that the program was commercially launched based on the findings of both Merzenich et al. (1996) and Tallal et al. (1996) despite these studies both having methodological limitations including small sample sizes. The meta-analysis com-
prised six high quality, randomised-control studies. Sample sizes ranged from 60 to 454, with participants having a mean age of 12.5 years. These studies, that somewhat improved upon the two studies by Merzenich et al. (1996) and Tallal et al. (1996), found no significant effect of the Fast ForWord program on any language outcome measure in comparison to control groups. This lack of evidence to show that temporal stretching of speech improves language outcomes weakens the case of the involvement of poor temporal processing in neurodevelopmental communication disorders. Based on the results of their meta-analysis, Strong et al. (2011) argue that the Fast ForWord program should not be endorsed until further and more substantial evidence is gathered. More randomised-controlled studies are required in order to pursue an understanding as to the true benefits of early intervention for neurodevelopmental communication disorders, and how auditory training programs can extend to improvement in educational attainment.

So far, this literature review has highlighted the importance of temporal synchronicity within the auditory brainstem for successful communication. Perhaps unsurprisingly, auditory evoked electrophysiological measures sensitive to temporal synchronicity have revealed temporal processing deficits in a subset of children and young adults with neurodevelopmental communication disorders. Given that electrophysiological measures are feasible for use with very young infants, they present a potentially useful biomarker for these disorders. Despite mixed views on the effectiveness of early intervention, the electrophysiological data collected in the NICU during newborn hearing screening (the ABR) is readily available and would provide a cost-effective method for the early identification of auditory temporal processing deficits. Bearing in mind the low cost that would be incurred by health care organisations, evidence against the apparent benefits of early intervention should not be taken as reason not to pursue the possibility that such neurodevelopmental communication disorders can be identified earlier than is currently attainable. Infants flagged as having auditory temporal processing deficits could be more closely monitored
during paediatric appointments throughout childhood for additional risk factors associated with the development of neurodevelopmental communication disorders. Considering the evidence that a subset of individuals diagnosed with these disorders demonstrate aberrant ABRs and given that data on functionality of the auditory brainstem is already collected through the NHSP, it seems logical to at least explore the possibility that the data could provide an insight into a child’s communication development in addition to their auditory development. As has already been discussed in this chapter, transient failure of the ABR may present one opportunity for the early detection of atypical temporal processing. However, the FFR is also sensitive to these deficits.

The FFR is not currently used clinically, despite evidence that it may be more sensitive to auditory temporal processing deficits than the currently used click-evoked ABR (King et al. 2002; Song et al., 2006; Russo et al., 2008, 2009). In particular, there are a subset of individuals who demonstrate disordered FFRs in response to complex stimuli despite having a normal click-evoked ABR (King et al., 2002; Song et al., 2006; Russo et al., 2008, 2009). Although transient failure of the ABR may reflect a delay in myelination that catches up once the response is retested, the measurement may not be sensitive enough to detect impaired myelination in neural populations that are sensitive to complex stimuli or in separate neural generators to those responsible for the click-evoked ABR. In support of this speculation, Efimov, Efimova and Rozhkovl (2014) found that whilst delayed CCT of the click-evoked ABR was detected in 22-25.5% of children with a neurodevelopmental communication disorder, 81% of children with ASD and 72% of children with a language disorder showed prolongation of wave VI, which is generated after wave V of the conventional click-evoked ABR. As discussed in Section 2.3 of this chapter, FFR deficits have been found in a subset of individuals with neurodevelopmental communication disorders. Given the response’s potential increased sensitivity to auditory temporal processing deficits, it also presents itself as a potentially useful biomarker for such disorders. The clinical
potential or the FFR as a biomarker for neurodevelopmental communication disorders and increased sensitivity of the FFR to auditory temporal processing deficits is discussed in the following section.

2.5 Clinical Potential of the FFR

Maturation of the FFR is far less understood than the maturation of the click-evoked ABR. Animal studies indicate that phase locking develops in a gradient fashion from low to high frequencies (Brugge, Anderson and Kitzes, 1978; Kettner, Feng and Brugge, 1985). The FFR reflects phase locking to both the envelope and TFS of a complex acoustic signal, and the ability to utilise both these temporal cues has been reported in children as young as 5 years of age using a behavioural discrimination task (Bertoncini, Serniclaes and Lorenzi, 2009). Levi, Folsom and Dobie (1995) found that the FFR was essentially adult like in 1 month old infants and Jeng et al. (2010) reported the speech-evoked FFR to be adult-like in its maturity and tracking accuracy by as young as 1 month old and is therefore likely to be mature in response to amplitude-modulated stimuli. These findings indicate that the FFR could be a suitable measurement of auditory brainstem integrity at a young age.

The FFR may have certain advantages over the click-evoked ABR as a biomarker and clinical tool. Despite being both useful and reliable, the ABR does have some limitations. For example, the click stimulus often used to elicit the response lacks frequency specificity and ecological validity. There is evidence that complex sounds such as speech are processed in a different manner to non-speech sounds in the auditory brainstem (Mody, Studdert-Kennedy and Brady, 1997), which is supported by the finding that the FFR is sometimes more sensitive to auditory temporal processing deficits in subjects with neurodevelopmental communication disorders than measurements of the click-evoked ABR when synthetic speech stimuli are used (King et al., 2002; Hayes et al., 2003; Russo et al., 2008, 2009; Azzam and Hassan, 2010). The reason as to why some subjects with neurodevel-
opmental communication disorders demonstrate normal auditory responses to click stimuli but not speech stimuli is still speculated. Banai, Abrams and Kraus (2007) have suggested that the effect may be due to the slower rise time of speech stimuli that may exacerbate any presence of neural desynchronisation. Vandermosten et al. (2011) believe that this phenomenon is due to differences in complexity between the two types of stimuli. These findings suggest that use of a more complex stimulus to assess the auditory brainstem of infants could reveal temporal processing deficits to which the click-evoked ABR may not be sensitive. Furthermore, as discussed in Section 2.3 of this Chapter, temporal cues such as the envelope and TFS of a speech signal are important for speech comprehension. These cues are reflected in the FFR but not the click-evoked ABR, which means that the FFR may provide information on temporal efficiency that the click-evoked ABR cannot.

Naylor (2003) has defined a biomarker as a biological characteristic that can be objectively measured and used to distinguish normal biological processes from pathogenic processes. An essential part of this, as highlighted by Mayeux (2004), is an understanding of normal distributions and between subject variability of any measure that has potential as a biomarker. Whilst both the click-evoked ABR and FFR can be objectively measured, the ability of the FFR to distinguish normal subjects from patient populations remains limited due to uncertainty regarding normal parameters. The low within and between-subject variability and high test-re-test reliability of the click-evoked ABR wave V latency in particular is what gives it an enormous strength in the clinical arena. The FFR would need to demonstrate such qualities in order to strengthen its clinical usefulness. Marsh, Brown and Smith (1975) have reported a low level of variability in FFR latencies collected from healthy human subjects and Batra, Kuwada and Maher (1986) suggested that such low variability in latency among normal subjects could make the FFR a sensitive indicator of midbrain or brainstem disorders that alter it. However, although subjects were repeatedly tested across several sessions, these studies were limited by small sample sizes, for example Batra, Kuwada and Maher
(1986) used only seven participants. Nevertheless, a review of the literature reveals high levels of variability across studies that have collected data on the FFR latency in healthy subjects. Early studies reported a latency of 2.5 to 6 ms (Marsh, Brown and Smith, 1975; Stillman, Crow and Moushegian, 1985). Glaser et al. (1976) reported a latency of around 5.4 ms and Batra, Kuwada and Maher (1986) have reported an FFR latency of 8.2 ms in response to continuous pure tones. Batra, Kuwada and Maher (1986) have suggested that the variability amongst FFR latencies may be due to the nature of the stimuli used. They highlight that studies which have found a shorter latency of around 6 ms have used tone burst rather than continuous tones, which may have made determining the true latency challenging. Indeed, Glaser et al. (1976) and Sohmer, Pratt and Kiniarti (1977) used tone burst stimuli in their studies and were the only ones to report shorter latencies than 7 ms.

There have also been studies that have sought to establish a normative latency value for the FFR to amplitude-modulated tones. Kuwada, Batra and Maher (1986) found that amplitude-modulated tones modulated between 100 and 350 Hz produce an FFR with a latency of between 7 and 9 ms. Dolphin and Mountain (1992) measured the latency of the FFR in Mongolian gerbils using a range of amplitude-modulated tones. It was found that responses obtained when using low modulation frequencies (< 50 Hz) produced a latency of 12.5 ms whereas the latency obtained when using higher modulation frequencies (50-180 Hz) was much slower at 6 ms. Purcell et al. (2004) found that tones amplitude-modulated at between 80-190 Hz produced an FFR with a latency of 8.6 ms. Unsurprisingly, variability across studies in regards to the latency of the FFR has extended to confusion over its neural generators. Generation sites are thought to be similar to those involved in generating wave V of the transient, click-evoked ABR, namely the lateral lemniscus (Galbraith, 1994) and inferior colliculus (Smith, Marsh and Brown, 1975; Stillman, Moushegian and Rupert, 1976; Glaser et al., 1976; Daly, Roeser and Moushegian, 1976), with others suggesting that it may have multiple generators (Kuwada, Batra and Maher, 1986; Dolphin and Mountain, 1992; John
and Picton, 2000). Sohmer, Pratt and Kinarti (1977) measured click-evoked ABRs and tone-burst evoked FFRs in normal subjects and subjects with an upper brainstem lesion. In normal subjects, it was found that FFR onset coincided with onset of waves IV or V of the click-evoked ABR. This result indicated an inferior colliculus generation site for the FFR. To further support this conclusion, it was found that in subjects with an upper brainstem lesion, absence of waves IV or V of the ABR was predictive of an absent FFR. Sohmer, Pratt and Kinarti (1977) concluded that the main neural generation site of the FFR must lie rostral to the superior olivary complex. However, this finding was later refuted by Hoorman et al. (1992) who reported a poor correlation between ABR wave V and FFR latencies. A lack of clarity over the neural generators of the FFR limits its clinical potential because it is not clear as to whether the FFR can reveal more about the efficiency of the auditory brainstem than the click-evoked ABR alone. It also limits the degree to which conclusions can be made as to where in the brainstem the pathology of an abnormal FFR may arise.

Perhaps the biggest contributors to the exploration of the FFR as a potentially useful clinical tool have been the research team at Northwestern University. They have published a plethora of papers leading to the overall conclusion that speech-evoked FFR in particular can both objectively and reliably identify children at risk of developing communication difficulties. Russo et al. (2008) boldly concluded that the FFR could potentially be used to screen for severe pragmatic deficits in infants and that auditory brainstem deficits could indicate a child at risk of ASD. This conclusion has led to the development of the BioMARK (formerly BioMap, Biological Marker of Auditory Processing; Abrams and Kraus, 2005) equipment that can be used by clinicians to measure the brainstem response to speech stimuli. Through the primary use of a synthetic speech syllable /da/, a set of waves have been identified that represent the onset of the speech-evoked FFR, its transient, phase-locked portion and its offset (see Figure 2.1). In particular, the BioMARK collects values for wave V
latency, wave A latency, V/A slope, first-formant frequencies and high frequencies. Scores of between 0-5 indicate normal brainstem timing, whereas scores of 6-22 indicate an abnormality. One advantage of the BioMARK is that data collection takes only around half an hour and children are able to watch a movie on low sound to keep them occupied and as still as possible (Rocha-Muniz, Befi-Lopes and Schochat, 2014). There is also evidence that the efficiency of the auditory brainstem to produce these waves may map onto real world perceptual abilities. For example, it has been suggested that the offset wave O of the speech-evoked FFR could be essential for understanding speech in noise. In older subjects, Anderson et al. (2013) found that the latency of the offset wave O could predict self-reported speech-in-noise performance. They postulate that this is due to deficits in the inhibitory processes of duration tuned neurons that are found in the inferior colliculus and higher in the auditory pathway (Casseday, Ehrlich and Covery, 2000). However, whilst wave V of the ABR has well established normative values throughout the literature, waves A, C and F are the only waves to currently have reliable and published normative values for the FFR evoked by the /da/ syllable (Russo et al., 2004; King et al., 2002) and it should be noted that these normative values are largely the product of just one laboratory, questioning their generalisability and subsequently, their potential usefulness in a clinical setting. Furthermore, they are limited to responses to just one speech syllable (/da/) and results are only generalisable to children.

A search of the literature reveals a limited number of studies that have investigated the usefulness of the BioMARK. Kumar and Singh (2015) found significant differences in absolute latencies of the FFR in response to the /da/ stimulus between children at risk of central auditory processing disorder without a reading deficit and typically developing controls. The two groups also differed significantly for BioMARK total scores, and onset latencies were significantly prolonged. However, the authors did question BioMARK’s sensitivity in detecting central auditory processing deficits, as it failed to identify some children who had been categorised as having such deficits by
scoring poorly on a screening checklist for auditory processing. In contrast, Billiet and Bellis (2011) found that two groups of dyslexic children, one with abnormal brainstem responses as classified by the BioMARK and one without, did not show any significant differences on behavioural tests of central auditory processing ability. This suggests that the BioMARK may be more sensitive to auditory processing deficits than behavioural assessments. However, it remains unclear as to whether the BioMARK is advantageous over behavioural measures designed to detect deficient auditory processing in the temporal domain.

Rocha-Muniz, Befi-Lopes and Schochat (2014) carried out the first study investigating the sensitivity and specificity of BioMARK in identifying children with auditory processing disorder, SLI and typically developing controls. Using a discriminant analysis they created a classification model to identify each of the three groups. With 72% sensitivity, a significant prolongation of the onset wave A, but typical amplitudes for the FFR to formants with high frequencies (>1240 Hz), classified those children with a diagnosis of auditory processing disorder. With 56% sensitivity, values below cut-off for the FFR amplitude to formants with high frequencies correctly classified those children with SLI. As might be expected, normal wave A latency and amplitudes to the FFR to formants with high frequencies classified typically developing children. The authors postulated that significant prolongation of the FFR onset waves V and A suggest that children with auditory processing disorder and SLI may have deficits in encoding sound in the lateral lemniscus and inferior colliculus within the auditory brainstem. These onset waves reflect the ability of the brainstem to fire synchronously during the transient events of a stimulus and thus suggest that these groups of children have a deficit in encoding temporal cues at the brainstem level. This study also suggests that the speech-evoked FFR could be a useful clinical tool in the detection of neurodevelopmental communication disorders. Similarly to Rocha-Muniz, Befi-Lopes and Schochat (2014), Kumar and Singh (2015) also found that wave V of the speech-evoked FFR was significant de-
layed. However, wave V of the click-ABR was within normal limits. This suggests that wave V of the ABR that is evoked by more complex stimuli could make a useful clinical tool for identifying temporal processing deficits than when it is elicited by simple click stimuli. However, it should be noted that although Rocha-Muniz, Befi-Lopes and Schochat (2014) found wave V of the speech-evoked FFR to be significantly prolonged in children with SLI in comparison to both children who were typically developing and children with auditory processing disorder, their discriminant analysis did not include it as a useful predictor in determining group membership. The FFR certainly has clinical potential as a biomarker for neurodevelopmental communication disorders. However, more research on its normative parameters is required for clinical use to be feasible.

2.6 Literature Review Summary

In summary, this literature review has discussed how a proportion of NICU infants demonstrate a transient failure of the click-evoked ABR at newborn hearing screening that recovers at diagnostic follow up. There is evidence to suggest that this transient failure may have a basis in the delayed myelination of the auditory brainstem. In turn, this may temporarily causes poor signal-to-noise ratio. A review of the literature finds that periods of auditory deprivation can impair neurodevelopment of the auditory brainstem, including temporal synchronicity. Therefore, this transient failure may indicate an early deficiency in auditory temporal processing that has a knock on effect on an infant’s subsequent communication development. The degree to which the auditory system is affected may account for why some subjects with a neurodevelopmental communication disorder demonstrate aberrant auditory brainstem responses whereas others do not. If the transient failure of the ABR indicates early myelination issues within the auditory brainstem that have a knock on effect on a child’s communication development then data already collected through the NHSP could be used to identify infants at risk of developing neurodevelopmental communication disorders. However, despite a link to the
development of ASD (Cohen et al., 2013), there remains a large gap in knowledge as to whether this transient failure is associated with the development of communication difficulties. The FFR has also been found to be disordered in a subset of children with neurodevelopmental disorders and in some cases, it appears more sensitive to processing deficits than the click-evoked ABR. The FFR is not currently used clinically. However, there are still a number of limitations on the potential clinical usefulness of the FFR, some of which the research in this thesis hopes to address.

2.7 Thesis Research Overview

The overarching aim of this thesis was to investigate the potential usefulness of auditory-evoked electrophysiological measures as biomarkers for neurodevelopmental communication disorders. In particular, we hypothesised that transient failure of the ABR at newborn screening is indicative of a delay in myelination of the auditory brainstem that may result in subtle auditory temporal processing deficits and the development of communication difficulties in later childhood. However, if the ABR normalises over time, the FFR may be a more sensitive, additional tool by which to identify atypical development in separate auditory brainstem structures or neural populations with preferences for complex stimuli.

In the chapters following Chapter Two, the research carried out in order to meet the overall aims of this thesis are presented in journal article format. Each paper is presented in a separate chapter and the first author is always the author of this thesis. Due to this format being used, it is possible that some concepts and literature will be repeated. The first study (Chapter Three) was a questionnaire study that sought to investigate whether children who show a transient failure of the automated ABR at newborn hearing screening are more likely to develop communication difficulties in later childhood. The second study (Chapter Four) was designed to investigate the potential clinical usefulness of the FFR, through comparison with wave V of the ABR, using a sample of normally hearing adults. This study also gave the op-
portunity to collect normative data for comparison purposes in the study in Chapter Five.

If auditory-evoked electrophysiological measures are to make useful biomarkers for neurodevelopmental communication disorders in later life then there should be sufficient evidence to suggest that a) individuals with such disorders demonstrate auditory temporal deficits and b) that electrophysiological measures are sensitive enough to detect such deficits in this population. Therefore, the third study (Chapter Five) sought to explore whether electrophysiological measures or a behavioural measure of temporal processing could distinguish adults with a neurodevelopmental communication disorder from a control group. In addition, data were collected from a group of adults with Multiple Sclerosis (MS) in order to explore whether adults with a neurodevelopmental communication disorder could be distinguished from adults with a confirmed demyelinating disorder. The purpose of this comparison was to explore the hypothesis that impaired myelination plays a role in neurodevelopmental communication disorders. In the three studies reported in Chapters Three to Five, the primary author (Terry) conducted the experiments, analysed the results and drafted the manuscripts. Authors Uus and Plack supervised Terry, advised on study design, analysis and provided guidance on both the interpretation of the results and the editing of manuscripts.
Chapter 3. Is Transient Failure of the Auditory Brainstem Response Associated with Developmental Communication Difficulties?

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This chapter was prepared for publication as a paper.
3.1 Abstract

The Newborn Hearing Screening Programme has identified a subset of intensive care unit graduates who show a transient failure of the auditory brainstem response (ABR) assessment at newborn hearing screening, which goes on to recover in the following weeks after screening. It is unclear as to whether this transient failure is clinically meaningful, however, there is evidence to suggest that it may reflect a delay in myelination and be linked to the development of communication difficulties in later childhood (Cohen et al., 2013). In collaboration with 11 NHS Trusts across England, 372 questionnaires were posted out to parents of children who had shown a transient failure of their ABR, and to parents of a control group. Otoacoustic emissions were normal in both groups and children were matched on sex and gestational age at time of screening. The questionnaire included a short version of the Children’s Communication Checklist 2 (CCC-2 Short), designed to assess the presence or absence of a communication difficulty. A total of 58 parents responded to the questionnaire. There was no significant difference between the two groups on scores of the CCC-2 Short, suggesting that transient failure of the ABR is not associated with the development of communication difficulties in later childhood.
3.2 Introduction

The Newborn Hearing Screening Programme (NHSP) was rolled out across the UK in 2001 and aims to identify permanent congenital hearing loss in infants as early as possible. In the UK, the NHSP has vastly improved on the previously used health visitor distraction screen that was administered at around 7-8 months of age, by reducing the average age of identification of hearing loss from 22 months (Fortnum and Davis, 1997) to 10 weeks (Uus and Bamford, 2006). Screening protocol for babies that are required to stay in the neonatal intensive care unit (NICU) for longer than 48 hours includes assessment of both their otoacoustic emissions (OAEs) and auditory brainstem response (ABR), due to a greater risk of auditory neuropathy spectrum disorder amongst this population (Berg et al., 2005; Xoinis et al., 2007). Measurement of the ABR at infancy could potentially provide insight into more than just a child’s risk of hearing loss. In particular, it has been found that a proportion of the NICU population, despite demonstrating normal OAEs, fail their ABR at initial assessment, but demonstrate a normal response in the following weeks (Uus, 2004; Psarommatis et al., 2006, 2011). The cause of this transient failure is unclear. It is possible that poor or noisy testing conditions on the ward may generate false-positive results. However, it has been suggested that the effect could be the result of the reversing of cellular damage caused by a hypoxic episode (Stein et al., 1983) and has been reported amongst infants recovering from hyperbilirubinemia (Wong, Chen and Wong, 2006). This transient failure may also be the result of a delay in the onset of myelination within the auditory brainstem. Indeed, NICU babies are exposed to a number of high risk conditions that have been found to be associated with immature myelination (Van Der Knaap and Valk, 2005). Roberts et al. (1982) reported that only one infant from a cohort of 75 NICU infants who failed their initial ABR assessment was subsequently diagnosed with hearing loss. The authors proposed that the initial, transient failure was the result of immaturity within the auditory brainstem. Berg et al. (2005) observed NICU hearing screen outcomes across 19 months in a
New York hospital and found that 24.1% of 477 graduates presented with a profile of present OAEs but an absent ABR in at least one ear. A logistic regression analysis failed to generate a model that could predict presentation of such a profile from risk factors that included gestational age, low birth weight, hyperbilirubinemia, a low Apgar score and anoxia. If these risk factors were unable to differentiate between babies who do and do not present with transient failure of the ABR, then delayed myelination within the auditory brainstem could be a plausible explanation. Myelination of the auditory brainstem is facilitated by two types of cell: Schwann cells and oligodendrocytes. Schwann cells are responsible for producing myelin within the auditory nerve (waves I-II of the ABR), whilst oligodendrocytes are responsible for producing myelin within the central auditory brainstem (waves III-V of the ABR, Rapin and Gravel, 2003). Myelination by oligodendrocytes has been shown to occur later than peripheral myelination (Moore, Perazzo and Braun, 1995, Moore and Linthicum, 2001). Therefore, a delay in the onset of myelination could theoretically result in an absent ABR that then recovers once myelination has had time ‘catch up’ and reach more rostral brainstem structures, such as the lateral lemniscus and inferior colliculus, which are thought to be responsible for the offset waves of the response (Starr, 1976).

Little research has been done to explore whether this transient failure is of clinical importance. However, it has been recently linked to communication difficulties in later childhood. Cohen et al. (2013) conducted a longitudinal study in which 74 NICU graduates were followed up until 4 months of age. Of this cohort, 46 were identified as having abnormal ABRs at initial testing and 28 were classified as having normal ABRs. The abnormal ABRs were characterised by significantly longer wave III absolute latencies and a significantly lengthened wave III-V inter-peak interval. All but one child in the abnormal ABR group went on to have a normal ABR before their hospital discharge date. It was found that 28% of children in the abnormal ABR group went on to receive a diagnosis of Autism Spectrum Disorder (ASD) compared to just 4% of children in the normal group, indicating that being in the abnormal ABR group gave an increased risk of
developing ASD. The results of this study suggest that abnormal ABRs that normalise could be of clinical importance in the domain of communication development.

Delayed myelination may result in poor signal-to-noise ratio of electrical signals along the auditory brainstem (Waxman, 1977; Inagaki et al., 1987; Rance, 2005), which would degrade auditory input during early development of the auditory system. Sensory deprivation has been found to impact on the production of myelin (Deremens, 1996; Li et al., 2011; Barrera et al., 2013). Therefore, despite recovery of the ABR, delayed myelination may impact upon the remaining myelination process, resulting in impaired myelination within the auditory brainstem. Impaired myelination has been found to have a detrimental effect on action potential timing fidelity whereas healthy myelination had been found to reduce spike jitter and promotes the precise temporal encoding of acoustic stimuli (Kim, Renden and Gersdorff, 2013). This is likely to be due to the faster propagation times of myelinated axons making them better equipped to transmit information with high temporal specificity. Transient failure of the ABR closely resembles a transient form of auditory neuropathy spectrum disorder (Starr et al., 1996), which has been associated with both temporal processing deficits in the auditory domain (Zeng et al., 1999; Rance, McKay and Grayden, 2004; Zeng, 2006) and communication difficulties, especially in noisy environments (Zeng, 2006; Rance et al., 2007). These same problems with temporal processing in the auditory domain have also been found in a subset of individuals with a diagnosed neurodevelopmental communication disorder, including ASD (McClelland et al., 1992; Lahat et al., 1995; Kwon et al., 2006; Azzam and Hassan, 2010; Basu, Krishnan and Weber-Fox, 2010; Roth et al., 2011).

It is important to explore whether this transient failure is clinically meaningful for a number of reasons. Firstly, it could mean that data collected by the NHSP could potentially be used to identify auditory temporal processing deficits and infants at risk of developing communication difficulties. Exploration of whether the data gathered
by the NHSP could facilitate earlier identification of communication difficulties is important because it would provide a cost and time effective method of identifying such deficits at an early stage in a child's development. As the NHSP has been so successful in reducing the age at which permanent congenital hearing impairment can be identified, it makes sense that it should be investigated as to whether the same data can be used for the early identification of more global impairments such as neurodevelopmental communication disorders for which communication difficulties are a central characteristic. Indeed, early intervention has been shown to be beneficial for such disorders (McGoey, Eckert and Dupaul, 2002; Woods and Wetherby, 2003; Schatschneider and Torgesen, 2004; Jones et al., 2007). Therefore, the aim of the current study was to provide preliminary data on whether there is an association between a transient failure of the ABR at newborn hearing screening and the development of a communication difficulty in later childhood.

3.3 Method and Materials

3.3.1 Recruitment

This study received full ethical approval from an NHS ethics committee (13/NW/0014) and was carried out in collaboration with 11 NHS Trusts throughout England. Initial contact was made by telephone by the principal investigator and Trusts that wished to become involved were subject to individual research and development approval processes before participant identification could begin. Collaborators from each trust agreed to make first contact with the parents of children who fit both the experimental group and control group inclusion criteria of the study. Suitability and contact information were accessed using the eScreener Plus (eSP) database, which holds all data collected through the NHSP. To be included in the experimental group a child needed to have:

- Been born between 1\textsuperscript{st} July 2003 and 30\textsuperscript{th} June 2009
• Spent a minimum of 48 hours in the NICU
• Had their audiological screen carried out using the NICU protocol
• Had a no clear response (NCR) in either one or both ears on the initial automated ABR assessment
• Had a clear response on their initial OAE assessment
• Passed their ABR assessment at diagnostic follow up

To be included in the control group a child needed to have:

• Been born between 1st July 2003 and 30th June 2009
• Spent a minimum of 48 hours in the NICU
• Had their audiological screen carried out using NICU protocol
• Had a clear response on both their initial automated ABR and OAE assessments

Collaborators were asked to identify the experimental group first and match them to control children based on sex and gestational age. Parents of children who fit our inclusion criteria for either the experimental or control group were sent a postal study pack. This pack included an invitation letter\textsuperscript{2}, participant information sheet\textsuperscript{3}, a questionnaire\textsuperscript{4} that included a copy of a short version\textsuperscript{5} of the Children’s Communication Checklist-2 (CCC-2 Short, Bishop, 1998; Bishop, 2003) and a consent form\textsuperscript{6}. Parents were requested to return the questionnaire and consent form in a free-post envelope that was provided. To encourage participation, parents who completed and returned the questionnaire to the research team were awarded with a £5.00 gift voucher for a popular online store.

\textsuperscript{2} Appendix A
\textsuperscript{3} Appendix B
\textsuperscript{4} Appendix C
\textsuperscript{5} Children’s Communication Checklist (CCC-2 Short) Bishop and Norbury © (2009) by Pearson, Assessment. Reproduced with permission. All rights reserved.
\textsuperscript{6} Appendix D
Revised in 2003, the CCC-2 was designed to act as a general screen for communication difficulties, particularly pragmatic and social interaction deficits (Norbury et al., 2004). The CCC-2 Short was chosen because the full version was deemed too lengthy to send out to parents and there were fears that the full version would decrease uptake. The questionnaire uses the following scoring system to ascertain the frequency with which a child demonstrates certain linguistic abilities:

Questions 1-6

0  Rarely or never (less than once a week)
1  Occasionally (once a week)
2  Regularly (once or twice a day)
3  Frequently or always (several times a day)

Examples of the statements in this section included “Gets the sequence of events muddled up when trying to tell a story or describe an event. E.g. if talking about a film they may describe the end before the beginning” and “Leaves off past-tense – ‘ed’ or other word endings.”

Questions 7-13

3  Rarely or never (less than once a week)
2  Occasionally (once a week)
1  Regularly (once or twice a day)
0  Frequently or always (several times a day)

Examples of statements in this section included “Speaks clearly, producing all speech sounds in a word accurately” and “Uses appropriate language to talk about future events (e.g. plans for tomorrow or plans for going on holiday).”

3.3.2 Sample

The target sample size was 163 in each group. A two group chi-square test with a 0.050 two sided significance level was found to
have 80% power to detect the difference between two groups when
the sample size in each group was 163. Therefore, the target of send-
ing out 800 questionnaires was set, given that the average question-
naire response rate is 20%. Unfortunately, due to logistical challenges
only a total of 372 questionnaires were eventually posted out.
58 questionnaires were returned in total, giving a response rate of
15.6%. There were 28 questionnaires returned from the control group
and 30 from the experimental group. Effect size for this sample was $d$
= 0.75. In the experimental group there were 20 males and 10 females
(mean age 88.5 months, range 58-123 months). For the control group
there were 17 males and 11 females (mean age 87.8 months, range 56-
123 months).

3.3.3 Analysis

Two children were excluded from analysis, one from the control
group and one from the experimental group. One child was excluded
because of a hearing loss and the other child was excluded because
English was not their first language. A total CCC-2 Short score was
calculated for each child, with reverse scoring for items 7-13. A high-
er score (max = 39) is associated with a communication difficulty. In a
preliminary analysis of the CCC-2 Short, a score of 5 or greater was
found to identify 94% of children with a communication difficulty and
a score of 4 or less identified 100% of typically developing children
(Bishop and Norbury, unpublished data). Therefore, for a chi-square
analysis, these cut-off scores were used to categorise subjects with the
presence or absence of a communication difficulty. This data was then
used to perform a chi-square analysis.

3.4 Results

3.4.1 Participant Descriptive Data

Mean descriptive data collected from the questionnaire can be
seen in Table 3.1. In the control group, one child had a diagnosis of
both dyslexia and auditory processing disorder, two children had a
diagnosis of autism and one child had a diagnosis of specific language impairment. In the experimental group, two children had a diagnosis of autism and one child had a diagnosis of attention-deficit hyperactivity disorder. This gave a total of four children in the control group with a clinically diagnosed neurodevelopmental communication disorder and three children in the experimental group. 72.4% of children in both the control and experimental condition were born prematurely.

Table 3.1

<table>
<thead>
<tr>
<th></th>
<th>Control (n=28)</th>
<th>Experimental (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CCC-2 short score</td>
<td>11.9</td>
<td>7.9</td>
</tr>
<tr>
<td>Age (months)</td>
<td>88.5</td>
<td>87.8</td>
</tr>
<tr>
<td>Weeks premature</td>
<td>6.7</td>
<td>5.2</td>
</tr>
<tr>
<td>Age of walking (months)</td>
<td>14.1</td>
<td>13.9</td>
</tr>
<tr>
<td>Age of talking (months)</td>
<td>12.9</td>
<td>11.9</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2552.5</td>
<td>2455.3</td>
</tr>
</tbody>
</table>

In the experimental group, 75.9% were born with labour complications and 51.7% required breathing assistance, compared to 55.2% of children in the control group being born with labour complications and only 37.9% requiring ventilation. 20.7% of children in the experimental group had been referred to a speech-language therapist compared to 48.3% of children in the control group.

3.4.2 Caregiver Demographics

In 84.2% of cases, the mother completed the questionnaire, and in 8.8% of cases it was the father. The highest level of educational achievement for the main caregiver was also assessed. 10.5% had no qualifications, 24.6% had achieved GCSE levels, 24.6% had achieved A levels, 14% had an undergraduate degree and 21.1% had achieved a
postgraduate degree. The highest percentage of questionnaires was
returned by parents under the care of the Pennine Acute Hospitals
NHS Trust, in particular the Bury (19.3%) and Rochdale catchment
areas (19.3%). The lowest numbers of questionnaires were returned by
parents under the care of the Blackpool Teaching Hospitals NHS
Foundation Trust catchment area (1.8%). Questionnaires were also
received from parents under the care of nine other NHS Trusts. 31%
of parents of children in the control group were concerned about their
child’s general development compared to just 20.7% of parents with
children in the experimental group. Other parental concerns and their
frequency in each group can be seen in Table 3.2.

Table 3.2

<table>
<thead>
<tr>
<th></th>
<th>Speaking</th>
<th>Listening</th>
<th>Communication</th>
<th>Reading/Writing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>31.0%</td>
<td>37.9%</td>
<td>31.0%</td>
<td>34.5%</td>
</tr>
<tr>
<td>Experimental group</td>
<td>13.8%</td>
<td>20.7%</td>
<td>13.8%</td>
<td>6.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Motor skills</th>
<th>Social skills</th>
<th>Learning</th>
<th>Behaviour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>31.0%</td>
<td>27.6%</td>
<td>31.0%</td>
<td>37.9%</td>
</tr>
<tr>
<td>Experimental group</td>
<td>3.4%</td>
<td>20.7%</td>
<td>13.8%</td>
<td>13.8%</td>
</tr>
</tbody>
</table>

3.4.3 Correlations

Table 3.3 shows the correlations that were conducted between
the CCC-2 Short total scores and the other variables collected from
the questionnaire. Point biserial correlations can only be run with
nominal variables that are dichotomous. Therefore, education of the
main caregiver was recoded into a dichotomous variable with the two
levels being whether the parent had attended university or not. Due to multiple comparisons, a Bonferroni correction was applied giving an alpha value of 0.002.

3.4.4 Means Comparison

Mean CCC-2 Short scores for the groups were compared using a means comparison analysis. Mean total scores for the CCC-2 Short can be seen in Table 3.1. It can be seen that contrary to our predictions, the control group had a higher mean score on the CCC-2 Short indicating a higher incidence of communication difficulties. A Pearson’s correlation found no age or gender effects. Total scores were not normally distributed for either group but could not be normalised using transformation algorithms. Therefore, a non-parametric test was used to carry out the analysis. A Mann-Whitney U test found no significant difference between the two conditions for CCC-2 Short scores ($Z = -1.074$, $n = 56$, $p = 0.283$). A post-hoc means comparison was carried out after excluding any children with a diagnosis of a developmental communication disorder. A Mann-Whitney U test found that there was still no significant difference between the two groups for CCC-2 Short scores ($Z = -1.121$, $n = 49$, $p = 0.262$).

3.4.5 Chi-square Analysis

As can be seen in Figure 3.1, an equal number of children in the control and experimental group were classed as having an absence of any communication difficulty. There were 10 children in the control group and 13 children in the experimental group who were classed as having the presence of a communication difficulty. Four children in the control group and three children in the experimental group had been diagnosed with a neurodevelopmental communication disorder. No significant relationship could be found between condition (experimental/control) and either the presence or absence of a communication difficulty. However, parental concern over general development was found to have a significant association with whether or not a child had the absence or presence of a communication difficulty.
Table 3.3

Correlations between CCC-2 Short Score and Other Measures Gathered from the Questionnaire Data

<table>
<thead>
<tr>
<th>Measure</th>
<th>Total CCC-2 short scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talking age</td>
<td>$r(38) = 0.220 \ p = 0.173$</td>
</tr>
<tr>
<td>Walking age</td>
<td>$r(49) = 0.058 \ p = 0.685$</td>
</tr>
<tr>
<td>Condition</td>
<td>$r(54) = -0.195, \ p = 0.150$</td>
</tr>
<tr>
<td>Education of care-giver</td>
<td>$r(52) = 0.281 \ p = 0.039$</td>
</tr>
<tr>
<td>Birth weight</td>
<td>$r(53) = 0.209 \ p = 0.125$</td>
</tr>
<tr>
<td>Full term</td>
<td>$r(54) = -0.022 \ p = 0.873$</td>
</tr>
<tr>
<td>Labour complications</td>
<td>$r(54) = -0.162 \ p = 0.232$</td>
</tr>
<tr>
<td>Physical disability and/or chronic illness</td>
<td>$r(54) = 0.254 \ p = 0.059$</td>
</tr>
<tr>
<td>Parental concern (general development)</td>
<td>$r(54) = 0.684^* \ p &lt; 0.001$</td>
</tr>
<tr>
<td>Therapist</td>
<td>$r(54) = 0.639^* \ p &lt; 0.001$</td>
</tr>
<tr>
<td>Statement of special education need</td>
<td>$r(54) = 0.624^* \ p &lt; 0.001$</td>
</tr>
<tr>
<td>School action</td>
<td>$r(47) = 0.413 \ p = 0.003$</td>
</tr>
<tr>
<td>Parental concern (speaking)</td>
<td>$r(54) = 0.598^* \ p &lt; 0.001$</td>
</tr>
<tr>
<td>Parental concern (listening)</td>
<td>$r(54) = 0.567^* \ p &lt; 0.001$</td>
</tr>
<tr>
<td>Parental concern (behaviour)</td>
<td>$r(54) = 0.684^* \ p &lt; 0.001$</td>
</tr>
<tr>
<td>Parental concern (motor skills)</td>
<td>$r(54) = 0.612^* \ p &lt; 0.001$</td>
</tr>
<tr>
<td>Parental concern (social skills)</td>
<td>$r(54) = 0.814^* \ p &lt; 0.001$</td>
</tr>
<tr>
<td>Parental concern (learning)</td>
<td>$r(54) = 0.692^* \ p &lt; 0.001$</td>
</tr>
<tr>
<td>Parental concern (reading/writing)</td>
<td>$r(54) = 0.661^* \ p &lt; 0.001$</td>
</tr>
<tr>
<td>Diagnosis of ASD</td>
<td>$r(56) = 0.471^* \ p &lt; 0.001$</td>
</tr>
<tr>
<td>Diagnosis of specific language impairment</td>
<td>$r(54) = 0.300 \ p = 0.025$</td>
</tr>
<tr>
<td>Diagnosis of ADHD</td>
<td>$r(54) = 0.119 \ p = 0.383$</td>
</tr>
<tr>
<td>Diagnosis of auditory processing disorder</td>
<td>$r(54) = -0.049 \ p = 0.717$</td>
</tr>
<tr>
<td>Ventilation</td>
<td>$r(52) = 0.004 \ p = 0.978$</td>
</tr>
<tr>
<td>Diagnosis of dyslexia</td>
<td>$r(54) = -0.049 \ p = 0.717$</td>
</tr>
<tr>
<td>Parental concern (communicating)</td>
<td>$r(54) = 0.720^* \ p &lt; 0.001$</td>
</tr>
<tr>
<td>Weeks premature</td>
<td>$r(39) = -0.178 \ p = 0.266$</td>
</tr>
</tbody>
</table>

Note. * $p < .001$
A 2 x 2 chi-square analysis was carried out with a value of 0.062 and an associated significance value of \( p = 0.893, df = 1 \).

Parental concerns over a number of different areas were found to highly correlate with CCC-2 Short score. Therefore, 2 x 2 chi-square analyses were run between these variables and whether subjects had an absence or presence of a communication difficulty. Due to multiple comparisons, a Bonferroni correction was applied giving an alpha of 0.005.

Table 3.4 shows the results of the significant associations that were found. Parental concern over general development was found to have the highest Cramer’s V of 0.563, meaning that 31.7% of the variation in frequencies of group membership (absence or presence of communication difficulty) can be explained by parental concern over general development. There was no significant relationship between communication ability and parental concern over speaking \( (X^2 = 6.560, df = 1, p = 0.010) \). Nor was there a significant relationship between whether a subject was classed as having an absence or presence of a communication difficulty, and parental concern over motor skills \( (X^2 = 6.495, df = 1, p = 0.011) \).

![Bar chart showing the number of experimental and control group children with either a presence or absence of a communication difficulty.](image-url)
3.5 Discussion

The results of the current study suggest that transient failure of the ABR at newborn hearing screening is not associated with development of a communication difficulty in later childhood. Around an equal number of the experimental and control group were found to have a clinical diagnosis of a neurodevelopmental communication disorder. Even with these children removed from the analysis, there was no difference in mean CCC-2 Short scores between the two groups. These results could be taken to suggest that the transient failure of the ABR at newborn hearing screening is not clinically meaningful. However, the current study recruited the parents of children who failed their initial ABR screen at newborn hearing screening based on the speculation that the failure is associated with delayed myelination at the time of testing. Yet it is also possible that environ-

<table>
<thead>
<tr>
<th>Variable</th>
<th>$X^2$</th>
<th>df</th>
<th>$p$</th>
<th>Cramer’s V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Listening</td>
<td>8.130</td>
<td>1</td>
<td>0.004</td>
<td>0.381</td>
</tr>
<tr>
<td>Communication</td>
<td>14.673*</td>
<td>1</td>
<td>&lt; 0.001</td>
<td>0.512</td>
</tr>
<tr>
<td>Learning</td>
<td>14.673*</td>
<td>1</td>
<td>&lt; 0.001</td>
<td>0.512</td>
</tr>
<tr>
<td>Social skills</td>
<td>16.178*</td>
<td>1</td>
<td>&lt; 0.001</td>
<td>0.537</td>
</tr>
<tr>
<td>Behaviour</td>
<td>9.022</td>
<td>1</td>
<td>0.003</td>
<td>0.401</td>
</tr>
<tr>
<td>Reading/writing</td>
<td>8.911</td>
<td>1</td>
<td>0.003</td>
<td>0.399</td>
</tr>
<tr>
<td>General Development</td>
<td>17.756*</td>
<td>1</td>
<td>0.001</td>
<td>0.563</td>
</tr>
</tbody>
</table>

Note. * $p < .001$
mental variables such as a noisy environment or blockage of the ear canal could have accounted for the transient failure and that it is not representative of a neurodevelopmental issue. However, it should be noted that the number of false-positives have fallen since the introduction of automated-ABR machines (Clemens and Davis, 2001), reducing the likelihood that these transient failures are a result of technological issues (Benito-Orejas et al., 2008).

ABR anomalies have also been associated with a number of medical conditions including perinatal asphyxia (Jiang et al., 2004) and low Apgar scores (Jiang et al., 2007). In the current questionnaire we were unable to establish whether these particular medical conditions had been present in each infant. However, it was found that parents of infants from the experimental group who did show the transient failure reported a higher incidence of both labour complications and breathing difficulties. Thus, these conditions may account for the transient ABR abnormality rather than a myelination delay. Teasing out the potential causes of this transient failure remains hugely challenging. Psarommatis et al. (2011) have suggested that the number of initial failures of the ABR could be reduced if screening is done one month after birth, giving any maturational delay time to catch up. In turn, this would reduce the number of false-positive cases that can cause unnecessary parental stress. However, dismissal of such a transient failure as purely ‘maturational’ could potentially overlook clinically important pathology (Uus, 2011), especially as a gap in knowledge remains as to its underlying cause.

There were further limitations in the current study that may be responsible for the lack of findings. The most prominent of these was undoubtedly that the study was underpowered. Effect size for the current study sample size was $d = 0.75$. According to Cohen (1988), an effect size of $d = 0.8$ represents a large effect. Any effect of the transient failure on communication development is likely to be small in scope and would therefore require a much larger data set to become apparent.

Postal questionnaires suffer from low response rates in general (Hox and De Leeuw, 1994) and in future, reminder letters may prove
useful for increasing response rates. The NHSP collects an enormous amount of data, with a recent newsletter from the Central Manchester NHS Foundation Trust estimating that 12,869 babies are screened every single week (‘Connect’ 2014). These data are stored on an internal database known as eSP, which was utilised for the current study. Access to these data was limited by a number of different gatekeepers and often challenging to access, despite the overwhelming evidence in the literature demonstrating auditory-evoked deficits in children with a diagnosed communication disorder. Preciousness over data was largely the reason that a postal study was required. We believe that serious consideration should be given to improving accessibility to the data for researchers to explore its potential in screening for more than just permanent congenital hearing loss. A larger sample would increase the power and scope of such a study.

Another potential study limitation lies in the sensitivity of the CCC-2 Short. The CCC-2 Short is a relatively novel measurement and may not have been sensitive enough to detect such difficulties in our sample. However, the longer CCC-2 version has been validated and found to successfully differentiate children with a neurodevelopmental communication disorder from controls (Geurts et al., 2004; Norbury et al., 2004). The CCC-2 Short was created by selecting the 13 most discriminating items from the CCC-2 using a validation sample that included children with language-learning impairment, ASD and typically developing children (aged 9-14 years). A standardisation sample was also used for children with a wider age range. However, the CCC-2 Short is yet to be validated on a large scale.

CCC-2 Short scores were found to be correlated with a number of different variables that were assessed on the questionnaire. Parental concern across a number of areas was most commonly associated with a higher CCC-2 Short score, including concern regarding general development, speaking, listening, communicating, learning, behaviour, motor skills, reading/writing and social skills. Chi-square analyses found that parental concern over listening, communication, learning, behaviour and social skills were significantly associated with the presence or absence of a communication difficulty. Parental concern over
general development had the strongest association, accounting for 31.7% of the variation in group classification (absence or presence of a communication difficulty). Parental concern over social skills and communication also accounted for a high percentage of variance, 28.8% and 26.2% respectively. These results suggest that parental concern may represent a clinically useful marker for the developmental communication difficulties. The use of parental concern as a screening technique has been suggested before (Glascoe, 1997), and Ozonoff et al. (2009) found that parental concern over development helped to predict whether infants would later be diagnosed with ASD. Parental concern has also been found to predictive of attention-deficit hyperactivity disorder (Bussing et al., 2003). Parental concern over communication development has sometimes been dismissed within the health care setting (Bultas, 2012). This may in part be due to the huge media attention that disorders such as ASD have received, causing unnecessary worry and over sensitivity in some parents. Indeed, parent-reported cases of ASD have significantly increased over the last decade (Blumberg et al., 2013). However, it is important to note a key limitation with this finding. Namely, parents of children already diagnosed with a communication disorder were reporting their concern after the diagnosis took place so it is likely that their concern was a result of the diagnosis and was not present beforehand. Nevertheless, there were parents who reported concern about their child’s general development in the absence of a diagnosis.

Additional limitations of this paper include the use of a self-reported postal questionnaire and risk of response bias. Some parents may have over- or under-played the extent of their child’s abilities. In a study that involved use of the Childhood Autism Spectrum Test as part of a parental questionnaire, Baron-Cohen et al. (2009) reported a ‘worried parent’ bias. Such a bias may also have affected the results of the current study. There may also have been a non-response bias, meaning that the parents who did take the time to respond to the questionnaire may have differed meaningfully from those who did not respond. For example, the caregiver who completed the questionnaire was almost always was female, meaning that the input of a male care-
giver was often overlooked. Furthermore, the questionnaire may have been biased toward stay-at-home parents who may have more time to observe their child’s behavior. The questionnaire was also highly biased toward English speaking parents. Although it should be noted that there was a good spread of responses from caregivers with a wide range of educational backgrounds. It is also possible that some parents did not correctly follow the instructions given in the questionnaire.

For example, one parent did not report any concerns about their child’s speech and language development yet did report that their child ‘rarely or never’ produced enjoyable or interesting conversations, or used appropriate language to talk about future or past events. Such an issue could possibly be avoided in the future by conducting telephone questionnaires with parents, which would ensure more confidence that the questions have been correctly understood. However, the results from the current study provide evidence that should encourage clinicians to take parental concern more seriously. In turn, it may be beneficial to provide more information to parents so that they are more educated and aware about the types of behaviours that could indicate the early stages of communication difficulties. This could be implemented into the NHSP through the use of leaflets provided at discharge from the hospital.

3.5.1 Conclusions

It remains unclear as to whether transient failure of the ABR at newborn screening is of clinical importance. Determining whether the failure is the result of a delay in myelination that may facilitate the development of communication difficulties is extremely challenging, due to so many variables possibly accounting for such a transient failure. Nevertheless, results of the current study suggest that parental concern regarding a child’s general and communication development may be a clinically useful marker for children at risk of developing a communication difficulty. We believe that more in depth research with much larger samples should be conducted in this area.
3.6 Acknowledgements

We would like to thank all of the NHS Trusts and collaborators that helped to make this study possible: Dr Jane Lyons (Pennine Acute Hospitals NHS Trust), Amanda Hall (University Hospitals Bristol NHS Foundation Trust), Paul Oddie (Salford Royal NHS Foundation Trust), Dr Patricia Taylor (Bridgewater Community Healthcare NHS Trust), Susan Donald (Countess of Chester Hospital NHS Foundation Trust), Colette Clarkson (Blackpool Teaching Hospitals NHS Foundation Trust), Lesley Peplow (University Hospitals Coventry and Warwickshire NHS Trust), Dr Gillian Painter (Central Manchester Hospitals NHS Foundation Trust), Andrea Curran (University Hospital of South Manchester NHS Foundation Trust). Special thanks also to all the parents who took the time to complete and return the questionnaire, your participation is very much appreciated and vital to research such as this. Special thanks also to Professor Courtenay Norbury for her permission in letting us use the short version of the CCC and her guidance in its analysis.
Chapter 4. An Examination of the Clinical Potential of the Frequency Following Response Through Comparison with the Auditory Brainstem Response

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This chapter was prepared for publication as a paper and recently underwent peer review at Hearing Research.
4.1 Abstract

Evidence suggests that the frequency following response (FFR) may be more sensitive to subtle auditory processing difficulties in individuals with neurodevelopmental communication disorders than the conventionally used, click evoked auditory brainstem response (ABR). However, normative data for the FFR are limited. The aim of the current study was to add to the pool of normative data and explore the clinical potential of the FFR through comparison with the click-evoked ABR. Participants comprising 29 normally hearing adults with no known neurological or communication disorders were presented with five amplitude modulated tones, with a carrier of 590 Hz and modulation rates of 95-135 Hz in 10 Hz increments. A novel stimulus design enabled recording of amplitude and latency for the FFR to both the temporal fine structure and envelope simultaneously. To determine latency, a group delay value was calculated for each participant by measuring the slope of the line relating FFR component phase to frequency. Amplitude and absolute latency were also collected for wave V of the click-evoked ABR. No correlation was found between click-evoked ABR latency and FFR latencies or between ABR and FFR amplitude data, except for a significant negative correlation between amplitude of the FFR to the upper side band (685-725 Hz) and amplitude of wave V of the click-evoked ABR. The FFR to the stimulus envelope and lower side band (455-495 Hz) were found to occur significantly later than wave V of the ABR. However, it remains unclear as to whether these results are a function of the cochlear traveling wave delay or separate neural generators within the subcortical auditory pathway. The current study suggests that whilst the FFR has clinical potential in a number of areas, issues still remain with testing time, reliability and between subject variability.

Keywords

Frequency following response; auditory brainstem response; communication disorders.
4.2 Introduction

The conventional click-evoked auditory brainstem response (ABR) comprises five clinically useful waves labeled I to V, which represent processing by different neural generators within the subcortical auditory pathway. The timing of each wave is highly replicable across subjects so that delays of even a fraction of a millisecond are of clinical importance (Hood, 1998). These characteristics have made the click-evoked ABR an electrophysiological gold standard measure used in both clinics and research for assessing the efficiency of this pathway. In research settings, the frequency following response (FFR) has also been used as a measure of subcortical auditory brainstem efficiency. It is a sustained, auditory evoked response that mimics the waveform of acoustic stimuli and reflects neural phase locking (Gardi, Merzenich and McKean, 1979), which is believed to represent temporal encoding (Levi, Folsom and Dobie, 1995). Currently, the FFR is not routinely used as a clinical tool despite evidence that it may be more sensitive to subtle auditory processing deficits than the conventional click-evoked ABR. In particular, research has demonstrated that when evoked by complex stimuli, the FFR is disordered in a subset of individuals with neurodevelopmental communication disorders despite this same subset often retaining a normal click-evoked ABR (King et al., 2002; Song et al., 2006; Russo et al, 2008, 2009). If the FFR is able to detect subtle auditory processing deficits amongst patients with a neurodevelopmental communication disorder that would normally go undetected by the traditionally used click-evoked ABR, then it may have clinical utility in the early identification of infants at risk of developing such a disorder. Researchers from Northwestern University, Illinois have taken a step toward using the FFR as a clinical tool with the development of the BioMARK (formerly BioMAP, Abrams and Kraus, 2005). This clinical tool uses a pre designated latency window to determine if the latency of the FFR falls within normal limits through comparison with control values taken from a sample of typically developing children aged 8-12 years old. Despite this step forward and evidence to suggest that BioMark can effectively identify children with a neurodevelopmental communication disorder
(Kumar and Singh, 2015) there is still limited evidence to support the use of the FFR as a clinical tool, and evidence regarding the effectiveness of BioMark is scarce and largely produced from just one research group. The potential clinical applications of the FFR are further hindered by a lack of normative latency values and a lack of clarity about neural correlates.

It has been suggested that the FFR has similar neural generators to wave V of the click-evoked ABR (Glaser et al. 1976; Sohmer, Pratt and Kinarti, 1977), namely the inferior colliculus (Smith, Marsh and Brown, 1975; Stillman, Moushegian and Rupert, 1976; Daly, Roeser and Moushegian, 1976). However, the evidence is not conclusive. For example, Gardi, Merzenich and McKean (1979) found that removal of both inferior colliculi did not affect production of the FFR and in a direct comparison study; Hoorman et al. (1992) reported a poor correlation between ABR and FFR latencies. Furthermore, Batra, Kuwada and Maher (1986) have reported an FFR latency of 8.2 ms in response to continuous pure tones, which is considerably longer than the average click-evoked wave V latency of around 5-6 ms (Norrix et al., 2012; Konrad-Martin et al., 2012).

Several studies have focused on establishing the latency of the envelope following response of the FFR in particular. Amplitude modulation is a common element in human speech (Dolphin and Mountain, 1992), and temporal cues in speech which consist of modulation frequencies of between 64 and 500 Hz are thought to be processed in the brainstem and responsible for encoding speech characteristics such as prosody and voicing (Giraud et al., 2000). Accurate encoding of both the envelope and temporal fine structure (TFS) of a stimulus is believed to be important for understanding speech (Rosen, 1992), and there is evidence that reduced sensitivity to changes in envelope modulations in particular may be associated with developmental communication difficulties (Benasich and Tallal, 2002, Russo et al., 2009). Using a sample of four normally hearing subjects (14-29 years) and six hearing impaired subjects (28-56 years), Kuwada, Batra and Maher (1986) concluded that tones amplitude modulated (AM) at
frequencies of between 100 and 350 Hz produce an envelope following response latency of between 7 and 9 ms. In a later animal study using Mongolian gerbils, Dolphin and Mountain (1992) reported a much shorter envelope following response latency of 6.6 ms for AM tones modulated at frequencies of 50-180 Hz. Purcell et al. (2004) studied a sample of 25 normally hearing female participants (18-43 years) and reported an envelope following response of 8.6 ms for AM tones modulated at between 80 and 190 Hz, which was longer than the FFR latency reported by Dolphin and Mountain (1992). However, it should be noted that the authors did not account for a 0.9 ms tubing delay. Collectively, these studies place the latency of the FFR to stimulus envelope at somewhere between 6 and 9 ms. Once again, this is a longer mean latency than is commonly found for wave V of the ABR, suggesting separate neural generators.

Comparison of the ABR and FFR is important if we are to understand more about how the FFR could potentially contribute to the clinical field, and increasing the pool of normative data that currently exists for the FFR is essential if this measurement is to be useful in the identification of possible pathologies. Furthermore, more certainty on the neural generators of the FFR and its components would be necessary in order to better pinpoint potential sites of lesion. Latency comparison with the conventional click-evoked ABR will help reveal more about neural generators of the FFR, potentially giving insight as to where FFR pathologies may arise from within the auditory brainstem.

The current study also aims to increase our understanding of the relation between the ABR and FFR through the use of a stimulus design that is able to simultaneously elicit the FFR to the envelope of a stimulus and the TFS. By adding and subtracting the FFR response to stimuli of opposite polarities these two components can be emphasised and separated (Huis in’t Veld, Osterhammel and Terkildsen, 1977; Yamada, Yamane and Kodera, 1977). It still remains debated as to whether TFS and envelope cues are processed by separate neural generators with respect to their roles in representing complex acoustic
signals. Evidence suggests that envelope and TFS cues may serve separate functions when it comes to speech and language proficiency (Shannon et al., 1995; Smith, Delgutte and Oxenham, 2002; Zeng et al., 2004). Establishment of whether these cues are generated by separate neural populations could be of clinical importance for infants at risk of developing neurodevelopmental communication disorders. For example, damage to neural populations responsible for generating the FFR to the envelope but not the TFS may have implications for the type of communication difficulties an individual may experience. This would provide clinically useful information that the conventional click-evoked ABR cannot. In the studies by Dolphin and Mountain (1992) and Purcell et al. (2004), magnitude and phase of the response were calculated using a fast Fourier transform analysis and a measure of group delay was obtained from unwrapping the phase points. The FFR is an ongoing response and as a result, response onset is challenging to pinpoint. However, for a fixed stimulus phase, the variation in the phase of a response to a sinusoidal acoustic stimulus as a function of frequency can be used to determine the group delay of the response (Gummer and Johnstone, 1984). Group delay is essentially a measure of the delay of the major neurophysiological response relative to arrival of the stimulus to the ear (Dolphin and Mountain, 1992). It is an objective and indirect measure of neural response latency, with the slope of the line relating phase to frequency reflecting how long after stimulus onset a response occurs, and hence where in the auditory pathway it is likely to have been generated. Using this method will generate a latency for phase locking to both the envelope and TFS, and allow insight into possible neural generators for each component. Comparison of the amplitude of the FFR components and wave V of the ABR will also provide more insight into the robustness of the FFR as a potential clinical measure. In addition, this paper will likely lend more insight into the potential usefulness of the FFR as a clinical tool in terms of testing times and practicability of use in a clinical setting. Therefore, this paper aims to address the following research questions, in a healthy, normally hearing adult population:
1. Does the envelope following response reflect the same neural generators as the TFS following response?

2. Does wave V of the ABR reflect the same neural generators as the FFR?

3. Do amplitudes of the ABR and FFR provide the same information?

4.3 Materials and Methods

4.3.1 Participants

A power analysis was carried out to determine adequate sample size. It was found that with an effect size of \( d = 0.6 \), a sample of 24 in each group would have 80% power to detect a difference between the two groups. Twenty-nine normally hearing adults took part in the study (PTA thresholds \( \leq 20\text{dB HL}, 250 \text{Hz}-8 \text{kHz} \) with a mean age of 24 years (age range 18-33 years). Tympanometry and otoacoustic emissions were assessed to ensure they fell within the normal range. All procedures were carried out according to the British Society of Audiology recommended guidelines (British Society of Audiology, 2011, 2013). All participants confirmed that they had not been diagnosed with any communication or neurological disorders. Each participant was allocated a three hour session and financial reimbursement was provided for time and travel expenses. The study was approved by a University of Manchester Ethics Committee (reference: 12283).

4.3.2 FFR Recordings

All electrophysiological testing took place within a double walled sound attenuating booth. Skin was prepared using alcohol wipes and a mild abrasive gel. The electrodes were then attached using Ten20 electro conductive gel and surgical tape was used to keep them in place. A vertical montage was used to collect responses using an electrode placed on the high forehead (Fz, active), a 7th vertebra
electrode (C7, reference), and a lower forehead electrode (FPz, ground). Once the electrodes were attached, participants were made comfortable in a reclining chair. Participants were asked to keep as still as possible during the testing session and many fell asleep throughout the duration of the testing period. Testing consisted of five conditions, each lasting around 8 minutes, with a short break between each session. During each condition, participants listened to one of five AM tones. In the frequency domain, the AM tones had components at the carrier frequency and at two adjacent side bands. The frequencies of the components in the five conditions used in the current study (in Hz) were: 495-590-685; 485-590-695; 475-590-705; 465-590-715 and 455-590-725. Each stimulus was 200 ms in duration (including 10 ms raised-cosine onset and offset ramps) and presented in alternating polarities separated by a 125 ms silent interval after each stimulus. Use of alternating polarities enabled separate extraction of the envelope and TFS responses. The overall stimulus level was 80 dB SPL and stimuli were presented to the right ear only. Presentation rate was 1.5/sec. The stimuli were presented using a TDT RP2.1 digital to analogue converter via Etymotic ER30 insert headphones and the transducers were located outside the sound booth to eliminate stimulus artefact. Recordings were made using a RA16 Medusa Base Station (Tucker-Davis Technologies, or TDT, Alachua, Florida, USA) and were band pass filtered online between 30 and 3000 Hz, and notch filtered at 50 Hz. Each condition was repeated three times, with each repetition consisting of 500 sweeps. Stimuli were presented in a random order to counteract any effects of restlessness from participants toward the end of testing.

4.3.3 ABR Recordings

Testing conditions and skin preparation were identical to those used for the FFR recordings. 100 μs alternating polarity clicks were presented at a rate of 11.1 per second and at a level of 80 dB nHL. ER3A insert headphones were used to present the stimuli to the right ear only. Electrodes were placed on the high forehead (Fz, active), the
right mastoid (reference) and the lower forehead (Fpz, ground). A clinical Interacoustics IABase 2000 machine was used to collect ABR recordings from participants. A high pass filter of 100 Hz and low pass filter of 3 kHz were applied and three grand averages of 2,000 sweeps were collected for each participant.

4.3.4 Analysis

4.3.4.1 FFR Latency and Amplitude

Average response waveforms for each condition were computed offline for each participant in MATLAB (The Mathworks, 2010). Average responses to the two polarities of each presented stimulus were then either added or subtracted from each other to produce an estimate of phase locking to the stimulus envelope and TFS respectively. The waveforms were then analysed using a discrete Fourier transform (DFT) with a frequency at the modulation rates (95, 105, 115, 125, 135) for the addition waveforms, and at the component frequencies for the subtraction waveforms. For the addition waveforms, corresponding to phase locking to the envelope, it was expected that a peak at the modulation value for the corresponding condition would be seen. For example, for condition one (modulated at 95 Hz), a peak at 95 Hz would be expected (Kuwada, Batra and Maher, 1986; Dolphin and Mountain, 1992). For the subtraction waveforms, corresponding to phase locking to the TFS, peaks at the carrier frequency of 590 Hz and at the two side bands were expected. To determine the latency of the envelope and TFS following responses, a MATLAB (Mathworks, 2010) script was run using the data generated from the five different stimuli.

The group delay value was defined as the slope of the linear regression of the phase of each component (in periods) plotted against frequency. The phase was unwrapped such that the linear fit gave the least sum of the squared residuals compared to a linear fit, with the

\footnotesize{7 For participants 4 and 9, only 4,000 sweeps were collected.}
condition that regression lines with slopes less than 3 ms and greater than 20 ms were not considered. An 18.2 ms tubing delay was accounted for in the MATLAB script used to calculate the group delay values, which gave the response latency relative to the ear canal. A frequency component was excluded from the group delay analysis if the response to this component was less than 3 SD above the noise floor (calculated as the average DFT power in the FFR in a band 5-33 Hz below the component frequency and 5-33 Hz above the component frequency). If fewer than three points remained after this procedure, the fit was discarded. For the FFR latency to the envelope, the data from 14 participants were discarded. For the FFR latency to the lower side band, the data from seven participants were discarded and for the FFR latency to the upper side band, 13 data sets were discarded. FFR amplitude was calculated as the amplitude of the DFT at each component frequency. For the FFR amplitude, two data sets were missing due to impaired data collection.

4.3.4.2 ABR Latency and Amplitude

Absolute latency for wave V of the ABR was computed offline for each participant. Waveforms were analysed by the first author and were checked a second time by an additional researcher who was blind to the results of the first analysis, thus providing a test retest analysis. There was no inconsistency between the two researchers for the peaks that were selected to represent wave V. Only after these two comparisons were data points finalised for analysis. The peak selection procedure for wave V had two steps. The first step involved plotting the waveform and selecting the peak of the wave that had been identified by the two separate researchers using a cursor. The cursor was then used to identify both the exact amplitude of the peak and the corresponding latency. Component amplitude (peak to following trough) data for wave V was obtained by reading the amplitude data point corresponding to the wave V peak latency and the following trough. Amplitude was then defined as the difference between the electric potentials obtained from each position. For wave V latency
and amplitude, only data for 18 participants could be collected due to participant attrition.

4.4 Results

4.4.1 Does the Envelope Following Response Reflect the Same Neural Generators as the TFS Following Response?

FFR latency for the envelope was not found to be significantly different from the latency of the TFS following response, nor were the latencies of the upper and lower side bands significantly different from each other.

Table 4.1 shows the mean latencies for the FFR to stimulus envelope and TFS as well as the latency ranges for each component. Due to discarded fits and participant attrition only a proportion of the total number of participants had values for each measure for comparison purposes. The numbers in brackets represent the standard error.

The mean waveform and spectra for the FFR to the envelope across the 23 participants with usable data can be seen in Figures 4.1 A and 4.1 C, whilst the mean waveform and spectra for the FFR to the TFS across the same participants can be seen in Figures 4.1 B and 4.1 D. Figure 4.2 gives the phase versus frequency plots for Subject 3. The straight line represents the linear regression of the phase of each component (in periods) plotted against frequency, and the slope represents the group delay value (the response latency relative to the ear canal). A Wilcoxon signed ranks test showed that the FFR latency for the envelope was not significantly different from the latency of the lower side band (TFS) \((n = 15, Z = -0.568, p = 0.570)\) nor the latency of the upper side band \((n = 11, Z = -0.356, p = 0.722)\). Neither were the latencies for the upper and lower side bands significantly different from each other \((n = 15, Z = -1.022, p = 0.307)\).

4.4.2 Does Wave V of the ABR Reflect the Same Neural Generators as the FFR?

Latency of the FFR to the stimulus envelope was found to occur significantly later than wave V of the click ABR, as was the latency of the FFR to the lower side band. However, latency of the FFR to the upper side band did not occur significantly later than wave V of the click ABR.
Table 4.1

**Summary of Mean Results**

<table>
<thead>
<tr>
<th>Measure</th>
<th>n</th>
<th>Mean latency (ms)</th>
<th>Latency range (ms)</th>
<th>n</th>
<th>Mean amplitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABR wave V</td>
<td>18</td>
<td>5.00 (0.0068)</td>
<td>4.37-5.52</td>
<td>18</td>
<td>0.726 (0.0741)</td>
</tr>
<tr>
<td>FFR to envelope</td>
<td>15</td>
<td>7.87 (0.7355)</td>
<td>4.68-14.11</td>
<td>27</td>
<td>0.067 (0.0103)</td>
</tr>
<tr>
<td>FFR to lower side band (TFS)</td>
<td>22</td>
<td>7.62 (0.3751)</td>
<td>4.58-13.14</td>
<td>27</td>
<td>0.029 (0.0030)</td>
</tr>
<tr>
<td>FFR to upper side band (TFS)</td>
<td>16</td>
<td>7.14 (0.8645)</td>
<td>3.54-16.47</td>
<td>27</td>
<td>0.010 (0.0019)</td>
</tr>
</tbody>
</table>

No significant correlations could be found between wave V of the click ABR and any of the FFR latency components.

Mean ABR wave V latency can be seen in Table 4.1. Figure 4.3 gives the mean click-evoked ABR waveform across 18 participants who had provided ABR data. A paired samples t-test found that latency of the FFR to the stimulus envelope was significantly longer than latency of wave V of the click ABR (t(8) = 2.721, p = 0.026). Latency of the FFR to the lower side band was also found to be significantly greater than the latency of wave V of the click ABR (n = 14, Z = -3.107, p = 0.002). However, a Wilcoxon signed ranks test found that there was no significant difference in latency between wave V of the click ABR and latency of the FFR to the upper side band (n = 9, z = -1.007, p = 0.314). There was no significant correlation (Pearson’s) found between the latency of the FFR to the stimulus envelope and latency of wave V of the click ABR (r(7) = 0.523, p = 0.149) nor was there a significant correlation (Spearman’s rho) found between the FFR to the lower side band and latency of wave V of the click ABR (r_s(12) = 0.241, p = 0.407). The latency of the FFR to the upper side
band also did not correlate with latency of wave V ($r_s(7) = 0.370, p = 0.327$).

4.4.3 Do Amplitudes of the ABR and FFR Provide the Same Information?

The final research question investigated whether the FFR and click-evoked ABR provide the same information in terms of amplitude. No significant correlations could be found between amplitude of wave V of the click ABR and either amplitude of the FFR to the stimulus envelope or amplitude of the FFR to the lower side band. However, there was a significant, negative correlation found between amplitude of wave V and amplitude of the FFR to the upper side band.

A (Spearman’s rho) correlation between amplitude of the FFR to the stimulus envelope and amplitude of wave V of the click ABR ($r_s(14) = 0.053, p = 0.846$) found no significant correlation nor was there a significant correlation (Pearson’s) between amplitude of the FFR to the lower side band and wave V ($r(14) = -0.032, p = 0.906$). However, there was a significant, negative correlation (Spearman’s rho) between the amplitude of the FFR to the upper side band and wave V amplitude ($r_s(16) = -0.473, p = 0.047$). A combined TFS value was computed by averaging the amplitudes of the lower and upper side band for each participant. There was no significant correlation between this value with the amplitude of wave V ($r(16) = -0.223, p = 0.375$).
Figure 4.1: Mean FFR waveforms and spectra across 23 participants with usable data for condition five. (A) Mean FFR waveform for added polarities (envelope). (B) Mean FFR waveform for subtracted polarities (TFS). (C) Mean FFR spectra for added polarities (envelope). (D) Mean FFR spectra for subtracted polarities (TFS).
Figure 4.2: FFR phase versus frequency plots for Subject 3. The straight line is the linear regression of the phase of each component (in periods) plotted against frequency, and the slope represents the group delay value (the response latency relative to the ear canal). (A) Envelope phase versus frequency plot. (B) Lower side band phase versus frequency plot. (C) Upper side band phase versus frequency plot.
Figure 4.3: Mean click-evoked ABR waveform across 18 participants who had provided ABR

4.5 Discussion

The current study aimed to explore the clinical potential of the FFR through comparison with the conventional click-evoked ABR. Latency of the FFR to the stimulus envelope was not significantly different from the latency of the FFR to the TFS for either the upper or lower side band frequencies. Similar latencies likely indicate that these FFR components share similar neural generators. The current study found an average FFR latency to stimulus envelope of 7.87 ms. This latency is in keeping with the envelope following response latencies reported by Kuwada, Batra and Maher (1986) and Purcell et al. (2004), and the overall FFR latency reported by Batra, Kuwada and Maher (1986). However, it is considerably longer than the 6.6 ms reported by Dolphin and Mountain (1992). This variance may in part be explained by the cochlear travelling wave delay. Transduction of signals through the auditory pathway is affected by the travelling wave of the basilar membrane, which results in latency of the FFR decreasing as carrier frequency increases (John and Picton, 2000; Ruggero and Temchin, 2007). Dolphin and Mountain (1992) used a carrier frequen-
cy of 1 kHz, which would have resulted in a shorter travelling wave delay than the 590 Hz carrier frequency used in the current study.

The second research question concerned whether wave V of the ABR reflects the same neural generators as the FFR. The FFRs to the envelope and the lower side band of the TFS (455-495 Hz) were found to occur significantly later than wave V of the ABR. In addition, neither of the latencies for these components were found to correlate with the latency of ABR wave V. The FFR to the TFS upper frequency side band (685-725 Hz) did not occur significantly later than wave V of the ABR. The lack of any correlation between the latency of the FFR components and wave V of the ABR supports the earlier findings of Hoorman et al. (1992) and Song et al. (2006) who also found no correlation between the two responses. Song et al. (2006) conclude that this lack of correlation indicates a separate processing component within the auditory brainstem that is unique to more complex stimuli.

The final research question was concerned with whether amplitudes of the ABR and FFR provide similar information. Only the amplitude of the FFR to the upper side band was found to significantly correlate with wave V amplitude, although negatively. No other significant correlations were found between any of the amplitude measures, although no strong conclusions can be drawn due to the small sample size. There has been little previous research in this area. However, the results are in contrast to those of Parthasarathy et al. (2014) who found that in young rats (3-6 months) amplitude of wave V was significantly correlated with envelope following responses modulated below 100 Hz. Further investigation with a larger sample is required to further understand the relationship between ABR and FFR amplitudes.

4.5.1 Separate Neural Generators or Cochlear Travelling Wave Delay?

The significant difference in latency between wave V of the ABR and both the FFR to the envelope and TFS lower side band (455-
495 Hz) found in the current study could be a function of the cochlear travelling wave delay rather than reflecting separate neural generators. The click stimulus used in the present experiment to elicit the ABR had a wide band spectrum with energy up to 10 kHz. Early research by Don and Eggermont (1978) has demonstrated that the end compound response generated by a click stimulus is dominated by responses at the basal end of the cochlea. The travelling wave delay at the 10 kHz place is thought to be around 0.5-1 ms in humans (Eggermont, 1979; Ruggero and Temchin). If we assume that the FFR in the current study originated from the 590 Hz place within the cochlea then it has been estimated that the cochlear travelling wave delay would be around 3.5 ms (Ruggero and Temchin, 2007). Each stimulus used to elicit the FFR in the current study had a 590 Hz carrier frequency. By subtracting 3.5 ms from both the envelope following response and TFS following response latencies, and 0.5 ms from the wave V mean latency, neural delays for the current study can be quantified. This would give all four measures a neural delay of between 3.64 and 4.50 ms. This is a crude calculation but suggests that FFR components and wave V of the conventional ABR may indeed share the same neural generators within the auditory pathway. Therefore, if the FFR does elicit the strongest cochlear response from the 590 Hz place then the cochlear travelling wave delay could explain why components of the FFR were found to be significantly longer in latency than wave V of the click-evoked ABR.

However, there is mixed evidence regarding whether the FFR does in fact reflect activity in the cochlear place corresponding to the carrier frequency used to elicit the response. It is generally established that for low level signal levels (< 50 dB SPL) the FFR is generated apically and near the cochlear place corresponding to the eliciting stimulus (Huis in’t Veld, Osterhammel and Terkildsen, 1977; Yamada et al., 1978). However, for high level stimuli (> 50 dB SPL) the picture is far less clear. For example, low frequency tones in the region of 500 Hz have been shown to excite cochlear regions 2-3 octaves basal to the frequency of stimulation (Rose et al., 1971; Rhode, 1978). Similar studies have found results to suggest that at high levels the
FFR to low frequency tones is generated by more basal activity (Yamada et al., 1978; Moushegian, Rupert and Stillman, 1978; Gardi and Merzenich, 1979). A more basal region with a characteristic frequency of say 2 kHz, which is near to the frequency of maximum sensitivity, has a travelling wave group delay of around 1.5 ms in humans (Ruggero and Temchin, 2007). Accounting for this length of travelling wave delay would see the components of the FFR have neural group delay values of between 5.64-6.37 ms, meaning that they still occur between 0.64-1.37 ms later than the wave V of the ABR and suggest separate neural generators.

The anatomical evidence regarding neural generators for the ABR and FFR remains inconclusive. Whilst there is evidence to suggest that the inferior colliculus is the major neural generator of the FFR (Smith, Marsh and Brown, 1975) and click-evoked ABR (Smith, Marsh and Brown, 1975; Stillman, Moushegian and Rupert, 1976; Glaser et al., 1976), there is also evidence to suggest that it is not involved in click-evoked ABR generation (Kiren et al., 1994) or generation of the FFR (Gardi, Merzenich and McKean, 1979). One possible explanation for the variance of results across studies is that there are multiple generators of the FFR itself, or that the FFR may have separate but also overlapping generators to the ABR. Gardi, Merzenich and McKean (1979) suggest that 50% of the FFR amplitude is generated within the cochlear nucleus, 20% generated from the superior olivary complex and 25% from the cochlea. Phase locked activity has even been reported as high in the auditory pathway as the medial geniculate body (Rouiller, de Ribaupierre and de Ribaupierre, 1979). Davis and Britt (1984) reported a low frequency (200-500 Hz) FFR of 6.8-7 ms in cats, the amplitude of which was reduced after bilateral ablation of the inferior colliculus. However, far more significant changes could be seen in the response after ablation of the lateral lemnisci, superior olivary complexes and cochlear nuclei. Indeed, the current study demonstrated an enormous range of latencies for all FFR components (3.54-16.47 ms), perhaps reflecting the varying influence of different neural generators. Although the group delay calculation in the current study was limited to a minimum latency of 3 ms, an elec-
trode that reflects multiple sources of the FFR with differing latencies will result in a summated response that would have a phase corresponding to the mean of phases from the individual generators, assuming equal response amplitude. In the case of equal amplitude sine waves, the addition of a sine wave with a phase of 90° and one with a phase of 270° would result in a sine wave with a phase of 180°. However, when amplitudes are unequal, the resulting wave will be weighted towards the phase of the sine wave that has the largest amplitude. If the FFR has multiple generators, then the strongest generator of any given individual response may weight the response and this could account for the variance amongst study results and reflect individual differences. This argument was put forward by both Davis and Hirsh (1976) who suggested that variations in FFR latencies are due to different travelling cochlear wave delays caused by multiple initiation sites along the basilar membrane, with each source having its own phase vector that could cancel out or enhance one another. The argument for multiple neural generators is further strengthened by evidence from studies that have used different electrode montages to record the FFR. For example, both Galbraith, Bagasan and Sulahian (2001) and Huis in’t Veld, Osterhammel and Terkildsen (1977) found that a vertical montage produces a less robust but longer latency FFR than a horizontal montage, and Stillman, Crow and Moushegian (1978) differentiated between two different scalp-recorded FFR that produced variable latencies. Nevertheless, multiple generators of the FFR along the auditory pathway are likely to have complex interactions and overlap in their produced activity making pin pointing exact generators challenging (Davis and Britt, 1984). It remains unclear as to whether the results of the current study demonstrate separate neural generators for the ABR wave V and FFR, or an effect of the cochlear travelling wave delay.

4.5.2 Clinical Potential of the FFR

Some individuals with neurodevelopmental communication disorders show aberrant FFRs, despite demonstrating a click-evoked ABR
within normal limits (King et al., 2002; Song et al., 2006; Russo et al., 2008, 2009). This suggests that the FFR can identify subtle auditory processing deficits that may be missed if the conventional click-evoked ABR alone is carried out. Although measurement of the FFR has not yet proven itself to be either fast or reliable enough to rival a measurement such as the ABR, these results suggest that the FFR could have clinical potential in certain areas such as the early identification of children at risk of developing neurodevelopmental communication disorders in later life. Previous researchers have suggested that it is the type of stimulus that can account for this phenomenon because these studies have used complex tones to elicit the FFR that better represent the complex acoustic signals of speech (Shannon et al., 1995; Alcantara et al., 2012) than a click stimulus, and can therefore better identify subclinical auditory processing deficits thought to play a role in communication disorders. However, based on the results of the current study, separate neural generators for the FFR and wave V of the ABR may also explain why some individuals demonstrate a normal wave V latency in the presence of a disordered FFR. In other words, damage to parts of the auditory brainstem responsible for generating all or part of the continuous FFR may not affect its ability to generate wave V of the transient ABR.

The current study found that the FFR to the envelope and lower side band of an AM tone occurs significantly later than latency of the ABR wave V. Furthermore, there were no correlations between the FFR and ABR in terms of latency. Neither were there correlations between the two measures in terms of amplitude, except for the significant negative relationship found between the amplitude of the FFR to the upper side band and wave V. However, the sample size was very small for the upper side band amplitude and when combined with the lower side band amplitude this correlation was no longer present. This evidence suggests that the FFR represents auditory processing in a different portion of the auditory brainstem to wave V of the click-evoked ABR. Although no strong conclusions can be drawn due to small sample sizes, this characteristic of the FFR would mean it has
clinical value in being able to reveal more about the efficiency of the subclinical auditory brainstem than the click-evoked ABR can alone.

In particular, the FFR could be a potentially useful addition to measurement of the ABR at diagnostic follow up appointments after referral from the Newborn Hearing Screening Programme. If the FFR can identify auditory temporal processing deficits that the ABR cannot, this would give clinicians more scope by which to flag children at possible risk of developing communication difficulties. One particular way that clinicians could act upon such information is by recommending children for auditory training programmes. There is evidence to suggest that such training can manipulate the neural pathways responsible for processing sound (Russo et al., 2005) and could help to minimise the negative impact on infants identified as having subtle auditory temporal processing difficulties. The FFR may also lend itself to improving site of lesion specificity in clinic. If the FFR does indeed have multiple generators throughout the auditory pathway (Huis in’t Veld, Osterhammel and Terkildsen, 1977; Stillman, Crow and Moushegian, 1978; Gardi, Merzenich and McKean, 1979; Galbraith, Bagasan and Sulahian, 2001), which each have frequency preferences that impact upon latency (John and Picton, 2000; Ruggero and Temchin, 2007), then stimuli of different frequencies could potentially be used to specify site of lesion. Despite its potential, the current study highlights a number of limitations that hinders the use of the FFR as a clinical tool. For example, the conventional click-evoked ABR recording remained a far quicker procedure than recording of the FFR, no data points had to be discarded from the recordings that were made of the ABR and variability in latency and amplitude was much lower for the click ABR data (see Table 4.2). The length of each stimulus used for the FFR recording was 325 ms (200 ms plus 125 ms silence). There were 1500 repetitions of each stimulus (five stimuli in total). The FFR to each stimulus took 8.13 minutes to record, giving a total recording time of 40.65 minutes not including 5 minute breaks between each stimulus.
In comparison, the ABR had a total testing time of just 9 minutes. One of the reasons that assessment of wave V of the conventional ABR has such value in the clinic is its high within and between subject reliability (Lauter and Karzon, 1990). Based on the results of this study, latency and amplitude of wave V of the click-evoked ABR continued to show far less variability in a normally hearing, healthy population than the FFR. Between subjects variability of FFR latency has previously been reported as very low (Smith, Marsh and Brown, 1975). Batra, Kuwada and Maher (1986) found that FFR latency variability was extremely low with a standard deviation of only 0.1 ms, leading the authors to conclude that the FFR has clinical potential for assessing the presence of pathology within the auditory pathway. This was not the case in the current study, although this could be explained by differences between studies in stimuli used to elicit the FFR. Too much variability means that it would remain challenging for clinicians to use the FFR as a means of identifying pathology within the auditory brainstem. More research with patient populations is required in order
to provide both researchers and clinicians with a benchmark by which to identify pathologies. Despite this between-subject variability, averaged latencies from the current study are generally in keeping with previous measures of FFR latency, suggesting that establishment of normative values is achievable. There is now good replicability across studies that normal variability of the latency of the FFR is between 6 and 9 ms.

4.5.3 Conclusions

The current study sought to explore the clinical potential of the FFR by examining its relationship with the conventional, click-evoked ABR. The findings can be summarised as follows:

- Stimulus envelope and TFS following responses of the FFR occurred at around the same time within the auditory pathway, with responses to the envelope and lower side band occurring significantly later than wave V of the ABR

- It remains unclear as to whether these latency differences are a function of the differences in cochlear travelling wave delay or separate neural generators along the auditory brainstem pathway

- There were no significant correlations found between latency of wave V and any of the FFR component latencies

- The FFR should be considered as a clinical measurement to complement the ABR. However, due to the time required to record a reliable response, and the high number of latency measures that had to be discarded due to noise, its feasibility as a routine clinical measurement is currently limited. The challenge remains in developing a sufficiently quick and reliable FFR measurement that would be feasible for clinical use amongst adult patients
4.6 Acknowledgements

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Chapter 5. Electrophysiological Measures of Auditory Temporal Processing as Potential Biomarkers for Neurodevelopmental Communication Disorders

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5.1 Abstract

A subset of individuals with neurodevelopmental communication disorders demonstrate auditory temporal processing deficits. These deficits may have a basis in impaired myelination that impacts upon temporary synchronicity. Therefore, the aim of this study was to investigate the potential usefulness of auditory-evoked electrophysiological measures, which may be sensitive to such deficits, as potential biomarkers for neurodevelopmental communication disorders. Participants comprised adults with a neurodevelopmental communication disorder \((n=21, \text{ mean age 27.8 years})\) and a control group free from any neurological or communication disorders \((n=29, \text{ mean age 24.3 years})\). A third subject group comprising adults with a demyelinating disorder was included \((n=19, \text{ mean age 48.9 years})\). Click-evoked auditory brainstem responses (ABR) were collected as well as the frequency following response (FFR) to five amplitude-modulated tones, each with a carrier of 590 Hz and modulation rates of 95-135 Hz in 10 Hz increments. Speech-in-noise ability was also assessed. Post-hoc tests found that when the communication disorder group was divided by diagnosis, only the Autism Spectrum Disorder (ASD) group were found to have significantly prolonged wave III-V inter-peak intervals and significantly worse speech-in-noise scores than the control group. Prolongation of the wave III-V inter-peak interval was also found in subjects with a demyelinating disorder. A logistic regression found that the speech-in-noise ability was the most important predictor of group membership (control or communication disorder). The findings of this study indicate that click-evoked ABR inter-peak intervals that reflect neuronal efficiency in the central auditory pathway and speech-in-noise ability may make useful biomarkers for ASD in particular.
5.2 Introduction

It is estimated that around 10% of children in the UK have communication difficulties (Law et al., 2000), which can be associated with a number of negative outcomes including poor literacy skills (Schuele, 2004), long term academic difficulties (Young et al., 2002) and poor employment prospects (Ruben, 2000). Communication difficulties are highly characteristic of several neurodevelopmental disorders including Autism Spectrum Disorder (ASD), dyslexia, Attention-Deficit Hyperactivity Disorder (ADHD) and Specific Language Impairment. The early identification of such disorders is now considered to be paramount given research to show that is vital to ensure early and effective intervention, which has been shown to improve outcomes in a range of areas (McGoey, Eckert and Dupaul, 2002; Woods and Wetherby, 2003; Schatschneider and Torgesen, 2004; Jones et al., 2007). Singh and Rose (2009) have endorsed the use of biomarkers for childhood disorders highlighting that they have the potential to increase the precision of a diagnosis and can capture children at risk before symptoms appear and begin to interfere with daily life. Potential candidates in the case of neurodevelopmental communication disorders are auditory-evoked electrophysiological measures. More specifically, the click-evoked auditory brainstem response (ABR) and frequency following response (FFR).

Research into the underlying neural correlates of neurodevelopmental communication disorders has shown that a subset of individuals with such disorders demonstrate temporal processing deficits in the auditory domain. For example, individuals diagnosed with ASD have been found to demonstrate both prolongation of absolute and inter-peak wave intervals of the click-evoked ABR, (Rosenhall et al., 2003; Kwon et al., 2006; Roth et al., 2011, 2012). Prolongation of the ABR wave V absolute latency and central transmission time (wave I-V inter-peak interval) have also been reported in individuals with ADHD (Lahat et al., 1995; Puente et al., 2002; Azzam and Hassan, 2010) and general language disorders (Malayeri et al., 2014). Children with neurodevelopmental communication disorders have also been shown to
have deficient FFRs, reflecting poor temporal encoding within the central portion of the auditory brainstem (Gardi, Merzenich and McKean, 1979; Levi, Folsom and Dobie, 1995). Children with ASD have shown reduced phase locking of the FFR (Russo et al., 2008, 2009). Poor phase locking to the amplitude modulations of a signal have been demonstrated in individuals with dyslexia (McAnally and Stein, 1996; Banai et al., 2009) and general language disorders (King et al., 2002; Song et al., 2006). In some studies, the click-evoked ABR was found to be normal whilst the FFR was disordered, suggesting that separate neural processes may be involved in processing simple versus complex stimuli (King et al., 2002; Song et al., 2006). This could mean that the FFR may be a more sensitive biomarker for these disorders than the click-evoked ABR, which is currently used clinically to measure efficiency of the auditory brainstem. Electrophysiological biomarkers would be particularly useful for a number of reasons. Firstly, they have an added advantage over behavioural measures because they do not require a conscious, behavioural response and can thus be used with relative ease on very young infants. The identification of most neurodevelopmental communication disorders currently relies on behavioural methods. The detection of ASD in particular relies on the observation skills of a caregiver who may or may not recognise signs such as failure of a child to respond to their own name (Ozonoff et al., 2009). Therefore, the addition of auditory-evoked electrophysiological measures could potentially enhance the current diagnostic tool kit of clinicians.

In support of the use of auditory-evoked electrophysiological measures as potential biomarkers for neurodevelopmental communication disorders, it has been suggested that the pathology involved in the auditory-temporal processing deficits seen in these patients may be identifiable at a young age. In particular, it has been postulated that delayed or impaired myelination of the auditory brainstem during important early developmental stages causes atypical responses to acoustic stimuli within the brainstem (Salamy, 1984; Harbord et al., 1990; McClelland et al., 1992). Amin et al. (2014) carried out a prospective, longitudinal study of 80 premature infants to investigate the potential
relationship between auditory pathway neural myelination and subsequent communication development. Healthy myelination was measured by the click-evoked ABR, specifically wave I-V inter-peak interval at 35 weeks post-menstrual age, and both receptive and expressive language abilities were assessed at three years corrected age by the Preschool Language Scale 4 (Zimmerman, Steiner and Pond, 2002). Inter-peak interval was found to be significantly associated with both expressive and receptive language ability. In particular, a one unit increase in the wave I-V inter-peak was associated with between a 5.4-5.5 decrease in receptive language scores and a 5.6-6.4 decrease in expressive language scores. These findings were in keeping with earlier studies (Cox et al., 1992; Desai et al., 1997) and provide evidence that the efficiency of early brainstem myelination may be associated with subsequent communication development. Basu, Krishnan and Weber-Fox (2009) have suggested that a delay in early myelination could be used to explain their findings of prolongation of ABR waves III and V with increased click repetition rate in children with specific language impairment. In particular, they postulate that such results reflect a neural conduction delay as a consequence of impaired myelination, drawing on evidence that the same exaggerated prolongation has been found in patients with a confirmed demyelinating disorder (Jacobson, Murray and Deppe, 1987). If the auditory-temporal deficits found in subjects with neurodevelopmental communication disorders are present in very young infancy, then electrophysiological measures could serve to flag infants at risk of developing such disorders. In turn, this would facilitate early intervention, which has been found to be beneficial for children diagnosed with a neurodevelopmental communication disorder.

In order to explore whether auditory-evoked electrophysiological measures would make useful biomarkers for neurodevelopmental communication disorders, this study aims to focus on three key areas. Firstly, can electrophysiological measures distinguish individuals with a neurodevelopmental communication disorder from a control population. Secondly, are electrophysiological measures more predictive of the presence of a neurodevelopmental communication disorder than a
behavioural measure? Electrophysiological measures would need to prove themselves as sensitive as behavioural measures in identifying such disorders in order to justify further research into their use as potential biomarkers. Finally, if the auditory temporal processing deficits found in individuals with neurodevelopmental communication disorders have a basis in impaired myelination then it might be expected that subjects with these disorders would demonstrate similar auditory brainstem pathology to subjects with a confirmed demyelinating disorder. Individuals with multiple sclerosis (MS) provide one such patient group. MS is a neurological disorder that attacks the central nervous system and destroys myelin, causing deficits in signal processing and inter-neuron communication (Marburg, 1906). Lesions of the brainstem are relatively easy to identify through symptoms such as nystagmus, dizziness and gait disturbance (Robinson and Rudge, 1977; Chiappa et al., 1980; Japaridze, Shakarishvili and Kevanishvili, 2002). MS affects myelination within the central nervous system so, as would be expected, latency of wave I of the ABR is often reported to be within normal limits in MS patients, whilst the central portion is prolonged (Japaridze, Shakarishvili and Kevanishvili, 2002). Robinson and Rudge (1975) found that 88% of a group of MS patients with a definite brainstem lesion and 76% with evidence of a brainstem lesion, had a prolonged latency of the ABR wave V. Chiappa et al. (1980) reported abnormal ABRs in 32% of a sample of MS patients, 55% of which had wave V abnormalities in particular. Similarly, Musiek et al. (1989) reported that 46.2% of a group of patients with MS had an absent or prolonged wave V despite having normal pure tone audiometry thresholds. Delayed ABR absolute and inter-peak intervals are not the only notable similarities between patients with demyelinating disorder and those with neurodevelopmental communication disorders. Both groups have also been known to show issues in detecting and understanding speech in noise (Alcantara et al., 2004; Ziegler et al., 2005; Lewis et al., 2006; Boets et al., 2007). Therefore, a self-report questionnaire measure of speech-in-noise was used for comparison purposes against electrophysiological measures in this paper.
1. **Research Questions**

1. Can measures of auditory temporal processing distinguish adults with a neurodevelopmental communication disorder from a control population and individuals with a confirmed demyelinating disorder?

2. Are electrophysiological measures of auditory temporary processing more predictive of the presence of a neurodevelopmental communication disorder than a behavioural measure?

### 5.3 Methods and Materials

This study was approved by an NHS research ethics committee (reference number 13/NW/0014).

#### 5.3.1 Participants

To determine sample size, a two group continuity corrected chi-square test with a 0.050 two-sided significance level was found to have 80% power to detect a difference between groups when the sample size was a minimum of 23 in each group. Due to recruiting difficulties, only a total of 19 participants with MS (mean age 48.9 years, age range 34-64 years, four males) and a total of 21 participants with a neurodevelopmental communication disorder (mean age 27.8 years, age range 20-49 years, seven males) took part in the study. Of these 21, seven participants had a diagnosis of dyslexia, nine had a diagnosis of ASD (high-functioning), four had a diagnosis of ADHD (one with a diagnosis of ADD) and one participant had a diagnosis of all three conditions (ADHD, ASD and dyslexia). The control group consisted of 29 normally hearing adults (mean age of 24.3 years, age range 18-33 years, six males) who were free from any neurological or communication disorders. All participants had normal hearing (PTA thresholds ≤ 20dB HL, 250 Hz-8 kHz). Tympanometry and otoacoustic emissions were also recorded to ensure they fell within the normal range. Participants for both patient groups were recruited for the study.
through an advert distributed via the University of Manchester student and staff intranet. Participants were also recruited through contacting relevant charities. Individuals interested in participation were provided with a participant information sheet and advised to contact the principal investigator if they wished to take part in the study. Each participant was allocated a three hour slot and a £15.00 reimbursement plus reasonable travel expenses. For participants in the MS patient group, a symptoms checklist\(^8\) was given to individuals interested in participating in the study. The checklist was designed to establish the presence of a brainstem lesion and included visual abnormalities such as nystagmus, the presence of which have been strongly associated with a high likelihood of brainstem lesions in MS (Robinson and Rudge, 1977). In order to be eligible for participation, participants were required to have at least two of the nine symptoms listed on the checklist. On arrival for their testing session, both the MS and communication disorder patient groups were asked to provide proof of their diagnosis in the form of a letter from either their GP, consultant or nurse.

5.3.2 ABR Recordings

A clinical Interacoustics IABase 2000 machine was used to collect ABR recordings from participants. All electrophysiological testing took place within a double-walled sound-attenuating booth. 100-μs alternating polarity clicks were presented at a rate of 11.1 per second and at a level of 80 dB nHL. ER3A insert headphones were used to present the stimuli to the right ear only. Skin was prepared using alcohol wipes and a mild abrasive gel. The electrodes were then attached using electro-conductive gel and surgical tape was used to keep them in place. The electrodes were placed on the high forehead (Fz, active), the right mastoid (reference) and the low forehead (Fpz, ground). Once the electrodes were attached, participants were made comfortable in a reclining chair and asked to keep as still as possible during the testing session to minimise myogenic interference. A high-pass filter of 100 Hz and low-pass filter of 3 kHz were applied online.

\(^8\) Appendix E
Three grand averages of 2,000 sweeps were collected for each participant.

5.3.3 FFR Recordings

Recording of FFR data was made using a RA16 Medusa Base Station (Tucker-Davis Technologies, or TDT, Alachua, Florida, USA). FFR recordings took place immediately after ABR recordings. Skin preparation was identical and a vertical montage was used to collect responses using an electrode placed on the high forehead (Fz, active), the 7th vertebra (C7, reference) and the lower forehead (FPz, ground). There were five conditions during which participants listened to one of five amplitude-modulated tones with equal-amplitude components at the carrier frequency and two adjacent side bands. The frequencies of the components for each condition used in the current study (in Hz) were: 495-590-685; 485-590-695; 475-590-705; 465-590-715 and 455-590-725. The overall stimulus level was 80 dB SPL. Each stimulus was 200 ms in duration (including 10 ms raised-cosine onset and offset ramps) and presented in alternating polarities separated by a 125 ms silent interval after each stimulus. Stimuli were presented in a random order to counteract any effects of restlessness from participants toward the end of testing. The stimuli were presented using a TDT RP2.1 digital to analogue converter via Etymotic ER30 insert headphones to the right ear only, with the transducers located outside the sound booth to limit the risk of stimulus artefact. Recordings were bandpass filtered online between 30 and 3000 Hz, and notch filtered at 50 Hz. Three sub-averages of 500 sweeps of each polarity were collected for each condition with a presentation rate of 1.5/sec.

5.3.4 The Speech, Spatial and Qualities of Hearing Scale Short Form (SSQ12)

Every participant was asked to complete a Speech, Spatial and Qualities of Hearing Scale short form questionnaire (SSQ12; Noble et al., 2013). This 12-item questionnaire contains sub-scales that assess an individual’s ability to detect and understand speech in noise, in-
cluding detecting target speech in the presence of multiple speech streams, sound localisation and the quality and naturalness of sound. The sub-scales represent nine of the ten sub-scales that are represented in the original and more comprehensive SSQ49 (Gatehouse and Noble, 2004). Questions 1-5 assess speech hearing, questions 6-8 assess spatial hearing and questions 9-12 assess quality of hearing. The successful detection of speech in noisy conditions has been shown to depend on the successful use of acoustic temporal cues (Shannon et al., 1995; Füllgrabe, Berthommier and Lorenzi, 2006). Therefore, a low score on the SSQ12 likely indicates behavioural consequences of poor auditory temporal processing.

5.3.5 ABR Analysis

Absolute latency for waves I, III and V of the ABR was computed offline for each participant. The peak selection procedure for each wave had three steps. The first step involved plotting the ABR waveform for each participant within a 4-10 ms time window. Secondly, the peak of the wave was chosen by the first author and was then checked a second time by an additional researcher who was blind to the condition of each participant, thus providing reliability. There was no inconsistency between researchers during this selection process. Only after these two comparisons were data points finalised for analysis. The cursor was then used to identify both the exact amplitude of the peak and the corresponding latency. Absolute latencies were then used to calculate inter-peak intervals. Component amplitude (peak to following trough) data for wave V was obtained by reading the electric potential using the computer cursor at the initial positive peak of each wave and the following trough. Data points were discarded if they were more or less than 2 SD from the mean. This was done for each group independently, using the relative mean and standard deviation.

5.3.6 FFR Analysis
Average response waveforms for each condition were computed offline for each participant in MATLAB (The Mathworks, 2010). The waveforms were then analysed using a discrete Fourier transform (DFT). To determine the latency of the FFR, a MATLAB (Mathworks, 2010) script was run using the data generated from the five different stimuli to produce a measure of group delay. Group delay can be defined as the slope of the linear regression of the phase of each component (in periods) plotted against frequency. The phase was unwrapped such that the linear fit gave the least sum of the squared residuals compared to a linear fit, with the condition that regression lines with slopes less than 3 ms and greater than 30 ms were not considered. The 18.2 ms tubing delay was accounted for in the MATLAB script used to calculate the group delay values, giving response latency relative to the ear canal. A frequency component was excluded from the group delay analysis if the response to this component was less than 3 SD above the noise floor (calculated as the SD of the DFT power in the FFR, measured in 2-Hz intervals, in bands 5-33 Hz below the component frequency and 5-33 Hz above the component frequency). If fewer than three points remained after this procedure, the fit was discarded. Data points for both latency and amplitude of the FFR components were then discarded if they were more or less than 2 SD from the mean. This was done for each group independently, using the mean and SD for each group. Signal-to-noise ratios (SNRs) were calculated as the ratios between the DFT amplitude at the component frequency divided by the mean DFT amplitude at the noise components. The SNRs were then converted to dB and averaged across conditions.

5.3.7 The SSQ12

Results for each group were scored separately and an average score for each participant was calculated. A lower score indicated more difficulty with speech-in-noise.
5.4 Results

5.4.1 Can measures of auditory temporal processing distinguish adults with a neurodevelopmental communication disorder from a control population and individuals with a confirmed demyelinating disorder?

Mean electrophysiological latencies and amplitudes as well as mean SSQ12 scores for all groups can be seen in Table 5.1.

Adults with a neurodevelopmental communication disorder could not be distinguished from a control population or adults with a confirmed demyelinating disorder on any click-ABR latency or amplitude component except the wave III-V inter-peak interval. Further analysis revealed that the wave III-V inter-peak interval was significantly prolonged in adults with a communication disorder when compared to the control group only. Furthermore, this prolongation of the wave III-V inter-peak interval was an effect of the ASD sub-group only. The communication disorder group could not be distinguished from the control group or the MS group on either FFR amplitude or latency.

There was a significant difference found between the three groups for SSQ12 scores. Post-hoc analysis found that this difference was between the communication disorder group and control group only, meaning that adults with a communication disorder had significantly worse SSQ12 scores than the control group. Post-hoc analysis showed that the communication disorder group had significantly worse scores on the speech scale of the SSQ12 only and that this was an effect of the ASD sub-group only.

5.4.1.1 ABR Comparisons

There was no statistically significant difference between groups for wave V latency as determined by a one-way ANOVA ($F(2,46) = 1.230, p = 0.302$).
Table 5.1

<table>
<thead>
<tr>
<th>Measure</th>
<th>Communication disorder group</th>
<th>n</th>
<th>MS group</th>
<th>n</th>
<th>Control group</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABR wave V latency (ms)</td>
<td>5.21</td>
<td>18</td>
<td>5.12</td>
<td>14</td>
<td>5.04</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>(0.087, 4.75-5.97)</td>
<td></td>
<td>(0.094, 4.27-5.59)</td>
<td></td>
<td>(0.061, 4.56-5.51)</td>
<td></td>
</tr>
<tr>
<td>ABR wave I-III inter-peak interval (ms)</td>
<td>2.40</td>
<td>16</td>
<td>2.03</td>
<td>10</td>
<td>2.06</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>(0.140, 1.90-3.40)</td>
<td></td>
<td>(0.041, 1.89-2.22)</td>
<td></td>
<td>(0.042, 1.73-2.38)</td>
<td></td>
</tr>
<tr>
<td>ABR wave III-V inter-peak interval (ms)</td>
<td>1.73</td>
<td>18</td>
<td>1.74</td>
<td>10</td>
<td>1.53</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>(0.035, 1.48-2.05)</td>
<td></td>
<td>(0.059, 1.28-2.12)</td>
<td></td>
<td>(0.054, 1.15-1.90)</td>
<td></td>
</tr>
<tr>
<td>ABR wave I-V inter-peak interval (ms)</td>
<td>4.02</td>
<td>15</td>
<td>3.81</td>
<td>10</td>
<td>3.59</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>(0.140, 3.47-5.14)</td>
<td></td>
<td>(0.067, 3.56-4.11)</td>
<td></td>
<td>(0.082, 2.99-4.18)</td>
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</tr>
<tr>
<td>ABR wave V amplitude (μV)</td>
<td>0.706</td>
<td>18</td>
<td>0.586</td>
<td>15</td>
<td>0.686</td>
<td>17</td>
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<tr>
<td></td>
<td>(0.056, 0.460-1.190)</td>
<td></td>
<td>(0.041, 0.526-1.043)</td>
<td></td>
<td>(0.148, 0.05-1.19)</td>
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<tr>
<td>FFR latency (ms)</td>
<td>7.60</td>
<td>17</td>
<td>6.17</td>
<td>11</td>
<td>7.66</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>(0.764, 5.23-14.29)</td>
<td></td>
<td>(0.444, 3.55-7.79)</td>
<td></td>
<td>(0.593, 3.49-13.92)</td>
<td></td>
</tr>
<tr>
<td>FFR amplitude (μV)</td>
<td>0.011</td>
<td>21</td>
<td>0.008</td>
<td>17</td>
<td>0.013</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>(0.001, 0.004-0.021)</td>
<td></td>
<td>(0.001, 0.003-0.019)</td>
<td></td>
<td>(0.001, 0.002-0.043)</td>
<td></td>
</tr>
<tr>
<td>FFR SNRs (dB)</td>
<td>9.17</td>
<td>21</td>
<td>6.28</td>
<td>18</td>
<td>11.58</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>(1.208, -1.37-15.96)</td>
<td></td>
<td>(1.174, -1.22-14.40)</td>
<td></td>
<td>(0.768, 4.05-17.65)</td>
<td></td>
</tr>
<tr>
<td>SSQ12 Score</td>
<td>6.40</td>
<td>18</td>
<td>7.21</td>
<td>11</td>
<td>7.52</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>(0.172, 4.80-7.80)</td>
<td></td>
<td>(0.552, 3.80-10.00)</td>
<td></td>
<td>(0.271, 4.60-9.30)</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* The values in brackets represent the standard error and the range of values. Due to discarded data, there were varying amounts of data available across subjects for each measure.
Wave I-III and I-V inter-peak interval data for the communication disorder group were not normally distributed and could not be normalised using transformation algorithms. Therefore, a non-parametric Kruskal-Wallis test was carried out in order to compare the means. There was no statistically significant difference between groups for wave I-V inter-peak interval ($X^2(2) = 4.549, p = 0.103$). Nor was a significant difference found for the three groups for wave I-III inter-peak interval ($X^2(2) = 3.700, p = 0.157$).

There was a statistically significant difference between groups for the wave III-V inter-peak interval as determined by a one-way ANOVA ($F(2,46) = 5.642, p = 0.001$). A Bonferroni post hoc test revealed that the significant difference was between the control and communication disorder groups ($p = 0.002$), meaning that the communication disorder group had a significantly longer wave III-V inter-peak interval than the control group.

Figure 5.1 shows the ABR mean waveforms across all three experimental groups. Pearson’s correlations found no association between age and inter-peak interval for either the control group or communication disorder group. An independent samples t-test found no significant difference between males and females for the inter-peak interval in the control group, however, there was a significant difference for the communication disorder group ($t(16) = -2.301, p = 0.035$). In particular, males had significantly longer wave III-V inter-peak intervals. To control for gender effects, an ANCOVA was run controlling for gender as a covariate, and found that the wave III-V inter-peak interval remained significantly longer in the communication disorder group compared to the control group ($F(1,31) = 8.661, p = 0.006$) after controlling for gender effects.

There was no significant difference between the three groups for wave V amplitude as determined by a one-way ANOVA ($F(2,47) = 1.556, p = 0.222$).

5.4.1.2 FFR Comparisons

Neither removal of outliers nor transformations algorithms were able to normally distribute the FFR latency data. Therefore, a non-
parametric Kruskal-Wallis test was used to compare FFR latency between all three groups. There was no significant difference between the three groups on this measure ($X^2(2) = 0.640, p = 0.726$).

FFR amplitude data were normalised using a log10 transform. There was a significant difference between groups as determined by a one-way ANOVA ($F(2,62) = 3.218, p = 0.047$). However, a Bonferroni post hoc test revealed that there was no significant difference between the control and communication disorder group ($p = 0.962$) nor between the communication disorder and MS group ($p = 0.405$).

There was a statistically significant difference between the three groups for FFR SNR as determined by a one-way ANOVA ($F(2,65) = 6.727, p = 0.002$). However, a Bonferroni post hoc test revealed that there was no significant difference for FFR SNR between the control group and communication disorder group ($p = 0.261$) nor between the MS and communication disorder group ($p = 0.200$).

5.4.1.3 SSQ12 Comparisons

There was a statistically significant difference between the three groups as determined by a one-way ANOVA ($F(2,47) = 6.299, p = 0.024$). A Bonferroni post hoc test showed that there was significant difference between the communication disorder and control groups ($p = 0.022$) but not MS and communication disorder groups ($p = 0.293$). This means that the communication disorder group had significantly worse SSQ12 scores than the control group.

Pearson’s correlations found no association between SSQ12 scores and age for either the control group or communication disorder group. Independent samples t-tests found no difference in gender effects for scores SSQ12 scores for either group. The SSQ12 uses three different internal scales to measure different aspects of hearing in noise. Means comparisons found that there was a significant difference between the communication disorder group and control group for the speech scale ($t(38) = 3.188, p = 0.003$), but not for the quality of hearing scale ($t(38) = 1.567, p = 0.125$) or spatial scale ($t(39) = -1.481, p = 0.147$).
Figure 5.1: Mean ABR waveforms across participants for each group. (A) Control group. (B) Communication disorder group. (C) MS group.
In order to further explore the differences between the communication disorder group and control group, the communication disorder group were divided into their respective diagnoses and comparisons were made for means of the two variables by which the communication disorder group and control group differed: the wave III-V inter-peak interval and SSQ12 scores. The subject with a diagnosis of all three disorders was excluded from the analysis.

5.4.1.4 SSQ12 Scores

There was a statistically significant difference between groups as determined by a one-way ANOVA ($F(3, 34) = 3.751, p = 0.020$). A Tukey HSD post-hoc test revealed that the ASD group had significantly lower SSQ12 scores than the control group ($p = 0.044$) but there were no statistical differences between any of the other groups included in the analysis. Figure 5.2 A shows mean SSQ12 scores for all groups included in the ANOVA.

5.4.1.5 Wave III-V Inter-Peak Interval

As gender was found to be associated with wave III-V inter-peak interval for the communication disorder group, an ANCOVA was run between each of the communication disorder sub-groups and control group, controlling for gender. There was a significant difference between group means ($F(3,30) = 4.405, p = 0.011$). Bonferroni post-hoc tests found that the only significant difference was between the ASD and control group ($p = 0.008$). No other significant differences between groups were found. Figure 5.2 B shows the distribution of wave III-V inter-peak intervals across all groups included in the ANCOVA.

5.4.2 Are Electrophysiological Measures of Auditory Temporary Processing more Predictive of the Presence of a Neurodevelopmental Communication Disorder than a Behavioural Measure?

SSQ12 scores were found to be a better predictor of the presence of a neurodevelopmental communication disorder than the wave III-V inter-peak interval.
Separate logistic regression models were computed to determine which was the most important predictor of group membership (control or communication disorder group). The wave III-V inter-peak interval of the click-evoked ABR was entered as the predictor variable in the first model and a test of the full model against a constant only model was statistically significant, indicating that wave III-V inter-peak interval can reliably distinguish between the two groups ($X^2 (1) = 8.879, p = 0.003$). This model explained 29.9% (Nagelkerke’s $R^2$) of the variance between groups and prediction success overall was 69.4% (64.7% specificity and 72.2% sensitivity). The Wald criterion demonstrated that wave III-V inter-peak interval made a significant contribution to prediction ($p = 0.014$). An Exp(B) of 354.031 showed that for every one unit increase in wave III-V inter-peak interval (ms), individuals are 354.031 times more likely to belong to the communication disorder group. The SSQ12 scores were entered as another predictor variable in a second model and a test of the full model against a constant only model was statistically significant, indicating that SSQ12 scores can reliably distinguish between the two groups ($X^2 (1) = 10.357, p = 0.001$). This model explained 31.2% (Nagelkerke’s $R^2$) of the variance between groups and prediction success overall was 66.7% (66.7% specificity and 66.7% sensitivity). The Wald criterion demonstrated that SSQ12 scores made a significant contribution to prediction ($p = 0.008$). An Exp(B) of 0.336 showed that for every one unit increase in SSQ12 score (improvement), individuals are 0.336 times less likely to belong to the communication disorder group. A lower $p$ value of 0.008 indicated that the SSQ12 scores are a better predictor of group membership than wave III-V inter-peak interval. To investigate whether the wave III-V inter-peak interval added a unique contribution to the prediction model outside of SSQ12 scores, a third logistic regression model was computed entering both measures as predictor variables. A test of the full model against a constant only model was statistically significant, indicating that this set of predictors reliably distinguished between the two groups ($X^2 (2) = 13.811, p = 0.01$). The model explained 48% (Nagelkerke $R^2$) of the variance between groups and prediction success overall was 80.6% (87.5% sensitivity and
73.3% specificity). The Wald criterion demonstrated that only SSQ12 scores made a significant contribution to prediction ($p = 0.017$). The Wald criterion p value for wave III-V inter-peak interval was $> 0.05$ ($p = 0.060$) showing that this measure did not add any unique contribution to the model over and above SSQ12 scores. Standardised coefficients were calculated for each variable using the method detailed in King (2007).

**Figure 5.2:** (A) Box plots showing distribution of SSQ scores by diagnosis. (B) Box plots showing distribution of wave III-V inter-peak latency of the click-evoked ABR by diagnosis.
The standardised coefficient for SSQ12 was found to be larger (-0.375) than for wave III-V inter-peak interval (0.283). This further demonstrates that SSQ12 scores are a more important predictor than wave III-V inter-peak interval.

5.4.3.4 MS and Control Group Comparisons

Means comparisons between the MS group and control group were conducted for measures that were found to distinguish the communication disorder group from controls. There was no difference for these two groups for SSQ12 scores ($t(30) = -0.577, p = 0.568$). However, wave III-V inter-peak interval was found to be significantly longer in the MS group than the control group ($t(29) = -2.535, p = 0.017$).

5.5 Discussion

The aim of this paper was to explore the potential usefulness of auditory-evoked electrophysiological measures as biomarkers of neurodevelopmental communication disorders. A control group and neurodevelopmental communication disorder group, comprising individuals with a diagnosis of ASD, dyslexia or ADHD, were compared using two auditory-evoked electrophysiological measures: the FFR and click-evoked ABR. The first focus of this study was to ascertain whether electrophysiological measures could distinguish adults with a neurodevelopmental communication disorder from a control group. Only the wave III-V inter-peak interval of the click-evoked ABR could distinguish the two groups. There was a significant correlation between gender and wave III-V inter-peak interval of the click-evoked ABR showing that a longer latency was associated with being male. This finding is in keeping with previous literature (Mitchell, Phillips and Trune, 1989; Dehan and Jerger, 1990). However, after controlling for the effect of gender the group differences in inter-peak interval remained statistically significant. However, a post-hoc analysis found that when the communication disorder group was split according to
diagnosis, it was only the ASD group that had a significantly prolonged wave III-V inter-peak interval in comparison to the control group. There were no significant differences between the control group and the dyslexia group or ADHD group for these two measures. However, it should be noted that the ADHD group in particular was very small (n = 4). The finding of a prolongation of the click-evoked wave III-V inter-peak interval in the ASD group also supports previous literature that used younger subjects (Kwon et al., 2006; Roth et al., 2011). Although it is impossible to know whether the III-V inter-peak prolongation was present in the current ASD sample during their childhood, based on the finding of such a prolongation in children with ASD, results from the current study could be taken to indicate that auditory temporal processing deficits are present in both children and adults diagnosed with ASD. This finding suggests that transmission of neural signals through the central auditory brainstem, as measured by the wave III-V inter-peak interval, could make a potentially useful biomarker for ASD in particular.

In contrast to previous literature, the communication disorder group could not be distinguished from the control group using FFR measures. Effect size for the sample size used for both FFR latency and amplitude was $d = 0.38$. According to Cohen (1988) an effect size of 0.2 represents a small effect. Therefore, sample size should have been adequate to detect even a small difference between groups. This suggests that that an underpowered study may not account for why no difference was found between the groups for FFR latency.

The difference in findings may be due to differences in stimuli used to evoke the FFR. In the current study, an amplitude-modulated tone was used, whereas in previous studies that have found differences in the FFR between subjects with a neurodevelopmental communication disorder and a control group, the choice of stimulus was the synthetic speech syllable /da/ (Jafari, Malayeri and Rostami, 2015; King et al., 2002; Cunningham et al., 2001). In particular, these previous studies found that subjects with a neurodevelopmental communication disorder differed from a control group for the onset and offset responses of the FFR to the /da/ syllable, whereas the sustained periodic
response between the onset and offset waves were unaffected (Jafari, Malayeri and Rostami, 2015; Cunningham et al., 2001). Indeed, based on previous research, Johnson, Nicol and Kraus (2005) highlight that a distinct pattern of inadequate representation of transient and temporally rapid activity and adequate representation of low frequency and sustained activity begins to emerge amongst a subset of individuals with neurodevelopmental communication disorders. Indeed, wave III-V inter-peak interval represents transient and rapid activity. The results from the current study demonstrate that latency of the onset response of the FFR to amplitude-modulated tones is not different between a communication disorder and control group. The finding that the FFR evoked by amplitude-modulated tones did not differentiate subjects with a communication disorder from a control group, whereas the FFR evoked by a synthetic speech syllable can, adds to the argument that speech may in some way be processed differently in the auditory brainstem than non-speech stimuli (Song et al., 2006). These results suggest that the FFR evoked by amplitude-modulated tones would not make a useful biomarker for neurodevelopmental communication disorders.

The second focus of the study was to establish whether auditory-evoked electrophysiological measures are more predictive of the presence of a neurodevelopmental communication disorder than a behavioural measure. It was found that the control and communication disorder groups could be distinguished using a self-report measure of speech-in-noise ability (SSQ12). In particular, the communication disorder group had significantly lower scores than the control group, indicating worse speech-in-noise ability. The SSQ12 has three subscales that represent different dimensions of speech-in-noise ability: speech hearing, spatial hearing and quality of hearing. A post-hoc test revealed that the significant difference between groups was the effect of a significant difference on the speech scale only. There was no significant difference between the two groups for the other two subscales. This suggests that individuals within the communication disorder group perform significantly worse than controls in situations that require attending to speech in noisy environments and when there are
multiple, competing speakers. However, locating sounds in noisy environments and maintaining the quality of sounds in a noisy environment appear unaffected. The second post-hoc analysis found that when the communication disorder group was split up by their diagnosis, only individuals in the ASD group were found to significantly differ from the control group for the SSQ12. The finding that the ASD group had a significantly worse ability than controls to hear speech in noisy conditions supports previous literature and is thought to reflect poor use of auditory temporal cues (Alcantara et al., 2004; Groen et al., 2009).

The electrophysiological (wave III-V inter-peak interval) and self-report (SSQ12) measure by which the communication disorder and control group could be distinguished were entered into logistic regressions as predictor variables. It was found that the speech-in-noise measure (SSQ12) was a more important predictor of group membership than wave III-V inter-peak interval. In particular, although wave III-V inter-peak interval was a significant predictor of group membership, it could not add any unique variance over and above the SSQ12. These results imply that the ability to successfully attend to speech in noisy environments and in the presence of contending speakers is an important predictor of the presence of a neurodevelopmental communication disorder. Interestingly, wave III-V inter-peak interval offered more sensitivity (72.2%) than the SSQ12 (66.7%) whereas the SSQ12 offered more specificity (66.7%) than inter-peak interval (64.7%). This suggests that the wave III-V inter-peak interval of the click-ABR could be more sensitive to detecting the presence of a neurodevelopmental communication disorder, whereas a self-report measure of temporal processing could be more sensitive to detecting the absence of such a disorder.

It has been proposed that the auditory temporal processing deficits experienced by individuals with a neurodevelopmental communication disorder could have a biological basis in the impairment of myelination of the auditory brainstem. Therefore, the aim of the final research question was to determine whether subjects with a neurodevelopmental communication disorder have similar deficits within the au-
ditory brainstem as subjects with a confirmed demyelinating disorder (MS). Mean wave III-V inter-peak interval of the click-evoked ABR was found to be significantly prolonged in the MS group when compared to the control group. This suggests that the MS group have a similar auditory brainstem pathology to the ASD group tested in the current study. This finding supports previous studies that have reported a similar pathology amongst MS patients (Stockard, Stockard and Sharbrough, 1977; Chiappa et al. 1980). A more recent study by Japaridze, Shakarishvili and Keyanishvili (2002) found inter-peak interval lengthening in 35% of 40 MS patients, the most common of which was lengthening of the wave III-V inter-peak interval, which would be expected if the central portion of the auditory brainstem was affected by demyelination. Wave I of the click-ABR is believed to be generated from the VIII cranial nerve within the peripheral nervous system, whereas wave III onwards is generated within the central nervous system (Starr, 1976). Wave I latency and wave I-III inter-peak interval was found to be within normal limits for both the communication disorder group and MS group, suggesting that the site of any myelination problem is likely to lie in the central nervous system. The peripheral and central nervous system are myelinated by different cells, namely Schwann cells and oligodendrocytes respectively. Unfortunately, no conclusions can be made about myelination based on the results of this study.

Nevertheless, Shah et al. (1978) found that deficient myelination in rats was represented by failure to achieve the shortening in ABR latencies with increasing age that was found in normally maturing rats. Furthermore, impaired myelination has also been found to considerably reduce transmission speed in neurons (Hess, 1997). Therefore, future research should focus on investigating whether early myelination impairment may be associated with auditory temporal processing deficits at the brainstem level.

If impaired myelination is a potential underlying pathology in the auditory temporal processing deficits exhibited by individuals with neurodevelopmental communication disorders, then this would strengthens the argument in favour of auditory-evoked electrophysio-
logical biomarkers that could detect the impact of such pathology at an early age.

It is important to note a number of limitations within the current study that may limit the generalisability of the findings. Firstly, the sample sizes were extremely small when the communication disorder group was split up according to diagnosis. Furthermore, subjects in this group were not assessed prior to participation in the study. Although subjects were required to provide proof of their diagnosis, there are some questions as to the validity of certain dyslexia and ADHD assessments in particular (Harrison, Edwards and Parker, 2007, 2008). In future studies, diagnoses should be confirmed through the researchers own assessments. Although every effort was made to explain the SSQ12 to each participant, it was a self-reported questionnaire that may have suffered from several limitations including the risk that some participants may have inaccurately reported their true experience with speech in noise. Furthermore, the SSQ12 only captures a snapshot of an individual’s speech in noise experience and assess speech-in-noise ability in a only a limited number of daily scenarios.

5.5.1 Conclusions

Findings from the current study imply that the wave III-V interpeak interval of the click-evoked ABR can distinguish individuals with ASD from a control group. Furthermore, this same prolongation of the III-V inter-peak interval was found in adults with a demyelinating disorder. A self-report questionnaire measure of speech-in-noise (SSQ12) was also able to distinguish these two groups and was found to be a more important predictor of group membership (presence or absence of a neurodevelopmental communication disorder) than wave III-V inter-peak interval, suggesting that electrophysiological biomarkers may not hold any advantage of a self-report marker for ASD. The SSQ12 is a self-report measure and would therefore require a child to be much older before it could be used to assess their speech-in-noise abilities. However, it may make a useful follow up tool for infants who are flagged as being at risk of neurodevelopmental communication disorders through electrophysiological measures. Indeed, a
model that included both the SSQ12 and wave III-V inter-peak interval gave the best sensitivity and specificity for predicting group membership.

It is important to note that electrophysiological measures of auditory temporal processing could not distinguish adults with dyslexia or ADHD from a control group. Despite findings of auditory temporal processing deficits in these disorders (Lahat et al., 1995; McAnally and Stein, 1996; Puente et al., 2002; Banai et al., 2009; Azzam and Hassan, 2010), this suggests that auditory-evoked electrophysiological measures may not make useful biomarkers for these particular disorders. Furthermore, the communication disorder group could only be distinguished from the control group based on one electrophysiological measure. These results most likely reflect the highly heterogeneous nature of neurodevelopmental communication disorders and their underlying pathologies.

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Chapter 6. General Discussion

6.1 Research Overview

The Newborn Hearing Screening Programme (NHSP) has proven ground breaking in its ability to identify children at risk of permanent congenital hearing impairment at a much earlier age than the previously used health visitor distraction test, and has improved outcomes for these children in a range of life areas (Kennedy et al., 2005; Uus and Bamford, 2006; Newton, 2013; Pimperton et al., 2014). One of the main aims of this thesis was to explore whether electrophysiological data collected from the NHSP could potentially be used to reveal more than just a child’s risk of hearing impairment. In the neonatal Intensive Care Unit (NICU), newborn hearing screening protocol includes assessment of both otoacoustic emissions (OAE) and the auditory brainstem response (ABR). There is a subset of NICU infants who show a transient failure of the ABR (Clemens, Davis and Bailey, 2000; Uus, 2004; Psarommatis et al., 2006, 2011), which has been associated with the development of Autism Spectrum Disorder (ASD, Cohen et al., 2013). The pathology behind this transient failure is debated. However, it may be the result of a delay in myelination that would temporarily affect production of the central components of the ABR until sufficient time has passed for myelination to ‘catch up.’ Although the ABR normalises in some cases, temporarily reduced neural activity has been shown to impact upon further myelination (Deremens et al., 1996) and in turn, impaired myelination may affect temporal synchronicity within the auditory brainstem (Waxman, 1977; Rance, 2005; Kim, Renden and Gersdorff, 2013). Given that a subset of children and young adults with neurodevelopmental communication disorders demonstrate auditory temporal processing deficits, transient failure of the ABR could act as a potentially useful biomarker for these disorders and provide a window into the potentially detrimental impact that early impairment in myelination may have on future neurodevelopment in the auditory pathway. Therefore, the aim of the study in Chapter Three was to investigate whether transient failure of
the automated ABR at newborn hearing screening was associated with the development of communication difficulties in later childhood. In order to investigate this, the communication abilities of children who had shown this transient failure of the ABR were compared with that of a control group who had shown normal ABRs at screening, using a short version of the Children’s Communication Checklist-2 (CCC-2 Short, Bishop, 1998; Bishop, 2003). This checklist is designed to detect the presence or absence of a communication difficulty using 13 questions that are completed by the child’s main caregiver.

In addition to the click-evoked ABR the frequency following response (FFR) has also been found to be disordered in subjects with neurodevelopmental communication disorders. The FFR is a transient, auditory-evoked measure that reflects the activity of phase-locked neurons and represents temporal encoding within the auditory brainstem (Rose et al., 1967; Gardi, Merzenich and McKeen, 1979). The FFR has been found to be disordered in some subjects with neurodevelopmental communication disorders who have normal ABRs to click stimuli (King et al. 2002; Song et al., 2006; Russo et al., 2008, 2009), suggesting that the FFR may be more sensitive than the click-evoked ABR to temporal processing deficits in this patient group. Given these findings and that this measure is sensitive to auditory temporal processing deficits, this presents the FFR as another potential biomarker for neurodevelopmental communication disorders. Therefore, the aim of the study in Chapter Four was to compare both latency and amplitude of the FFR with latency of wave V of the click-evoked ABR to investigate whether these measures reflect processing in separate neural populations. Despite evidence that the FFR may be more sensitive to auditory temporal processing deficits than the click-evoked ABR, this measurement is not currently used in a clinical setting. Therefore, another aim of the study in Chapter Four was to explore the clinical feasibility of the FFR in comparison to the click-evoked ABR, which is currently used to assess auditory brainstem integrity in infants referred through the NHSP.

In the study in Chapter Five, the FFR was further examined as a potential biomarker for neurodevelopmental communication disorders
by investigating its ability to distinguish individuals with a neurodevelopmental communication disorder from a control population. In addition, participants completed a self-report questionnaire measure of auditory temporal processing, which assesses speech-in-noise ability. The purpose of this additional measure was to further evaluate the potential usefulness of auditory-evoked electrophysiological measures as potential biomarkers for neurodevelopmental communication disorder by investigating whether these measures were a more important predictor of the presence of a neurodevelopmental communication disorder than a self-report measure. The study in Chapter Five also included participants with a demyelinating disorder. If the auditory temporal processing deficits found in neurodevelopmental communication disorders have a basis in impaired myelination then it might be expected that individuals with such disorders demonstrate similar auditory brainstem pathology to individuals with a demyelinating disorder. The results of the studies in Chapters Three through to Five will be discussed in more detail in the following sections.

6.2 Is Transient Failure of the ABR Clinically Meaningful?

The study in Chapter Three was novel in its attempt to investigate whether transient failure of the automated ABR at newborn hearing screening is associated with communication difficulties in children before they reach 10 years of age. However, the results of the study suggest that there is no association between transient failure of the automated ABR at newborn hearing screening and development of communication difficulties. In particular, no significant difference was found between the experimental and control groups on CCC-2 Short scores. Sixteen children in the experimental group (transient failure) were found to have the presence of a communication difficulty compared to 14 children in the control group (no transient failure). However, this difference was not statistically significant.

These findings are in contrast to those of Cohen et al. (2013) who found the transient failure was associated with a later diagnosis of ASD. The size of any effect of a transient failure of the ABR is
likely to be small and due to the limited sample size of the study in Chapter Three, it is possible that any true effect was missed. Furthermore, although the original version of the CCC-2 has been validated (Geurts et al., 2004; Norbury et al., 2004), studies measuring the sensitivity and specificity of the shortened version are yet to be carried out. Empirical investigation into whether the transient failure of the ABR is clinically meaningful is extremely challenging. Based on previous research, the hypothesis proposed in Chapter One suggests that transient failure of the ABR could be indicative of a delay in myelination, which may temporarily reduce conduction of neural impulses (Waxman, 1977; Inagaki et al., 1987; Rance, 2005). Subsequently, this may impair the myelination process (Demerens et al., 1996) in auditory brainstem structures more rostral to the site of delayed onset and affect temporal synchronicity (Waxman, 1977; Rance, 2005).

However, there are a number of alternative explanations as to why infants may show this transient failure that are unrelated to neurological pathology, including middle ear problems (Hall and Grose, 1993), a noisy testing environment, or an unsettled infant that may cause myogenic interference. Therefore, results should be interpreted as extremely preliminary and due to the limitations of the study, the absence of an association is not necessarily indicative that the transient failure is not of clinical importance. The question remains as to why some infants show a temporary abnormality of the ABR and whether a period of transient failure has an impact on future neurodevelopment in the auditory brainstem. Psarommatis et al. (2011) have suggested that delaying screening by one month could reduce the number of cases of these transient failures by allowing the auditory brainstem to mature. However, if a transient failure is of clinical significance then such a move would run the risk of missing important clinical information. Furthermore, delaying screening would pose logistic difficulties in terms of recalling infants and families, which in turn would result in lower numbers of infants being screened. Future research should aim to use a much larger sample in order to explore whether the transient failure is clinically meaningful. This is discussed further in Section 6.5 of this chapter.
6.3 Is There Evidence of Impaired Myelin in the Auditory Brainstem of Subjects with Neurodevelopmental Communication Disorders?

The hypothesis discussed in Chapter One suggests that transient failure of the ABR may be indicative of delayed myelination that may impair further myelination of the auditory brainstem. This hypothesis is extremely challenging to address and unfortunately, no conclusions can be made as to the involvement of impaired myelin in the auditory brainstem of subjects with neurodevelopmental communication disorders based on the results found in this thesis. However, the study in Chapter Five was novel in its direct comparison of subjects with a neurodevelopmental communication disorder and those with a demyelinating disorder. Multiple Sclerosis (MS) is one such disorder in which myelin of the central nervous system is destroyed (Marburg, 1906). The results of this study showed that both the MS group and a group of adults with ASD were found to have significant prolongation of the wave III-V inter-peak interval of the click-evoked ABR compared to a control group. This finding in the MS group supports previous literature. Both Stockard et al. (1977) and Chiappa et al. (1980) found that the majority of their subjects with MS who had delayed click-evoked ABR latencies showed prolongations for the wave III-V inter-peak interval only. The prolongation of the wave III-V inter-peak interval in patients with MS is likely due to a transmission deficit within neurons that lie between the superior olivary complex (wave III) and inferior colliculus (wave V) (Starr, 1976; Starr et al., 1977). This pattern of prolongation was also found in the ASD group. Speed of transmission through neurons is a good indicator of the thickness of myelin (Waxman, 1980). Therefore, prolonged transmission time found in the ASD group could also indicate a reduction in myelin in the pathway responsible for producing waves III-V, although this is purely speculation.

The theory that neurodevelopmental communication disorders have a biological basis in impaired myelination which might be detected at an early stage is extremely challenging to explore empirical-
ly. Ideally, studies investigating this hypothesis would need to be longitudinal in nature and would require expensive imaging techniques to accurately track changes in myelination of the auditory brainstem. However, if impaired myelination and atypical ABRs in infancy are risk factors for these disorders, auditory-evoked electrophysiological measures could help clinicians track more closely the developmental trajectories of infants who show atypical ABRs.

Given that healthy myelination is thought to be an integral part of the development of temporal processing abilities (Waxman, 1977; Rance, 2005; Kim, Renden and Gersdorff, 2013), and that auditory temporal deficits are found in subjects with neurodevelopmental communication disorders, it would be of high clinical importance to identify such impairment as early as possible. Furthermore, such impairment would be detectable at an earlier stage through auditory-evoked electrophysiological measures than behavioural measures, which require a child to be older.

Secondly, it is possible that impaired myelination within auditory brainstem structures responsible for the click-evoked ABR are being overlooked in clinical settings. Personal communication with a number of NHS audiologists has revealed that when an infant is currently referred from the NHSP to an audiologist, click-evoked ABR inter-peak intervals are not assessed unless they are grossly prolonged. Therefore, it is possible that a subtle auditory temporal processing deficit, in the form of a transmission delay in the central portion of the auditory brainstem, is being missed by clinicians during standard measurement of the ABR. Prolongation of the wave III-V inter-peak interval of the click-evoked ABR in subjects with ASD supports previous findings (Wong and Wong, 1991; Rosenhall et al., 2003; Kwon et al., 2006). Furthermore, Cohen et al. (2013) found that it was infants who showed a transient prolongation of the wave III-V inter-peak interval in particular who were more likely to be diagnosed with ASD by 4 months of age, and Amin et al. (2014) found that wave I-V inter-peak interval was significantly associated with later receptive and expressive language skills. Furthermore, absolute latency of wave V was not found to distinguish the communication disorder group
from the control group in the study in Chapter Three. Taken together, this evidence suggests that wave III-V inter-peak interval of the click-evoked ABR may make a useful biomarker for ASD in particular. Using inter-peak interval as a clinical tool could also be useful as it would allow clinicians to monitor the shortening of transmission time, which is a hallmark of normal maturation within the auditory brainstem (Salamy and McKean, 1976; Starr et al., 1977; Rotteveel et al., 1987).

It should be noted that a self-report questionnaire measure of speech-in-noise was found to be a more important predictor of whether an individual belonged to either the control group or communication disorder group. In particular, the ASD group showed significantly worse speech-in-noise ability than the control group. Diagnostic criteria used by the latest version of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) is primarily based on behavioural symptoms and the results from the study in Chapter Five suggest that self-report questionnaire measures of speech-in-noise may be useful for detecting infants at risk of ASD in particular. However, speech-in-noise difficulties have been reported in almost all neurodevelopmental communication disorders (Alcántara et al., 2004; Ziegler et al., 2009; Schafer et al., 2013). Speech-in-noise abilities could be assessed and monitored once children reach a classroom environment. Problems with processing speech-in-noise could have a number of negative impacts for children and would make classroom environments extremely challenging. Indeed, even normally hearing children without communication difficulties have been found to struggle to understand speech in an environment that mimics the noise levels experienced in most classrooms (Jamieson et al., 2004). If identified early, the negative impact of speech-in-noise difficulties for children with neurodevelopmental communication disorders could perhaps be reduced. However, one major drawback of using primarily behavioural measures to identify neurodevelopmental communication disorders is that by the time a child reaches an age at which these measures are feasible for use, the critical age for plasticity within the auditory brainstem (42 months) may have passed (Sharma, Nash and
Dorman, 2009). For example, Goin-Kochel, Mackintosh and Myers (2006) reported an average age of diagnosis for ASD of 4.5 years. Although behavioural screens give clinicians the tools to diagnose conditions such as ASD before two years of age, in reality children are usually only diagnosed at four years, on average two years after the parents have begun to show concern over their child’s development (Mandell, Novak and Zubritsky, 2005). In contrast, auditory evoked electrophysiological measures would offer an opportunity to detect auditory temporal processing deficits at an earlier age than behavioural measures. This is of the utmost importance given that early interventions have been shown to be beneficial for children with neurodevelopmental communication disorders (McGoey, Eckert and Dupaul, 2002; Woods and Wetherby, 2003; Hayes et al., 2003; Schatschneider and Torgesen, 2004; Howard et al., 2005).

6.4 Does the FFR Have Clinical Potential as a Biomarker for Neurodevelopmental Communication Disorders?

The FFR has been found to be disordered in subjects with neurodevelopmental communication disorders (King et al., 2002; Russo et al., 2008; Basu, Krishnan and Weber-Fox, 2010, Jafari, Malayeri and Rostami, 2015), occasionally in the presence of a normal ABR to click stimuli (King et al., 2002; Hayes et al., 2003; Song et al., 2006; Russo et al., 2008, 2009). This suggests that the FFR could be more sensitive than the click-evoked ABR to auditory temporal processing deficits in this patient group, and may offer a window into pathology in different auditory brainstem structures that respond to more complex stimuli. Therefore, the second main aim of this thesis was to explore the clinical potential of the FFR as a biomarker for neurodevelopmental communication disorders. The parameters of a healthy FFR must be established in order to detect any pathology that may affect its production. In particular, a lack of clarity regarding the neural generators and latency of a normal FFR limits its clinical usefulness. Therefore, the aim of the study in Chapter Four was to examine the clinical potential of the FFR through comparison with the click-evoked ABR.
The FFR reflects phase-locked activity to both the stimulus envelope and temporal fine structure (TFS). The study in Chapter Four was novel in its comparison between the latency and amplitude of the click-evoked ABR and FFR to both stimulus envelope and temporal fine structure (TFS) in a normally hearing population. The FFR to five different amplitude-modulated tones each with a carrier frequency of 590 Hz and modulated at rates of between 95-135 Hz, was recorded in a healthy and normally hearing population. The results showed that latency of the FFR to the envelope and lower side band of the temporal fine structure (TFS) (455-495 Hz region) of the stimulus occurred significantly later than wave V of the click-evoked ABR.

Although it could not be established as to whether this difference in latency was the result of separate neural generators or the cochlear travelling wave delay, weighing up the evidence suggests that separate neural generators are the most likely explanation. In particular, there is evidence that a tone of around 500 Hz can excite cochlear regions that are 2-3 octaves basal to the frequency of stimulation (Huis in’t Veld, Osterhammel and Terkildsen, 1977; Rhode, 1978; Gardi and Merzenich, 1979), which would reduce the cochlear travelling wave delay from around 3.5 ms to 1.5 ms (Ruggero and Temchin, 2007). Given that the traveling wave delay of the click-evoked ABR is thought to be around 0.5-1 ms (Eggermont, 1979; Ruggero and Temchin, 2007), this would give both measures a similar travelling wave delay and suggests that separate neural generators account for the longer latency of the FFR. This finding presents the FFR as a tool that may reflect the integrity of separate neural populations than the click-evoked ABR wave V. For the control group, average FFR latency was found to be 7.66 ms. Further studies are required in order to establish whether this latency is similar in other control populations. However, this latency is over 2.50 ms greater than the average click-evoked ABR latency for the control group found in the study in Chapter Four (5.04 ms). The finding brings to question the conclusions of previous papers that neural generators of the FFR are the same as the generators for the click-evoked ABR wave V (Glaser et al. 1976; Sohmer, Pratt and Kinarti, 1977). This finding is important in the context of the use-
fulness of auditory-evoked electrophysiological measures as biomarkers for neurodevelopmental communication disorders because it demonstrates that the FFR reflects temporal processing in more rostral brainstem structures than the click-evoked ABR. Given that FFR deficits are found in children with these disorders, the click-evoked ABR alone could potentially miss auditory temporal processing deficits in infancy in these more rostral structures.

However, the study in Chapter Five found that the FFR could not distinguish a control group from a communication disorder group. At face value, this could suggest that the FFR would not make a useful biomarker for neurodevelopmental communication disorders. However, there are several explanations as to why there were no FFR deficits found in the communication disorder group. Firstly, it may be due to a difference in stimuli used across studies. Although many of the studies that have recorded the FFR in subjects with a neurodevelopmental communication disorder have elicited the response using the synthetic speech syllable /da/ (King et al., 2002; Song et al., 2006; Russo et al., 2008, 2009), the FFR can also be elicited by amplitude-modulated tones, which are thought to accurately represent the acoustic properties of speech (Shannon et al., 1995) and can mimic temporal features of speech such as the fluctuation of envelope cues (Alcántara et al., 2012). Furthermore, temporal cues in speech which consist of amplitude modulation frequencies of between 64 and 500 Hz are thought to be responsible for encoding prosody and voicing and believed to be processed in the brainstem (Giraud et al., 2000). The study in Chapter Five was unable to replicate previous findings of a prolonged FFR in individuals with a neurodevelopmental communication disorder could be seen to support previous claims that speech stimuli are somehow processed differently in the auditory brainstem than non-speech stimuli (Song et al., 2006). Both Leonard (1998) and Rosen (2003) have argued that research pertaining to poor temporal processing of non-speech stimuli cannot be linked to future neurodevelopmental communication disorders. If the FFR is to be used as a potential biomarker for neurodevelopmental communication disorders then it is possible that the type of stimuli used to evoke the response
could be important in order to detect pathology. However, there appears to be no other studies that have investigated the FFR evoked by amplitude-modulated tones in individuals with neurodevelopmental communication disorders, meaning that the results from the study in Chapter Five must be interpreted with caution and further research with similar patient groups and stimuli are encouraged. Secondly, there is always the possibility that there were no auditory processing deficits in the sample used in the study in Chapter Five. However, this explanation is somewhat hindered by the finding of a prolongation of the click-evoked ABR wave III-V inter-peak interval, indicating that an auditory processing deficit was present in this group. In previous studies, a disordered FFR has often only been identified in a subset of children with neurodevelopmental communication disorders (King et al., 2002; Johnson et al., 2005; Banai, Abrams and Kraus, 2007; Billiet and Bellis, 2011). Therefore, it is possible that the adults in the study in Chapter Five represent the population of individuals with these disorders who do not have auditory temporal processing deficits. This highlights one limitation of the FFR as a potential biomarker for neurodevelopmental communication disorders. Another possible explanation as to the contrast in findings in the study in Chapter Five in comparison to previous literature is the age of the subjects that were used. Studies that have reported FFR deficits in subjects with neurodevelopmental communication disorders have all used children, whereas the study in Chapter Five used an adult sample. To the authors’ knowledge, there are no other studies that have investigated the FFR in adults with neurodevelopmental communication disorders. Our findings suggest that they are not present in this population. Furthermore, as disordered FFRs are only found in a subset of children with these disorders, it may be best used cautiously as a predictive biomarker by which clinicians may identify infants at risk given the presence of other important risk factors such as genetic susceptibility.

Another noteworthy limitation for the use of the FFR as a biomarker for neurodevelopmental communication disorders is the likelihood that the response has multiple generators, with reports of generation sites as caudal as the cochlea and as rostral as the medial ge-
niculate body (Gardi, Merzenich and McKean, 1979; Davis and Britt, 1984; Rouiller, de Ribaupierre and de Ribaupierre, 1979). Davis and Hirsh (1976) have suggested that variations in FFR latencies reported across studies could be due to different travelling cochlear wave delays caused by multiple initiation sites along the basilar membrane. The FFR is a sustained response and so measuring its onset is challenging and the use of one latency value may not accurately represent the possibly multiple generators within the auditory brainstem. This could potentially limit the potential of the FFR as a clinical tool because differences in latency may reflect normal variable responses from multiple generators rather than indicate a delay in neural transmission. Nevertheless, this limitation could be reduced if electrode montages during assessments are kept constant to ensure a response from similar neural generators or through the use of a stimulus that produces a replicable FFR waveform, such as the /da/ syllable that is currently utilised by the BioMARK tool (Abrams and Kraus, 2005).

Nevertheless, the novel stimulus design used in the study in Chapter Four that enabled the recording of the envelope following response and TFS following response simultaneously may have clinical utility. Being able to separately identify whether the envelope or TFS following response is delayed could allow insight into the nature of the language difficulty an individual may experience based on evidence that the TFS and envelope following responses have separate roles in speech perception and communication (Smith, Delgutte and Oxenham, 2002; Zeng et al., 2004; Lorenzi et al., 2006). In turn, this could result in better strategies of care for individuals at risk of developing such communication difficulties.

Much more research is required to either support or challenge the use of the FFR as a clinical tool. The results from the current thesis support the hypothesis that speech stimuli can identify auditory temporal processing deficits that non-speech stimuli cannot. Although these results should be interpreted with caution due to small sample sizes and a lack of previous literature that have evoked the FFR using amplitude-modulated tones. A number of further limitations in the po-
tential use of the FFR as a clinical tool were noted from both the studies in Chapters Four and Five. For example, recording of the FFR had a total testing time of almost 41 minutes and a high number of responses had to be discarded because of noise in the data. Neither of these characteristics would make the FFR a particularly attractive tool for use in the clinic where time is of the essence. Study two also demonstrated that variability remained much higher for the FFR in comparison to the click-evoked ABR. Given these limitations, the FFR would not currently make a useful biomarker for neurodevelopmental communication disorders. Nevertheless, a tool such as the BioMARK (Abrams and Kraus, 2005) would overcome some of the limitations found in the use of the FFR in the papers in this thesis, such as a prolonged testing time and lack of normal parameters by which to identify pathology. Furthermore, with growing evidence that complex stimuli are processed by separate auditory brainstem structures, the click-evoked ABR may be severely limited in what it can tell us about the integrity of the auditory brainstem of infants. However, in conclusion, the FFR still suffers from severe limitations that would inhibit its use within a clinical setting.

6.5 Future Directions

The overall aim of the studies in this thesis was to investigate the potential usefulness of auditory evoked electrophysiological measures as potential biomarkers for neurodevelopmental communication disorders. In particular, the NHSP collects data (the ABR) from NICU graduates that may serve to flag poor temporal synchronicity which is found amongst subjects with these disorders. There remains a gap in knowledge as to whether transient failure of the ABR at newborn hearing screening is clinically meaningful. The study in Chapter Three was limited by a small sample size, primarily due to difficulties in accessing the data required for the study. NHS Trusts may wish to look to review the ease with which such data can be accessed by research teams. Data collection was especially challenging due to a high number of gate-keepers and high variability in research and develop-
ment approval procedures across different NHS Trusts. A national, anonymised ‘big data’ source that could be accessed by research teams with approved projects would prove extremely useful and could be used to track children longitudinally to identify any links between auditory evoked electrophysiological data collected at newborn screening and future global development. This could be relatively easy to achieve by distributing consent forms to parents prior to screening. The NHSP has a unique advantage to be able to capture potentially useful data on the temporal resolution of an infant’s auditory brainstem, and given the overwhelming evidence for auditory brainstem involvement in neurodevelopmental communication disorders, further research in this area is highly encouraged.

Further research into why only a subset of individuals with neurodevelopmental communication disorders show auditory temporal processing deficits is highly encouraged in order to expand knowledge about the usefulness of auditory evoked electrophysiological responses as biomarkers for such disorders. Individuals diagnosed with these disorders who do demonstrate auditory temporal processing deficits may represent a unique trajectory of communication and linguistic development. If substantiated, this perspective would have several important clinical applications. Tomblin (2008) has argued that it may be better to assess an individual’s ability to function within society on an individual level rather than using standardised tests based around what is considered as a normal developmental trajectory for speech and language, opinions of which are heavily influenced by culture (Norbury and Sparks, 2012). If children with neurodevelopmental communication disorders and auditory processing deficits do present a unique patient group, then the early identification of this group through auditory-evoked electrophysiological measures could help toward this individualisation and tailoring of appropriate treatment to maximise positive outcomes.

In Chapter Two, it was highlighted that many neurodevelopmental communication disorders are highly co-morbid and are similar in the nature of the communication difficulties they experience. The results of the study in Chapter Five found that only adults diagnosed
with ASD had a significantly prolonged wave III-V inter-peak interval and scored significantly worse on a self-report questionnaire measure of speech-in-noise when compared to both a control group and a group of adults with a diagnosis of dyslexia or ADHD. These findings are in contrast to those studies that found the wave III-V inter-peak interval to be prolonged in subjects with ADHD (Jafari, Malayeri and Rostami, 2015). However, it does support McAnally and Stein (1996) who found the click-evoked ABR to be normal in dyslexic patients. This suggests that auditory-evoked electrophysiological measures may not be useful for detecting neurodevelopmental communication disorders such as dyslexia or ADHD. Much more research is needed in this area. The study in Chapter Five showed speech-in-noise ability and wave III-V inter-peak intervals to be significant predictors of group membership between a group of adults with neurodevelopmental communication disorders and a control group. Furthermore, it was a group of adults with ASD in particular who had both significantly worse speech-in-noise ability and prolonged wave III-V inter-peak intervals in comparison to a control group. Taken together, these three measures could make a potentially useful battery for the early identification of ASD, which could be explored in future research.

In addition, the results of the study in Chapter Three suggest that parental concern regarding general development could be important in the early identification of communication difficulties, although the result should be interpreted with caution. Parental concern over a number of different developmental areas including communication, social skills and learning were significantly correlated with presence of a communication difficulty. Parental concern has been found to predict a diagnosis of ADHD (Bussing et al., 2003) and ASD (Ozonoff et al., 2009). Yet despite evidence of its potential usefulness, Young, Brewer and Pattison (2003) found there to be a significant delay between when a parent first reported suspicions of ASD in their child and a clinical diagnosis by a professional. Furthermore, parental concerns in this area have been found to be dismissed by some health care professionals (Bultas, 2012). Mandell, Novak and Zubritsky (2005) found that parental concern over the presence of a hearing im-
pairment was associated with an increase in diagnosis age for children with ASD, suggesting that parental concern about auditory deficits was not taken particularly seriously by professionals and resulted in a delay in diagnosis. This is worrying in light of the results of the studies in both Chapters Three and Five of this thesis, which found that not only is parental concern associated with the presence of a communication difficulty but that auditory processing deficits are present in adults with autism. Better parental education about the early behavioural warning signs of neurodevelopmental communication disorders could be easily implemented into the NHSP through better parental education on the signs and early behavioural characteristics of neurodevelopmental communication disorders.

There are perhaps some ethical concerns regarding the use of electrophysiological measures as biomarkers for neurodevelopmental communication disorders that should be noted by future researchers. For example, the use of auditory evoked electrophysiological measures to flag infants who should be more closely monitored for signs of developing a neurodevelopmental communication disorder should be pursued with care. Closer monitoring of infants may cause undue parental stress if the suspected presence of such a disorder is not accurate. Therefore, far more solid evidence would be required to justify the use of auditory-evoked electrophysiological measures as biomarkers for neurodevelopmental communication disorders. As highlighted by Walsh et al. (2011) some biomarkers are associated with a range of neurodevelopmental disorders and can lack specificity. However, auditory-evoked electrophysiological measure could be looked upon as biomarkers of susceptibility to the development of communication difficulties in general. This may go some way in overcoming the extremely heterogeneous nature of neurodevelopmental communication disorders.

6.6 Overall Conclusions
The main conclusions drawn from this thesis can be summarised as follows:
• Transient failure of the click-evoked ABR at newborn hearing screening was found not to be associated with the later development of communication difficulties. However, this study was preliminary and limited by a small sample size. As such, no definitive conclusions as to whether transient failure of the ABR is clinically meaningful can be made. Further research with a ‘big data’ source is recommended.

• The hypothesis that impaired myelination underlies the auditory temporal deficit in individuals with neurodevelopmental communication disorders remains challenging to investigate.

• Prolongation of the inter-peak interval of waves III-V of the click-evoked ABR and poor speech-in-noise ability could be clinically useful in identifying infants at risk of developing ASD.

• The FFR was not able to distinguish a group of subjects with a neurodevelopmental communication disorder from a control group, limiting its potential as a biomarker for these disorders. Furthermore, issues in practicability remain when it comes to using the FFR as a clinical tool.

• This thesis has provided evidence that can encourage new research into potential new markers (click III-V inter-peak interval/self-report questionnaire measuring speech-in-noise ability/parental concern) for neurodevelopmental communication disorders.

In sum, the pursuit of meaningful biomarkers for neurodevelopmental communication disorders is complex, with both ethical and logistical challenges. However, given the overwhelming evidence for auditory brainstem involvement in these disorders, population-based studies with much larger samples are highly encouraged in order to further explore the potential of auditory evoked electrophysiological...
measures as biomarkers for neurodevelopmental communication disorders.
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Appendices

Appendix A

*Invitation letter used in the study in Chapter Three:*

[Insert relevant NHS Trust logo here]
[Insert Manchester University logo here]
[Insert relevant NHS Trust address here]

[Date]

R.E. [Insert Child’s name here]

Dear [insert parents’ names here]

Our NHS Trust is currently working in collaboration with The University of Manchester on a research study for which you and your child, named above, have been selected as potential participants. You may remember that when your child was born they had their hearing screened whilst still in hospital. Your child’s result at this screening is the reason you and your child have been selected as potential participants.

Your participation is voluntary and will simply require you to fill out a short questionnaire that is designed to measure the communication strengths and weaknesses of your child. You may choose to complete this questionnaire by post, online or by telephone. The enclosed participant information sheet provides further information about this study. Please read this carefully if you are interested in taking part. Please note, if you choose not to take part this will not affect your access to our care services here at the Trust.

This study has been approved by an NHS Ethics Committee (13/NW/0014) and you are welcome to speak to a member of the research team at any time if you have any queries.

THE QUESTIONNAIRE IS INCLUDED IN THIS PACK AND CAN BE FOUND ON YELLOW PAPER. PLEASE COMPLETE THE
QUESTIONNAIRE, ALONG WITH THE ENCLOSED CONSENT FORM (PINK PAPER) AND RETURN THEM BOTH IN THE PROVIDED PRE-PAID ENVELOPE.

Thank you for taking time to read this letter and we look forward to hearing from you.

Yours sincerely,
Appendix B

Participant Information Sheet used in the study in Chapter Three:

PARTICIPANT INFORMATION SHEET

Predictive Value of the Newborn ABR Screen for Developmental Communication Difficulties in Children

Please take the time to carefully read through all the information so that you can make an informed decision as to whether or not you would like to take part.

What is the purpose of this study?

You may remember that your child had their hearing tested when they were a few days old. We are interested in whether the results of this test may have some kind of relationship with their later communication development. You have been invited to take part in this study because the results of (one of) your child’s hearing screening results fits one of the categories that we are interested in. You do not have to take part in this study. Participation is completely voluntary. If you decide to take part, you should also note that are you free to withdraw from taking part at any time.

What will I be required to do?

The study requires you to complete a simple questionnaire (enclosed on yellow paper) so that we can gather information about your child’s general development and their communication strengths and weaknesses. It is important for you to note that this is not a diagnostic tool. Your child will not be diagnosed with any kind of communication disorder.

What are the possible benefits of taking part?

There will be no direct benefit to your child as a result of taking part. However, you will receive a £5 Amazon gift voucher for completing the questionnaire. Furthermore, completing the questionnaire may help identify whether or not your child is within or below average limits for communication abilities within their age group. This could
be an invaluable tool in helping you improve your child’s communication skills and both their educational and social outlook. Perhaps your child has been diagnosed with a communication disorder or you know someone who has. If this is the case, by taking part you could be helping to further knowledge on disorders such as autism and ADHD, and their origins. This in turn could improve management of the disorders and help toward a better quality of life for anyone diagnosed with a communication disorder.

*Are there any risks?*

There are no risks involved in this study and any information collected about you and your child during the course of the research will be kept strictly confidential and will never be disclosed to third parties. If on completing the questionnaire you have any concerns regarding your child’s development, or you encounter any distress on answering the questions, please speak directly to your local GP or your child’s paediatrician for advice and support.

*What will happen to the results of the research study?*

The results of the study will be used for part of a PhD qualification and published in a journal article. We will be happy to send you a summary of the results once the study is completed.

*Who has reviewed the study?*

The study has undergone scientific review within The University of Manchester and has been reviewed by a NHS Research Ethics Committee who has given this study a favourable opinion (reference 13/NW/0014).

*Who should I contact if I wish to obtain further information?*

If you have any questions about the study or any general enquiries, please contact Anna Terry on 0161 275 3507 or anna.terry@postgrad.manchester.ac.uk.

For independent advice on participating in research you can contact the Patient Advice and Liaison Service (PALS):

Phone: 0161 276 4261
Email: adult.pals@cmmc.nhs.uk
Website: [http://www.pals.nhs.uk](http://www.pals.nhs.uk)

If you have a concern about any aspect of this study, please feel free to contact a member of the research team on 0161 275 3507. If they are unable to resolve your concern or you wish to make a complaint regarding the study, please contact a University Research Practice and Governance Co-ordinator on 0161 2757583 or 0161 2758093 or by email to research-governance@manchester.ac.uk.
Appendix C

Validated questionnaire used in the study in Chapter Three:

Thank you for deciding to take part in our research study. The questionnaire can be completed in your own time and returned in the pre-paid envelope provided. Please try and return the questionnaire no later than three weeks from the date you received it. If you wish to complete it online please go to [insert address here] or contact a member of the research team if you would like to complete it over the phone.

Part One: General Questions

Your child’s D.O.B: • • . • . • • •  
Your child’s name:  
Your child’s sex Please tick one: • Male • Female  

Today’s date:  
Home postcode:  
Your name (person completing the questionnaire):  

Please describe your relationship to the child (e.g. mother, father, grandmother etc.):  

What is the highest educational level of the child’s main caregiver? Please tick one:  

- No qualifications  
- GCSE/O Levels  
- AS Level  
- A Level (or equivalent)  
- Undergraduate degree  
- Postgraduate degree  

If known, please provide the birth weight of your child in lbs and oz:  

lbs oz or g  

Was the child born full term (at 38-42 weeks)? Please tick one  

- YES  
- NO  

If no, please state how many weeks early the baby was:  

weeks early  

Were there any complications during the labour?  

- YES  
- NO  

If yes, please give details below:
Was your child ventilated during his/her time in intensive care?
YES  NO

Has s/he any physical disability or chronic illness? Please tick one
YES  NO

If yes, please give details below:

Do you have any concerns regarding your child’s general development?

Please tick one:

YES  NO
If yes, please give details below:
At what age did your child begin to walk?
months.
At what age did your child say his/her first word?
months

Part Two: The Children’s Communication Checklist Short Version

Children’s Communication Checklist (CCC-2 Short) Bishop and Norbury © (2009) by Pearson, Assessment. Reproduced with permission. All rights reserved.

The CCC-S is a brief screening instrument designed to help us identify children with potential speech, language and communication needs. It is helpful to find out how the child behaves in everyday situations, and whether adults who know the child well have any concerns about the child’s development. Please help us by completing the all questions that you can.

There are 7 questions about the child’s environment and about any developmental concerns or any extra help the child may be receiving. Please read each question carefully and tick all of the boxes that apply. On the other side of the sheet, there are 13 statements describing how children communicate. Please read the instructions carefully to know how to rate these items.

All these questions must be answered in relation to the child detailed above.

Q1: Is your child combining words into phrases or sentences?
Yes ☐ No ☐

Q2: Is English the main language spoken at home? Yes ☐
No ☐
If no, what is the child’s home language:

Q3: Has your child ever been seen by a speech-language therapist or educational psychologist?
Yes □ No □

Q4: Does your child have a statement of special educational need?
Yes □ No □

If yes, what is the problem?

If yes, what is the primary need code on the statement?

Q5: Is your child being monitored for school action? Yes □ No □

If yes, what is the problem?

Q6: Have you ever been concerned about your child’s skills in any of the following areas?

   a. Speaking □ f. Fine/Gross motor skills □
   b. Listening □ g. Social skills □
   c. Communication □ h. Learning □
   d. Reading/writing □ i. Other (please specify) □
   e. Behaviour □ j. NO CONCERNS □

Q7: What specific diagnoses has your child received from outside agencies? (please tick all that apply):

   a. Hearing Impairment □ e. Specific Language Impairment □
   b. Autism (Autistic Spectrum) □ f. Dyslexia (Reading) Impairment □
   c. Down syndrome □ g. Dyspraxia □
   d. Other □ h. Attention Deficit/Hyperactivity □
   i. Auditory Processing Disorder □

Please specify if ‘other’: j. NO KNOWN DIAGNOSES □

For items 8-13, please indicate how frequently your child makes the following errors by writing a number in the box to the right of the statement as follows (do not leave any items blank). FOR THESE
ITEMS A HIGHER NUMBER SUGGESTS GREATER DIFFICULTY:

0 rarely or never (less than once a week)
1 occasionally (once a week)
2 regularly (once or twice a day)
3 frequently or always (several times a day)

8. Forgets words s/he knows, e.g. instead of “rhinoceros” may say, “that animal with a horn.” [ ]

9. Uses terms like “he” or “it” without making it clear what s/he is talking about. E.g. when talking about a film may say ‘he was really great’ without explaining who ‘he’ is. [ ]

10. Misses the point of jokes and puns (though may be amused by humour such as slapstick). [ ]

11. Leaves off past-tense –‘ed’ or other word endings [ ]

12. Takes in just one or two words of a sentence, so misinterprets what has been said. E.g. if someone says ‘I want to go skating next week’, may think they have been or want to go now. [ ]

13. Gets the sequence of events muddled up when trying to tell a story or describe an event. E.g. if talking about a film they may describe the end before the beginning. [ ]

Items 14-20 ask about communicative strengths, or things your child does well. Please respond 0, 1, 2, or 3 as before, but this time, A HIGHER NUMBER SUGGESTS GREATER SKILL.

14. Uses appropriate language to talk about future events (e.g. plans for tomorrow or plans for going on holiday.

15. You can have an enjoyable, interesting conversation with him/her. [ ]

16. Can produce long and complicated sentences such as: “When we went to the park I had a go on the swings”; “I saw a girl holding a spotty umbrella”. [ ]

17. Uses words that refer to whole classes of objects, rather than a specific item; e.g. refers to chairs, tables and drawers as “furniture” or apples, bananas and pears as “fruit” [ ]
18. Speaks clearly, producing all speech sounds in a word accurately. [   ]

19. Explains a past event (e.g. what s/he did at school or what happened at a party) clearly. [   ]

20. When answering a question, provides just the right amount of information, without being overly precise or too vague. [   ]

*That is the end of the questionnaire. Thank you for taking the time to complete it, your time and effort are greatly appreciated.*
Appendix D

Consent form used in the study in Chapter Three:

CONSENT FORM
Predictive Value of the Newborn ABR Screen for Developmental Communication Difficulties in Children

Our reference: YORK

IF YOU WOULD LIKE TO PARTICIPATE IN OUR STUDY, PLEASE COMPLETE AND SIGN THIS FORM.

A pre-paid envelope is enclosed in which you can return this form along with the completed questionnaire. Thank you. Please tick the box if you agree.

I confirm that I have read the participant information sheet regarding the above study and would like to participate.  

I confirm that I understand that the data from the questionnaire may be published anonymously as part of a PhD project.

I understand that relevant sections of anonymous data collected during the study may be looked at by other individuals from the University of Manchester and from regulatory authorities. I give permission for these individuals to access this anonymous data if necessary.

I am happy to be contacted about this study and any related follow up research for this project.

Please print your name:  
Please sign here:  
Date:  
Email or Telephone:  

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----------------------------------------------------------------------------------

THANK YOU
Appendix E

*Brainstem lesion checklist used for the study in Chapter Five:*

To assess your suitability for our study, please complete the following checklist
Do your symptoms consist of any of the following (please tick all that apply):

1. Vertigo (feeling as though your surroundings are spinning) □
2. Blurred vision □
3. Hearing problems □
4. Dizziness □
5. Slurred speech □
6. A lack of co-ordination □
7. Tremors or involuntary shaking □
8. Nystagmus (involuntary eye movements) □
9. Internuclear Ophthalmoplegia (problems with gaze) □