THE AUDITORY BRAINSTEM RESPONSE IN HEALTHY ADULTS AND ADULTS WITH ALCOHOL DEPENDENCE SYNDROME

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Abstract

The Auditory Brainstem Response (ABR) assesses brainstem function. This thesis explores the click and speech ABR in both healthy adults and adults with alcohol dependence syndrome (ADS).

Experiment One undertook auditory-cognitive assessment including ABRs, of 60 healthy adults (30 women), aged 18-30 years. For waves III and V of the click ABR, women's responses were earlier than men's by 0.14ms and 0.19ms. For the speech ABR, onset and offset measures were earlier in women by at least 0.43ms. No effect for left vs. right ear was found in either case. Inter-rater reliability was found to be high (ICC2,1 ≥0.89) for the click ABR and good (ICC2,1 ≥0.75) for six of the seven peaks of the speech ABR. A comparison of ABRs to those from an older group of 12 adults aged 31-49 years (six women, matched control group for Experiment Two) found the stimulus to response lag for the speech ABR, was earlier (0.78ms) in the older women but within the expected range. Click and speech ABRs were repeated after 12 weeks and the representation of F0 for women was greater by 4.8 μV at the second recording.

Experiment Two assessed the auditory-cognitive profile and ABRs of 16 adults (six women) aged 29-49 years, undergoing a treatment and rehabilitation programme for people with ADS. All participants had hearing thresholds within normal limits, but exhibited deficits in auditory-cognitive profiles compared to matched, healthy adults, including their click and speech ABRs. For the click ABR, men had significant delays in wave III (0.18ms) and wave V (0.22ms). For women there were significant delays for wave I (0.11ms) and wave V (0.22ms). For the speech ABR, men had significant delays in the onset measures of waves V (0.40ms) and A (0.36ms). Women had significant delays in waves V (0.45ms), A (0.48ms) E (0.66ms) and O (0.42ms). Testing was repeated after 12 weeks of abstinence and significant improvements in the click and speech ABR were observed. For men, average click ABR latencies improved for wave III (0.12ms) and wave V (0.22ms) and for women, wave V (0.08ms) improved. Significant improvements were also found for discrete peak and onset measures of the speech ABRs for both men and women. For men, average speech ABR latencies improved for wave A (0.23ms) and the duration of the VA complex (0.15ms). For women there were improvements in wave V (0.10ms), A (0.12ms) and E (0.33ms).

These results add to the body of knowledge about the ABR and support its value as a clinical tool. They also provide new information about auditory-cognitive function in adults with ADS, for whom beneficial effects of abstinence are demonstrated. The ABR has a potential role in identifying people most at risk of alcohol related brain damage and in monitoring recovery with abstinence.

Keywords

Auditory Brainstem Response, Frequency Following Response, Speech ABR, Reliability, Alcohol Dependence Syndrome, Abstinence.

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Abbreviations

ABR	Auditory brainstem response
ADS	Alcohol dependence syndrome
AEP	Auditory evoked potential
AI	Auditory cortex
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APD	Auditory processing disorder
ARBD	Alcohol related brain damage
ASD	Autistic spectrum disorder
AST	Aspartate aminotransferase
AUD	Alcohol use disorder
AVCN	Anteroventral cochlear nucleus
BAC	Blood alcohol concentration
CANS	Central auditory nervous system
CIC	Central area of the inferior colliculus
Click ABR	Click evoked auditory brainstem response
CM	Cochlear microphonic
CN	Cochlear nucleus
CNS	Central nervous system
CPA	Cerebellopontine angle
CPM	Central pontine myelinolysis
CT	Computed tomography
CVC	Consonant vowel consonant
DCN	Dorsal cochlear nucleus
DD	Dichotic digits
DPOAE	Distortion product otoacoustic emission
DPST	Duration pattern sequence test
DTI	Diffusion tensor imaging
E	Envelope
EEG	Electroencephalogram
EPSP	Excitatory postsynaptic potential
ERP	Event related potential

F0	Fundamental frequency
F1	First formant
F2	Second formant
FFR	Frequency following response
GABA	Gamma-Aminobutyric acid
GDT	Gap detection threshold
GGT	Gamma-Glutamyltransferase
IC	Inferior colliculus
ICC	Central nucleus of the inferior colliculus
ICC	Intraclass correlation coefficient
ISI	Inter stimulus interval
LL	Lateral lemniscus
LSO	Lateral superior olive
MCV	Mean corpuscular volume
MBD	Marchiafava–Bignami disease
MEG	Magnetoencephalography
MGB	Medial geniculate body
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MSO	Medial superior olive
MTNB	Medial nucleus of the trapezoid body
NMDA	*N*-methyl-d-aspartate
OAE	Otoacoustic emission
PDS	Persistent developmental stuttering
PET	Positron Emission Tomography
PI	Performance intensity
PPST	Pitch pattern sequence test
PTA	Pure tone audiometry
PVCN	Posteroventral cochlear nucleus
REA	Right ear advantage
RGDT	Random gap detection test
RMS	Root mean square
ROC	Receiver Operator Characteristic
SADQ	Severity of alcohol dependence questionnaire
SDT	Speech detection threshold

SIN	Speech in noise
SNHL	Sensorineural hearing loss
SNR	Signal to noise ratio
SOAE	Spontaneous otoacoustic emission
SOC	Superior olivary complex
SPECT	Single photon emission computed tomography
SPL	Sound pressure level
Speech ABR	Speech evoked auditory brainstem response
SRT	Speech recognition threshold
TEOAE	Transient evoked otoacoustic emission
TFS	Temporal fine structure
VCN	Ventral cochlear nucleus
vMGB	Ventral medial geniculate body
WAIS	Wechsler adult intelligence scale
WE	Wernicke’s encephalopathy
WKS	Wernicke Korsakoff syndrome
WIN	Words in noise
WMC	Working memory capacity

Chapter One: Thesis Overview

1.1 Introduction

The tools used to perform a standard hearing assessment capture hearing sensitivity but fail to capture the sizable role of central auditory processing (Musiek et al. 2017). This is a significant limitation because of the inter-related roles of hearing sensitivity, cognitive and central auditory processing in sound perception and recognition. A recently developed tool within the research community, the speech Auditory Brainstem Response (speech ABR), may offer promise in addressing this gap. The movement of tools from the research to the clinical setting requires justification and validation. For the speech ABR, there are a number of research issues concerning reliability and recording parameters, which remain unresolved.

Clinical utility in the healthcare setting refers to the "ability of a screening or diagnostic test to prevent or ameliorate adverse health outcomes through the adoption of efficacious treatments conditioned on test results" (Grosse and Khoury 2006, p.448). It is also a measure of the value that clinicians place on the information that a clinical tool provides (Bossuyt et al. 2012). There has been criticism of the quality of both the design and reporting of studies introducing new clinical tools. Without appropriate evaluation in the research domain, these tools can be prematurely introduced into clinical use resulting in unnecessary testing and inaccurate diagnoses (Bossuyt et al. 2003; Vermiglio 2016). Not only should patient health information be provided but also proof that using a certain test could improve outcome, enhance quality of care, improve efficiency or be more cost effective (Bossuyt et al. 2012).

When considering how accurate a test (or combination of tests) is, it should be evaluated against a reference standard. The reference standard is that which is currently considered to be the optimum way of determining the presence, or absence, of any particular condition. It may be a single method, or a suite of methods that are used to establish a diagnosis. Using the word 'test' can be misleading as it refers to any method used that provides additional information about a patient's condition. It can include everything from the clinical history taking, physical examination and results of other assessments that have been used. Apart from diagnosis, the results of a test may lead to further diagnostic testing or a change in, or even cessation of,

treatment. How accurate the new test under evaluation is, is determined by the amount of agreement with the results of the reference test(s). Accuracy can be expressed in different ways including sensitivity and specificity, likelihood ratios, diagnostic odds ratio, and the area under a receiver operator characteristic (ROC) curve (Bossuyt et al. 2003).

In this thesis, I explore the clinical utility of the Auditory Brainstem Response (ABR) when evoked by both a click and a speech-like stimulus. The click evoked ABR (click ABR) has a long history of clinical use and is a well-established tool for assessing brainstem function (Jacobson 1985; Hood 1998; Burkard et al. 2007; Hall 2007; Stone et al. 2009). There is increasing interest in the use of more complex stimuli to elicit the response (Skoe et al. 2010; Tarsenko et al. 2014; Nielzén et al. 2016; Manouilenko et al. 2017). Unlike the click ABR, there is little standardisation of the complex stimuli used to elicit the response and little exploration of the factors that might influence the response (Hood 1998; Hall 2007). Although it may only be a change in stimulus that is eliciting the response, the accompanying studies that assess the effects of changes in recording and subject factors are often lacking in the published research. This limits the value that clinicians can derive from such testing. In order to address this the overarching aims of this thesis are:

1. To assess the reliability of the speech ABR. Establishing confidence in inter-rater reliability and test re-test repeatability is a mandatory precursor to addressing the central aims of the thesis.
2. To assess the impact of patient-related parameters on speech ABR measures, by experimental examination. This will support the principled development of a clinical protocol.
3. To examine, through clinical trial, the comparative value of using the click and speech ABR to measure and monitor neural function in people with alcohol dependence syndrome.

The aims have been addressed using two experiments. Experiment One has been designed to examine aims one and two, with aim three addressed by Experiment Two. A more detailed overview of the thesis structure is provided in the following section.

1.2 Thesis Structure

A review of the literature relevant to this study is presented in chapter two, which is composed of four sections. The opening section is descriptive, designed to provide the reader with a fundamental understanding of the auditory pathways and how we hear. It also describes the development of a test battery that can be used to assess a person's auditory-cognitive profile. These details are required, as both Experiments One and Two are using tools which assess different aspects of cognitive function and the auditory pathway. The following section is also descriptive in nature, providing a history and overview of the use of the click ABR. This section presents many of the stimulus, recording and participant factors that have been explored in the quest to verify both research and clinical utility. The subsequent literature review sections contain a critical appraisal of the literature that has been published in relation to Experiments One and Two. The first provides an overview of the speech ABR, followed by a critical review of its use in the research and clinical environment. The second provides an overview of alcohol use and its effects on the human brain. Within this section, there is also a critical review of the clinical utility of the click and speech ABR in relation to alcohol consumption.

Chapter three pertains to Experiment One and consists of four sections. These sections address the aims that relate to factors that need to be considered, if the speech ABR is to have research or clinical utility. In the first section the participants, methods and a description of the auditory-cognitive profile for healthy young adults are presented. The following section explores the inter-rater reliability of the speech ABR and a comparison with that of the click ABR. The final two sections contain investigations pertaining to participant factors that are not adequately understood, or addressed, in the existing literature. The first of these includes explorations of the difference in the speech ABRs of men and women and differences in the speech ABRs from left and right ears. The final section includes a comparison of speech ABRs from adults aged 18-30 years, with those from adults aged 31-49 years. An exploration of test-retest repeatability is also presented.

Chapter four presents Experiment Two and consists of five sections. These sections address the aims that pertain to the utility of the ABR in a clinical population. The first section characterises the auditory-cognitive profile of adults with alcohol dependence syndrome (ADS). The following section contains studies of the click and speech ABR in adults with ADS. This is followed by a repeat of these explorations but

after a period of abstinence from alcohol. The final section presents a study examining the relationships between drinking history, auditory-cognitive profile and the ABRs.

The final chapter of this thesis provides a discussion of the results of the studies contained in Experiments One and Two. This discussion includes an interpretation of the findings and their implications for the utility of the ABR within the research and clinical domains.

Chapter Two: Literature Review

Chapter two comprises a review of literature related to Experiments One and two. The first section of this literature review is descriptive, designed to provide the reader with a fundamental understanding of the auditory pathway. The auditory system is described in relation to anatomy and physiology. This is followed by a discussion of the additional but inter-related roles of auditory processing and cognition, when considering speech perception.

2.1 The Auditory System and Hearing

Sounds vary in intensity, frequency and timing, and it is possible to distinguish sounds of interest even in competing noise (Appler and Goodrich 2011). This is accomplished by the ear and associated auditory pathways. Traditionally, the ascending auditory system (i.e. the pathway taken by an incoming auditory stimulus to its interpretation in the cortex) is subdivided into two sections: the peripheral auditory system and the central auditory nervous system (CANS) (Musiek 1994). Section 2.1 provides a descriptive and functional overview of the key components of the auditory system (the peripheral 2.1.1 and the CANS 2.1.2) as well as neural communication within the brain. The ear is the most complex of our sensory organs and a more detailed account of the anatomy of the auditory pathways is presented by Møller (2014).

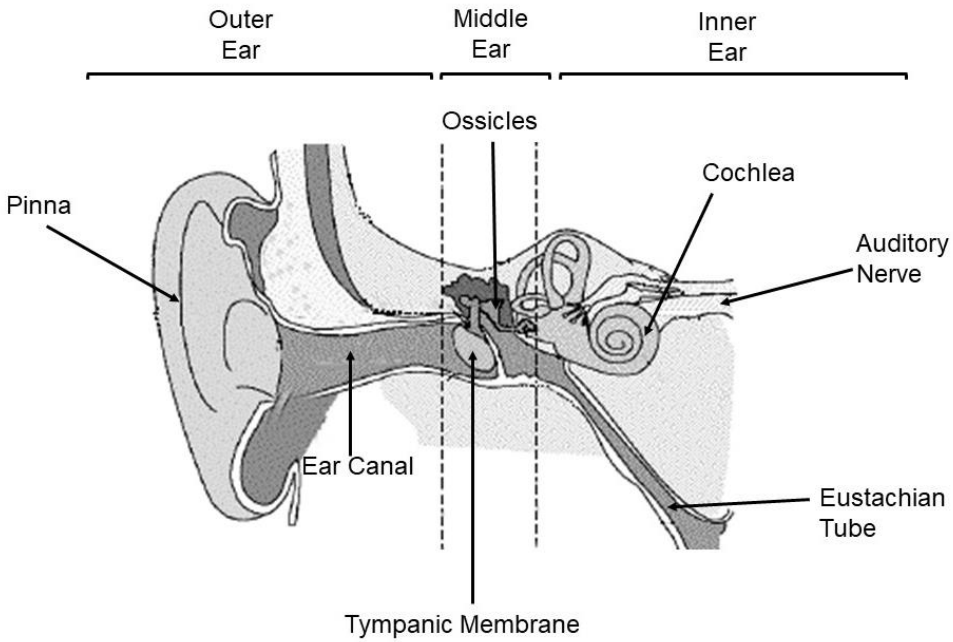
2.1.1 The Peripheral Auditory System

The peripheral auditory system can be subdivided into three anatomically and functionally discrete sections (Fig. 1): the outer ear, the middle ear and the inner ear (Buser and Imbert 1992; Brownstein et al. 2012). The auditory pathway starts at the outer ear, consisting of the pinna/auricle and the external auditory meatus (ear canal). Sound waves arrive at the pinna and the location of origin is determined by interaural differences in the time and intensity for sounds in the horizontal plane. For sounds in the sagittal plane, localisation occurs as a result of monaural changes in the signal spectrum. A role of the pinna is therefore, to receive sounds, localise them in the sagittal plane and allow the listener to determine whether a sound source is in front

of them or behind them (Baiduc et al. 2013). The physical properties of the pinna also result in amplification of the sound by around 20 dB for frequencies from 2,000 to 5,000 Hz (Bess and Humes 2009).

Figure 1. The Outer, Middle and Inner Ear

(Adapted from Hass 2013, Chapter One, Section 13)



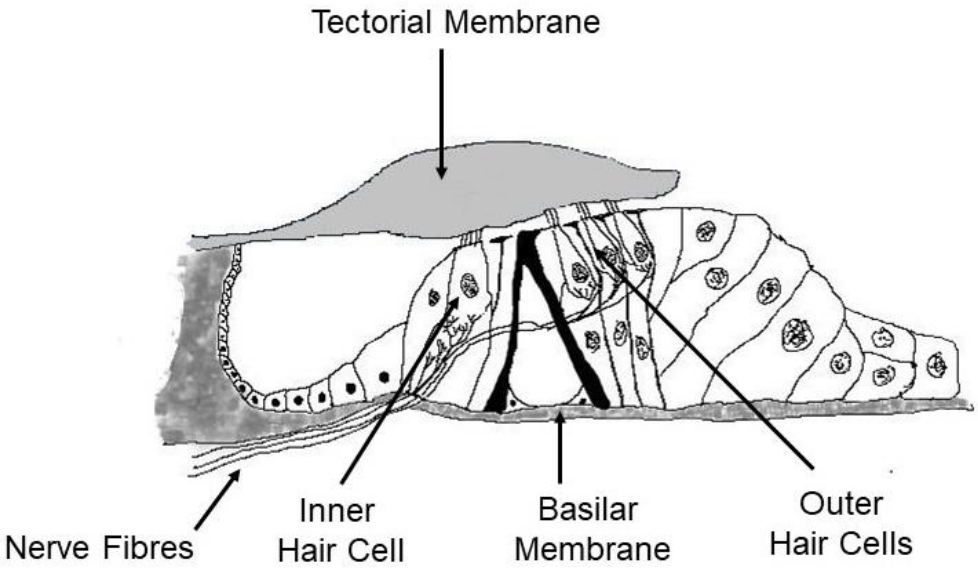
Sound is then directed along the external auditory meatus and arrives at the tympanic membrane (ear drum). The ear canal acts as a resonator, providing a boost of at least 10 dB for incoming sounds in the region of 2500 to 2700 Hz, dependant on the size of the canal (Silva et al. 2014). The tympanic membrane is oval and conical in shape and forms part of a system designed to overcome the impedance mismatch that occurs between sound travelling in air and sounds entering the fluid filled inner ear. Firstly, the tympanic membrane vibrates in response to sound. The vibrations set three tiny bones, the ossicles (malleus, incus, stapes), into motion. This results in a back-and-forth movement, which begins the conversion and transmission of the incoming sound waves to mechanical energy. The final result of this bone movement is pressure of the footplate of the stapes, on the oval window of the cochlea. A lever action is created which has the effect of making a very small contribution to the recovery of sound energy that would otherwise be lost through the impedance mismatch (Bess and Humes 2009). Secondly, the more important contribution to

overcoming the impedance mismatch is related to the relative size of the tympanic membrane and the membrane of the oval window. The tympanic membrane has a surface area of around 55 mm^2, whilst the oval window has a surface area in the region of 3.2 mm^2. This results in a 17:1 difference in surface area and an increase in gain of around 25 dB for sounds between 100 and 2500Hz (Seikel et al. 2013). Together with the gains provided by the pinna, external auditory meatus and middle ear, the loss of 30dB in sound pressure that is caused by sound transferring from air to fluid, is mostly overcome for sounds between 100 and 5000 Hz, which are key for speech perception (Bess and Humes 2009). It is at this point that the sound enters the inner ear as a travelling wave.

The cochlea, containing the sensory organ of hearing, is often described as a coiled, snail-shaped structure (Brownstein et al. 2012). It is divided into three, fluid-filled compartments with the middle compartment, the scala media, lying between the scala tympani and scala vestibuli. The organ of Corti, which sits on the basilar membrane and contains the receptor cells, lies within the scala media (Pickles 1988; Buser and Imbert 1992) (Fig. 2). When the oval window vibrates a travelling wave is established which causes the scala media and the structures within it, to be displaced. The basilar membrane is not uniform along its length, being stiffer and narrower at the base and wider and more elastic at the apex (Kim and Koo 2015). This change in physical property along its length, results in different areas of the basilar membrane responding maximally to different frequencies at different places. The stiffer basal end responds maximally to high frequencies and the converse is true for the more elastic, apical end (Møller 2014). This results in there being a characteristic frequency place, with maximum displacement of the basilar membrane occurring for each frequency at its characteristic frequency place (Appler and Goodrich 2011; Baiduc et al. 2013). This arrangement of a specific place for a specific frequency is referred to as tonotopic organisation and continues throughout the auditory pathway (Bess and Humes 2009; Shera 2015).

Figure 2. The Organ of Corti

(Imaged created by C. Johnson)



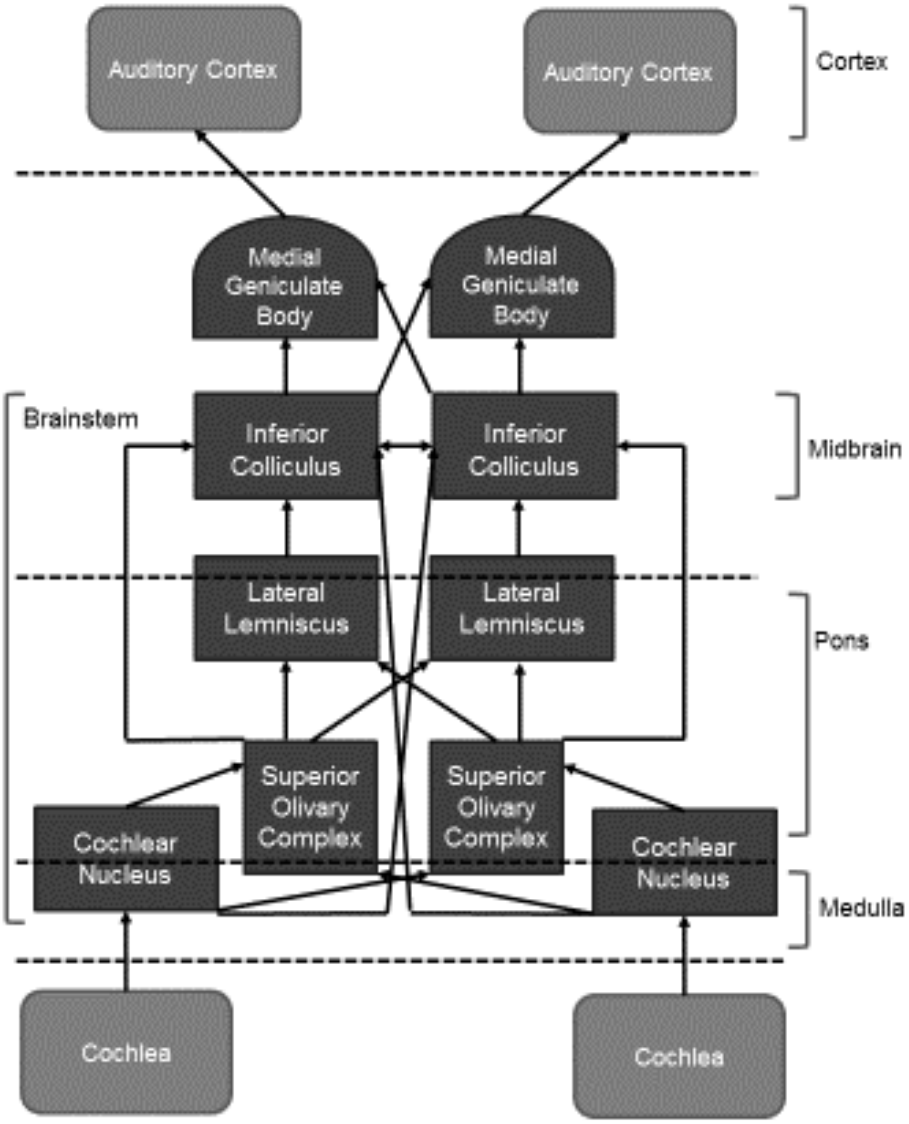
The receptor cells within the organ of Corti are called hair cells, as they have cilia protruding from the tops of the cell. There is a single row of inner hair cells and three to five rows of outer hair cells (Pickles 1988). Afferent nerve fibres primarily innervate the inner hair cells, whilst the outer hair cells mostly connect with efferent nerve fibres. The key role of the hair cells is the amplification of the incoming signal and its conversion from mechanical energy to electrical energy. This is the form of energy that can be deciphered by the brain (Møller 2014).

2.1.2 The Central Auditory Nervous System and the Brain

The primary function of the peripheral auditory system is to transduce acoustic energy, received at the pinnae, into fine-grained electrical impulses (Chisholm et al. 2003). The neural impulses produced are then transmitted by the VIIIth cranial nerve, synapsing in the brainstem and then travelling through a number of nuclei in the auditory brainstem before reaching the auditory cortex (Fig. 3). This happens in an ordered fashion with different nuclei and cell types providing the resolution and organisation needed for sound recognition, localisation and differentiation (Phillips 2007). Perception occurs when the cortical neurons have performed a detailed analysis of the features of the incoming signal (Plack 2005).

Figure 3. The Ascending Auditory Pathways

(Imaged created by C Johnson)



The ascending pathway is sometimes also referred to as the afferent, or corticopetal, pathway (Marsh and Campbell 2016). The organ of Corti is connected to the brainstem by means of the auditory nerve, a branch of the VIIIth cranial nerve (Nayagam et al. 2011). The majority of spiral ganglion neurons make connections with multiple cell types in the first nucleus of the auditory pathway, which is ipsilateral to the ear of presentation, the Cochlear Nucleus (CN) (Appler and Goodrich 2011). The CN can be subdivided into the Ventral Cochlear Nucleus (VCN) and the layered

Dorsal Cochlear Nucleus (DCN). This is the first of the more complex processing stages with the CN thought to be undertaking a number of processing tasks. The large variety of cell types are associated with a large variety of response types. These include tuning properties, preservation or degradation of temporal resolution, intensity function, coding of complex sounds and tonotopic organisation (Rouiller 1997). From here, neural projections of the VCN connect to the Superior Olivary Complex (SOC) and those from the DCN connect to the Inferior Colliculus (IC). It is at the level of the SOC that there is a convergence of information from both ears (Phillips 2007).

The SOC comprises a number of nuclei and those receiving input from the CN are the Medial Nucleus of the Trapezoid Body (MNTB), the Medial Superior Olive (MSO) and the Lateral Superior Olive (LSO). Their primary functions are thought to be tonotopicity and sound localisation, as the SOC receives information about interaural delays (Buser and Imbert 1992). From here and the CN, the axons of the neurons form a bundle, called the Lateral Lemniscus (LL). The LL is the most conspicuous tract in the ascending auditory pathway. There are three nuclei in the LL and they receive input from the CN and the contralateral LL but the majority arise from the SOC. As many of these neurons connect to the contralateral Inferior Colliculus (IC), it is thought that LL has a role in binaural hearing (Møller 2014). All ascending information passes via the central nucleus of the IC, the ICC, and the ICC connect to each other. This connection allows for analysis of timing differences of sounds arriving at each ear and therefore sound localisation. The ICC is also a layered structure, preserving tonotopic organisation (Phillips 2007).

All previously described nuclei in the CANS reside in the brainstem, whereas the neurons leaving the IC synapse at the Medial Geniculate Body (MGB) in the thalamus, or directly in the auditory cortex. The MGB receives information from the ipsilateral and contralateral ICC and the ventral MGB (vMGB) contains neurons which are frequency specific (Buser and Imbert 1992). From here, the axons project to the auditory cortical fields and the primary auditory cortex (AI). When considering hearing and the human brain, it is the auditory cortex that is of particular interest. The auditory cortex is the part of the cortex involved in hearing and is located in the superior part of the temporal lobe. It is not a singular brain area but contains of a network of associated areas that all have a role in decoding sound (Baars and Gage 2013; Hackett 2015). The main auditory area includes the AI and the AI connects with other areas of the cortex involved in information processing. The AI is a layered structure located deep within the temporal lobe (Hackett 2011). The function of the auditory

cortex is to detect sounds, determine the location of sound sources and recognise the identity of sound sources, their meaning and relevance (Møller 2014). Different types of neurons have different functions within the auditory system. Their different response properties enable the coding of frequency, intensity, timing information and spatial information (Phillips 2007). The majority of neurons in the cortex respond to binaural inputs, which are required for decoding of complex hearing processes. The input from both ears is not represented in the same way within each hemisphere. The right ear has a much larger, or stronger representation, in the left hemisphere than the left ear, and vice versa. The auditory cortex should not be considered the termination of the auditory pathway. Instead, it can be conceived to be a hub for sound processing, which interacts with other brain areas, across the hemispheres, as well as the descending auditory pathways (Baars and Gage 2013). Sound information is distributed across the network of cortex areas and the decoding is mediated, resulting in the awareness and perception of sound (Hackett 2015).

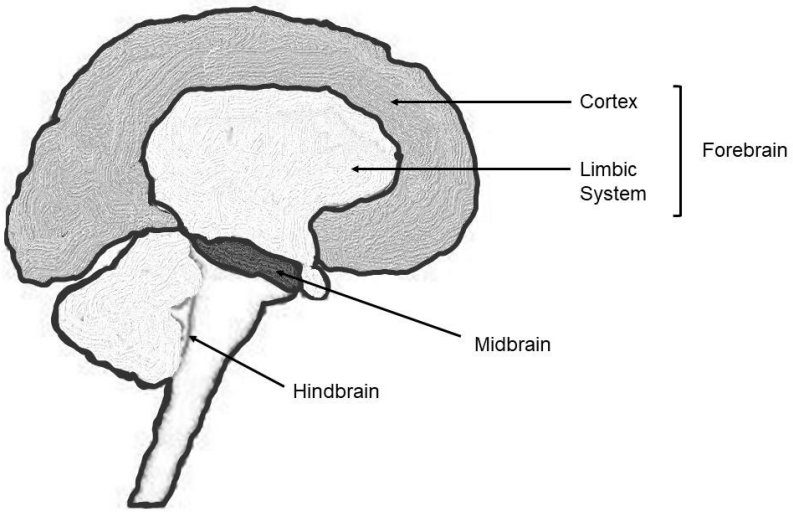
Most people have a dominant hemisphere for many aspects of speech processing (Slevc et al. 2011). For around 95% of right-handed people and almost 80% of left handed people, it is the left hemisphere (Oliveira et al. 2017). This results in a reported right ear listening advantage, as the auditory pathway from the right ear to the left hemisphere is more direct. The majority of the route from the left ear travels in the contralateral pathway through the brainstem, arriving in the right hemisphere. Interhemispheric transfer occurs mainly via the corpus callosum (Hinkley et al. 2016). However routes are not fixed, it is vital to understand that plasticity is a feature of brain function. Neural plasticity refers to “the ability of neurons to change in form and function in response to alterations in their environment” (Kaas 2001, p.10542). This means that the neural map alters over the adult lifespan, this can be as a result of injury, experience and the aging process (Sharma et al. 2013).

There is also an equally complex network of neurons carrying information from the auditory cortex to the periphery, referred to as the descending auditory pathway, the efferent pathway or the corticofugal pathway (Terreros and Delano 2015). These ascending and descending networks are not independent. It is thought that there is a series of dynamic loops in which changes in activity at higher levels in the brain affect neural coding at lower levels. Therefore, signal processing is fine-tuned by these loop systems (Bajo and King 2013). The afferent auditory pathways to the brain are presented in simplified format in figure three.

Like any other anatomical structure, the brain can be divided into different parts or regions and this can be done in different ways. A basic categorisation is that the brain consists of the hindbrain, midbrain, and forebrain (Fig. 4). The cerebrum is the largest structure, accounting for more than three quarters of brain volume and is divided into two hemispheres (Carter 2014). The cerebrum, hippocampus, amygdala, thalamus and hypothalamus constitute the forebrain. The neocortex comprises the folded outer layers of the cerebral hemispheres and consists of grey matter surrounding the deeper white matter of the cerebrum (Eggermont 2007; Nieuwenhuys et al. 2007). There are grooves (sulci) and wrinkles (gyri) on the surface of the cerebral hemispheres which greatly increases its area. The midbrain contains nuclei called the basal ganglia and along with the pons and medulla forms the brainstem. The hindbrain consists of the pons, the cerebellum and the medulla (Nieuwenhuys et al. 2007; Carter 2014).

Figure 4. The Brain

(Imaged created by C. Johnson)



The human brain is estimated to contain around 86 billion nerve cells (neurons) (Azevedo et al. 2009). The majority of neurons in the human brain are interconnected and work together to control the behaviour of the human body, with respect to internal/external and motor/sensory stimuli (ibid; Kumar and Bhuvaneswari 2012). This behaviour control also relies on the presence of as many supporting cells (glial cells) (Azevedo et al. 2009; von Bartheld et al. 2016). The neurons connect to each other via synapses, with neural activity resulting in synaptic transmissions

(Jernigan and Stiles 2017). It has been estimated that the number of connections, known as synapses, is more than a hundred trillion and these connections are not random (Eroglu and Barres 2010). The primary function of neurons is communication and messages are passed through the neural network via chemical or, less commonly, electrical synapses. The synapses mediate the flow of information between neurons (Hormuzdi et al. 2004). Neurons communicate by generating electrophysiological signals known as action potentials, which are translated into neurochemical signals at synapses and transmitted to other neurons (Baslow 2009). There is a resultant postsynaptic potential, which may be inhibitory or excitatory, generated in the form of a change in the membrane potential (an electrical potential) and induced by the opening of ion channels. Communication within the nervous system generally takes place by transmission of these action potentials (Watson et al. 2010). Although there is some individual variation, the neurons are arranged precisely in a complex structural network, which in turn results in a complex, interacting, functional network (Cao et al. 2014; Glasser et al. 2016).

When a brief sound stimulus, like a click, is presented to the ear, the hair cells along the basilar membrane of the cochlea (see Fig. 2) depolarise. This results in the membrane potentials of neurons of the eighth nerve changing and this is called the excitatory postsynaptic potential (EPSP). In addition, the action potential firing rate alters and this is determined by the amplitude of the EPSP. Differences between the potentials on the inside and outside of a cell result in a small current passing through the cell membrane (Davis-Gunter et al. 2001). Knowledge of these processes led to the development of a tool that assesses conduction time of an auditory stimulus through the auditory brainstem pathways, the ABR. The ABR will be explored in section 2.2.

2.1.3 Development of an Auditory-Cognitive Model

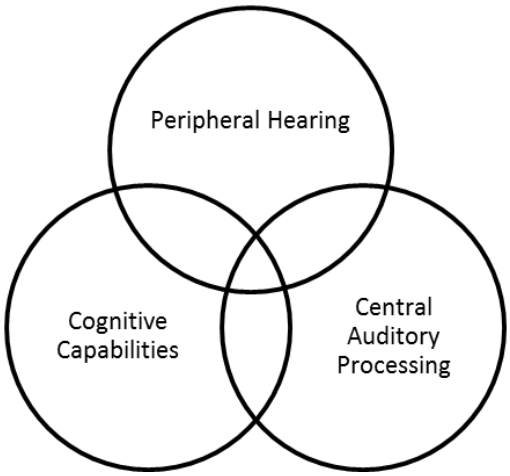
Researchers exploring auditory perception often choose to study speech perception in children or in older adults, to see how it differs from that of typical adult listeners. As the participants within this study are adults, it is pertinent to explore the current ideas about speech perception in the adult population. It may also be useful because people with alcohol dependency are considered to be at risk from premature aging (Spencer and Hutchison 1999). The Working Group on Speech Understanding and Aging (CHABA 1988) proposed three models which might be used to explain age

related hearing loss. These three models were: changes to peripheral hearing, changes in the structure of the brain stem and forebrain, and changes in cognition (Golding et al. 2006). Alternative terminology is peripheral hearing loss, central auditory processing decline and cognitive decline (Stach et al. 2009). The historical dissociation into three areas has resulted in researchers taking a 'site-of-lesion' approach, in an attempt to identify changes in these different areas and how they affect speech perception. While three individual models have been identified, it is recognised that they are usefully conceived as comprising an inter-related triad.

A hybridisation of these models may be conceptualised as an auditory-cognitive model (Pichora-Fuller 2003; Pichora-Fuller and Singh 2006; Pichora-Fuller et al. 2016) (Fig. 5). This is an alternative conceptual 'processing' approach, which aims to understand how lower-level sensory processes interact with higher-level cognitive processes (Pichora-Fuller and Singh 2006). Research has found that restoring the audibility of sounds using hearing aids is not sufficient to overcome listening difficulties and that there is therefore, a requirement to investigate these auditory-cognitive interactions (Pichora-Fuller et al. 2016). It has only been relatively recently that audiologists have begun to consider the interaction between auditory processes and cognition. The term cognitive hearing science has been used to describe this area of interdisciplinary research (Arlinger et al. 2009). In the following section (2.1.4), the development of a test battery which aims to explore these inter-related areas of the auditory-cognitive profile is presented.

Figure 5. The Auditory-Cognitive Model

(Imaged created by C. Johnson)



2.1.4 Development of the Assessment Battery

An audiologist has a wide range of tests available for assessing the auditory pathways and hearing status of an individual, or their 'auditory ability' (Kidd et al. 2007). An individual auditory-cognitive profile can be compiled from the results of a range of tests, with the aim being to create an understanding of a person's functional hearing and identify any pathologies present. The profile can then guide both parties in the selection of an appropriate remediation strategy, if required (Lecluyse et al. 2013). Some tests, such as pure tone audiometry, assess the entire auditory pathways whilst others are focussed on more localised areas. The tests used as part of an auditory assessment may be behavioural, relying on the individual responding to the stimulus in some way, or physiological (Katz 2015). It is standard practice within audiology to use behavioural and physiological tests to provide a method of cross checking results (Jerger and Hayes 1976). Each test is selected and performed for a specific purpose and there must be sound justification for their inclusion in a test battery (Dillon et al. 2012). In Experiment One, aspects of recording the speech ABR will be explored for people with no known deficits in hearing, including auditory processing capabilities and aspects of cognition that are important for understanding speech. This requires consideration of the appropriate testing for establishing an auditory-cognitive profile for participants.

Whilst there are many tests available for assessing various aspects of audition, some are more applicable for clinical use than others. The more tests that are performed, the higher the likelihood of false positives occurring, or chance abnormal findings. There is also a higher fatigue burden on both the individual being tested and the tester (Dillon et al. 2012). The development of a test battery suitable for constructing an auditory-cognitive profile therefore requires careful consideration. The guiding principles of the development of this test battery were that the assessments must be suitable for clinical use and must be able to provide an overview of elements known to contribute to difficulties processing speech sounds. Individual tests needed to be simple for participants to perform, be well validated with normative data available and not take an excessive amount of time to administer. The test battery used in this research has been devised to provide a measure of the integrity of the auditory pathways, hearing status in quiet and noisy conditions and the auditory processing capabilities of each individual. As per the auditory-cognitive model

discussed in section 2.1.3 and as the speech ABR is thought to reflect aspects of higher level processing, cognitive tests have been included in this assessment.

2.1.4.1 Clinical Interview

The clinical interview or case history has often been described as the 'first test' in the audiologist's assessment battery (Rosenberg 1978). As hearing can be affected by a number of external and internal factors, a case history provides information on an individual's life experiences that may have influenced their hearing and listening abilities. This initial assessment is primarily used to gather information about a participant's hearing history and general health. A secondary aim is to aid in determination of whether any participants do not meet the inclusion criteria for the study.

2.1.4.2 Otoscopy

Otoscopy is the visual inspection of the pinna and surrounding skin, external auditory meatus and tympanic membrane using an otoscope. This procedure aids in the identification of any pathology or anomalies of the outer ear, tympanic membrane and to a lesser extent the middle ear. Visual inspection of the ear is essential to identify any contraindications for further audiometric assessment (British Society of Audiology 2010).

2.1.4.3 Hearing Threshold Assessment

Pure tone audiometry (PTA) is the gold standard clinical tool used for assessment of hearing thresholds (MacLennan-Smith 2013; Beck et al. 2014). PTA is used to measure the absolute threshold, or the level of a pure tone that can just be heard by the subject. It is based on a psychophysical method of limits and used to identify the lowest sound intensity that can be detected by the subject, at least fifty per cent of the time (Harell 2002; Gelfand 2009). A 'modified Hughson-Westlake procedure' as proposed by Carhart and Jerger (1959) is generally used in the clinical environment. In the UK, clinicians follow the recommended procedure for pure tone air and bone conduction threshold audiometry with and without masking (British Society of Audiology 2011).

2.1.4.4 Tympanometry

Tympanometry is an objective means of analysing middle ear function. It is defined as 'the dynamic measure of acoustic immittance in the external ear canal as a function of changes in air pressure in the ear canal' (ANSI, S3.39 1987). Liden (1969) advocated the use of tympanometry for the diagnosis of middle ear lesions and Jerger (1970) published the first clinical findings. Pathology of components of the middle ear system can alter the characteristics of the system, resulting in changes in acoustic admittance, which can be measured using tympanometry. Results are often plotted in the form of a tympanogram, with compliance (ml or mmho) on the y-axis and ear canal pressure on the x-axis. The classification system for tympanograms commonly used today was developed by Liden (1969) and Jerger (1970). Tympanogram 'types' are often used to identify middle ear problems such as tympanic membrane perforation, fluid in the middle ear cavity, reduced mobility of the tympanic membrane (due to the presence of scar-tissue) or the ear bones (due to otosclerosis), or hypermobility as a result of ossicular discontinuity (Hunter and Sanford 2015).

2.1.4.5 Otoacoustic Emission Testing

'Otoacoustic emissions' is the name given to the sounds made by outer hair cells as they actively respond to auditory stimulation. Otoacoustic emission testing (OAEs) was developed by Kemp in the late 1970s (Kemp 2002) when he found that sounds of cochlear origin could be recorded from the outer ear canal. These low-level sounds are thought to reflect the non-linear, active processes of the cochlea. These processes are considered to be responsible for the "high sensitivity, sharp frequency selectivity and wide dynamic range of the human auditory system (Norton 1992)" (Keppler et al. 2010, p. 99). This is achieved as a result of outer hair cell motility, which works to enhance the movements of the basilar membrane and is especially important at low-input levels (Brownell 1990). OAEs are generated by outer hair cells, which do not themselves activate primary auditory nerve fibres, however there is a strong relationship between the absence of OAEs and hearing loss (Kemp 2002). These sounds can be recorded using commercially available equipment, utilising a miniature probe and microphone held in place at the entrance to the external auditory meatus via an eartip. OAE testing provides a straightforward, efficient non-invasive

and objective indication of cochlear function, as OAEs are known to disappear with inner ear damage (ibid.).

OAEs can be classified in accordance with their eliciting stimulus. Spontaneous OAEs (SOAEs) are recordable without external stimulation, whilst the most commonly used clinical methods of eliciting OAEs are Transient-Evoked OAEs (TEOAEs) and Distortion Product OAE's (DPOAEs). TEOAEs are elicited by brief, transient stimuli, usually in the form of clicks and responses are strongest and easiest to detect in the speech frequency band, 1–4 kHz for ears with hearing better than 30 dBHL (Bonfils et al. 1990; Probst et al. 1991; Lonsbury-Martin et al. 1991; Kemp 2002). DPOAEs are elicited by simultaneous presentation of two pure tones that are close in frequency, with primaries classified as f1 and f2 and with levels L1 and L2, respectively. They are generated as a result of the nonlinear response properties of the basilar membrane and are considered to indicate the presence of compression (Prieve and Fitzgerald 2015). The frequency range of the DPOAEs extends mostly from 1 to 8 kHz and DPOAEs are absent in ears with hearing loss greater than 55 dB HL (Lonsbury-Martin et al. 1991; Gorga et al. 1997; Lonsbury-Martin and Martin 2003).

The TEOAE and DPOAE techniques complement each other. They can be used for the objective assessment of hearing status in difficult-to-test subjects, objective estimation of the degree of hearing loss, assessing damage that has not yet resulted in hearing loss (Marshall et al. 2001) and as a valuable tool in the audiological diagnostic test battery, to determine the site of lesion (Lonsbury-Martin and Martin 2003). If TEOAEs are present and there are no other concerns regarding hearing status, then it may not be valuable to proceed with DPOAE testing.

2.1.4.6 Speech Testing

Speech, as opposed to pure tones, is the auditory stimulus through which we communicate. The ability to classify a person's auditory function based solely on the audiogram has been questioned (van Esch et al. 2013; McCaslin 2017). Speech audiometry has historically been used to cross-check the results of pure tone audiometry. It has been found that there is usually high correlation between thresholds for speech and pure tones, with only minimal differences between the thresholds. However, it is often not possible to predict the difficulty that a hearing impaired listener will have with speech discrimination in noisy conditions, from the results of pure tone

or speech audiometry alone (Killion and Niquette 2000). Indeed, Carhart and Tillman (1970) emphasised the value of measuring speech recognition performance in background noise as an 'ecological measure' of communication disability (Wilson et al. 2004). Speech perception in noise becomes more difficult still if the noise fluctuates (De Laat and Plomp 1983; Festen and Plomp 1990; Versfeld and Dreschler 2002; Darwin 2008; Kilman et al. 2015).

Speech testing can be performed using single words or sentences. Using sentences provides additional context which may aid in speech perception, however it also adds cognitive load which may negate the benefit of context (Wilson et al. 2007). As it is known that people who score similarly in word recognition tasks in quiet can perform very differently in a background noise situation (Beattie et al. 1997), it is proposed that all participants undertake speech perception testing in fluctuating noise. The fluctuating noise will be multi-talker babble, as this is known to be an effective masker for speech perception (Silbert 2014). The purpose of performing speech-in-noise testing is to establish whether they have a signal to noise ratio (SNR) loss (Killion et al. 2004), which may affect speech perception in everyday situations (van Esch et al. 2013). SNR loss can be defined as "the dB difference in SNR between an individual hearing impaired listener and a control group of normal hearing listeners, for a specified level of performance" (Grant and Walden 2013 p. 260).

For Experiments One and Two, the sentence tests offer an appropriate method of assessing 'real world' ability. There are a number of commercially available speech tests, offering the facility to test speech recognition in quiet and noisy conditions. Differing amounts of normative data exist for each and some have versions recorded in different languages or accents. Most commercially available tests presented in English have been recorded using American English. A potential source of enhanced difficulty may stem from listeners being presented with speech material in an unfamiliar accent (Adank et al. 2009; Dawes 2011). For the purpose of assessing how people perform in their daily lives, a commercial test recorded in a British accent will be used. This test has been developed as a software package by Faulkner (1998) for the Institute of Hearing Research (IHR). The tests use Bamford Kowal Bench open-set sentences presented in a mainstream 'Received Pronunciation' English male or female accent (Bench et al. 1979; Bench et al. 1987).

Speech audiometry, as a less sensitive measure of everyday difficulty will only be performed for people exhibiting a SNR loss, to determine the threshold for speech recognition (Rosenhall et al. 2011). If it is found that these individuals show a

discrepancy in results between pure tone and speech audiometry, then this may be as a result of a cognitive, language or central auditory disorder (ASHA 1996). For speech audiometry the AB monosyllabic word test will be used. This is an open set speech perception test consisting of lists of ten words, recorded in 'standard British southern' pronunciation by a male speaker. Each word is constructed as a consonant vowel consonant (CVC) word and all words are developed from the 10 vowels and 20 consonants that most frequently occur in Boothroyd's own vocabulary of CVC words (Boothroyd 1968).

2.1.4.7 Auditory Processing Disorder Screening Battery

The speech ABR is reported to be sensitive to deficits in auditory processing capabilities (Billet and Bellis 2011). The British Society of Audiology's (2011) position statement on APD does not provide a concise definition or explicit recommendations about testing. In their 2007 position statement, the British Society of Audiology recommended that an APD test battery should include assessments that evaluate non-speech auditory processing along two or more dimensions. These tests may take the form of discrimination, temporal resolution, and binaural interaction assessments. They also advocated the use of speech perception tests, measures of cognition and an audiological assessment to complement this battery.

Results from studies looking at auditory processing in animals with known lesions, contributed to the development of various psychophysical tests designed to assess auditory processing (Musiek 1994). One difficulty with using test batteries has been that the definition of auditory processing disorder has been revised over the years and may continue to be revised. It is known that deficits in memory or attention, can have a negative impact on APD test performance (Hällgren et al. 2001). It is also known that peripheral hearing loss has a potential negative impact on APD tests (Divenyi and Haupt, 1997; Humes et al. 1996; Musiek et al. 1990; Musiek et al. 1991; Neijenhuis et al. 2004). Tests that have been demonstrated to be less affected by peripheral hearing loss include dichotic digit tasks and frequency patterning tasks (AAA 2010). As previously mentioned, performance on speech based assessments may be influenced by using recordings in non-native accents (Dawes 2011). A test with a low linguistic load, such as the dichotic digits test may offer an acceptable option. The inclusion of this test would also offer a way of assessing hemisphere dominance for speech processing.

In 2000, a consensus was reached at a conference in America, regarding the minimum test battery required for diagnosing auditory processing disorders. The battery should contain a dichotic task, a duration pattern sequence test, and a temporal gap detection test (Jerger and Musiek 2000). Earlier work performed in elderly patients with and without Alzheimer's disease, with similar hearing thresholds, found that although sentence identification was similar, there were significant differences in performance on tests of auditory processing, including dichotic digits, pitch patterns and duration patterns (Strouse et al. 1995).Therefore it is necessary to adequately explore these elements of hearing. A compact disc of commercially available tests, with normative data available from Auditec Inc., including dichotic digits, pitch pattern sequence, duration pattern sequence and random gap detection, will be used In Experiments One and Two, to assess auditory processing capabilities. These tests of auditory processing are discussed individually, in the following sections.

2.1.4.7.1 Pattern Tests

Spoken language contains linguistic content comprising the lexicon, semantic relations and syntax as well as supra-segmental information, provided by stress, intonation and duration patterns (Medwetsky 2002). It has been found that these two types of information are processed somewhat differently during speech perception, with linguistic content being mostly processed within the left hemisphere and supra-segmental information being mostly processed within the right hemisphere (Musiek and Lamb 1994). Successful perception of spoken language therefore requires integration of these types of information, across processing areas of the brain. The ability to discriminate supra-segmental auditory information such as frequency, intensity or duration has been used to assess how well this process of integration is occurring.

The three tone duration pattern sequence test (DPST) was developed by Musiek et al. (1990) and measures auditory pattern identification. The pitch pattern sequence test (PPST) was developed by Pinheiro (1977) and assesses temporal sequencing, which is the ability of a person to process two or more auditory stimuli in their order of presentation (Pinheiro and Musiek 1985). Essentially these tests require the functioning of both cerebral hemispheres and the corpus callosum (Musiek et al. 1980). As previously mentioned, this is related to the understanding that the right

hemisphere recognises the acoustic pattern and the left hemisphere has a greater role in speech and language processing (Bhatnagar and Andy 1995), as well as temporal sequencing (Swisher and Hirsh 1972; Pinheiro and Musiek 1985). For both of these tests, both hemispheres are required to decode a pattern in order to make an appropriate verbal response. The majority of acoustic information is carried in auditory pathways that are received in the contralateral hemisphere to the ear that received the information. Therefore, in order for acoustic stimuli presented to the left ear to be processed in the left hemisphere, the information must cross the corpus callosum. Patients with known lesions affecting auditory areas of either hemisphere or the corpus callosum perform poorly on this test (Musiek 1994). For some patients, the test results improve if they are asked to 'hum' the response as opposed to responding in words. In this case, the lesion location is likely to be the corpus callosum. It is thought that the processes underlying pitch pattern sequence recognition differ from those underlying duration pattern sequence recognition, as they appear better suited to identifying different cerebral lesions, with the DPST being shown to be sensitive in detecting cerebral and brainstem lesions in addition to impaired auditory cortex function (ibid.).

The accompanying Auditec Inc. manual for the DPST states that ''from work carried out by Musiek et al. (Musiek et al. 1990) it appears that the range of scores considered to demonstrate normal performance is 67-100% correct'' (Auditec Inc. n.d. p1). The accompanying Auditec Inc manual for the PPST suggests a range of 88-100% for adults indicates normal performance.

2.1.4.7.2 Dichotic Digits

Dichotic listening tests have been developed to assess auditory integration ability, specifically the efficiency of transfer of auditory-linguistic information between the two hemispheres of the brain. These tests involve the presentation of different stimuli (e.g. digits, nonsense syllables, spondees, monosyllabic words, and sentences) to both ears at the same time and were first introduced by Broadbent (1954) and later refined by Kimura (1961a, 1961b). Kimura proposed a model to illustrate how the central auditory nervous system processes dichotic information. With the contralateral pathways being more extensive, these pathways would be dominant, with acoustic stimuli being more effectively transmitted to the hemisphere contralateral to the ear of presentation (Medwetsky 2002). Dichotic listening tests are

purported to be sensitive to cerebral and interhemispheric lesions (Musiek and Weihing 2011), as well as brainstem lesions (Katz 1962; Jerger and Jerger 1974; Keith 1977; Musiek 1983).

One of the more commonly used dichotic speech tests in an APD screening or diagnostic assessment battery, is the dichotic digits test. Presenting digits to two ears simultaneously to examine auditory processing, was first carried out over fifty years ago. Results from early studies found that this method appeared to demonstrate a right ear listening advantage and that people with known lesions in the central auditory pathway could be identified (Musiek 1983). Patients with right temporal lobe lesions are found to have contralateral deficits and patients with left hemisphere lesions have bilateral or contralateral deficits. Left ear deficits are more commonly reported and have been found in patients with compromised interhemispheric transfer.

The dichotic digits test has a good level of test-retest reliability, is sensitive to memory impairment and results do not seem to be affected by hearing loss up to a moderate level (Gates et al. 2008). For this version of the test, a normal value for adults is given by Auditec Inc. as scores between 82-100% correct.

2.1.4.7.3 Random Gap Detection Test

Temporal resolution is the term used to describe the ability of the auditory system to respond to dynamic fluctuations in the envelope of a sound stimulus over time (Musiek et al. 2005). It has been suggested that it is disruptions in this process that may give rise to the difficulties experienced by older adults, when listening in background noise (Pichora-Fuller et al. 1995; Snell 1997; Pichora-Fuller 2003). As such, it has been proposed that diagnostic test batteries should include assessments of temporal resolution (ASHA 1996; Jerger and Musiek 2000). The use of gap detection paradigms to meet this need have been explored (Strouse et al. 1998; Bertoli et al. 2002; Musiek et al. 2005). Psychophysical gap detection paradigms require the listener to respond when they detect a silent interval (gap) between two carrier stimuli, with the shortest detectable interval being the gap detection threshold (GDT) (Schneider and Hamstra 1999; Musiek et al. 2005). The commercially available random gap detection test (RGDT) was developed by Keith (2000a) to provide clinicians with a standardised, quick way of assessing temporal processing disorders. Gap detection thresholds can be calculated for individual tones of 500Hz, 1000Hz,

2000Hz and 4000Hz, or a composite score can be calculated as an average of these. The inclusion of the RGDT for clicks, enables the clinician to calculate a gap detection threshold for gaps in noise. For this particular test “a normal gap detection threshold for both tones and clicks is considered to be between 2 and 20 milliseconds (msec)” (Keith 2000b, p.8).

2.1.4.8 Cognitive Tests

Cognitive performance assessment for older adults with hearing loss, or who have difficulty understanding speech, especially in background noise, has only recently come to prominence in the field of audiology. Some of the first work looking at incorporating cognitive assessment and developing a suitable test battery was published in the late 1980s (van Rooij et al. 1989). Traditionally, audiologists in the United Kingdom do not perform any cognitive testing when they construct a hearing profile. However, identifying cognitive deficits in audiology patients could explain some of the speech understanding difficulties experienced by adults that cannot be explained by their level of hearing loss (Vaughan et al. 2008). Recent work carried out by the HearCom project (Houtgast and Kramer 2007) has looked at developing a test battery suitable for building an auditory profile. They have acknowledged that at best only 60% of the variance seen in speech recognition scores in noise can be attributed to peripheral pathology. Therefore, they are advocating the inclusion of cognitive assessment when creating an auditory profile. Of the work completed evaluating speech understanding difficulties in older adults and the cognitive domains, it appears that working memory and processing speed declines are hallmarks of this particular problem (Vaughan et al. 2008).

In order to determine the relative contributions of hearing loss, auditory processing deficit or cognitive processing deficit to a problem hearing speech, each area should be investigated. The purpose of this research is not to identify participants with cognitive decline or to quantify intelligence, but to give a broad overview of cognitive processing capabilities, which may affect speech understanding. The Wechsler Adult Intelligence Scale-III (WAIS-III^{UK}) provides a way for qualified practitioners to assess cognitive function in a standardised way over a variety of cognitive domains. It has been described as being one of the best known and most widely used individually administered test of general intellectual ability (Johnson and Rust 2003). The WAIS-III^{UK} can be used to assess general thinking and reasoning

skills. Normative data has been collected for adults up to and including 89 years of age and this data allows comparison with how an individual's performance compares with others considered typical of their age.

Practitioners have recognised that administering the full WAIS test battery may not always be necessary or feasible and much research has been published looking at the use of particular subtests. The full WAIS-III^{UK} is comprised of 14 subtests designed to give measures of verbal comprehension, perceptual organisation, working memory and processing speed (Wechsler 1997). Scores are provided for interpreting intellectual functioning, determined by the number of subtests administered. If all subtests are carried out, then both IQ and Index scores can be calculated. If a selection of subtests is administered, then only one or the other of these scores can be calculated. Researchers have looked at using short forms of the WAIS-III^{UK}, and using between two and seven of the subtests, depending on desired outcome, is possible as a screen (Schrimsher et al. 2008). This particular battery was developed to gain an overview of the participants' cognitive capabilities. A selection of verbal and performance subtests were chosen to provide information on verbal comprehension, memory and processing speed as these are areas identified as being key for speech comprehension (Vaughan et al. 2008).

All cognitive tests in both Experiment One and Two were administered by an audiologist, under the supervision of a registered clinical psychologist, in accordance with the instructions given in the administration and scoring manual (Wechsler 1997). Raw scores on each test are converted to scaled scores with a mean of 10 and a standard deviation of 3. These scaled scores can then be used to look at specific domains of cognitive functioning (Table 1).

Table 1. WAIS-III^{UK} Subtests Grouped According to Indexes

Verbal Comprehension	Working Memory	Processing Speed
Vocabulary	Digit Span	Digit Symbol Coding
	Letter-Number Sequencing	Symbol Search

2.1.4.8.1 The Vocabulary Test

The ability to define words, relying on the extent to which a person has learned, understood and is able to express their understanding, is considered to be one of the best single measures of intelligence. Throughout the lifespan, it remains one of the most stable abilities (Ardila 2007). Verbal comprehension is a requirement for successful spoken communication and a deficit in this area, could negatively affect communication abilities (Arlinger et al. 2009).

2.1.4.8.2 Digit Symbol Coding

The digit symbol-coding subtest is multifaceted in nature, requiring a number of abilities, such as visual-motor coordination, motor and mental speed and visual working memory, for acceptable performance. The two functions researched most thoroughly include processing speed and memory. There is a known age-related decline in digit symbol-coding scores (Ardila 2007) and this is mostly explained by a decline in processing speed with a smaller contribution from a decline in memory (Joy et al. 2004).

2.1.4.8.3 Digit Span Forwards and Backwards

The digit span test from the WAIS-III^{UK} has been described as assessing aspects of attention, concentration, mental control and memory (Wechsler 1997). Measures of forward and backward digit span are among the oldest and most widely used tests of short-term verbal memory (Richardson 2007). It is thought that the ability to perform the test forwards and backwards is underpinned by different processes with the forward digit recall being a short-term memory task and the backward recall task measuring working memory (St. Clair-Thompson 2010).

2.1.4.8.4 Symbol Search

The symbol search subtest is designed to assess information processing speed and visual perception. Acceptable scores require both rapid and accurate processing of non-verbal, visual information in the form of symbols that have no language related meaning. As previously discussed, the subtests that assess speed

of information processing, or how fast the brain can think, show the greatest decline with aging (Ryan et al. 2000; Ardila 2007) and appear to be related to the difficulties that some older adults may experience with understanding speech (Vaughan et al. 2008).

2.1.4.8.5 Letter-Number Sequencing

As per the digit span subtests, letter number sequencing is thought to assess aspects of cognition such as auditory working memory, attention, concentration and mental control (Vaughan et al. 2008). It is believed to be supplemental to the digit span assessment with additional unique contributions relating to processing speed and visual spatial working memory (Crowe 2000). The letter-number sequence test has been investigated in relation to hearing loss and was found to be the neurocognitive variable most strongly associated with performance on a sentence test. The authors concluded that this subtest had clinical utility as it may address questions relating to attention (Vaughan et al. 2008).

2.1.4.9 The Auditory Brainstem Response

Using a combination of click ABR and speech ABR provides a possible method for differentiating between suspected disorders (Skoe and Kraus 2010a). It is not possible to fully interpret the results of the speech ABR without knowing whether the click ABR falls within ‘normal’ limits. The ABR is used to assess neural integrity within the brainstem (Hood 1998), whereas the speech ABR is thought to be useful in assessing disorders that feature higher level language processes (Song et al. 2006; Skoe and Kraus 2010a). The onset responses of the speech ABR should be highly correlated with that of wave V-Vn of the click ABR. Performing a click ABR prior to performing a speech ABR is therefore essential.

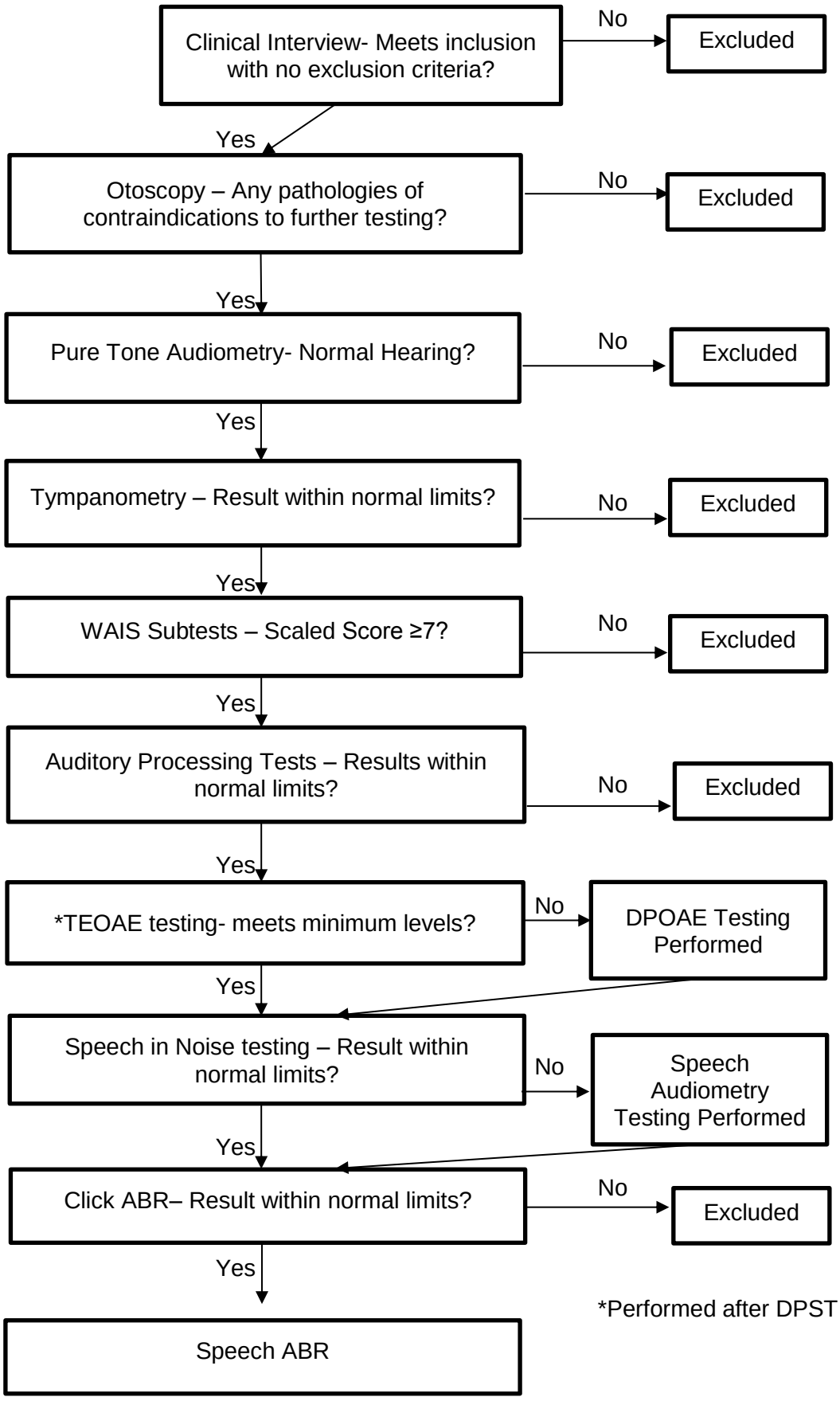
2.1.5 Finalisation of the Assessment Battery

It is usual to control for unwanted order effects that may affect test results, by randomising test order for all participants. This minimises the risk that performing one test may affect performance in the others (Katz and Tillery 2005). However, with audiological testing this is not always possible as some tests are a pre-requisite for

others. For example, otoscopy should always precede audiological assessment, to establish whether there are any contra-indications for performing certain tests (BSA 2011; Rappaport and Provençal 2002). It is a requirement of APD tests to know something about hearing thresholds in order to establish an appropriate presentation level (Musiek et al. 1991). The decision was taken to perform the assessments in a predetermined order for all participants and a flowchart of assessment strategy is provided (Fig. 6). The methods used for performing each of the tests that comprise the auditory-cognitive profile are detailed in Experiment One, section 3.1.2.

There now follows, in section 2.2, a descriptive overview of the click ABR, its history, the underlying neural generators and factors that affect results.

Figure 6. Flowchart of Assessment Process



2.2 The Click Auditory Brainstem Response

This section of the literature review is dedicated to the click Auditory Brainstem Response (click ABR). The click ABR can conceivably be thought of as contributing to the overall auditory-cognitive profile, however for the purposes of Experiments One and Two it will be treated separately.

2.2.1 The Electroencephalogram and the History of the ABR

Neurons are constantly active, undergoing internal voltage changes. It is the balance of excitation and inhibition that each cell receives which determines whether brain behaviour can be classed as 'sleeping' or 'awake.' Excitation in a sleeping brain is the result of internal processing whereas, excitation in an awake brain is the result of sensory stimulation (Steriade 2001). The electroencephalogram (EEG) is the recording of electrical activity within the brain (Remijn et al. 2014). In other words, it is the recording of the electrical activity generated by neurons, as a result of processing activities. Individual electric changes are too small to be detected at the scalp, unless many cells are undergoing these changes synchronously (Eggermont 2007). If enough fluctuating potentials summate and are conducted to the scalp, they can be recorded (Fisch 2005). Changes in brain behavioural state lead to changes in the EEG and the resultant recording is also dependent on the location of the electrodes (Eggermont 2007). The 10-20 system is an internationally recognised system of electrode placement to standardise EEG recording. This specification of placement provides for total coverage of the scalp, allows for variation in head size across the lifespan and for those with micro or macrocephaly (Chong et al. 2007). The distance between electrodes is based on the measurement of the skull from front to back and left to right. The numbers 10 and 20 refer to the fact that the distances between the electrodes are within 10 or 20% of these overall measurements. Although the standard is to use 21 recording electrodes and one ground electrode, it is a flexible system. Each electrode is given a letter as follows: frontopolar (Fp), frontal (F), central (C), parietal (P), occipital (O) and auricular (A). They are also given a subscript, which denotes whether placement is midline or a lateral placement (Fisch 2005).

The first EEG recordings took place in the 1920s and in the 1930s it was found that responses to auditory stimuli could be detected within the electroencephalogram

(Davis 1939). Auditory evoked potentials (AEPs) measure discrete changes in electrical voltage that occur throughout the central auditory nervous system in response to an auditory stimulus. AEPs can be subdivided into near-field and far-field potentials. Near-field potentials are recorded from electrodes placed directly on structures within the auditory nervous system. Far-field potentials are recorded from electrodes placed on the scalp (Møller 2014). AEPs can also be subdivided depending on the timescale in which the response arises, after stimulus presentation. For adults, early latency responses occur within the first 10 milliseconds following stimulation and include electrocochleography and the auditory brainstem response. Middle latency responses occur between 12 and 75 milliseconds after stimulus presentation. Long latency responses occur after 75 milliseconds and include tests referred to as event related potentials (ERPs). ERPs are influenced by the subject's state of attention or arousal (Burkard and Secor 2002). Auditory ERPs are often still in the research domain, as inter-subject variability is high and experiments often need to be designed depending on the question being asked (Woodman 2010; Jerger 2016). The early recording of AEPs was restricted to long latency potentials, as the shorter latency potentials have very small amplitudes which could not be detected (Eggermont 2007). Over the years, the development of technology has reached a point at which electrical responses to auditory stimulus in the region of less than 2 μvolts can be reliably and repeatedly recorded, non-invasively (Pratt 2003). This technique includes the averaging of responses from the repetitious presentation of many (usually) identical stimuli. This averaging technique relies on the evoked waveform being very similar for each stimulus presentation, whilst the background EEG changes more randomly. The result is that the responses to the auditory stimulus summate leading to increased amplitude of the waveform, whilst the background noise is cancelled out. There is a relationship between the location of the signal generated and the amplitude of the recorded response. The closer the activated neurons are to the scalp, the larger the recorded potential (Eggermont 2007).

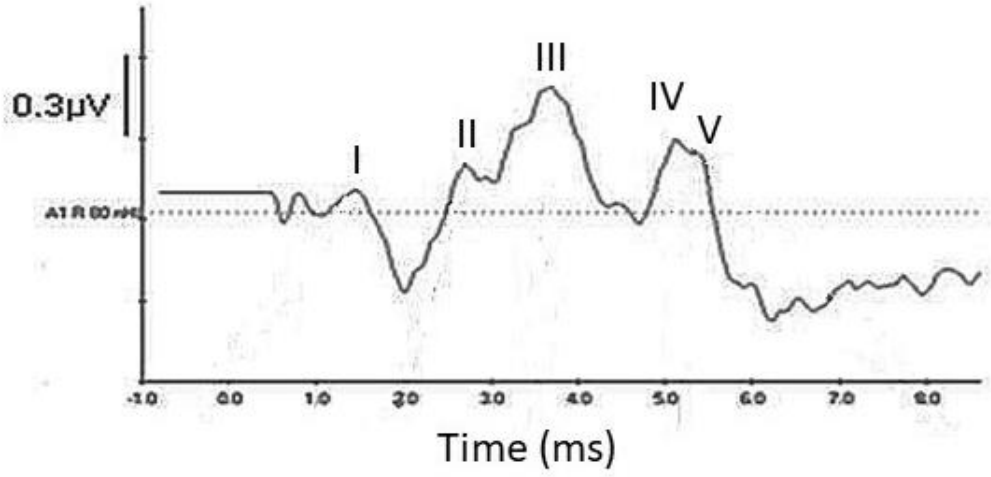
One of the most routinely used AEPs is the Auditory Brainstem Response (ABR). It is thought that Kiang (1961) first demonstrated the existence of the ABR. However, the response was not characterised until later and became of immediate interest (Jewett et al. 1970; Jewett and Williston 1971). Jewett (1994) presents a personal account of the events leading to this work and the initial classification of the ABR as an artefact. The ABR captures neural responses in the brainstem elicited by exposure to a sound stimulus. As first developed, the stimulus was a simple fast onset

click (click ABR) with the response measuring the degree of synchronous neural firing at stimulus onset (Grose et al. 2007). The evoked brainstem response is considered to be reliable and repeatable, with the latencies and amplitudes of the response wave falling within a restricted range for people with 'normal' neurologic function (Schwartz et al. 1994). The response waveform (see Fig. 7 for an example) comprises between 5 to 7 peaks (Jewett and Williston 1971) and is influenced by the characteristics of the stimulus itself, the recording factors and the listener (Hood 1998). Peaks I, III and V are usually discernible in people with normal hearing, whilst waves II, IV, and VI may, or may not, be detectable (Levine et al.1993). However, it is interesting to note that ABR labelling convention is not consistent with labelling for other sensory evoked potentials. With the ABR, only peaks deviating from the baseline in one direction are labelled, whereas in other evoked potentials both positive and negative peaks are labelled with the letters P and N, respectively. The P or the N is followed by a number that is equivalent to the typical latency value for that component of the waveform (Møller 2014).

The ABR peaks are a representation of the far-field recording of neural onset responses (Burkard et al. 2007) and because both ear and brainstem pathology influence the recording in characteristic ways, the test is considered to be suitable for diagnostic purposes. Both the presence or absence of peaks and the nature of the wave itself (peak amplitude and peak latencies) can be used to assess neurologic function throughout the auditory brainstem pathways and identify neurological dysfunction. In the clinical setting, the ABR is the most commonly used auditory far-field potential (Møller 2014). The ABR has been shown to be of clinical value in estimating hearing thresholds, site of lesion testing and intraoperative monitoring (Burkard and Secor 2002). A more recent focus of ABR testing has been to improve the quality of the response recorded, reduce the time of acquisition and eliminate errors made by operator judgement (Hall and Rupp 1997). It has been described as "a unique diagnostic dimension that has transcended interdisciplinary boundaries" (Jacobsen 1985, p.3). It allows us to study a sensory system in relation to the potentials evoked by aspects of a sound and the effect this has on the neural activity along the pathway (Eggermont 2007) and this makes it of interest to people working in many disciplines.

Figure 7. The Auditory Brainstem Response

(click ABR tracing recorded by C. Johnson)



2.2.2 Generators of the click ABR

In order for a test such as the ABR to be diagnostically useful, there needs to be knowledge about the neural generators of the response and the influence of any pathologies. It has not been straightforward to identify the neural generators of the ABR because of the recording method used and the fact that there are large numbers of nerve tracts and auditory nuclei within the auditory pathway (Fig. 3). From the level of the cochlear nucleus and throughout the brainstem, some of the afferent auditory neurons cross the midline of the brain and synapse contralaterally. This results in multiple pathways from the auditory periphery to the cortex, some of which are more direct than others (McFadden et al. 2010). If an electrode is placed on any neural structure in the ascending auditory pathway, a sound evoked electrical potential can be recorded from that structure (Møller 2014). When using a far-field recording method, it is possible that more than one neural generator is contributing to the recording. The activity detected by an electrode is therefore, a sample of electrical activity generated by neurons from different areas of the brain. What also needs to be considered is that far-field potentials are only generated when most of the currents produced by individual neurons are produced synchronously and are flowing in the same spatial direction. We can therefore only measure these far-field potentials from structures that are spatially aligned (Eggermont 2015).

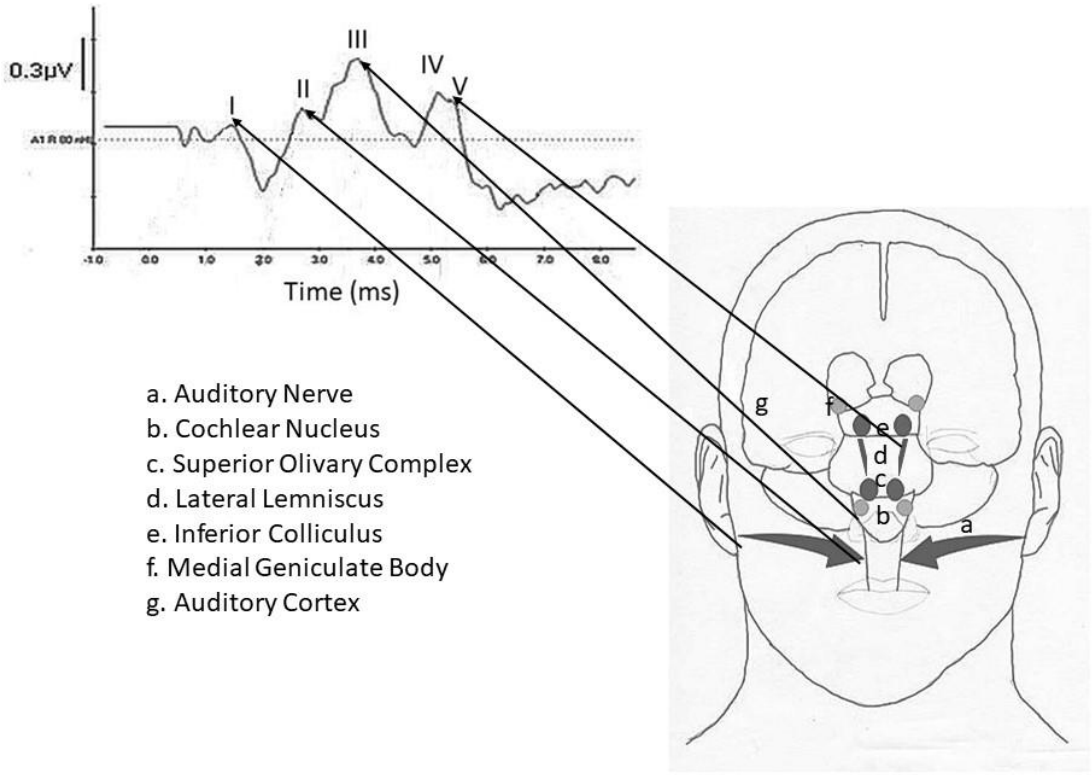
As previously discussed, when the ABR is recorded from the scalp of an adult, usually between the vertex and the earlobe or mastoid, there are five peaks that occur within 10 ms of the sound stimulus being presented. These peaks are conventionally labelled with Roman numerals I to V as per Jewett and Williston (1971). These individual peaks have been the focus of neural generator studies. Most of these studies have either relied on recording directly from neural structures during surgery, from studies of people with known lesions, or from animal models (Parkkonen et al. 2009). ABRs are usually recorded with three or four electrodes, typically placed at the vertex, forehead, and either on the earlobes or the mastoids. The resulting amplitudes of the ABR peaks depend on the orientation of the pair of electrodes from which the ABR is recorded. It should be remembered that even though many structures will be generating electrical activity, not all will contribute to the far-field recording (Møller 2014). It is possible to use many more electrodes for recording AEPs, resulting in multiple recording sites. This high-density approach allows for more location specificity of the neural generators that are contributing to the signal recorded at the scalp (Bidelman 2015). It is now also possible in the research environment, to use a combination of AEP and functional magnetic resonance imaging (fMRI) in an attempt to combine a technique which has high temporal resolution with a technique which has better spatial resolution of the signal (Scarff et al. 2004; Milner et al. 2014).

The different peaks within the ABR are generated by neural activity in the cochlea, the auditory nerve, nerve tracts and the auditory nuclei of the ascending auditory pathways (Fig. 8) (Møller 2014). Neural generator studies have tended to focus on the auditory nuclei. However, we know that far-field potentials can originate when action potential activity passes between media with different conductance. They can also originate when there is a change in structure or a bend in the nerve tract (Stegeman et al. 1987). It is not presently known whether the peaks of the ABR are generated by nerve tracts (white matter) or the auditory nuclei (gray matter) (Møller 2014). Apart from peaks I and II which originate from the distal and proximal ends of the auditory nerve (Stockard et al. 1978; Møller and Jannetta 1982), all the other peaks, when recorded from the scalp, have multiple generator sites (Parkkonen et al. 2009). Specifically, peak I is the compound action potential of the auditory nerve (Eggermont 2007). Peak III appears to be generated at the level of the Pons and is primarily thought to arise from the cochlear nucleus on the same side as the ear of stimulation (Hall 2007; Møller 2014). There is some debate about whether there is any contribution from the Superior Olivary Complex within later publications (Hall

2007; Parkkonen et al. 2009; Møller 2013). Peak IV is less well investigated and its generators are not clearly understood. The current evidence suggests that contributions arise from the superior olivary complex (Møller 2014). It is thought that peak V arises from the lateral lemniscus termination at the inferior colliculus, and from within the inferior colliculus, contralateral to the ear being stimulated. Combined ABR and fMRI analysis supports this conclusion (Parkkonen et al. 2009).

Figure 8. The Neural Generators of the ABR

(Image created by C. Johnson)



2.2.3 Recording the ABR

Many factors, including the subject themselves, affect the ABR waveform. In order to record the ABR a stimulus is required, a transducer for delivering the stimulus, electrodes for recording the response and a way of isolating the response from other unwanted noise (Schwartz et al. 1994). The choice of electrode montage, recording filter, bandwidth, stimulus repetition rate and other ABR recording and stimulus parameters differ depending on whether the ABR is performed for otoneurological

assessment or for threshold seeking. Previous research has shown that subject factors including sex, age and hearing loss affect ABR results (Jerger and Hall 1980; Rosenhall et al. 1986; Keith and Greville 1987; Thornton 1987; Jerger and Johnson 1988; Watson 1996; Hultcrantz et al. 2006; Jiang et al. 2009; Konrad-Martin et al. 2012). A review of these individual factors is presented in the following sections.

2.2.3.1 Stimulus Factors

The ABR is evoked by an auditory stimulus, or more precisely, by changes in the stimulus. These changes can be the onset or offset of a sound, any amplitude modulation and its frequency content or any frequency modulation (Eggermont 2007). There are a number of factors to consider when deciding what type of stimulus will be optimal for recording an ABR. Whether the stimulus is a click, tone burst or speech signal can affect the recording achieved. The frequency of the stimulus, its polarity, how long it lasts, how often it is presented and at what intensity level, all need to be taken into account (Hood 1998; Hall 2007). The stimulus requires presentation monaurally or binaurally, either through insert earphones, headphones, bone conduction or via speakers (Pratt 2003). As the ABR involves far field recording, it is advantageous to elicit a strong and synchronous response. A stimulus, which has a rapid onset and energy over a range of frequencies, will elicit synchronous firing from a large number of neurons (Sininger and Cone-Wesson 2002). When trying to assess how well the auditory pathway is functioning, it is beneficial to record electrical activity from as many neurons firing as possible with a synchronous onset time. Therefore, a transient, broadband stimulus such as a click is well suited to diagnostic testing, as the ABR should represent the optimal functioning of the auditory pathway (Møller 2014). Analysis of click duration has found that a 100 μs click has a broad enough bandwidth with similar spectrum, to a transducer excited by broadband noise and this is generally used when recording the click ABR (Burkard and Secor 2002). This use of a defined click stimulus allows for results to be compared to clinical normative data and even minor differences from optimal performance can be detected and may indicate pathology (Schwartz et al. 1994). If a click is used then the resulting response is thought to correspond to the hearing region from 500 to 4000 Hz (Stapells and Oates 1997). The higher the frequency content of a stimulus, the shorter the latency of the ABR trace. This is because the travelling wave reaches the basal region of the cochlear stimulating firing more quickly than it reaches the apical regions associated

with the lower frequencies (Sininger 1992). The ABR waveform generated by a tone pip is smaller, broader and has longer latencies than the ABR waveform generated by a click, particularly with lower frequencies (Mason et al. 2002).

The rate at which the stimulus is presented can affect both the latency and the amplitude of the ABR recording. The stimulus must be presented repeatedly in order to average the response over time to a level where it can be isolated from other noise. For diagnostic testing, it has been conventional to use a relatively slow click rate, in order to allow the neurons to recover between firing and maintain a good level of synchronicity. This is thought to provide a picture of the optimal performance of the system and allow comparison to normative data. However, it has been proposed that a more rapid rate which allows less time for neural recovery between firing can significantly delay the latency of wave V if there is pathology present, although this method is not commonly adopted (Ackley et al. 2006). A click rate of somewhere around 10 per second is thought to help with identification of wave I, yet still maintains a reasonable acquisition time for patient comfort (Burkard and Secor 2002). When recording an ABR, consideration must be given to the surrounding recording environment, as there will be mains electricity lines in the room, as well as the electrical noise from the recording equipment. Therefore, it is advisable to use a cycle rate that does not have the potential to be confused with other electrical noise. A rate of 11.1 stimuli per second has been suggested for diagnostic purposes (Hood 1998).

The polarity of the stimulus can be altered by changing the diaphragm position within the transducer, delivering the stimulus in either a condensation, rarefaction or alternating phase. A stimulus presented in rarefaction phase may result in a marginally shorter latency and increased amplitude of the early components of the ABR compared to a stimulus presented in the condensation phase (Hall 2007). The ABR may differ considerably when presented in either the rarefaction or condensation mode, for people with cochlear hearing loss (Møller and Jho 1991). It is possible to present the stimuli in alternating phases, which may result in the cancellation of stimulus related artefact on averaging (Hall 2007).

Another factor to consider in stimulus presentation is the intensity level. Commonly used intensity measures are ‘peak equivalent SPL’ (PeSPL) and dB above the normal hearing threshold (dB HL). PeSPL is the value given to a click, which has the same peak sound pressure as the root mean square (RMS) sound pressure of a pure tone. A decrease in intensity usually results in an increase in latency and amplitude, until the point at which threshold is approached and wave morphology is

no longer discernible (Hood 1998; Zhang et al. 2004). Wave V is affected less than waves I and III and may be the only discernible peak when stimuli are presented at low intensity levels (Møller 2014). As previously mentioned with diagnostic testing, the intensity should be high to excite as many neurons to fire as possible, without bringing discomfort to the client. The maximum stimulus intensity level of clinically available ABR recording equipment is in the region of 95 –100 dB nHL. However, it is recommended that testing commence at between 70 and 90 dB nHL (Burkard and Secor 2002). If the stimulus is presented to both ears simultaneously then the amplitude of waves recorded can be as much as 60% higher than when presented to one ear alone. There is no data at present that indicates a change in latency for binaural versus monaural recording. For both diagnostic and threshold estimation testing, each ear should be evaluated in isolation (Hood 1998). If a person has a severe to profound level of hearing loss, then it may not be possible to record any wave morphology.

2.2.3.2 Recording Factors

Electrodes are used to record the ABR and these are usually applied to the mastoid or ear lobes and vertex (Cz) or high forehead (Fz). Usually three electrodes are required per recording channel (Burkard and Secor 2002). One electrode acts as the non-inverting electrode and can be placed at Cz or Fz, one as the inverting electrode and placed on the ear lobe or mastoid of the ear to be stimulated. The third electrode is placed on the contralateral earlobe or mastoid and acts as a ground. However, this electrode montage only allows for single channel recording. The electrodes are placed to maximise the recording of electrical potentials in the area of interest, which should allow individual wave components to be distinguished (Schwartz et al. 1994). It is also possible to record in the vertical plane between both ears, which results in a lowering of the amplitude of wave V whilst preserving the amplitude of wave I (Hood 1998). This montage is not generally used for threshold estimation or diagnostic testing.

Once the potentials have been acquired they have to be separated from all other sources of noise, which involves boosting the signal to noise ratio. The signal of interest is in the region of 1μ V, therefore processing is necessary to isolate it from other noise sources. This can be achieved by differential amplification, time-domain averaging, filtering and the rejection of artefacts (Schwartz et al. 1994). Low and

balanced impedances between electrodes will optimise the performance of the differential amplifier. For diagnostic testing, impedances of less than 5 KΩ are required (Stevens 2002). Time-domain averaging involves repetition of the recording to allow averaging over time, which will enhance the signal to noise ratio. This is also referred to as the number of sweeps and for ABR recording at high intensities, between 1000 and 2000 sweeps is usually sufficient. If the intensity rate is decreased then the number of sweeps may be increased, although there will come a point when further averaging does not appreciably alter the result (Hood 1998). Each sweep requires a set time duration and there are known normal time periods for acquiring an ABR for adults and infants. This is to some extent dependant on stimuli, with click stimuli requiring 10-12 ms in adults and 15-20 ms in infants, whilst toneburst stimuli require 15-20ms in adults and 20-25 ms in infants (Burkard and Secor 2002).

Another way of reducing noise and reducing the number of stimulus presentations needed is by filtering out elements that do not contain the response. Filtering alters the appearance of components of the ABR, so filters should be selected to enhance the peaks that are of interest, without changing their latencies (Møller 2014). In order to decide on the filter settings, the frequency of the required elements needs determining. This has been evaluated as a bandpass of between 30 and at least 1500 Hz. Schwartz et al (1994) suggest that if the high pass cut off is raised from 30 Hz to 100 or 150 Hz, there is an enhancement of waves I-III, which can be appropriate for diagnostic testing. Hall (2007) provides a suggested protocol for clinical measurement of the ABR and advises that the low pass filter be set to 3000Hz unless there is excessive high frequency artefact present, in which case it should be reduced to 1500Hz.

2.2.3.3 Subject Factors

There are a number of factors to be considered in relation to the person undergoing click ABR assessment. The click ABR essentially becomes adult-like by about the age of two years and adult normative data is routinely used for children above the age of eighteen months (Hood 1998). There are changes that occur after this period with the response finally stabilising at around age 12 (Skoe et al. 2015a; Sharma et al. 2016). It can be difficult to establish the effect of age on the ABR because, as we get older our hearing also deteriorates (Jerger and Hall 1980; Jerger and Johnson 1988; Lightfoot 1993). There is not a clear consensus on how the ABR

changes with age, researchers are still trying to understand the interactions between age, hearing loss and other recording parameters. The degree and configuration of the hearing loss also has an impact and older adults with better hearing may or may not have increased latencies depending on the condition of the auditory pathways. One of the difficulties of working with people with hearing loss, is that it can be difficult to detect early peaks, such as I and III (Konrad-Martin et al. 2012). It appears that between the ages of 25 and 55, ABR wave latencies increase in the order of 0.1 to 0.2ms (Jerger and Hall 1980). When compared to 21-30 year olds, click ABR wave V results do not become significantly different until people reach between 50 and 60 years of age (Skoe et al. 2015a). Hall (2007) has reviewed the literature and found that researchers report an increase in the I-V interpeak interval between the ages of 60 to 80 years. However, in a more recent study of people aged 71 to 96 years old, when hearing loss was controlled for, wave V of the click ABR did not vary by age (Gates et al. 2008). In general, it would appear that slight changes in latency are found for individual peaks and the interpeak intervals with aging, although the pattern varies. This may also be partly attributable to sex specific changes, with males reported to have greater changes (Jerger and Johnson 1988). Decreases in the amplitude of individual peaks with aging are reported, with wave I being more affected (Konrad-Martin et al. 2012)

As discussed, the click ABR is relatively stable in adults without hearing loss up until around age 50 years (Skoe et al. 2015a). The impact of conductive and sensorineural hearing loss (SNHL) on the click ABR is well known and can be differentiated using the click ABR (Steinhoff et al. 1988; Baldwin and Watkin 2014). Short-term conductive hearing loss results in a shift in absolute peak latencies, with inter-peak latencies remaining the same (Fria and Sabo 1980). Long-term conductive hearing loss can affect the inter-peak latencies (Hall and Grose 1993). The click ABR in people with sensorineural hearing loss (SNHL) depends on the degree and configuration of the loss. With increasing hearing loss, ABR components increase in latency, the inter-peak intervals increase and waves decrease in amplitude. If the level of loss is severe to profound it can be difficult, if not impossible, to record the click ABR (Keith and Greville 1987; Hood 1988).

It is of interest to note that there has been recent criticism of researchers using the ABR and either not reporting the sex of their subjects, or not taking sex into consideration in analyses of results (Stamper and Johnson 2015). There is a wealth of literature that underpins the finding that sex differences exist in the adult click ABR

(Jerger and Hall 1980; Rosenhamer et al. 1980; Edwards et al. 1983; Jerger and Johnson 1988; Durrant et al. 1990; Watson 1996). Sex differences in adult ABRs are reported throughout the literature for the amplitude of waves I and V (Kjaer 1979; Michalewski et al. 1980). There are conflicting results about the latency of wave I with some researchers finding no differences between men and women (Chao et al. 2008; Stamper and Johnson 2015), whilst others find differences across waves I, III and V (Lourenço et al. 2008). It has been identified that the effect of sex is present for wave I but that it is smaller (Don et al. 1993). It is generally accepted that the individual wave peaks from wave III onwards and interpeak latencies are significantly shorter in women (Hall 2007). Researchers propose that these differences between the sexes may be a result of physical size, including the length of the cochlea and/or hormonal influences (Aoyagi et al. 1990; Yadav et al. 2002; Hultcrantz et al. 2006; McFadden et al. 2010; Krizman et al. 2012a). It is, therefore, important to either have sex specific normative data or to balance the number of males and females contributing to a clinical normative data set (Hall 2007).

There is little evidence to show any clinically significant differences in the right and left ear responses to the click ABR for adults with normal hearing (DeVries and Decker 1988; McFadden et al. 2010; Vander Werff and Burns 2011). Some researchers have suggested that there is perhaps an earlier and larger but not clinically significantly different response to the click ABR, when the stimulus is presented to the right ear (Levine and McGaffigen 1983; Levine et al. 1988). Indeed, one of the ways to determine whether responses are normal is to compare right and left ear data from an individual, as they should be the same (Hood 1998). When using the ABR for either diagnostic or threshold estimation testing, each ear should be evaluated in isolation. This raises the question about whether masking of the non-test ear is required. Sound can travel through the skull by bone vibration and if loud enough, can stimulate the non-test cochlea (Yacullo 1999). The ABR is often recorded at high sound intensities and therefore there is the potential for contribution from the non-test cochlea. Evidence from ABRs recorded from the test ear and non-test ear in normal hearing young adults has found that wave I was often not recordable from the contralateral side. Waves III and V are recordable but are not significantly different in amplitude or latency from the test ear (Rosenhamer and Holmkvist 1982). The current advice is that masking is not required for diagnostic testing, if testing a person with hearing within normal limits bilaterally. However, consideration must be given to the

fact that testing from either ear may include contributions from the non-test ear (Hall 2007).

It has long been accepted that the click ABR is not influenced by attention (Picton et al. 1971; Picton et al. 1974; Kuk and Abbas 1989). It has been investigated during sleep, with no or limited changes occurring. Any limited changes are thought to be as a result of the response being less obscured by myogenic activity (Osterhammel et al. 1985; Campbell and Bartoli 1986). In contrast, there is some evidence that the ABR may be affected by attention depending on stimulus and recording conditions (Lukas 1981). Ikeda et al. (2008) proposed that using low intensity, short trial lengths and tone pips may aid in assessing the effect of attention but that it is difficult to identify the attention effect at the auditory periphery using traditional click ABR methods. There is very little evidence that the click ABR is affected by experience, as the wave latencies fall within a restricted range for adults with normal hearing. There is very limited evidence that better adult readers have longer wave V latencies, when a fast stimulus presentation rate is used (31.25 - 64.5 Hz). The researchers urge caution when interpreting this data as hearing was only screened and actual hearing thresholds may have been significantly different within the test population (Skoe et al. 2017).

The ABR is considered a robust response because there are little, if any, effects of the level of consciousness, medications, general anaesthesia, or muscle paralyzing agents (Stone et al. 2017). Relatively few medications are known to have an effect on the ABR, as most modify cortical activity only. Medications such as psychotherapeutics which are used to treat conditions such as depression, anxiety, or psychosis do not significantly impact on the ABR (Hall 2007). Chloral hydrate is a sedative used for ABR testing in infants and is not thought to affect the ABR (Valenzuela et al. 2016). Diazepam (Valium) is a commonly prescribed anti-anxiety drug and it is thought to have, at most, a minimal impact on the ABR. Adams et al. (1985) found a small increase in the interpeak latency of I to V but no change in amplitude. Valium has been used for recording the ABR in patients who have high anxiety levels and cannot relax enough to allow artefact free recording (Hall 2007). No real effects of poly-drug use were found in a study looking at people with addiction, instead it was the psychiatric status of the patient that was important (Patrick and Struve 1994). Patients with epilepsy taking anticonvulsants such as phenytoin are known to have prolonged interpeak latencies (Chan et al. 1990; Panjwani et al. 1996). There is limited data on the effects of thiamine, with one study (n=2) advocating that

thiamine can result in reduced latency of ABR peaks in infants with thiamine deficiency (Lonsdale et al. 1979). There are reported links between thiamine metabolism and brainstem function. Thiamine-responsive megaloblastic anaemia is a rare syndrome characterised by the presence of diabetes mellitus, megaloblastic anaemia, and sensorineural deafness (Bay et al. 2010). There is extremely limited evidence that a diagnosis prior to age two months and treatment with thiamine may prevent the progressive sensorineural hearing loss associated with this syndrome (Önal et al. 2009). The effect of nicotine on the ABR has been investigated for both adult non-smokers and smokers and was found to have no effect (Kumar and Tandon 1996; Harkrider et al. 2001). In one study, an acute effect of nicotine was found on the amplitude of wave V only (Knott 1987). However, smoking and passive smoking may be associated with hearing loss and hearing loss will have an effect on the ABR (Dawes et al. 2014).

2.2.4 Repeatability of the ABR

In order for a test to be clinically valuable it must be deemed to be repeatable, generating the same information between test sessions unless there has been a change as a result of intervention, development or pathology (Song et al. 2011; Hornickel et al. 2012a). It is uncommon to find a clinical measure that is absolutely reliable, as not only can the instruments and the people using them be fallible but there can be inconsistencies in the way in which the people being tested respond (Bruton et al. 2000). In the case of the ABR, interpretation of the waveform includes assessment of morphology, peak latency, inter-peak latency and amplitude measures. With respect to the waveform, what is being measured is usually the time elapsed between the presentation of the stimulus and the peak of interest. Hall (2007 p. 216) provides a commentary on the 'Art of Peak Picking'. Either the clinician marks the peak at the point on the waveform, which has the maximum amplitude in the time window of interest, or they select the last point on the peak before the negative slope. There are pros and cons to using both methods, but the key is to be consistent in the method of choice. Amplitude can be difficult to assess, as again, there are two options for marking maximum and minimum amplitude. It can be marked from the maximum peak point to the minimum of the following trough (Davis 1976), or from the peak point to a set baseline. Interpeak intervals are calculated between marked peak points, usually between wave I and wave III, wave III and wave V and between wave I and

wave V (McFadden et al 2010). The I to V interpeak interval has been referred to as ‘central conduction time’ or brainstem transmission time and is used to establish if there is any pathology along the auditory pathway from the auditory nerve, through the brainstem (Gorga et al. 1988).

The ABR is described as being an objective test because no active response is required from the person being tested (Anderson et al. 2013a). However, as previously discussed, there can be a subjective element to marking the waveform. As with most auditory evoked potential recording the customary method of response detection, requires the two or more responses to be superimposed and visually examined for reliability (Golding et al. 2009; Sutton and Lightfoot 2013). There are a number of methods that can be used to automate detection of the ABR including correlation, template matching or comparing the variance of the averaged waveform to that of the background noise level. When looking at the signal compared to the background noise, this can be achieved using a single point, (Fsp), or by looking at multiple points (Fmp) (Cone-Wesson et al. 2002; Sutton and Lightfoot 2013). Although newborn hearing screening equipment employs techniques for the automated detection of a response (Cebulla and Stürzebecher 2013), it remains the case that diagnostically, the method used to determine the presence or absence of a response is visual inspection of the waveform (Sutton and Lightfoot 2013). As such, although the ABR is often referred to as an objective test, there is a subjective element involved in interpretation of the waveform (Sininger 1993). There are a number of ways in which consistency in interpretation of recordings can be measured. Intra-rater agreement is used to determine the agreement among repeated administrations of the same diagnostic test performed by a single individual. Inter-rater agreement is used when different raters apply the same instrument or procedure when assessing the same subjects. A small number of studies have been published focussing on the consistency of a single rater when performing repeated analysis of waveforms and inter-rater agreement when presented with the same waveforms. From these studies intra-rater agreement for the click ABR ranges from 79% to 100% and inter-rater agreement ranges from 81% to 100% (Kjaer 1979; Rossman and Cashman 1985; Champlin 1992; Pratt et al. 1995; Olsen et al. 1997; Naves et al. 2012a; Naves et al. 2012b). There is some variation in the results, which is attributed to the analysis criteria used and the repeatability of the waveforms. When raters are asked to make a judgement on normal as opposed to abnormal, rather than a decision on actual latency, then agreement appears to be higher. When raters are asked to make

decisions regarding hearing threshold estimation then high levels of variability between raters can be found (Vidler and Parker 2004). There are also a number of studies looking at objective measures of response detection compared with subjective measures; however, these focus on variability between raters and objective methods (Elberling and Don 1984; Mason 1984; Arnold 1985; Valdes-Sosa et al. 1987; Pool and Finitzo 1989; Sininger 1993; Ozdamar et al. 1994).

Studies using the ABR have demonstrated that intra-subject repeatability is high with only small differences in latency being demonstrated between tests on the same subject (Kavanagh et al. 1988; Oyler et al. 1991). The latencies of the response wave fall within a restricted range for people with 'normal' neurologic function (Schwartz et al. 1994). Abnormal results may include a complete absence of a waveform, increased latencies of one of more waves, with or without a decrease in amplitude and differences in latencies between responses from the right and left ears (Kjaer 1979). The clinical importance of amplitude is limited, as there can be substantial variability in this measure (Hall 2007). As the click ABR is a test which is widely available, the equipment easily portable and the response provoked deemed to be reliable and repeatable, it has been used in many investigational studies and has a current global use in universal newborn hearing screening programmes.

2.3 The Speech Auditory Brainstem Response

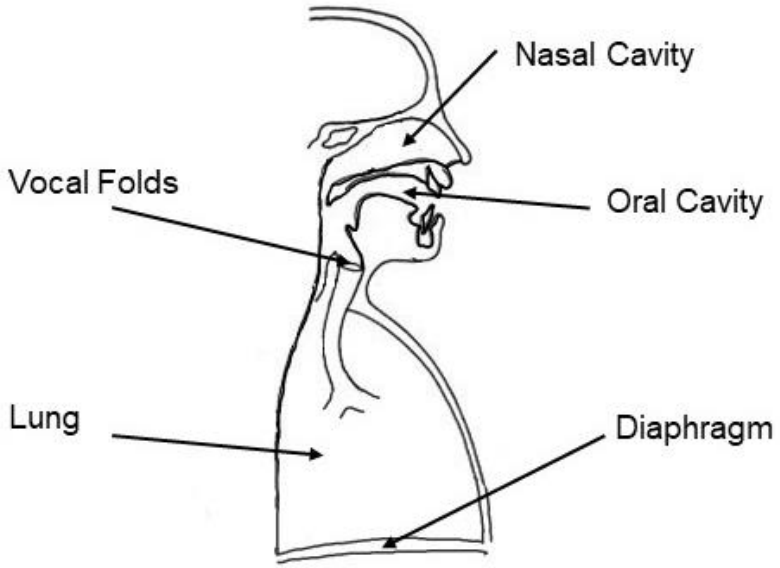
This section of the literature review is dedicated to the speech Auditory Brainstem Response (speech ABR). The speech ABR is a recent evolution of the ABR and as such does not have a current role in standard clinical assessment batteries. The purpose of this section is to introduce the reader to the speech ABR and provide a critical analysis of literature relevant to Experiments One and Two.

It is known that the click ABR is an appropriate tool for assessing neural synchrony in the auditory nerve and through the brainstem (Stone et al. 2009). However, the 'real-world' scenario is the precise ability to encode complex sounds, including speech (Russo et al. 2004). Processing of speech material appears to be more affected by a disruption in the central auditory nervous system (CANS) pathway, than processing of non-speech stimuli (Bellis et al. 2000; Jerger and Musiek 2000; Song et al. 2006). Processing speech stimuli, as opposed to click stimuli, places a greater demand on the system, in terms of increased desynchronising effects on neural phase locking (Song et al. 2011). It is now known that neural encoding of more complex stimuli can also be assessed non-invasively, by adapting the ABR procedure and using periodic stimuli, such as a short speech or speech-like stimulus (Greenberg 1980; Galbraith et al. 1995; Skoe and Kraus 2010a). In this section, the speech ABR will be explored in relation to: its development as a means for assessment, where it comes from (neural generators), what it represents, considerations for testing and what is already known about its use as a clinical tool.

Until relatively recently, the most commonly used stimulus to elicit the ABR has been a click. The click ABR, its use and the stimulus itself, have been described previously. When considering auditory stimuli, speech is usually the signal of interest for human interaction. Unlike pure tones and clicks, speech comprises complex sound waves, with information transmitted by ongoing yet precise, spectral changes over time (Abrams and Kraus 2015). For voiced speech sounds, the speech signal is created at the vocal folds and after travelling through the vocal tract, is produced at speaker's mouth (Fig. 9).

Figure 9. Speech Production

Adapted from Zelman (2011, p.35)



The 'source filter model' is routinely used to describe properties of speech (Stevens et al. 1953; Fant 1960; Kraus and Nicol 2005). Source information provides extra-linguistic information, allowing the listener to identify aspects about the speaker such as their sex, age and emotional state (Johar 2016) and is formed by the pulsing of the vocal folds (Smith and Patterson 2005). Linguistic information is created by the filtering that occurs in the vocal tract and at the articulators (Stevens 1997). Simple units within spoken language are consonant-vowel (CV) and consonant-vowel-consonant (CVC) combinations (MacNeilage and Davis 2000) and particular filter shapes help to create the differences between them (Kraus and Nicol 2005).

When considering the process of speech perception, the consonants carry most of the information leading to word identification. The louder and more stable frequency vowel sounds provide accent and intonation information (Toro et al. 2008). Researchers often use CV combinations, or syllables, to investigate aspects of speech perception. Perception of stop consonants (e.g. /t/, /d/, /k/), where a period of silence is followed by a burst of sound, has been shown to be especially vulnerable in clinical populations (Tallal and Piercy 1975; Russo et al. 2009) and to disruption by noise (Russo et al. 2004). This is why researchers have been using 'speech-like syllables' involving this group of sounds e.g. /ta/, /da/, /kee/, as stimuli in experiments investigating speech perception. In particular, the syllable /da/ has become routinely used as a stimulus (Nuttall et al. 2015; Sanfins and Colella-Santos 2016). The

formation of /da/ requires changing from an alveolar place of articulation for the stop-burst (plosive) of the /d/, to the back of the mouth for the vowel sound /a/. This type of CV transition can be perceptually challenging, as a result of the rapidly changing spectro-temporal content and low amplitude of the /d/ compared to the /a/ (Tallal 1980; Alwan et al. 2011; White-Schwoch and Kraus 2013). There is increasing interest in the use of these types of stimuli to investigate sound encoding at the level of the brainstem by using speech ABR. An overview of the speech ABR is presented in the following section.

2.3.1 Overview of the Speech ABR

Different types of stimuli are now being used to investigate sound encoding at the level of the brainstem (Dau et al. 2000; Cunningham et al. 2001; Aiken and Picton 2008; Akhoun et al. 2008a; Swaminathan et al. 2008; Strait et al. 2009; Skoe and Kraus 2010b; Wang et al. 2010; Won et al. 2016). This type of testing may be referred to as the speech ABR, complex ABR, frequency following response or envelope following response, depending on the stimulus used. For the purposes of the current research, speech is the signal of interest. When analysing the speech ABR, consideration needs to be given to the structure of speech. Speech includes a low-frequency spectro-temporal 'envelope' in the 2-8 Hz range, 'periodicity' information in the 100-400 Hz range and underlying temporal fine structure (TFS) (Rosen 1992). Researchers have been interested in looking at the slowly varying temporal feature, referred to as the periodicity envelope, which overlies the more rapidly varying temporal features (the TFS) (Ananthakrishnan et al. 2016). When using a stimulus like /da/, the response will reflect the periodicity of the envelope of the syllable as well as contributions from the vowel harmonics of the repeated syllable (Marsh and Campbell 2016).

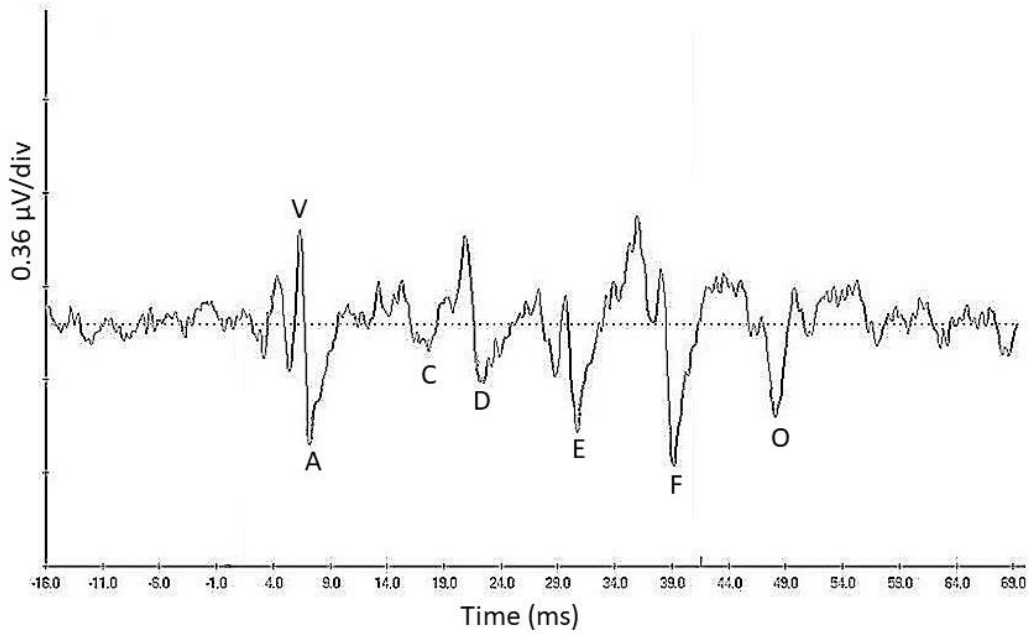
The speech ABR comprises a waveform that has distinct response components, the onset response (similar to a click ABR), the frequency following response and the offset (Fig. 10). The term 'frequency-following response' (FFR) is routinely used to describe a response that follows the spectral frequency of the stimulus, or the frequency of its envelope (Aiken and Picton 2008; Easwar et al. 2015; Varghese et al. 2015). The FFR has been proposed as a biomarker for conditions featuring abnormal auditory processing (Coffey et al. 2016). It has been recorded using pure tones (Moushegian et al. 1973; Galbraith and Brown 1990), tonal sweeps

(Krishnan and Parkinson 2000; Basu et al. 2010; Clinard and Cotter 2015), vowels (Aiken and Picton 2008; Laroche et al. 2013; Won et al. 2016), consonant-vowel syllables (Johnson et al. 2008a; Skoe et al. 2015a), continuous speech (Reichenbach et al. 2016) and other vocalisations (Strait et al. 2009). The FFR reflects ongoing, synchronous neural firing in response to the periodic auditory stimuli and the response mimics the harmonic aspects of the stimulus (Marsh and Worden 1968; Moushegian et al. 1973; Ananthanarayan and Durrant 1992; Aiken and Picton 2008; Chandrasekaran and Kraus 2010). FFRs elicited by speech sounds can be played back as an audio signal and are recognisable as low pass filtered speech (Galbraith et al. 1995; Weiss and Bidelman 2015). The generator process appears to extract the envelope and the fundamental frequency of the stimulus with the resulting FFR locking to the fundamental frequency of the vowel portion (Marsh and Campbell 2016). The resulting waveform is dominated by the representation of the lower frequencies of the stimulus and this relates to the fact that there is an upper limit of phase locking in the rostral brainstem, in the region of 1.5 to 2 kHz (Krishnan 2002; Picton 2010).

By using more complex stimuli, like speech, researchers have found that they are able to detect abnormalities in the brainstem response to sound that are not evident when using simple stimuli (Banai et al. 2007; Filippini and Schochat 2009; Kouni et al. 2013; White-Schwoch and Kraus 2013; Tahaei et al. 2014). These differences occur not only in the timing of the response but also in the way that the stimulus characteristics are encoded and this appears to offer a way of differentiating between typical and clinical populations.

Figure 10. The Speech Auditory Brainstem Response

(speech ABR tracing recorded by C. Johnson)



2.3.2 Proposed Clinical Utility

The introduction of newborn hearing screening programmes has resulted in a resurgence in the use of ABR recording. As previously discussed, the ABR has been in clinical use for many years, as the equipment is portable, it is a non-invasive procedure and it is deemed to provide an objective measure of the electrophysiological response of the neural components of the brainstem (Hood 1998). However, speech ABR waveforms are more complex and require identification of different components to those elicited by click, tone bursts, tone pips or chirps (Skoe and Kraus 2010a). A limited amount of research has been undertaken to assess the reliability of these ABR responses, when elicited using complex sounds (Johnson et al. 2005; Song et al. 2011; Hornickel et al. 2012a). It is surmised that the reliability of these responses will not be as high as for those evoked by clicks, as these stimuli are more complex and dynamic in terms of spectral and temporal information. It also appears evident that the responses are influenced by participants' experience and therefore more subject to individual differences (White-Schwoch et al. 2013; Strait et al. 2013; Krizman et al. 2015a; Skoe et al. 2015b). When reliability was studied, it was found that aspects of analysis that relied on manual identification of the

waveforms, or the subjective view of the rater, produced the weakest reliabilities. It has been demonstrated that reliability indices for the speech ABR are comparable to those of behavioural tests of auditory processing (Hornickel et al. 2012b). Whilst it appears that there can be good intra-subject repeatability when eliciting responses using more complex stimuli (Song et al. 2011), nothing is known about inter-rater agreement when analysing these waveforms.

One of the proposed benefits of the speech ABR, when compared to behavioural tests of auditory processing, is that it is essentially a passive experience for the participant, requiring co-operation but no active cognitive involvement. Tests of auditory processing usually require a subjective response from the listener to indicate what they have or have not heard and may equally be assessing cognitive skills (Humes 2005; Martin et al. 2008; Cox et al. 2008). The speech ABR has the potential advantage of teasing out these contributions and offering an objective way of assessing sub-cortical, auditory processing of speech-like sounds (Russo et al. 2004).

A tool developed for clinical use by researchers at the Auditory Science Laboratory, Northwestern University is the BioMARK (Johnson et al. 2005), and this was commercialised by Natus Medical Incorporated. BioMARK was initially marketed as a clinical tool for the assessment of children with dyslexia, auditory processing disorders (APD), specific language impairment (SLI) and learning disability (LD). It was claimed that the research group had “extensively characterized the brainstem response to a 40-ms syllable, /da/” (Kraus and Nicol 2005, p.177). As a result of the commercial availability of the BioMARK system, there have been a number of studies undertaken globally, which have used the same 40 ms synthetic speech syllable /da/. The /da/ stimulus is a five-formant synthesised syllable (Klatt 1976) which begins with a high frequency (2500, 3500 and 4000 Hz) burst in the first 10 ms. This is then followed by a ramped voiced period, containing the fundamental frequency (F0) (103–125 Hz). During this voiced period there is a transition reflecting the change in place of articulation and this is captured by linearly changing formant frequencies, with the first formant (F1) ramping up from 220 to 720Hz and the second formant (F2) ramping down from 1700 to 1240Hz (Skoe and Kraus 2013). There is no actual steady-state vowel portion in the stimulus, however the perception is of the syllable /da/, and this terminology will be used throughout this document (Dhar et al. 2009; Krizman et al. 2015b).

Before any tool can be deemed to be clinically useful there must be data available on what the results represent and an understanding of any factors that might influence the results (Skoe and Kraus 2010a; Rocha-Muniz et al. 2016; Sanfins and Colella-Santos 2016). There are still some questions to be answered about the speech ABR and these are highlighted in the following section. This section includes a discussion about what the response is and the proposed neural generators, followed by a section on stimulus, recording and subject factors, as per Hood (1998). As this is the only tool developed for clinical use, a literature review in section 2.3.7 features the issues and results reported for this particular stimulus.

2.3.3 Components of the Speech ABR

The typical speech-evoked brainstem response to a 40 ms /da/, is a waveform with a pattern of voltage fluctuations (King et al. 2002). The waveform comprises seven identifiable peaks, labelled V, A, C, D, E, F, and O (Fig. 10), with individual peaks occurring 7- 8 ms after the equivalent stimulus characteristic (Johnson et al. 2007). This period of time has been proposed to reflect transmission delay between the ear and rostral brainstem structures (Chandrasekaran and Kraus 2010; Skoe and Kraus 2010a). Waves V and A are thought to reflect the onset of the response with wave C being the transition region and denoting the change from the burst to the periodic portion of the syllable (vowel). Waves D, E, and F mark the periodic region (i.e., FFR), from which the fundamental frequency of the stimulus can be extracted. There are small voltage fluctuations between D, E and F and it is proposed that these represent the encoding of higher frequency information (formants) (Hornickel et al. 2009). The phase-locking properties of the brainstem neurons to both the fundamental frequency and its harmonics, are therefore characterised by the FFR region (Krishnan 2002; Russo et al. 2004; Vander Werff and Burns 2011). The final wave is O and represents the offset of the response. The envelope boundary in relation to voicing can be denoted by looking at the latencies of wave C and wave O (Dhar et al. 2009; Skoe and Kraus 2010a). Aspects of the waveform in relation to onset (latencies of V and A), spectro-temporal measures (latencies of D, E, F), envelope (latencies of C and O), pitch (D to F inter-peak latencies and F0 amplitude) have been routinely used in waveform analysis. The response has been described in terms of the temporal and amplitude properties of the waveform, including peak latency, inter-peak interval, slope and root-mean-square amplitude of activation and

frequency-domain analysis (Johnson et al. 2005). In the case of a CV stimulus, such as /da/, these measures can be used to assess features including the onset noise burst, formant transition, and steady-state vowel.

Analysis of a complex sound by a healthy cochlea results in a series of bandpass-filtered signals that relate to a position on the basilar membrane. The bandpass signal can be evaluated using the Hilbert transform to create the analytic signal, which provides a representation of the magnitude of the envelope of the signal at that time, and the instantaneous frequency of the signal. Therefore, based on the Hilbert transform the temporal information can be divided into its envelope (E) and fine structure (TFS) with E representing the amplitude contour of the signal over time and TFS representing rapid oscillations with rate close to the centre frequency of the analysed band (Moore 2008; Wang et al. 2015). There is evidence to suggest that TFS may have a role in pitch perception (Smith et al. 2002; Moore 2008). Therefore, the FFR can be subdivided into either an 'envelope FFR' or a 'spectral FFR' (Krishnan 2002; Aiken and Picton 2008; Anderson et al. 2013b). However, there are now questions being raised about what some of these measures actually reflect (Gockel et al. 2011; Varghese et al. 2015; Coffey et al. 2016). A review of these areas of debate is included in the sections below.

2.3.4 Generators of the Speech ABR

The generators of each of the click ABR components are reasonably well understood and have been discussed previously (2.2.2) (Jewett 1994; Hood 1998: Møller 2014). Despite its current use in research and potential for clinical use, the neural origins of the speech ABR are not entirely clear (Coffey et al. 2016). There is debate in the literature about the differences between the transient and sustained brainstem evoked potentials. The onset response, or the VA complex, is often cited as being analogous to the click-evoked wave V-Vn complex (Johnson et al. 2005; Song et al. 2006; Skoe and Kraus 2010a). The onset response reflects the movement of the sound signal from the periphery, through the auditory nerve and up to the cortex. When the FFR was first explored, there were concerns that it was a stimulus related artefact (Akhoun et al. 2008b; Campbell et al. 2012; Plack et al. 2014). However, the response is thought to occur too late for that possibility (Moushegian et al. 1973) and it is not elicited when the stimulus delivery tube is clamped (Plack et al. 2014). In the 'convolution model' of the FFR, it is proposed that the FFR may just

represent a set of repeated onset responses. In this model, the neural generators of the FFR are the same as for the transient ABR and relate to the overlapping of waves IV and V (Dau 2003; Bidelman 2015). This model was recently tested and has not been found to be supported (Bidelman 2015).

The first putative primary generator of the FFR was identified as being the inferior colliculus (Smith et al. 1975; Sohmer et al. 1977), however later research called this into question, placing the primary generator at a lower brainstem level (Hoormann et al. 1992). Chandrasekaran and Kraus (2010), presented arguments against the neural generators being at the cochlea or cortex level and concluded that 'far field' recorded onset and frequency following responses reflected multiple sources in the rostral brainstem including the lateral lemniscus (LL), cochlear nucleus (CN), and inferior colliculus (IC). It is likely that the choice of electrode configuration has an influence on the anatomical sources that are detected (Plack et al. 2014; Bidelman 2015). The assumption that the generator is at the level of the IC comes, in part, from the 6-8 ms delay seen in the response, after stimulus presentation. This time period is consistent with the time required for the signal to travel to the IC (Moushegian et al. 1973; Galbraith et al. 2000; Chandrasekaran and Kraus 2010). Lesion and ablation of the IC in humans eliminates the far field recorded FFR (Sohmer et al. 1977; Davis and Britt 1984). The stimulus duration exceeds that of a click, so the time window of the recorded response is in the range of 50ms, resulting in an overlap with later AEPs (Cunningham et al. 2001). However, the frequency content of the speech ABR is higher than would be evident from a middle latency or cortical response, which lends credence to a brainstem origin (Johnson et al. 2005). In addition, the speech ABR response closely mimics the acoustic features of the speech stimulus presented, whereas cortical responses can be shaped by internal cognitive processes, such as attention (Hood 1998).

Cochlear origins have been ruled out on the basis that the FFR does not behave in the same way as the cochlear microphonic (CM), for example it is not sensitive to stimulus presentation rate (Worden and Marsh 1968). Indeed, the onset response and the FFR respond differently to changes in presentation rate (Krizman et al. 2010; Neupane et al. 2014; Al Osman et al. 2016) and stimulus intensity (Galbraith and Brown 1990; Picton et al. 1981; Akhoun et al. 2008b). As both the onset response and FFR vary with both behavioural and clinical measures (Kraus and Nicol 2005; Coffey et al. 2016) they should be conceptualised as functionally distinct

responses that arise from different neural generators in the auditory pathway (Krizman et al. 2010; Bidelman 2015).

Cortical generators have been ruled out on the basis of the timing of the response being too early and on the fact that FFR contains phase-locked activity that is above the upper limit of phase locking from neurons in the cortex (Aiken and Picton 2008; Akhoun et al. 2008b). The amplitude of the FFR, typically in the nanovolt range is much smaller than that seen for cortical responses and requires many more stimulus presentations to establish the typical wave morphology. The FFR is repeatable and does not reduce in amplitude with increasing numbers of stimulus presentations, unlike cortical responses (Chandrasekaran and Kraus 2010). Also, the ABR was thought to become 'adult-like' by about age 2 years, whereas cortical responses are slower to mature (Hood 1998; Hall 2007). However, there is now a wealth of evidence that the FFR is moderated by learning and experience, which do involve areas within the cortex (Musacchia et al. 2006; Tzounopoulos and Kraus 2009; Strait et al. 2009; Skoe et al. 2013).

The brainstem processes information from the ascending auditory system (afferent, corticopetal) and via descending connections (efferent, corticofugal). These corticopetal and corticofugal systems are interrelated and have been conceptualised as a "hierarchy of dynamic corticopetal-corticofugal loops" which filter ascending and descending information (Bajo and King 2013; Marsh and Campbell 2016, p.6). Learning and experience effects, which have been demonstrated using the speech ABR, have been attributed to modulation of subcortical processes by the efferent pathway from the cortex and researchers have interpreted the FFR as being of purely subcortical origin (Coffey et al. 2016). Recent research calls this conclusion into question. Inhibition and enhancement of the FFR have been observed (Hairston et al. 2013), the FFR cannot be entirely explained by the convolution model (Bidelman 2015) and changes occur in the FFR into adolescence (Skoe et al. 2015a). The upper limit of phase locking in the auditory cortex has also been shown by intracranial recording to be around 200 Hz (Bellier et al. 2015). Magnetoencephalography (MEG) techniques have been employed to localise generating sites, as they are more precisely able to assess the anatomical sources than ABR techniques (Parkkonen et al. 2009). A finding of recent research is that there is a right-lateralized FFR originating in the cortex, in addition to contributions from nuclei within the brainstem (Coffey et al. 2016). The researchers propose that this might be related to pitch processing and that the subtle aspects of periodicity in the FFR are related to processes in the right

auditory cortex. As there is an apparent dissociation between the processing of the spectral content of the stimulus and the envelope information, it is possible that these are represented in different anatomical areas of the brain (ibid.).

2.3.5 Recording the Speech ABR

A tutorial for recording the speech ABR has been provided by Skoe and Kraus (2010a) and they discuss the effects of various stimulus, recording and response analysis factors. An overview, updated or expanded where applicable, is presented here.

2.3.5.1 Stimulus Factors

As per the click ABR, changes in factors relating to the stimulus can result in changes in the response. A number of studies have been published which use various stimulus intensity levels to explore the latency-intensity function of the speech ABR (Hoorman et al. 1992; Krishnan 2002; Akhoun et al. 2008b; Archana et al. 2015; Ananthakrishnan et al. 2016). Systematic increases in peak latency and decreases in amplitude are observed for the click ABR, with decreasing intensity of stimulus presentation (Picton et al. 1981; Hall 2007). Whilst both the onset response and FFR also show latency shifts with changes in stimulus intensity, the latency-intensity function for the FFR is steeper than for the onset response. In the study by Krishnan (2002), it was found that at all intensities tested, the FFR spectrum for different vowels was dominated by the response peaks at F1 with smaller F2 harmonics. The amplitudes of the harmonics increased as intensity was increased, but not at the same rate. This amplitude gain is affected by sensorineural hearing loss (Archana et al. 2015; Ananthakrishnan et al. 2016). The current conclusion is that the onset response and FFR are differentially affected by changes in presentation level of the stimulus (Skoe and Kraus 2010a).

There have been many studies published which explore the effect of stimulus presentation rate on the click ABR. Testing with stimulus rates up to 20/s have little effect. Once past this, latencies increase and amplitudes decrease as presentation rate increases (for a review see Hall 2007). The onset response of the speech ABR shows an increase in latency with increasing rate, even at rates of less than 20/s. There is a selective effect of increasing rate on components of the FFR, with the

magnitude of the higher frequency components of the response decreasing but not the magnitude of the frequencies corresponding to F0 (Krizman et al. 2010; Al Osman et al. 2016). This may be affected by the aging process, with some changes in the representation of F0 with rate, when comparing older to younger adults (Neupane et al. 2014).

In the majority of studies, it is typically an envelope (E) FFR that is recorded (Aiken and Picton 2008). The reason for this is that using alternating responses is thought to eliminate the cochlear microphonic, reduce stimulus related artefact and enhance lower-frequency components that are phase-locked to the envelope. Using a fixed-phase stimulus is thought to result in responses phase-locked to the spectral components (Aiken and Picton 2008; Skoe and Kraus 2010). In relation to the speech ABR, researchers have investigated the representation of both E and TFS cues by the addition and subtraction of brainstem responses when presented in alternating polarities (Aiken and Picton 2008; Gockel et al. 2011; Anderson et al. 2013b; Ananthakrishnan et al. 2016). Questions have been raised about whether it is possible to separate these responses, what each of these components actually represent and their relative contributions to the FFR (Skoe and Kraus 2010a; Gockel et al. 2011; Plack et al. 2014; Bidelman 2016). There is a concern that a subtracted response may reflect stimulus artefact (Plack et al. 2014). It is agreed that the FFR reflects temporal information that could be used to estimate pitch, what is not clear is whether this is a reflection of the neural processes involved in pitch extraction or whether it only reflects the neural representation of sounds in the auditory periphery. What can be concluded is that information, which may be used by the brain to identify pitch, is present and detectable using the FFR. However, there is no evidence that pitch is extracted subcortically. The FFR cannot be used to make claims regarding pitch processing in the brainstem beyond what is already occurring in the auditory periphery and it probably does not provide a representation of any additional pitch processing at brainstem level (Gockel et al. 2011; Plack et al. 2014).

The click ABR is an onset response, which should not be affected by the duration of the click. If the ABR is not elicited by a click, then the rise time and duration will affect the onset response (Hood 1998). The FFR is influenced by the eliciting stimulus frequency and duration. There are many different stimuli of differing durations in use, for example the long (170 ms) and short (40 ms) /da/ (Song et al. 2011). Using short duration (<100 ms) stimuli minimizes recording time but a longer duration stimulus lends itself to being more natural. Onset measures are unlikely to

be influenced by cortical activity but according to recent research (Coffey et al. 2016), it is likely that responses to stimuli of longer duration (>80ms) may contain a cortical contribution. The authors do concede that more research is required to confirm these findings and clarify the respective roles of subcortical and cortical processing (ibid.). It is recommended that use of any 'new' stimulus requires robust piloting (Skoe and Kraus 2010a).

2.3.5.2 Recording Factors

Consideration must be given to the electrode montage to be employed and its effect on recording, as well as reducing unwanted sources of artefact. For both click and speech ABR recording it is typical to use a single differential electrode channel, with active (noninverting), reference (inverting), and ground electrodes. As previously discussed, the electrodes are usually placed on a mastoid or earlobe (reference), a frontocentral scalp location (active), such as high forehead and another cephalic location for ground (e.g. contralateral mastoid/earlobe) (Krishnan 2007; Aiken and Picton 2008; Skoe and Kraus 2010a; Bidelman 2015). This configuration is referred to as a vertical montage because it is aligned to the vertical dipole of the brainstem and it is likely that neural activity from rostral brainstem structures contribute to the response (Galbraith 1994). A horizontal montage would have right and left mastoids/earlobes as the reference and active electrodes; these are aligned to the horizontal dipole of the brainstem and will record neural activity from more peripheral areas of the auditory pathway, including the cochlea, auditory nerve and lower brainstem (Aiken and Picton 2008). Multichannel analysis by Bidelman (2015) suggests that the optimal montage for FFR recording would be to use a Fz or Fpz electrode with a non-cephalic site to minimize peripheral contributions to the response. It is thought that single-channel recordings, using the common methodologies are still an efficient way to record the FFR but may overestimate the amplitude of brainstem contributions (ibid.).

As previously discussed, care must be taken to minimise the presence of artefact in the response. Sources of artefact have been identified as power supplies, physiological activity, contribution from the cochlear microphonic and electromagnetic leakage from the transducers (Skoe and Kraus 2010a). There are steps that can be taken to minimise the possibility of response contamination with artefact. These include: making sure that electrode impedances are balanced and below 5 kΩ,

ensuring the electrode wires and transducers are not in contact by using insert earphones with tubing to separate the transducer from the electrodes, rejecting large amplitude responses that may represent physiological activity, averaging the signal over many trials and adding the responses to alternating polarity presentations (Akhoun et al. 2008b, Skoe and Kraus 2010a; Campbell et al. 2012; Plack et al. 2014). Some researchers have advocated the use of electromagnetic shielding of transducers and have employed purpose built faraday cages (Akhoun et al 2008b) or used expensive custom earphones (Campbell et al. 2012). Akhoun et al. (2008b) detected the presence of artefact using insert earphones in some recordings but this type of artefact in the response can be detected visually (Skoe et al. 2010a). One way to assess whether this may be a problem is to run a recording with the tube to the insert earphone clamped, in order to measure the artefact level (Plack et al. 2014).

2.3.5.3 Subject Factors

There are a number of subject factors that can influence the speech ABR. Historically, the click ABR has been described as becoming adult-like by about the age of two years (Johnson et al. 2010) and stabilising at around age 12 (Skoe et al. 2015; Sharma et al. 2016). Between the ages of 25 and 55, ABR wave latencies increase by 0.1 to 0.2ms (Jerger and Hall 1980). When compared to 21-30 year olds and click ABR wave V results do not become significantly different until people reach between 50 and 60 years of age (Skoe et al. 2015a). The complex ABR has been considered to be a potential tool in further exploring the effects of ageing. A number of studies have been published which have found that the complex ABR is less robust in older adults compared to younger adults (Clinard et al. 2010; Clinard and Tremblay 2013; Vander Werff and Burns 2011; Anderson et al. 2011; Skoe et al. 2015; Clinard and Cotter 2015; Sanju et al. 2017a). In relation to the speech ABR, differences have been found for the onset response, response-to response correlation and root-mean-square amplitude (Vander Werff and Burns 2011; Anderson et al. 2011; Clinard and Tremblay 2013; Skoe et al. 2015; Presacco et al. 2016; Schoof and Rosen 2016). Difficulties with speech processing that do not coincide with poor hearing thresholds, as is sometimes evidenced in older adults, have been linked to a loss of temporal precision of sound processing within the brainstem (Anderson et al. 2011; Anderson et al. 2013a; Sanju et al. 2017a).

The speech ABR is also thought to be stable in adults without hearing loss, up to the age band of 50 to 60 years (Skoe et al. 2015). In a study comparing young people (ages 15 to 25 years) to middle aged people (ages 40 to 60 years), it was found that wave V was later in middle aged people and encoding of F1 and F2 was less robust (Sanju et al. 2017a). The research group state that middle aged adults have poorer encoding of some aspects of speech compared to young adults. However, the lower age group includes people whose responses have not yet reached maturity, so this comparison of 'adults' is not valid (Krizman et al 2015b). Song et al. (2011) studied test–retest reliability over a period of 1 to 10 weeks for the 40 ms /da/ stimulus, in a group of adults aged 19 to 36 years and found no significant differences in the responses between the two test dates. There have also been longitudinal training studies performed with adults, looking at whether auditory training has an effect on the speech ABR. As part of these studies the speech ABR has been recorded between 1 week and 6 months post initial assessment (e.g. Song et al. 2012; Anderson et al. 2013c; Skoe et al. 2014). The results of these studies do not show any significant differences in the speech ABR response for the control group, if no intervention or pathological change has occurred in the time period studied.

The impact of conductive and sensorineural hearing loss (SNHL) on the click ABR has been discussed previously (2.2.3). The speech ABR, like the click ABR, is thought to be stable in adults without hearing loss up until age 50 years (Skoe et al. 2015). The effect of SNHL on the speech ABR is reported to be an increase in latency of the onset response but no effect on the latencies or amplitudes of waves comprising the FFR (Nada et al. 2016). However, there is an apparent change in the balance of envelope and temporal fine structure (TFS) features, with a potentially greater degradation of the neural representation of TFS in the FFR (Vander Werff and Burns 2011; Anderson et al. 2013b; Ananthakrishnan et al. 2016).

There is a wealth of literature that underpins the finding that sex differences exist in the click ABR, with females having earlier wave latencies than males (e.g. Jerger and Hall 1980; Jerger and Johnson 1988; Durrant et al. 1990; Watson 1996). Differences between the onset and FFR responses have been found for males and females, with the onset response being larger and faster for females than males but the FFR being the same for both (Hoorman et al. 1992; Krizman et al. 2012a; Ahadi et al. 2014a; Liu et al. 2017). It is therefore, important to have sex specific normative data available when using this tool in a clinical setting (Ahadi et al. 2014a).

There is little evidence to show any clinically significant differences in the right and left ear responses to the click ABR. It would appear that there is little evidence to suggest a right ear listening advantage (REA) for click stimuli at the level of the brainstem (Vander Werff and Burns 2011). At the level of the cortex, more complex stimuli appear to be processed preferentially by either auditory cortex (AC), depending on the element being evaluated. Fast temporal modulations appear to be largely processed in the left AC with fine grained frequency analysis tending to engage the right AC more strongly (Zatorre and Belin 2001; Schönwiesner et al. 2005; Schönwiesner et al. 2007; McGettigan and Scott 2012).

For many people there is a known REA when listening to competing speech signals, played to each ear simultaneously (Schmithorst et al. 2013). Schwartz and Tallal (1980) presented two sets of stop consonants randomly to each ear. One set had typical 40-msec formant transitions, whilst the other had extended 80 ms formant transitions. For the 40 ms set, the REA was found but for the 80 ms set the magnitude of this effect decreased. The conclusion was that the right ear advantage can be observed for signals which require processing of rapid acoustic changes (ibid; Hornickel et al. 2009).

In relation to the FFR component, there has been some debate in the literature about asymmetry of these responses. In a study of eight women, 500Hz tone bursts were used to elicit a FFR at different sensation levels and participants were found to have asymmetric FFRs at each level. However, the response with the greatest magnitude did not consistently come from either ear and this was seen as providing evidence that cortical processing asymmetries were related to asymmetric processing within the brain stem (Ballachanda et al. 1994). A more recent study with 12 adults (nine females) found that FFR peak latencies, elicited by a 40 ms /da/, were earlier for right ear presentation, although inter-peak latencies were the same. In terms of frequency encoding, the response relating to coding of the first formant of the syllable was more robust for the right ear. The conclusion drawn was that the right ear advantage extends to the brainstem, specifically when speech stimuli are employed (Hornickel et al. 2009). One study has replicated these findings (Sinha et al. 2010a) but they have not been replicated in further studies. More recent research has not demonstrated any ear differences when using the same 40 ms /da/ stimulus (Vander Werff and Burns 2011; Ahadi et al. 2014b; Sanju et al. 2017b).

The stimulus can also be presented to both ears at the same time, which results in it being perceived to be louder. The speech ABR recorded to binaural

stimulation provides a more robust response (Skoe and Kraus 2010a). The binaural interaction component of the speech ABR can be recorded but whilst it appears to be present in the onset response, there is more variability within the frequency following portion of the response (Uppunda et al. 2015).

Tests of auditory processing or speech perception usually require a subjective response from the listener to indicate what they have or have not heard. There is known interaction between language processing, in terms of pragmatics, semantics, syntax, phonetics, phonology and prosody and other non-auditory attributes (e.g. cognitive skills) required for language perception (Friederici 2011). As previously discussed, it is possible that some tests thought to be assessing auditory processing may equally be assessing cognitive skills (Pichora-Fuller 2003; Humes 2005). An objective measure of speech processing, that is not influenced by the cognitive abilities of the listener, would be of benefit. The speech ABR has been described as being of use in assessing the processing of complex auditory stimuli at a subcortical level, which would therefore not be affected by attentional state (Bidelman 2015). Functional MRI studies have demonstrated that inferior colliculus (IC) activity is modulated by selective attention to auditory stimuli (Rinne et al. 2008) and the IC is thought to be a contributor to both the onset response of the speech ABR and the FFR. Marsh and Campbell (2016) propose a 'New Early Filter Model' in which they suggest that "corticofugal modulation of corticopetal-corticofugal loops leads to an attentional selection crucially affecting the level of the rostral brainstem" (Marsh and Campbell 2016, p.136).

Differences in the FFR have been demonstrated when employing comparisons of attending or not attending to sound, or attending to one auditory stream in the presence of another (Galbraith and Arroyo 1993; Galbraith and Kane 1993; Galbraith and Doan 1995; Galbraith et al. 1998, 2003; Hoormann et al. 2004). Researchers investigating a specific component of the FFR, the previously mentioned E FFR, have challenged the interpretation of these findings. Researchers looked at the strength of E FFR phase locking when participants were asked to listen to spoken digits presented monaurally, then to selectively listen when competing digits were presented to the other ear and finally to ignore the auditory stimuli and perform an analogous visual task. Attention related changes in alpha activity were found via cortical EEG recording; however, no differences were seen in the E FFRs. The researchers concluded that effects of attentional state could not be demonstrated using E FFRs (Varghese et al. 2015). Whilst selective attention effects have been

reported for E FFRs, there were individual differences in these effects, either in a positive or negative direction (Lehmann and Schönwiesner 2014). These contradictory findings and questions about the analysis of results in the previous studies, specifically those by Galbraith and Arroyo (1993) and Galbraith and Doan (1995), have called into question the FFR's sensitivity to attention (Varghese et al. 2015). It is also argued that experiencing different emotions during testing leaves the speech ABR largely unaltered (Wang et al. 2010).

Whilst the click ABR is an exogenous response, characterised by the stimulus and recording parameters, the speech ABR could contain both an exogenous and endogenous response, as it may be modified by internal cognitive processes (Hood 1998). In an attempt to control for attention during testing and reduce physiological contaminants, it is usual practice for research participants to watch a movie or read a book. If watching a movie, the soundtrack is played at <40 dB SPL, so as not to mask the presentation of the stimulus of interest, or subtitles are used (Skoe and Kraus 2010a).

One of the purported benefits of the speech ABR is the ability to detect differences in populations that cannot be detected using the click ABR (Song et al. 2008; Billet and Bellis 2011) and in the majority of studies looking at the speech ABR, the criteria for exclusion is an abnormal click evoked wave V. The speech ABR is reportedly shaped by auditory experience and is coupled to cognitive functions involving language and music (for a review see Skoe and Kraus 2010a). It is claimed that musicians and bilingual people have better auditory processing abilities. The changes seen are reported to be in the form of more robust encoding of F0 for bilinguals and speakers of tonal languages and selectively enhanced encoding of harmonics for musicians (Bidelman et al. 2011; Krizman et al. 2012b; Strait and Kraus 2014; Weiss and Bidelman 2015). Poor socioeconomic status and poor literacy skills have also been linked to deficits in the speech ABR, such as degraded encoding of TFS but not of F0, poorer phase distinction for different stop consonants and poorer response consistency (Hornickel et al. 2012c; White-Schwoch and Kraus 2013; Kraus et al. 2014; Skoe et al. 2017). This apparent experience dependent plasticity (Krishnan et al. 2012) could be a confounding factor when attempting to use the speech ABR as a clinical tool. However, one of the criticisms of the studies that musical training can improve neural encoding is that there is a lack of information about any improvement in speech perception or literacy. Evans et al. (2014) provide a critique of a number of studies on the basis of the wide array of outcome measures

used in interpreting the complex ABR waveforms and the lack of supporting evidence of behavioural improvement. They also express concerns regarding group sizes and lack of control groups.

One of the areas that has been proposed as requiring assessment in relation to speech perception skills, is working memory capacity (WMC). It is particularly useful to use tests that involve retaining a memory load whilst concurrently requiring mental processing, as these are more affected by cognitive decline. It has been proposed that tests such as backward digit span or letter number sequencing should form part of a speech perception assessment battery (Bopp and Verhaeghen 2005; Vaughan 2008; Marsh and Campbell 2016). Kraus and Anderson (2013) also argue that cognitive screening should be a component of the audiology test battery. There is now a feeling that perhaps the terminology that has been employed in relation to the speech ABR, including various derivations of 'the auditory brainstem response to complex sounds (cABR)', should be revisited as "this terminology undermines the integrated and experience-dependent nature of the activity it indexes" (Kraus and White Schwoch 2015, p.644-645).

2.3.6 Repeatability of the Speech ABR

There have been questions raised about the repeatability of the speech ABR. In a study of test-retest reliability, the speech ABR in children aged eight to thirteen was performed twice, with a year between each assessment (Hornickel et al. 2012a). The conclusions of this study were that the response timing and spectral encoding were highly replicable over the period of one year. However, their results were questioned as 92% of the reported correlations failed to reach a level (0.70) considered to be acceptable by clinical standards and the methods for deriving the results were considering sub-optimal (McFarland and Cacace 2012). The authors of the original study replied, arguing that a correlation coefficient of 0.60 was suitable for group analysis, and that 0.70 would be necessary for clinical diagnosis. They suggested that a smaller subset of measures which reached 0.70 be used when considering clinical diagnosis. It was also argued that the developmental age of the children and the long test-retest interval were factors, which may have resulted in reduced test-retest reliability (Hornickel et al. 2012b).

The repeatability of the speech ABR to the standard /da/ in adults appears to be confirmed by the test-retest reliability data presented by Song et al (2011). This

study looked at speech ABR results in forty-five adults age 19-36, tested at two different times (41 ± 34 days) and found no significant differences in the response between the data from the two tests. There are no further studies of this type in adults, therefore the assertion of test-retest reliability is based on a single study.

This completes the exploration of the different stimulus, recording and participant factors that have the potential to affect the speech ABR waveform. A critical review of the literature that has been published using the BioMARK stimulus in adults is presented in the following section.

2.3.7 A Review of Studies using the 40 ms /da/ Stimulus

The use of more complex stimuli to elicit the onset and frequency following responses is still in its infancy and the majority of recent research in this area has been conducted by a limited number of research groups. Both between and within these groups, researchers have taken different approaches to collecting and analysing the data (Skoe and Kraus 2010a). A recent review of the literature on speech-evoked auditory brainstem responses has been published (Sanfins and Colella-Santos 2016). This particular review was carried out to find articles published between 2005 and 2015, relating to the following search terms: speech ABR, ABR-speech, speech auditory brainstem response, auditory evoked potential to speech, speech-evoked brainstem response, complex sounds, and cABR. Articles were excluded if they were reviews or case studies, were not published in English, or if the subjects were animals and 21 articles were selected for review. As a result of the review they concluded that the speech ABR is “objective, fast, and can be applied from early childhood. It is equally effective in different languages, and can provide differential diagnoses of diseases with similar symptoms” (ibid. p.7).

However, there are many more articles featuring speech ABR than were identified for the review by Sanfins and Colella-Santos (2016). This is probably because of the differences in terminology used by research teams. The purpose of the following review is to explore studies that have all used a version of the 40ms /da/ stimulus (marketed to clinicians as ‘BioMARK’). Due to the apparent delay in maturation of the response, the review will include studies that have included participants that are 16 years of age or older (Krizman et al. 2015b). By looking at original research studies which have broadly utilised the same stimulus, and often the same analysis techniques, comparisons can be made and conclusions drawn. As it is

known that this stimulus was developed by researchers at the Auditory Neuroscience Laboratory of Northwestern University, it seemed appropriate to work through their publication list (www.brainvolts.northwestern.edu/publications.php). The first use of a precursor to the 40 ms /da/ stimulus was by Cunningham et al. (2001), therefore the search timeline was limited to 2000 to 2017. Fifteen studies were identified from this publication list that used the 40 ms /da/ to evoke the speech ABR in adults. A search for 'speech ABR' was then performed in Pubmed, limiting the results to publications since 2000, in humans and published in English. 208 results were returned, a review of the abstracts found 23 articles were related to the speech ABR. Of these, seven concerned adults and were not from the Auditory Neuroscience Laboratory of Northwestern University research group. A further search using the search term '40 ms da' and the same filter settings, returned 154 results, of which only a further 3 were relevant and not already identified. Similar searches were performed in Google Scholar and by reviewing the citations and reference lists of the already identified articles, this increased the total number of articles found from 26 to 44 (70% increase). The final number of original articles that have used the 40 ms /da/ (or a 40 ms version of it) for speech ABR testing in adults totals 44 (see Appendix 1).

What is clear from this group of publications is that the research comes from a small pool of research groups. Of the 44 papers identified, sixteen originate from researchers who are currently or have previously worked at Northwestern University. Fifteen originate from researchers working in, or conjunction with the All India Institute of Speech and Hearing. Five originate from researchers working within Iran or Tehran Universities of Medical Sciences and the rest come from groups associated with Manipal University India, the University of California, Davis, the University of Ottawa, the University of Sao Paulo, Syracuse University, the Universiti Sains Malaysia and Capital Medical University, Beijing. What is less clear is how much data is presented that represents data from the same participants but is being used to answer different questions. For example, the data presented by Skoe et al. (2015a) includes data from the previously published studies and these are listed. However, it is not always possible to tell this from other studies. It is possible that the individual numbers of participants that contribute to this larger pool of data, is less than it might first appear.

The 44 studies can be broadly subdivided into three themes including research about the relationship to peripheral processes, research regarding the exploration of the recording technique and collection of normative data and finally research that explores the speech ABR in different groups of people. The following discussion

provides a critical review of the research by the identified themes. Where papers have already been used to contribute to the discussions above, they will only be briefly covered in this section.

2.3.7.1 The Speech ABR and its Relationship with Peripheral Processes

Dhar et al. (2009) and Rana and Barman (2011) looked at the relationship between different types of otoacoustic emissions (OAEs) and the speech ABR. For the study using Distortion Product OAEs (DPOAEs), it was found that aspects of the FFR including composite measures of harmonics (F1 and HF), spectrotemporal measures (latencies of D, E and F), and Envelope Boundary (latency of C to O), were related to cochlear function, as measured by DPOAEs. There was a negative relationship between envelope boundary and DPOAE structure (Dhar et al. 2009). However, this relies on the inclusion of peak C in the results. This peak is often excluded from analyses for being unreliable in terms of identification and is not reported in later studies (Hornickel et al. 2009; Skoe and Kraus 2013; Skoe et al. 2015a; Zakaria et al. 2016). There is some unusual normative data presented by Rana and Barman (2011, see Table II p. 914) who report extremely wide latency ranges for nearly all peaks. This is highly unusual in ABR testing and calls the data presented into question. The conclusion drawn from both studies is that the use of OAE testing might help to distinguish between peripheral and central auditory nervous system dysfunction.

2.3.7.2 Exploration of the Recording Technique, Analysis and Acquisition of Normative data

Campbell et al. (2012) have investigated recording an artefact free response, ensuring that the response is genuine and not contaminated by leakage from the transducer. The conclusions drawn were that one or more techniques should be used, which may include counter-phasing, shielding, and referencing. Whilst the stimulus used in this study is described as a 40 ms /da/ stimulus, there is no further information presented about the stimulus characteristics.

In an attempt to tease out the roles of high frequency harmonics and the stimulus envelope in encoding of speech ABRs, Gnanateja and Ranjan (2012) made changes to the standard /da/ stimulus. In one assessment they used high pass filtering

with a cut-off frequency of 1700 Hz, to correspond to the second formant frequency of the signal. They then compared the responses to the standard /da/ with the filtered /da/ and found no significant differences in the representation of F0, F1, and F2 when looking at respective amplitudes. In the second assessment they used a Hilbert transform to produce a stimulus only containing the fine structure of the vowel, with the new stimulus being the same as the standard stimulus, up until the vowel onset portion. They then ran a comparison between the responses to the standard /da/ and to the transformed stimulus and found significant differences in the representation of F0, F1, and F2 when looking at respective amplitudes. However, the differences for F1 and F2 may not have remained significant, had a correction been made for multiple comparisons. The researchers concluded that the FFR is coded primarily by the stimulus envelope. In a second study, Gnanateja et al. (2013) attempted to address the influence of spectral similarity and context on the encoding of FFRs. They used three stimuli presented in different paradigms, a same-spectral-structure (SSS) paradigm and a different-spectral-structure (DSS) paradigm. In the SSS paradigm, the same stimulus was presented repetitively, being either the standard /da/ or the filtered /da/ from the previous study. In the DSS paradigm the filtered /da/ was presented alongside the standard /da/ at a ratio of 1:3. FFR's evoked by the DSS paradigm differed to those evoked by the SSS paradigm, which suggests that different auditory neural mechanisms were involved. As the only difference in the stimulus was spectral structure, the authors conclude that this is a parameter cueing the context dependent, sub-cortical encoding of speech.

There have previously been attempts to model the ABR to transient stimuli in an attempt to understand the neural processes in the auditory pathway (Rønne et al. 2012. Jafarpisheh et al. (2014) present a dynamic model of the speech ABR which uses fuzzy logic in representing nonlinear mapping that occurs between the stimulus and the response. This model only applies to use of the standard /da/ in 'normal' participants and does not have the rules in place to account for the role of experience. The authors acknowledge that this type of modelling approach is not commonly used in clinical diagnosis but that this may change in the future.

Normative data for the speech ABR to /da/ is presented by Skoe et al. (2015a). The purpose of the study was to examine stability and plasticity of auditory brainstem function across the lifespan, although the oldest individual in the study is 72 years old. The data is grouped by decade but it is not possible to tell from the data presented where the cut off points are, for example there is a group of 30-40 year olds and a

group of 40-50 year olds. There would appear to be an overlap for the data for 40 year olds. Also, in the group of 30-40 year olds, 78% of the 32 participants were women and as it is known that men and women have different responses, these figures must be used with caution. In contrast, it would appear that there is poorer speech encoding for some aspects of speech in middle aged listeners (40-60 years old) than in young listeners (15-25 years old) (Sanju et al. 2017a). When comparing the results from the two groups it was determined that wave V latency was longer and there was less robust encoding of F1 and F2 for the middle aged listeners. However, it has already been shown by Krizman et al. (2015) that there is a decrease in the spectral representation of the evoking syllable between adolescence and adulthood. It is therefore not a surprising result when comparing a group containing adolescents to a group of middle-aged people.

The repeatability of the speech ABR to the standard /da/ in adults is confirmed by the test-retest reliability data presented by Song et al (2011). This study examined speech ABR results in adults aged 19-36 years, tested at two different times. No significant differences were found between the speech ABR responses recorded at the two time points.

A number of studies have looked at using the /da/ stimulus with adults whose native language is not American English. They have either used the standard BioMARK /da/ (Karawani and Banai 2010; Sinha and Basavaraj 2010a), or they have created an alternative /da/ in line with the standard stimulus but using characteristics of the native language (Rocha et al. 2010; Ansari and Rangasayee 2015a, Ansari and Rangasayee 2015b, Ansari and Rangasayee 2016). No significant differences in speakers of non-tonal languages have been found when using the standard /da/ (Karawani and Banai 2010; Ansari and Rangasayee 2015b). For some of the papers, only data relating to the onset of the speech ABR is used (Rocha et al. 2010; Ansari and Rangasayee 2016), or an incomplete set of wave data is presented (Sinha and Basavaraj 2010a) which does not allow for comprehensive comparison.

Expanding on these studies, one study has looked at the speech ABR in relation to ethnicity. In many countries, populations comprise people of different races, irrespective of whether they share the same language. In most clinical settings the assessments used must be suitable for use with the majority of the population. In a country like Malaysia, the two main ethnic groups are Malay and Chinese and whilst no differences were found between their speech ABRs, the results were different to that for Caucasian males (Zakaria et al. 2016). What is not fully explained within this

paper is that the Malay males and Chinese males may or may not differ in their use of language. The Malay language is non tonal whereas Chinese languages, such as Mandarin, are. The discussion about language use and its relevance to previous published work on the FFR is covered briefly, yet would seem to be of critical importance in interpreting the data and its implications.

2.3.7.3 Effects of Stimulus Factors

The effect of rate of presentation on the response evoked by a standard /da/ has been investigated (Krizman et al. 2010; Neupane et al. 2014). When considering the ABR, the slower a stimulus is presented, the longer the recording time but the better the wave morphology (Hood 1998). The standard recording rate for the speech ABR to /da/ is 11 Hz (either 10.9 or 11.1 Hz) and when the participant is quiet and the artefact rejection rate is low, it will take around nine minutes to record 6000 trials. In relation to clinical utility, the test needs to be conducted in a reasonable time period for expecting a patient to sit still but also provide the level of detail required for analysis. There are differential effects seen in the speech ABR response when moving between presentation rates of 6.9, 10.9 and 15.4 Hz. There is increased latency of the onset as presentation rate increases, as well as a decrease in the response magnitude of the higher frequencies but not those corresponding to F0 (Krizman et al. 2010). It would appear that the standard rate does provide the morphology required to assess the response but presentation rate can be slowed if further investigation is required. Compared to recording the click ABR, there is an issue with making these types of changes within a recording session. It is possible to visually analyse a click ABR response and understand whether a change in presentation rate might be helpful. However, some analysis of the speech ABR waveform is performed offline, using an open source Matlab toolbox that is provided by the research team at Northwestern University (Skoe and Kraus 2010a). Until the waveform has been labelled, converted to an ASCII (American Standard Code for Information Interchange) file (Rana and Barman 2011) and then imported into the toolbox for analyses, it is not possible to fully appreciate what the response looks like and it would not be practical within a clinical session to keep stopping testing, to perform analyses.

The only study looking specifically at the effect of polarity found that the amplitude of the first formant and high frequency components was reduced in the alternating polarity condition. An interesting finding of this study was poor detection of

peak O, the offset peak (Kumar et al. 2013). The offset peak was mentioned but findings not reported by Sinha and Basavaraj (2010) and was only identified in 10% of participants with hearing impairment compared to 94% of normal hearing participants (Ansari et al. 2016). It is uncommon that researchers report difficulties with identification of wave O when using the standard /da/. The authors attribute this to using a different electrode montage, as they used the vertex for non-inverting electrode, the lower forehead for the inverting electrode and the nasion for the ground electrode (Kumar et al. 2013). As the authors did not find significant differences between the responses elicited by rarefaction or condensation polarities, they conclude that the speech ABR can be recorded using a single polarity. However, no mention is made of the fact that researchers typically use alternating polarity to aid in elimination of stimulus artefact.

2.3.7.4 Effects of Subject Factors

There is interest in what the speech ABR can tell us about the aging process. Vander Werff and Burns (2011) looked at the response to the standard /da/ in adults aged 61 to 78 years versus adults aged 20 to 26 years. They found that the older adults had significantly smaller onset and delayed offset responses for the speech ABR. Although there were also differences in the FFR, these were accounted for by the disparity in hearing thresholds. Anderson et al. (2013b) compared two groups of older (aged ~60-71 years) participants, with 'normal hearing' and hearing loss. They tried to control for the effect of hearing loss by using both the standard /da/ and an amplified /da/. They also looked at the effect of noise on the speech ABR response. They found that compared to the normal hearing group, there was an imbalance between the E and TFS representation in older adults with hearing loss, with the E FFR being enhanced. Questions have been raised about the validity of this approach and whether it is actually possible to separate the waveform into envelope and temporal fine structure components in this way (Plack et al. 2014).

In relation to the effects of hearing loss on the speech ABR, Ansari and Rangasayee (2016) looked at the onset measures and found that they were significantly different for people with SNHL. Archana et al. (2015) also looked at the onset responses and the latency intensity function in people with SNHL and concluded that the speech ABR could be used to look at the abnormal loudness growth (recruitment) experienced by some people with hearing loss. It is not known

why neither study reported the FFR measures. However, if the speech ABR is to be used clinically, a hearing assessment must be performed to determine auditory function, otherwise the results cannot be reliably analysed.

Four papers have been published which explore the responses to the standard /da/, for men and women (Krizman et al. 2012a; Ahadi et al. 2014a; Jalaei et al. 2017; Liu et al 2017). Differences were found between the waveforms in all studies, with women having earlier and larger onset responses, as well as more robust and better representation of fundamental and first formant frequency information. In the study by Jalaei et al. (2017) head size was also measured. They found differences in the transient but not the sustained features of the speech ABR and these differences were only slightly affected when head size was controlled for. These sex differences are an important finding, as it suggests that there should be different normative data used for men and women. It would also mean that if researchers are comparing groups, then it is important to consider the sex distribution within these groups. If the groups were not balanced, then significant differences found could occur as a result of sex differences.

As previously discussed, there are conflicting reports about whether there is subcortical laterality in brainstem responses. There have been five papers published using the standard /da/ which explore this issue (Hornickel et al. 2009; Sinha and Basavaraj 2010a; Vander Werff and Burns 2011; Ahadi et al. 2014b; Sanju et al. 2017b). Hornickel et al. (2009) concluded that responses to right ear presentation occurred earlier than those for left in the FFR and that there was more robust frequency encoding of F0 when stimuli were presented to the right ear. However, it is unlikely that these results would remain statistically significant if corrections for multiple comparisons were applied. These results were confirmed by Sinha and Basavaraj (2010), however full statistical analyses are not reported. More recent studies have not found significant differences between the responses for the right and left ears (Vander Werff and Burns 2011; Ahadi et al. 2014a; Sanju et al. 2017b). This remains a question that requires clarification.

In many studies of the speech ABR, the participant groups are restricted to those who are right handed (Dhar et al. 2009; Hornickel et al. 2009; Sinha and Basavaraj 2010a; Ahadi et al. 2014a; Ahadi et al. 2014b; Jafari and Malayeri 2014; Jafarpisheh et al. 2014; Tahaei et al. 2014; Ansari and Rangasayee 2015a; Ansari and Rangasayee 2015b; Zakaria et al. 2016; Sanju et al. 2017b). This is because of the relationship between handedness and cerebral hemisphere dominance for

speech processing. Around 90% of people are right handed and the majority of these (>90%) will have left hemisphere dominance for speech processing (Strauss and Wada 1983; Morgan and McManus 1988; Oliveira et al. 2017). At least 70% of left-handed people also have left hemisphere dominance for speech processing (Corballis 2014). In relation to the speech ABR, if there is lateral asymmetry then different normative data might be required for each ear and knowing about individual hemisphere dominance for language processing will be required. To assess this, researchers have been using strategies such as dichotic listening tests, which involve presenting two different stimuli, to each ear at the same time (Musiek 1983), or more recently using fMRI techniques (Hugdahl 2011).

Skoe and Kraus (2010a) suggest that the use of binaural stimulation to elicit the speech ABR results in a response with larger amplitudes. They advocate the use of binaural presentation of stimuli, to reflect what happens in real world listening. The finding that binaural presentation results in a larger amplitude of speech ABR response has been confirmed by Ahadi et al. (2014a). Therefore, it depends on the question being asked, as to whether the stimulus is presented monaurally or binaurally. If there are specific questions about the auditory pathways then individual responses from each ear will be required, however if researchers are looking more generally at speech perception then binaural stimulation may be the preferred option.

2.3.7.5 Exploration of the Speech ABR in Different Groups of Adults

Differences in the speech ABR between men and women and older and younger adults have already been explored in the previous section. Researchers have also used the standard /da/ to explore groups of people with better or worse than normal auditory perception abilities. Musicians have been widely studied, including studies performed with the standard /da/ (Strait et al. 2009; Parbery-Clark et al. 2013; Skoe and Kraus 2013; Kumar et al. 2017). Experienced musicians are likely to have earlier latencies of the onset response and higher amplitudes of encoding of F0 than non-musicians (Kumar et al. 2017). It may not be that these responses from musicians fall out with normative data limits, for example in the study by Strait et al. (2009), a normal response to the standard /da/ was a requirement for participant inclusion, even though the participants were musicians. Therefore, knowing whether a patient has musical experience equivalent to over 3 years of training during their lifetime (Parbery-Clark et al. 2013), might be helpful in interpretation of results.

In contrast, a study has also been undertaken exploring the speech ABR in people who are amusic and comparing the response to people without musical experience (Lehmann et al. 2015). The researchers employed the addition and subtraction method of producing an E FFR and a TFS FFR and concluded that onset responses were slower and that fine-grained processing differed from the normal range in people with congenital amusia. The increase in latency was related to increasing severity of amusia. An interesting aspect of this study is that although the standard 40 ms /da/ was used and the research group included members of the Auditory Neuroscience Laboratory, Northwestern University, standard wave nomenclature was not used. Instead of troughs being labelled A through to O, the most prominent peaks were labelled one through seven. It is therefore, not possible to make a direct comparison with results of other studies.

Difficulties processing speech in noisy conditions that exceed what is expected from pure tone threshold levels are not uncommon, especially as people age. Separating out the contributions from ageing, hearing loss, central auditory processing and cognitive ability is not straightforward (Goossens et al. 2017). The speech ABR has been used to investigate this, as it was believed that it could offer a way of separating out the auditory processing element. In a case study of two older adults, Anderson and Kraus (2010) found that speech ABR from the person with good speech in noise (SIN) perception abilities had earlier peak latencies and more robust F0 representation. In a further study Anderson et al (2013) looked at the onset latency, the VA slope, offset latency, and response morphology (cross-correlation of the stimulus and response waveforms) for middle aged and older adults and found that the speech ABR predicted more of the variance in self-reported SIN difficulties than either a test of SIN (QuickSIN) or a person's pure tone hearing thresholds. Similarly, Lagacé et al. (2016), explored whether there was a link between speech ABR in noise results and the Words in Noise (WIN) test. The onset responses were compared to results from the WIN test presented at three different signal to noise levels. Although there was an increase in the latency and a decrease in the amplitude of the onset response when presented in noise, there was no apparent link between the WIN scores and the onset speech ABR results.

Whilst people vary in their abilities to process speech in noise, they also vary in their acceptable noise levels, which are the levels of noise that they are prepared to tolerate when listening to speech (Koch et al. 2016). It has been proposed that this may be as a result of differences in afferent and efferent processing (Rishiq et al.

2012). Shetty et al. (2014) found that there was a higher VA amplitude in a group of people with higher ANL scores than for those with low ANL scores but no analysis of the FFR was performed.

There are very few studies performed with adults from 'clinical' populations. Skoe et al (2017) performed a study looking at a link between reading ability and ABR waveforms in adults with diverse but unimpaired reading levels. They found that reading ability was linked to wave V latency for both the click and speech ABR. However, it would seem that these latencies were within the normative range. Jafari and Malayeri (2014) carried out a study comparing the speech ABR from people who were congenitally blind with normal sighted people. They found that the blind participants had earlier and larger responses to the /da/ syllable for both the onset and FFR components of the speech ABR. They attributed this finding to a compensatory mechanism by which the blind participants had enhanced neural representation and neural synchronisation of speech stimuli. Tahaei et al. (2014) compared the speech ABR in people with persistent developmental stuttering (PDS) with a control group. They found that people with PDS had longer latencies for the onset and offset peaks but no differences in the sustained measures compared to the control group. Mishra et al. (2015) compared the speech ABR in people with normal hearing but absent acoustic reflexes with a control group and found no differences in the response, either for the onset or sustained components.

A study comparing the speech ABR in healthy, middle aged adults and those with a diagnosis of diabetes mellitus type II was performed by Sanju et al. (2017b). They found a significant delay in latencies of waves V, A, D, E, F and O, although no information was provided about the sex of the participants. They did not analyse any further attributes of the speech ABR. They concluded that these delays could not be attributed to the aging process, as the waveforms of the clinical group differed from the age matched control group. They state that "click-evoked ABR latency analysis was done to check the baseline neural response and the absolute and inter-peak latencies were cross-checked against adult normative values" (p. 79). However, they do not provide anything other than a single sample click ABR waveform in the results section. They go on to state that "as the findings correlated with existing click-evoked ABR findings in diabetic individuals, the utility of S-ABR as a tool in this clinical population has been established" (p. 81). The authors did not provide this evidence from their own study, as they did not provide any results or analysis of the click-ABR for their participants. Instead, they used findings from existing literature to support this

claim. If there was a correlation of click ABR and speech ABR findings, it should have been reported in the results section. The lack of this data and the reference to previous literature does not support their statement that the utility of this speech ABR in this population has been established. Therefore, it can be concluded that at the present time, there are no examples of aspects of the commercially available speech ABR being used as an established 'biomarker' in adult clinical populations.

2.3.8 Relevance of the Findings to the Current Study

From the above review of the literature, it would appear that if using the speech ABR as a clinical tool, there are some points to consider. There is no current evidence to suggest that the standard recording or analysis techniques need to be altered, when used with people with normal pure tone hearing thresholds (Skoe and Kraus 2010a). In relation to reliability and waveform marking, there needs to be evidence that inter-rater agreement is at an acceptable level for this to be a useful tool. There perhaps also needs to be further evidence of the repeatability of the speech ABR in adults over time. There is one study that appears to suggest that young and middle-aged adults have some differences in speech encoding (Sanju et al. 2017a) and a larger study that does not show this result (Skoe et al. 2015a). Clinicians will need to know exactly what normative data is needed, as it would appear that separate normative data is required for men and women but this may need to be further broken down by ear of stimulus presentation. There are further considerations in relation to the patients themselves, as it is thought that the speech ABR reflects aspects of cognitive communication abilities, hearing thresholds, auditory experience and auditory processing (Tzounopoulos and Kraus 2009; Skoe and Kraus 2010b; Kraus and Nicol 2014; Tarasenko et al. 2014; Krizman et al. 2015a). When exploring the speech ABR in healthy adults, these aspects need to be taken into account. Patients would need to undergo a hearing assessment, including a speech-in-noise test, as hearing impairment and auditory processing deficits are likely to have an impact on the speech ABR. It is also likely that people with specific language impairments will have abnormal speech ABR's, so participants need to be asked about this before their speech ABR can be interpreted, or included in a normative data set. There should be a way of identifying whether any abnormalities in the speech ABR can be related to peripheral dysfunction and this can be potentially answered by the inclusion of OAE testing. Until the question about potential lateral asymmetry is conclusively answered,

it would appear that clinicians will need to record handedness and perform a dichotic listening test to assess hemispheric dominance for speech processing. When taking the patient history, it would also seem appropriate to ask about language use (bilingualism, tonal language) and musicianship. Aspects of cognitive function also need to be considered, such as processing speed and working memory. When considering how to analyse the speech ABR, the evidence suggests that it is not currently advisable to split the response into an E FFR and a TFS FFR (Gockel et al. 2011). In both Experiments One and Two, responses to opposite-polarity stimuli will be added as this approach minimises stimulus artefacts (Aiken and Picton 2008; Skoe and Kraus 2010a). Taking this approach eliminates the ability to discuss the contributions of envelope or temporal fine structure information to the FFR.

2.4 The Click and Speech ABR in Adults with Alcohol Dependence Syndrome

In this section of the literature review, the utility of both the click and speech ABR in a clinical population will be investigated. People who have received a diagnosis of Alcohol Dependence Syndrome (ADS) have not only been exposed to a neurotoxin (Scheepers 1997) but may also experience abnormal sound processing (Monnot et al. 2001; Uekermann et al. 2005; Uekermann and Daum 2008). The reasons for choosing to study this particular clinical population are explored more fully in the sections below. Firstly, the place of alcohol in society in general is discussed, and this is followed by an exploration of the current situation in Scotland, specifically in relation to harmful drinking. The effects of harmful drinking on the brain and difficulties with diagnosis are then considered. This is followed by a review of the literature in relation to what is already known about the ABR in this population and why using speech to elicit the ABR may be appropriate. Finally, the aims of Experiments One and Two are presented.

2.4.1 Alcohol in Society

> "Alcohol is both a tonic and a poison. It all depends upon the dose"
> (Pinder 2008 p.S31)

Humans have been consuming alcoholic beverages for at least 10,000 years (Room et al. 2005; McGovern 2009; Hanson 2013). Alcohol has been used medicinally, in religious practices and recreationally (Crocq 2007). It is still a drug of everyday use because it is generally socially acceptable, available and legal (Hicks and Zucker 2014). Whether someone drinks alcohol or not, is determined by their individual socio-cultural situation and there can be differences in drinking behaviours between different cultural groups (Bhaskar and Kumar 2014). Alcohol has the ability to alter a person's consciousness, mood or thinking processes. With over 2 billion users globally, it is one of the world's most commonly used psychoactive drugs, alongside caffeine and tobacco (WHO 2014). The mortality rate attributable to this is approximately 3.3 million people every year (ibid.). Whilst there are consequences of drinking at harmful levels, there can also be benefits to both the economy and the individual.

2.4.1.1 The Pros and Cons of Alcohol Consumption

In the UK, the alcohol industry is worth £45 billion to the economy and provides in the region of 600,000 jobs (Cameron and Truss 2016). People describe the benefits of drinking alcohol in relation to pleasure, relaxation and socialising (Nicholson et al. 2017). However, it is also believed to cost the UK economy at least £21 billion with around £4.5 billion relating to healthcare costs (IAS 2016). There is a trade-off between the benefits and consequences of alcohol consumption, so when determining public health strategies, policy makers consult risk curves. The difficulty relating to alcohol consumption is that this curve is J shaped with respect to total mortality. This means that people who regularly consume small amounts of alcohol have a lower risk of mortality than abstainers (Chokshi et al. 2015). Between 2013 and 2016, the UK Chief Medical Officers undertook a review of the evidence base in relation to alcohol and health. As a result of their work new 'Low Risk Drinking Guidelines' were produced (Department of Health 2016). Their research concluded that benefits from drinking alcohol were less than previously envisaged and only held true for a minority of the population. Indeed, drinking any amount of alcohol increases the risk of various types of cancer, including cancers of the mouth, throat, large bowel and liver. The new guidelines highlight that there is no safe drinking limit but that a maximum of 14 units per week for both men and women, spread over at least three days poses a low risk to health.

Whilst moderate drinking has been related to a reduced risk of more than twenty different health conditions (Fekjaer 2013), it is known that it is causally related to more than 200 diseases and types of injuries (WHO 2014). The chronic, heavy use of alcohol increases the risk of damage to organs and immune functions, most notably in the pancreas, liver and brain (Spanagel 2009). As a neurotoxin (Scheepers 1997) alcohol can cause nerve damage and negatively impact on brain physiology, structure and function leading to insomnia, memory loss, depression, cognitive impairment or development of dementia (Mannelli and Pae 2007). It is of note that women are more likely to experience physical illnesses and more severe cognitive and motor impairment with significantly lower cumulative alcohol doses compared with men (Ceylan-Isik et al. 2010). It is therefore interesting, that the recommended maximum drinking guidelines have the same total units for both men and women.

Alcohol consumption has been reported to be the "third largest risk factor for disease and disability" (WHO 2011 p. x) and the costs to society are difficult to

quantify. Not only is there an impact on the health and quality of life of drinkers but this extends to others affected by the drinker's behaviour (Thavorncharoensap et al., 2009; Rehm 2011; Johnston et al. 2012; Bellis et al. 2015). The negative social impact of alcohol misuse is widely acknowledged. Indeed, it has been suggested that for societies, alcohol is the most harmful misused substance (McCartney et al. 2016). This seems to be a particular problem for Scotland with the Scottish Government recognising that "as a nation our relationship with alcohol has become unbalanced" (Scottish Government 2012 p.1).

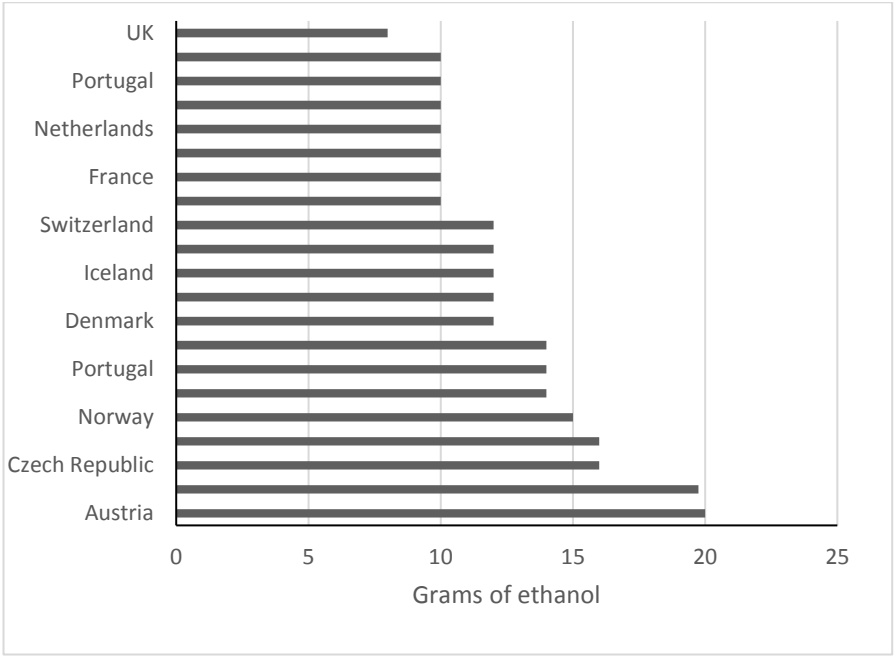
2.4.1.2 Alcohol Use in Scotland, a Particular Problem

The current First Minister of Scotland, Nicola Sturgeon has said that 'for too long, too many Scots have been drinking themselves into an early grave' (Carson 2015, p 12). Based on alcohol sales figures for 2007, it has been reported that Scotland had the eighth highest consumption of alcohol per capita globally, with an average consumption of 11.8 litres (1,180 units per annum or 22.7 units per week) of pure alcohol, per adult (Scottish Government 2009). It has been estimated that alcohol misuse is costing the Scottish economy between £3.56 billion per year (York Health Economics Consortium 2010) and £7.2 billion per year (Johnston et al. 2012). Recent alcohol sales data suggests that the current average consumption stands at 10.5 L of pure alcohol per adult, compared to the global average of 6.2 L per adult. If non-drinkers are excluded from calculations, this figure rises to 12.5L (1250 units per annum, or 24 units per week) per adult drinker, per annum (WHO 2014; NHS Health Scotland 2017). The World Health Organisation has reported that in the UK the average consumption is 11.6 litres per adult (WHO 2014) and it is known that average alcohol sales are 17% higher in Scotland than in England and Wales (NHS Health Scotland 2017).

Scotland has higher levels of physical or mental harm caused either entirely or partly by alcohol than the rest of the UK and most of Europe and around 5% of all deaths in Scotland can be attributed to alcohol (Scottish Government 2013). Alcohol-related deaths are 54% higher in Scotland than in England and Wales (NHS Health Scotland 2017). It has previously been estimated that around 50% of men and 39% of women in Scotland exceed drinking benchmarks (Beeston et al. 2011). Data based on self-report suggest that 22% of men and 16% of women are drinking at hazardous or harmful levels (see section 2.4.2 for definitions) (Scottish

Government 2017) and that around 7% of the population has alcohol dependence syndrome (ADS) (SIGN 74 2003). Recent data corroborates these figures with 18% of the adult drinking population reporting drinking at hazardous levels, or greater (NHS Health Scotland 2017). However, prevalence figures are believed to be an under estimate, as self-reported drinking figures only account for 52% of alcohol sales (ibid.). It is interesting to note that in a recent survey, around half of Scottish adults could not accurately identify the number of units in different alcoholic drinks, so asking people how many units they are consuming may not produce accurate figures (Sharp et al. 2014). The concept of units is not universal, with many countries opting to use the term 'standard drink' and some countries not having a definition of how much alcohol is in a standard drink (WHO 2014; Mongan and Long 2015). The differences across various countries are illustrated in figure 11 (data derived from WHO 2014; Mongan and Long 2015). For consistency within this study, from this point forward grams of ethanol will be used instead of the term units, as the unit is not a standard measure globally.

Figure 11. Maximum Number of Grams of Ethanol per Standard Drink by Country



In relation to health harm caused by alcohol, 23,400 individuals were admitted to hospital in 2015/2016, some of whom were admitted multiple times (NHS Health Scotland 2017). There were 7,327 deaths from alcohol-specific causes in the UK in

2016, equating to a rate of 11.7 deaths per 100,000 population. Scotland has the highest rate of alcohol-related deaths in the UK. For every 100,000 of the population, the death rates attributable to alcohol in Scotland are 30 for males and 14 for females (ONS 2017). The Scottish Government monitor these statistics with the aim being to assess the success of their Alcohol Framework for Action strategy (Scottish Government 2009). Key elements of this strategy are to reduce alcohol consumption and to provide an improved level and quality of treatment and support. The NHS, voluntary and private service providers in Scotland offer both residential and community based detoxification programmes. However, an audit in 2009 of NHS services in Scotland found no consistency in what was being offered and also that the level of spend across different geographical areas did not necessarily reflect the level of need (Audit Scotland 2009). One of the issues in providing services is a difficulty in formally identifying those with alcohol dependency and those at risk of developing alcohol-related brain damage (ARBD) (Wilson et al. 2011). The diagnosis remains heavily reliant on the 'clinical' interview (Schuckit et al. 2009; SIGN 74 2003) which is problematic given the substantial evidence showing that questionnaires and other self-reported measures tend to underestimate alcohol consumption (Alling et al. 2005; Chick and Kemppainen 2007). Services need to be allocated appropriate levels of funding and be able to spend their budgets more effectively. For this to happen, there needs to be a more objective way of establishing who and how many people are dependent on alcohol. Alcohol use disorders are subdivided in relation to risk of harm and the following section provides an overview of the categories of alcohol dependence as an alcohol use disorder.

2.4.2 Alcohol Use Disorders

Alcohol use disorders (AUD) are characterised by the consumption of large quantities of alcohol, despite the knowledge that this can be both harmful and lead to addiction. Long-term alcohol use results in changes within the brain and concomitant behavioural changes. These behavioural changes include a diminished level of control, inability to escape adverse consequences and preoccupation with alcohol consumption (Crews and Vetreno 2014). AUDs are classified by the World Health Organization's International Classification of Diseases (ICD-10, WHO 2016) and include hazardous alcohol use, harmful alcohol use and alcohol dependence in ascending risk of harm (Section V, F10). Hazardous use in itself is not a diagnostic

term but describes a pattern of drinking alcohol that can lead to increased harm. It can be applied to those drinking more than the 14 units (112 g of pure alcohol) per week guideline. This harm may be in relation to physical or mental health, or more broadly negative social consequences (NICE 2010a). In contrast, harmful drinking and alcohol dependence are terms with associated diagnostic criteria. Harmful drinking is a 'pattern of drinking that is causing damage to health' (ICD-10, Chapter V, F10.1) and it must be proven that the health of the person in question has actually been damaged by their pattern of drinking but negative social consequences are not a factor in diagnosis. According to ICD-10, a diagnosis of alcohol dependence syndrome (ADS) is made when an individual displays a 'cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value' (Chapter V, F10.2). The participants in Experiment Two have all received a diagnosis of ADS and so this diagnosis and its consequences will be described more fully in the following sections. However, in relation to the literature terminology is unspecific. There is a history of use of the term 'alcoholic' without any associated definition of what this terminology relates to. This is a current concern within the field of alcohol research (Room 2011). When considering the literature, it is perhaps more useful to use the broad term of AUD in order to capture this wide variability.

2.4.2.1 Alcohol Dependence

Alcohol dependence is a multifaceted disorder with both genetic and environmental risk factors and there are individual differences in vulnerability (Bhaskar and Kumar 2014). Evidence from twin studies suggests that alcohol dependence has a heritability of 50–60% (Kendler et al. 1997) and there is also a shared susceptibility to nicotine dependence (Dick et al. 2007). People with a dependence on alcohol may experience cravings for it, tolerance of it and withdrawal symptoms if unable to access it (ICD-10). Identifying people with ADS is problematic as current available biological measures, such as liver function tests, are known to be "poor indicators of the presence of harmful or dependent drinking" (NICE [CG115] 2011 p.5). Biochemical biomarkers for alcohol consumption used in the UK commonly include Gamma-Glutamyltransferase (GGT), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP) and Mean Corpuscular

Volume (MCV) (Sharpe et al. 1996; SIGN 74 2003). GGT is a glycoprotein found in liver cells and elevation of GGT levels indicates liver disease. However, elevated levels only appear in up to 50% of chronic, heavy drinkers. AST, ALT and ALP are enzymes and an elevation in blood levels can indicate heavy drinking, however they are less sensitive than GGT. MCV is a measure of the volume of red blood cells and people with alcohol dependence tend to have values higher than the normal range. The usefulness of this measure is limited by the fact that MCV remains high even after months of abstinence (SIGN 74 2003; Peterson 2004).

Guidelines for diagnosis, assessment and management of harmful drinking and alcohol dependence recommend the use of the Severity of Alcohol Dependence Questionnaire (SADQ) to determine who may require assisted alcohol withdrawal (NICE [CG115] 2011). It is reported that the typical age range for the emergence of an AUD is 18-29 years (Le Berre et al. 2014). This age range coincides with the period during which the brain is thought to reach maturation, or become adult-like (Somerville 2016). In relation to the individual, it is of the utmost importance that the people most at risk of developing Alcohol-Related Brain Damage (ARBD) are able to be identified and receive the appropriate treatment. It is believed that the same damage observed in male brains can be elicited in female brains by shorter duration of drinking and at lower doses (Neiman 1998; Ceylan-Isik et al. 2010; Vatsalya et al. 2017). There is acknowledgement within the literature that research on alcohol use disorders and its related harms has largely been undertaken with male participants (Brighton et al. 2016). Historically, it has been the case that men are more likely to have alcohol dependency than women. However, it is claimed that death rates for females with ADS are between 50-100 percent higher than for men (Walter et al. 2003). These differences are thought to arise from both sex (biological) and gender (psycho-socio-cultural) factors (Erol and Karpyak 2015). An overview of how alcohol is thought to affect the brain is presented in the following section.

2.4.3 Alcohol and the Brain

As described in 2.1.2, the human brain is estimated to contain around 86 billion neuronal cells and at least as many support cells (Azevedo et al. 2009). With the assistance of the support cells, the neurons connect to each other via synapses, with neural activity resulting in synaptic transmissions (Jernigan and Stiles 2017). The neurons are arranged in complex structural networks, which in turn results in complex,

interacting, functional networks (Cao et al. 2014). It is worth noting that although the human brain is becoming increasingly well mapped, there is some individual variation in structural and function organisation (Glasser et al. 2016).

It is now known that a history of exposure to excessive amounts of alcohol affects all cell types within the brain. We know that drinking at harmful levels can result in atrophy of different areas within the brain, leading to a reduction in brain weight (Erdozain et al. 2014). Recent research has supported the introduction of the reduced limit of alcohol intake in the UK, finding that even moderate levels of drinking result in hippocampal atrophy. The researchers also found no protective effects of light drinking on brain structure, when comparing results to those of abstainers (Topiwala et al. 2017).

Investigation of the impact on brain volume of alcohol use must take into account pattern of use, genetic variation and nutritional status (Le Berre et al. 2014). It is likely that inflammatory processes play a significant role in this decline in brain volume (Persidsky et al. 2014) and the result is widespread damage to a number of highly strategic neural circuits, including the brainstem (Cadaveira et al. 1994; Verma et al. 2006). A brief introduction to alcohol related pathological processes is presented in the following sections.

2.4.3.1 The Effects of Alcohol on the Brain

It is a consistent finding that people with a history of an AUD can present with substantial changes in brain structure and in function (Dager et al. 2015; Keil et al. 2015). Alcohol is a relatively simple compound that is able to cross the bloodbrain barrier and interact with a variety of proteins in the brain (Bhaskar and Kumar 2014; Keil et al. 2015). Pathology can result from the direct neurotoxic action of alcohol, which may vary depending on the pattern and type of drink consumed, or by indirect effects arising from liver disease, genetic profile, socio-economic status and poor vitamin absorption (Thomson 2000; Le Berre et al. 2014; Sutherland et al. 2014). This results in patterns of damage with coinciding pathologies that are not necessarily alcohol-specific and make diagnosis more difficult (Keil et al. 2015). Our knowledge about the alcohol related pathological processes that occur in the brain is increasing (Rosenbloom and Pfefferbaum 2008; Kumar et al. 2009; Sutherland et al. 2014; McCorkindale et al. 2016) and this is essential in understanding and preventing alcohol related brain damage (ARBD).

2.4.3.2 Alcohol Related Brain Damage

ARBD results from chronic drinking at harmful levels (Sutherland et al. 2014) and it is becoming evident that drinking at moderate levels over a long period of time can result in structural changes (Topiwala et al. 2017). ARBD is an umbrella term, which encompasses various associated psychoneurological and cognitive conditions. Prevalence data varies, as patterns of drinking differ between cultural groups and between the sexes, even within cultural groups (Aziz 2014; Bhaskar and Kumar 2014). ARBD is more commonly seen in drinkers in the 40 - 50 age range, with women presenting up to a decade younger than men (Wise 2014). For women with ADS, brain damage progress more rapidly than is the case for men (Walter et al. 2003). ARBD incorporates a range of conditions including alcohol-related dementia, Korsakoff's syndrome, Wernicke's encephalopathy (WE), alcohol-related brain injury, hepatic encephalopathy, Marchiafava–Bignami disease (MBD), central pontine myelinolysis (CPM) and alcohol amnesic syndrome (Zahr et al. 2011; Aziz 2014; Cao et al. 2014).

The structural changes evident in the brains of people with ARBD include a reduction in grey matter and white matter volumes (Sutherland et al. 2014; McCorkindale et al. 2016) accompanied by shrinkage of the cerebellum, frontal, medial temporal, and parietal lobes. There is a general association between the amount of alcohol consumption and the level of atrophy, with the amount of alcohol drunk per day being a factor in predicting harm (Harding et al. 1996; Gonzalez-Reimers et al. 2014; Le Berre et al. 2014). In the study by Topiwala et al. (2017) drinking 112g of alcohol per week (14 UK units) regularly, resulted in a decrease in hippocampal volume. This level of drinking is at the limit of the current guidelines of the UK Chief Medical Officers. It is thought that subcortical structures including the amygdala, hippocampus, ventral striatum, dorsal striatum, thalamus and caudate nuclei may be particularly susceptible to the deleterious effects of alcohol (Jernigan et al. 1991; Buhler and Mann 2011; Dager et al. 2015). It is also possible that prior to developing an AUD, these particular structures exhibit deficits that may contribute to its development and continuation (Squeglia et al. 2012; Segobin et al. 2014; Dager et al. 2015).

Differences have been reported on the effects of alcohol on the brain, between men and women. Whilst both sexes display the reductions in brain volumes described above, women seem to be more susceptible to the neurotoxic effects of alcohol. It

would appear that brain shrinkage and associated cognitive dysfunction progresses faster in women (Hommer 2003; Prendergast 2004).

2.4.3.3 The Pathophysiological Mechanisms of ARBD

The current proposed pathophysiological mechanisms that lead to ARBD have been summarised in a review by Zahr et al. (2011). Post mortem pathological studies, in vivo imaging studies, molecular studies and presentation of clinical and psychological features have all been used to explore aspects of ARBD (Harper 2009). Gross structural changes in the brain can be demonstrated using various imaging techniques (Erdozain et al. 2014; Keil et al. 2015). The molecular mechanisms underlying ARBD are still poorly understood and as yet there are no conclusive molecular markers (Byun et al. 2014; Ignacio et al. 2015; McCorkindale et al. 2016). A sequence of alterations in brain structure in relation to alcohol use is presented by Keil et al. (2015). Early changes include the atrophy of the superior cerebellum and the frontal white matter. There are different reports regarding atrophy of white and grey matter, however it is considered that there is a greater level of white matter atrophy (McCorkindale et al. 2016). The largest white matter tract, the corpus callosum, has been shown to be abnormally sparse in people with an AUD (Monnig et al. 2014). The supratentorial frontal, infratentorial pontine, and cerebellar regions exhibit white matter atrophy, whilst the superior portions of the cerebellum and the thalamic nuclei exhibit grey matter atrophy (Keil et al. 2015). It is interesting to note that studies that have looked at the populations of specific countries have found different associations between volumes of certain areas of the brain and history of alcohol consumption. This is thought to be influenced by drinking patterns, cultural norms and nutrition, which all lead to heterogeneity in the effects of alcohol on the brain (Le Berre et al. 2014).

Synapses are considered to be particularly susceptible to the deleterious effects of alcohol (Roberto and Varodayan 2017). Alcohol affects the activity of both the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and the excitatory neurotransmitter, glutamate (Weintraub 2017). *N*-methyl-D-aspartate (NMDA) is a glutamate receptor and chronic drinking leads to up-regulation of the NMDA and down regulation of the GABA receptors, resulting in tolerance. Withdrawal from alcohol results in an increase in NMDA receptor function and a loss of the GABA inhibitory effect. The results is hyper-stimulation of the central nervous system, which manifests

clinically as autonomic excitability (e.g. auditory hallucinations) and psychomotor agitation (e.g. purposeless movement, tremors) (Long et al. 2017).

Even with our current level of knowledge about ARBD, it is estimated that 80-90% of cases are not diagnosed (Royal College of Psychiatrists et al. 2014). If a diagnosis of ARBD occurs, the lack of biomarkers for early ARBD further impacts on the selection and monitoring of any intervention (Ignacio et al. 2015). Thiamine deficiency, often as a result of chronic consumption of alcohol at harmful levels, can lead to Wernicke encephalopathy (WE) or Wernicke-Korsakoff syndrome (WKS). Wernicke encephalopathy is an acute neurological disorder and early identification and treatment is required in order to avoid irreversible brain damage (Busani et al. 2014; Erdozain et al. 2014). Treatment includes thiamine replacement and failure to administer adequate doses of thiamine results in death in up to 20% of patients (Latt and Dore 2014). The treatment regime prescribed by NICE (2010b) for patients at risk of developing WE is lacking in detail. Practitioners have called for universally accepted guidelines that provide information on the optimal dose, mode and frequency of administration and duration of treatment (Latt and Dore 2014).

When looking at effects of alcohol on brain structures, another fact to consider is that chronic smoking often accompanies chronic drinking (Hasin and Grant 2015). As previously discussed, there is a shared susceptibility to nicotine dependence (Dick et al. 2007). It is useful to try and delineate any effects that can be attributed to smoking. It is estimated that 80% of people with alcohol dependence also smoke (Kalman et al. 2005). Tobacco products may also contain neuroactive substances which may lead to brain atrophy. As such it is possible that negative affects attributed to alcohol may instead have been caused by smoking. McCorkindale et al. (2016) explored this possibility in autopsied human brains but concluded that smoking by itself as well as a combination of smoking and alcohol showed no additional effect on brain atrophy.

2.4.4 Functional Damage: Clinical and Psychological Features of ARBD

Chronic heavy drinking can lead to brain atrophy that results in progressive cognitive decline and changes in personality (Keil et al. 2015). Diagnosis of ARBD relies on the presence of these characteristics and includes an assessment of cognitive function (NICE 2011). It is reported that changes in cognitive function can occur after drinking at harmful levels for a period of five years (Royal College of

Psychiatrists et al. 2014). In the UK higher risk drinking levels, whether they lead to dependence or not, are an average of 280 g of alcohol per week for women and 400g for men (NICE 2010a). Although it would appear that drinking at lower levels of 56g of alcohol per week can lead to decline in lexical fluency (Topiwala et al. 2017). There are variations in the reported prevalence of cognitive impairment in people with an AUD, however the figures for mild cognitive impairment range from 50-80% (Gonzalez-Reimers et al. 2014). It is also known that even with similar patterns of drinking, the risk of brain atrophy increases after people reach 50 years of age (Keil et al. 2015).

Changes in cognitive function commonly include deficits in executive function (Sullivan et al. 2000; Christiansen et al. 2013) affecting decision making (Loeber et al. 2009; Crews and Vetreno 2014), emotional regulation, impulsivity (Oscar-Berman and Marinkovic 2007) working memory, attention, concentration (Kopera et al. 2012), processing new or complex information (verbal and visual); abstract problem solving and visual-spatial processing (Kim et al. 2014). ARBD is also associated with confusion, apathy, depression, irritability and an impaired sense of smell (Aziz 2014; Cao et al. 2014; Erdozain et al. 2014; McCorkindale et al. 2016). These kinds of deficits, especially in higher order functions, suggest that damage to the frontal lobe has occurred (Le Berre et al. 2014; McCorkindale et al. 2016). In addition, an inability to cease alcohol consumption, not helped by impaired decision-making, motivation, planning and impulse inhibition, also implies that damage has occurred in the prefrontal cortex and limbic systems (Crews and Vetreno 2014). Obvious clinical signs of ARBD include tremors and postural instability (Keil et al. 2015).

2.4.5 The Effects of Abstinence

Many studies of people with an AUD are carried out once detoxification from alcohol has occurred. This withdrawal process itself, results in changes that researchers should be aware of. Withdrawal can be conceived as a sudden halt in chronic, heavy drinking which can initiate symptoms including anxiety, sweating, vomiting, tremors, seizures, and may even prove fatal (Long et al. 2017; Weintraub 2017). For people deemed to be at risk of seizures or delirium tremens, a medically assisted withdrawal should take place in the hospital environment. Benzodiazepine, carbamazepine or clomethiazole may be used to treat symptoms (NICE [CG100] 2010b). The Ritson Clinic is a 12 bed, detoxification ward within the Royal Edinburgh

Hospital. For a patient admitted with significant withdrawal symptoms the treatment would be started with the benzodiazepine, Chlordiazepoxide. Diazepam is prescribed in the event of seizure. Metoclopramide is prescribed to help with nausea and vomiting, Loperamide for the prevention of diarrhoea and paracetamol for pain relief. The patient will receive Pabrinex, which is a solution containing thiamine hydrochloride, riboflavin, pyridoxine hydrochloride and nicotinamide (B vitamins); ascorbic acid (vitamin C); and glucose. After three days this is changed to oral thiamine unless confusion is still evident. After two weeks the patient will be offered Acamprosate, for neuroprotection. The duration of the hospital stay is usually around 7-10 days but may be longer if required (Appendix 2). The effects of the withdrawal process are discussed in the following section.

2.4.5.1 Effects of Withdrawal

There is an increasing amount of information available about the actual effect of the withdrawal process. The symptoms occur because of an increase in NMDA receptor function and a reduction in the inhibition of GABA-A receptors, the results of which are autonomic excitability and psychomotor agitation (Crooks and Peery 2012; Roberto and Varodayan 2017). These symptoms of withdrawal can be so unpleasant that the person consumes alcohol again, to gain relief from them. Even if withdrawal is successful, people who have a history of AUD can experience motor deficits due to compromised cerebellar function and it is though that the withdrawal process itself may be a contributing factor (Jung 2015).

The brain is especially vulnerable to the effects of alcohol during adolescence (Barron et al. 2005). Concerns about the effects of alcohol on the adolescent brain prompted the Scottish Health Action on Alcohol Problems (SHAAP) group to dedicate a seminar to this topic. Although there is some contradictory evidence, it seems that harmful drinking at this time may result in significant frontal cortical degeneration (Crews and Vetreno 2014). Recent research has found reduced prefrontal cortex and cerebellar volumes, as well as white matter atrophy in adolescents and young adults who are drinking heavily (Cservenka and Brumback 2017). It is also possible that adolescents and young adults may experience cycles of heavy drinking and abstinence, otherwise known as binge drinking (Byrd 2016). Whilst this type of consumption is not limited to younger adults, in effect, this is the same as undergoing

a series of withdrawals and may result in cell death within the brain (Obernier et al. 2002; O'Daly et al. 2012; Cservenka and Brumback 2017).

2.4.5.2 The Role of Thiamine

We take in thiamine (vitamin B1) through our food and it is essential for healthy metabolism and brain function (Abdou and Hazell 2015). In particular, thiamine is an essential co-factor for the metabolism of carbohydrates. Chronic alcohol consumption results in thiamine deficiency as a result of reduced nutritional intake, decreased absorption and impaired utilisation of carbohydrates (Latt and Dore 2014). Chronic, heavy drinking is the primary cause of thiamine depletion in the developed world (Liu et al. 2017). At least 25-31% of people with an alcohol use disorder have thiamine depletion but it is often only diagnosed post-mortem. Depletion affects both the nervous and cardiovascular systems. If depletion reaches a severe level then a person may develop WE, which presents with symptoms of confusion, lack of co-ordination of muscle movements and weakness or paralysis of eye muscles (Sachdeva et al. 2015). As previously discussed (section 5.4.2.1), if left untreated the patient may go on to develop Wernicke Korsakoff syndrome (WKS). This is characterised by the development of irreversible consequences including dementia and gait abnormalities (Gossman and Newton 2017). Up to 20% of people with WKS will need to be cared for but WE is treatable with thiamine replacement. By treating the WE, the progression to WKS can be avoided (Latt and Dore 2014). Unfortunately, the majority of cases of WE are not diagnosed, which has led to thiamine becoming a routine treatment for patients admitted to hospital with an alcohol use disorder (NICE [CG100] 2010a).

2.4.5.3 Reversibility of Changes in the Brain

Although there is a known risk of relapse (Crews and Vetreno 2014), ARBD is non-progressive if abstinence and an appropriate level of nutrition are maintained (Aziz 2014). The brain damage associated with chronic, heavy drinking is potentially reversible with abstinence (Zahr et al. 2011; Segobin et al. 2014; Keil et al. 2015; Wang et al. 2016). It takes up to seven days for the symptoms of alcohol withdrawal to conclude (Long et al. 2017) and it is thought that the earliest weeks of abstinence coincide with the greatest level of brain volume regeneration (Wang et al. 2016). It is

known that increases in white matter are evident within days of abstinence (Keil et al. 2015), although neural plasticity varies across the different regions of the brain (Segobin et al. 2014). It is also possible that smoking status affects the pattern of recovery of cerebral white matter (Gazdzinski et al. 2010). These changes are accompanied by an improvement in cognitive ability, memory, and visuo-motor coordination (Kopera et al. 2012; Segobin et al. 2014), which is indicative of alcohol related disrupted neuronal connectivity, as opposed to extensive neuronal loss (McCorkindale et al. 2016).

Up to 75% of people with ARBD can expect to have improved function and recovery occurs during the first three months of abstinence (Gonzalez-Reimers et al. 2014; Royal College of Psychiatrists et al. 2014). People with the greatest degeneration require urgent intervention (Le Berre et al 2014). Therefore, it is critical that people with AUDs are diagnosed early and ideally intervention takes place before ARBD occurs (Aziz 2014). However, due to the heterogeneity of the population in relation to individual differences and differences in presentation of symptoms, this is not an easy task. The question is how to recognise the clinical antecedents that lead to ARBD?

2.4.6 Exploring the Brain in People With AUDs

Neuroimaging techniques, such as Magnetic Resonance Imaging (MRI), Functional Magnetic Resonance Imaging (fMRI), Magnetic Resonance Spectroscopy (MRS), Diffusion Tensor Imaging (DTI), Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), Computed Tomography (CT), Diffusion-Weighted Magnetic Resonance (DW-MRI) have increased our understanding of disease processes associated with AUDs. However, each method has both advantages and disadvantages and in order to establish a comprehensive picture of brain function, these imaging tools need to be used in a complementary way. This is not currently realistic at the individual assessment and treatment level, due to the costs involved and these techniques tend to remain in the research domain (Bühler and Mann 2011).

Also within the research domain are the electrophysiological tests where the response is generated at the level of the cortex. These tests can be useful for monitoring of individuals but inter-subject variability tends to be high and standard clinical equipment is often not able to run these tests. As such they are possibly more

appropriate to be considered in terms of clinical research, rather than current clinical application (Woodman 2010; Jerger 2016). Before these kinds of tests can be used routinely in clinical practice there need to be some basic protocols and stimuli developed that can have widespread use. Interpreting the results of these studies can be hampered by the need to consider the effects of attention and context (Stapells 2009; Sussman et al. 2013). This is not the case for auditory evoked potentials which arise from the subcortical areas.

It is known that people with an AUD have reduced subcortical volumes (Bühler and Mann 2011) and there have been studies performed to establish whether such abnormalities reverse with abstinence (Dager et al. 2015). The ABR may offer a quick and cost-effective way of exploring the impact of alcohol and abstinence on brainstem functioning. There may be clinical value to using such a measure of functioning as an objective way of monitoring neural impact. An EEG approach to recording the electrical activity of the brain and brainstem non-invasively, has been widely used in studies of pathological mechanisms, including ARBD. As previously discussed, the techniques can be relatively quick, convenient, inexpensive and offer excellent temporal resolution (Cao et al. 2014). Monitoring brainstem function in people considered to have an alcohol use disorder has been of interest over the last thirty years (Beglieter et al. 1981; Chu et al. 1982; Chan et al. 1985; Nickel and Riedel 1987; Cadaveira et al. 1994; Verma et al. 2006) but has produced conflicting findings. It is known that click ABR findings in patients with WKS, cerebellar degeneration, and cerebellar ataxia are abnormal (Rosenhamer and Silfverskiold 1980; Chu et al. 1982; Chan et al. 1985; Nickel and Riedel 1987). In addition, 40% of patients with long-term ADS were found to have abnormalities in the auditory brainstem response, even though they had no diagnosis of WKS or alcohol-related neurological disease. This would indicate that although these patients had clinically verifiable brainstem disease, as demonstrated using the click ABR, they had no outward sign of neurological disease (Verma et al. 2006). Therefore, the relationship is not equivocal, with abnormal ABR results demonstrated in some patients with ADS and not others. This suggests that there may be a role for ABR in detecting early stage damage, which exists before a patient develops symptoms. In the following section, a review of the current findings relating to the ABR and people with an AUD is provided.

2.4.6.1 Alcohol and Hearing

The effect that hearing loss has on the ABR has been discussed in section 2.2.3. When considering whether a diagnostic tool is likely to be useful, it is important to explore any potentially confounding factors. There is disagreement within the literature about the effect of alcohol consumption on hearing. Acute alcohol consumption for people without a diagnosis in ADS is reported to lead to a temporary threshold shift (Upile et al. 2007). Alcohol has been highlighted as a potential risk factor for hearing loss because it has a depressive effect on the central nervous system and lead to deficits in nutritional status. As discussed in the preceding sections, it might be expected that chronic consumption results in peripheral nerve degeneration and alteration of brain structure. Although research using the ABR in people with an AUD has been published since the late 1970s, the effect of alcohol on hearing thresholds was still unclear some twenty years later (Brant et al. 1996). Some researchers have not found any effect of alcohol on hearing thresholds, either in men or women (Brant et al. 1996; Curhan et al. 2011; Curhan et al. 2015), whilst others have found a harmful effect of drinking alcohol for men (Rosenhall et al. 1993). There are also studies that have shown that drinking low to moderate levels of alcohol has a protective effect on hearing thresholds (Popelka et al. 2000; Itoh et al 2001; Fransen et al. 2008; Gopinath et al. 2010; Dawes et al. 2014; Rigters et al. 2016). The most recently published study in this area looked at drinking moderate levels of alcohol and found that this had a protective effect on hearing threshold levels in women (Lin et al. 2017). The disagreement between the results of these studies may arise because they are hampered by difficulties in characterisation of history and type of alcohol consumption and differences in measurement and classification of hearing loss. Curhan et al. (2011, 2015) raise the interesting issues of vitamin intake and hearing loss and hearing loss in relation to type of alcohol consumed. In a previous study their research team had found that vitamin B12 might have a protective effect in men over the age of 60 years (Shargorodsky et al. 2010). They therefore explored this observation in the subsequent study and found lower intake of vitamin B12, and higher consumption of spirits was associated with an increased risk of hearing loss (Curhan et al. 2011). They then went on to explore the relationship between alcohol and hearing loss in women. They found that when looking at overall alcohol consumption in women, there was no link with hearing loss. However, when they looked at type of alcohol consumed, they found a modest association between hearing loss and

drinking beer and a modest protective effect for those drinking wine (Curhan et al. 2015). It may therefore be prudent to look more closely at the types of alcohol consumed, when considering potential damage to the auditory system.

For people with alcohol dependence the link between alcohol and hearing thresholds is also unclear. Early work found that alcohol could not solely account for hearing loss (Nordahl 1964). A review of various studies found that although high frequency hearing loss was often reported, the actual relationship between chronic, heavy alcohol consumption and peripheral hearing loss was unclear (Spitzer 1981). A difficulty is that people with an AUD may also have experienced head trauma, noise exposure or taken ototoxic medication, which can also result in hearing loss (Rosenhall et al. 1993; Crawford 1997). Other studies have suggested that there is a link between high levels of drinking and hearing loss, predominantly high frequency hearing loss (Wheeler et al. 1980; Gołabek and Niedzielska 1984; Niedzielska et al. 2001; Verma et al. 2006; Ribeiro et al. 2007). There is a lack of detailed alcohol consumption history in many of these studies, which makes drawing conclusions difficult.

A method for monitoring outer hair cell function in the cochlea is transient evoked otoacoustic emission testing (TEOAE) (see section 2.1.4). This has been incorporated into some of the hearing assessments, as it offers a way of assessing site of lesion. TEOAEs have only been used in two studies related to alcohol and hearing and both studies concluded that there was damage to outer hair cells, attributable to alcohol (Niedzielska et al. 2001; Ribiero et al. 2007). However, there was no control group used in the earlier study and there were no criteria provided for diagnosis of an AUD. Length of drinking history but not quantity of alcohol consumed was reported and participants had been abstinent for one to nine months (Niedzielska et al. 2001). In the second study, although there were control groups, these were not matched for sex and the participants were diagnosed as ‘alcoholics’ on the basis of drinking more than one litre of unspecified alcoholic beverage per day. No mention was made of length of drinking history, or any quantification of pure alcohol consumed. Although it was stated that the subjects were in a period of abstinence, no further details were provided on length of abstinence. The poor reporting of the alcohol history in both studies does not allow conclusions to be made, that are generalisable.

What may be an important factor for hearing, as raised by a previous study on vitamin intake (Shargorodsky et al. 2010), is the role of thiamine. It does appear that there is some interest in thiamine containing products in therapy for hearing loss of a

neural nature (Korienko and Korienko 2011). Roger's syndrome (Thiamine responsive megaloblastic anemia) which results from a deficiency in a thiamine transporter protein, comprises a triad of anemia, diabetes mellitus and sensorineural deafness. Treatment is by daily ingestion of thiamine, however this does not seem to prevent or reverse any hearing loss (Oishi and Diaz 1993). The lack of consensus in the literature regarding AUDs and hearing loss dictates that hearing thresholds should be evaluated before any electrophysiological testing, using auditory stimulus, is conducted.

2.4.6.2 Alcohol and Central Auditory Processing

As alcohol is a neurotoxin, it is not unreasonable to anticipate that central auditory processing might be affected by chronic, heavy drinking. Surprisingly, there are few papers that address this question in people with an AUD and those that do have employed electrophysiological studies. There is little published evidence on behavioural tests of auditory processing. The acute effect of alcohol on healthy controls has been investigated and it has been found that discrimination ability in difficult listening conditions is adversely affected by alcohol consumption (Fitzpatrick and Eviatar 1980). Spitzer and Ventry (1980) found deficits in a range of speech processing tasks in people with an AUD. Spitzer (1981) looked at the evidence available at the time and concluded that whilst there had been research on the acute effects of alcohol, there were few studies assessing the auditory processing abilities of people with an AUD. The Short Increment Sensitivity Index (SISI) assesses a person's ability to detect 1 dB increment in tones at various frequencies and has some use in determining whether a lesion is at the level of the cochlear or in retrocochlear regions (Jerger et al. 1959). This test was used as part of a battery to assess hearing ability in people with AUD (Gołabek and Niedzielska 1984). Results suggested that 70% of the ears examined had a hearing loss and that the source of the hearing losses were mostly retrocochlear. In a study by Steiger et al. (1985) looking at the ability of people with an AUD to recognise speech in a competing speech situation, it was found that abstinent patients' performance was affected. However, this recovered after several months of abstinence. A difficulty with this study is that very few patients remained abstinent and of the 49 originally tested, only six were re-tested. It is therefore difficult to know if recovery was genuine and generalisable.

Another interesting result is that there may be different effects of acute alcohol consumption on auditory processing, depending on the frequency of stimulus used. Pearson et al. (1999) found changes in discrimination thresholds between different frequency stimuli, with a much higher increase in discrimination thresholds for stimuli greater than 1000Hz. They concluded that variations of the effects of alcohol in the literature may be attributable to different stimuli being used. Behavioural tests of auditory processing can be affected by deficits in cognitive function because they usually require a response from the person being tested. This makes it difficult to know whether results are as a result of alcohol consumption, or a pre-existing cognitive deficit.

2.4.7 Alcohol Related Changes in the ABR

A literature search was performed in order to understand the current evidence base and identify any areas of discord. A search for 'Auditory AND Evoked AND Alcohol*' was performed in Pubmed and this returned a total of 386 results. The search was then limited to humans and papers published in English which reduced the returned results to 288. A review of the abstracts found 28 papers that contained original data and described using the ABR in people who had consumed alcohol. If the articles related to children or polysubstance use, they were excluded from this review. A similar search was performed in Google Scholar and by reviewing the citations and reference lists of the already identified articles; an additional seven articles were identified. The final number of original articles that have used the ABR in adults in relation to alcohol consumption totals 35 (see appendix 3). Of these 35 articles, 15 have been published by five research groups. The participants have been located in North America (12 studies), Europe (17 studies), Asia (4 studies) and Australia (2 studies). The majority of the articles were published between 1976 and 1999 with only four articles published in the last 17 years and none since 2006. During this time, there have been advances in technology and software and a better understanding of the effects of stimulus, recording and subject factors. There have also been attempts to improve reporting of diagnostic studies (Bossuyt et al. 2015) and the terminology relating to AUDs (ICD-10).

The maximum total number of adults included in these studies is 1059, as there is some replication of reporting of participant details across papers by the same authors or research groups (Chan et al. 1985; Hammond et al. 1986; Cadaveira et

al.1991; Cadaveira et al.1992; Cadaveira et al. 1994). Of these 1059 cases, only 138 are reported as being female. It is important to note that sex data is not reported in nine of the 35 studies, totalling 237 participants. This is potentially an issue, as there are different normative data sets required for males and females and it also means that there is actually very little known about the ABR in women in relation to alcohol.
The majority of these studies have taken place after withdrawal from alcohol. However, the duration of abstinence ranges from as little as 72 hours, to up to 12 months (Cadaveira et al. 1994; Smith and Riechelmann 2004). The studies can broadly be divided into four themes including research on the effects of social drinking, adults with AUD both with and without overt neurological symptoms and the effects of abstinence over time. Standards are now in place for the reporting of diagnostic accuracy studies. For example, there are Standards for Reporting Diagnostic Accuracy Studies (STARD) and Consolidated Standards of Reporting Trials (CONSORT) (Bossuyt et al. 2015). The literature from these four areas of research on the effects of social drinking, adults with AUD both with and without overt neurological symptoms and the effects of abstinence over time will now be critically reviewed.

2.4.7.1 The ABR and Social Drinking

One of the earliest studies published on the effects of alcohol on the ABR in humans, is of a research team acting as participants (Squires et al. 1978). The six, normal hearing male participants ingested alcohol in doses related to their normal levels of consumption and weight, in an attempt to achieve a similar level of intoxication in each participant (stated as 0.55 -1.65 ml of alcohol per Kg of body weight). The ABR was recorded pre-dosing and post alcohol dosing serially, until 2 hours had passed. Blood samples were taken to establish the levels of alcohol, which ranged from 44 to 144 mg/100 ml. A comparison was made between responses from the right and left ears and no differences were found, so the data was pooled. There was a significant increase in latencies from peaks III to VII, although for each subject latencies remained within the normal limits. It is interesting to note that the shift in latencies did not relate to the individual blood alcohol levels and the authors concluded that the ABR response might be a more sensitive measure of the effect of alcohol on the nervous system than blood alcohol level readings. The authors propose that using higher dosing levels of alcohol might result in further prolongation of waves,

however there are ethical consideration with this type of research. The style of this paper renders it difficult to extract pertinent information, as there are no sub-sections.

The effect of alcohol, dose and time was measured in nine, male, light to moderately heavy social drinkers with normal hearing (Church and Williams 1982). On different days each participant had a baseline ABR recorded before being given either a high (1.0g 190 proof ethyl alcohol/ Kg body weight), moderate (0.5g ethanol /Kg) or placebo (5 ml alcohol floated on orange juice) dose of alcohol and blood alcohol concentration (BAC) was measured at regular intervals. The ABR was then recorded at intervals up to around 445 minutes post ingestion until the BAC had diminished to at least 20 mg%. It is not stated how the results from left and right ears were treated, although the statistical analyses suggest that the data was pooled. Similarly to the results of the study by Squires et al. (1978), there were significant increases in absolute latencies of peaks II to VII after alcohol ingestion, with the maximum latency changes occurring between one and two hours after ingestion. There was no effect of dose within waves I to V of the ABR. Although significant levels of prolongation of waves were reported, no comment was made as to whether these remained within the normal expected range. In contrast to the study by Squires et al. (1978), the authors concluded that click ABR latencies were not as good at capturing the effects of intoxication, as blood alcohol concentrations.

The results of both of these studies indicate that absolute latencies of waves III to V will be affected by alcohol consumption in men. There is no corresponding data for women. This needs to be taken into account when undertaking research with people with ADS. Recent alcohol consumption will have an effect on absolute latencies of ABRs. The remainder of the studies in this review record the ABR after a period of initial withdrawal from alcohol.

2.4.7.2 The ABR in People with an AUD, Without Obvious CNS signs

When considering the clinical utility of either the click or speech ABR, it is essential to know whether either of these tools can provide information on brainstem pathology that occurs before overt symptoms appear. The following discussion is a review of studies that have explored the click ABR in people identified by the historic term ‘alcoholic’.

The click ABR was recorded in 17 patients who met the research diagnostic criteria for ‘alcoholism,’ alongside 17 healthy control participants, matched for age,

sex and education (Begleiter et al. 1981). The patients had an 'average' drinking history of 16 years but had been abstinent for three weeks and medication-free for two weeks. The methods for collecting the ABR were described in detail but the polarity of the stimuli and the initial hearing thresholds were not reported. The researchers did not find any differences between the recordings from left and right ears, so pooled the data. They found that wave I was the same for both the patients and controls but that there were significant increases in latencies from waves II through to V and a corresponding overall increase in the interpeak latencies. They concluded that there was a significant difference in brainstem transmission time between the patients and the healthy controls, even though the patients had no overt symptoms of CNS damage. As there was no difference in wave I, they concluded that the deficit was not at the periphery but at the level of the medulla and pontine formation. However, it is not possible to state this explicitly, if there is no assessment of hearing status. The results of this study led the researchers to propose that the click ABR could provide essential information about the progress of deficits in the brainstem and the potential of recovery with abstinence. This was the first published paper in this area and it prompted further studies.

In contrast to the above mentioned study, no latency differences were found in the ABRs of 33 patients with ADS when compared to a healthy control group (Reilly et al. 1983). No information is provided about the patients, except that they were taking part in a 28 day 'alcohol problem' treatment programme. The researchers noted that previous studies that had found differences had much narrower latency ranges for 'normal' function, whereas they were looking for differences of 2.5-3 S.D.s from that of the control means. Although click ABRs were recorded from the right and left ears, it is not clear from the analysis how this data was handled. It was noted that waveform morphology was different (subjective rating on a Likert scale) but that this resolved after a period of three weeks of abstinence. The authors attribute differences in results between their study and that of Begleiter et al. (1981) to be a function of medication (Antabuse and Librium) taken by their study participants, differences in ABR technique or more likely a difference in the population tested. They described their population as being those enrolled in a community rehabilitation programme. However, nothing is specified in relation to eligibility criteria, diagnosis, or alcohol history. It is very difficult for a reader to know whether these participants were 'alcoholics', as suggested by the title of the paper.

Again, in contrast to the first publication, no significant differences in ABRs in 14 patients with ADS (DSM-III) were found when compared to 14 healthy controls, with sex not being specified (Spitzer and Newman 1987). Data from left and right ears were treated separately. Although Spitzer and Newman did not find differences with respect to wave latencies they did report a much higher level of variability in the waveforms from the clinical group. In this particular study, the ABRs were recorded ten days post detoxification. The age range for the participants differed between the clinical group and healthy controls, as did the hearing thresholds. The authors state that the healthy adults had hearing thresholds within normal limits but that the clinical group had hearing within normal limits for their age. Without knowing more about the participants, it is not possible to draw conclusions about this study. An imbalance between males and females could be a factor, as sex is not stated.

A further study comparing the ABRs of 26 patients with alcohol dependency (DSM-III) to those who had been exposed to lead and mercury, as well as to healthy controls was undertaken (Lille et al. 1988). In this study the recording parameters were changed from a previous study by the same research group (Lille et al. 1987), as the ABRs were recorded at 60 dB above the subjective hearing levels, as opposed to 20 dB above. The actual hearing thresholds were not discussed. The participants had been abstinent for an average of 10 days. An increased interpeak interval for I-V was found in one participant only who had been exposed to lead but also had alcohol dependency. No further details are presented about the ABR results. As no details are presented including criteria for normal or abnormal, it is impossible to consider whether the results are reliable.

In the first of the subsequent studies to find significant prolongation in the click ABR, 15 patients (two women), described as 'alcoholics' (DSM-III) and fifteen age and sex matched controls were assessed (Dìaz et al. 1990). The patients were reported to have been abstinent for around one month. All participants were reported to have hearing thresholds of less than 65 dB SPL, although further details are not provided. The details for recording the ABR are presented in sufficient detail to allow for study repetition. As with the study by Begleiter et al. (1981), wave V was delayed in the patients compared to the controls and the I-V and III-V interpeak intervals were prolonged. Of the fifteen patients, three (20%) had clinically abnormal values of wave V and two had clinically abnormal increases in interpeak intervals. Abnormal values were defined as being more than 2.5 S.Ds. from the control group mean. This does

not take into account any sex differences in the click ABR. It is not stated whether the abnormal results were found in the male or female participants.

As a result of conflicting evidence, a study of the click ABR in 44 male patients with alcohol dependency was undertaken (Meinck et al. 1990). The group alcohol history is briefly described. The ABRs from these male patients were compared to a group of 40 healthy controls, 23 of which were female. Four patients were excluded for having ABR latencies with a variability of > 5%. No differences were found between right and left ears, so data was pooled. The criteria for abnormality were individual latencies ≥2.5 S.D. with respect to the mean of the control group. The ABRs for the patient group were significantly later for waves III, V and for I-V interwave intervals were significantly longer. ABRs were considered to be abnormal in 45% of patients. However, they were being compared to a control group of whom more than half were female. The data from the control group would contain ABR latencies that could be expected to be significantly shorter than those for males. It is not surprising that comparing a group of males to a mixed control group would produce significant differences, irrespective of alcohol use.

Aspects of utility of the ABR in identifying early CNS dysfunction as well as premature aging were explored in 32 ‘alcoholic’ patients (DSM-III) aged 23-57 years, with a history of at least eight years of heavy alcohol consumption. Healthy participants (n=32) who were matched for age, sex and education, were also recruited (Cadaveira et al. 1991, 1992). The procedure for recording the ABR is presented in detail and it would be possible to repeat this investigation, however no mention is made of the participants’ hearing thresholds. The patients were abstinent from alcohol for at least 25 days before the ABR was recorded. There were significant differences found between the groups in wave V latencies and interpeak latencies and these were unaffected by age. It was found that wave V values were outside normal limits for 18 of the 32 (56%) patients. The authors concluded that the ABR is a potentially useful tool for studying changes that are happening at an earlier age.

The study with the largest number of participants was a comparison of the ABR in men (n=133) and women (n=70) with ADS (DSM-III) (Worner and Lechtenberg 1992). ABR recording details are not provided, so it would not be possible to make any meaningful comparisons with results from other studies. The age profile and years of diagnosis of ADS differed between the groups of men and women. The women were younger and had fewer years of history of ADS. No details are provided about the timing of the recordings, only that the ABRs were recorded in people admitted for

detoxification. There were significant differences in waves III and V of the ABRs between men and women. The groups were reported as having latencies falling within the normal limits for the particular laboratory, although no details are provided about what these were. Although this study is potentially a very useful contribution to the knowledge base, the lack of detail provided makes it difficult to interpret these results in a meaningful way.

In a continuation of the research looking at adults with ADS, a question was raised as to whether there was a subgroup more at risk. People with both an alcohol use and antisocial personality disorder may be at greater risk of brain damage because of existing impaired, frontal lobe function (Kuruoğlu et al. 1996). ABR testing was performed with 40 male patients with alcohol dependency, 15 of which met the DSM-III-R criteria for antisocial personality disorder. Ten age and education matched, abstinent controls were also recruited. No information is presented about hearing status other than stimuli were presented at 60 dB above their subjective hearing threshold. Waves III and V were significantly prolonged in the alcohol dependant participants, as were the interpeak intervals of I-III, III-V and I–V. Abnormal ABRs were found in 17.5 % of the patients. The authors found that both the amount of alcohol ingested daily and length of drinking history correlated with wave V latency ($r = 0.262$, $p < 0.05$) and I-V interval ($r = 0.272$, p, 0.05). With respect to interpretation of size correlation coefficients, these would be considered to be negligible levels of correlation (Mukaka 2012). No differences were found between those patients with a single diagnosis of alcohol dependence versus those with both alcohol dependence and antisocial personality disorder.

It was considered possible that the differences in the literature may have arisen from differences in the nutritional status of participants. A study comparing ABRs from 40 well-nourished males with alcohol dependency (DSM-III-R) and 20 healthy, abstinent males was undertaken by Nicolás et al. (1997). The men with ADS all reported consuming a daily dose of at least 100g of ethanol for the preceding two years. Recordings were carried out 10 days after hospital admission and the details of the recording technique are described, although hearing thresholds are not discussed. Significant prolongation of waves I, III and V was found, alongside prolongation of interpeak I - III, III-V, and I-V intervals, when compared to the control group. There was also a decrease in amplitude of the individual waves. Seven of the 40 (17.5 %) patients had an abnormal wave V latency and these particular patients reported a significantly higher amount of alcohol consumption than those without

abnormal values. The authors concluded that their lower prevalence of abnormal findings, compared to other studies, could be attributed a variety of factors relating to the heterogeneity of this particular population. Factors might include the degree of neurological impairment, degree and history of alcohol dependency and whether or not a participant could be classified as thiamine deficient, which was not thought to be the case for the subjects tested in this particular study. Reilly et al. (1983) have also raised this issue of heterogeneity within this population. This is an important point for consideration, as the classification of people according to criteria does suggest that the target condition is quite specific (Vermiglio 2016).

In a departure from the interest in click ABRs for diagnostic purposes, the concept of hearing loss in people with alcohol dependency was broached by Gołąbek and Niedzielska (1984). This study was followed up by an attempt to evaluate the degree and place of damage (Niedzielska et al. 2001). Patients (sex not stated) with alcohol dependency (n=30), the criteria for which was receiving therapy and who had been abstinent for between one and nine months, were assessed. The assessments included pure tone audiometry, tympanometry, acoustic reflex testing, transient otoacoustic emission testing and ABR testing. The description of all elements of the test battery is too brief to enable replication. Hearing thresholds were within normal limits in only eight of the 30 participants. Wave I was prolonged in 28 ears, wave III was prolonged in 50 ears and wave V was prolonged in 54 ears. Interpeak interval I–III was prolonged in 30 ears, III–V was prolonged in 28 ears and I-V was prolonged in 41 ears, however no criteria for these decisions are discussed. This limits the interpretation of this data, as there is no definition or rationale provided for the criteria.

A further paper specifically addressing hearing status in people with ADS, used ABR as part of the hearing profile (Verma et al. 2006). In this study, 20 people with ADS (ICD-10) were recruited, as well as control groups of social drinkers and abstainers. The patient group was aged 30 to 60 years and it was found that this group had significantly elevated hearing thresholds at higher frequencies with half of them having some level of hearing loss. Criteria were provided for categorising the ABR as normal or abnormal and abnormal results were found for 40% of the patient group. An important omission is that there is no sex data reported for any of the participants and the control groups were only stated to be matched for age. Mean absolute latency of waves III and V, as well as the I-V interpeak interval were prolonged in the patient group but the wording of the results is ambiguous in relation to whether this was a significant difference. There is also a query regarding the

stimulus type used, which is reported as being a pure tone click. Clicks are by nature broadband stimuli. The results for the social drinkers and abstainers were said to be similar but no statistical analyses are reported. The authors concluded that people with ADS but no overt symptoms of neurological disease may have abnormal ABRs, indicating damage caused by chronic, heavy alcohol consumption. However, 50% of the patients had abnormal hearing test results yet there is no discussion of the impact of hearing loss on click ABR results. It is therefore not possible to state that any damage is caused by alcohol consumption.

It can be seen from these results that there is still a degree of uncertainty about the clinical utility of the click ABR in this population of people with ADS but no overt CNS signs. This can partly be explained by some of the issues discussed within the reviews of these studies and these are discussed further in section 2.4.7.5.

2.4.7.3 The ABR in people with an AUD with CNS signs and/or Liver Disease

In an attempt to understand the relationship of click ABR results with pathology, studies have been designed to look at the click ABR in patients with more severe symptoms. Chu and Squires (1980), recruited 52 patients (13 female) with AUD (no criteria given), both with and without overt CNS signs to be assessed using ABR. The recording procedure was described, apart from the polarity of the click stimulus used. The age range of patients was 20 to 75 years of age but no discussion is presented about hearing thresholds. The only consideration is that intensity of level of stimulus presentation was increased if identification of wave components was not possible. The researchers used a >4.4 ms conduction time between wave I and V as the criterion for abnormality without any justification or reference in support. Using this criterion, it was found that conduction time was abnormal in nearly half of the participants, although this dropped to 13% for those with no neurological signs. This study does not discuss the effects of sex, aging or hearing loss on the ABR nor is there any attempt to justify what might be considered ‘normal’ in a population without a history of AUD.

A further study by this research group (Chu et al. 1982) repeats the research already performed and the methods of recording the ABR were as for the previous study (see Chu and Squires 1980). For this study, 66 patients with a history of AUD were recruited of which 15 were female. It is not possible to determine whether these were entirely different participants from those in the previous study. The patients were

grouped according to absence or presence of neurological symptoms and age. It is apparent that a threshold ABR was performed to evaluate hearing but this applies to evaluating high frequency loss only and it was determined that four patients had at least a severe level of unilateral hearing loss. Different criteria for normal function are also presented for those below and above 50 years of age and references are provided as evidence for this. No mention is made of having separate normative data for males or females. It was found that 41% of participants had abnormal brainstem responses (> mean of interpeak intervals for normal function ± 2.5-3 SD, depending on age). Of interest is that abnormalities were unilateral in 21 patients and that incidence of abnormalities increased both with age and with the number of neurological complications. This makes it unclear as to whether age alone is a factor, or whether this is simply a function of the length of history of AUD. Abnormal brainstem responses were also found in 30% of patients without WE or neurological signs. The authors concluded that many patients with AUD may have brainstem lesions without accompanying symptoms.

The above study by Chu et al. (1982) was further developed to look at any correlation between the electrophysiological findings and morphological alterations using computed tomography (CT) (Chu 1985). People with an unspecified history of AUD (n=45), with no diagnosis criteria provided, of which 13 had been abstinent for at least two years, were included in this study. No mention is made of whether they also contributed to data in the previous study and the male to female ratio was 3:1. There is acknowledged bias within the study, as the participants who had received a CT scan were more likely to have experienced neurological complications. The methods of recording the ABR were as for the previous study (Chu et al. 1982). Abnormal brainstem responses were found in 53% of participants (> mean of interpeak intervals for normal function ± 2.5-3 SD, depending on age). Four of the 13 participants who had been abstinent had abnormal responses. The results of the study were that abnormal brainstem responses correlated with an increased size of brainstem cisterns and potentially brainstem atrophy. This is perhaps an unsurprising result and it would have been interesting to understand more about the drinking history. This series of research papers fails to address factors relating to the effects of sex, aging or hearing loss on the click ABR. Indeed, it is stated that one subject had a severe unilateral hearing loss but no details are provided about any hearing assessments or whether this participant was excluded from the study.

A further study by members of the same research group (Chu and Yang 1987), focussed on the effects of liver disease on ABRs. Patients with an AUD and liver disease but no known neurological disease (n=41), were recruited to participate in the study. The methods of recording were similar to previous studies (Chu and Squires 1980; Chu et al. 1982; Chu 1985). Again, it is unclear about the sex of the participants or how many of the participants may have had a hearing loss. The patients were subdivided into four groups dependant on the severity of their liver disease. Regardless of group, the interpeak latencies of waves I-III, III-V and I-V were prolonged, although the mean results fell within the normal limits, as compared to a group of 18 healthy, age and sex matched controls. There were no differences in peak or interpeak latencies between the groups. Therefore, their conclusion was that liver disease did not affect the ABR.

Another research group investigated the ABR in 13 patients with ADS (not defined), exhibiting slow tremor and cerebellar ataxia (Rosenhamer and Silverskiöld 1980). Seven of the patients had normal hearing thresholds up to 4000HZ. Although the sex of the patients is not reported, the ABR recording parameters are presented in sufficient detail to allow reproduction of this study. The criteria for a normal ABR result are stated, for analysis of the I-V interpeak interval. Ten of the patients had a significantly increased I-V interpeak interval but there was no increase in absolute latency of wave I. Two of the patients had abnormal ABR results (15%). The patients all had visible symptoms of disease in a motor system. The authors concluded that the ABR could be used to confirm changes occurring in a sensory system.

Wernicke's Encephalopathy (WE) can be considered to be a clinical emergency, requiring urgent treatment (Day and del Campo 2014). ABRs were recorded for 56 patients with AUD but without WE. Of these, 24 patients had evidence of cerebellar degeneration. Additionally, ABRs were recorded for 25 patients with WE but in all cases recording took place after two weeks of abstinence (Chan et al. 1985). Four of the participants with an AUD were female. A control group of healthy men (n=37) and women (n=40) were also recruited. All participants had their hearing thresholds measured and a threshold ABR performed before to ensure that participants had normal or near normal hearing thresholds. The details for recording the ABR are presented in a way which would enable the study to be reproduced. Of the 32 (13%) patients with AUD but without WE, four had abnormal ABR results, although the I-V interpeak latency was significantly prolonged for this group. Of the 24 patients with AUD and evidence of cerebellar degeneration, six (25%) had

abnormal ABR results but both the III–V and the I-V interpeak intervals were significantly prolonged. Twelve (48%) of the patients with WE had abnormal ABR results and there were significant increases in the I-III and I-V interpeak latencies. Of the patients with WE, 16 underwent thiamine treatment and remained abstinent and were re-tested after six months. Of these only two (13%) had abnormal ABRs and the interpeak latencies for the group were significantly shorter than at original testing. The authors discuss the importance of defining the criteria for 'abnormality', whether that be the mean +2 SD or the mean +3SD.

Optimum parameters for recording the ABR have been explored in patients with Wernicke-Korsakoff syndrome and patients with Multiple Sclerosis (MS) (Hammond et al. 1986). ABRs were recorded with both rarefaction and condensation polarities in control participants with normal hearing, WKS patients and MS patients. Limited details are provided about the hearing of the patient groups, with the ABRs being recorded at 65 dB above the subjective click threshold for that ear. For the control group, only wave I in females was significantly different when recorded in rarefaction, as compared to condensation polarity. The results for patients with WKS and MS were mixed, 12 of the 25 WKS patients had abnormalities, with the majority of these abnormalities found in the wave I-III area. The authors concluded that sex and stimulus polarity should be taken into account when establishing control data. It was not stated how many of the 12 patients with abnormalities were female. This seems to be a common omission in studies and raises questions about how generalisable the results are.

In a continuation of the research in patients with Korsakoff syndrome (KS), a comparison was made between 29 male patients with KS, aged 50 years (± 5.25 years) and 30 healthy, male controls aged 31 years (± 7.37 years) (Nickel and Riedel 1987). All participants were reported as having normal hearing up to 2000 Hz. The patients with KS had significantly increased interpeak intervals for waves I-III and I-V. It was found that using the interpeak interval data (I – VI) and a discrimination point of six msec, specificity of the ABR was 87% and sensitivity was 62%. The authors make a statement that the mean age differences batween the groups is not an issue, as per Chu (1985). They do not discuss whether there were any differences in hearing thresholds above 2000 Hz. It is not clear why the authors decided on 2000 Hz as a cut-off point. The click ABR is reported to best represent the zone of hearing of between 1000 and 4000 Hz (Hurley et al. 2005), with the greatest agreement in the

2000-4000hz region (Hood 1998). If there is hearing loss present above 2000hz, this will affect the click ABR and the impact will be determined by the severity of the loss.

Building on the previous research in the utility of ABRs in patients with Wernicke's encephalopathy, Haas and Nickel (1991) undertook a prospective study of patients with clinical signs of WE. They recorded ABRs from 22 patients with WE, 28 patients with delirium tremens and 30 healthy controls over a five-year time period. Although they state that they recorded the ABR at 70 dB HL for normal hearing participants, they don't expand on how many had normal hearing or what they did if a hearing loss was present. They found that delayed interpeak latencies were a feature of the delirium tremens and WE groups and that using a cut-off point of 4.5ms for the I-V interval, resulted in a sensitivity of 86% and an efficiency of 92% for discriminating between control participants and those with delirium tremens or those with WE. Testing was performed serially over eight days at the acute stage of the participants' illness and a reduction in latencies and interpeak latencies was observed. They concluded that interpeak latencies for waves I–V of the ABR could be extremely useful for early diagnosis of WE.

Click ABRs have been recorded in a mixed group of patients, in relation to CNS signs. The ABRs of eleven males meeting the DSM-II criteria for alcohol dependence, were recorded at 10-20 days post alcohol withdrawal (Lille et al. 1987). Five of the patients had overt signs of CNS damage. An additional 20 age matched, healthy control participants were also recruited. There was no significant differences reported between the control and patient group but the ABRs were considered to be abnormal in 2 patients with CNS signs (18.2%), in which the I-V interpeak intervals were + 3 S.D. above the mean of the controls. It is noteworthy that recording took place at 20 dB sensation level. In an early study by Squires et al (1978), recordings took place at 55 and 75 dB above threshold for normal hearing and it was found that wave I could not be identified in the traces recorded at the lower intensity. It is questionable whether the tracings recorded at 20 dB above threshold, could result in clear waveforms. It is interesting, as previously mentioned, that in the subsequent study by Lille et al. (1988) the intensity of stimulus presentation is 60dB sensation level. This change in protocol suggests that the research team were not confident in the use of the lower presentation intensity level.

Differences in the ABR profiles for patients with central pontine myelinolysis (CPM) have been reported, with earlier click ABR waves being affected. Nine male patients with alcohol dependence who had developed CPM were recruited to

participate in ABR testing (Mochizuki et al. 2003). An additional 14 male patients with alcohol dependence but no diagnosis of CPM and 14 healthy males also took part in the assessment. There is a lack of detail of the ABR recording and hearing status is not discussed. The interpeak latencies of waves I–III for the patients with CPM were significantly longer than for the healthy controls and for the patients with alcohol dependence but no diagnosis of CPM. These intervals were also considered to be abnormal in five of the eight (62.5%) patients with a diagnosis of CPM.

Finally, ABRs were recorded from 38 male patients, 19 of whom were head and neck tumour patients, the tumours thought to be a result of long term, heavy alcohol consumption (Smith and Riechelmann 2004). Daily alcohol consumption assessment was treated in detail. Behaviour was defined in relation to pure alcohol consumption as low risk being 0-30 g (3.75 units), risky being 30-60g (3.75 – 7.5 units), dangerous being 60-120g (7.5 – 15 units) and high risk being greater than 120g (>15 units). Hearing assessments were performed prior to ABR recordings and people with a hearing loss of > 10 dB relative to their age profile in ISO 7029 and ISO 8253-3, were excluded. The other 19 patients were attending a plastic surgery clinic and although their profile of drinking behaviour was less risky, there was a small level of overlap (0-49g vs. 0-210g per day). Absolute latencies of waves III and V, as well as the interpeak intervals of I-III and I-V were significantly prolonged in the patient group with head and neck tumours. There was also a logarithmic relationship between interpeak interval I-V and cumulative alcohol consumption. Cumulative alcohol consumption was defined by looking at average consumption of beer, wine and spirits in periods of decades and adjusting for drink type to establish the amount of pure alcohol consumed.

2.4.7.4 The ABR and Abstinence over Time

There are very few longitudinal studies of the click ABR in adults with an AUD. Two men, each with at least a 30-year history of heavy drinking were diagnosed with suspected central pontine myelinolysis (CPM). ABRs were recorded serially over a 20-week period from initial admission to hospital for case one and over a three month period for case two. The early ABR recordings were used to support the diagnosis and it was found that an initial lengthened wave I-V interval returned to a ‘normal’ value within a 12 week period in both cases (Stockard et al. 1976). The methods of recording are described in a reasonable level of detail, although the polarity of the

click is not reported and the level of presentation is said to be varied but this is not specified further. There is no discussion about the hearing thresholds of the two cases, although the clicks were generally presented at 60 dB sensation level. There is also a very limited description about their alcohol consumption. These results are specific to two cases of men with AUDs who have suspected CPM so are not generalisable to a wider population. However, the authors conclude that the results provide evidence of pontine remyelination after 12 weeks of abstinence.

Serial ABR testing was carried out in two men with a long history of heavy drinking who had been admitted to hospital with a diagnosis of Wernicke's disease (Erkulwater and Condon 1989). Patient one had a 36-year history of heavy alcohol consumption, details of consumption history for patient two were not specified. It was not considered possible to obtain accurate hearing thresholds, so ABRs were recorded at high intensities in an attempt to mitigate any effect of hearing loss. The ABRs were recorded weekly whilst the patients were undergoing thiamine treatment, until the patients were discharged. Initially only wave I could be reliably identified in the traces. Waves II to V became apparent in later recordings. The abnormal waveform for patient one returned to within normal limits within a one-month period. The abnormal waveform for patient two was still outside normal limits at the end of treatment, although improvements in latencies had been observed.

The previously mentioned studies by Cadaveira et al. (1991,1992) were continued and the group was followed over a one-year time period. Twelve patients remained abstinent for one year and their ABRs were recorded at intervals during this time. All but two of the patients click ABR wave values returned to within normal limits over the 12 months.

These studies provide information about potential recovery with abstinence. It would appear that recovery can occur in as little as one month but for some people results can still be considered to be abnormal after 12 months. The evidence here is sparse and could be of real interest to clinicians when deciding on treatment and rehabilitation. In many cases, these programmes have set time periods but a more person-centred approach may be to tailor the programme to the persons recovery needs.

2.4.7.5 Common Issues across the Studies

There is a lack of consensus in the literature regarding click ABR results in people with ADS. It appears that click ABR results are abnormal when there are overt signs of CNS involvement and the higher the number of CNS signs, the greater the number of abnormalities in the ABR. However, these results stem from a series of studies were age, sex and hearing status are not adequately addressed. The differences evident from results of people with ADS but no overt CNS signs may also be attributable to unknown deficits within the hearing profile of participants, differences in the method of acquiring the ABR and individual differences in disease progress. These factors will now be discussed in the following sections.

2.4.7.5.1 Age of Participants

It is known that click ABR peak and interpeak latencies increase with age, with significant differences becoming apparent in adults over the age of 50 years (Skoe et al. 2015a). Age is therefore a potentially confounding factor when considering whether alcohol affects the click ABR. Of the reviewed studies, at least 20 have clinical population groups which include adults under and over the age of 50 years. In many cases there is an age matched control group. However, it is not always possible to tell if age has been considered as a confounding factor. In the series of studies by Chu et al. (Chu and Squires 1980; Chu et al. 1982), age is discussed but the relationship between age and years of drinking history is not straightforward. Age and years of drinking history are not always related and it is difficult to understand how these variables interact and whether one or both are the important variable when considering changes in the ABR.

2.4.7.5.2 Sex of Participants

As previously discussed, of the 35 studies only 26 provide details of the sex of the participants. It can only be confirmed that the click ABR has been studied in 138 women with an AUD. It can therefore be concluded that there is currently very little known about the ABR in women, in relation to alcohol. It's also useful to understand normative data sets and whether they are for men, women or balanced across the sexes. An imbalance in group compositions can affect results. Ideally,

different normative data sets are required for males and females but this is not mentioned specifically in any of the studies. In the one study looking at male female differences, the researchers refer to the normative data for their clinic, without specifying what this is.

2.4.7.5.3 Drinking History

There is a lack of detail and sometimes lack of diagnostic criteria for the patients with an AUD. Of the 33 studies relating to patients, only 22 provide any diagnostic criteria for the AUD in question. There is a historical use of the term 'alcoholic' without any description of how this label has been applied. Most studies report average length of dinking history but only two studies report types of beverages consumed. There is a lack of quantification of pattern of drinking behaviour or attempts to define daily or cumulative dose of pure alcohol. There is also a wide variation both within and between the studies in the length of abstinence before testing occurred and how abstinence was monitored.

The concept of heterogeneity within the population with an AUD is highlighted (Reilly et al. 1983; Nicolás et al. 1997). When looking to apply any diagnostic tool in a population, there must be a well-defined clinical population (Bossut et al. 2015). Although the diagnosis of an AUD is now made in accordance with written criteria (e.g. DSM-5, ICD-10), there is still large variability in the drinking histories that result in a diagnosis. The existing literature lacks the detail required to enable results to be applied more globally. This is an issue that requires addressing within the research field.

2.4.7.5.4 Hearing Status

Details of any peripheral hearing assessment were lacking in over half of the studies and PTA was only carried out in seven of the 35 studies. Hearing was reported as being normal for the participants in four of these studies (Church and Williams 1982; Chan et al. 1985; Nickel and Riedel 1987; Spitzer and Newman 1987) and abnormal in the remaining three studies (Rosenhamer and Silfverskiold 1980; Niedzielska et al. 2001; Verma et al. 2006). This issue is of great concern, as it is not possible to fully attribute prolongation or abnormalities in ABR results to alcohol consumption if hearing loss has not been ruled out as a confounding factor.

2.4.7.5.5 Recording Parameters

The small numbers of studies in humans in this field, the differences in the quantification of alcohol consumption history and some methodological differences across studies in recording the ABR, have meant that it is currently not possible to assess how reliable this tool is within this population. An overview of the recording parameters for each study is provided in appendix 3. When considering these parameters, the most common stimulus used was the 0.1 msec click (18 studies). However, stimulus type was not specified in 12 studies. Intensity levels were generally high (at least 60 dB SL or 60 dB nHL), apart from a single study by Lille et al. (1987) but were not reported in four studies. The most commonly used bandpass filter settings of 100/150 to 3000 were used in 15 studies but not reported in five studies. A click presentation rate of between 10 and 20 Hz was used in 27 of the studies but not reported for six studies. An overview of the effects of changing these recording parameters has been presented in section 2.2.3. What can be stated is that there is a lack of consistency in the ABR recording protocols used and poor reporting of protocols for some studies. This stems in part from the historical nature of these studies, reporting of ABR studies has improved, as has the understanding of the effects of changing these parameters (Hood 1998).

From this review, it can be concluded that there are promising indications that the ABR could be useful in detecting damage before clinical signs exist. The ABR is appealing because recording does not place a heavy burden on the patient and this is particularly attractive when someone is feeling unwell during the process of withdrawal. A reliable, non-invasive, inexpensive, marker of early stage alcohol-induced brain cell damage could be a useful tool in both diagnosis and informing patient management. It would be interesting to understand whether recent changes in the use of more complex auditory stimuli would offer a more effective assessment. To date there is limited data available for the speech ABR response in adults. It has generally been used to assess typically developing adults and changes associated with the ageing process, there are no reports of use for those with ADS.

2.4.8 The Speech ABR and Alcohol

Successful social interaction relies on our ability to gauge intent, attitude or emotional tone, when someone else is speaking. Non-linguistic aspects of speech

including stress, timing, intonation pattern, pitch rhythm and pausing provide this emotional tone and are described as prosody. Affective prosody, is the term used to describe those aspects of speech which convey the emotional tone of language. Accuracy of prosody perception has been found to be impaired in people with Autistic Spectrum Disorder (ASD), Schizophrenia, Dementia and ADS (Uekermann and Daum 2008). Monnot (2001) found that people with an AUD who had gone through detoxification and been alcohol free for 3 weeks, were less able to understand the emotional tone in other people's speech and were therefore more likely to make errors that negatively impacted on social interactions. Deficits in affective prosody perception were found to be related to the age at which intense alcohol exposure commenced, as well as the length of drinking history. This finding has been used to investigate alcohol toxicity in terms of its effects on the brain. There is an interesting question to consider about cause and effect. Is it possible that pre-existing deficits in affective prosody or speech processing more generally, that negatively impacts on social interactions, could be a risk factor for developing ADS?

Whilst the click ABR is known to be useful in examining the integrity of the auditory brainstem, speech stimuli are more useful for deficits related to language processing (Song et al. 2006). One prosodic element of spoken language is pitch alteration and researchers have claimed that the speech ABR has a use in exploring deficits in prosody that are known to be experienced by children with ASD. Russo et al. (2008) investigated the subcortical representations of speech in a group of children with ASD. They claimed that as pitch is the psychophysical correlate of fundamental frequency (F0), speech syllables with descending and ascending pitch contours could be to explore deficits in speech encoding that would be critical for understanding emotional intent. They concluded that some children with ASD exhibited deficient brainstem encoding of pitch. This was indicated by aberrant pitch tracking and reduced neural phase locking to the stimulus (Russo et al 2008; Russo et al 2009). However, recent published research has highlighted that it is incorrect to assume that the frequency following response (FFR) reflects the perception of pitch. The FFR cannot be used to make claims regarding auditory processing in the brainstem beyond what is already occurring in the auditory periphery, and it does not provide a representation of pitch (Gockel et al. 2011).

There has been no research on the speech ABR in adults with ADS. An aim of this research is to investigate whether using a speech stimulus to elicit the ABR offers any different or additional information, in terms of a biomarker for ADS, than

can be detected using the click ABR. Deficits have been found in the speech ABR in some individual's with ASD that are not detected with the click ABR (Russo et al. 2008; Russo et al. 2009). As behavioural deficits in affective prosody perception are found in people with ASD and people with ADS, the additional use of speech to elicit the response seems to be an appropriate area of investigation.

2.5 Aims of Experiments One and Two

The aim of Experiment One is to generate some control data for men and women with no demonstrable deficits in auditory or cognitive function. As part of this, the following questions will be addressed:

1. What is the inter-rater agreement for speech ABR?
2. What is the effect of ear of presentation on the speech ABR?
3. What is the effect of sex on the speech ABR?
4. What is the effect of age (18-30 vs. 31-49 years) on the speech ABR?
5. What is the between session repeatability of the speech ABR?

In Experiment Two the auditory brainstem response (ABR) of a group of people diagnosed with ADS will be recorded as they enter a treatment and rehabilitation programme and again after 12 weeks of abstinence from alcohol. This will allow the impact of alcohol and abstinence on auditory brainstem functioning and the value of using measures of functioning as an objective way of monitoring neural impact, to be assessed. This study will use both the click and the speech stimulus /da/ to elicit the response. The degree to which one of these measures may provide superior sensitivity and specificity with regard to alcohol use, will be examined with a view to determining the degree to which using either or both measures proves optimal. In order to achieve this the following questions will be addressed:

1. In what ways do people diagnosed with alcohol dependence syndrome, who have normal hearing sensitivity, differ in their auditory-cognitive profile compared to healthy adults?
2. Is the auditory brainstem response of people diagnosed with alcohol dependence syndrome different from that of healthy adults?

- a. when responding to click stimuli
- b. when responding to speech stimuli

3. What are the changes in 1 and 2, following adherence to a 12 week alcohol abstinence programme?
4. What is the relationship between drinking history and measures in 1, 2, and 3?

Chapter Three: Experiment One

As discussed in section 2.3, using more complex stimuli may allow the detection of abnormalities in the brainstem response to sound, that are not evident when using simple stimuli. It would appear that the speech ABR may be a useful tool for exploring and monitoring brainstem function in people for whom speech processing may be compromised. However, in order for a test to be clinically valuable it must be deemed to be reliable with changes occurring only as a result of intervention, development or pathology (Song et al. 2011; Hornickel et al. 2012ab). Clarification is required for certain aspects of interpretation and findings, in relation to the speech ABR. The purpose of Experiment One is to explore those aspects of the speech ABR that require clarification, when consideration is being given to collecting data from healthy adults. This process includes an assessment of inter-rater reliability, the generation of separate data for men and women, an exploration of the potential need for ear specific data, a comparison of results from adults in different age ranges and an assessment of test-retest reliability

This section presents the methods and descriptive statistics that relate to the auditory-cognitive profile of young adults with typical hearing sensitivity. In the following section (3.1), the participants will be introduced and the methods for the individual tests used, will be described. Each of the tests presented below has a body of literature exploring its clinical use. It is beyond the scope of this project to provide an in-depth review of the individual assessment tools and an overview has been presented in section two (2.1.4). A detailed description of the procedures that were used for performing testing, data analysis and the presentation of the results is presented in the following sections. The tests themselves can be subdivided into behavioural assessments, physiological assessments and assessments of cognitive function. However, they are presented below grouped by tests of cognitive function and tests of auditory processing. For precise order of assessment, please see figure six in section two (2.1.5).

Subsequent sections contain the results, analysis and interpretation of the data gathered by the methods described below. The general and descriptive statistics include information about the participants and the results from the auditory-cognitive profile test battery and the click ABR. An exploration of the speech ABR is presented in section 3.3.

3.1 The Auditory-Cognitive Profile and ABR Assessment

The following section details the participants and the methods used to perform the individual tests of the auditory-cognitive profile and ABR assessments.

3.1.1 Participants

69 adults (35 Females, 34 Males) aged 18-30 years were recruited by advertisement within Queen Margaret University and by word of mouth. To be included, the participants had to meet the following criteria:

- Age 18 to 30 years old.
- Monolingual native English speaker.
- No history of occupational noise exposure or ototoxic medication.
- No diagnosis of dyslexia, any specific language impairment or autistic spectrum disorder.
- Otologically normal bilaterally (according to EN ISO 7029:2017), following otoscopy performed in accordance with the BSA (2010) recommended procedure for ear examination.
- Pure tone hearing thresholds for 250, 500, 1000, 2000, 4000 Hz and 8000 of no greater than 20 dB HL bilaterally.
- Transient evoked otoacoustic emissions (TEOAEs) present in at least three frequency bands with a signal-to-noise ratio of at least 3 dB and with overall reproducibility of 70% or higher.
- No evidence of central auditory processing difficulties, defined as scoring outside the ‘normal’ range on any test of the subtests of auditory processing.
- Right handed by self-report or Edinburgh Handedness Inventory or left handed with no evidence of left ear advantage using dichotic digit testing.
- All Wechsler Adult Intelligence Scale subtest scaled scores to be ≥7.
- No history of neurological disorders such as multiple sclerosis, Huntington’s disease, or major head trauma.
- No diagnosis of depression.
- No diagnosis of alcohol use disorder
- Normal click-evoked brainstem response latencies (see section 3.1.3.7, table 11), measured by an alternating polarity, 100-μs click stimulus, presented at 80 dB HL, at a rate of 13.1 Hz with bandpass filters of 150-3000Hz.

Five women were subsequently excluded from the study, one for being bilingual, one for having a unilateral mild conductive loss, one for having a bilateral mild high frequency sensorineural hearing loss and two for scoring below the normal values for auditory processing tests. Four men were subsequently excluded from the study, three for scoring at below normal levels on a WAIS subtest, one of whom also scored below normal level for an auditory processing test and a further one who scored below the normal levels for an auditory processing test. This resulted in sixty younger adults (30 Females, 30 Males) aged 18-30 years (mean age 23.6 yrs, S.D. 3.8 yrs) participating in this exploratory study.

All assessments were performed in a single session within a private double walled sound proofed room (Industrial Acoustics Corporation, Staines, Middlesex, UK). The studies in Experiment One were conducted with the approval of the Ethics Committee of Queen Margaret University and all participants signed a consent form prior to data collection.

3.1.1.1 Sources of Error and Bias

The following considerations influenced the design of the study.

3.1.1.1.1 Sampling Effect

The group of participants selected to contribute to the control data should be representative of adults with a profile of normal auditory function and normal cognitive ability. This was achieved by recruiting a sufficient number of both male and female participants within a defined age range who met strict inclusion criteria in relation to their hearing acuity and functional hearing.

3.1.1.1.2 Bias and Compensation

As the control participants were required to have scores of > 6 on subtests of the WAIS, and hearing thresholds of no greater than 20 dB HL they might not represent the general population of adults. The majority of participants were University students and as such, the data presented should be considered as control data as opposed to normative data. It is possible that participants' performances could be affected by learning effects and/or fatigue. As some tests are pre-requisites for

others, the decision was made to present tests in a set order and allow for breaks as required in an attempt to mitigate fatigue. The final assessment is a physiological assessment, which does not require a response from the participant. However, it may be that this particular measure is affected by alertness or attention and participants were asked to watch a DVD of their choice in an attempt to compensate for this.

3.1.2 Methods

The methods used to construct the auditory profile of healthy participants are presented in the following sections.

3.1.2.1 Clinical Interview Procedure

In this research project, a standard case history form was used to identify any contraindications to proceeding with testing, inform the audiometric assessment and aid in interpretation of subsequent test results. The case history form, comprised of five subsections includes questions relating to demographics, employment and social history, general health and audiovestibular function. There were an additional four non-standard questions asked, as a result of the literature review which included fluency in other languages, musicianship, handedness and highest level of qualification attained. A more generic question about physical and emotional health was also asked and at this point participants were specifically asked about any diagnoses of depression, alcohol dependence syndrome, or specific language impairment. This question also allowed participants to mention any further information regarding their history that they felt pertinent (Appendix 4). All participants completed an interview based on the case history form.

3.1.2.2 Otoscopy Procedure

In order to detect pathology or contraindications for further testing, an examination of the ears and surrounding areas was performed in accordance with British Society of Audiology (2010) guidelines for ear examinations, for all participants. Examination of the ears was carried out using a Heine otoscope with disposable speculae. The participant remained seated during the procedure, which took around one minute per ear.

3.1.2.3 Pure Tone Audiometry Procedure

Pure-tone hearing thresholds were measured at 0.25, 0.5, 1, 2, 4, and 8 kHz using a model GSI 61; Grason-Stadler, Milford, NH audiometer and Telephonics TDH-50P headphones, calibrated according to ISO-389-1 (2000). If there was a gap of 20dB or more between two adjacent frequencies, intermediate frequencies were tested. The test was performed in accordance with the recommended procedure of the British Society of Audiology (2011). The threshold was obtained when the participant responded to the lowest intensity, by pressing a button, at least fifty per cent of the time on the ascending presentations. Bone conduction audiometry was performed using a radioear B71 bone vibrator at 0.5, 1, 2 and 4 kHz as per the above BSA procedure, if air conduction thresholds at these frequencies were worse than 19 dB HL. Masking was employed as recommended by the above mentioned British Society of Audiology procedure, if required. All thresholds were plotted on an audiogram with respect to frequency (Hz) and intensity (dB HL). Hearing was categorised in terms of the descriptors developed by the BSA (2011 p. 26, see Table 2). The participant remained seated throughout the procedure, which took on average around 10 minutes and all participants had their hearing threshold levels assessed.

Table 2. Audiometric Descriptors (British Society of Audiology 2011 p.26)

Descriptor	Average hearing threshold levels (dB HL)
Mild hearing loss	20 - 40
Moderate hearing loss	41 - 70
Severe hearing loss	71 - 95
Profound hearing loss	> 95

3.1.2.4 Tympanometry Procedure

This is an examination used to assess the condition of the middle ear, the mobility of the eardrum (tympanic membrane) and the conduction bones (ossicles) by creating variations of air pressure in the ear canal, whilst a low tone is played (Fowler and Shanks 2002). Tympanometry is an objective test of middle-ear function and does not require a response from the participant. The movement of the tympanic membrane is measured when a tone and small amount of air is introduced into the external

auditory meatus. A small ear tip was used to create an airtight seal between the tympanometer probe and the external auditory meatus. The pressure in the meatus was then changed incrementally from + 200 daPa to at least -200 daPa and a constant 226Hz tone was presented during this air pressure change. This procedure was performed using a tympanometer (model GSI Tympstar; Grason-Stadler, Milford, NH) meeting the performance and calibration requirements of BS EN 60645–5 and in accordance with the BSA recommended protocol for Tympanometry (British Society of Audiology 2013). Measures of ear canal volume, tympanic membrane compliance and the air pressure corresponding to maximum compliance value, were obtained in the form of a tympanogram and recorded manually as individual values. Classification of the tympanogram was made according to the Jerger classification system (Jerger 1970). The participant remained seated throughout the procedure, which took around two minutes per ear and all participants had their middle ear function assessed.

3.1.2.5 Cognitive Assessment

The selection of tests for the cognitive assessment is described in section two (2.1.4). All tests are subtests from the Wechsler Adult Intelligence Scale-III (WAIS-III^{UK}).

3.1.2.5.1 Vocabulary Test Procedure

The vocabulary test consisted of a list of words that the participant was asked to define. There were 30 test items and all participants were presented the same words in the same order, if the practice items were completed correctly. As per the instructions, the first three words were used in reverse sequence if the participant scored less than two points on the first two test items administered. Each word was presented visually and verbally and responses were scored as per the administration and scoring manual (Wechsler 1997), in terms of complexity and demonstration of abstract thinking. The test was discontinued if a participant failed to score any points on six consecutive words. The score was determined by adding up the points allocated for each word and then converted to a scaled score, as per the administration and scoring manual (Wechsler 1997) and all participants undertook the vocabulary assessment.

3.1.2.5.2 Digit Symbol Coding Procedure

The Digit Symbol Coding test consists of individual boxes numbered one to nine, which are uniquely paired with a symbol and the participants must fill in the matching symbol for each number.

For practice, the participant was instructed to use the given key and to copy each symbol into the corresponding numbered box, randomised from one to eight. They were then asked to complete as many of these codings as possible, in the order presented in the workbook, within 120 seconds. The score was determined by the correct number of codings achieved within the set time limit. The score was then converted to a scaled score, as per the administration and scoring manual (Wechsler 1997) and all participants undertook this assessment.

3.1.2.5.3 Digit Span Forwards and Backwards Procedure

The digit span forwards and backwards test comprises two separately administered components and both were completed for each participant. Digit span forward was administered first with the tester reading a series of number sequences, with the numbers being presented at a rate of one per second and the participant was asked to repeat exactly what they heard in the correct order of presentation. This sequence increased in duration from two numbers to a maximum of nine numbers, depending on whether the participant was able to repeat two trials successfully. Secondly, the same process was repeated but the participant was asked to repeat the numbers in reverse order, up to a possible maximum of eight numbers. The task was discontinued if the subject made errors in both trials of a given sequence length. Scores of 0, 1 and 2 were allocated based on the participant's response. If the participant failed to correctly repeat a digit sequence for both trials of a given length, a score 0 was given. When subjects failed to correctly repeat the digit sequence in one of the trials a score 1 was given and when subjects repeated the digit sequence correctly for both trials a score 2 was given. The scores of each the digit span forward and backwards test were summed to produce the raw score. The score was then converted to a scaled score, as per the administration and scoring manual (Wechsler 1997).

3.1.2.5.4 Symbol Search Procedure

The symbol search test comprises five pages, the first being a demonstration and practice page and the subsequent four each containing fifteen rows of symbols. The symbols are arranged in rows with a column of two symbols to the left of the page, a column of five symbols in the centre of the page and a yes and no answer box to the right-hand side of the page. The correct answer is yes, if the set of five symbols includes either of the two symbols on the left.

After demonstration and practice, the participant was asked to mark either the yes or no checkbox with a pencil in response to as many items as possible, within a 120 second time period. Matches occur at a rate of 50%, and total correct positive responses marked within the test period were counted to provide the raw score. The score was then converted to a scaled score, as per the administration and scoring manual (Wechsler 1997) and all participants undertook this assessment.

3.1.2.5.5 Letter-Number Sequencing Procedure

The tester read a sequence containing both numbers and letters and the participant was asked to reorder the stimuli by first repeating the numbers in ascending order and then the letters in alphabetical order. The sequence increased in duration from two items, a letter and a number to eight items, comprising four interspersed random letters and numbers. There were three trials for each sequence length and testing was discontinued if the participant could not correctly repeat all three sequences in each trial. Scores of 0, 1, 2 and 3 were allocated based on the participant's response. If the participant failed to correctly order and repeat a sequence for all 3 trials of a given length, a score 0 was given. When subjects failed to correctly reorder and repeat the sequence in 2 of the trials, a score 1 was given and when subjects failed to correctly reorder and repeat the sequence in 1 of the trials a score of 2 was given. A score of 3 was awarded when the participant correctly reordered and repeated the sequences for all 3 trials. Raw scores were calculated, depending on the number of trials correctly completed. The score was then converted to a scaled score, as per the administration and scoring manual (Wechsler 1997) and all participants undertook this assessment.

3.1.2.6 Auditory Processing Assessment

The selection of tests for the auditory processing assessment is described in section two (2.1.4). Assessment of auditory processing ability was undertaken using the compilation CD produced by Auditec Inc. (St. Louis, Mo., USA). All material relating to the tests of auditory processing was played on a Toshiba DVD player (Model no. SD-270EKB2) routed through the previously mentioned audiometer. The audiometer was calibrated using a 1000 Hz test tone on the CD, to present the test items at 0 on the volume unit (VU) meter (Brandy 2002).

3.1.2.6.1 Duration Pattern Sequence Test (DPST) Procedure

The DPST involves the presentation of series of three 1000 Hz tones of either 500 ms or 250 ms to each ear separately. In each trial, two of the three tones are of the same duration, with the other one being of a different duration. The 500 ms tone is the long tone (L) and the 250 ms is the short tone (S).

Thirty trials were presented to each ear using a combination of tone lengths, which could be LLS, LSL, SLL, SSL, SLS, or LSS. The trials were presented at 50 dB sensation level (SL), relative to the participants 1000 Hz threshold for that ear. The trials were presented in the order that they appear on the CD, although they are randomly arranged on the CD. Ten practice items were presented to each ear, to ensure that the participant could distinguish between the long and short tones, before the trials of thirty per ear began. The participant was asked to repeat the pattern of tones heard, using the descriptors long and short. Responses were marked as correct if the participant correctly identified the pattern, correct if they correctly identified the pattern but reversed the terminology long and short (reversal), or incorrect if they did not repeat the correct pattern. The number of correct and reversal responses were summed and then converted to a percentage score.

3.1.2.6.2 Pitch Pattern Sequence Test (PPST) Procedure

The pitch pattern sequence test uses series of three tone burst patterns. In each presentation, the one variable is the frequency of the tone presented. Of the three tones presented one will be of a different frequency to the other two. Tones of 1430 Hz are described as high (H) and of 880 Hz, as low (L). There are 150

milliseconds between each tone in the series of three and seven seconds between each series of tones.

The tones were presented at 50 dB sensation level (SL) relative to the participant's 1 kHz threshold for the ear to be tested. A set of ten practice tests were administered to ensure that the participant could distinguish the difference between the high and low tones before 30 trials were presented to each ear in turn. The series' were presented monaurally in the order that they appear on the CD, however the prepared material is randomised with respect to the tone burst combinations. If after 30 trials the participant's score was less than 90%, a further 30 trials were presented to that ear. Musiek (1994) found that participants may perform better on a second set of 30, for this particular test.

The participants were asked to repeat the pattern of tones heard using the words high or low to describe each pattern. The series combinations possible were HLH, HHL, HLL, LHL, LLH and LHH. The trial was marked correct if repeated accurately, as a reversal (if the sequence was correct but the high and low were reversed) or as incorrect if the pattern was not recognised. The number of correct and reversal responses were summed and then converted to a percentage score.

3.1.2.6.3 Dichotic Digits Procedure

Two different pairs of sequential digits were presented to each ear at the same time, at 50 dB SL relative to the PTA average of 500Hz, 1000Hz and 2000Hz for that ear. The pre-recorded material consists of pairs of numbers for presentation to each ear that are drawn from a pool of 1-9, excluding the number 7. The scoring of the participant's response was as per the scoring method described by Keith (1984). The participant was asked to repeat back all the digits heard, in any order. The response was marked as correct for each digit that was correctly repeated. Practice items included 10 double digits presented in the dichotic condition. 40 double digits were then presented and if all numbers were correctly repeated a score of 100% was given. The right ear score (RES) and the left ear score (LES) were calculated with the RES being the percentage of correctly repeated digits presented to the right ear and vice versa for the LES. By subtracting the LES from the RES, an ear advantage value could be calculated. All participants undertook this assessment.

3.1.2.6.4 Random Gap Detection Test (RGDT) Procedure

Stimuli comprising pairs of tones or clicks were presented binaurally, at 55 dB HL for all participants. The stimulus pairs were presented at 4.5-second intervals to allow time for participants to respond. Participants were asked to report whether they heard one or two stimuli in each presentation. Subtest one was a practice consisting of 500 Hz tone pairs with interstimulus interval (ISIs) presented in ascending order from 0-40 ms and this was used to familiarise the participant with the test. For the test runs (500-4000Hz) the ISI between each pair of tones increased and decreased in duration randomly. Subtest two consisted of four trials for the 500 Hz, 1000 Hz, 2000 Hz and 4000Hz tones. Subtest three was a practice for click stimuli with ISIs presented in ascending order from 0-40 ms and finally subtest four was the RGDT for clicks. The silent interval between the two tones or clicks ranged from 0 to 40 ms (0, 2, 5, 10, 15, 20, 25, 30, and 40 ms) randomly presented, although the test order was not randomised. Administration of the tests and scoring were carried out in accordance with the RGDT administration manual (Keith 2001). Responses were marked as 1 when the subject reported that they had heard one tone and 2 when they heard two tones. Thresholds were obtained by identifying from the score sheet the interval in milliseconds when the subject consistently commenced detection of two stimuli instead of one. A composite gap detection threshold (GDT) was calculated for the tones and a GDT for the clicks.

3.1.2.7 Otoacoustic Emissions Procedures

Transient evoked otoacoutic emissions (TEOAE) were collected for each participant unless there were contraindications to doing so, using an Otodynamics ILO292 Echoport analyser (Otodynamics Ltd, Hatfield UK), with ILO V6 clinical OAE software. Distortion-product otoacoustic emission (DPOAE) testing was only carried out if a participant did not have TEOAEs of at least 3 dB in three out of the five frequency bands tested. DPOAE testing was performed immediately after TEOAE testing for each ear, if required, using the same equipment as for TEOAE testing.

3.1.2.7.1 TEOAE Procedure

TEOAEs were elicited using conventional nonlinear clicks (80μs duration, 50 repetitions/s) presented at 84dB (± 3dB) peak equivalent in accordance with the technical manual and 260 responses were averaged for each participant with the noise rejection level set at 4 mPa. Prior to data collection the probe was calibrated using the software and 1 cm^3 calibration chamber supplied by the equipment manufacturer. The 'checkfit' mode was used prior to recording commencing, to ensure the best possible fit of the probe and that the appropriate stimulus level and stimulus waveform had been achieved. TEOAEs are usually evaluated with respect to the signal to noise ratios and percentage reproducibility or correlation estimate and these are used to determine the quality of the response. The ILO292 utilises two alternative buffers, A and B to average responses. The measure of reproducibility can be defined as the correlation coefficient between the A and B buffers. Noise is estimated from the difference between the waveforms stored in the A and B buffers and the signal is estimated from the sum of the A and B buffers, divided by two. Stability is a measure of probe fit or change in the stimulus over the recording period. For this study, measurements with stimulus stability of at least 90% were considered acceptable. The emission and noise amplitudes were analysed in half-octave frequency bands centred at 1.0, 1.4, 2.0, 2.8, and 4.0 kHz. A TEOAE was considered to be present if its amplitude was 3 dB above the level of the noise floor (Keppler et al. 2010), with overall reproducibility 70% or more across frequencies (Hall 2015). For a participant to be included, a TEOAE amplitude of 3 dB above the noise floor had to be present in three out of five of the frequency bands tested. All 60 participants were able to undertake this assessment for both ears.

3.1.2.7.2 DPOAE Procedure

For DPOAE assessment a two-tone stimulus complex (f1 and f2) was automatically swept across the f2 frequency range of 8000 Hz through to 1000 Hz. The frequency ratio (f2/f1) was 1.22, as this ratio has been shown to elicit the largest DPOAE levels across subjects (Probst et al. 1991). The intensity levels of the lower (L1) and higher frequency (L2) primary tones was fixed at 65 and 55 dB SPL respectively (Gorga et al. 1997). DPOAE responses were recorded at frequencies of 1, 1.5, 2, 3, 4, 6 and 8 kHz. A measurement-based stopping rule was used during

data collection, with measurement stopping after 60 seconds of artefact-free averaging (Gorga et al. 2005; Thorson et al. 2012). DPOAEs were considered to be present when the emission amplitude at individual frequencies was at least 6 dB higher than its associated noise amplitude (SNR≥6 dB).

3.1.2.8 Speech-In-Noise Testing Procedure

Speech Test Presenter (SPTester) BKB IHRSL version 2.05 software was used to present recorded BKB sentences with the participant seated at a distance of one metre directly in front of the speaker. There are 21 lists each containing 16 sentences, which can be presented in an adaptive manner or at fixed level, using a male or female voice. Using an adaptive methodology, results in a reduced time taken to determine threshold.

The adaptive BKB male test was selected, with female babble as background noise and two lists were administered per participant, with the score being the average for both lists. The sentences were presented with an initial speech level of 50 dB and a noise level of 70 dB SPL. The noise level was held constant, whilst the speech level was initially increased in 5 dB steps until the participant was able to identify all keywords. Testing continued with one-up-one-down adaptive level control and a step size of 2 dB. Participants were required to repeat as much of the sentence as they had heard. Keywords in the sentences were scored and if all keywords were identified, the sentence was given a correct score. The adaptive programme operates under a system of rules, with the rule being applied at the end of each trial depending on whether sufficient correct responses have been accumulated. Once all sentences have been played, an estimated threshold is calculated by taking the average either of the last number-to-score trials, or of the last number-to-score trials at which reversals occurred. This calculation is performed by the software. Lists 6 and 21 were presented for each participant and the average of the two lists were used as an overall estimate of threshold. It was expected that adult listeners should be able to achieve a 50% correct score at a SNR of 0dB or better.

3.1.2.9 Speech Audiometry Testing Procedure

Speech audiometry was performed in a similar manner to pure tone audiometry. A number of word lists were presented at different intensity levels in order

to plot a performance-intensity (PI) function. The aim was to determine at what level an individual could detect that speech was present at least 50% of the time, otherwise known as the speech detection threshold (SDT) and at what level an individual could understand what was being said, at least 50% of the time, otherwise known as the speech recognition threshold (SRT). The speech recognition threshold (50% correct point) is estimated from the PI function curve.

Speech audiometry was performed using the same audiometer and headphones, as used in pure-tone audiometry. The procedure for performing speech audiometry with monosyllabic word lists was undertaken as per guidelines (Evans, 1997 p. 147-149). This testing only occurred if a person scored above 0 dB on the Speech in Noise assessment. The calibration tone was played via the previously described Toshiba DVD player through channel A of the audiometer and the input to the audiometer was adjusted to generate a 0 dB VU reading for the calibration tone. The Dial setting (Ds) was calculated by averaging the results of the air conduction thresholds for 500Hz, 1000Hz, 2000Hz and 4000Hz. The masking dial setting (Dm) was calculated as per the formula provided by Evans (1997, p. 148). The first list was then presented at 30 dB above the Ds and the Dm was adjusted accordingly. The participant's repetition of a test word was recorded and the three phonemes scored as correct or incorrect. Any additions, omissions or substitutions were scored as incorrect (Boothroyd 2008). Once the list was scored, if 100% responses were correct, the Ds and DM were reduced by 10 dB and the procedure was repeated until scores of 10% or less were obtained. When a person could not achieve 100% score on the first list, the presentation level was increased in 10dB steps until a roll over in score occurred, the identification level of three adjacent test level was 95% or more, or the uncomfortable loudness level was reached. Scores were then plotted to produce a PI function curve. The process was undertaken for both ears individually.

3.1.2.10 Click ABR Procedure

A calibrated Bio-Logic Nav Pro system with AEP version 7.0 data acquisition software (Natus Medical, Inc. Mundelein, IL), was used for all ABR data collection. For the click ABR, 100 µs clicks were delivered to participants via standard Bio-logic insert earphones (580-SINSER-012) fitted with foam tips. A vertical montage of three disposable electrodes, high forehead (Fz non-inverting), Mastoid (M1 or M2, inverting), and Mastoid (M1 or M2, Common) electrode placement was used in

accordance with the 10-20 International system for scalp mapping (Klem et al. 1999). This combination of electrode placement was suitable for single channel recording of diagnostic ABRs in adults (Beattie et al. 1986) and allowed for better skin contact than when using vertex (Cz) placement with disposable electrodes in adults. Each participant had these areas of skin cleansed and exfoliated using Nuprep paste, to provide a good contact surface for the electrodes, as it is known that the outermost layer dead skin layer can act as an electrical insulator (ASHA 1987). Disposable electrodes were chosen, to best reflect current practice in the NHS in the United Kingdom. The electrodes were attached to these areas and the wires were braided to minimise artefacts. Prior to testing commencing, an impedance check was run to ensure that all three electrodes were registering impedances of less than 5 kΩ and were within 2kΩ of each other.

Testing was carried out in a dark room, with the participant asked to relax in a reclining chair, with their eyes closed and their head and neck fully supported. Participants were instructed to ignore the auditory stimulus. An alternating 100 μs click stimulus was presented at a rate of 13.1Hz, as low presentation rates allow more recovery time between firings and help maintain optimum synchronicity (Stach et al. 1994). This particular rate was chosen to minimise the electrical noise from any 50Hz mains sources in the area. A presentation intensity of 80dB nHL was chosen to ensure the maximum level of neural synchrony was achieved. It is known that for the ABR to be recorded, the participant will generally require less than 70 dB loss at 2 to 4 kHz (Cueva 2004).

As the ABR response is small in comparison to other electrical noise generated within the body, a range of techniques were used to process the signal. These included the use of filters to capture information in the frequency range of interest and the use of averaging to increase the signal to noise ratio. As per recommendations for diagnostic ABR recording, a time window of 10.66 ms, and a bandpass filter of 150-3000Hz were chosen (Stach et al. 1994). A minimum of two blocks of 1024 sweeps were collected for each ear, to provide two comparable waveforms. Online artefact rejection was set to ±23μV and the sampling rate was 24000Hz. This protocol has been used previously within this clinic and there is an established normative data set for this equipment.

All participants underwent ABR assessment and once two comparable waveforms were collected, the grand average waveform for the left ear and the right ear were calculated and analysis was performed. The latencies of waves I, III and V

were marked for each set of waveforms, allowing interpeak latencies to be calculated. The peak method was used for waves I and III and the shoulder method for wave V, in an attempt to prevent the mislabelling of wave IV as wave V. Latency decisions were made using the following criteria, based on data collected for adults (Hall 2007) and for adults with and without hearing loss (Burkard and Sims 2001):

- For wave I, the point of maximum positivity between 1 and 2 ms.
- For wave III, the point of maximum positivity between 3 and 4 ms.
- For wave V, the shoulder of the point of maximum positivity between 5 and 6 ms.

3.1.2.11 Speech ABR Procedure

Speech ABR recording followed immediately after recording the click ABR and as such the electrode configuration and insert earphone used, as described in section 3.1.2.10, remained the same. Prior to each recording session, the /da/ stimulus was calibrated to 80 dB SPL using a Cassella CEL-254 sound level meter coupled to an insert earphone adaptor. The SPL was sampled over a 60 second period to obtain an average.

All responses were recorded using the BioMARK default setting within the Navigator Pro AEP system. Recordings were performed in accordance with the procedures reviewed in the previous section (see Skoe and Kraus 2010a). Before full recording commenced, a run of 500 trails with the insert earphone tubes clamped shut was performed to check for any artefact. During testing the participants were advised that they should relax as much as possible but minimise any movement whilst the /da/ was playing. They wore one insert earphone at any one time and this allowed them to watch a DVD of their choice, played at a background level of no greater than 40 dB SPL. This method was employed in an attempt to facilitate relaxation and to control their level of alertness (Hornickel et al. 2009a,b; Krizman et al. 2010). The five formant speech syllable /da/ was played through the insert earphones. As previously described, it consists of an initial 5ms onset burst, with the fundamental frequency (F0) rising linearly from 103 to 125Hz, the first formant (F1) rising from 220 to 720Hz, the second formant (F2), decreases from 1700 to 1240Hz, the third formant (F3) decreases from 2580 to 2500Hz whilst the fourth formant (F4) and the fifth formant (F5) remain constant at 3600hz and 4500Hz for the duration of the stimulus (Krizman

et al. 2012a; Skoe and Kraus 2013). The stimulus was presented at a rate of 10.9 Hz in alternating polarities to minimize any stimulus artefact and the presence of the cochlear microphonic (Russo et al. 2004; Aiken and Picton 2008). With summed responses, the envelope following response was enhanced (Aiken and Picton 2008; Skoe and Kraus 2010a; Campbell et al. 2012).

Online artefact rejection was set to ±23μV and three blocks of 2000 sweeps were collected for each ear at 80 dB SPL. Responses were averaged using a 85.33 ms window, including 15 ms of pre-stimulus activity. The responses were bandpass filtered online from 100-2000 Hz (Butterworth filter, 12 dB/octave, zero phaseshift) and digitally sampled at 12000 Hz (Anderson et al. 2013). The guidelines presented in the technical manual were adhered to regarding the acceptable artefact rejection rate, with the aim being to maintain an artefact rejection rate of below 10% but including responses with up to 20% rejection if this proved to be unachievable (AEP Systems User's and Service Manual p.207). For each participant, a grand average of the speech ABRs for the left ear and for the right ear was calculated. The grand averages were converted to ASCII format using the 'AEP to ASCII' software function (Bio-Logic Systems Corp. version 1.3.0). These files could then be imported into the Brainstem Toolbox software (Skoe and Kraus 2010). This software runs on the MATLAB® version 2007a, MathWorks Inc., Natick, MA) platform and contains custom routines developed by Erika Skoe and Trent Nicol (Brainstem Toolbox 2008), which can be used to perform analyses of the waveform. This approach to analysis follows that of the team at the Auditory Neuroscience Laboratory at Northwestern University (Russo et al. 2009; Skoe and Kraus 2010a; Krizman et al. 2012a).

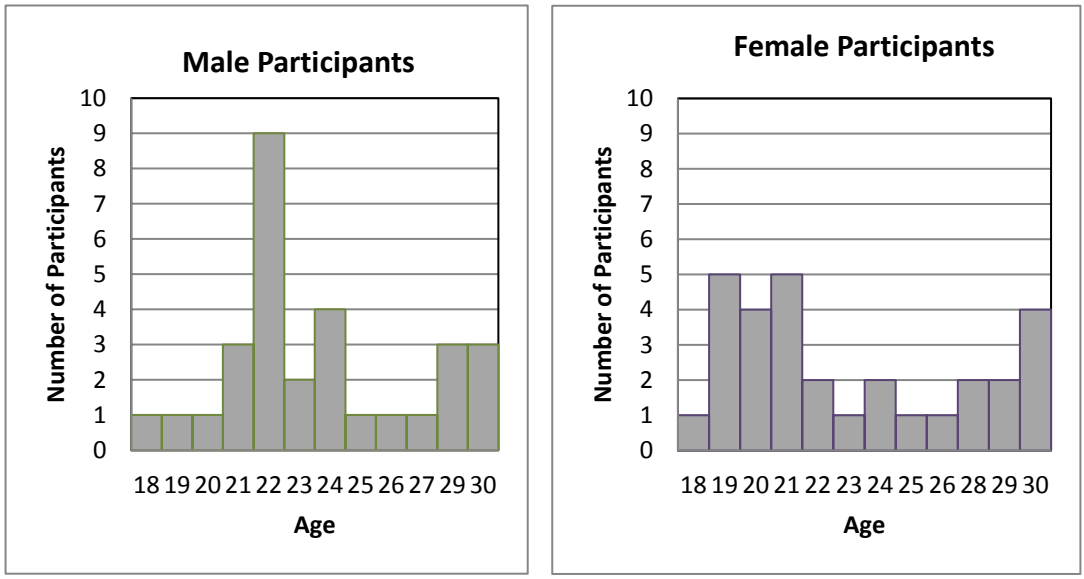
3.1.3 Results and Analysis of the Auditory-Cognitive Profile of Participants

The following discussion of results relates to the 60 participants who met the inclusion criteria, as set out in section 3.1.1 and all participants completed all aspects of testing. In all cases prior to analysis the Shapiro-Wilks Francia test was applied to established that the data for males and females was normally distributed. The results of speech ABR testing are presented in sections 3.2 and 3.3.

3.1.3.1 Age Profile of Participants

Data is presented from the 30 male and 30 female participants whose results contributed to generating control data for healthy adults. All 60 participants completed all aspects of the auditory-cognitive profile assessment. The mean age of the male participants was 23.83 years (S.D. 3.41) and the mean age of the female participants was 23.27 years (S.D. 4.13). The age profile of the participants is presented in figure 12.

Figure 12. Age Profile of the Participants



3.1.3.2 Pure Tone Audiometry

To meet the inclusion criteria an individual's pure tone hearing thresholds for 250 Hz, 500 Hz 1000 Hz, 2000 Hz, 4000 Hz and 8000 Hz could be no greater than 20 dB HL bilaterally. Results for the right ears and left ears for the male participants are presented in the figures below (Figs. 13 to 16).

Figure 13. Pure Tone Audiometry Results for Males (Mean and S.D.): Right Ear

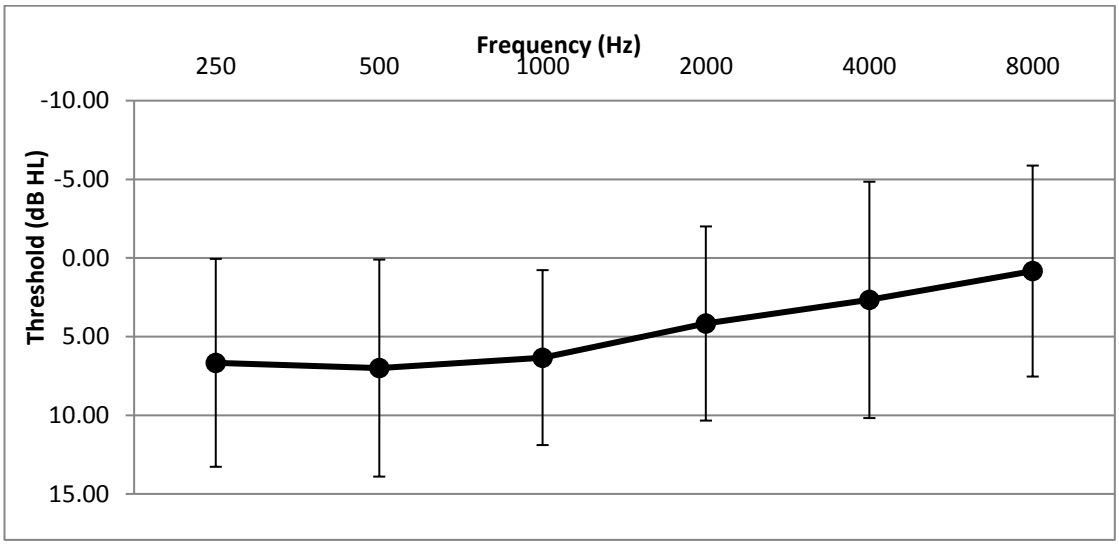
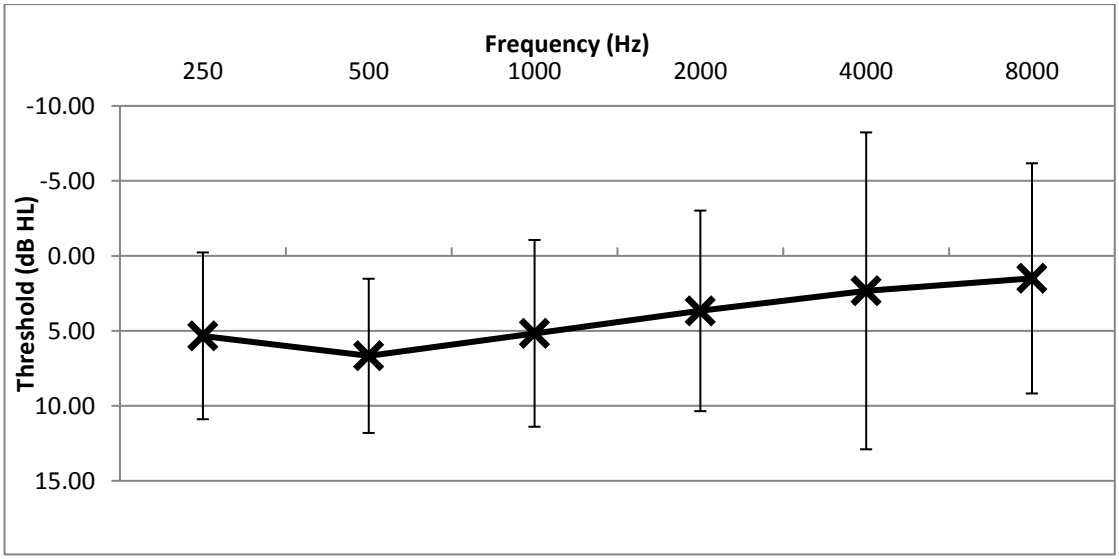


Figure 14. Pure Tone Audiometry Results for Males (Mean and S.D.): Left Ear



Results for the right ears and left ears for the female participants are presented in the figures below.

Figure 15. Pure Tone Audiometry Results for Females (Mean and S.D.): Right Ear

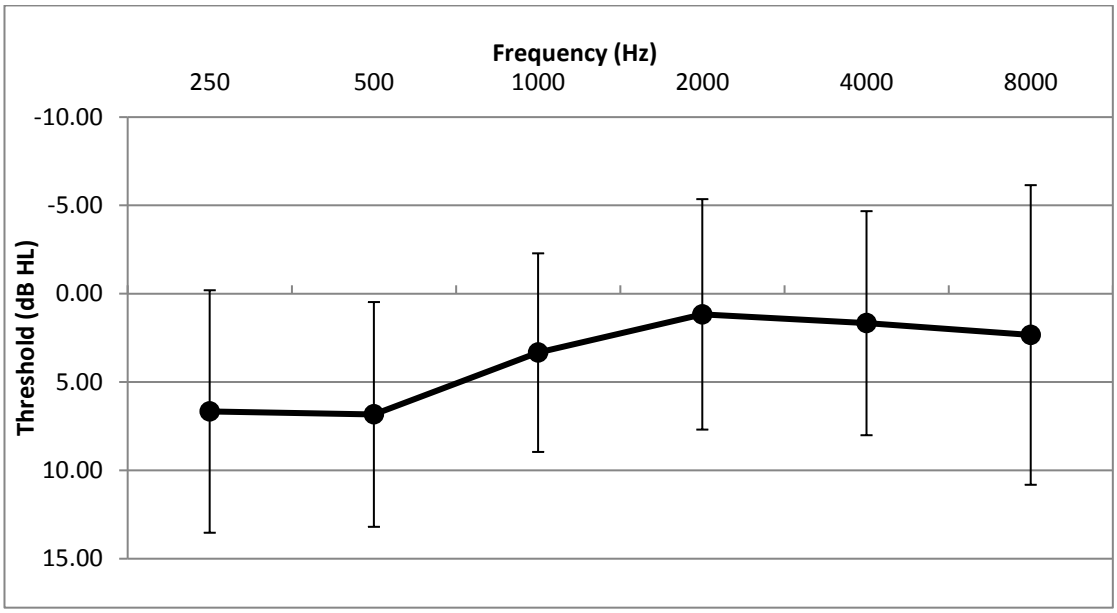
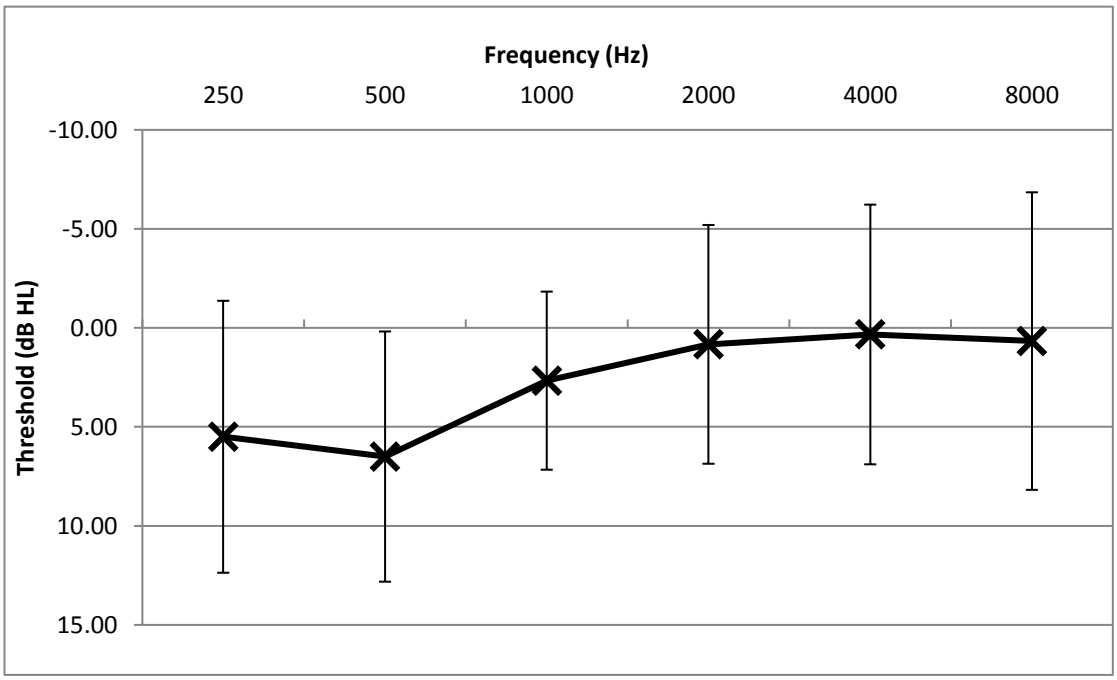


Figure 16. Pure Tone Audiometry Results for Females (Mean and S.D.): Left Ear



3.1.3.2.1 Interpretation of Results for Pure Tone Audiometry

Data for the healthy adults (age 18-30 years) are presented in table two for comparison with other results from UK adults in this age range. ISO 7029:2017 is an

international standard that presents the 'statistical distribution of hearing thresholds related to age and gender.' This data is based on a review of twenty-one studies from around the world that have published hearing threshold data, recorded since 1980. Table D.1 in Annex D of the standard provides the statistical distribution of hearing threshold deviations. The median value for adults aged 30 years is 0dB deviation from 0, up to 2000Hz. At 2000 Hz we could expect a deviation of 1dB for 50% of males. At 2000Hz it is 1dB for both males and females and at 8000Hz it is 2dB for males and 1 dB for females. The maximum deviation from 0 from the frequencies of interest is 11dB for 10 % of females aged 30 (ISO 7029:2017). Lutman and Davis (1994) revisited the expected hearing thresholds for adults in the age range of 18 to 30 years. Data for young adults who have been screened as being 'otologically normal', with no evidence of pathology are presented in brackets (Table 3). They did not find any significant differences between males and females, which would imply that the data is not gender specific.

Table 3. Average PTA results of Participants from Experiment One and from the Study by Lutman and Davis (in brackets).

	250Hz	500Hz	1000Hz	2000Hz	4000Hz	8000Hz
Median	5.0 (8.0)	5.0 (5.0)	5.0 (2.5)	0.0 (4.0)	0.0 (6.5)	0.0 (8.5)
Mean	6.0 (8.4)	6.8 (5.5)	4.4 (4.1)	2.5 (4.5)	1.8 (8.0)	1.3 (9.6)
S.D.	6.4 (4.2)	6.1 (4.4)	5.6 (4.2)	6.4 (4.6)	7.9 (6.9)	7.6 (7.9)

The results of pure tone audiometry testing for the 60 adults included within this study are comparable with the findings presented by Lutman and Davis (1994). The group of adults in this study has better pure tone hearing thresholds at the higher frequencies, approaching the 0 dB benchmark (ISO 7029: 2017).

3.1.3.3 Cognitive Assessment

The mean values of the scaled score results for the subtests of the WAIS-III^{UK} assessment are presented in the following table (Table 4).

Table 4. Mean Values for Scaled Scores from Subtests of the WAIS-III^{UK}

WAIS-III^{UK} Subtest	Males (S.D.)	Females (S.D.)
Vocabulary	12.1 (0.27)	11.6 (0.26)
Digit-Symbol Coding	9.8 (0.44)	11.8 (0.39)
Digit Span	11.4 (0.46)	11.1 (0.53)
Symbol Search	11.3 (0.37)	12.2 (0.42)
Letter-Number Sequencing	11.4 (0.37)	11.5 (0.42)

3.1.3.3.1 Interpretation of Results of the Cognitive Assessment

Age related scaled scores on the WAIS-III^{UK} allow comparison of scores to the 'standardisation sample' provided in the WAIS-III^{UK} administration and scoring manual (Wechsler 1997). Scaled scores have a mean of ten and a standard deviation of three. All individual scores were above the lower cut off point of seven, indicating that no individuals were performing below the lower acceptable limit for normal function on any of the subtests administered.

3.1.3.4 Auditory Processing Capability Assessment

The mean values for the individual auditory processing tests are presented in individual tables within the following section. Auditory temporal processing and patterning can be assessed by the duration pattern sequence and pitch pattern sequence tests. A combination of duration pattern sequence test and pitch pattern sequence test can identify lesions in either hemisphere and/or the corpus callosum (Musiek 1994). Auditory temporal resolution can be assessed by the Random Gap Detection Test which is purported to be sensitive to lesions within the central auditory nervous system (Boscariol et al. 2009). Binaural integration can be assessed by the dichotic digits test, which is thought to be sensitive to cerebral and interhemispheric lesions, as well as brainstem lesions (Musiek 1983).

3.1.3.4.1 Results of Duration Pattern Sequence Testing

The results of the DPST are presented in table five below and all participants undertook this assessment.

Table 5. Results of Duration Pattern Sequence Testing (Mean and S.D.)

DPST Score	Males		Females	
	Right Ear (S.D.)	Left Ear (S.D.)	Right Ear (S.D.)	Left Ear (S.D.)
Mean % Correct	95.7 (6.96)	93.8 (7.10)	95.1 (8.39)	95.2 (6.00)

3.1.3.4.1.1 Interpretation of Results

Auditec provide a suggested cut off for scores of 67% or lower to be considered outside normal limits. All individual scores were above 70%, indicating that all individuals performed within accepted normal limits for this test of pattern processing.

3.1.3.4.2 Results of Pitch Pattern Sequence Testing

The results of the PPST are presented in table six below and all participants undertook this assessment.

Table 6. Results of Pitch Pattern Sequence Testing (Mean and S.D.)

PPST Score	Males		Females	
	Right Ear (S.D.)	Left Ear (S.D.)	Right Ear (S.D.)	Left Ear (S.D.)
Mean % Correct	98.9 (2.81)	98.6 (3.12)	99.2 (1.89)	99.8 (0.84)

3.1.3.4.2.1 Interpretation of Results

Auditec suggest that scores are within normal limits if they fall between 88 and 100%. All individual scores were above 90%, indicating that all individuals performed within accepted normal limits for this test of pattern processing.

3.1.3.4.3 Results of Dichotic Digits Testing

The results of the dichotic digits assessment are presented in table seven below and all participants undertook this assessment.

Table 7. Results of Dichotic Digits Testing (Mean and S.D.)

DD Score	Males		Females	
	Right Ear (S.D.)	Left Ear (S.D.)	Right Ear (S.D.)	Left Ear (S.D.)
Mean % Correct	96.8 (3.16)	95.6 (3.92)	96.7 (3.90)	95.4 (4.60)

3.1.3.4.3.1 Interpretation of Results

Auditec suggest that scores are within normal limits if they fall between 82 and 100%. All individual scores were above 85%, indicating that all individuals performed within accepted normal limits for this test of pattern processing.

3.1.3.4.4 Results of Random Gap Detection Testing

The results of the RGDT are presented in table eight below and all participants undertook this assessment.

Table 8. Results of Random Gap Detection Testing (Mean and S.D.)

Measures of RGD	Males		Females	
	Tones (S.D.)	Click (S.D.)	Tones (S.D.)	Click (S.D.)
Mean RGDT threshold in ms	5.48 (2.79)	6.13 (4.43)	6.08 (2.57)	6.63 (3.63)

3.1.3.4.4.1 Interpretation of Results

Auditec suggest that gap detection results are within normal limits if they fall under 20ms. All individual scores were within this limit, indicating all individuals performed within accepted normal limits for this test of gap detection. These results are comparable with a recent study by Sousa et al. (2012) who found that for normal hearing adults aged 18 to 25 years, the average RGDT for tones was 6.72 ms and the mean RGDT for clicks was 6.43 ms.

3.1.3.5 TEOAE Testing

The results of TEOAE and DPOAE testing are often used as an objective cross-check to confirm the evidence of normal hearing, as indicated by PTA results. A TEOAE was considered to be present if its amplitude was 3 dB above the level of the noise floor, with stability of 90% and overall reproducibility 70% or more across frequencies (Keppler et al. 2010; Hall 2015). The results are presented in table nine.

Table 9. Results of TEOAE Testing (Mean and S.D.)

TEOAE Measure	Males		Females	
	Right Ear (S.D.)	Left Ear (S.D.)	Right Ear (S.D.)	Left Ear (S.D.)
Reproducibility	88.03 (10.1)	88.97 (9.25)	93.37 (6.17)	92.67 (7.08)
Stability	99.43 (0.57)	98.97 (1.10)	98.80 (2.07)	98.90 (1.16)
1.0kHz	12.57 (8.26)	11.28 (7.13)	11.16 (7.40)	13.10 (7.68)
1.4kHz	14.53 (7.30)	13.57 (7.34)	15.08 (8.00)	15.81 (6.4)
2.0kHz	11.67 (7.78)	13.19 (6.79)	15.75 (4.87)	15.74 (5.72)
2.8kHz	10.15 (7.40)	10.10 (7.50)	16.25 (4.82)	13.98 (6.03)
4.0kHz	7.48 (7.24)	7.56 (6.75)	10.16 (6.32)	11.29 (5.86)

3.1.3.5.1 Interpretation of Results of TEOAE Testing

All participants had a TEOAE present at 3 dB above the level of the noise floor in at least 3 out of 5 frequency bands, with reproducibility of response at greater than 70%. This would indicate that all participants had hearing threshold levels, at these frequencies, of 25-30 dB HL or better (Probst and Harris 1993) and this is in agreement with the results of pure tone audiometry testing. As all participants met the criteria for presence of TEOAEs, DPOAE testing was not performed.

3.1.3.6 Results of Speech-In-Noise Assessment

As some people can have ‘normal hearing’ as measured using PTA but still perform poorly in difficult listening situations, a speech-in-noise assessment was used to assess whether any participants had a signal to noise ratio (SNR) loss. All participants undertook this assessment and the results are presented in table ten.

Table 10. Results from the Speech in Noise Assessment (Mean and S.D.)

SIN Measure	Males (S.D.)	Females (S.D.)
Mean SRT for 50% correct score in decibels	-4.13 (1.31)	-4.03 (1.27)

3.1.3.6.1 Interpretation of results

A signal to noise ratio loss occurs if a person's speech reception threshold in background noise is in excess of what would be expected for someone with 'normal' hearing. There are no normative results provided with the version of BKB speech-in-noise test used in this assessment. However, previous data from this clinic for adults with normal hearing found that the mean SRT value was -3, with a standard deviation of 1. A score of 0 seems to be an appropriate cut off value for use with adults without measurable hearing loss. As can be seen from table ten, all adults within this study had SRT scores of less than 0 dB and therefore further speech audiometry in quiet was not performed.

3.1.3.7 Results of Click Evoked Auditory Brainstem Response Testing

It is established best practice to use local clinical normative data for assessing ABR results (Hall 2007). Typically, when looking at speech ABR, the criterion for the click ABR is a 'normal' wave V latency (e.g. Dhar et al. 2009; Song et al. 2011). For the protocol used in this study, the normative data results previously collected within Queen Margaret University for adults aged 18 to 30 years are presented in table 11.

Table 11. Normative Data for QMU Clinic (Mean and S.D.)

ABR Component	Sex	Mean latency in ms (S.D.)	Range: ± 2 S.D.
Wave V	Male	5.55 (0.23)	5.09 - 6.01
	Female	5.42 (0.23)	4.96 - 5.88

3.1.3.7.1 Latency of Click ABR Responses

Two audiologists independently marked the grand average ABR waveform data derived from the 60 participants (Vidler and Parker 2004) and this resulted in a data set of 120 waveforms for the click evoked ABR. For all waveforms, the examiners

were asked to complete a table to indicate whether they felt replicable waves were present in the constituent traces that contributed to the grand averaged waveform. For the click ABR the examiners were in agreement that waves I, III and V could be reliably identified in 100% of waveforms.

For a participant to be included within this study, their individual ABR wave V latency results for click ABR testing had to fall within the ranges outlined in table eleven. All 60 participants met these criteria and their results are detailed in table 12. Applying the Shapiro-Wilks Francia test established that the click ABR data for males and females was normally distributed.

3.1.3.7.1.1 Within and Between Participant Effects

A mixed ANOVA was performed with repeated measures to look at within subject differences in the latency and amplitude values of the click ABR recorded from right and left ears, as well as between subject differences in respect to sex. No significant differences were found between the responses from the right and left ears. There was a significant difference in the click ABR responses between men and women $F(1, 58) = 29.83$, $p = <0.001$.

Performing post hoc, independent samples t-tests on the click ABR and applying a Bonferroni correction for multiple comparisons, confirms that all measures apart from the interpeak latency of waves III-V are significantly different in men and women (Table 12). For waves III and V of the click ABR, women's responses were earlier than men's by 0.14ms and 0.19ms. As no significant differences were detected, whether using right or left ear presentation to elicit the response, right ear only has been used for the comparison of waveforms from males and females.

Table 12. Comparison of Latency Values for the Click ABR for Men and Women (Right Ear, Mean and S.D.)

Mean ABR Component latency in ms	Male (S.D.)	Female (S.D.)	t	p
Wave I	1.57 (0.12)	1.50(0.09)	3.21	0.002*
Wave III	3.72 (0.14)	3.58 (0.14)	5.42	<0.001*
Wave V	5.64 (0.15)	5.45 (0.17)	6.66	<0.001*
Waves I-III	2.15 (0.14)	2.08 (0.14)	2.94	0.004*
Waves III-V	1.92 (0.16)	1.87 (0.16)	1.95	0.054
Waves I-V	4.07 (0.19)	3.94 (0.16)	4.01	<0.001*

* Result remains significant after correcting for multiple comparisons

It is also the case that the amplitudes of waves I and III were significantly higher for women than men (Table 13). Wave I was higher by 0.04 µV and wave III was higher by 0.08 µV for the women.

Table 13. Comparison of Amplitude Values for the Click ABR for Men and Women (Right Ear, Mean and S.D.)

Mean ABR Component Amplitude in µV	Male (S.D.)	Female (S.D.)	t	p
I	0.04 (0.08)	0.08 (0.07)	-2.73	0.007*
III	0.19 (0.10)	0.27 (0.11)	-4.31	<0.001*
V	0.05 (0.10)	0.05 (0.11)	0.21	0.836

* Result remains significant after correcting for multiple comparisons

3.1.3.7.1.2 Interpretation of Click ABR Results

The ABR wave data is consistent with the previously reported normal range for adult subjects (Jacobson 1985; Hall 2007; Hood 1998). Latency data from the right and left ears should be comparable if hearing is within the normal range or symmetrical in nature. Differences in absolute latency from the left and the right ears are often used to detect retrocochlear pathology. For the interaural Wave V latency, there should be no more a than 0.3–0.4 ms millisecond difference between ears (ASHA 1987). In this study, no significant differences were found between the peak latencies of the right and left ears for men and women. However, there is a wealth of evidence to support the finding of differences in ABR waveforms between men and women. In general, waveforms recorded from female subjects have shorter latencies and larger amplitudes across the adult lifespan (Jerger and Hall 1980). Wave I latency is usually the least affected, resulting in shorter I-V interpeak latencies for women. There are two proposed explanations for this effect, the first being that women tend to have smaller head sizes, therefore the distance between generator sites is shorter, so the time taken to travel is less and the amplitude recorded greater, if the electrode is closer to the generator site. The second relating to the fact that there are physiologic and biochemical differences between men and women, which affect neurotransmission (Hall 2007; Hornickel et al. 2009). The sex differences found for the click ABR within this study are in agreement with the literature published on this topic.

Amplitude data is considered to have minimal clinical importance (Hall 2007) because of the substantial normal variability of this measure. There are a number of reasons for this variability including choice of site of electrode placement, effects of 'subject' movement, filter bandwidth, peak picking criteria and choice of amplitude measurement. The conclusion of studies of effects of electrode placement has been that much larger response amplitudes will be recorded when using Cz as opposed to a high-forehead placement (ibid.). As previously discussed, 'peak picking' approaches can vary from the maximum amplitude approach to the shoulder approach, with the maximum amplitude approach resulting in higher amplitude measurements. Depending on whether amplitudes are recorded using a peak to trough method or a peak to baseline method, will also have an impact on amplitude size. In this study, the shoulder method of peak picking was used in association with the baseline generated by the system manufacturer's software. The amplitude data has been recorded to allow for comparisons with the participants comprising the clinical group in the second part of this study.

Whilst there is no apparent requirement for separate ear related normative data, it is prudent to have separate data for men and women, as the upper latency range for men is higher than for women, as can be seen in the table below (Table 14).

Table 14. Latency Range for Click ABR Measures for Men and Women (Pooled Ear Data).

ABR Component	Latency Range in ms (Mean ± 2SD)	
	Men	Women
Wave I	1.33 - 1.81	1.32 - 1.68
Wave III	3.44 - 4.00	3.30 - 3.86
Wave V	5.34 - 5.94	5.11 – 5.79
I-III	1.87 - 2.43	1.80 – 2.36
III-V	1.6 - 2.24	1.55 – 2.19
I-V	3.69 - 4.45	3.62 – 4.26

3.1.4 Summary

The aim of this part of the study was to generate some control data for men and women with no demonstrable deficits in auditory or cognitive function. The results of the auditory-cognitive profile assessment indicated that the 60 adults included in

this study had auditory-cognitive profiles typical for their age. There was no evidence of hearing impairment or a deficit in cognitive function that might negatively affect speech perception and recognition.

3.2 Inter-Rater Reliability of the Speech ABR

The aim of this section within Experiment One is to answer the research question which arose from the literature review undertaken in section two. The research question is: What is the inter-rater agreement for the speech ABR?

3.2.1 Participants

Three experienced audiologists, including the researcher were asked to mark the grand average click and speech ABR waveform data, as per the procedures detailed in section 3.2.2.3.

3.2.2 Methods

The following section details the participants and the methods used to perform an inter-rater reliability assessment of the speech ABR.

3.2.2.2 ABR Data Collection Procedures

The procedures for collecting the click and speech ABR waveforms are detailed in sections 3.1.2.10 and 3.1.2.11.

3.2.2.3 Waveform Marking Procedure

Three audiologists analysed the grand average ABR waveform data derived from 30 of the participants. This constituted a data set of 60 waveforms for the click ABR and 60 waveforms for the speech ABR. Each rater was blind to the identity and sex of the participants. The examiners were asked to label waves I, III and V of the click ABR waveforms in accordance with Hall (2007). The peak method was used for waves I and III and the shoulder method for wave V in an attempt to prevent the mislabelling of wave IV as wave V. For the purposes of analysis, the two 1024 sweep trials were used as a guide for marking the calculated waveform. The zoom function was used at its maximum to assist in identifying the proper location for waveform marking. Reviewing the individual waveforms allowed reproducibility of the waves to be assessed and aided in peak picking decisions.

The examiners were asked to label the speech ABR waveforms in accordance with the guidance presented by Skoe and Kraus (2010a).The analysis consisted of the visual inspection of the waveforms and identification, where possible, of waves V, A, C, D, E, F and O (Johnson et al. 2005; Kraus and Nicol 2005; Skoe and Kraus 2010a). For the purposes of analysis, the three 2000 sweep trials were used as a guide for marking the calculated waveform (grand average of 6000 sweeps). The zoom function was used at its maximum to assist in identifying the proper location for waveform marking. For all waveforms the examiners were asked to complete a table to indicate whether they felt replicable waves were present in the constituent traces that contributed to the grand averaged waveform.

3.2.3 Results and Analysis for the Click ABR

All raters were able to reliably identify 100% of individual peaks in the click ABR waveforms. To determine inter-rater reliability, comparisons were made between the raters marked waveforms. A two-way random effects single measure model (ICC2,1) with 95% confidence interval (CI) was used to calculate the intraclass correlation coefficients using SPSS, version 19 (Table 15). This formula was used as waveforms were labelled by all three raters and each rater analysed each waveform on a single occasion. The absolute agreement definition was used to account for any potential systematic bias that might occur between raters.

Table 15. Intraclass Correlation Coefficients for Click ABR Waveform Marking

ABR Component	Left Ear ICC (95% CI)	Right Ear ICC (95% CI)
Wave I	0.92 (0.87-0.96)	0.89 (0.78-0.94)
Wave III	0.96 (0.92-0.98)	0.98 (0.96-0.99)
Wave V	0.95 (0.90-0.97)	0.91 (0.85-0.96)

3.2.3.1 Interpretation of Results for the Click ABR

For this study the ICC coefficients were assessed in accordance with Currier (1990) with the following classification of: 0.90–0.99: high reliability, 0.80–0.89: good reliability, 0.70–0.79: fair reliability, and ≤ 0.69: poor reliability. For the click ABR waveforms the ICC coefficient was ≥0.89 in all cases, with only wave I for the right ear falling below high reliability, with an ICC coefficient of 0.89 (Table 15). As

previously established, the ABR when elicited by click has an inter-rater agreement in excess of 81% (Kjaer 1979; Rossman and Cashman 1985; Pratt et al. 1995; Olsen et al. 1997; Naves et al. 2012a; Naves et al. 2012b). In this study we found that the majority of waves had high inter-rater reliability, with only one in the good reliability category. These findings are in accordance with claims in the general ABR literature that the ABR is reliable and it also demonstrates that the raters in this study were suitably experienced in labelling click ABR waveforms.

3.2.4 Results and Analysis for the Speech ABR

The inter-rater reliability assessment was performed as per section 3.2.3. The results for the speech ABR waveform marking are presented in the following table (Table 16).

Table 16. Intraclass Correlation Coefficients for Speech ABR Waveform Marking

Speech ABR Component	Left Ear ICC (95% CI)	Right Ear ICC (95% CI)
Wave V	0.93 (0.88-0.96)	0.97 (0.94-0.98)
Wave A	0.87 (0.78-0.93)	0.92 (0.85-0.96)
Wave C	0.45 (0.23-0.66)	0.59 (0.39-0.76)
Wave D	0.75 (0.60-0.86)	0.75 (0.60-0.86)
Wave E	0.99 (0.99-0.99)	0.89 (0.81-0.94)
Wave F	0.83 (0.71-0.91)	0.96 (0.92-0.98)
Wave O	0.98 (0.96-0.99)	0.99 (0.98-1.00)

For all waveforms the examiners were asked to complete a table to indicate whether they felt replicable peaks were present in the constituent traces that contributed to the grand averaged waveform. The raters were able to identify the peaks in the waveforms as detailed in table 17.

Table 17. Average Detectability (%) of Individual Peaks of the Speech ABR in Healthy Control Participants

Transient Measure	V	A	C	D	E	F	O
Average % detectability	100	100	95	97	100	98	98

3.2.4.1 Interpretation of Results for the Speech ABR

For the waveforms elicited by the more complex stimulus /da/, $ICC_{2,1}$ was high for waves V, E and O for the left ear (0.93-0.99) and for waves V, A, F and O for the right ear (0.92-0.99). $ICC_{2,1}$ was good for waves A and F for the left ear (0.83-0.87) and wave E for the right ear (0.89). $ICC_{2,1}$ was fair for waves D for the left and right ears (0.75). Waves C for both the left and right ear had poor reliability. For all waves except wave E, the inter-rater reliability was at least as good or better for those traces recorded from the right ear, than for those recorded from the left ear.

As discussed in section two (2.3.7), wave C is often excluded from results as it is not reliably identifiable (Hornickel et al. 2009; Skoe and Kraus 2013; Skoe et al. 2015a; Zakaria et al. 2016). From the findings regarding inter-rater reliability assessment, it would appear that this is not a reliable feature of the waveform recorded from healthy adults with no hearing loss. It is, therefore, of limited use in assessment of the waveform. This has an impact on waveform analysis, as wave C should be excluded. The time window for analysis of the FFR must be reduced from the standard of 11.4–40.6 ms to a period of 21.9–40.6 ms (Hornickel et al. 2009). This time window encompasses the range of latencies observed for peaks D, E, and F but excludes the inclusion of the wave C area of the waveform.

3.2.5 Addressing the Research Question

It has been found that the inter-rater agreement coefficient for the speech ABR to /da/ is at least 0.75 for all discrete elements, except for wave C. At present, there is no consensus on acceptable values for ICC coefficients in relation to test utility. Chinn (1991) recommends an intra-class correlation coefficient of at least 0.6, if a measure is to be useful. A clinically acceptable correlation has been proposed as being 0.75 or 0.80 (Shrout and Fleiss 1979), with Fleiss (1981) and Cicchetti and

Sparrow (1981) proposing the following classification: < 0.40 = poor, 0.40 – 0.59 = fair, 0.60 – 0.74 = good,> 0.74 = excellent. For this study the ICC coefficients were assessed in accordance with Currier (1990) and the results would suggest that waves V, A, D, E, F and O have sufficient inter-rater reliabilities to be considered when performing analyses. This finding calls into question any previously published findings which rely on the inclusion of wave C, when drawing conclusions. Specifically wave C is thought to represent the onset of the voicing and alongside wave O marks the boundary of the envelope (Johnson et al. 2005; Dhar et al. 2009). Analyses which rely on looking at the envelope boundary (Dhar et al. 2009), are therefore based on an unreliable measure.

3.3 Speech ABRs from the Right and Left Ears of Men and Women

The aim of this section within Experiment One is to answer research questions about specific participant factors which arose from the literature review undertaken in section two. Specifically, the research questions to be answered are:

- What is the effect of ear of presentation on the speech ABR?
- What is the effect of sex on the speech ABR?

3.3.1 Participants

Details of the 60 participants have been provided in section 3.1.1.

3.3.2 Methods

The following section details the participants and the methods used to answer the research questions relating to potential ear and sex differences in the speech ABR.

3.3.2.2 Speech ABR Procedure

The procedure used to collect and mark the speech ABR waveforms has been described in section 3.1.2.11. Two experienced audiologists independently marked the grand average ABR waveform data derived from the 60 participants (Vidler and Parker 2004) and this resulted in a data set of 120 waveforms for the speech ABR. If the two raters were not in accordance regarding marking of a peak latency, the peak was marked as ‘not reliable’ and excluded from analyses. Peaks were also marked as ‘not reliable’ if they were smaller than the average amplitude of the pre-stimulus baseline activity and therefore excluded from analyses.

3.3.3 Data Analysis and Results

The data analysis and results relating to discrete peak, composite onset measure, stimulus to response correlation and spectral encoding measures of the speech ABR, are presented in the following sections.

3.3.3.1 Discrete Peak and Composite Onset Measures Analysis

A mixed ANOVA with repeated measures for ear and between participant effects for sex was performed. The intention was to assess any within subject differences of the discrete peak and composite onset measures of the speech ABR recorded from right and left ears, as well as between subject differences in respect to sex. No significant differences were found between the responses from the right and left ears. There was a significant difference in these measures of the speech ABR responses between men and women $F(1, 58) = 34.37$, $p = <0.001$.

Performing post hoc independent samples t-tests on the discrete peaks of the speech ABR and correcting for multiple comparisons confirmed that many of the discrete peak measures apart from waves D and E (sustained portion) are significantly different in men and women (Table 18). The interpeak latencies within the FFR portions of the waveform are not different between men and women. However, the slope of the onset response is different between men and women. As no significant differences were detected whether using right or left ear presentation to elicit the response, right ear only has been used for the comparison of waveforms from males and females.

Table 18. Discrete Peak and Composite Onset Measures of the Speech ABR for Men and Women (Right Ear, Mean and S.D.)

Speech ABR Component	Male (S.D.)	Female (S.D.)	t	p
wave V (ms)	6.98 (0.29)	6.55 (0.26)	6.09	<0.001*
wave A (ms)	7.95 (0.30)	7.46 (0.33)	5.98	<0.001*
wave D (ms)	22.99 (0.85)	22.68 (0.82)	1.44	0.154
wave E (ms)	31.33 (0.53)	31.03 (0.50)	2.21	0.031
wave F (ms)	39.95 (0.48)	39.40 (0.37)	4.93	<0.001*
wave O (ms)	48.60 (0.53)	48.13 (0.34)	4.08	<0.001*
wave D-E	8.34 (0.93)	8.36 (0.75)	-0.08	0.939
wave E-F	8.62 (0.67)	8.37 (0.38)	1.77	0.081
VA Duration (ms)	1.00 (0.28)	0.92 (0.14)	1.415	0.162
VA Amplitude (µV)	0.26 (0.10)	0.33 (0.10)	-2.470	0.016
VA Slope (ms/ µV)	-0.27 (0.09)	-0.36 (0.12)	3.506	0.001*

* Result remains significant after correcting for multiple comparisons

3.3.3.1.1 Interpretation of Discrete Peak and Composite Onset Measures Analysis

There is no evidence of an effect of ear on the discrete peak or composite onset measures of the speech ABR, provided hearing levels are within 'normal' limits. However, there are differences in the speech ABR between men and women. Measures relating to the onset and offset features of the response are different, whilst the measures relating to the FFR portion of the waveform are largely the same.

As no differences were detected, whether using right or left ear presentation to elicit the response, right ear only has been used for the comparison of waveforms from males and females. Independent sample, two-tail t-tests were used to investigate the speech ABR response between males and females for the dependent variables listed. Results are reported with a Bonferroni-corrected significance criterion for multiple comparisons ($a = 0.0033$). Differences were found in the timing of the onset peaks with females having significantly earlier peak latencies at peaks V ($t(59) = 6.09$, $p < 0.001$) and A ($t(59) = 5.98$ $p < 0.001$) compared to males (Table 18). Significant differences were also found in the timing of the other peaks including the FFR peak F ($t(59) = 4.93$, $p < 0.001$) and the offset peak O ($t(59) = 4.08$, $p < 0.001$). Onset and offset measures were earlier in women by at least 0.43ms. There were no significant differences found in the interpeak interval of the FFR peaks corresponding to the period of the fundamental frequency, D to E or E to F between males and females.

The response to the onset of /da/ was further analysed using composite measures including the slope, VA peak to trough amplitude and interpeak interval. The slope from peak V to peak A was significantly different between males and females ($t(59) = 3.506$, $p = 0.001$), with males having shallower slopes. No differences were found in the VA peak to trough amplitude or the interpeak interval.

3.3.3.2 Stimulus to Response Correlations and Spectral Encoding Measures Analysis

The FFR was analysed in terms of magnitude and correlation to the stimulus, using the previously mentioned custom MATLAB routines. These measures provide insight into the general extent of sustained neural activity and phase-locking capabilities of the underlying neural population. A cross-correlational technique was used to shift the response in time until a maximum correlation between the stimulus

and response occurred. This allowed the stimulus-to-response correlation (SR corr), which provides information on the degree to which the response mimics the stimulus, as well as the amount of delay or shift (SR lag) to be calculated.

A Fourier transform analysis was performed and the size of the neural response over the time period was calculated. The signal to noise ratio, a comparison of the pre-stimulus activity compared to the response activity, should be > 1, and ideally >1.5, if the response is to be accepted as genuine (Skoe and Kraus 2010a). Additionally, the average magnitude of spectral components was calculated for three frequency ranges including the fundamental frequency (F0) 103–120 Hz, first formant (F1) 455–720 Hz, and high frequency (HF) 721–1154 Hz.

3.3.3.2.1 Within and Between Participant Effects

A mixed ANOVA with repeated measures for ear and between participant effects for sex, was performed. The aim was to look at within subject differences of the SR correlation and spectral encoding measures of the speech ABR recorded from right and left ears, as well as between subject differences in respect to sex. No significant differences were found between these particular responses from the right and left ears, of the speech ABR between men and women (Table 19).

Table 19. Spectral Encoding Measures of the FFR for Men and Women (Right Ear, Mean and S.D.)

Speech ABR Component		Male (S.D.)	Female (S.D.)
Correlation measures	SR corr (20–40 ms)	0.105 (0.04)	0.102 (0.05)
	SR lag	8.48 (0.85)	8.38 (0.70)
Amplitude Measures (μV)	SNR	2.65 (0.87)	2.48 (0.78)
	F0 (21.9–40.6 ms)	12.702 (10.55)	10.590 (4.22)
	F1 (21.9–40.6 ms)	1.256 (0.48)	1.403 (0.50)
	HF (21.9–40.6 ms)	0.487 (0.13)	0.594 (0.21)

As Krizman et al. (2012a) identified a difference in the representation of HF (amplitude measure representing high frequency) only between men and woman a planned independent samples t-tests on the spectral amplitude measures of the speech ABR was performed. After applying a Bonferroni correction for multiple

comparisons, no significant differences were found between the spectral amplitude measures for men and women (Table 20).

Table 20. Spectral Amplitude Measures (Right Ear, Mean and S.D.)

Spectral Magnitude in μV	Men (S.D.)	Women (S.D.)	t	p
F_0	12.702 (10.55)	10.590 (4.22)	1.017	0.313
F_1	1.256 (0.48)	1.403 (0.50)	-1.153	0.254
HF	0.487 (0.13)	0.594 (0.21)	-2.380	0.021

3.3.3.2.2 Interpretation of Stimulus to Response Correlations and Spectral Encoding Measures Analysis

There was no significant difference found in the stimulus to response correlations from either the right or left ears, or between the sexes. A fast Fourier transform was performed over the 22–40 ms range of the response (excluding wave C), to evaluate spectral encoding. No significant differences were found in the encoding in any of the ranges evaluated. There were, therefore, no effects of ear of presentation or sex, on these features of the speech ABR for healthy adults with 'normal hearing'.

3.3.4 Addressing the Research Questions

The results of the analyses of discrete peaks, composite onset measures, stimulus to response correlations and spectral encoding measures with respect to both ear and sex are discussed in the following sections.

3.3.4.1 Effect of Ear

In contrast to Hornickel et al (2009) but in keeping with Vander Werff and Burns (2011), Ahadi et al. (2014b) and Sanju et al. (2017b) no significant ear differences could be detected when using the speech stimulus /da/ to elicit the ABR. The claims made by Hornickel et al. (2009) were that there was evidence of more robust frequency encoding in the right ear, as well as earlier processing of the FFR

region of the response. They concluded that there was left lateralisation for elements of speech processing, at the level of the brainstem. As previously discussed, these findings would not have remained significant if a correction for multiple comparisons had been applied. From the results of the testing of the 60 adults in the present study, there appear to be no differences between the speech ABR waveforms from right and left ears. It would seem that there is no requirement for separate ear data and this also means that the speech ABR can be used irrespective of hemisphere dominance. This finding is important, as the tool is more suitable for clinical use if people can be tested without initial assessment of hemisphere dominance.

3.3.4.2 Effect of Subject Sex

Differences have been found in the onset and offset elements of the speech-evoked ABR between males and females. Whilst wave F does differ between the males and females in this study, there is no difference in the inter-peak latencies of the elements comprising the FFR. These findings are in agreement with those by Krizman et al. (2012a) and Ahadi et al. (2014b) who also found sex-related differences between the onset measures but not in the sustained measures of the response. Women have earlier onset measures but the interpeak latencies of the FFR portion of the response are the same for men and women. Unlike the findings of Krizamn et al. (2012a) and Ahadi et al (2014a), there was no difference in the spectral amplitude measures, with men and women having equally robust encoding. Although there was an approach towards significance for the higher frequency spectral magnitude ($t(58)= -2.38$, $p= 0.021$), this does not remain a significant finding once a correction for multiple comparisons is applied. In light of these findings, sex specific control or normative data is advisable if the speech ABR is to be used in the clinical environment.

3.4 Repeatability and Effect of Age on ABRs in Healthy Adults

The aim of this section within Experiment One is to answer research questions that may be of concern when considering repeated testing, or performing longitudinal studies. The specific research questions being answered within this section are:

- What is the effect of age (18-30 vs. 31-49 years) on the speech ABR?
- What is the between session repeatability of the speech ABR?

The following section details the participants and the methods used to answer the research questions relating to testing the speech ABR over time.

3.4.1 Participants

Fourteen adults in the 31-49 year age group were recruited by word of mouth to participate in this part of the study. These adults were recruited in line with the criteria established in section 3.1.1, apart from the age range and they had no diagnosis of Alcohol Dependence Syndrome. Two males were subsequently excluded from the study, both for having a bilateral mild to moderate level of sensorineural hearing loss. This resulted in data from 12 adults (six females, six males) aged 33 to 49 years (mean age 42.1 yrs, S.D. 4.93 yrs) contributing to this part of the study. Of these 12 adults, nine (five women), aged 33 to 49 years (mean age 43.4 yrs, S.D. 4.90 yrs), completed two assessments that were undertaken 12 weeks apart.

3.4.1.1 Sources of Error and Bias

The following considerations influenced the design of the study.

3.4.1.1.1 Sampling Effect

The group of participants selected to contribute to the control data should be representative of adults with a profile of normal auditory function and normal cognitive ability. This was achieved by recruiting both male and female participants within a defined age range (31-49 years) who met strict inclusion criteria in relation to their hearing acuity and functional hearing.

3.4.1.1.2 Bias and Compensation

As the control participants were required to have scores of > 6 on subtests of the WAIS, and hearing thresholds of no greater than 20 dB HL they might not represent the general population of adults. The data presented should be considered as control data as opposed to normative data.

3.4.2 Methods

All tests that comprise the auditory-cognitive profile assessment were carried out as per the methods previously presented in section 3.1.2.

3.4.2.1 Click ABR Procedure

The click ABRs were recorded as per the methods previously presented in section 3.1.2.10. For the purposes of analysis, the two 1024 sweep trials were used as a guide for marking the calculated waveforms. The zoom function was used at its maximum to assist in identifying the proper location for waveform marking. Reviewing the individual waveforms aided in peak picking decisions. If the two raters were not in accordance regarding marking of a peak latency, the peak was marked as ‘not reliable’ and excluded from analyses. Peaks were also marked as ‘not reliable’ if they were smaller than the average amplitude of the pre-stimulus baseline activity and therefore excluded from analyses. This resulted in a data set of 24 click ABR waveforms from right and left ears recorded at baseline and 18 click ABR waveforms from right and left ears recorded at follow-up assessment.

3.4.2.2 Speech ABR Procedure

The speech ABRs were recorded as per the methods previously presented in section 3.1.2.11. For the purposes of analysis, the three 2000 sweep trials were used as a guide for marking the calculated waveforms. The zoom function was used at its maximum to assist in identifying the proper location for waveform marking. If the two raters were not in accordance regarding marking of a peak latency, the peak was marked as ‘not reliable’ and excluded from analyses. Peaks were also marked as ‘not reliable’ if they were smaller than the average amplitude of the pre-stimulus baseline

activity and therefore excluded from analyses. This resulted in a data set of 24 speech ABR waveforms from right and left ears recorded at baseline and 18 speech ABR waveforms from right and left ears recorded at follow-up assessment.

3.4.3 Results and Analysis of the Auditory-Cognitive Profile

The following section provides the results and analysis for the auditory-cognitive profile. In all cases prior to analysis the Shapiro-Wilks Francia test was applied to establish that the data for males and females was normally distributed.

3.4.3.1 Age Profile of Participants

Data is presented from the six male and six female participants whose results contributed to generating control data for healthy adults (Figs.17 and 18). All 12 participants completed all aspects of the auditory-cognitive profile assessment. The mean age of the male participants was 43.2 years (S.D. 4.62) and the mean age of the female participants was 41.0 years (S.D. 5.40).

Figure 17. Age Profile of Male Participants

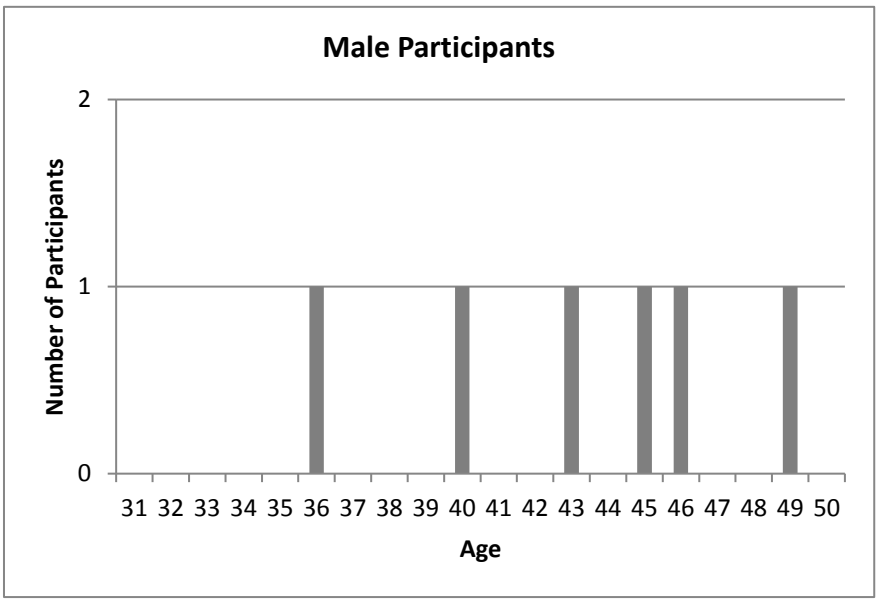
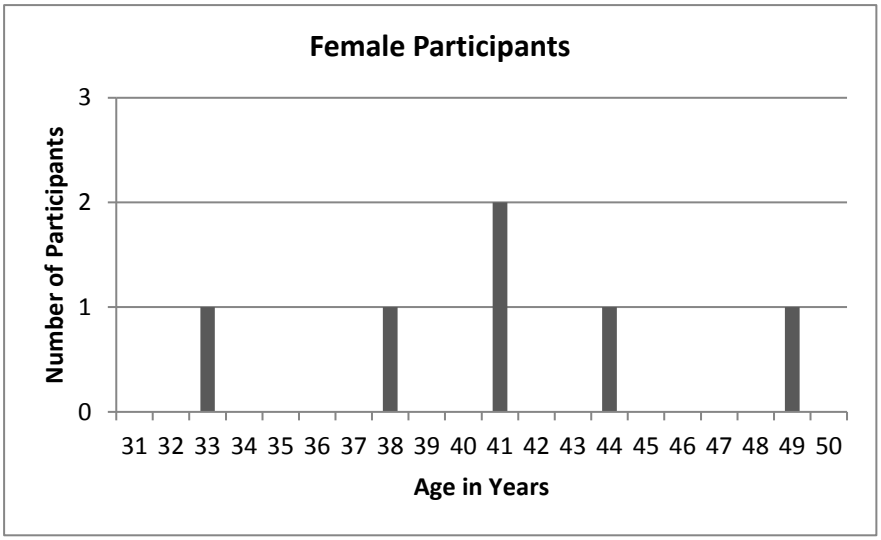


Figure 18. Age Profile of Female Participants



3.4.3.2 Pure Tone Audiometry of Participants

To meet the inclusion criteria an individual's pure tone hearing thresholds for 250 Hz, 500 Hz 1000 Hz, 2000 Hz, 4000 Hz and 8000 Hz could be no greater than 20 dB HL bilaterally. Results for the right ears and left ears for the male participants recorded at baseline, are presented in the figures below (Figures 19 to 22).

Figure 19. Pure Tone Audiometry Results for Males (Right Ear, Mean and S.D.)

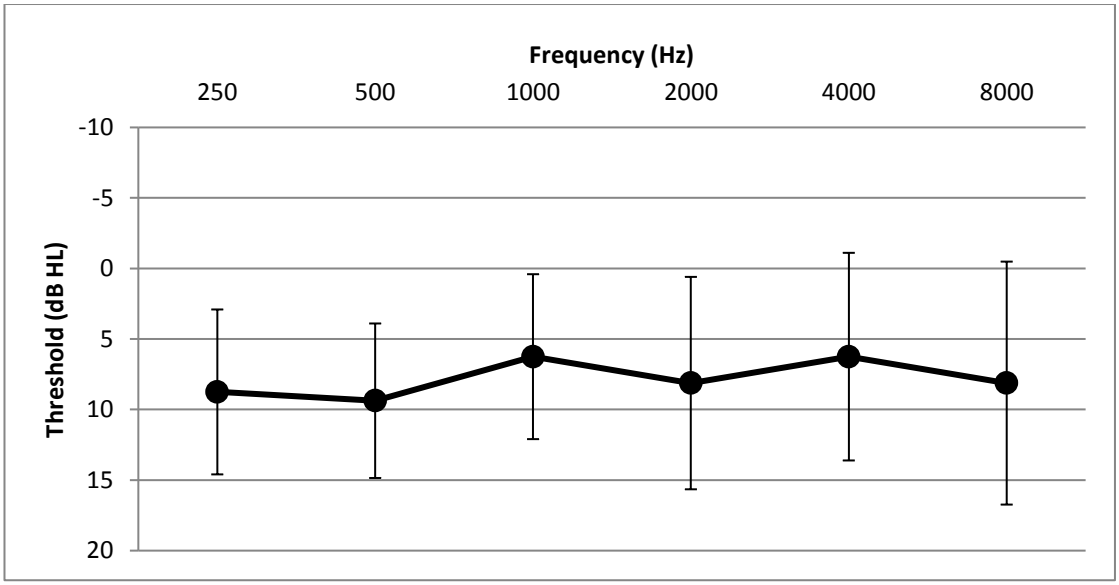
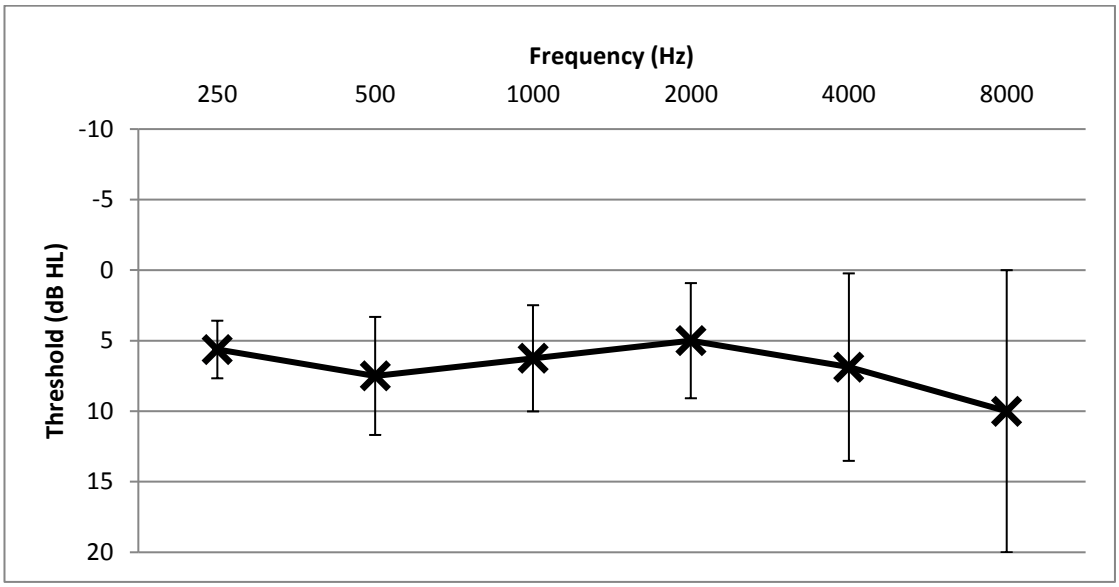


Figure 20. Pure Tone Audiometry Results for Males (Left Ear, Mean and S.D.)



Results for the right ears and left ears for the female participants recorded at baseline, are presented in the following figures.

Figure 21. Pure Tone Audiometry Results for Females (Right Ear, Mean and S.D.)

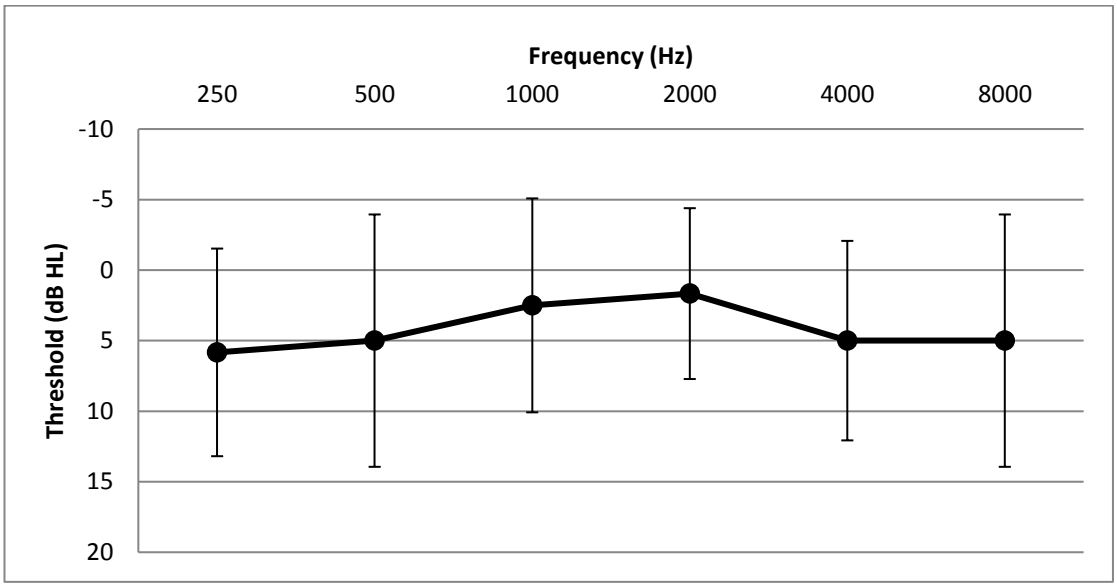
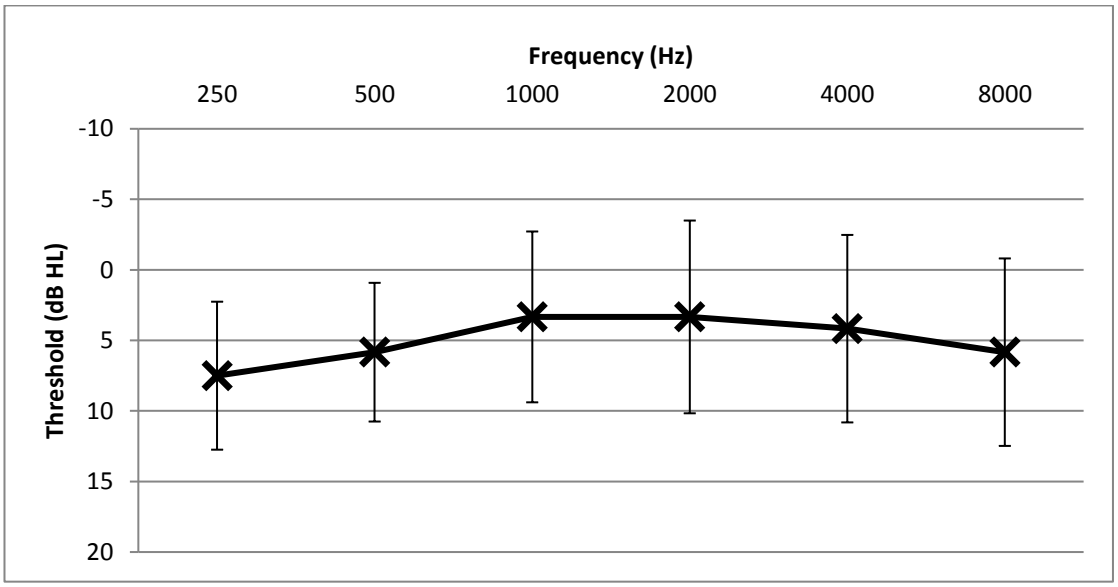


Figure 22. Pure Tone Audiometry Results for Females (Left Ear, Mean and S.D.)



3.4.3.2.1 Comparison of PTA results between Baseline Measure and Second Assessment

Although all results were within the limits for normal hearing, mixed ANOVA with repeated measures for time and between participants effects for sex was performed. This was undertaken in order to establish whether hearing thresholds had changed over the 12 week period. No significant changes were detected between the air conduction thresholds at baseline testing and at second assessment, either for males of females.

3.4.3.2.2 Interpretation of Results for PTA

The results of pure tone audiometry testing for adults included within this study are as would be expected from ISO7029:2017. All participants had thresholds of 20 dB HL or less for each frequency point and no participants had thresholds meeting any of the British Society of Audiology descriptors of hearing loss (British Society of Audiology 2011, p. 22).

3.4.3.3 Cognitive Assessment of Healthy Adults

The mean values of the scaled score results for the subtests of the WAIS-III^{UK} assessment are presented in tables 21 and 22.

Table 21. Values for Scaled Scores from Subtests of the WAIS-III^{UK} at Baseline (Mean and S.D.)

WAIS-III^{UK} Subtest	Males (S.D.)	Females (S.D.)
Vocabulary	11.0 (1.26)	12.3 (1.63)
Digit- Symbol Coding	11.2 (2.23)	11.5 (0.56)
Digit Span	10.3 (0.82)	10.2 (1.60)
Symbol Search	11.7 (1.21)	11.5 (1.38)
Letter- Number Sequencing	10.5 (1.38)	10.5 (1.38)

Table 22. Values for Scaled Scores from Subtests of the WAIS-III^{UK} at Second Assessment (Mean and S.D.)

WAIS-III^{UK} Subtest	Males (S.D.)	Females (S.D.)
Vocabulary	11.8 (0.96)	12.4 (1.82)
Digit- Symbol Coding	12.3 (0.96)	11.6 (0.55)
Digit Span	10.8 (0.50)	10.6 (0.89)
Symbol Search	11.8 (1.50)	11.8 (1.30)
Letter- Number Sequencing	11.0 (0.82)	11.0 (1.22)

3.4.3.3.1 Comparison of Cognitive Assessment Results between Baseline and Second Assessment

Although all results were within the accepted limits for normal function, a mixed ANOVA was performed with repeated measures for time and between participant effects for sex. This was undertaken to establish whether cognitive function had changed over the 12 week period. A significant change was detected between the performance at baseline testing and at second assessment, $F(1, 7)= 16.33$, $p = 0.005$ for the assessment overall but no significant difference between men and women. Post hoc, paired samples t-tests were performed and although results of two of the subtests approached significance, there were no significant changes at the individual test level (Table 23).

Table 23. Results of Cognitive Assessments at Baseline and Follow-Up (Mean and S.D.)

WAIS-III^{UK} Subtest	Baseline (S.D.)	Second Assessment (S.D.)	t	p
Vocabulary	11.78 (1.48)	12.11 (1.45)	-2.000	0.081
Digit- Symbol Coding	11.89 (0.78)	11.89 (0.78)	-	-
Digit Span	10.33 (1.32)	10.67 (0.71)	-1.414	0.195
Symbol Search	11.67 (1.41)	11.78 (1.30)	-1.000	0.347
Letter- Number Sequencing	10.67 (1.22)	11.00 (1.00)	-2.000	0.081

3.4.3.3.2 Interpretation of Results of the Cognitive Assessment

All individual scaled scores were above the lower cut off point of 7 (Wechsler 1997), indicating that no individuals were performing below the lower acceptable limit for normal function on any of the subtests administered. It has previously been determined that test-retest repeatability is good for this particular age group, when repeating the test after a two to 12 week period (The Psychological Corporation 2002, p. 59). For the current study, there was no evidence of a practice effect that affected the results of the second assessment.

3.4.3.4 Auditory Processing Capability Assessment

The mean values for the individual auditory processing tests are presented in tables 24 to 31 within the following section. Applying the Shapiro-Wilks Francia test established that with the exception of the RGDT data, the results were not normally distributed. For these variables, the Wilcoxon Signed-ranks test was used to compare the values at baseline assessment to those after a period of 12 weeks.

3.4.3.4.1 Results of Duration Pattern Sequence Testing

The results of the Duration Pattern Sequence Test are presented in table 24 below and all participants undertook this assessment.

Table 24. Results of Duration Pattern Sequence Testing (Mean and S.D.)

DPST Score	Males		Females	
	Right Ear (S.D.)	Left Ear (S.D.)	Right Ear (S.D.)	Left Ear (S.D.)
% Correct, Baseline	99.6 (0.88)	98.2 (2.69)	98.3 (2.58)	96.8 (2.81)
% Correct, Second Assessment	99.4 (1.25)	99.4 (1.25)	100.0 (0.00)	98.5 (1.37)

3.4.3.4.1.1 Comparison of Duration Pattern Sequence Testing Results between Baseline Measure and Second Assessment

The Wilcoxon Signed-ranks test was used to compare the values at baseline assessment to those after a period of 12 weeks (Table 25).

Table 25. Comparison of Duration Pattern Sequence Testing Results between Baseline and Follow-Up (Mean and S.D.)

DPST Score	Baseline (S.D.)	Second Assessment (S.D.)	z	p
% Correct, Right Ear	98.61 (2.20)	99.72 (0.83)	-1.414	0.157
% Correct, Left Ear	97.31 (2.76)	98.89 (1.32)	-2.121	0.034

3.4.3.4.1.2 Interpretation of Results

All scores were above 70%, indicating that all individuals performed within accepted normal limits for this test of pattern processing. After applying a Bonferroni correction for multiple comparisons, there was no significant difference between the test results recorded at baseline and after 12 weeks.

3.4.3.4.2 Results of Pitch Pattern Sequence Testing

The results of the Pitch Pattern Sequence Testing are presented in table 26 below and all participants undertook this assessment.

Table 26. Results of Pitch Pattern Sequence Testing (Mean and S.D.)

PPST Score	Males		Females	
	Right Ear (S.D.)	Left Ear (S.D.)	Right Ear (S.D.)	Left Ear (S.D.)
% Correct, Baseline	100.0 (0.00)	99.7 (0.88)	98.6 (2.21)	99.2 (2.04)
% Correct, Second Assessment	100.0 (0.00)	100.0 (0.00)	99.5 (1.12)	100.0 (0.00)

3.4.3.4.2.1 Comparison of Pitch Pattern Sequence Testing Results between Baseline Measure and Second Assessment

The Wilcoxon Signed-ranks test was used to compare the values at baseline assessment to those after a period of 12 weeks (Table 27).

Table 27. Comparison of Pitch Pattern Sequence Testing Results between Baseline and Follow-Up (Mean and S.D.)

PPST Score	Baseline (S.D.)	Second Assessment (S.D.)	z	p
% Correct, Right Ear	99.1 (1.88)	99.7 (0.83)	-1.342	0.180
% Correct, Left Ear	99.2 (1.77)	100.0 (0.00)	-1.342	0.180

3.4.3.4.2.2 Interpretation of Results

All scores were at 95% or above, indicating that all individuals performed within accepted normal limits for this test of pattern processing. There were no significant differences in the results recorded at baseline and second assessment, although results are towards ceiling levels for this assessment.

3.4.3.4.3 Results of Dichotic Digits Testing

The results of the dichotic digits assessment are presented below (Table 28) and all participants undertook this assessment.

Table 28. Results of Dichotic Digits Testing (Mean and S.D.)

DD Score	Males		Females	
	Right Ear (S.D.)	Left Ear (S.D.)	Right Ear (S.D.)	Left Ear (S.D.)
% Correct, Baseline	98.1 (2.22)	97.8 (2.48)	98.3 (2.04)	97.1 (1.88)
% Correct, Second Assessment	100.0 (0.00)	98.8 (1.44)	99.5 (1.12)	98.5 (2.24)

3.4.3.4.3.1 Comparison of Duration Pattern Sequence Testing Results between Baseline Measure and Second Assessment

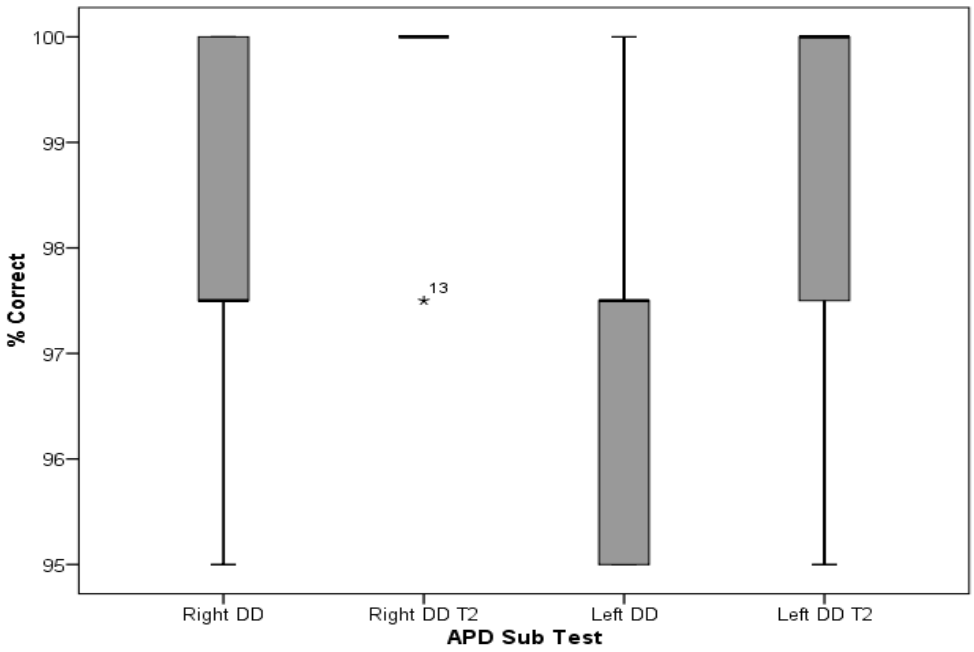
The Wilcoxon Signed-ranks test was used to compare the values at baseline assessment to those after a period of 12 weeks (Table 29).

Table 29. Comparison of Dichotic Digit Testing Results between Baseline and Follow-Up (Mean and S.D.)

DD Score	Baseline (S.D.)	Second Assessment (S.D.)	z	p
% Correct, Right Ear	98.1 (2.08)	99.7 (0.83)	-1.857	0.063
% Correct, Left Ear	96.9 (2.08)	98.6 (1.82)	-2.449	0.014*

* Result remains significant after correcting for multiple comparisons

Figure 23. Results of Dichotic Digits Testing at Baseline and Follow-Up



Where DD is dichotic digits and T2 is second assessment

3.4.3.4.3.2 Interpretation of Results

All scores were at 95% or above, indicating that all individuals performed within accepted normal limits for this test of pattern processing. Although all results were towards the upper limit, there was a significant improvement in the left ear score, even after correcting for multiple comparisons (Figure 23). It is therefore possible that there is a practice effect evident for this particular test.

3.4.3.4.4 Results of Random Gap Detection Testing

The results of the Random Gap Detection Testing (RGDT) are presented below (Table 30) and all participants undertook this assessment.

Table 30. Results of Random Gap Detection Testing (Mean and S.D.)

RGDT Threshold	Males		Females	
	Tonal Threshold (S.D.)	Click Threshold (S.D.)	Tonal Threshold (S.D.)	Click Threshold (S.D.)
Mean (ms), Baseline	5.94 (1.85)	6.25 (2.31)	7.29 (3.00)	5.00 (0.00)
Mean (ms), Second Assessment	4.38 (1.56)	6.25 (2.50)	7.00 (3.14)	5.00 (0.00)

3.4.3.4.4.1 Comparison of Random Gap Detection Testing Results between Baseline and Follow-Up

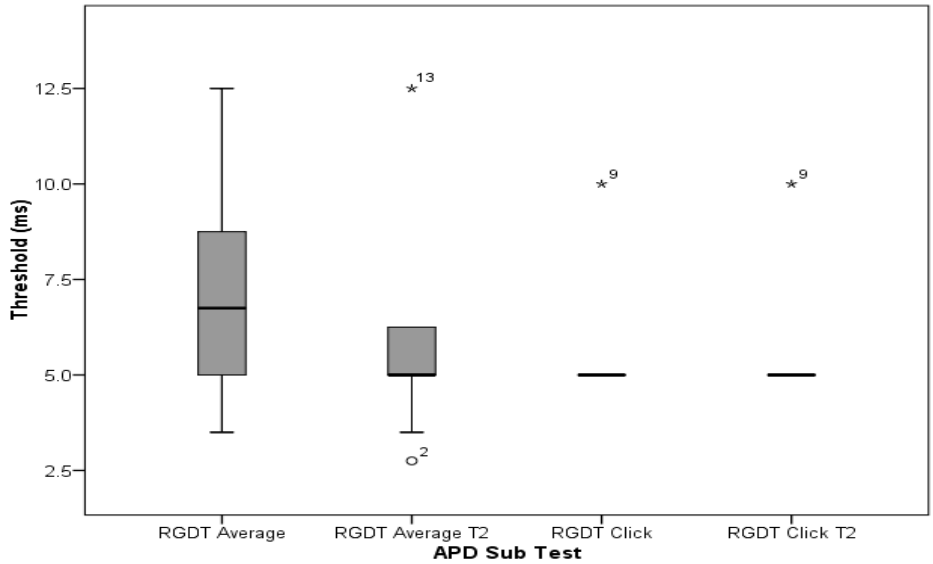
A paired samples t-test was used to compare the values at baseline assessment to those after a period of 12 weeks (Table 31).

Table 31. Comparison of Random Gap Detection Testing Results between Baseline and Follow-Up (Mean and S.D.)

RGDT Threshold	Baseline (S.D.)	Second Assessment (S.D.)	t	p
Mean of Threshold for Tones (ms)	6.81 (2.93)	5.83 (2.78)	2.723	0.026*
Click Threshold (ms)	5.56 (1.67)	5.56 (1.67)	-	-

* Result remains significant after correcting for multiple comparisons

Figure 24. Results of Random Gap Detection Testing at Baseline and Follow-Up



Where RGDT is Random Gap Detection Test and T2 is second assessment

3.4.3.4.4.2 Interpretation of Results

All individuals performed within accepted normal limits for these tests of gap detection. There was no difference in the mean click threshold across the group. However, there was a significant improvement in the mean of the average threshold for tones presented at 500, 1000, 2000 and 4000 Hz (Figure 24) at the second assessment. This is unlikely to be a result of a practice effect, as the same improvement was not evident for the RGDT for clicks.

3.4.3.5 TEOAE Testing in Healthy Control Participants

The results of TEOAE testing were used as an objective cross-check to confirm the evidence of normal hearing, as indicated by PTA results (Table 32).

Table 32. TEOAE Results (Mean and S.D.)

TEOAE Measure	Males (S.D.)	Females (S.D.)
Reproducibility %	91.13 (6.13)	92.50 (3.82)
Stability %	98.63 (2.53)	99.25 (1.46)
Response at 1.0kHz SPL	11.39 (4.66)	11.39 (3.97)
Response at 1.4kHz SPL	16.05 (4.05)	17.20 (3.34)
Response at 2.0kHz SPL	13.89 (3.94)	17.25 (2.91)
Response at 2.8kHz SPL	10.31 (5.41)	11.34 (4.53)
Response at 4.0kHz SPL	9.74 (5.19)	8.09 (4.63)

3.4.3.5.1 Comparison of TEOAE Testing Results between Baseline Measure and Second Assessment

A mixed ANOVA with repeated measures for time and between participants effects for sex was performed to establish whether TEOAEs had changed over the 12 week period. There was no significant difference in the TEOAE results over time or by sex.

3.4.3.5.2 Interpretation of Results of TEOAE Testing

All participants had a TEOAE present at 3 dB above the level of the noise floor in at least 3 out of 5 frequency bands, with reproducibility of response at greater than 70%. This would indicate that all participants had hearing threshold levels at these frequencies, of 25-30 dB HL or better (Probst and Harris 1993), this is in agreement with the results of pure tone audiometry testing. TEOAE results were stable over time. As all participants met the criteria for presence of TEOAEs, DPOAE testing was not performed.

3.4.3.6 Speech-In-Noise Assessment

As some people can have ‘normal hearing’ as measured using PTA but still perform poorly in difficult listening situations, a speech-in-noise assessment was used to assess whether any participants had a signal to noise ratio (SNR) loss. All

participants SRT results were below 0 dB and the average values for males and females are presented in the following table (Table 33).

Table 33. Results from the Speech in Noise Assessment (Mean and S.D.)

SRT Score	Males (S.D.)	Females (S.D.)
Mean 50% correct score (dB) Baseline	-4.75 (1.28)	-4.67 (1.21)
Mean 50% correct score (dB) Second Assessment	-5.75 (0.50)	-5.00 (1.22)

3.4.3.6.1 Comparison of Speech-In-Noise Testing Results between Baseline Measure and Second Assessment

A paired samples t-test was performed for the group and no differences were found between the results at baseline and at second assessment ($t(8) = 1.84$ $p = 0.104$).

3.4.3.6.2 Interpretation of Results

All adults within this study had SRT scores of less than 0 dB which can be considered to be normal and therefore further speech audiometry in quiet was not performed. There was no change in performance over a 12 week period.

3.4.4 Results and Analysis of Click ABR Testing

In this section, a control data set will be presented for the individual waves at baseline and at follow-up and this will be compared to the data set from section 3.1.3.7.

3.4.4.1 Latency and Amplitude of Click ABR Responses

Two audiologists independently marked the grand average ABR waveform data derived from all participants (Vidler and Parker 2004) and this resulted in a data set of 24 waveforms for the click evoked ABR. The examiners were asked to complete a table to indicate whether they felt replicable waves were present in the constituent

traces that contributed to all grand averaged waveforms. For the click ABR, the examiners were in agreement that waves I, III and V could be reliably identified in 100% of waveforms. Applying the Shapiro-Wilks Francia test established that the click ABR data for males and females was normally distributed. Latency and amplitude data for the control group, are presented in the tables below (Tables 34 and 35) and the data is collapsed to include both ears.

Table 34. Latency Results from the Click ABR Assessment, Data Pooled for Ear (Mean and S.D.)

ABR Component	Males (S.D.)	Females (S.D.)
Wave I latency (ms)	1.56 (0.09)	1.48 (0.06)
Wave III latency (ms)	3.64 (0.10)	3.60 (0.06)
Wave V latency (ms)	5.61 (0.13)	5.27 (0.17)

Table 35. Amplitude Results from the Click ABR Assessment, Data Pooled for Ear (Mean and S.D.)

ABR Component	Males (S.D.)	Females (S.D.)
Wave I amplitude (μV)	0.05 (0.10)	0.12 (0.15)
Wave III amplitude (μV)	0.20 (0.12)	0.18 (0.15)
Wave V amplitude (μV)	0.06 (0.08)	0.09 (0.12)

3.4.4.1.1 Comparing the Control Data for Two Groups of Healthy Adults

Independent samples t-tests found no significant differences between the ABR latencies between the two groups of healthy adults (ages 18-30 yrs and ages 31-49 yrs), except for wave V for females. It was found that the group of six older women had a slightly shorter wave V latency ($t(70) = 3.32$, $p = 0.001$), which remained after corrections for multiple comparisons were applied.

Table 36. Latency Range for Click ABR Components for Males

ABR Component	Latency Range in ms (Mean ± 2SD)	
	Men (age 18-30)	Men (age 31-49)
Wave I	1.33 - 1.81	1.38 - 1.74
Wave III	3.44 - 4.00	3.44 - 3.84
Wave V	5.34 - 5.94	5.35 - 5.87
I-III	1.87 - 2.43	1.74 - 2.42
III-V	1.6 - 2.24	1.69 - 2.25
I-V	3.69 - 4.45	3.69 - 4.41

Table 37. Latency Range for Click ABR Components for Females

ABR Component	Latency Range in ms (Mean ± 2SD)	
	Women (age 18-30)	Women (age 31-49)
Wave I	1.32 - 1.68	1.36 - 1.60
Wave III	3.30 - 3.86	3.48 - 3.72
Wave V	5.11 - 5.79	4.93 - 5.61
I-III	1.80 - 2.36	1.95 - 2.31
III-V	1.55 - 2.19	1.27 - 2.07
I-V	3.62 - 4.26	3.52 - 4.08

3.4.4.1.2 Interpretation of Baseline Click ABR Results

Although the wave V data for the six healthy older females was slightly shorter than for the larger group of younger healthy participants, the data from the older control group within the upper limits for the younger healthy adults. This is in agreement with the results of the study by Skoe et al. (2015a) who only found a significant lengthening in the click evoked wave V once people reached the age 50-60 year bracket. It is therefore possible to use the larger set of click ABR control data from younger adults for a comparison with the participants with ADS in Experiment Two. The upper limits of the wave latency data generated in section 3.1.3 will be used to define the upper limit of what would typically be expected for a healthy adult with normal hearing.

3.4.4.2 Effects of Time on the Click ABR Measures

The click ABRs were recorded from a subset of nine healthy adults, aged 33-49 years (see section 3.4.1), 12 weeks after the initial ABR recordings took place (Table 38). A mixed ANOVA with repeated measures for time and between participant effects for sex was performed. This was undertaken to look at within subject differences in the latency values of the click ABR recorded from both ears at baseline and second assessment, as well as between subject differences in respect to sex. No differences were found between the absolute or interpeak intervals between baseline and second assessment. As expected, there was a significant difference in the click ABR responses between men and women $F(1, 16) = 20.26$, $p = <0.001$.

Table 38. Comparison of Click ABR Results between Baseline and Follow-Up (Mean and S.D.)

ABR Wave latency (ms)	Males		Females	
	Baseline (S.D.)	Second Assessment (S.D.)	Baseline (S.D.)	Second Assessment (S.D.)
I	1.66 (0.06)	1.66 (0.08)	1.48 (0.07)	1.47 (0.09)
III	3.56 (0.04)	3.58 (0.06)	3.61 (0.04)	3.63 (0.05)
V	5.54 (0.05)	5.56 (0.05)	5.27 (0.19)	5.24 (0.11)
I-III	1.90 (0.08)	1.92 (0.14)	2.13 (0.10)	2.16 (0.11)
III-V	1.97 (0.08)	1.98 (0.07)	1.66 (0.21)	1.61 (0.11)
I-V	3.87 (0.10)	3.90 (0.11)	3.78 (0.14)	3.77 (0.07)

3.4.4.3 Interpretation of Results of the Study of Repeatability of the Click ABR

In healthy, normal hearing adults it is not expected that the ABR will change over time until after adults reach their 5-6th decade (Skoe et al. 2015a). The results from the above study confirm that the click ABR is repeatable in healthy, normal hearing adults over a 12 week period.

3.4.5 Results and Analysis of Speech ABR Testing

In this section, a control data set will be presented for the speech ABR measures at baseline and at follow-up and this will be compared to the data set

presented in section 3.3.3. Two audiologists independently marked the grand average speech ABR waveform data derived from all participants (Vidler and Parker 2004) and this resulted in a data set of 24 waveforms for the speech evoked ABR. Applying the Shapiro-Wilks Francia test established that the speech ABR data for males and females was normally distributed.

3.4.5.1 Discrete Peak and Composite Onset Measures Analysis

Latencies and amplitudes of discrete peaks were evaluated, in addition to three composite measures of neural synchrony to the onset of the stimulus (Table 39). The composite measures included V to A interpeak latency, V to A peak-to-trough amplitude, and the slope of the VA complex (change in peak amplitude over time). Independent samples t-tests found no significant differences between the absolute wave latencies, or the VA complex measures of the speech ABR, between the younger and older adults.

Table 39. Discrete Peak and Composite Onset Measures of the Speech ABR, Data Pooled for Ear (Mean and S.D.)

Speech ABR Component	Male (S.D.)	Female (S.D.)
wave V (ms)	6.96 (0.36)	6.61 (0.23)
wave A (ms)	7.75 (0.40)	7.40 (0.29)
wave D (ms)	23.48 (0.45)	23.28 (0.63)
wave E (ms)	31.68 (0.75)	30.88 (0.49)
wave F (ms)	39.83 (0.68)	39.45 (0.29)
wave O (ms)	48.88 (0.43)	48.46 (0.50)
wave D-E (ms)	8.20 (0.63)	7.56 (0.79)
wave E-F (ms)	8.15 (0.86)	8.59 (0.53)
VA Duration (ms)	0.89 (0.26)	0.82 (0.17)
VA Amplitude (µV)	0.22 (0.09)	0.28 (0.11)
VA Slope (ms/ µV)	-0.26 (0.11)	-0.34 (0.15)

3.4.5.1.1 Comparing the Discrete Peak and Composite Onset Measures for Healthy Adults Aged 18-30 years and Aged 31-49 years

Independent samples t-tests found no significant differences in the speech ABR peak latencies between the two groups of healthy adults.

3.4.5.1.2 Interpretation of Discrete Peak and Composite Onset Measures Results

The discrete peak and composite onset measures of the speech ABR from the older adults (31-49 yrs) is not significantly different from that of the younger adults (18-30 yrs). This is in agreement with the results of the study by Skoe et al. (2015a) who only found a significant lengthening in the waves A, D and E once people reached the age 50-60 year bracket. It is therefore possible to use the larger set of control data for a comparison with the participants with ADS in Experiment Two. The upper limits of the wave latency data presented in section 3.3.3 will be used to define the upper limit of what would typically be expected for a healthy adult with normal hearing.

3.4.5.2 Stimulus to Response Correlation and Spectral Encoding Measures Analysis

The FFR was analysed in terms of magnitude and correlation to the stimulus, using the previously mentioned custom MATLAB routines (Table 40).

Table 40. Stimulus to Response Correlation and Spectral Encoding Measures, data Collapsed from Both Ears (Mean and S.D.)

Speech ABR Component		Male (SD)	Female (SD)
Correlation measures	SR corr (20–40 ms)	0.113 (0.06)	0.103 (0.07)
	SR lag	7.70 (1.02)	7.60 (0.60)
Amplitude Measures (μV)	SNR	1.85 (0.33)	1.98 (0.45)
	F_0 (21.9–40.6 ms)	5.901 (2.54)	6.954 (3.91)
	F_1 (21.9–40.6 ms)	1.116 (0.44)	1.277 (0.34)
	HF (21.9–40.6 ms)	0.414 (0.07)	0.507 (0.14)

3.4.5.2.1 Comparing the Stimulus to Response Correlation and Spectral Encoding Measures for Healthy Adults Aged 13-30 years and Aged 31-49 years

Independent samples t-tests found a significant difference between the SR Lag for the women in study one and the healthy women in study two ($t(70) = 3.56$, $p = 0.001$), which remained after corrections for multiple comparisons were applied. No significant differences were found between these measures for the healthy men in study one and in study two.

3.4.5.2.2 Interpretation of Stimulus to Response Correlation and Spectral Encoding Measures Results

There were no differences in the SR correlation and spectral encoding measures of the speech ABR from the younger (18-30 yrs) and older (31-49 yrs) adults, except for the SR Lag in women. The SR lag is the amount of time that the signal needs to be shifted with respect to the stationary signal that produces the greatest coherence between the signals and is usually in the region of 7-10 ms (Hornickel et al. 2009). This measure can be used to look at response consistency and provides an indication of phase locking capability (Mourad et al. 2016). This was shorter in the healthy older women, however for both age groups the SR lag for the female participants was within the expected range. This difference will be taken into consideration when assessing the SR lag for women with ADS in Experiment Two.

3.4.5.3 Effects of Time on the Discrete Peak and Composite Onset Measures

To establish whether the speech ABRs had changed over the 12 week period, two-way ANOVAs with repeated measures for time were performed. These measures were recorded from both ears at baseline and second assessment. For the nine participants (33-49 yrs) who completed both assessments a significant difference was found for these measures between the baseline and second assessment $F(1,7)=7.52$, $p=0.029$ for men only.

Post hoc paired samples t tests were performed on the transient measures of the speech ABR for males and females. Although two measures involving wave F approached significance for males, there were no significant differences found for these measures recorded from the males or the females (Tables 41 and 42).

Table 41. Comparison of Discrete Peak and Composite Onset Measures for Males between Baseline and Follow-Up (Mean and S.D.)

Speech ABR Component	Baseline (S.D.)	Second Assessment (S.D.)	t	p
wave V (ms)	7.01 (0.34)	7.05 (0.25)	-0.294	0.777
wave A (ms)	7.82 (0.27)	7.83 (0.17)	-0.053	0.959
wave D (ms)	23.71 (0.37)	23.83 (0.33)	-0.898	0.399
wave E (ms)	31.89 (0.71)	31.81 (0.86)	0.588	0.575
wave F (ms)	39.95 (0.75)	39.47 (0.41)	2.021	0.083
wave O (ms)	48.57 (0.50)	48.35 (0.55)	1.202	0.268
wave D-E ms	8.18 (0.68)	7.98 (0.84)	1.870	0.104
wave E-F ms	8.06 (1.09)	7.66 (1.08)	1.986	0.087
VA Duration (ms)	0.81 (0.23)	0.77 (0.22)	0.355	0.733
VA Amplitude (µV)	0.231 (0.09)	0.211 (0.08)	0.422	0.685
VA Slope (ms/ µV)	-0.289 (0.11)	-0.271 (0.08)	-0.332	0.750

Table 42. Comparison of Discrete Peak and Composite Onset Measures for Females between Baseline and Follow-Up (Mean and S.D.)

Speech ABR Component	Baseline (SD)	2nd Assessment (SD)	t	p
wave V (ms)	6.67 (0.29)	6.40 (0.14)	2.221	0.053
wave A (ms)	7.49 (0.33)	7.32 (0.14)	1.584	0.148
wave D (ms)	23.27 (0.59)	23.27 (0.65)	-0.019	0.986
wave E (ms)	30.79 (0.44)	30.82 (0.39)	-0.483	0.641
wave F (ms)	39.57 (0.20)	39.66 (0.24)	-1.038	0.326
wave O (ms)	48.74 (0.22)	48.75 (0.23)	-0.084	0.935
wave D-E ms	7.47 (0.64)	7.56 (0.68)	-0.707	0.498
wave E-F ms	8.81 (0.41)	8.84 (0.40)	-0.424	0.682
VA Duration (ms)	0.86 (0.13)	0.92 (0.11)	-0.926	0.379
VA Amplitude (µV)	0.253 (0.09)	0.314 (0.04)	-1.657	0.132
VA Slope (ms/ µV)	-0.292 (0.09)	-0.345 (0.05)	1.743	0.115

3.4.5.3.1 Interpretation of the Repeatability of the Discrete Peak and Composite Onset Measures

The post hoc analysis found no significant differences between the discrete peak and composite onset measures of the speech ABR when performed at baseline and 12 weeks later. This indicates that these measures are stable over time.

3.4.5.4 Effects of Time on the Stimulus to Response Correlation and Spectral Encoding Measures

Two-way ANOVAs with repeated measures for time were performed to assess any differences in the stimulus to response correlation and spectral encoding measures over time. These measures were recorded from both ears at baseline and second assessment, for the nine participants (33-49 yrs) who completed both assessments. A significant difference was found between these measures between baseline and second assessment $F(1,9)=13.76$, $p=0.005$ for women only.

Post hoc, paired samples t-tests were performed on the SR correlation and spectral encoding measures of the speech ABR for males and females. No significant differences were found for these measures recorded from the males, once corrections for multiple comparison had been applied (Table 43). Even after corrections for multiple comparison had been applied, a significant difference in the amplitude of F0 remained for the women, with the amplitude higher at second assessment (Table 44).

Table 43. Comparison of Assessment of Stimulus to Response Correlation and Spectral Encoding Measures for Males between Baseline and Follow-Up (Mean and S.D.)

Speech ABR Component	Baseline (SD)	2nd assessment (SD)	t	p
SR corr (20–40 ms)	0.118 (0.06)	0.113 (0.04)	0.151	0.884
SR lag	7.31 (0.79)	8.59 (1.19)	-3.16	0.016
SNR	1.76 (0.31)	1.50 (0.22)	1.40	0.205
F0 (21.9–40.6 ms)	5.23 (2.02)	4.90 (2.30)	0.643	0.541
F1 (21.9–40.6 ms)	1.08 (0.48)	1.14 (0.13)	-0.461	0.659
HF (21.9–40.6 ms)	0.423 (0.07)	0.417 (0.07)	0.148	0.887

Table 44. Comparison of Assessment of Stimulus to Response Correlation and Spectral Encoding Measures for Females between Baseline and Follow-Up (Mean and S.D.)

Speech ABR Component	Baseline (SD)	2nd assessment (SD)	t	p
SR corr (20–40 ms)	0.097 (0.07)	0.081 (0.05)	0.539	0.603
SR lag	7.43 (0.67)	7.60 (0.90)	-0.638	0.539
SNR	1.74 (0.33)	2.52 (0.61)	-2.57	0.030
F0 (21.9–40.6 ms)	5.26 (3.08)	10.06 (3.97)	-3.65	0.005*
F1 (21.9–40.6 ms)	1.14 (0.31)	1.51 (0.30)	-2.26	0.050
HF (21.9–40.6 ms)	0.452 (0.12)	0.556 (0.13)	-1.59	0.146

3.4.5.4.1 Interpretation of the Repeatability of the Stimulus to Response Correlation and Spectral Encoding Measures

There was only one significant difference found in any of these measures of the speech ABR when recorded at two separate time points, 12 weeks apart. The amplitude of the portion of the response representing F0 was greater in women by 4.8 μV at second assessment. Therefore, the majority of measures are stable over a 12 week period, however amplitude data for F0 may vary over time.

3.4.6 Addressing the Research Questions

An aim of this study was to assess whether separate control data for men and women with no demonstrable deficits in auditory or cognitive function was necessary when looking at adults aged 31-49 years of age, compared to adults aged 18-30 years. The results of the auditory-cognitive profile assessment indicated that for all of the adults forming the older control group, there was no evidence of hearing impairment or a deficit in cognitive function that might affect speech perception and recognition. Follow up testing of nine individuals, found no changes in hearing thresholds, cognitive function, or speech in noise recognition. There were some improvements in the scores on the dichotic digits assessments that might indicate a practice effect. However, results were close to ceiling for the individual tests. Results from the older, healthy participant group (31-49 yrs) were compared to those of the younger healthy participants group (18-30 yrs). The results from the group of older

adults were, for most measures, not found to be significantly different from those from the younger group of adults. For the two significant differences established for the females, the results were within the limits established for the younger control group. It is therefore appropriate to use the data from the larger control group to define the limits that would be expected for normal adults.

A second aim of this study was to assess whether changes in results occurred over time. A 12 week period was chosen, as this is the length of the rehabilitation programme offered by the Lothians and Edinburgh Abstinence Programme (LEAP). The participants in Experiment Two are enrolled in this treatment and rehabilitation programme. There were some improvements seen in the results of the APD tests and this might be attributable to a practice effect. This will be taken into account when looking at the follow-up test data for the participants with ADS. All but one of the seventeen speech ABR measures were repeatable over time. Caution needs to be applied when looking at the representation of F0 in the waveform. A difference between assessments was only found for women, which may be a feature of a small sample size but needs to be taken into consideration when analysing speech ABR results.

Chapter Four: Experiment Two

At present, there is no objective, quick and inexpensive way of assessing the effect of harmful drinking on the brain. As discussed in section two, it would appear that the click ABR may offer a way of assessing and monitoring neural damage relating to harmful alcohol consumption. It would also appear that the speech ABR allows the detection of abnormalities in the brainstem response to sound, not evident when using the click stimuli. As there are unresolved questions about whether or not people with an AUD have significantly prolonged brainstem conduction time for sound, further research comparing the click and speech ABR in this population, is required. The purpose of Experiment Two is to explore both the click and speech ABR in adults with a diagnosis of alcohol dependence syndrome. A reminder of the aims and research questions are as follows:

An aim of Experiment Two is to assess the impact of alcohol and abstinence on auditory brainstem functioning and the value of using measures of functioning as an objective way of monitoring neural impact. As part of this, the following questions will be addressed:

1. In what ways do people diagnosed with alcohol dependence syndrome, who have normal hearing sensitivity differ in their auditory-cognitive profile compared to healthy adults?

2. Is the auditory brainstem response of people diagnosed with alcohol dependence syndrome different from that of healthy adults?

    a. when responding to click stimuli

    b. when responding to speech stimuli

3. What are the changes in 1 and 2, following adherence to a 12 week alcohol abstinence programme.

4. What is the relationship between drinking history and measures in 1, 2, and 3?

This section presents the methods and analyses that relate to the auditory-cognitive profile of adults with ADS. The methods for the individual tests used, has been described in section three (3.1.2). For precise order of assessment, please see figure six, section two (2.1.5). All studies within Experiment Two were conducted with

the approval of the Ethics Committee of Queen Margaret University, as well as approval from the NHS Research Ethics committee (15/WA/0019 IRAS 156480) (Appendix 5) and all participants signed a consent form prior to data collection.

4.1 Effects of Alcohol on the Auditory-Cognitive Profile of Adults with Alcohol Dependence Syndrome

This section aims to answer the research question 'in what ways do people diagnosed with alcohol dependence syndrome, who have normal hearing sensitivity, differ in their auditory-cognitive profile compared to healthy adults?'

Descriptive statistics that relate to the auditory-cognitive profile of adults with ADS but with typical hearing sensitivity, performed at baseline assessment, are presented.

4.1.1 Participants

Eighteen adults (7 Females, 11 Males) aged 29-49 years, with a history of excessive consumption of alcohol, attending an abstinence programme were recruited. The participants were patients who had received a diagnosis of ADS and had committed to taking part in the Lothians & Edinburgh Abstinence Programme (LEAP). Years of problem drinking ranged from four to thirty (mean = 14.3 years). The patients were either admitted to the Ritson Clinic for alcohol detoxification before taking part in the LEAP programme, or patients who had managed to reduce their drinking without a medically assisted detoxification and were being admitted directly to LEAP. The Ritson Clinic is a 12 bed detoxification ward based in the Royal Edinburgh Hospital. The ward is for people for whom it is unsafe to detox in the community and the average stay is ten days. LEAP supports those who wish to stop taking alcohol and / or other illicit drugs, with a treatment and rehabilitation day programme lasting twelve weeks and involving daily, structured activities (see http://www.nhslothian.scot.nhs.uk/services/a-z/leap/Pages/default.aspx).

The inclusion criteria for Experiment Two was as follows:

- A patient of LEAP with a diagnosis of ADS, undergoing detoxification and taking part in an abstinence programme.
- Aged 18-50 years.
- Native British Speaker.

The Exclusion Criteria for Experiment Two were:

- A diagnosis of hearing loss or a hearing aid wearer (hearing thresholds ≥20 dB HL for 250, 500, 1000, 2000, 4000 and 8000 Hz) either pre-existing or established at baseline testing.
- A diagnosis of alcohol related brain damage or Wernicke-Korsakoff syndrome.
- A diagnosis of psychosis.
- A history of addiction to illicit substances other than alcohol.
- Uncorrected visual impairment that would prevent reading during testing.
- A diagnosis of dyslexia, any specific language impairment or autistic spectrum disorder.
- A history of neurological disorders such as multiple sclerosis, Huntington's disease, or major head trauma.
- A diagnosis of dementia or Alzheimer's disease.
- Pregnancy.

One woman and one man were subsequently excluded from the study, for having a bilateral, mild to moderate level of sensorineural hearing loss. This resulted in 16 adults (6 Females, 10 Males) aged 29-49 years (mean age 40.9 yrs, S.D. 6.56 yrs) participating in this exploratory study.

4.1.1.1. Sources of Error and Bias

The following considerations influenced the design of the study.

4.1.1.1.1. Sampling effect

The criteria for inclusion in the study group were a diagnosis of ADS, entry into a rehabilitation programme and normal hearing thresholds. There was no requirement for the participants in the study group to have normal auditory processing or normal cognitive ability. The reason for this is that it is known that people with ADS may experience difficulties in cognitive performance and perform more poorly on tests from the WAIS-III^{UK} when compared to standard age scaled results (Lin et al. 2010).

4.1.1.1.2 Bias and compensation

The data from the study participants reflects data from adults aged 29 to 49, without a diagnosis of dyslexia, any specific language impairment or autistic spectrum

disorder, or having experienced major head trauma. It is known that there is a link between learning difficulties and substance misuse (Jhanjee 2015). As people with dyslexia or any specific language impairment were excluded, this study does not capture the full range of people likely to have ADS.

For any participant to be included in this study their hearing thresholds had to be ≤20 dB HL. Patients with known hearing losses were not included in this study, as the hearing loss could have an effect on the ABR results. It is possible that people with ADS are at risk of hearing loss (Gołąbek and Niedzielska 1984; Verma et al. 2006) and this study does not capture the extent of this issue.

4.1.2 Methods

All testing was carried out as described in section three, details of which can be found in 3.1.2. The only differences being the location of testing, the addition of evaluation of history of alcohol consumption (see 4.1.2.1) and the number of times testing was performed. Testing was either carried out in a quiet interview room within the Ritson Clinic in the Royal Edinburgh Hospital, or in a quiet counselling room within LEAP in the Astley Ainslie Hospital. Neither of these rooms are soundproofed but they are used for confidential patient discussions and are located in quiet areas of the respective hospitals.

4.1.2.1 Alcohol Consumption History

In order to assess whether differences in the history of alcohol consumption resulted in differences in the ABR waveforms, patients' records were accessed with consent. The alcohol history profile was derived by looking at information including when they first came into contact with health services in relation to alcohol consumption. Patients may have completed the Severity of Dependence Scale (SDS), they may have had Clinical Outcomes in Routine Evaluation (CORE) and there may also be results from blood tests such as gamma-glutamyl transpeptidase (GGT), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and mean corpuscular volume (MCV) (see section two, 2.4.2.1). The clinic normative ranges for these tests were 10-55 for GGT, 10-50 for ALT, 40-125 for ALP and 78-98 for MCV. During the abstinence programme patients may have also been screened by breathalyser or urine/saliva test. This information was used to complete a drinking profile for each

patient. It is assumed that patients volunteering for participation will be abstaining from alcohol consumption and the recreational use of other illicit drugs, as per their programme requirements. The patients' records were checked at the follow up appointment to establish whether any alcohol use had been detected during this time. In the rare event that the care team determined or suspected a patient to have consumed alcohol during the treatment and rehabilitation programme, they were withdrawn from the study. This occurred for participant number ten, whose data only contributes to baseline assessment.

4.1.3 Results and Analysis of the Auditory-Cognitive Profile

The following section provides the results and analysis for the auditory-cognitive profile of adults with ADS. In all cases prior to analysis the Shapiro-Wilks Francia test was applied to establish that the data for males and females was normally distributed.

4.1.3.1 Age Profile of Participants with ADS

Data is presented from the ten male and six female participants with ADS. All sixteen participants completed all aspects of the auditory-cognitive profile assessment. The mean age of the male participants was 41.2 years (SD 7.54) and the mean age of the female participants was 40.5 years (SD 5.09). The age profile of participants is presented in the following figures (Figs. 25 and 26).

Figure 25. Age Profile of Male Participants with ADS

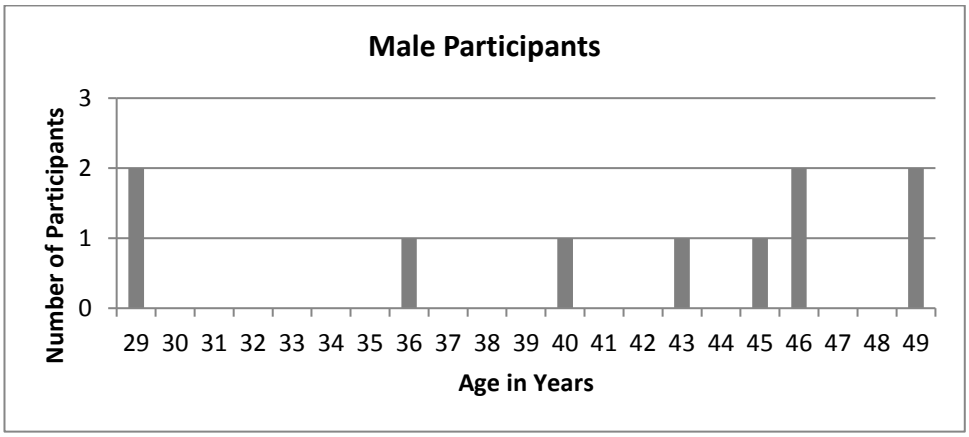
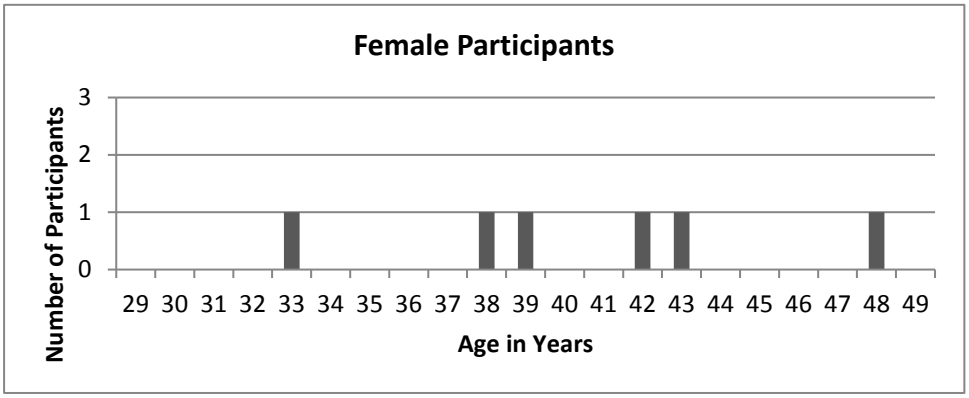


Figure 26. Age Profile of Female Participants with ADS



4.1.3.2 Alcohol Profile of the Participants with ADS

The drinking history of the individual participants with ADS is presented in the following table (Table 45). Details include the sex, age, age of first alcoholic drink, age at which drinking became problematic, years of chronic, heavy drinking, recent drinking behaviour, whether thiamine has been prescribed, markers for alcohol (see section 2.4.2), smoking status any other pertinent history.

Table 45. Alcohol Profile of the Participants with ADS

ID	Sex	Age (yrs)	Age of first drink (yrs)	Years of chronic, heavy drinking	Recent drinking behaviour (grams of alcohol /day)	Thiamine	Marker for Alcohol	Smoker	Other Information
1	Male	45	15	24	Up to 5 lts cider / day (~200 grams/ day)	No	MCV=92 GGT=89	No	Left school at 15 without qualifications. No previous abstinence.
2	Male	40	10	18	Bottle of Buckfast and 4 cans Strongbow / day (~148 grams/ day)	Yes	MCV=98 ALP=160	Yes	Left school at 15 without qualifications. Detoxification in 2009, remained abstinent for 5 months.
3	Male	29	18	11	4 lts cider and up to 2 bottles of wine / day (160 - 304 grams/ day)	Yes	Not in notes	Yes	Self detox in 2012, admitted to A&E. CORE 10 Score: 11, SDS: 8
4	Male	29	10	7	1 litre of vodka / day (300 grams / day)	Yes	MCV=115 GGT=298	Yes	Detoxification in Ritson clinic in 2014. Has tried self-detoxification but only lasts 1 week without alcohol. CORE 10 Score: 19, SDS:13

Table 45 continued

ID	Sex	Age (yrs)	Age of first drink (yrs)	Years of chronic, heavy drinking	Recent drinking behaviour	Thiamine	Marker for Alcohol	Smoker	Other Information
5	Female	39	NR	10	At least ½ litre vodka / day (5/7 days) (0-150 grams/ day)	No	Not in notes	No	
6	Female	38	18	5	1 litre of vodka / day (5/7) (0 -300 grams/ day)	Yes	Not in notes	No	2 previous detoxifications, with maximum period of abstinence of about 5 weeks.
7	Male	46	14	25	1-2 litres of cider and a bottle of vodka / day (248 - 288 grams/ day)	Yes	MCV=97 ALT=74 GGT=276	Yes	Came to the attention of health services in 2004 for 'problem drinking.' Two previous detoxifications in the Ritson clinic, plus a community detox in 2015. CORE 10 Score: 10, SDS: 14
8	Female	33	18	4	1 bottle vodka / day (208 grams/ day)	No	MCV=92 ALT=124 GGT=200	Yes	Started irregular binge drinking at about age 24. One previous detox in the Ritson clinic.

Table 45 continued

ID	Sex	Age (yrs)	Age of first drink (yrs)	Years of chronic, heavy drinking	Recent drinking behaviour (grams of alcohol/day)	Thiamine	Marker for Alcohol	Smoker	Other Information
9	Female	42	12	23	6-8 pints of Stella Artois and 4 pints of Innis & Gunn / day (262 – 307 grams/ day)	Yes	MCV=91 ALT=49 GGT=158	Yes	First detoxification at age 19, at least two further detoxifications.
10	Male	36	NR	5	1 bottle of vodka / day (208 grams/ day)	Yes	GGT=159	Yes	Five previous seizures due to alcohol withdrawal in last 2.5 years.
11	Male	46	10	26	1 Lt vodka / day (300 grams/ day)	No	Not in notes	Yes	Was abstinent for 4 years until recently and has had 3 previous detoxifications. CORE-10 Score: 31
12	Male	43	NR	16	0 or 1-2 Litres of vodka / day, depending on money (0-600 grams/ day)	Yes	No values outside normal limits.	Yes	Four previous seizures due to alcohol withdrawal. Detoxification in Ritson clinic, 7 years ago.

Table 45 continued

ID	Sex	Age (yrs)	Age of first drink (yrs)	Years of chronic, heavy drinking	Recent drinking behaviour	Thiamine	Marker for Alcohol	Smoker	Other Information
13	Female	43	14	4	2 bottles of wine / day (~144 grams/ day)	No	Not in notes	Yes	CORE-10 Score: 20, SDS: 10
14	Male	49	14	15	6 lts cider / day and ½ bottle of vodka in addition at weekend. (240 - 344 grams/ day)	Yes	Not in notes	Yes	Left school at 15. Previous admission to Ritson clinic. SDS: 14
15	Male	49	15	30	4 cans of lager and 1 bottle of vodka / day. (~272 grams/ day).	No	Not in notes	Yes	Came to the attention of health services in 2012 for 'problem drinking.' CORE-10 Score: 21, SDS: 10
16	Female	48	NR	6	1.5-4 bottles of wine / day (but usually 2). (108 - 288 grams/ day).	No	MCV=92 ALT=180 GGT=401	Yes	Has previous contact with services for alcohol use, that predates 6 years declared heavy drinking. CORE-10 Score: 26, SDS: 13

4.1.3.3 Pure Tone Audiometry

To meet the inclusion criteria an individual's pure tone hearing thresholds for 250 Hz, 500 Hz 1000 Hz, 2000 Hz, 4000 Hz and 8000 Hz could be no greater than 20 dB HL bilaterally. Results for the right ears and left ears for the male participants are presented in figures 27 and 28 below.

Figure 27. Pure Tone Audiometry Results for Males (Right Ear, Mean and S.D.)

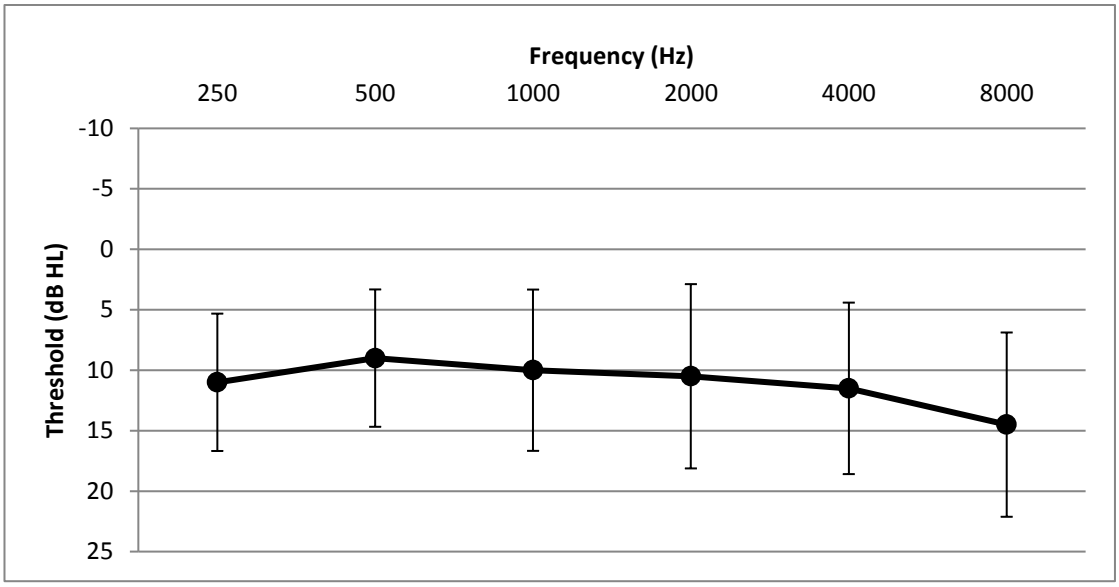
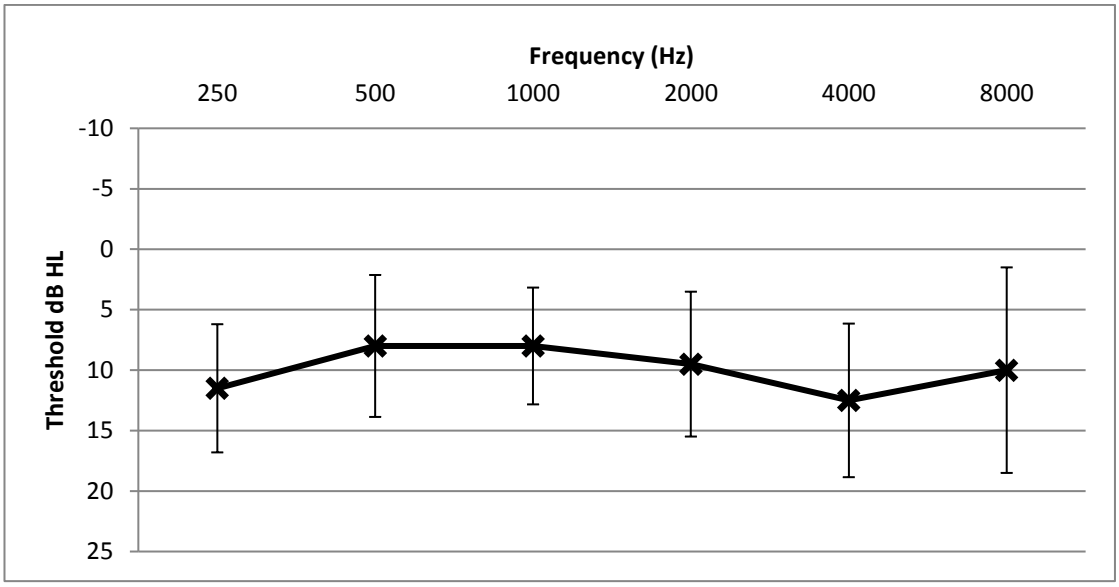


Figure 28. Pure Tone Audiometry Results for Males (Left Ear, Mean and S.D.)



Results for the right and left ears for the female participants are presented in the figures 29 and 30 below.

Figure 29. Pure Tone Audiometry Results for Females (Right Ear, Mean and S.D.)

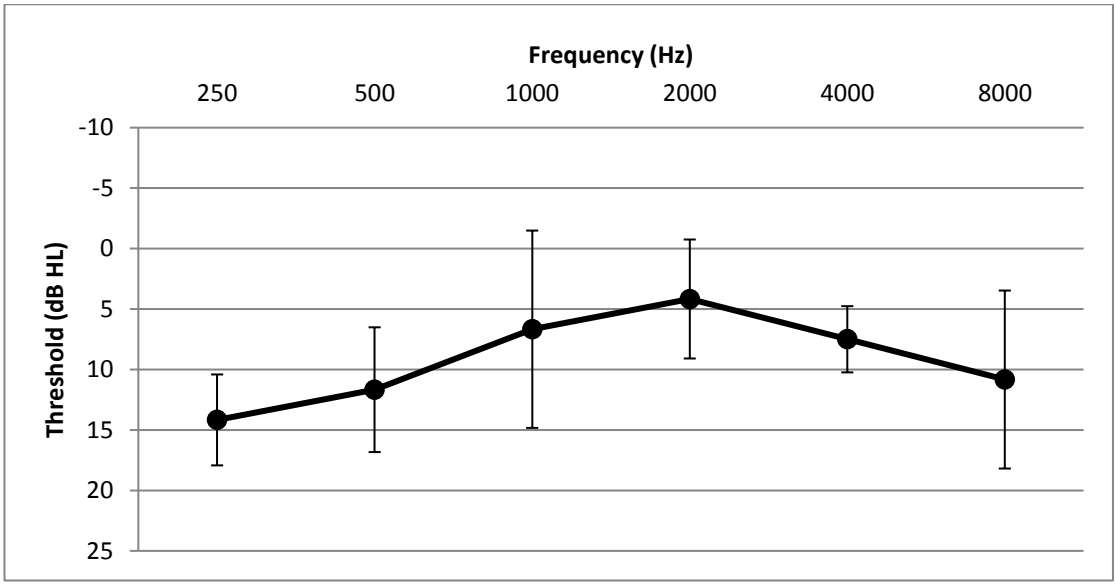
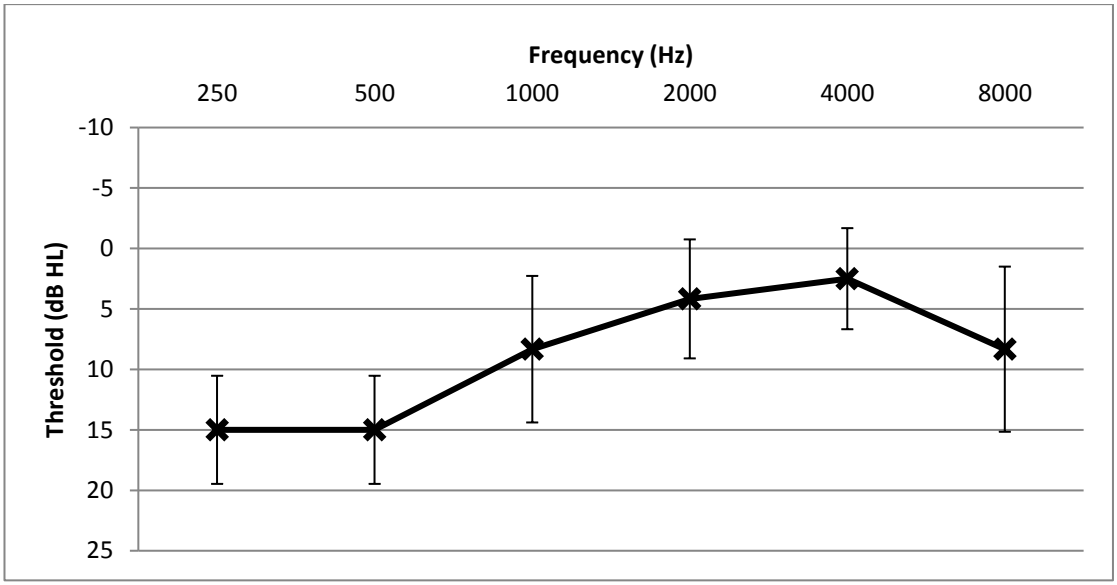


Figure 30. Pure Tone Audiometry Results for Females (Left Ear, Mean and S.D.)



4.1.3.3.1 Interpretation of Results for PTA

All participants had thresholds of 20 dB HL or better for each frequency point and no participants had thresholds meeting any of the BSA descriptors of hearing loss (British Society of Audiology 2011, p. 22). The results of pure tone audiometry testing for the adults with ADS included within this study are as would be expected from ISO7029:2017.

4.1.3.4 Cognitive Assessment

The mean values of the scaled score results for the subtests of the WAIS-III^{UK} assessment are presented in table 46 below.

Table 46. Results of Cognitive Assessments at Baseline (Mean and S.D.)

WAIS-III^{UK} Subtest	Males (S.D.)	Females (S.D.)
Vocabulary	7.30 (3.30)	8.67 (2.25)
Digit- Symbol Coding	7.50 (2.64)	9.00 (2.28)
Digit Span	7.50 (3.06)	9.50 (2.07)
Symbol Search	8.70 (2.67)	9.00 (2.28)
Letter- Number Sequencing	6.50 (2.72)	9.83 (2.48)

4.1.3.4.1 Interpretation of Results of the Cognitive Assessment

Eight (50%) participants scored below the lower cut off point of seven (Psychological Corporation 1997), for one or more of the subtests when measured at baseline assessment. As discussed in section 2.4.4, this is to be expected for people with a diagnosis of ADS (Kopera et al. 2012). Details of the scores for these individuals are presented in table 47.

Table 47. Summary of Results for Individuals with WAIS-III^{UK} Subtest Scores outside Normal Limits (in Bold).

ID	SEX	Vocabulary	Digit Symbol coding	Digit Span	Symbol Search	Letter Number Sequencing
1	Male	**3**	**4**	**4**	**5**	**3**
4	Male	10	7	8	8	**4**
7	Male	9	8	**4**	7	**5**
9	Female	**5**	8	8	9	8
10	Male	**5**	**5**	**6**	7	7
12	Male	9	7	14	9	**6**
13	Female	9	**6**	9	7	13
14	Male	**2**	**6**	**5**	7	**3**

4.1.3.5 Auditory Processing Capability Assessment

The mean values for the individual auditory processing tests are presented in tables within the following section. The data for all APD tests (except RGDT) was not normally distributed.

4.1.3.5.1 Results of Duration Pattern Sequence Testing

The results of DPST are presented below (Table 48) and all participants undertook this assessment.

Table 48. Results of Duration Pattern Sequence Testing at Baseline (Mean and S.D.)

DPST Score	Males		Females	
	Right Ear (S.D.)	Left Ear (S.D.)	Right Ear (S.D.)	Left Ear (S.D.)
% Correct	74.17 (22.64)	73.50 (22.46)	83.89 (29.73)	82.78 (22.94)

4.1.3.5.1.1 Interpretation of Results

Five participants (31%) scored below the lower cut off point of 67% when measured at baseline assessment. Details of the scores for these individuals are presented in the table below (Table 49).

Table 49. Summary of Results for Individuals with DPST Scores outside Normal Limits (in Bold)

ID	SEX	Right Ear, % Correct	Left Ear, % Correct
1	Male	**35.00**	**45.00**
7	Male	83.33	**56.67**
9	Female	**23.33**	**36.67**
14	Male	**63.33**	**53.33**
15	Male	**40.00**	**40.00**

4.1.3.5.2 Results of Pitch Pattern Sequence Testing

The results of the PPST are presented below (Table 50) and all participants undertook this assessment.

Table 50. Results of Pitch Pattern Sequence Testing at Baseline (Mean and S.D.)

PPST Score	Males		Females	
	Right Ear (S.D.)	Left Ear (S.D.)	Right Ear (S.D.)	Left Ear (S.D.)
% Correct	76.17 (25.83)	79.00 (21.03)	96.95 (5.42)	96.67 (8.16)

4.1.3.5.2.1 Interpretation of Results

Six participants (38%) scored below the lower cut off point of 88% when measured at baseline assessment. Details of the scores for these individuals are presented in the table below (Table 51).

Table 51. Summary of Results for Individuals with PPST Scores outside Normal Limits (in Bold).

ID	SEX	Right Ear, % Correct	Left Ear, % Correct
1	Male	**35.00**	**40.00**
7	Male	**66.67**	**83.33**
9	Female	**86.67**	**80.00**
12	Male	**80.00**	**70.00**
14	Male	**35.00**	**50.00**
15	Male	**60.00**	**70.00**

4.1.3.5.3 Results of Dichotic Digits Testing

The results of the dichotic digits assessment are presented below (Table 52) and all participants undertook this assessment.

Table 52. Results of Dichotic Digits Testing at Baseline (Mean and S.D.)

DD Score	Males		Females	
	Right Ear (S.D.)	Left Ear (S.D.)	Right Ear (S.D.)	Left Ear (S.D.)
% Correct	89.50 (11.04)	68.25 (26.46)	87.92 (8.58)	87.08 (8.28)

4.1.3.5.3.1 Interpretation of Results

Nine (56%) participants scored below the lower cut off point of 82% when measured at baseline assessment. Details of the scores for these individuals are presented in the table below (Table 53).

Table 53. Summary of Results for Individuals with DD Test Scores outside Normal Limits (in Bold)

ID	SEX	Right Ear, % Correct	Left Ear, % Correct
1	Male	**65.00**	**37.50**
2	Male	95.00	**80.00**
5	Female	**77.50**	85.00
7	Male	87.50	**47.50**
9	Female	90.00	**80.00**
10	Male	95.00	**27.50**
12	Male	**80.00**	**62.50**
14	Male	82.50	**50.00**
16	Female	**77.50**	**77.50**

4.1.3.5.4 Results of Random Gap Detection Testing

The results of the RGDT are presented below (Table 54) and all participants undertook this assessment. One participant had results outside the limits of the test and no gap detection threshold could be calculated at baseline testing.

Table 54. Results of Random Gap Detection Testing at Baseline (Mean and S.D.)

RGDT Threshold	Males		Females	
	Tonal Threshold (S.D.)	Click Threshold (S.D.)	Tonal Threshold (S.D.)	Click Threshold (S.D.)
Mean (ms)	12.19 (5.14)	12.22 (10.93)	11.54 (4.09)	11.17 (7.49)

4.1.3.5.4.1 Interpretation of Results

Four (25%) participants had a RGDT threshold of 20 ms or more when measured at baseline assessment. Details of the individual scores for these individuals are presented below (Table 55).

Table 55. Summary of Results for Individuals with RGD Test Scores outside Normal Limits (in Bold)

ID	SEX	Average Threshold (ms)	Click Threshold (ms)
1	Male	**23.00**	**40.00**
6	Female	11.25	**20.00**
9	Female	18.75	**20.00**
15	Male	**>40**	**>40**

4.1.3.6 TEOAE Testing

The results of TEOAE testing (Table 56) were used as an objective cross-check to confirm the evidence of normal hearing, as indicated by PTA results.

Table 56. TEOAE results at Baseline (Mean and S.D.)

TEOAE Measure	Males	Females
Reproducibility % (SD)	82.89 (9.31)	83.80 (8.70)
Stability % (SD)	97.60 (2.30)	98.10 (1.57)
Response at 1.0kHz SPL (SD)	9.21 (6.75)	6.47 (5.49)
Response at 1.4kHz SPL (SD)	12.56 (6.80)	11.81 (4.75)
Response at 2.0kHz SPL (SD)	10.69 (5.37)	10.68 (4.75)
Response at 2.8kHz SPL (SD)	9.62 (6.61)	6.65 (3.28)
Response at 4.0kHz SPL (SD)	6.92 (6.10)	8.35 (5.60)

4.1.3.6.1 Interpretation of Results of TEOAE Testing

All participants had a TEOAE present at 3 dB above the level of the noise floor in at least 3 out of 5 frequency bands, with reproducibility of response at greater than 70%. This would indicate that all participants had hearing threshold levels at these frequencies of 25-30 dB HL or better (Probst and Harris 1993) and this is in agreement with the results of pure tone audiometry testing. As all participants met the criteria for presence of TEOAEs, DPOAE testing was not performed.

4.1.3.7 Results of Speech-In-Noise Assessment

A speech-in-noise assessment was used to assess whether any participants had a signal to noise ratio (SNR) loss. All participants SRT results were below 0dB and are presented in table 57.

Table 57. Results from the Speech- in- Noise Assessment (Mean and S.D.)

SRT Score	Males (S.D.)	Females (S.D.)
Mean 50% correct score (dB), Baseline	-3.10 (0.88)	-3.67 (1.21)
Mean 50% correct score (dB), Second Assessment	-3.50 (1.05)	-4.00 (1.41)

4.1.3.7.1 Interpretation of Results

All adults within this study had SRT scores of less than 0 dB which can be considered to be normal and therefore further speech audiometry in quiet was not performed.

4.1.4 Addressing the Research Question

The aim of this study was to explore the auditory-cognitive profiles of adults with ADS, who have normal hearing sensitivity. There is an apparent heterogeneity within the results from the participants with ADS (Table 58). Of the sixteen participants, eight (50%) had at least one result below normal limits for the cognitive assessment at baseline testing and eleven (69%) had at least one result below normal limits for the auditory processing assessment. The results of the auditory-cognitive profile assessment indicate that only three of the sixteen adults (19%) who participated in baseline testing exhibited no evidence of a deficit in cognitive function or auditory processing that might affect speech perception and recognition. However, none had any diagnosis of specific language impairment.

Table 58. Summary of Deficits in the Auditory-Cognitive Profile of Individual Participants

ID	Sex	No. of Cognitive assessments outside normal limits	No. of APD assessments outside normal limits
1	Male	5	4
2	Male	0	1
3	Male	0	0
4	Male	1	0
5	Female	0	1
6	Female	0	1
7	Male	2	3
8	Female	0	0
9	Female	1	4
10	Male	3	1
11	Male	0	0
12	Male	1	2
13	Female	1	0
14	Male	4	3
15	Male	0	3
16	Female	0	1

4.1.4.1The Auditory-Cognitive Profile in People with ADS

In what ways do people diagnosed with alcohol dependence syndrome, who have normal hearing sensitivity differ in their auditory-cognitive profile compared to healthy adults? Although the participants within this study were selected on the basis of having 'normal' hearing thresholds when measured by pure tone audiometry, it is apparent that for those with ADS the auditory-cognitive profile is not typical. Of the five WAIS subtests used for the cognitive assessment, all resulted in at least one person being identified with a deficit. A combination of the Vocabulary, Digit-Symbol Coding and Letter Number Sequencing subtests only would have identified all people with a below typical subtest result. Of the four auditory processing tests used, all resulted in at least one person being identified with a deficit. A combination of the Dichotic Digits and Random Gap Detection subtests would have identified all people

with a below typical subtest result. To expand on this, the RGDT for clicks identifies more of the people with deficits than the RGDT for tonal stimuli and therefore it may be possible to use this subtest for screening, as opposed to additionally testing with all four tones.

The measures recorded within this study have demonstrated that aspects of auditory processing and cognition that may affect speech processing, can be impaired in people with ADS. Of the sixteen people tested, thirteen (81%) had deficits in either auditory processing or aspects of cognition and five people (31%) had deficits in both. The majority of people tested on entering the LEAP programme, did not have 'typical' auditory-cognitive profiles for their age and sex and the potential impact of this will be discussed in chapter five.

4.2 The Auditory Brainstem Responses of Adults with Alcohol Dependence Syndrome

The aim of this section is to answer research questions relating to both the click and speech ABRs in people with ADS. Specifically, the research question to be addressed is:
Is the auditory brainstem response of people diagnosed with alcohol dependence syndrome different from that of healthy adults?

a. when responding to click stimuli
b. when responding to speech stimuli

Section 4.2.3 onwards contains the results, analysis and interpretation of the data gathered by the described methods. The analyses include a comparison of the baseline ABR results with the control data generated in chapter three.

4.2.1 Participants

The participants with a diagnosis of ADS have been described in section 4.1.1.

4.2.2 Methods

All testing was carried out as described in section three, details of which can be found in section 3.1.2. The only differences being the location of testing and the number of times testing was performed. Testing was either carried out in a quiet interview room within the Ritson Clinic in the Royal Edinburgh Hospital, or in a quiet counselling room within LEAP in the Astley Ainslie Hospital. Neither of these rooms are soundproofed but they are used for confidential patient discussions and are located in quiet areas of the respective hospitals.

4.2.2.1 Click ABR Procedure

The click ABR recording took place after the speech-in-noise assessment, as per figure six, section two (2.1.5). The methods for collecting the click ABR data have been described in section three (3.1.2.10).

4.2.2.2 Speech ABR Procedure

The speech ABR recording took place after click ABR recording, as per figure six, section two (2.1.5). The methods for collecting the speech ABR data have been described in section three (3.1.2.11).

4.2.3 Results and Analysis of Click ABR Testing

The following section provides the results and analysis of the click ABR for adults with ADS when compared to the ABRs of healthy adults from Experiment One. In all cases prior to analysis the Shapiro-Wilks Francia test was applied to establish that the data for males and females was normally distributed.

4.2.3.1 The Click ABR in People with ADS

Two audiologists independently marked the grand average ABR waveform data derived from all participants (Vidler and Parker 2004). The data set was comprised of 32 waveforms from 32 ears. For all waveforms the examiners were asked to complete a table to indicate whether they felt replicable waves were present in the constituent traces that contributed to the grand averaged waveform. For the click ABR the examiners were in agreement that waves I, III and V could be reliably identified in 100% of waveforms. Latency and amplitude data for the participants with ADS, are presented in the tables below (Tables 59 and 60). Amplitude is relative to a Baseline within the software.

Table 59. Latency Results from the Baseline Click ABR Assessment, Data Pooled for Ear (Mean and S.D.)

ABR Component (ms)	Males (S.D.)	Females (S.D.)
Wave I latency	1.64 (0.15)	1.61 (0.10)
Wave III latency	3.90 (0.16)	3.69 (0.16)
Wave V latency	5.86 (0.22)	5.67 (0.23)
I-III latency	2.28 (0.12)	2.08 (0.11)
III-V latency	1.96 (0.18)	1.98 (0.14)
I-V latency	4.24 (0.16)	4.06 (0.15)

Table 60. Amplitude Results from the Click ABR Assessment, Data Pooled for Ear (Mean and S.D.)

ABR Component (μV)	Males (S.D.)	Females (S.D.)
Wave I amplitude	0.073 (0.10)	0.073 (0.07)
Wave III amplitude	0.175 (0.12)	0.155 (0.08)
Wave V amplitude	0.048 (0.08)	-0.030 (0.10)

4.2.3.2 Comparing the Control data for Healthy Adults from Experiment One and Adults with ADS from Experiment Two

Apart from wave I, independent samples t-tests found significant differences for the ABR latencies between the healthy males in Experiment One and those with ADS in Experiment Two. Both waves III ($t(78)= -4.93$, $p < 0.001$) and Wave V ($t(78) = -5.00$, $p < 0.001$), were significantly delayed in the men with ADS. The interpeak intervals of waves I to III ($t(78) = -3.83$ $p < 0.001$), and I to V (($t(78) = -3.52$ $p = 0.001$) were significantly prolonged and all these differences remained after corrections for multiple comparisons were applied. There were no significant differences in the amplitudes of the waves between the two groups. The latency ranges for the men in Experiment One and Experiment Two are provided in table 61.

Table 61. Latency Range for Click ABR Components for Males

ABR Component	Latency Range in ms (Mean ± 2SD)	
	Healthy Men	Men with ADS
Wave I	1.33 - 1.81	1.34 - 1.94
Wave III	3.44 - 4.00	3.58 - 4.22
Wave V	5.34 - 5.94	5.42 - 6.30
I-III	1.87 - 2.43	2.04 - 2.52
III-V	1.6 - 2.24	1.6 - 2.32
I-V	3.69 - 4.45	3.92 - 4.56

Of the 10 men with ADS, two (20%) had wave I latency outside normal limits unilaterally. Four (40%) had wave III latency outside normal limits, of which one was bilaterally. Four (40%) had wave V latency outside normal limits, three of which were

bilaterally (Table 62). Two (20%) had a prolonged I-III interpeak interval unilaterally, and one (10%) had a prolonged III-V interpeak interval unilaterally and one (10%) had a prolonged I-V interpeak interval unilaterally (Table 63).

Table 62. Summary of Results for Men with ABR Peak Latencies Outside Normal Limits

ID	Right Ear			Left ear		
	I	III	V	I	III	V
4			✓			✓
7		✓			✓	
10			✓		✓	✓
12	✓		✓		✓	✓
15				✓	✓	✓

Where ✓ represents positive for a result outside normal limits.

Table 63. Summary of Results for Men with ABR Interpeak Latencies Outside Normal Limits

ID	Right Ear			Left Ear		
	I-III	III-V	I-V	I-III	III-V	I-V
1				✓		
2				✓		
4		✓	✓			

Where ✓ represents positive for a result outside normal limits.

Independent samples t-tests found significant differences for the ABR latencies between the healthy females in Experiment One and the females with ADS in Experiment Two. Waves I ($t(70)= -3.81$, $p < 0.001$) and V ($t(70) = -3.94$, $p < 0.001$), were significantly delayed in the females with ADS and these differences remained after corrections for multiple comparisons were applied. There were no significant differences in the amplitudes of the waves between the two groups. The latency ranges for the women in Experiment One and Experiment Two are provided below (Table 64).

Table 64. Latency Range for Click ABR Components for Females

ABR Component	Latency Range in ms (Mean ± 2SD)	
	Women (age 18-30)	Women with ADS
Wave I	1.32 - 1.68	1.41 – 1.81
Wave III	3.30 - 3.86	3.37 – 4.01
Wave V	5.11 - 5.79	5.21 – 6.13
I-III	1.80 - 2.36	1.86 - 2.30
III-V	1.55 - 2.19	1.70 - 2.26
I-V	3.62 - 4.26	3.76 - 4.36

Of the 6 women with ADS, three (50%) had wave I latency outside normal limits of which one was bilaterally (Table 65). Of these three, one (17%) had all waves outside normal limits bilaterally, and a prolonged I-V interpeak interval unilaterally (Table 66).

Table 65. Summary of Results for Women with ABR Peak Latencies Outside Normal Limits

ID	Right Ear			Left ear		
	I	III	V	I	III	V
8	✓					
13				✓		
16	✓	✓	✓	✓	✓	✓

Where ✓ represents positive for a result outside normal limits.

Table 66. Summary of Results for Women with ABR Interpeak Latencies Outside Normal Limits

ID	Right Ear			Left Ear		
	I-III	III-V	I-V	I-III	III-V	I-V
16			✓			

Where ✓ represents positive for a result outside normal limits.

4.2.3.3 Interpretation of Click ABR Latency and Amplitude Data

The neural brainstem response to click stimuli of people diagnosed with ADS, is different to that of healthy adults.

4.2.4 Results and Analysis of Speech ABR Testing

The data set generated consists of 32 speech ABR waveforms from 32 ears. For all waveforms the raters were asked to complete a table to indicate whether they felt replicable waves were present in the constituent traces that contributed to the grand averaged waveform. The raters were able to identify the waves in at least two out of three traces, as detailed below (Table 67).

Table 67. Average Detectability (%) of Individual Peaks of the Speech ABR in Participants with ADS

Transient Measure	V	A	D	E	F	O
Average % detectability	100	100	98	100	100	100

4.2.4.1 Discrete Peak and Composite Onset Measures Analysis

Latencies and amplitudes of discrete peaks were evaluated, in addition to three composite measures of neural synchrony to the onset of the stimulus. The composite measures included V to A interpeak latency, V to A peak-to-trough amplitude, and the slope of the VA complex (change in peak amplitude over time). The mean latency values for these measures, pooled for ears, is presented in the table below (Table 68).

Table 68. Discrete Peak and Composite Onset Measures of the Speech ABR for Men and Women (Mean and S.D.)

Speech ABR Component	Male (S.D.)	Female (S.D.)
wave V (ms)	7.34 (0.38)	7.01 (0.39)
wave A (ms)	8.30 (0.36)	7.95 (0.36)
wave D (ms)	23.02 (0.39)	22.90 (0.56)
wave E (ms)	31.64 (0.46)	31.66 (0.60)
wave F (ms)	40.02 (0.58)	39.76 (0.48)
wave O (ms)	48.77 (0.41)	48.54 (0.17)
wave D-E (ms)	8.62 (0.60)	8.77 (0.55)
wave E-F (ms)	8.38 (0.53)	8.10 (0.71)
VA Duration (ms)	0.964 (0.19)	0.944 (0.19)
VA Amplitude (µV)	0.195 (0.08)	0.179 (0.08)
VA Slope (ms/ µV)	-0.200 (0.09)	-0.193 (0.09)

4.2.4.2 Comparing the Control data for Healthy Adults from Experiment One and Adults with ADS from Experiment Two

Independent samples t-tests found significant differences for the speech ABR peak latencies between the healthy males in Experiment One and the males with ADS from Experiment Two. Both waves V and A, were significantly delayed in the adults with ADS (Table 69). Whilst other measures also resulted in significant differences, these differences do not remain significant when results are reported with a Bonferroni-corrected significance criterion for multiple comparisons (a = 0.0045).

Table 69. Comparison of Speech ABR Discrete Peak and Onset Measures between Healthy Male Control Participants and Men with ADS (Mean and S.D.)

Speech ABR Component	Healthy Men (SD)	Men with ADS (SD)	t	p
wave V (ms)	6.94 (0.26)	7.34 (0.38)	-5.14	< 0.001*
wave A (ms)	7.94 (0.30)	8.30 (0.36)	-4.43	< 0.001*
wave D (ms)	23.00 (0.74)	23.02 (0.39)	-0.098	0.922
wave E (ms)	31.28 (0.49)	31.64 (0.46)	-2.88	0.005
wave F (ms)	39.86 (0.44)	40.02 (0.58)	-1.34	0.184
wave O (ms)	48.62 (0.47)	48.77 (0.41)	-1.34	0.185
wave D-E (ms)	8.28 (0.79)	8.62 (0.60)	-1.75	0.084
wave E-F (ms)	8.57 (0.56)	8.38 (0.53)	1.34	0.185
VA Duration (ms)	1.01 (0.27)	0.964 (0.19)	0.734	0.465
VA Amplitude (μV)	0.257 (0.09)	0.195 (0.08)	2.64	0.010
VA Slope (ms/ μV)	-0.261 (0.09)	-0.198 (0.09)	-2.65	0.010

* Result remains significant after correcting for multiple comparisons

Table 70. Data Ranges for Discrete Peak and Onset Measures in Men from Experiment One and Men with ADS from Experiment Two

Speech ABR Component	Range (Mean ± 2SD)	
	Healthy Men	Men with ADS
wave V (ms)	6.42 – 7.46	6.58 – 8.10
wave A (ms)	7.34 – 8.54	7.58 – 9.02
wave D (ms)	21.52 – 24.48	22.24 – 23.80
wave E (ms)	30.30 – 32.26	30.72 – 32.56
wave F (ms)	38.98 – 40.74	38.86 – 41.18
wave O (ms)	47.68 – 49.56	47.95 – 49.59
wave D-E (ms)	6.7 – 9.86	7.42 – 9.82
wave E-F (ms)	7.45 – 9.69	7.32 – 9.44
VA Duration (ms)	0.47 – 1.55	0.58 – 1.34
VA Amplitude (μV)	0.077 – 0.437	0.035 – 0.355
VA Slope (ms/ μV)	-0.441 - -0.081	-0.378 - -0.018

Independent samples t-tests found significant differences for the discrete peak and composite onset measures between the healthy females in Experiment One and

the females with ADS from Experiment Two (Table 71). With the majority of these differences remaining after corrections for multiple comparisons were applied.

Table 71. Comparison of Speech ABR Discrete Peak and Onset Measures between Healthy Female Control Participants and Women with ADS (Mean and S.D.)

Speech ABR Component	Healthy Women (SD)	Women with ADS (SD)	t	p
wave V (ms)	6.56 (0.27)	7.01 (0.39)	-4.88	< 0.001*
wave A (ms)	7.47 (0.31)	7.95 (0.36)	-4.85	< 0.001*
wave D (ms)	22.72 (0.76)	22.90 (0.56)	-0.761	0.449
wave E (ms)	31.00 (0.61)	31.66 (0.60)	-3.43	0.001*
wave F (ms)	39.41 (0.44)	39.76 (0.48)	-2.47	0.016
wave O (ms)	48.12 (0.40)	48.54 (0.17)	-3.57	0.001*
wave D-E (ms)	8.28 (0.79)	8.77 (0.55)	-2.03	0.046
wave E-F (ms)	8.42 (0.50)	8.10 (0.71)	1.86	0.067
VA Duration (ms)	0.905 (0.14)	0.944 (0.19)	-0.812	0.420
VA Amplitude (µV)	0.307 (0.10)	0.179 (0.08)	4.16	< 0.001*
VA Slope (ms/ µV)	-0.346 (0.12)	-0.193 (0.09)	-4.20	< 0.001*

* Result remains significant after correcting for multiple comparisons

Table 72. Data Ranges for Discrete Peak and Onset Measures in Women from Experiment One and Women with ADS from Experiment Two

Speech ABR Component	Range (Mean ± 2SD)	
	Healthy Women	Women with ADS
wave V (ms)	6.02 – 7.10	6.23 – 7.79
wave A (ms)	6.85 – 8.09	7.23 – 8.67
wave D (ms)	21.20 – 24.24	21.78 – 24.02
wave E (ms)	29.78 – 32.22	30.46 – 32.86
wave F (ms)	38.53 – 40.29	38.80 - 40.72
wave O (ms)	47.32 – 48.92	48.20 – 48.88
wave D-E (ms)	6.7 – 9.86	7.67 – 9.87
wave E-F (ms)	7.42 – 9.42	6.68 – 9.52
VA Duration (ms)	0.625 – 1.185	0.564 – 1.324
VA Amplitude (µV)	0.107- 0.507	0.019 – 0.339
VA Slope (ms/ µV)	-0.586 - -0.106	-0.373 - -0.013

4.2.4.3 Interpretation of Results for Discrete Peak and Composite Onset Measures

Differences are found in the transient onset measures for the speech ABR for both men and women with ADS when compared to the healthy, control group. There were additional differences between the healthy women and women with ADS in the composite onset measure and the offset measures. Of the ten men with ADS, four (40%) had wave V outside normal limits, of which two were bilaterally (20%). Three (30%) had wave A outside normal limits, of which one (10%) was bilaterally. One (10%) had wave E outside normal limits unilaterally and three (30%) had wave F outside normal limits unilaterally. One (10%) had wave O outside normal limits unilaterally. One (10%) had the interpeak interval for D to E outside normal limits unilaterally. One (10%) had an abnormally low amplitude for the VA complex, unilaterally, and two (20%) had abnormally shallow slopes for the VA complex unilaterally. Of the six women with ADS, three (50%) had wave V outside normal limits, of which two were bilaterally (33%). Three (50%) had wave A outside normal limits, bilaterally. Two (33%) had wave E outside normal limits unilaterally and one (17 %) had wave F outside normal limits unilaterally. One (17%) had the interpeak interval for E to F outside normal limits unilaterally. Two (33%) had an abnormally long duration for the VA complex, unilaterally. Two (33%) had an abnormally low amplitude for the VA complex, unilaterally, and one (17%) had an abnormally shallow slope for the VA complex unilaterally.

4.2.4.4 Stimulus to Response Correlation and Spectral Encoding Measures

The FFR was analysed in terms of magnitude and correlation to the stimulus, as in Experiment One.

4.2.4.4.1 Within and Between Participant Effects

A mixed ANOVA with repeated measures for ear and between participant effects for sex was performed. This was undertaken to look at within subject differences of the SR correlation and spectral encoding measures of the speech ABR recorded from right and left ears, as well as between subject differences with respect to sex. No differences were found between the responses from the right and left ears

or between men and women. The mean values for each measure are presented below and the data was collapsed across ears (Table 73).

Table 73. SR Correlation and Spectral Encoding Measures of the FFR for Men and Women (Mean and S.D.)

Speech ABR Component		Male	Female
Correlation measures	SR corr (20–40 ms) (SD)	0.094 (0.04)	0.098 (0.04)
	SR lag (SD)	8.67 (0.98)	8.42 (1.14)
Amplitude Measures (μV)	SNR (SD)	1.88 (0.48)	1.45 (0.21)
	F0 (21.9–40.6 ms) (SD)	8.29 (6.85)	6.26 (3.45)
	F1 (21.9–40.6 ms) (SD)	1.41 (0.43)	1.06 (0.25)
	HF (21.9–40.6 ms) (SD)	0.405 (0.11)	0.446 (0.11)

4.2.4.5 Comparing the Control data for Healthy Adults from Experiment One and Adults with ADS from Experiment Two

Independent samples t-tests found no significant differences for the SR correlation and spectral encoding measures of the speech ABR, between the two groups of men (Table 74). Results are reported with a Bonferroni corrected significance criterion for multiple comparisons (a = 0.008).

Table 74. Comparison of SR Correlation and Spectral Encoding Measures of the FFR for Healthy Male Control Participants and Men with ADS (Mean and S.D.)

Speech ABR Component	Healthy men (SD)	Men with ADS (SD)	t	p
SR corr (20–40 ms)	0.103 (0.04)	0.094 (0.04)	0.866	0.378
SR lag	8.35 (0.93)	8.67 (0.98)	-1.28	0.203
SNR	2.48 (0.80)	1.88 (0.48)	1.76	0.083
F0 (21.9–40.6 ms)	11.14 (8.91)	8.29 (6.85)	1.30	0.197
F1 (21.9–40.6 ms)	1.24 (0.42)	1.41 (0.43)	0.859	0.393
HF (21.9–40.6 ms)	0.485 (0.13)	0.405 (0.11)	2.481	0.015

Table 75. Data Ranges for SR Correlation and Spectral Encoding Measures in Men from Experiment One and Men with ADS from Experiment Two

Speech ABR Component	Range (Mean ± 2SD)	
	Healthy Men	Men with ADS
SR corr (20–40 ms)	0.023 – 0.183	0.014 – 0.174
SR lag	6.49 – 10.21	6.71 – 10.63
SNR	0.88 – 4.08	0.92 – 2.84
F_0 (21.9–40.6 ms)	-	-
F_1 (21.9–40.6 ms)	0.40 – 2.08	0.55 – 2.27
HF (21.9–40.6 ms)	0.225 – 0.745	0.185 – 0.625

Independent samples t-tests found significant differences for SR correlation and spectral encoding measures of the speech ABR between the healthy females in both groups (Table 76). The signal to noise ratio was higher and the amplitude of the response for F0 was higher in the females in Experiment One. Whilst other measures also resulted in significant differences, these differences do not remain significant when results are reported with a Bonferroni-corrected significance criterion for multiple comparisons (a = 0.008).

Table 76. Comparison of SR Correlation and Spectral Encoding Measures of the FFR for Healthy Female Control Participants and Women with ADS (Mean and S.D.)

Speech ABR Component	Healthy Women (SD)	Women with ADS (SD)	t	p
SR corr (20–40 ms)	0.109 (0.04)	0.098 (0.04)	0.791	0.432
SR lag	8.38 (0.71)	8.42 (1.14)	-0.181	0.857
SNR	2.42 (0.82)	1.45 (0.21)	3.970	< 0.001*
F0 (21.9–40.6 ms)	10.27 (3.92)	6.26 (3.45)	3.299	0.002*
F1 (21.9–40.6 ms)	1.45 (0.55)	1.06 (0.25)	2.335	0.022
HF (21.9–40.6 ms)	0.594 (0.21)	0.446 (0.11)	2.402	0.019

* Result remains significant after correcting for multiple comparisons

Table 77. Data Ranges for SR Correlation and Spectral Encoding Measures in Women from Experiment One and Women with ADS from Experiment Two

Speech ABR Component	Range (Mean ± 2SD)	
	Healthy Women	Women with ADS
SR corr (20–40 ms)	0.029 – 0.189	0.018 – 0.178
SR lag	6.96 – 9.80	6.14 – 10.70
SNR	0.78 – 4.06	1.03 – 1.87
F0 (21.9–40.6 ms)	2.43 – 18.11	-
F1 (21.9–40.6 ms)	0.350 – 2.55	0.56 – 1.56
HF (21.9–40.6 ms)	0.174 – 1.01	0.226 – 0.666

4.2.4.6 Interpretation of Results for SR Correlation and Spectral Encoding Measures

No significant differences were found in the encoding in any of the ranges evaluated between the healthy males and those with ADS. Of the 10 men with ADS, only one (10%) had any of these measures outside the normal range, with a low stimulus to response correlation unilaterally. There were differences in the SNR and F0 amplitude between the healthy women and women with ADS. It would appear that the response is not as robust and spectral encoding is poorer in women with ADS, compared to healthy women of the same age. Of the six women with ADS, two (33%) had wave F0 amplitudes below normal limits unilaterally.

4.2.4.7 Summary of Speech ABR Results

The Speech ABR results for adults with ADS are significantly different from those of healthy adults, across a number of measures. Differences common for both men and women occur at the VA complex, with the latencies of these onset peaks being significantly prolonged in adults with ADS. A summary of the measures outside 'normal' limits, for individual participants is presented in table 78.

Table 78. Speech ABR Measures Outside 'Normal' Limits, for Individual Participants with ADS

ID	SEX	Right Ear –No. of speech ABR measures outside normal limits	Left Ear –No. of speech ABR measures outside normal limits
1	Male	0	2
4	Male	3	2
5	Female	3	2
6	Female	3	4
8	Female	2	2
9	Female	1	1
10	Male	1	1
12	Male	3	3
13	Female	1	0
15	Male	0	5
16	Female	2	3

4.2.5 Addressing the Research Questions

The aim of this study was to explore the click and speech ABRs of adults with ADS, who have normal hearing sensitivity. Significant differences have been found in both the click ABR and the speech ABR for adults with ADS when compared to healthy adults. The differences indicate a prolongation of brainstem conduction time. These differences will be discussed more fully in chapter five.

4.2.5.1 Click ABRs in Adults with ADS

Is the auditory brainstem response to click stimuli of people diagnosed with alcohol dependence syndrome different from that of healthy adults? It has been found that the click ABR for people with ADS is different to that of the typical population and that men and women exhibit different ABR profiles. Men with ADS had significant delays in wave III (0.18ms) and wave V (0.22ms) and the interpeak intervals for I-III and I-V were prolonged by at least 0.13 ms. For women with ADS, wave I was delayed by 0.11ms and wave V was delayed by 0.22ms. For both men and women, it can be

expected that there is a significant delay in wave V. Not everyone will have results outside 'normal' limits but we can expect that 40% of men will have wave's III and V latencies outside normal limits and 50% of women will have a wave I latency outside normal limits. Results outside 'normal' limits were found in seven of the ten (70%) male participants and three of the six (50%) female participants. What is interesting is that not all 'abnormal' results are bilateral, and therefore assessment of both ears is required. It is possible to say that using the click ABR in people with ADS can detect deficits in neural processing that are not 'clinically' evident. A discussion about the sites of lesion and the utility of the click ABR in identifying lesions will be presented in chapter five.

4.2.5.2 Speech ABRs in Adults with ADS

Is the auditory brainstem response to speech stimuli of people diagnosed with alcohol dependence syndrome different from that of healthy adults? For the speech ABR, there are also significant differences between the results from healthy adults and those from adults with ADS. Again, there were slightly different profiles for the speech ABRs from men and women. For men, it was the onset measures that were significantly delayed. However, for women there were more measures affected, including a delayed offset response and less robust measures of spectral encoding. Men had significant delays in the onset measures of waves V (0.40ms) and A (0.36ms). Women had significant delays in waves V (0.45ms), A (0.48ms) E (0.66ms) and O (0.42ms). Results outside 'normal' limits were found in five of the ten (50%) male participants and all six (100%) female participants. These results will be discussed more fully in chapter five.

4.3 Effects of Abstinence on the Auditory-Cognitive Profile of Adults with Alcohol Dependence Syndrome

The aim of this section is to answer the research question 'what is the change in the auditory-cognitive profile of people with ADS following adherence to a 12 week alcohol abstinence programme?' The results, analysis and interpretation of the data gathered by the methods previously described, is presented. The general and descriptive statistics include information about the participants and the results from the auditory-cognitive profile test battery performed at second assessment. A comparison with results at baseline testing is also presented.

4.3.1 Participants

The participants with a diagnosis of ADS have been described in section 4.1.1. Of the 16 adults who took part in baseline assessment, eleven (69%) adhered to the twelve week rehabilitation programme and completed the second assessment (6 men, 5 women). No patient who completed the first assessment and the twelve week programme, declined to take part in the second assessment. Details of the individual participants can be found in the following table (Table 79) and their alcohol profiles have been presented in section 4.1.3.

Table 79. Details of Participants Taking Part in Follow-Up Testing

Participant ID	Sex	Age
1	Male	45
3	Male	29
4	Male	29
6	Female	38
7	Male	46
8	Female	33
9	Female	42
11	Male	46
13	Female	43
15	Male	49
16	Female	48

4.3.2 Methods

All testing was carried out as described in section three (3.1.2). This second assessment for adults with ADS took place within the final week of the twelve week rehabilitation programme. Testing occurred in a quiet counselling room within LEAP in the Astley Ainslie Hospital. These counselling rooms were not soundproofed but they are used for confidential patient discussions and are located in a quiet area of the hospital.

4.3.3 Results and Analysis of the Auditory-Cognitive Profile at Follow-Up Assessment

The following section provides the results and analysis for the auditory-cognitive profile of adults with ADS, after a period of twelve weeks of abstinence. In all cases prior to analysis the Shapiro-Wilks Francia test was applied to establish that the data for males and females was normally distributed.

4.3.3.1 Comparison of PTA Results between Baseline Measure and Second Assessment

All results were within the limits for normal hearing at second assessment. Data was pooled for ear and a mixed ANOVA with repeated measures for time and between participant effects for sex, was performed. This was undertaken in order to establish whether hearing thresholds had changed over the twelve week period. There was a significant difference between the thresholds at baseline and second assessment, $F(1,20)= 5.85$, $p=0.025$.

Post hoc, paired samples t-tests were performed for the group to establish which thresholds had changed. After applying a Bonferroni correction for multiple comparisons, a small but significant change was detected between the air conduction thresholds at baseline testing and at second assessment at 250Hz only, $t(21)= 3.38$, $p=0.003$.

4.3.3.1.1 Interpretation of PTA Results

There was a slight but significant improvement in the hearing threshold result at 250Hz but it is unlikely that this could affect the click or speech ABR results in any appreciable way.

4.3.3.2 Comparison of Cognitive Assessment Results between Baseline and Second Assessment

The results of second assessment testing are detailed in table 80. A mixed ANOVA with repeated measures for time and between participants effects for sex was performed. This was undertaken to establish whether cognitive function had changed over the twelve week period. There was a significant difference in the results of the WAIS-UK^{III} subtests over time $F(1, 9) = 17.25$, $p = <0.002$ but no significant difference between men and women.

Performing post hoc, independent samples t-tests on the WAIS-UK^{III} subtests found significant improvements in performance on everything but the vocabulary subtest (Table 80). However, these differences did not remain significant after applying a Bonferroni correction for multiple comparisons. Two of the five (40%) participants who had deficits in scores but attended follow-up assessment, had subtest scores that had returned to within normal limits after the twelve week period.

Table 80. Results of Cognitive Assessments at Baseline and Follow-Up (Mean and S.D.)

WAIS-III^{UK} Subtest	Baseline (S.D.)	Second Assessment (S.D.)	t	p
Vocabulary	8.63 (2.80)	8.73 (2.83)	-1.000	0.341
Digit- Symbol Coding	8.55 (2.81)	9.64 (2.34)	-2.963	0.014
Digit Span	7.91 (2.39)	8.73 (2.15)	-3.105	0.011
Symbol Search	9.09 (2.84)	10.36 (1.86)	-3.130	0.011
Letter- Number Sequencing	7.91 (2.91)	9.18 (2.09)	-2.283	0.046

Details of the scores for individuals with identified deficits at baseline and who completed follow-up testing, are presented in table 81.

Table 81. Summary of Results for Individuals with WAIS-III^{UK} Subtest Scores outside Normal Limits (in Bold).

ID	SEX	Vocabulary T1/T2	Digit Symbol coding T1/T2	Digit Span T1/T2	Symbol Search T1/T2	Letter Number Sequencing T1/T2
1	Male	**3 / 3**	**4 / 6**	**4 / 4**	**5** / 8	**3 / 5**
4	Male	10 / 10	7 / 8	8 / 8	8 / 8	**4** / 8
7	Male	9 / 9	8 / 8	**4 / 6**	7 / 10	**5** / 10
9	Female	**5 / 5**	8 / 8	8 / 9	9 / 9	8 / 8
13	Female	9 / 10	**6** / 7	9 / 9	7 / 9	13 / 13

4.3.3.3 Auditory Processing Capability Assessment

The mean values for the individual auditory processing tests are presented in tables within the following section. The data for all APD tests (except RGDT) was not normally distributed. For these variables, the Wilcoxon Signed-ranks test was used to compare the values as baseline assessment to those after a period of twelve weeks.

4.3.3.3.1 Results of Duration Pattern Sequence Testing

The results of DPST performed at second assessment are presented below (Table 82).

Table 82. Results of Duration Pattern Sequence Testing at Second Assessment (Mean and S.D.)

DPST Score	Males		Females	
	Right Ear (S.D.)	Left Ear (S.D.)	Right Ear (S.D.)	Left Ear (S.D.)
% Correct	80.06 (23.32)	77.22 (28.08)	94.00 (10.84)	92.00 (12.42)

4.3.3.3.1.1 Comparison of Duration Pattern Sequence Testing Results between Baseline Measure and Second Assessment

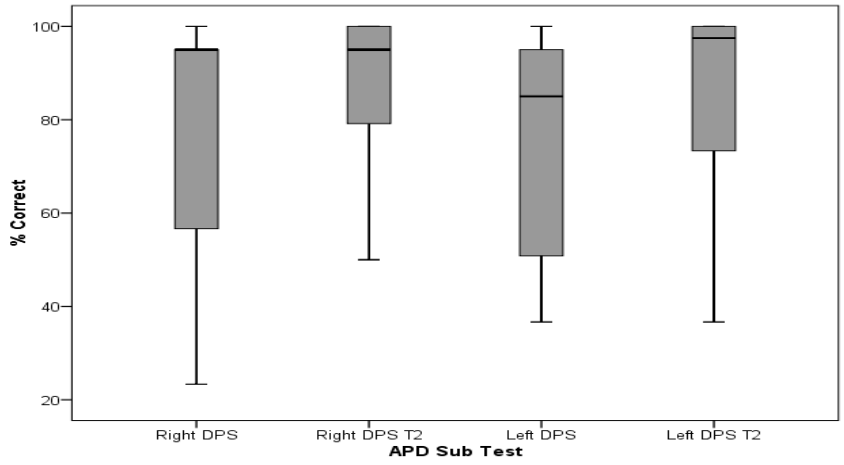
The Wilcoxon Signed-ranks test was used to compare the values at baseline assessment to those after a period of twelve weeks (Table 83).

Table 83. Comparison of Duration Pattern Sequence Testing Results between Baseline and Second Assessment (Mean and S.D.)

DPST	Baseline (S.D.)	Second Assessment (S.D.)	z	p
% Correct, Right Ear	75.91 (29.00)	86.39 (19.29)	-2.384	0.017*
% Correct, Left Ear	75.15 (25.15)	83.94 (22.71)	-2.298	0.022*

* Result remains significant after correcting for multiple comparisons

Figure 31. DPST Results at Baseline and After Twelve Weeks



Where DPS is Duration Pattern Sequence and T2 is second assessment

4.3.3.3.1.2 Interpretation of Results

There were significant improvements in scores after the twelve week period and two participants had results that had returned to within normal limits, at the end of the twelve week period (Table 84).

Table 84. Summary of Results for Individuals with DPST Scores outside Normal Limits (in Bold)

ID	SEX	Right Ear, % Correct T1 / T2	Left Ear, % Correct T1 / T2
1	Male	**35.00 / 52.00**	**45.00 / 36.67**
7	Male	83.33 / 83.33	**56.67** / 76.67
9	Female	**23.33** / 75.00	**36.67** / 70.00
15	Male	**40.00 / 50.00**	**40.00 / 50.00**

4.3.3.3.2 Results of Pitch Pattern Sequence Testing

The results of PPST performed at second assessment are presented below (Table 85).

Table 85. Results of Pitch Pattern Sequence Testing at Second Assessment (Mean and S.D.)

PPST Score	Males		Females	
	Right Ear (S.D.)	Left Ear (S.D.)	Right Ear (S.D.)	Left Ear (S.D.)
% Correct	81.39 (23.49)	88.33 (13.83)	99.00 (2.24)	99.00 (2.24)

4.3.3.3.2.1 Comparison of Pitch Pattern Sequence Testing Results between Baseline and Second Assessment

The Wilcoxon Signed-ranks test was used to compare the values at baseline assessment to those after a period of twelve weeks (Table 86).

Table 86. Comparison of Pitch Pattern Sequence Testing Results between Baseline and Second Assessment (Mean and S.D.)

PPST	Baseline (S.D.)	Second Assessment (S.D.)	z	p
% Correct, Right Ear	85.76 (22.15)	89.39 (19.04)	-2.041	0.041
% Correct, Left Ear	86.67 (18.50)	93.18 (11.34)	-2.207	0.027

4.3.3.3.2.2 Interpretation of Results

After correcting for multiple comparisons, there was no significant improvement in the scores after the 12 week period. However, one of the participants had results that had returned to within normal limits during this time (Table 87).

Table 87. Summary of Results for Individuals with PPST Scores outside Normal Limits (in Bold).

ID	SEX	Right Ear, % Correct T1 / T2	Left Ear, % Correct T1 / T2
1	Male	**35.00 / 43.33**	**40.00 / 63.33**
7	Male	**66.67 / 80.00**	**83.33 / 86.67**
9	Female	**86.67** / 95.00	**80.00** / 95.00
15	Male	**60.00 / 65.00**	**70.00 / 80.00**

4.3.3.3.3 Results of Dichotic Digits Testing

The results of the dichotic digits assessment performed at follow-up, are presented below (Table 88).

Table 88. Results of Dichotic Digits Testing at Second Assessment (Mean and S.D.)

DD Score	Males		Females	
	Right Ear (S.D.)	Left Ear (S.D.)	Right Ear (S.D.)	Left Ear (S.D.)
% Correct	90.83 (13.93)	85.42 (21.00)	98.00 (2.74)	96.00 (3.79)

4.3.3.3.3.1 Comparison of Dichotic Digit Testing Results between Baseline and Second Assessment

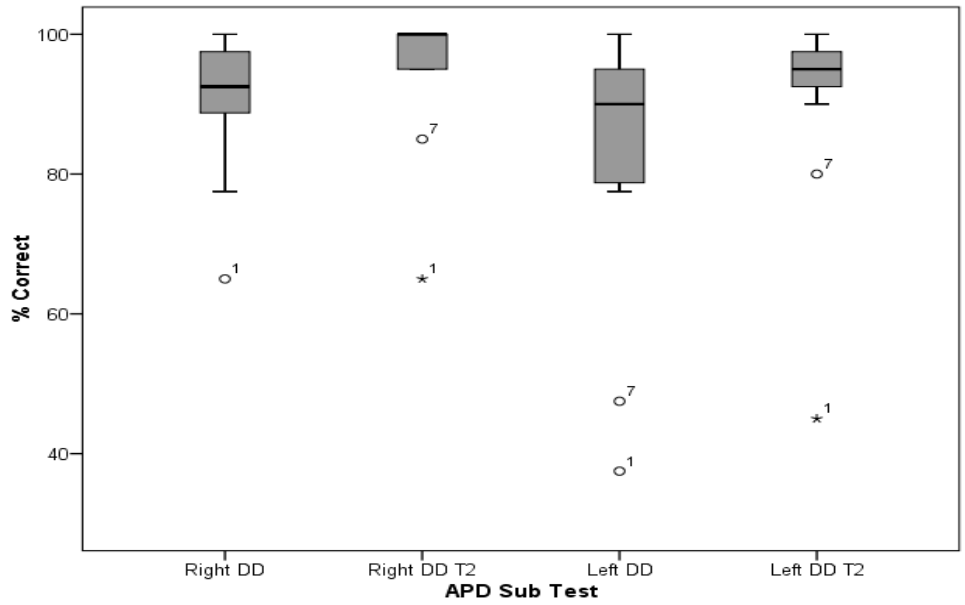
The Wilcoxon Signed-ranks test was used to compare the values at baseline assessment to those after a period of twelve weeks (Table 89).

Table 89. Comparison of Dichotic Digit Testing Results between Baseline and Second Assessment (Mean and S.D.)

PPST	Baseline	Second Assessment	z	p
Right Ear % (SD)	90.23 (10.63)	94.09 (10.68)	-1.980	0.048
Left Ear % (SD)	81.82 (20.74)	90.23 (16.03)	-2.673	0.008*

* Result remains significant after correcting for multiple comparisons

Figure 32. DD Test Results at Baseline and After Twelve Weeks



Where DD is Dichotic Digits and T2 is second assessment

4.3.3.3.3.2 Interpretation of Results

After correcting for multiple comparisons, there was a significant improvement in the scores for the left ear. Two of the participants had results that had returned to within normal limits after the twelve week period of abstinence (Table 90).

Table 90. Summary of Results for Individuals with DD Test Scores outside Normal Limits (in Bold)

ID	SEX	Right Ear, % Correct T1 / T2	Left Ear, % Correct T1 / T2
1	Male	**65.00 / 65.00**	**37.50 / 45.00**
7	Male	87.50 / 85.00	**47.50** / **80.00**
9	Female	90.00 / 95.00	**80.00** / 90.00
16	Female	**77.50** /100.00	**77.50** / 97.50

4.3.3.3.4 Results of Random Gap Detection Testing

The results of the RGDT at second assessment are presented below (Table 91).

Table 91. Results of Random Gap Detection Testing (Mean and S.D.)

RGDT Threshold	Males		Females	
	Tonal Threshold (S.D.)	Click Threshold (S.D.)	Tonal Threshold (S.D.)	Click Threshold (S.D.)
Mean (ms)	10.10 (6.01)	16.00 (13.42)	10.35 (2.20)	7.40 (5.13)

4.3.3.3.4.1 Comparison of Random Gap Detection Testing Results between Baseline and Second Assessment

A paired samples, t-test was used to compare the values at baseline assessment to those after a period of twelve weeks (Table 92).

Table 92. Comparison of Random Gap Detection Testing Results between Baseline and Second Assessment (Mean and S.D.)

RGDT Threshold	Baseline (S.D.)	Second Assessment (S.D.)	t	p
Mean of Threshold for Tones (ms)	12.35 (5.08)	10.23 (4.27)	2.014	0.075
Click Threshold (ms)	14.20 (10.74)	11.70 (10.59)	1.627	0.138

4.3.3.3.4.2 Interpretation of Results

There was no significant improvement in the scores over the twelve week period. Two of the participants had results that had returned to within normal limits. Details of the individual scores for these individuals are presented below (Table 93).

Table 93. Summary of Results for Individuals with RGD Test Scores Outside Normal Limits (in Bold)

ID	SEX	Average Threshold (ms) T1 / T2	Click Threshold (ms) T1 / T2
1	Male	**23.00 / 20.50**	**40.00 / 40.00**
6	Female	11.25 / 11.25	**20.00** / 15.00
9	Female	18.75 / 10.00	**20.00** / 5.00
15	Male	**>40 / >40**	**>40** / 5.00

4.3.3.4 Comparison of TEOAE Testing Results between Baseline Measure and Second assessment

A mixed ANOVA with repeated measures for time and between participants effect for sex was performed. This was undertaken to establish whether TEOAEs had changed over the twelve week period. There was no significant difference in the TEOAE results over time.

4.3.3.4.1 Interpretation of Results of TEOAE Testing

All participants had normal TEOAE results both at the beginning and the end of their treatment and rehabilitation programme. This is as would be expected from the pure tone audiometry results.

4.3.3.5 Results of Speech-In-Noise Assessment

As per at baseline testing, all participants SRT results were below 0dB and are presented in table 94.

Table 94. Results from the Speech- in- Noise Assessment at Follow-Up (Mean and S.D.)

SRT Score	Males (S.D.)	Females (S.D.)
Mean 50% correct score (dB)	-3.50 (1.05)	-4.00 (1.41)

4.3.3.5.1 Comparison of Speech-in-Noise Assessment Results between Baseline and Second Assessment

A paired samples, t-test was performed for the group and no differences were found between the results at baseline and at second assessment ($t(10) = 0.559$, $p = 0.588$).

4.3.3.5.2 Interpretation of Results

There was no change in the performance on the speech- in-noise assessment during the twelve week period.

4.3.4 Addressing the Research Question

The aim of this study was to explore whether there were any changes in the auditory-cognitive profile of the participants with ADS after twelve weeks of abstinence. Although there is some improvement for the group as a whole over the twelve week period, the situation is different when appraised at the individual level (Table 95). Eleven participants completed the twelve week rehabilitation programme and attended for second assessment. For the cognitive assessments, six (55%) scored within the normal range. Of the remaining five, four (80%) had improvement in the number of subtests scored as ‘normal’ at follow up. For the auditory processing assessment, five (45%) scored within the normal range. Of the remaining six, four (67%) had improvement in the number of subtests scored as ‘normal’ at follow up. Eight of the eleven adults (73%) who took part in follow up testing, had results outside normal limits at baseline assessment. Of these eight, four (50%) had results that had returned to within the normal ranges after the twelve week period of abstinence.

Table 95. Aspects of the Auditory-Cognitive Profile Outside 'Normal' Limits at Follow-Up

ID	Sex	No. of Cognitive assessments outside normal limits T1 / T2	No. of APD assessments outside normal limits T1 / T2
1	Male	5 / 4	4 / 4
3	Male	0 / 0	0 / 0
4	Male	1 / 0	0 / 0
6	Female	0 / 0	1 / 0
7	Male	2 / 1	3 / 2
8	Female	0 / 0	0 / 0
9	Female	1 / 1	4 / 0
11	Male	0 / 0	0 / 0
13	Female	1 / 0	0 / 0
15	Male	0 / 0	3 / 3
16	Female	0 / 0	1 / 0

4.3.4.1 The Auditory-Cognitive Profile in People with ADS

What is the change in the auditory-cognitive profile of people with ADS following adherence to a 12 week alcohol abstinence programme?

There were significant improvements in the results of the WAIS-III^{UK} subtests over the twelve week period. Eight (50%) of the participants with ADS had below expected values on the cognitive assessment initially. Of these eight, five attended for second assessment and two (40%) had 'normal' scores at the second assessment. Eleven (69%) of the participants with ADS had below expected values on the auditory processing assessment initially. There were significant improvements in aspects of auditory processing including both the duration pattern sequence test results and dichotic digits test results. Of these eleven, six attended for second assessment and three (50%) had 'normal' scores at the second assessment. For the healthy population described in section three, there was some improvement in the auditory processing assessment after twelve weeks, indicating a small practice effect but not for the WAIS subtests. We could expect an increase in Dichotic Digits score of around 2% and an increase in Random Gap Detection Threshold for Tones of around one millisecond. The increase in dichotic digits score for people with ADS over a twelve week period of abstinence was in the region of

4% for the right ear and 9% for the left ear, so it was greater than what could reasonably be attributed to a practice effect. In section 4.1.4.1, it was stated that using the Random Gap Detection subtests for clicks only, would have identified all people with a below typical subtest result for this particular screening measure. No practice effect was detected for this subtest within the RGDT screening battery.

Whilst there is significant improvement with abstinence, not all people with ADS will have scores within the 'normal' range after a period of twelve weeks of abstinence (Table 96). It is possible that their scores, prior to commencing harmful drinking, may not have been within the 'normal' range and this will be explored further in the discussion chapter (chapter five).

Table 96. Individual Participant Results for the Cognitive and Auditory Processing Assessments

ID	Cognitive Assessment at T1	Auditory Processing Assessment at T1	Cognitive Assessment at T2	Auditory Processing Assessment at T2
1 (M)	✓	✓	✓	✓
3 (M)				
4 (M)	✓			
6 (F)		✓		
7 (M)	✓	✓	✓	✓
8 (F)				
9 (F)	✓	✓	✓	
11 (M)				
13 (F)	✓			
15 (M)		✓		✓
16 (F)		✓		

Where ✓ represents positive for a result outside normal limits.

4.4 Effects of Abstinence on the ABRs of Adults with Alcohol Dependence Syndrome

The aim of this section is to establish whether there is any change in the click and speech ABRs of people with ADS, following adherence to a 12 week alcohol abstinence programme. The general and descriptive statistics describe the results of the ABRs performed at second assessment. A comparison of the ABRs with the results recorded at baseline testing is also presented. The research questions being addressed are:

- What is the change in the click ABR following adherence to a 12 week alcohol abstinence programme?
- What is the change in the speech ABR following adherence to a 12 week alcohol abstinence programme?

4.4.1 Participants

The participants (n=11) have been introduced in the section 4.3.1. All participants who underwent the second assessment of the auditory-cognitive profile, also had click and speech ABR recording performed.

4.4.2 Methods

This second assessment for adults with ADS took place within the final week of the twelve week rehabilitation programme. Testing occurred in the aforementioned quiet counselling rooms within LEAP, in the Astley Ainslie Hospital.

4.4.2.1 ABR Recording Procedure

All ABR testing was carried out as described in section three (subsections 3.1.2.10 and 3.1.2.11). ABR waveforms were recorded from eleven participants, totalling 22 waveforms for the click and for the speech ABR.

4.4.3 Results and Analysis of the Click ABR at Follow-Up Compared with Baseline Assessment

As previously described, two audiologists independently marked the grand average ABR waveform data derived from all participants (Vidler and Parker 2004). This totalled 12 waveforms for the men and 10 waveforms for the women. For all waveforms the examiners were asked to complete a table to indicate whether they felt replicable waves were present in the constituent traces that contributed to the grand averaged waveform. For the click ABR the examiners were in agreement that waves I, III and V could be reliably identified in 100% of waveforms. The latency values are presented in table 97. In all cases prior to analysis the Shapiro-Wilks Francia test was applied to established that the data for males and females was normally distributed.

To establish whether the click ABRs had changed over the 12 week period, two-way ANOVAs with repeated measures for time were performed. There was a significant improvement in the latency results over time for both women $F(1, 9) = 7.93$, $p= 0.02$ and men $F(1,11) = 11.68$, $p= 0.006$. There was no difference in the amplitude results over time for either men or women.

Performing post hoc paired samples t tests on the individual ABR waves found significant improvements in wave V latency ($t(9)=2.64$, $p=0.027$) for females. However, these differences did not remain significant after applying a Bonferroni correction for multiple comparisons.

Table 97. Comparison of Click ABR Results between Baseline and Follow-Up (Mean and S.D.)

ABR Wave latency (ms)	Males		Females	
	Baseline (S.D.)	Second Assessment (S.D.)	Baseline (S.D.)	Second Assessment (S.D.)
Wave I	1.61 (0.17)	1.61 (0.18)	1.62 (0.11)	1.57 (0.09)
Wave III	3.88 (0.16)	3.76 (0.21)	3.70 (0.18)	3.64 (0.09)
Wave V	5.78 (0.24)	5.56 (0.28)	5.66 (0.25)	5.58 (0.24)
Interpeak I-III	2.27 (0.13)	2.14 (0.27)	2.08 (0.12)	2.06 (0.05)
Interpeak III-V	1.90 (0.20)	1.79 (0.46)	1.96 (0.14)	1.94 (0.21)
Interpeak I-V	4.17 (0.18)	3.94 (0.29)	4.04 (0.16)	4.01 (0.19)

4.4.3.1 Interpretation of Click ABR Results

There is a significant, overall improvement in the click ABR results for both males and females. For men, average click ABR latencies improved for wave III (0.12ms) and wave V (0.22ms) and for women, wave V (0.08ms) improved. When considered at the individual level, of the ten adults who had at least one ABR measure outside the normal range, seven completed follow up testing. Six of these seven had improvements in at least one measure of latency to within the normal range and three of the seven had ABRs that had fully returned to within the normal range within the 12 week period (Table 98).

Table 98. Comparison of Number of ABR Components Outside Normal Limits at Baseline and Second Assessment

ID	SEX	Right Ear – No. of ABR measures outside normal limits T1 / T2	Left Ear – No. of ABR waves measures outside normal limits T1 / T2
1	Male	0 / 0	1 / 0
4	Male	3 / 0	1 / 0
7	Male	1 / 1	1 / 0
8	Female	1 / 0	0 / 0
13	Female	0 / 0	1 / 1
15	Male	0 / 0	3 / 2
16	Female	4 / 1	3 / 1

4.4.4 Results and Analysis of the Speech ABR at Follow-Up Compared with Baseline Assessment

Two examiners were asked to label the /da/ evoked waveforms in accordance with the guidance presented by Skoe and Kraus (2010a). For all waveforms the examiners were in agreement that individual peaks could be reliably identified in 100% of waveforms. Latencies and amplitudes of discrete peaks were evaluated, in addition to three composite measures of neural synchrony to the onset of the stimulus. The composite measures included V to A interpeak latency, V to A peak-to-trough

amplitude, and the slope of the VA complex. The mean latency values for these measures collapsed across ears, is presented in the following table (Table 99).

Table 99. Discrete Peak and Composite Onset Measures of the Speech ABR for Men and Women (Mean and S.D.)

Speech ABR Component	Male (S.D.)	Female (S.D.)
wave V (ms)	7.34 (0.38)	7.01 (0.39)
wave A (ms)	8.30 (0.36)	7.95 (0.36)
wave D (ms)	23.02 (0.39)	22.90 (0.56)
wave E (ms)	31.64 (0.46)	31.66 (0.60)
wave F (ms)	40.02 (0.58)	39.76 (0.48)
wave O (ms)	48.77 (0.41)	48.54 (0.17)
wave D-E (ms)	8.62 (0.60)	8.77 (0.55)
wave E-F (ms)	8.38 (0.53)	8.10 (0.71)
VA Duration (ms)	0.964 (0.19)	0.944 (0.19)
VA Amplitude (μV)	0.195 (0.08)	0.179 (0.08)
VA Slope (ms/ μV)	-0.200 (0.09)	-0.193 (0.09)

Two-way, repeated measures ANOVAs were performed to establish whether any discrete peak or composite onset measures of the speech ABR changed over the 12 week period. There was a significant improvement in these results over time for both women $F(1, 9) = 9.60$, $p= 0.013$ and men $F(1,11) = 18.17$, $p= 0.001$.

Performing post hoc, paired samples t-tests on the individual speech ABR components found significant improvements in wave A latency ($t(11)=4.50$, $p=0.001$) for men only (Tables 100 and 101).

Table 100. Comparison of Discrete Peak and Composite Onset Measures between Baseline and Follow-Up for Males with ADS (Mean and S.D.)

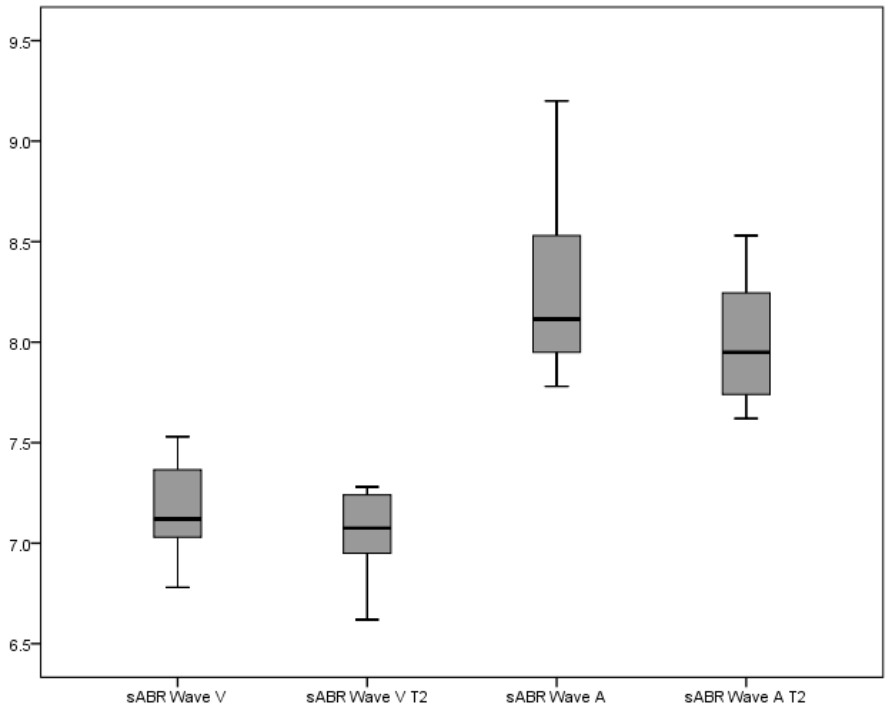
Speech ABR Component	Baseline (SD)	2nd Assessment (SD)	t	p
wave V (ms)	7.28 (0.45)	7.20 (0.45)	1.947	0.078
wave A (ms)	8.28 (0.43)	8.05 (0.42)	4.498	0.001*
wave D (ms)	22.93 (0.44)	22.80 (0.43)	1.310	0.217
wave E (ms)	31.68 (0.53)	31.55 (0.46)	1.225	0.246
wave F (ms)	40.00 (0.52)	39.97 (0.44)	0.543	0.598
wave O (ms)	48.77 (0.50)	48.59 (0.52)	2.146	0.055
wave D-E ms	8.75 (0.66)	8.74 (0.32)	0.050	0.961
wave E-F ms	8.33 (0.51)	8.42 (0.13)	-0.670	0.517
VA Duration (ms)	0.993 (0.22)	0.847 (0.20)	2.572	0.026
VA Amplitude (µV)	0.201 (0.10)	0.187 (0.09)	0.502	0.626
VA Slope (ms/ µV)	-0.196 (0.11)	-0.218 (0.09)	0.746	0.471

* Result remains significant after correcting for multiple comparisons

Table 101. Comparison of Discrete Peak and Composite Onset Measures between Baseline and Follow-Up for Females with ADS (Mean and S.D.)

Speech ABR Component	Baseline (SD)	2nd Assessment (SD)	t	p
wave V (ms)	6.88 (0.28)	6.78 (0.27)	1.227	0.251
wave A (ms)	7.87 (0.33)	7.75 (0.29)	1.463	0.177
wave D (ms)	22.99 (0.56)	23.07 (0.46)	-0.513	0.620
wave E (ms)	31.66 (0.66)	31.33 (0.69)	1.632	0.137
wave F (ms)	39.89 (0.40)	39.69 (0.43)	1.568	0.151
wave O (ms)	48.51 (0.17)	48.45 (0.26)	0.986	0.350
wave D-E ms	8.67 (0.55)	8.26 (0.90)	1.389	0.198
wave E-F ms	8.23 (0.71)	8.36 (0.80)	-0.658	0.527
VA Duration (ms)	0.983 (0.19)	0.967 (0.42)	0.154	0.881
VA Amplitude (µV)	0.194 (0.08)	0.229 (0.07)	-1.097	0.301
VA Slope (ms/ µV)	-0.204 (0.10)	-0.250 (0.07)	2.255	0.051

Figure 33. Changes with Abstinence for the Onset Response for Men with ADS



Two-way, repeated measures ANOVAs were performed to establish whether any SR correlation or spectral encoding measures of the speech ABR changed over the 12 week period. No differences in these measures were found for the either the men or the women.

4.4.4.1 Interpretation of Speech ABR Results

There was an overall improvement in the speech ABR measures over the twelve week period of abstinence for both the men and women with ADS. For men, average speech ABR latencies improved for wave A (0.23ms) and the duration of the VA complex (0.15ms). For women there were improvements in wave V (0.10ms), A (0.12ms) and E (0.33ms). At baseline testing 11 of the 16 adults (69%) with ADS had at least one speech ABR measure outside the normal range and eight of these completed follow up testing. Of these eight, seven had improvements in at least one measure of the speech ABR to within the normal range and five of the eight had speech ABRs that had fully returned to within the normal range within the 12 week period (Table 102).

Table 102. Number of Results Outside Normal Limits for Adults with ADS at Baseline and at Follow-Up Testing

ID	SEX	Right Ear – No. of speech ABR measures outside normal limits T1 / T2	Left Ear – No. of speech ABR measures outside normal limits T1 / T2
1	Male	0 / 0	2 / 0
4	Male	3 / 0	2 / 2
6	Female	3 / 2	4 / 3
8	Female	2 / 0	2 / 0
9	Female	1 / 0	1 / 0
13	Female	1 / 0	0 / 0
15	Male	0 / 0	5 / 5
16	Female	2 / 0	3 / 0

4.4.5 Addressing the Research Questions

The aim of this section was to establish whether there is any change in the click and speech ABRs of people with ADS, following adherence to a 12 week alcohol abstinence programme. Repeating the ABR recordings at the end of a twelve week period of abstinence found significant improvements in the click and speech ABR, although not everyone had ABRs within normal limits.

4.5 Drinking History, the Auditory-Cognitive Profile and the ABR

The aim of this section is to establish the relationship between drinking history and measures of the auditory-cognitive profile, click and speech ABR. Further analysis is required to be able to answer any questions relating to drinking history, the auditory-cognitive profile and the ABR results. This will form the study presented in the sections below.

4.5.1 Participants

The details of the participants with ADS have been presented in section 4.1.1. Of the people with ADS tested, 14 (88%) had at least one result outside the normal range for the suite of tests performed. The description of the drinking history for each participant has been provided in section 4.1.3, table 45. The participants completing follow-up testing have been described in section 4.3.1.

4.5.2 Methods

The methods of collection for the tests comprising the auditory-cognitive battery and for the click and speech ABRs have been previously described in section three, (3.1.2). Data collection took place in either the Ritson Clinic or in LEAP, as detailed in section four (4.1.2).

4.5.3 Results and Analysis of Drinking History and Baseline Assessments

Pearson or Spearman's Rank correlations were used to explore whether there was any relationship between the number of years of alcohol consumption, or the grams of alcohol consumed and the four aspects of the auditory-cognitive profile detailed in tables 103 and 104. The correlation coefficients were categorised as per Mukaka (2012).

Table 103. The Drinking Profile and Summary of Results Outside 'Normal' Limits at Baseline

ID	Alcohol History (yrs)	Grams/day	Results Outside Normal Limits			
			Cognitive Assessment	Auditory Processing Assessment	Click ABR	Speech ABR
1 (M)	24	200	✓	✓	✓	✓
2 (M)	18	148		✓	✓	
3 (M)	11	160-304				
4 (M)	7	300	✓		✓	✓
5 (F)	10	0-150		✓		✓
6 (F)	5	0-300		✓		✓
7 (M)	25	248-288	✓	✓	✓	
8 (F)	4	208			✓	✓
9 (F)	23	262-307	✓	✓		✓
10 (M)	5	208	✓	✓	✓	✓
11 (M)	26	300				
12 (M)	16	0-600	✓	✓	✓	✓
13 (F)	4	144	✓		✓	✓
14 (M)	15	240-344	✓	✓		
15 (M)	30	272		✓	✓	✓
16 (F)	6	108-288		✓	✓	✓

Where ✓ represents positive for at least one result outside normal limits.

Table 104. The Drinking Profile and Summary of Results Outside 'Normal' Limits at Second Assessment

ID	Alcohol History (yrs)	Grams/day	Results Outside Normal Limits			
			Cognitive Assessment	Auditory Processing Assessment	Click ABR	Speech ABR
1 (M)	24	200	✓	✓		
3 (M)	11	160-304				
4 (M)	7	300				✓
6 (F)	5	0-300				✓
7 (M)	25	248-288	✓	✓	✓	
8 (F)	4	208				
9 (F)	23	262-307	✓			
11 (M)	26	300				
13 (F)	4	144			✓	
15 (M)	30	272		✓	✓	✓
16 (F)	6	108-288			✓	

Where ✓ represents positive for at least one result outside normal limits.

4.5.3.1 The Drinking History and the Cognitive Assessment Recorded at Baseline

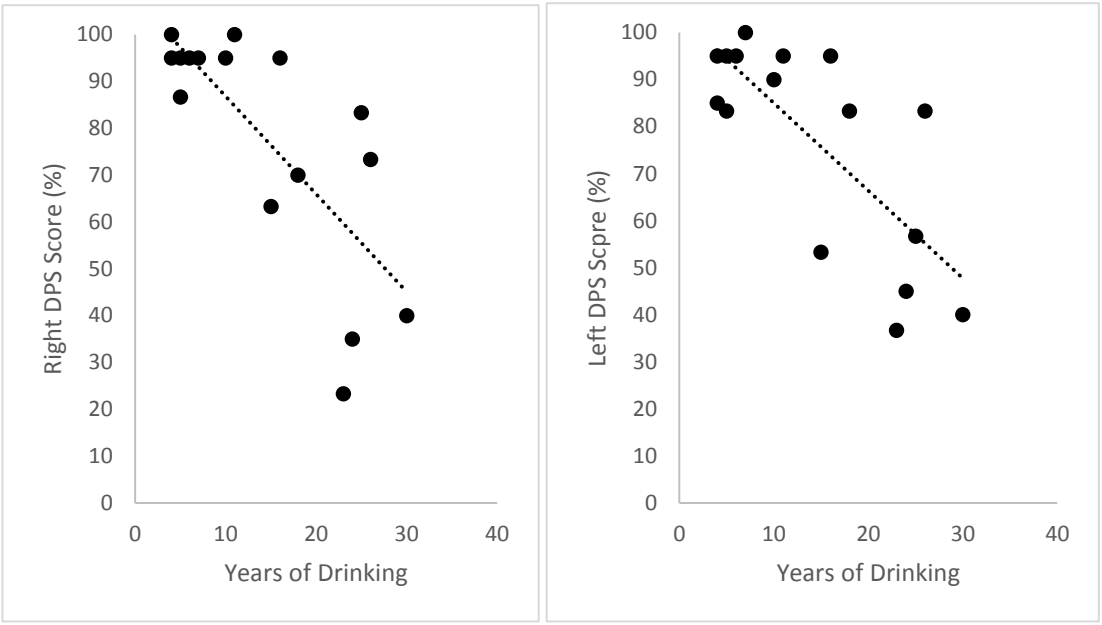
No relationships were found between either the length of drinking history, or the daily alcohol consumption for number of results outside normal limits for the cognitive assessment at baseline, when using Pearson correlation. There was also no relationship detected between the individual assessment results and the length of drinking history, or the daily alcohol consumption.

4.5.3.2 The Drinking History and the Auditory Processing Assessment at Baseline

Spearman's Rank correlation found a moderate, positive relationship between the number of years of heavy alcohol consumption and the number of abnormal results found using the Auditory Processing Assessment Battery, $r = 0.56$, $n = 16$, $p = 0.023$. Looking at the individual scores for each of the APD assessment, this was

found to be driven largely by the scores for the Duration Pattern Sequence Testing and to a lesser extent the Pitch Pattern sequence testing. Spearman's Rank correlation found a high, negative relationship between the number of years of heavy alcohol consumption and the scores on the Duration Pattern Sequence Tests, r = -0.72, n = 16, p = 0.002 for the right ear and a moderate negative relationship, r = -0.65, n = 16, p = 0.006 for the left ear (Fig. 34). A moderate, negative relationship was found between the number of years of heavy drinking and the scores of the Pitch Pattern Sequence Tests, r = -0.55, n = 16, p = 0.026 for the right ear and r = -0.54 for the left ear, n=16, p = 0.031.

Figure 34. The Relationship between Scores of the Duration Pattern Sequence Test and Number of Years of Heavy Drinking.



4.5.3.3 The Drinking History and the Click ABR at Baseline

Using Pearson correlation, a low, negative correlation was found for the maximum grams of alcohol consumed per day and interpeak interval measures of the click ABR for the I to V interval, r = -0.44, n = 22, p = 0.041 only.

4.5.3.4 The Drinking History and the Speech ABR at Baseline

There was only one other relationship found between results and years of drinking, or daily, maximum grams of alcohol consumed. For measures of the speech ABR, Pearson correlation found a moderate, positive relationship between the stimulus response lag and the maximum, daily grams of alcohol consumed, $r = 0.57$, $n = 16$, $p = 0.022$ for the right ear only.

4.5.3.5 Interpretation of Results at Baseline Assessment

It is important to consider that the grams of alcohol were those recorded before cessation of drinking began and that they are conservative estimates. In many cases, the drinking history included only a general description of the type of alcohol consumed. For example, if someone was drinking 'cider', alcohol by volume typically ranges from 3 to 8%, depending on the type of cider consumed. When specific brands or types were not mentioned in the patient's drinking history, a conservative estimate was used.

4.5.4 Results and Analysis of Drinking History and Follow-Up Assessments

Pearson or Spearman's Rank correlations were used to explore whether there was any relationship between the number of years of alcohol consumption or the daily alcohol consumption and the four aspects of the auditory-cognitive profile. An additional consideration at this point was whether participants had been prescribed thiamine, as part of their treatment programme (Table 105).

Table 105. Summary of Drinking History, Thiamine Prescription and Abnormalities at Follow-Up Assessment

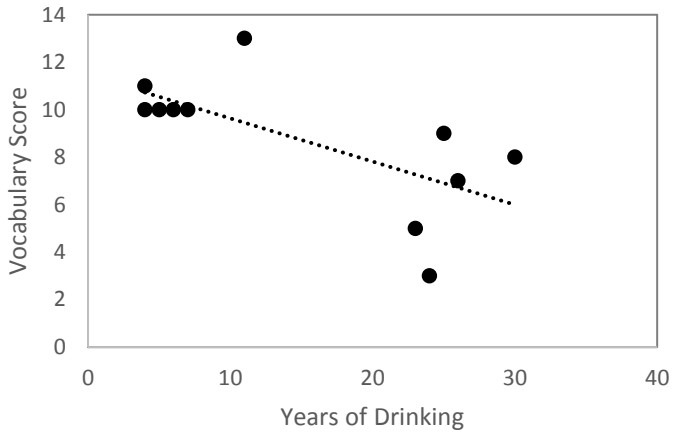
ID	Alcohol History (yrs)	Grams per day	Thiamine	Cognitive Assessment	Auditory Processing Assessment	Click ABR	Speech ABR
1 (M)	24	200	No	✓	✓		
3 (M)	11	160-304	Yes				
4 (M)	7	300	Yes				✓
6 (F)	5	0-300	Yes				✓
7 (M)	25	248-288	Yes	✓	✓	✓	
8 (F)	4	208	No				
9 (F)	23	262-307	Yes	✓			
11 (M)	26	300	No				
13 (F)	4	144	No			✓	
15 (M)	30	272	No		✓	✓	✓
16 (F)	6	108-288	No			✓	

Where ✓ represents positive for at least one result outside normal limits.

4.5.4.1 The Drinking History and the Cognitive Assessment at Follow-Up

Pearson correlation found a moderate, positive relationship between the number of years of heavy alcohol consumption and the number of abnormal results at follow-up for the WAIS subtests, $r = 0.61$, $n = 11$, $p = 0.047$. Looking at the individual scores for each of the WAIS subtests, this was found to be driven by the scores for the Vocabulary subtest (Fig. 35). Pearson correlation found a moderate, negative relationship between the number of years of heavy alcohol consumption and the scores on the Vocabulary subtest, $r = -0.67$, $n = 11$, $p = 0.022$.

Figure 35. Relationship Between WAIS-III^{UK} Vocabulary Scores and Years of Heavy Drinking



4.5.4.2 The Drinking History and the Auditory Processing Assessment at Follow-Up

Spearman's Rank correlation found a moderate, negative relationship between the number of years of heavy drinking and the number of abnormal APD subtest results, r = 0.67, n=11, p = 0.026. There was a high, negative relationship between years of heavy drinking and the score for right ear of the Duration Pattern Sequence Test, r = -0.70, n=11, p = 0.016. A moderate, negative relationship was also found between the number of years of heavy drinking and the scores for the Pitch Pattern Sequence Test, r = -0.67, n = 11, p = 0.026 for the right ear and r = - 0.68, n = 11, p = 0.022 for the left ear.

4.5.4.3 The Drinking History and the Click ABR at Follow-Up

Pearson correlation found moderate, negative relationships between the maximum, daily grams of alcohol consumed and measures of the click ABR results for the right ear only. Moderate, negative relationships was found for wave V, r = -0.62, n = 11, p = 0.040, the interpeak interval III to V, r = -0.63, n = 11, p = 0.037 and the interpeak interval I to V, r = -0.66, n = 11, p = 0.028.

4.5.4.4 The Drinking History and the Speech ABR at Follow-Up

For the speech ABR after twelve weeks of abstinence, Pearson correlation showed a moderate, negative relationship between some sustained measures for the left ear and average grams of alcohol consumed. Moderate, negative relationships were found for the stimulus to response correlation, r = -0.68, n = 11, p = 0.022 and for the Stimulus Response lag, r = -0.60, n=11, p = 0.049. There was also a moderate, negative relationship between the transient measure of VA amplitude for the left ear and the average grams of alcohol consumed, r = -0.66, n =11, p = 0.026.

4.5.4.5 The Role of Thiamine

One further aspect of the drinking profile that merits discussion is whether or not there was any difference in the follow-up testing results for people taking thiamine. Spearman's Rank correlation found no relationship between scores on the cognitive or auditory processing assessments and whether or not someone took thiamine. An example of the wave V click ABR latencies and whether or not someone took thiamine is presented in the figures below (Figs. 36 and 37). From these figures, it can be seen that the people taking thiamine tended to have shorter wave V click ABR latencies after a period of abstinence.

Figure 36. Wave V Latency Results from the Ears of Men Taking Thiamine

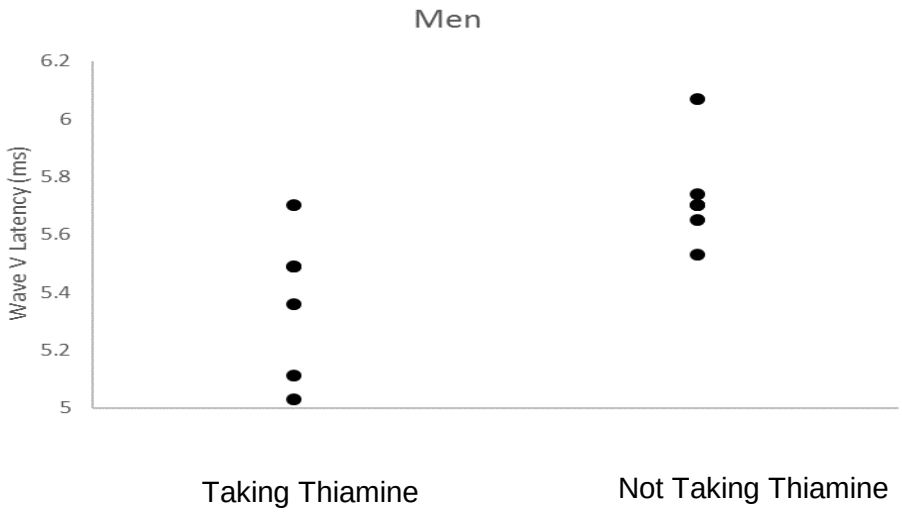
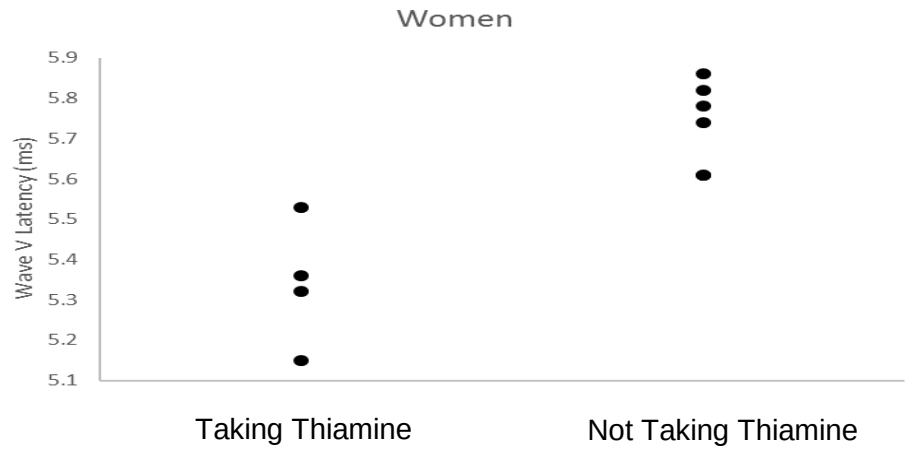


Figure 37. Wave V Latency Results from the Ears of Women Taking Thiamine



It is potentially problematic to perform analysis of the ABR results because of the differences in latencies between men and women and due caution needs to be applied to results. Independent samples t-tests found significant differences for the follow-up test results for the click ABR between the people taking thiamine and those not taking thiamine (n=22, d.f.=20). With the majority of these differences remaining after corrections for multiple comparisons were applied (Table 106).

Table 106. Difference for the Click ABR between People Taking and Not Taking Thiamine

ABR Wave Latency (ms)	No Thiamine Group (SD)	Thiamine Group (SD)	t	p
I	1.60 (0.17)	1.59 (0.10)	0.240	0.813
III	3.61 (0.09)	3.81 (0.18)	-3.453	0.003*
V	5.73 (0.14)	5.35 (0.21)	5.063	<0.001*
I-III	2.01 (0.20)	2.23 (0.11)	-3.085	0.006*
III-V	2.13 (0.17)	1.54 (0.26)	6.333	<0.001*
I-V	4.13 (0.10)	3.77 (0.22)	5.094	<0.001*

* Result remains significant after correcting for multiple comparisons

For the significant differences, apart from the earlier wave III in those not taking thiamine, the interpeak intervals for waves III-V and I-V are shorter in those

taking thiamine and the absolute latency of wave V is earlier. There were no significant differences found for measures of the speech ABR and those taking thiamine.

4.5.4.6 Interpretation of Results at Follow-Up

More relationships were found between drinking history and abnormalities at follow-up, than at baseline assessment. Correlations do not infer causality, only the presence and direction of a relationship. The scores on the vocabulary test from the WAIS-III^{UK}, recorded after a period of abstinence is linked to the number of years of heavy drinking. As can be seen in figure 35, this is a negative relationship with the vocabulary scores decreasing as the years of heavy drinking increase. The vocabulary subtest is considered to be one of the best measures of intelligence and tends to remain stable across the lifespan (Ardila 2007).

The relationship between the results of the auditory processing assessment and drinking history is similar to that found at baseline testing. Scores on the duration and pitch pattern sequence tests tend to be lower with increased years of drinking. The results for the click ABR are similar to those found for baseline assessment, except apply to the right ear only. There are some relationships between the speech ABR results and the average grams of alcohol consumed. These appear in the stimulus to response measures and provide a measure of the degree of phase locking within the brainstem. It would appear that how well the response matches the stimulus and the degree of phase locking, decreases with increasing quantity of alcohol consumption.

There is an indication that taking thiamine and shorter wave V latencies are related, however this requires further investigation with larger group sizes.

4.5.5 Addressing the Research Questions

The broad aim of Experiment Two was to explore the utility of both the click and speech ABR in a clinical population. The clinical population chosen was adults with a diagnosis of alcohol dependence syndrome. There is no current, clinical tool that can predict who may be at risk of developing alcohol related brain damage. The ABR offers a quick, inexpensive and non-invasive way to assess brainstem function. The progression of ARBD is not well understood but it is possible that deficits at brainstem level may be present before overt clinical signs are apparent. There have

been studies using the ABR with this population, with varied results. As it is also known that poor affective prosody processing is a feature of this syndrome (Monnot et al. 2001; Uekermann et al. 2005), then using a speech like stimulus might offer a more sensitive measure of brainstem function. The results of the studies within Experiment Two confirm that the ABR is able to detect deficits in people with ADS who have no overt clinical features. Both the click and speech ABR are delayed in people with ADS compared to healthy adults. It would appear that the speech ABR is a more sensitive tool for use in this particular clinical population. The speech ABR identifies 69% of people and the click ABR identifies 63% of people with ADS as having deficits in processing auditory stimuli at the level of the brainstem. This indicates that there is deterioration in the auditory processing pathway, within the brainstem in people with ADS. Repeating the ABR recordings at the end of a twelve week period of abstinence found significant improvements in the click and speech ABR, although not everyone had ABRs within normal limits. It had previously been found in Experiment One, that ABR responses were repeatable in the healthy control participants over the twelve week period and this repeatability would be a requirement of any clinical tool.

Using either the Auditory Processing Battery or the Speech ABR identifies 69% of the adults with ADS as having a measurable deficit. If these two elements are combined, with criteria of either having a deficit on an auditory processing test and / or a measure of the speech ABR, this rises to 88% sensitivity. It is more difficult to address the issue of specificity, as one of the aims of Experiment One was to establish a set of control data. The exclusion criteria for the study resulted in healthy participants being excluded if they scored outside normal limits on tests of auditory processing. However, the older adults (ages 31-49 years) recruited for Experiment One, were being assessed to establish if their results fell within the previously determined data. If this dual criteria was applied specificity would be 100%, as none of these adults would have been identified. The question of specificity requires further exploration with a larger population of typical, healthy adults.

When considering the question '*What is the relationship between drinking history and effects of abstinence on any of the measures assessed?'* Eight (73%) of the eleven people with ADS who completed the programme had at least one result still outside the normal range for the tests performed. Pearson or Spearman's Rank correlations were used to explore whether there was any relationship between the number of years of alcohol consumption or the number of units consumed and the

four aspects of the auditory-cognitive profile have previously been detailed in table 105. It would appear that there were more relationships between the measures and drinking history at follow-up, than at baseline assessment.

Chapter Five: Discussion

The overarching aim of this thesis was to investigate the click and speech ABR in people with alcohol dependence syndrome. Two separate but linked experiments were designed in order to achieve this. The aim of Experiment One was to explore some of the uncertainties within the literature relating to control data, which might prevent the adoption of the speech ABR as a clinical tool. Experiment One was developed to establish the inter-rater agreement for the speech ABR, whether separate normative or control data is required for the left and right ears and for men and women and whether the speech ABR is repeatable over time. The broad aim of Experiment Two was to explore the utility of the speech ABR in a clinical population. Adults with a diagnosis of alcohol dependence syndrome were chosen as the clinical population, for a combination of three reasons. There is debate in the literature about the results of ABR testing in this population (see section 2.4.7), there is evidence that speech processing is known to be affected in adults with an alcohol use disorder and finally, there is an urgent need for a clinical tool that can identify adults at risk of developing alcohol related brain damage. Experiment Two was developed to assess both the impact of alcohol and abstinence on auditory brainstem functioning and the value of using such measures of functioning as an objective way of monitoring neural impact.

The aim of this section is to discuss and apply the findings of both these experiments in order to answer questions about the general clinical utility of the ABR. The results of the individual studies for healthy adults are discussed in section 5.1, with section 5.2 containing the discussion of results from the studies pertaining to adults with ADS. The final section of the thesis (5.3) presents the conclusion to the overarching aims listed in section one (1.1).

5.1 The Speech ABR in Healthy Adults

A review of the current evidence base relating to the speech ABR was presented in section two. This included a scoping review of the particular use of the single clinically available tool, the BioMARK. However, a concerning conclusion was that there is a paucity of studies in adult, clinical populations. Clearly for a tool to be deemed clinically useful, it must be rigorously evaluated (Bossuyt et al. 2003) and

whilst Kraus and Nicol (2005) state that the response to /da/ has been extensively characterised, this is not the same as rigorous evaluation. The results of the scoping review highlighted key questions about the requirements for control data:

1. What is the inter-rater agreement for speech ABR?
2. What is the effect of ear of presentation on the speech ABR?
3. What is the effect of sex on the speech ABR?
4. What is the effect of age (18-30 vs. 31-49 years) on the speech ABR?
5. What is the between session repeatability of the speech ABR?

Each of these questions was addressed by collecting control data for men and women with no demonstrable deficits in auditory or cognitive function. A discussion of the results pertaining to each of these research questions is presented in the following sections (section 5.1.1 to 5.1.4).

5.1.1 Inter-Rater Agreement for the Speech ABR

Three experienced, qualified audiologists undertook blind waveform marking for both the click and speech ABRs and the results were compared in order to calculate the inter-rater agreement. Inter-rater agreement for the click ABR was anticipated to be high, as it has been found to be in excess of 81% based on previous studies (Kjaer 1979; Rossman and Cashman 1985; Pratt et al. 1995; Olsen et al. 1997; Naves et al. 2012a; Naves et al. 2012b). For this study the intraclass correlation coefficient was used to estimate inter-rater reliability. Different researchers provide different descriptions of what the acceptable level of reliability is, for example Cicchetti (1994), would describe an ICC of between 0.75 and 1.00 as excellent. Koo and Li (2016) suggest that values between 0.75 and 0.9 indicate good reliability and values greater than 0.90 indicate excellent reliability. Most sources are in agreement with the minimum acceptable ICC coefficient for reliability being 0.75, as suggested by Shrout and Fleiss (1979).The results of the current study showed that waves I, III and V had an ICC coefficient of 0.89 or greater. This would class the inter-rater reliability of the click ABR as high (Currier 1990). It also gives a confidence that the raters were suitably experienced in labelling click ABR waveforms. The results for the speech ABR waveform marking found that detectability of waves V, A, C, D, E, F and O was at least 95%. However, they were not all marked in the same place across the three

markers. The inter-rater agreement for the speech ABR was high for all individual waves, except D and C. In answer to the question about the inter-rater reliability, the results suggest that for waveforms elicited by the BioMARK 40 ms /da/ stimulus, (presented at 80 dB SPL to normal hearing ears), the inter-rater agreement is at a level acceptable for clinical use and comparable to the click ABR, with the exception of wave C. As a consequence of these results, a decision was made to exclude wave C from any further analysis. This new knowledge has important implications, as it suggests that researchers need to be vigilant when looking at the current literature using this particular stimulus to elicit the speech ABR. It has been stated that the envelope boundary in relation to voicing can be denoted by looking at the latencies of wave C and wave O (Dhar et al. 2009; Skoe and Kraus 2010a). However, if wave C cannot be reliably identified then this also renders this measure of envelope boundary as unreliable. This has consequences for findings that relate cochlear function to the speech ABR, as presented by Dhar et al. (2009), in so far as DPOAE structure cannot be concluded to be significantly related to the speech ABR envelope boundary. This result also has implications for anyone using custom stimuli to elicit the ABR response. It is imperative that aspects of reliability are fully assessed before results can be analysed.

5.1.2 Repeatability of the Speech ABR

The results of Experiment One indicate that there is an acceptable inter-rater reliability for the speech ABR. It has been proposed that test-retest repeatability indices for the speech ABR are good and comparable to those of other behavioural tests of auditory processing (Hornickel et al. 2012b). The results of the study published by Hornickel et al. (2012a) looking at test-retest repeatability over the period of a year in the speech ABR in school aged children were questioned. As there was some uncertainty about test-retest repeatability (McFarland and Cacace 2012) and due to the longitudinal nature of Experiment Two, it was decided to incorporate this element into Experiment One. There was only one difference in the speech ABRs, for women when recorded twelve weeks apart. The majority of measures are stable over a twelve week period, however amplitude data for F0 may vary over time. These results are in keeping with those reported by Song et al. (2011).

5.1.3 Subcortical Laterality

One area where there has been a lack of consensus in the research base, is whether the cortical asymmetry for language processing (Häberling et al. 2016) extends to the brainstem. At present there are two published studies (n= 32) (Hornickel et al. 2009; Sinha et al. 2010a) that support there being differences in the speech ABR for the right and left ears and three published studies (n= 107) (Vander Werff and Burns 2011; Ahadi et al. 2014b; Sanju et al. 2017b) that have not found any differences. In the present work, the results of testing of 60 adults found no significant differences between all components of the speech ABR for the right and left ears. This is an important finding. Not only does it make both the assessment process and application of normative data more straightforward but it also clarifies whether or not there is subcortical laterality for speech processing. In relation to clinical assessment, the restriction to testing only right-handed people, or needing to perform assessment of hemisphere dominance for language processing is removed. There would appear to be no right ear advantage for processing of speech sounds at the level of the brainstem. An interesting caveat to this finding, is that longer stimuli (>80ms) may elicit a response that includes a cortical component and therefore differences in results may be seen if longer speech-like stimuli are employed. However, the origin of the difference would be at the level of the cortex (Coffey et al. 2016).

5.1.4 Sex Differences in the Speech ABR

The results of all studies that have explored sex differences in the speech ABR have found differences between the speech ABRs from men and women (n = 153) (Krizman et al. 2012a; Ahadi et al. 2014a; Jalaei et al. 2017). In all three published studies it was found that women's onset responses were earlier and larger, with no differences in the sustained portion of the response. The results of Experiment One (n=60), found that measures relating to the onset and offset features of the response were different between men and women. However, the measures relating to the FFR (sustained) portion of the waveform were largely the same. These results mirror those found in previous studies, therefore it confirms the requirement for separate normative data sets for men and women. It is not surprising that there is a difference in the onset responses, as the click ABR wave V–Vn complex is thought to be largely analogous

to the speech ABR wave V-A complex (Song et al. 2006; Skoe and Kraus 2010a). As it is known that there are latency differences in wave V of the click ABR between men and women (Jerger and Hall 1980; Rosenhamer et al. 1980; Edwards et al. 1983; Jerger and Johnson 1988; Durrant et al. 1990; Watson 1996), then these differences should also be evident in the onset response of the speech ABR.

5.1.5 Requirements for Normative Data for Men and Women

As previously discussed, for any assessment to be clinically useful, the clinician requires data defining what the response should look like for a healthy person. It is important to consider how the results change over the lifespan and whether different normative data is needed for certain age groups, or indeed different sexes. When the ABR first came into use, studies were published characterising the waveform and what could be accepted as 'normal' (Hall 2007). Although there is normative data provided within text books (e.g. Hood 1998, Hall 2007) the guidance for clinicians is to collect normative data which takes into account their own test environment and equipment (Hall 2007). The decision is then where to apply the cut off criteria, which are usually two to three standard deviations from the mean value. If using two standard deviations it is expected that 5% of the population will be outside the limits and if using three standard deviations, this falls to less than 0.5%. The decision may be guided by the percentage of the population that are expected to be affected by the condition of interest.

From the results of the studies in Experiment One, the recommendations for any normative or control data are that separate data is required for men and women but ear specific data is not required. With respect to age it was found that the speech ABR for adults aged 31-49 years fell within the results generated for adults aged 18-30 years. This is in agreement with previous published data (Skoe et al. 2015a). It would be necessary to establish normative data for participants older than 49 years and this has implications for both research and clinical utility. When reporting speech ABR studies, age should be stated and effects of age controlled for. If this is not done, then any reported effects may be as a result of aging.

5.2 The Auditory-Cognitive Profile and ABRs in Adults with ADS

The concept of clinical utility was introduced in section one and relates to the usefulness of test results in informing decision making that can prevent or improve

health outcomes (Grosse and Khoury 2006). Knowledge about the diagnostic accuracy of the test in question underpins this decision process. There are three elements required when undertaking any form of diagnostic accuracy study. These include the condition of interest, a potential test and thirdly, a reference standard to which to compare the results of testing (Bossuyt et al. 2003). There are different components to consider when seeking to establish the ability of a new test to correctly identify the presence of the condition of interest. The results of testing of healthy people should be different to those of people with the target condition and the sensitivity and specificity of the new test should be determined (Vermiglio 2016).

For Experiment Two the use of the speech ABR was evaluated with a clinical population: adults with a diagnosis of ADS. It is believed that using a more complex stimulus to elicit the brainstem response offers a more 'real-world' scenario (Russo et al. 2004), giving insight into speech specific processing abilities. Researchers have found that the speech ABR is able to detect subtle neurological differences, which are not evident when using the simple click stimuli (Banai et al. 2007; Filippini and Schochat 2009; Kouni et al. 2013; White-Schwoch and Kraus 2013; Tahaei et al. 2014). These differences occur not only in the timing of the response but also in the way that speech is encoded and this appears to offer a way of differentiating between typical and clinical populations. Processing of speech material appears to be more affected by a disruption in the central auditory nervous system (CANS) pathway than processing of non-speech stimuli (Bellis et al. 2000; Jerger and Musiek 2000; Song et al. 2006). Early research using the speech ABR has been largely focussed on children with specific language impairments or those with a diagnosis of Autistic Spectrum Disorder (King et al. 2002; Wible et al. 2004; Banai et al. 2005; Russo et al. 2009). It would appear from this literature that there may be some value in using this type of testing for people with a clinical profile that includes deficits in speech processing ability. Adults with ADS fit this profile, as it is known that they can exhibit deficits in processing information related to prosody (Monnot 2001; Uekermann and Daum 2008). There is also a history of using click ABR testing within this population with varying results and this uncertainty required clarification. Perhaps most importantly, there is an urgent need for a tool that can monitor the neural impact of chronic, heavy drinking and the potential impact of subsequent reduced drinking or abstention.

The results of the scoping review of click ABR use in this population, presented in chapter two, highlighted the following questions:

1. In what ways do people diagnosed with alcohol dependence syndrome, who have normal hearing sensitivity differ in their auditory-cognitive profile compared to healthy adults?
2. Is the auditory brainstem response of people diagnosed with alcohol dependence syndrome different from that of healthy adults?

- a. when responding to click stimuli
- b. when responding to speech stimuli

3. What are the changes in 1 and 2, following adherence to a 12 week alcohol abstinence programme.
4. What is the relationship between drinking history and measures in 1, 2, and 3?

Experiment Two was designed to address these areas, both to answer questions about the click ABR in this population and whether or not using speech to elicit the ABR offers any advantages.

Data was collected from a group of 16 men and women with a diagnosis of ADS. Eleven of these participants undertook a second assessment at the end of their 12 week treatment and rehabilitation programme. The discussion of the results of the individual studies pertaining to Experiment Two are presented in the following sections (section 5.2.1 to 5.2.9).

5.2.1 The Auditory-Cognitive Profile in People with ADS

Although all participants in Experiment Two were included on the basis of having no measurable hearing loss when assessed by Pure Tone Audiometry (British Society of Audiology 2011), differences were found between their auditory-cognitive profiles and those of healthy adults. Of the adults with ADS, 81% had deficits in either auditory processing or aspects of cognition and 31% had deficits in both. It is important that clinicians working with people with ADS are aware of the consequences of these deficits. The majority of people entering the treatment and rehabilitation programme are likely to have deficits that can affect speech processing.

It is known that quality of communication between healthcare providers and their patients' influences patient outcomes. Verbal communication can be thought of as a range of processes and behaviours that occur when people are engaging in transmission and understanding of information (O'Hagan et al. 2014). Effective

communication has a positive effect on the emotional and physical well-being of the patient (Stewart 1995), as well as adherence to their treatment (Zolnierek and Dimatteo 2009). People with auditory processing deficits generally have difficulties in more complex listening situations. They report problems with understanding rapid speech or speech in background noise and may have difficulty with understanding verbal instructions (Jerger and Musiek 2000; Chermak 2002). Research in older adults has found that changes in auditory processing ability may have a greater effect on speech perception than changes in hearing thresholds (Ohlemiller 2004). There is also an associated increase in listening effort for those with deficits in auditory processing. Increased listening effort results in fatigue (McGarrigle et al. 2014), negatively impacting both on a patient's ability to communicate and their well-being. Lemke and Besser (2016) propose considering listening effort in relation to situational influences, the listener's auditory and cognitive resources and the listener's personal state. There are, therefore, a number of considerations for a clinician when practicing patient-centred communication. The clinician should understand the communication needs of the patient, evaluate the environment in which communication is taking place and ascertain how the patient is currently feeling. What is missing in many healthcare settings is a deep understanding of these aspects of communication.

It is not typical for a hearing assessment to take place in healthcare settings unless there is an obvious concern that someone is not hearing. There is also a lack of understanding of the more subtle aspects of decline in the auditory-cognitive profile. This is evident when considering that caregivers incorrectly identify the symptoms of hearing loss, confusing them with cognitive dysfunction (Shoup and Roeser 2000) and that dementia is significantly over-estimated in adults with untreated hearing loss (Weinstein and Amstel 1986). This has been attributed to the fact that most assessments are presented orally and difficulty in hearing results in poor performance, giving rise to an overestimation of the level of cognitive impairment (Qian et al. 2016; Roalf and Moberg 2016). The results of Experiment Two indicate that even if hearing thresholds do not indicate a hearing loss, the majority of people entering a treatment and rehabilitation programme for people with ADS will experience some deficit in auditory and / or cognitive skills. Even when speech is audible and can be understood, listening will potentially be effortful, tiring, or stressful (Pichora-Fuller et al. 2016). Consideration needs to be given to activities where the listening environment may prove difficult for communication. For example, group discussions in large, reverberant rooms will require additional listening effort. If a

person has been taking part in rehabilitation sessions during the day that have required increased listening effort, then establishing or maintaining effective communication in sessions at the end of the day may be more challenging.

Although patients were excluded if they had a diagnosis of a specific language impairment, for some people the deficits seen in aspects relating to speech processing may have pre-existed their harmful relationship with alcohol. A number of studies have identified ongoing vulnerability in psychological functioning for people who experienced early language difficulties. There is evidence that early language delay has an adverse outcome for literacy skills, and leads to poorer educational attainment (Johnson et al. 2010). In a recently published prospective study, it was found that poor and deteriorating childhood vocabulary profiles are associated with psychosocial outcomes in adulthood, including alcohol dependence (Armstrong et al. 2017). It is only quite recently that the need to consider preventative treatment programmes has been raised (CASA 2000). Of the sixteen people with ADS who took part in Experiment Two, four (Participants 1,7,11 and 14) talked about difficulties understanding school work and leaving with few or no qualifications. This affected their self-esteem and confidence in social situations. To quote one participant, 'I always felt really stupid but when I drank alcohol it made me relax and I felt like I fitted in, it gave me confidence' (Participant 1). Individuals with 'mild intellectual disability' or 'borderline intellectual functioning' are known to be an 'at risk group' for alcohol addiction (Didden 2017). When considering drinking history and results at follow-up assessment, there was a moderate, negative relationship between the number of years of heavy drinking and the vocabulary sub-test from the WAIS-III^{UK}. The vocabulary subtest is considered to be one of the best measures of intelligence and tends to remain stable across the lifespan (Ardila 2007). If the results of this sub-test had remained stable over the lifespan, then participants one and nine possibly had lower than average pre-drinking scores.

It is known that people experiencing anxiety may use substances such as alcohol, to self-medicate (Goodwin et al. 2002). If, for some people, it is difficulty with language or learning that has resulted in the lack of confidence, then it is worth considering how to ameliorate this underlying issue. The particular battery of tests used in Experiment Two may provide clinicians with information about who may need a more specific language assessment. When considering clinical utility, as discussed in section one (1.1), it is important to evaluate how tests lead to changes in outcome that are valuable to patients. It is possible that using these tests may indicate that

some patients require different measures to be incorporated into their treatment and rehabilitation programmes (Bossuyt et al. 2012). For example, if someone has undiagnosed difficulties with language and learning, simply receiving a diagnosis can allow them to re-interpret their difficulties (Armstrong and Humphrey 2009). There is evidence that in school settings, that pre-diagnosis, some children have been labelled by their teacher or peers as “stupid, lazy or slow” (Humphrey 2002 p. 35). It has been proposed that receiving a diagnosis of dyslexia can be psychologically beneficial, as this diagnosis provides a legitimate explanation for difficulties experienced (Riddick 2000). A diagnosis offers the opportunity to begin remediation activities and to look at coping strategies that may alleviate some of the anxiety felt in certain situations (de Beer et al. 2014). It also allows for more patient-centred communication in order to meet the information needs of individuals.

5.2.2 The Click Auditory Brainstem Response in People with ADS

The results of Experiment Two, for a population of sixteen adults with ADS, show that there is a delay in waves III and V for men and in waves I and V for women, when compared to healthy adults. For men only, there was an increase in the I-III and I-V interpeak intervals. Ten patients (63%) had abnormal click ABRs, of which three were women. A greater percentage of men (70%) than women (50%) had at least one measure outside normal limits for the click ABR. The review of the literature, presented in section two, demonstrated a lack of consensus in the effects of chronic, heavy drinking on the click ABR. An overview of the results of previous studies of people with ADS but no overt neurological symptoms, together with the results of Experiment Two is presented in table 107.

Table 107. Results of ABR Studies in Patients with ADS

Authors (Year of Publication)	Patients	Results
Chu and Squires (1980)	Sub-group of 8 patients with ADS but no overt neurological complications.	12% had abnormal increased I-V interpeak interval.

Table 107 Continued

Authors (Year of Publication)	Patients	Results
Begleiter et al. (1981)	17 male patients with ADS	Wave I normal, subsequent waves delayed.
Chu et al. (1982)	Sub-group of 17 patients with ADS but no overt neurological complications.	12% had abnormal increased interpeak intervals.
Reilly et al. (1983)	33 patients with ADS	No difference between ABRs from a healthy control group and ABRs from patients group.
Chan et al. (1985)	Subgroup of 32 patients with ADS but no overt neurological complications.	Increased I-V interpeak intervals compared to healthy controls. 13% had 'abnormal' ABRs.
Spitzer and Newman (1987)	14 patients with ADS	No difference in latencies between ABRs from a healthy control group and ABRs from patients group. Some difference in waveform morphology.
Lille et al. (1988)	26 patients with ADS	No difference in latencies between ABRs from a healthy control group and ABRs from patients group.
Diaz et al. (1990)	15 patients with ADS	Wave V latencies, III-V and I-V interpeak intervals were prolonged but values within normal range.
Meinck et al. (1990)	44 male patients with ADS	Wave I, III and V latencies, and I-V interpeak intervals were prolonged. 18 patients (45%) had delayed ABR components.

Table 107 Continued

Authors (Year of Publication)	Patients	Results
Cadaveria et al. (1991)	32 patients with ADS	Wave V latency and interpeak intervals III-V and I-V were significantly prolonged. 18 patients (56%) had abnormal ABRs
Cadaveria et al. (1992)	32 male patients with ADS	Wave V latency and interpeak intervals III-V and I-V were significantly prolonged. 15 patients (47%) had abnormal ABRs.
Worner and Lechtenberg (1992)	203 patients with ADS (70 female)	All results within normal limits.
Kuruoğlu et al. (1996)	40 male patients with ADS	Waves III and V latency and interpeak intervals I-III, III-V and I-V were significantly prolonged. 7 patients (17.5%) patients had abnormal ABRs.
Nicolás et al. (1997)	40 male patients with ADS	Waves I, III and V latency and interpeak intervals I-III, III-V and I-V were significantly prolonged. 7 patients (17.5%) patients had abnormal wave Vs.
Niedzielska et al. (2001)	30 patients with ADS	46.7% of waves I prolonged, 83% of waves III prolonged and 90% of waves V prolonged. 50% of interpeak intervals I-III prolonged, 46.7% of III-V prolonged and 68.3% of I-V were prolonged.

Table 107 Continued

Authors (Year of Publication)	Patients	Results
Mochizuki et al. (2003)	Subgroup of 14 male patients with ADS but no overt neurological complications.	No difference in latencies between ABRs from a healthy control group and ABRs from patients group.
Verma et al. (2006)	20 patients with ADS	Tendency for longer waves III, V and interpeak interval I-V. 8 patients (40%) had abnormal ABRs.
Experiment Two (Clinical)	16 patients with ADS (6 female)	For men waves III and V were delayed and the interpeak intervals I-III and I-V were prolonged. For women, waves I and V were delayed. 10 patients (63%) had abnormal ABRs.

As highlighted in section two (2.4.7), there is no overwhelming agreement in the results. The recording parameters are detailed in appendix three and eight of the studies have used quite similar recording techniques. These include the use of a 0.1 msec click, presented at around 11Hz, with high pass filter settings in the range of 100-200 Hz and low pass filter settings in the range of 3000-3200Hz (Chu and Squires 1980; Chu et al. 1982; Chan et al. 1985; Diaz et al. 1990; Meinck et al. 1990; Cadaveria et al.1991, 1992; Nicolás et al.1997). The results of all of these eight studies confirm some prolongation in measures of the ABR in patients with ADS. Apart from the study by Diaz et al. (1990), the ABR results for people with ADS were significantly different from what would be expected of healthy adults. There is a common finding that the I-V interpeak interval is prolonged in adults with ADS. The results of Experiment Two are in agreement with the findings for studies with similar ABR recording parameters.

Although the study by Smith and Richelman (2004) discusses possible gender effects, they excluded females to mitigate this. It is known that the effects of alcohol on males and females differ (see section two, 2.4) with brain damage progressing

more rapidly in women (Ceylan-Isik et al. 2010). It is interesting that the study by Worner and Lechtenberg (1992) which had a large number of female participants, did not find any difference between their laboratory control data and the results of the ABRs in people with ADS. It is difficult to appraise this study as no details of the method for recording the ABR are reported, or of how it was evaluated. The importance of having either separate male and female control data, or balanced control data has been previously discussed (Hall 2007). To the author's knowledge Experiment Two is the first study in which full details of the ABRs in both males and females with ADS are presented. For both sexes, at least 50% of patients had abnormal click ABRs. However, although wave V was delayed both in males and females, there appeared to be some differences in earlier waves. There are a number of studies that report a prolonged wave III in males (Meinck et al.1990; Begleiter et al.1991; Kuruoğlu et al.1996; Nicolás et al. 1997) which was also found in Experiment Two. Although there have been studies that reported a prolonged wave I, sex data was not consistently reported.

A discussion of the generators of the click ABR waves was presented in section two (2.2.2). Although numbers in Experiment Two are limited when divided into males and females, there is preliminary evidence of differences in the ABR results for men and women with ADS, compared to healthy adults. For men the central conduction time from peak I to peak V is increased. Wave I occurs at the expected latency but the subsequent waves are delayed. Waves III and / or V were delayed in 40% of men. It is not straightforward to relate these findings to underlying neural generators because of the multiple generator sites contributing to far-field recordings. It would appear that the pathology is occurring not at the periphery but within the brainstem, from the level of the cochlear nucleus onwards. It could be conceived that a delay at wave III would have the effect of delaying the appearance of wave V. It has been shown however, that it is possible for early waves to be delayed without affecting the latency of wave V (Patrick and Struve 1994). Indeed, for participant seven in this study, there was a delayed wave III without a corresponding delay at wave V. In the case of most of the male participants with ADS who had abnormal results it would appear that for the right ear it was only wave V that was affected, whilst for the left ear it was wave III and wave V. This indicates that there can be both pathology at the level of the cochlear nucleus and at the level of the inferior colliculus. It is interesting to note these asymmetrical differences and speculate that pathology tends to appear at the inferior colliculus level prior to lower regions within the brainstem. One of the

proposed models of ARBD is that the right hemisphere is more susceptible to the negative effects of alcohol (Sanhueza et al. 2011). When considering the auditory pathways, it is contributions from the left ear that arrive in the right hemisphere. This raises a question regarding the entire pathway being more susceptible to the effects of alcohol. To determine if there is a pattern in the appearance of pathological results a larger, prospective study would be a worthwhile undertaking.

The situation for the women with ADS is somewhat different, although both waves I and V were delayed compared to the female controls, the more common abnormal finding was an increased latency in wave I. This would indicate pathology occurring at the level of the periphery as well as within the upper brainstem. All participants had hearing thresholds within 'normal' limits but the indications are that sub-clinical damage has occurred that is affecting transmission of the signal through the auditory nerve. Otoacoustic emission testing, thought to be a measure of outer hair cell function, was normal for all participants. This deficit could therefore be occurring as early as the inner hair cells or first neural synapses from the inner hair cells. In order to assess the compound action potential of the auditory nerve and enhance the investigation of wave I abnormalities, it might be of interest to perform electrocochleography (ECochG). This is an auditory evoked potential that can be employed for recording the electrical responses from the cochlear hair cells and auditory nerve (Santarelli and Arslan 2013). The recording parameters are similar to those of the ABR, however the active electrode needs to be placed as close to the cochlea as possible. The least invasive way of achieving this is to place an electrode against the tympanic membrane. There would need to be a consideration of the clinical justification for this procedure, in relation to the knowledge provided. It may help to answer questions in relation to hearing loss and ADS (Verma et al. 2006).

There is a known difference in the effect of alcohol on the brain, between the sexes. Although women with ADS generally drink lower amounts of alcohol, they tend to exhibit more severe brain damage (Ceylan-Isik et al. 2010) and the progression of damage appears to be faster (Hommer 2003; Prendergast 2004). For this particular population, 50% of women had at least one abnormal click ABR measure, whereas it was 70% for the men tested. This raises an issue of the heterogeneity of the general population with ADS. There are a number of interacting factors, which can lead to alcohol dependency, including genetics, environment, personality characteristics and psychiatric comorbidities (Zahr et al. 2011). There are also wide variations in the age at which drinking commenced, the age at which drinking became problematic, the

type of alcohol consumed and the pattern of drinking (Strunin et al. 2007). In addition to this, the nutritional status of the person will affect damage to the brain, with thiamine deficiency leading to Wernicke–Korsakoff syndrome (Martin et al. 2003). Although there is a label of 'alcohol dependence syndrome', this describes a set of characteristics and behaviours (ICD-10, Chapter V, F10.2). People can take very different pathways before receiving a diagnosis of ADS. One of the reasons why there is such a variation in the literature may be attributable to differences in recording techniques and often poor reporting of patient details and methods. It is acknowledged that there is also confusion around the terminology used within the field of substance use disorders (Room 2011).

5.2.3 The Speech Auditory Brainstem Response in People with ADS

The results of Experiment Two, for a population of sixteen adults with ADS show that there is a delay in waves V and A of the speech ABR for both men and women, when compared to healthy adults. For the composite onset measures of VA amplitude and slope, women with ADS had significantly lower amplitudes and shallower slopes, than for the healthy women. Although these results were also significant for men, they did not remain so once a correction for multiple comparisons was applied. For peaks falling within the sustained portion of the speech ABR response, waves E and O were significantly later for females, when compared to healthy women. The results for men were also significant for peak E but did not remain so, once a correction for multiple comparisons was applied. The findings that the peaks relating to the onset of the response were significantly different in people with ADS is perhaps not surprising. The VA complex, is thought to be largely analogous to the click-evoked wave V-Vn complex (Wible et al. 2004; Johnson et al. 2005; Song et al. 2006; Skoe and Kraus 2010a). There is a significant correlation between the latencies of wave V when recorded by click and speech ABR in the general population. However, this is not the case for a sub-group of individuals with learning difficulties and abnormal speech ABRs. These findings suggest that brainstem structures do respond differently to click and speech stimuli (Song et al. 2006). As wave V was found to be significantly delayed in the click ABRs of people with ADS, then if the VA complex is largely analogous to this, it should be delayed in the speech ABR for people with ADS. In Experiment Two, every person with an abnormal (delayed) wave measure of V for the click ABR, also had an abnormal (delayed)

measure for wave V of the speech ABR (Table 108). In addition, two women with normal wave Vs for the click ABR, had abnormalities (delays) in the wave Vs of the speech ABR. This is the first indication that the speech ABR may offer a more sensitive measure of neural function than the click ABR in this population. Click and speech stimuli impose different encoding demands on the brainstem. This kind of result has been found in when comparing the click ABR and speech ABR both in children and in adults (King et al. 2002; Song et al. 2006; Johnson et al. 2007; Sanju et al. 2017b). The findings of Experiment Two confirm that there can be abnormal neural encoding of speech, in the presence of a normal click ABR. There can also be the opposite situation where a person can have an abnormal ABR but a normal speech ABR. In this study this occurred for participants two and seven. When looking at where the abnormal result occurred, in both case it was related to either wave III or the I-III interpeak interval in the click ABR. The neural generator site affected is therefore at a lower point in the brainstem than that thought to be responsible for the speech ABR response.

Table 108. Click and Speech Wave V Abnormalities for Individual Participants with ADS

ID (Sex)	Click ABR		Speech ABR	
	V Right	V left	V Right	V Left
4 (M)	✓	✓	✓	✓
5 (F)			✓	✓
6 (F)			✓	
10 (M)	✓	✓		✓
12 (M)	✓	✓	✓	✓
15 (M)		✓		✓
16 (F)	✓	✓	✓	✓

Where ✓ represents positive for a result outside normal limits.

In relation to the measures from the sustained portion of the response, which reflects the response to the vowel, it appears that this area may also be affected by alcohol dependency. This study demonstrated apparent sex differences in the encoding of the slow elements of speech. Adults with ADS have less synchronous neural activity in relation to rapidly changing features of the /da/. Women also appear to have compromised neural phase-locking to the slower components of speech. The

response for women with ADS was less robust than for the healthy women. The signal to noise ratio and the representation of F0 were less robust. When returning to the discussion of the 'source filter' model in section two (2.3), it has been proposed that there are two different information processing streams. The source characteristics of speech relay non-linguistic information including the sex, emotional state, attitude and identity of the speaker. The filter characteristics relay the linguistic content, the building blocks of vowels and consonants. This results in two processing pathways, one for the responses to the acoustic filter characteristics of the syllable and one for the source (Kraus and Nicol 2005). As it is known that both the onset response and FFR vary with both behavioural and clinical measures (Kraus and Nicol 2005; Coffey et al. 2016) they should also be conceptualised as functionally distinct responses that arise from different neural generators in the auditory pathway (Krizman et al. 2010; Bidelman 2015). The results of Experiment Two also indicate that there are at least two pathways, which are differentially affected. It would be interesting to determine whether one pathway is more sensitive to the effects of alcohol than the other. Although there were significant differences for the men for the slower, source components, they did not remain on correction for multiple comparisons. In order to determine if a degradation in processing of fast components of speech precedes a degradation of encoding of the slower components, a larger, prospective study would be required. As with the click ABR, when relating the speech ABR back to its proposed neural generators it would appear that deficits in these pathways may arise from the lateral lemniscus and/or inferior colliculus (Chandrasekaran and Kraus 2010). If, as can be seen from the results, both source and filter pathways are affected, then recognition of speech and speaker intention may be affected (Krishnamurti et al. 2013).

As opposed to the click ABR, which has six latency measures for each ear, the speech ABR has seventeen different measures. In this study, people with ADS had deficits which occurred across fourteen of these measures. Most commonly, the abnormal results were in the VA complex area (64%), however if just the VA complex is used, or even combined with the discrete peak latency measures (89% of all abnormalities), not all people with abnormal results would be identified. There was one individual (Participant 13) who only had an abnormality on the SR correlation and spectral encoding measures. Clinically, it would be more straightforward to use the speech ABR as a diagnostic tool, if additional analyses in Matlab were not required. The BioMARK module allows the calculation of the aspects related to the VA complex.

Removing the analysis of aspects related to stimulus to response correlation and spectral encoding would reduce the sensitivity of the speech ABR from 69% to 63%. If the criteria for a positive diagnosis were an abnormality on either the auditory processing tests or the discrete peak or composite onset measures of the speech ABR only, this would reduce the sensitivity from 88% to 81%. A larger study would be needed to determine whether performing all the additional analysis in MATLAB is warranted, for people with ADS.

In total, eleven people with ADS (69%) had at least one measure outside normal limits for the speech ABR. Of these, five of the men (50%) had at least one measure outside normal limits. However, a key finding is that all 6 women (100%) had at least one measure outside the normal limits. It would appear that the differences that were evident in the click ABR results between men and women are also evident in the speech ABR results. Previous research, in addition to the results of Experiment One, have found that sex differences are evident in the speech ABRs, with the onset response generally earlier and more robust for females (Krizman et al. 2012a; Ahadi et al. 2014a; Jalaei et al. 2017; Liu et al. 2017). Although it was the onset responses that were commonly affected in people with ADS, as discussed, there is a difference between men and women in the sustained portion of the response. It would appear that phase locking is more impaired in the women with ADS than for the men. When contemplating sex differences, consideration should be given to the fact that for some men (Patients two and seven) the abnormalities in the click ABR measures encompassed wave III and there were no abnormal speech ABR measures. It may be the case that the speech ABR is better suited to capturing damage to neural pathways in women and the click ABR is better suited to capturing damage in men. As recording of both responses can be carried out sequentially and the speech ABR captures deficits in people not always identified with the click ABR, the recommendation would be to run both tests.

5.2.4 Changes in the Auditory-Cognitive Profile with Abstinence

There were significant improvements in the results of both the auditory processing assessments and cognitive assessments after twelve weeks of abstinence. A practice effect has been ruled out by analysing the results of the study with the healthy adults (section three, 3.4). Baseline testing found 81% of people experienced difficulties with either one or both areas of the auditory-cognitive profile.

Eight participants who presented with at least one deficit in either the auditory processing or cognitive assessment attended for follow-up assessment. Of these, four (50%) still had at least one deficit at follow-up testing and two participants (25%) retained deficits in both areas (Table 96). No participant had any atypical results at follow-up testing that weren't already apparent at baseline testing. When considering the initial pool of eleven who completed two assessments, 36% experienced difficulties with aspects of the auditory-cognitive profile at follow-up, compared to the initial 81%. For two of the people who were still experiencing difficulties in areas of the auditory-cognitive profile, there were no corresponding deficits in either the click or speech ABR after twelve weeks of abstinence. As previously discussed, it is not possible to rule out whether these particular subjects had difficulties in these areas at the cortical level, that were pre-existing. However, they may benefit from additional support for these problem areas, in order to successfully avoid relapse. Didden (2017) finds that the evidence base of what constitutes effective intervention for this group is small and generally of poor quality. He is of the opinion that treatment will only be effective, if consideration is given to both the addiction and the cognitive status of the patient.

5.2.5 Changes in the Click ABR with Abstinence

There were significant improvements in the click ABR results for both men and women with ADS. Of the initial ten people with at least one abnormal measure, seven completed follow-up testing. No one had any measures outside the normal range at follow-up testing, that weren't already apparent at baseline testing. Six of the seven participants had improvements in at least one measure of latency, to within the normal range. Three of the seven had click ABRs that had fully returned to within the normal range within the 12 week period. There are few longitudinal ABR studies in people with ADS and there is limited data that the ABR improves with abstinence over time (Porjesz and Begleiter 1985; Haas and Nickel 1991; Cadaveira et al. 1994). One difficulty in comparing the results of these studies is the differences in timescales for abstinence. Most published studies of people with ADS take place once the patient is abstinent but that can be anything from a matter of days, to years. The study by Porjesz and Begletier (1985) is in the form of a review but discusses their own findings for an unspecified group of people with ADS who had been abstinent for one month. They found significant delays in the click ABR from waves II onwards, after a month

of abstinence. A study looking at recovery with abstinence over the period of a week for patients with WE, found shortening in the I-V interpeak interval for the click ABR. In a study including patients with ADS who had been abstinent for between two and ten years, it was found that the click ABR was abnormal in 31% of those patients (Chu 1985). A group of patients with ADS had click ABRs recorded after one, five and twelve months of abstinence (Cadaveira et al. 1994). The results of this study found that although improvement took place in the one to five month period, it was more notable in the five to twelve month period. Twelve, male participants were abstinent for the full year. Of that twelve, 42% had abnormal ABR results after one month, 25% had abnormal ABR results after five months and 17% had abnormal ABR results after one year of abstinence. The results of Experiment Two found that after twelve weeks four of the eleven participants (36%), who completed follow-up testing, still had at least one abnormal measure for the click ABR. These results are in line with those of the previous longitudinal studies (Chu 1985; Cadaveira et al. 1994).

What is not always reported within the published studies is whether patients were taking thiamine and if so, for how long. There are reported links between thiamine metabolism and brainstem function, with thiamine deficiency having deleterious effects on glia, myelin and microvasculature (de la Monte and Kril 2014). In the case of the four patients who still had atypical click ABR responses, three were not taking thiamine. The single patient who was taking thiamine, was patient seven, who was one of only two patients to have deficits present at wave III and not wave V. Hammond et al. (1986) noted the benefits of thiamine treatment in their patients with WKS and Haas and Nickel (1991) have stated that thiamine is effective in the treatment of WE if administered at the acute stage. A group of patients with ADS but no measurable thiamine deficiency had click ABR assessment on entering a clinic for assistance with terminating their drinking. There were significant differences in their ABR results for waves I, III and V and 17.5% had abnormal values for wave five (Nicolás et al. 1997). One of the only studies to look specifically at the effects of thiamine concluded that, together with abstinence, treatment with thiamine aided in the improvement of ABR results for patients with WKS (Chan et al. 1985). However, there was no control group present and it was not stated whether patients with ADS but no diagnosis of WKS, received any thiamine treatment. In this case, the study design does not allow any conclusion as to whether it is the effects of thiamine, or abstinence that have resulted in improvements. The click and / or speech ABR could

be investigated for effectiveness in monitoring the effects of thiamine and may provide clinicians with evidence for when a medication regimen can cease.

5.2.6 Changes in the Speech ABR with Abstinence

There was an overall improvement in the speech ABR measures over the twelve week period of abstinence, for both the men and women with ADS. Of the eleven adults who completed two assessments, eight had at least one measure of the speech ABR outside normal limits at baseline and this had reduced to three at the end of the twelve week period. There are no similar published studies to compare these findings with, however the number of people still exhibiting deficits within this timescale is similar to those for the click ABR studies (Chu 1985; Cadaveira et al. 1994). What is of interest, is that there are differences between the click ABR results and the speech ABR results in relation to the patients remaining affected. For participant four, the click ABR has returned to normal, whilst wave V of the speech was still late unilaterally. For participant six, wave A has moved into normal limits unilaterally. For patient fifteen both the click and speech ABR have a number of measures that remain outside normal limits unilaterally. It therefore appears that improvements have occurred, however the timescale may be too short for full recovery, if full recovery is indeed to happen. It is interesting that for two females who had normal speech ABRs at follow-up testing, the click ABRs were still outside normal limits. For one of these patients, it was a deficit at wave I that remained unilaterally. It would appear that the click ABR and speech ABR are complimentary in monitoring recovery of brainstem function in adults with ADS, entering a treatment and rehabilitation programme. Using both measures allows aspects of auditory nerve and brainstem function to be monitored.

The recovery in brainstem function, as monitored by the speech ABR is encouraging. Of the three participants that had remaining deficits, all three had deficits relating to the VA complex. Again, this indicates that there may be no need to perform further analysis of the waveform in Matlab to assess dysfunction. The difference between using the click ABR and the speech ABR in relation to the wave V, may be a consequence of only labelling the vertex positive peak V and not Vn of the click ABR. It is likely that the vertex negative wave also has diagnostic value, as it will have its own neural generator (Møller 2014). This result of poor neural encoding of the onset complex has implications for speech perception. ‘Acoustic onsets’ have

received particular attention in the speech perception literature and the early speech ABR literature (Russo et al. 2004; Wible et al. 2004; Banai et al. 2005). It has been proposed that there is a link between perception and the representation of acoustic onsets in the speech ABR. An abnormal representation of speech onset results in deficits, which result in difficulties distinguishing between consonants that are similar (Abrams and Kraus 2015). For the people with ADS who retained this marker, the results of the cognitive assessment were normal. Although the cognitive assessment was not comprehensive, it did assess aspects of cognitive function related to speech processing. For these people, it would appear that there is dyssynchrony of the signal in the rostral brainstem.

5.2.7 The Effects of Drinking History

Although the age profiles of participants in Experiment Two were similar, the average number of years of drinking history for the men in this study was 17.7 (5-30 years) and for the women was 8.7 (4-23 years). The patient notes contained the age at which drinking commenced, the age at which drinking became problematic and the typical drinking behaviour prior to programme entry. Additional information for some patients included the Severity of Dependence Scale (SDS) score. The SDS is a five-item questionnaire, with a maximum score of 15. The suggested cut-off score to indicate alcohol dependence is three or above (Lawrinson et al. 2007). Seven of the participants had SDS scores recorded in the notes. These scores ranged from eight to fourteen. When trying to categorise the drinking history of the patient group, all patients could be classified as having high-risk consumption behaviour, as they invariably consumed more than 120g of alcohol per day (Bühringer et al. 2002).

Of the tests conducted as part of the assessment battery, it was the tests of auditory processing that were found to have the strongest correlations with the number of years of heavy alcohol consumption. In particular, there was a moderate to high negative relationship between scores for the Duration Pattern Sequence Test (DPST), and years of problem drinking. The DPST requires the functioning of the auditory pathways including both cerebral hemispheres and the corpus callosum. The duration pattern test is known to be able to identify lesions that the pitch pattern sequence test cannot, with the converse also being true. The DPST has been shown to be more sensitive in detecting cerebral, brainstem and impaired auditory cortex function (Musiek 1994). The DPST is a test of the entire auditory pathway, as the test

requires the stimuli to be heard, understood and a response verbalised. Of the five patients identified with a deficit on the DPST, four had deficits on either the click ABR, the speech ABR or both. It is not possible to identify the site of lesion more precisely, except to say that for participant fourteen, it is unlikely to be in the brainstem area. The DPST is not likely to identify any additional participants with processing deficits, than have already been identified using the Dichotic Digits test and the Random Gap Detection test for Clicks. However, it does seem to provide interesting additional information regarding the relationship with years of problem drinking.

Of the published studies looking at the click ABR and cumulative effects of alcohol, only two have reported a link (Nicolás et. al. 1997; Smith and Riechelmann 2004). It has been reported that an abnormal wave V is evident with a higher total lifetime dose of ethanol per Kg of body weight (Nicolás et. al. 1997). In this particular study, the participants were divided into two groups, those with wave V abnormalities and those without and the lifetime dose of ethanol per Kg of bodyweight was compared. It was not possible to perform this type of analysis in Experiment Two, as the weight for each participant was not always included in the case notes. There was also an imbalance in group sizes, for those with click ABR wave V abnormalities. The second study to report a link used a more detailed breakdown of lifetime history of alcohol consumption (Smith and Riechelmann 2004). They found that there was a logarithmic relationship between cumulative lifelong exposure and the I to V interpeak interval. However, this relationship was weaker when age was controlled for. Again, this is not possible for Experiment Two, as this level of detail about drinking history was not present in the notes. A low, negative correlation was found for the maximum grams of alcohol consumed per day and interpeak interval measures of the click ABR for the I to V interval recorded at baseline. As discussed, it may be that had the knowledge of the alcohol history been more detailed, a stronger relationship may have been apparent. However, other researchers have been unable to find patterns when using a variety of event related potential assessments and have concluded that clinical effects vary greatly between individuals (Cadaveira et al. 1994).

There are some interesting differences in the click ABR profiles of those taking thiamine, compared to those who are not, after for the period of abstinence. These results are based on small numbers and must be interpreted with caution. It would appear that there is greater recovery of wave V latency in those people taking thiamine and this is worthy of further research. If this is indeed the case, the ABR could be used as a biomarker to measure the beneficial effects of thiamine on

brainstem function. This was not the case for the speech ABR at follow-up, although that might be expected, as there appeared to have been more recovery to within normal limits for this measure.

5.2.8 Recommendations for a Clinical Assessment Battery

Drawing on the information discussed throughout Experiment Two, it would appear that the questions posed in relation to diagnosis, could be answered by using the following abbreviated, assessment battery:

- History Taking
- Otoscopy
- Tympanometry
- Screening Audiometry performed at 20dB HL.
- TEOAEs
- WAIS III Subtests: Vocabulary, Digit Symbol Coding, Letter Number Sequencing
- Auditory processing Subtests: Dichotic Digits, Random Gap Detection Test for Clicks
- Click ABR
- Speech ABR

The following proved not to be distinguishing: Symbol search, digit span forwards and backwards, the duration and pitch pattern sequence tests, the random gap detection test for tones and the speech in noise test

This abbreviated, assessment battery would take less than one and a quarter hours to complete. Whilst it would provide the required details about abnormalities, scores on tests such as the DPST appear to be linked to years of drinking. These results may be of interest to clinicians when drinking history is vague or information is conflicting.

5.2.9 Clinical Utility of the Speech ABR in Adults with Alcohol Dependence Syndrome

The concept of clinical utility was introduced in section one. A test, or suite of tests, can be clinical useful if they provide patient health information as well as proof

of improved outcome, enhanced quality of care, improved efficiency or cost effectiveness (Bossuyt et al. 2012). Currently the diagnosis of ADS relies on a clinician making a judgement about a set of behaviours (ICD-10). There is no standard treatment and rehabilitation programme in Scotland or the UK. There is an identified difference in the provision and scope of treatment and rehabilitation programmes throughout Scotland (Audit Scotland 2009), as well as a lack of evidence of effectiveness more generally (Didden 2017). It has been proposed that treatment will only be effective, if consideration is given to both the addiction and the cognitive status of the patient (ibid.).

It would appear that assessing a person's auditory-cognitive profile, including the use of the click and speech ABR can provide additional information about a patient's health. It can also provide information, which might allow a treatment programme to be more person-centred. For example, it might highlight underlying cognitive deficits for which coping strategies might be appropriate, or indicate the need for a more comprehensive language assessment. It will identify auditory processing difficulties, encouraging consideration of communication strategies for both the patient and the treatment provider. The use of the ABRs provides information about the health of the brainstem and provides an indication of brain damage that might not otherwise be evident. These tools also offer a way to monitor the effectiveness of the treatment programme. The ABRs could be used as a biomarker to measure the beneficial effects of thiamine on brainstem function, allowing for a tailored treatment regime.

Performing an auditory-cognitive assessment battery, without the ABRs will identify 69% of people with abnormalities. By including the speech ABR this rises to identification of 81%-88% of adults with ADS. This is dependent on whether abnormalities of the discrete peak and composite onset measures of the speech ABR, or abnormalities of all measures of the speech ABR are used. All participants with abnormalities in the click ABR also had either an abnormality in the tests of auditory processing or the discrete peak and composite onset measures of the speech ABR. The speech ABR, therefore adds valuable information, not provided by the other assessments.

The full assessment battery performed in both Experiments One and Two took in the region of two, to two and a half hours to complete. The participants in Experiment Two stated that they enjoyed undertaking the assessments and all participants who remained in the treatment and rehabilitation programme elected to

undergo follow-up assessment. The retention rate for this study was high (69%) compared to other studies that have involved working with people with ADS (Gill et al. 2016). A potential criticism of the definitions of clinical utility is that they appear to be tailored to the clinicians' perspective. The participant feedback was that that they valued the information that the test battery provided. For those that attended follow-up testing, all asked about improvement in their results. They considered that the tests provided a way for them to monitor their own progress. To quote one participant (Participant 13), 'I knew I felt better but this proves it, doesn't it? This is proof that doing this (*programme*) was the right thing for me.'

5.3 Conclusions

The purpose of this section is to present the conclusions relating to the overarching aims of this thesis.

The overarching aims were:

1. To assess the reliability of the speech ABR. Establishing confidence in inter-rater and test re-test reliability is a mandatory precursor to addressing the central aims of the thesis.
2. To assess the impact of patient-related parameters on speech ABR measures, by experimental examination. This will support the principled development of a clinical protocol.
3. To examine, through clinical trial, the comparative value of using the click and speech ABR to measure and monitor neural function in people with alcohol dependence syndrome.

The speech ABR has been shown to be stable over a period of twelve weeks in adults aged 31-49 years. A unique contribution of this thesis was to provide inter-rater reliability data for the speech ABR. This has not been considered in the wider literature and the findings highlight the importance of undertaking this assessment. Before analysis of ABR results can be attempted, for any new stimulus used, inter-rater reliability must be performed.

In relation to considerations about ABR recording, it was found that the previous assertion that there is sub-cortical laterality of speech encoding (Hornickel et al. 2009), is incorrect. This is clinically helpful, as it negates the potential requirement for separate normative data for right and left ears. In a number of the research studies, participants have been excluded if they are left handed or exhibit right hemisphere dominance for speech processing. This would render the speech ABR of limited use clinically, if it could not be used in the general population. As per findings for the click ABR, separate normative data is required for men and women, although this is not commonly reflected in the published studies. Again, this is important clinically, as using normative data derived mostly from one sex at the expense of the other, will lead to either men being incorrectly identified with abnormalities or abnormalities not being detected for women. It would appear that

normative data is valid for that 18-49 years age range but further research is required to supplement that provided by Skoe et al. (2015a) regarding the aging population.

Both the click and speech ABR appear to have a valuable role to offer clinicians working with people with ADS. This is a unique contribution, as the speech ABR has not been applied with this population previously. The click and speech ABR can provide a measure of neural function not currently available and potentially identify those most at risk of alcohol related brain damage. They can also provide a way to monitor recovery and have a potential role in monitoring the beneficial effects of thiamine on brainstem function. Their inclusion into a wider auditory-cognitive assessment provides both the patient and clinician with patient health information as well as proof of improved outcome and potentially enhanced quality of care. Quality of care enhancements can arise from being able to tailor the treatment programme to meet the patient's communication needs. An auditory-cognitive assessment may also identify patients who may benefit from more in-depth language based assessment. If performing the auditory-cognitive profile assessment does enable more effective, person-centred treatment, this could result in fewer relapses and therefore offer a more cost-effective approach to patient care.

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Appendices

The appendices for Experiments One and Two are presented as follows:

Appendix One. Table of Studies Using the 40 ms /da/ Stimulus
Appendix Two. Abbreviated Version Of Treatment AS Usual in the Ritson Clinic
Appendix Three. Table of ABR and Alcohol Studies
Appendix Four. History Questionnaire
Appendix Five. IRAS Ethical Approval

Appendix One. Table of Studies Using the 40ms /da/ Stimulus

Authors (Year of Publication)	Subjects	Speech ABR Collection Protocol	Research Question(s)	Conclusions
Dhar et al. (2009)	28 adults (ages 19–30 years, mean = 25; 17 women) Right handed, normal hearing.	Standard /da/ at 80.3 dB SPL, alternating polarities at 10.9 Hz. Vertical montage Bandpass filtered: 100 to 2000 Hz 6000 artefact-free trials	Is there a relationship between DPOAE measures and Speech ABR measures?	Relationships with the DPOAE measures were found for sABR measures except onset and Pitch. Therefore aspects of the speech ABR are related to, or covary with, cochlear function.
Hornickel et al. (2009)	12 adults (ages 21–30 years, mean = 25.67; 9 women) Right handed, normal hearing.	Standard /da/ at 80.3 dB SPL, alternating polarities at 10.9 Hz. Vertical montage Bandpass filtered: 100 to 2000 Hz 6000 artefact-free trials	Is there a difference between left and right ear subcortical encoding of a speech like stimulus?	Responses to right ear presentation occurred earlier than those for left in the FFR. More robust frequency encoding of F0 when stimuli were presented to the right ear than the left ear. Therefore there is subcortical left lateralization of some aspects of speech processing.
Strait et al. (2009)	30 adults (ages 19-35 years, mean = 24.7; 18 women). Normal hearing, normal response to /da/.	Biomark recording protocol	What are the influences of musical experience on neural processing of emotionally relevant sounds?	Normal response to 40 ms /da/ for inclusion purposes only. Musicians exhibit enhanced perception of emotion in speech.
Anderson and Kraus (2010)	2 adults (ages 61 and 62 years).	Biomark recording protocol	Do adults with poor speech in noise (SIN) perception have deficits in the speech ABR?	Good SIN perception resulted in earlier peak latencies and more robust F0 representation.

Appendix One. Table of Studies Using the 40ms /da/ Stimulus Continued

Authors (Year of Publication)	Subjects	Speech ABR Collection Protocol	Research Question(s)	Conclusions
Karawani and Banai (2010)	37 adults (ages 18-28 years, mean = 23.5; 27 women. Native Hebrew and Arabic speakers, normal hearing.	Standard /da/ at 80 dB SPL, alternating polarities at 10.9 Hz. Vertical montage Bandpass filtered: 100 to 2000 Hz 6000 artefact-free trials	What does the speech ABR look like when collected using the US protocol for native Hebrew and Arabic speaker?	The speech ABR to the 40 ms /da/ does not differ between speakers of English and speakers of Arabic or Hebrew.
Krizman et al. (2010)	18 adults (ages 21-33, mean = 26; 9 women) Normal hearing.	Standard /da/ at 80.3 dB SPL, alternating polarities at 15.4, 10.9 and 6.9 Hz. Vertical montage Bandpass filtered: 100 to 2000 Hz 6000 artefact-free trials	What is the effect of stimulus presentation rate on the speech ABR?	There are differential effects on the onset and FFR. Increased latency of the onset was seen as presentation rate increased. The FFR was also rate dependent, response magnitude of the higher frequencies but not those corresponding to $F_{0,}$ decreased as rate increased.
Rocha et al. (2010)	50 adults (ages 19-32, mean = 23.6; 28 women) Normal hearing.	/da/ produced to resemble standard stimulus. Presented through headphones, at 75 dB HL, at 11 Hz Vertical montage 2000 trials	What does the speech ABR look like for typical adults?	Normative data for onset measures published.

Appendix One. Table of Studies Using the 40ms /da/ Stimulus Continued

Authors (Year of Publication)	Subjects	Speech ABR Collection Protocol	Research Question(s)	Conclusions
Sinha and Basavaraj (2010b)	30 adults (ages 18-25 years) Normal hearing.	/da/ produced to resemble standard stimulus at 80 dB nHL, alternating polarities at 7.1 Hz. Vertical montage Bandpass filtered: 30 to 3000 Hz 2000 trials	What does the speech ABR look like for typical adults?	Normative data for onset measures published. No correlation found between click ABR wave V and speech ABR wave V.
Sinha and Basavaraj (2010a)	20 adults (ages 18-30 years, mean =22; 20 women). Normal hearing, right handed.	Standard /da/ at 80 dB SPL, alternating polarities at 9.1 Hz. Vertical montage Bandpass filtered: 100 to 3000 Hz 3000 trials	Is there a difference between left and right ear subcortical encoding of a speech like stimulus?	No difference in onset responses. Responses to right ear presentation occurred earlier in the FFR. More robust frequency encoding of F0 and harmonics for the right ear than the left ear. Therefore there is subcortical left lateralization of some aspects of speech processing.
Rana and Barman (2011)	35 adults (ages 18-23 years) Normal hearing.	Standard /da/ at 80 dB SPL, alternating polarities at 9.1 Hz. Vertical montage Bandpass filtered: 100 to 3000 Hz 3000 trials	Is there a relationship between TEOAE measures and Speech ABR measures?	There is no correlation between TEOAE amplitudes and the various components of the speech ABR, apart from speech ABR wave V latency and TEOAE global emission strength.

Appendix One. Table of Studies Using the 40ms /da/ Stimulus Continued

Authors (Year of Publication)	Subjects	Speech ABR Collection Protocol	Research Question(s)	Conclusions
Song et al. (2011)	45 adults (ages 19-36 years, mean = 24.5; 29 women). Normal hearing.	Standard /da/ at 80.3 dB SPL (magnetic shielding) alternating polarities at 10.9 Hz. Vertical montage 6000 artefact-free trials	What is the test-retest reliability of the speech ABR?	There is no significant variability in any of the components of the speech ABR within individuals, across different recording sessions.
Vander Werff and Burns (2011)	Group 1: 19 adults (ages 20-26 years; 13 women) Normal hearing Group 2: 18 older adults (ages 61-78 years; 17 women) Hearing thresholds ≤ 25 db HL.	Standard /da/ at 82 dB SPL, alternating polarities at 10.9 Hz. Vertical montage Bandpass filtered: 100 to 2000 Hz 3000 artefact-free trials	Is there a difference in the speech ABR between younger and older adults?	Older adults had significantly smaller onset and delayed offset responses for the speech ABR. Differences in the FFR were accounted for by the disparity in hearing thresholds.
Campbell et al. (2012)	15 adults (ages 18-28, mean =22.5; 9 women) Normal hearing.	40 ms /da/ (not described) 8 trains of 480 40 ms da Offline bandpass filtered 70- to 2000-Hz	What methods can be used to eliminate artefact?	Speech ABRs can be recorded using high-fidelity insert earphones as long as one or more techniques are used to remove stimulus transduction artifact.

Appendix One. Table of Studies Using the 40ms /da/ Stimulus Continued

Authors (Year of Publication)	Subjects	Speech ABR Collection Protocol	Research Question(s)	Conclusions
Gnanateja and Ranjan (2012)	Test 1: 13 adults (ages 18-24 years) Normal Hearing Test 2: 15 adults (ages 18-27 years) Normal hearing.	Standard /da/ and filtered /da/ presented at 80 dB SPL at 10.9 Hz Vertical montage 4000 trials	What are the roles of high frequency harmonics and stimulus envelope in the encoding of the speech ABR?	FFRs evoked by the 2 stimuli were not different in spectrum. The envelope is key for the coding of the FFR.
Krizman et al. (2012a)	76 adults (ages 22-29 years, mean = 24.7 years; 38 women) Normal hearing.	Standard /da/ at 80 dB SPL, alternating polarities at 10.9 Hz.	Are there differences in the speech ABR for men and women?	There are sex differences in the fast acoustic components of the speech ABR with women having earlier and more robust responses.
Anderson et al. (2013a)	111 adults (ages 45 - 78 years, mean = 61.1; 64 women).	Standard /da/ presented at 80.3 dB SPL or normalized for HL (electromagnetic shielding), alternating polarities at 10.9 Hz Vertical montage Bandpass filtered: 100 to 2000 Hz 6000 trials	Can the speech ABR predict subjective ratings of SIN understanding using the Speech, Spatial and Qualities of Hearing Scale?	The speech ABR recorded in noise can be used, alongside other measures, to predict self-reported difficulties with listening in noise.

Appendix One. Table of Studies Using the 40ms /da/ Stimulus Continued

Authors (Year of Publication)	Subjects	Speech ABR Collection Protocol	Research Question(s)	Conclusions
Anderson et al. (2013b)	Group 1: 15 adults (ages 61-68 years, mean =64; 10 women) Normal hearing to 4000Hz Group 2: 15 adults (ages 60-71 years, mean =64; 8 women) Mild to moderate SNHL.	Standard /da/ presented at 80.3 dB SPL or normalized for HL (electromagnetic shielding) binaurally, alternating polarities at 10.9 Hz Vertical montage Bandpass filtered: 100 to 2000 Hz 6000 trials	How does hearing loss affect the speech ABR?	Compared to the normal hearing group, there was an imbalance between the E and TFS representation. The E following response is enhanced.
Anderson et al. (2013c)	58 adults (ages 55-79; 35 women). Divided into normal hearing and hearing impaired groups.	Standard /da/ presented at 80.3 dB SPL or normalized for HL (electromagnetic shielding), alternating polarities at 10.9 Hz Vertical montage Bandpass filtered: 100 to 2000 Hz 6000 trials	Does the speech ABR change for older adults who have undertaken an auditory training programme?	After training the previously seen enhancement of the E following response is reduced and approaches that of older adults with normal hearing. There was no change in the speech ABR for the control group.
Gnanateja et al. (2013)	14 adults (ages 17-25 years; 7 women) Normal hearing.	Standard /da/ and filtered /da/ presented at 80 dB SPL at 10.9 Hz Vertical montage 4000 trials	How are a series of regular and irregular stimuli encoded using speech ABR?	The brainstem can encode pitch even with little acoustic information below the second formant frequency.

Appendix One. Table of Studies Using the 40ms /da/ Stimulus Continued

Authors (Year of Publication)	Subjects	Speech ABR Collection Protocol	Research Question(s)	Conclusions
Kumar et al. (2013)	17 adults (ages 17-30 years, mean =20.7; 9 women) Normal hearing.	Standard /da/ presented at 80 dB SPL, binaurally, alternating polarities at 7.1 Hz. Vertical montage Bandpass filtered: 50 to 1500 Hz 6000 trials	What is the effect of stimulus polarity on the speech ABR?	There is a differential effect of polarity on the speech ABR. Latency measures and amplitude of the F0 response were not different across polarities. The amplitude of the F1 and HF components was reduced in the alternating polarity condition.
Parbery-Clark et al. (2013)	30 adults (ages 18-22; 19 women) Normal hearing. Divided into musicians and non-musicians.	Standard /da/ presented at 70 dB SPL, left ear, right ear and diotically. Vertical montage Offline Bandpass filtered: 70 to 2000 Hz 6000 trials	To what extent does binaural processing contribute to the speech in noise listening advantage evident in musicians?	Musicians' had better speech-in-noise perception in the diotic but not the monaural conditions.
Skoe and Kraus (2013)	770 people (ages 0.25-72.41 years) Normal hearing. Divided into musicians and non-musicians.	Standard /da/ at 80 dB SPL, alternating polarities at 10.9 Hz. 6000 trials	Is experience-dependent plasticity enhanced during periods of developmental change?	Experience-dependent plasticity is greatest during critical periods in development, for certain components of the speech ABR including onset latency, high-frequency phase-locking, and response consistency.

Appendix One. Table of Studies Using the 40ms /da/ Stimulus Continued

Authors (Year of Publication)	Subjects	Speech ABR Collection Protocol	Research Question(s)	Conclusions
Ahadi et al. (2014a)	48 adults (ages 20-28 years, mean =22.8; 25 women) Persian speakers, normal hearing, right handed.	Standard /da/ presented at 80 dB SPL, binaurally, alternating polarities at 10.9 Hz. Vertical montage Bandpass filtered: 100 to 2000 Hz 6000 trials	Are there differences in the speech ABR for men and women?	Women had earlier and larger onset responses as well as more robust and better representation of fundamental and first formant frequency information.
Ahadi et al. (2014b)	48 adults (ages 20-28 years, mean =22.8; 25 women) Persian speakers, normal hearing, right handed.	Standard /da/ presented at 80 dB SPL, left ear, right ear and diotically, alternating polarities at 10.9 Hz. Vertical montage Bandpass filtered: 100 to 2000 Hz 6000 trials	What are the effects of stimulus presentation mode and ear of presentation on the speech ABR?	Shorter right ear latency were observed two peaks, but response timing was similar across presentation modes. Binaural stimulation resulted in a response of larger amplitude. No real evidence of lateral asymmetry.

Appendix One. Table of Studies Using the 40ms /da/ Stimulus Continued

Authors (Year of Publication)	Subjects	Speech ABR Collection Protocol	Research Question(s)	Conclusions
Jafari and Malayeri (2014)	Group 1: 26 adults (ages 26-40 years, mean =35; 10 women) Congenitally blind, Hearing ≤25 dB HL Group 2: 24 adults (ages 26-40 years, mean = 33; 10 women) Normal sighted, normal hearing. All Persian speakers, right handed	Standard /da/ presented at 80 dB SPL, alternating polarities at 10.9 Hz. Vertical montage Bandpass filtered: 100 to 2000 Hz 4000 trials	What are the effects of congenital blindness on the speech ABR?	The blind subjects had earlier and larger responses to the /da/ syllable with better responses observed for both the onset and FFR.
Jafarpisheh et al. (2014).	40 adults (ages 20-28 years, mean =22.8; 18 women) Persian speakers, normal hearing, right handed	Standard /da/ presented at 80 dB SPL, binaurally, alternating polarities at 10.9 Hz. Vertical montage Bandpass filtered: 100 to 2000 Hz 6000 trials	Can the speech ABR be modelled using fuzzy logic?	Nonlinear fuzzy based dynamic extraction of the signal is a valid approach for generating features of the speech ABR.

Appendix One. Table of Studies Using the 40ms /da/ Stimulus Continued

Authors (Year of Publication)	Subjects	Speech ABR Collection Protocol	Research Question(s)	Conclusions
Neupane et al. (2014)	Group 1: 42 adults (ages 18-30) Group 2: 42 adults (ages 40-60)	Standard /da/ at 80 dB SPL, alternating polarities at 15.4, 10.9 and 6.9 Hz. Vertical montage Bandpass filtered: 100 to 3000 Hz 2000 artefact-free trials	Is there a difference between the effect of repetition rate on the speech ABR in younger and middle aged individuals?	Wave V was prolonged for middle-aged individuals for all three-repetition rates and increasing the repetition rate to 15.4 detrimentally affected the encoding of F_0 in middle-aged individuals, compared to presentation at 6.9 Hz.
Shetty et al. (2014)	23 adults divided into groups based on ANL score.	40 ms /da/ (not described) presented at 65 dB nHL, alternating polarities at 7.1 Hz. Vertical montage Bandpass filtered: 100 to 3000 Hz 2000 trials	Is there a relationship between acceptable noise level, speech ABR and cortical signal to noise ratios?	No differences were found in SNRs in the waveforms of the speech ABR and LLR between low and high ANL groups. The amplitude of V-A of the speech ABR and N1-P2 of LLR were both larger in the high ANL group.

Appendix One. Table of Studies Using the 40ms /da/ Stimulus Continued

Authors (Year of Publication)	Subjects	Speech ABR Collection Protocol	Research Question(s)	Conclusions
Tahaei et al. (2014)	Group 1: 25 adults with PDS (ages 16-35, mean = 24.5 years; 4 women) Group 2: 25 fluent adults (ages 16-35 years, mean = 22.4; 4 women) Persian speakers, normal hearing, right handed.	Standard /da/ presented at 80 dB SPL, alternating polarities at 10.9 Hz. Vertical montage Bandpass filtered: 100 to 2000 Hz 6000 trials	Does the speech ABR differ from that expected of typical adults for people with persistent developmental stuttering (PDS)?	Subjects with PDS had significantly longer latencies for the onset and offset peaks compared to the control group. There were no differences in the sustained measures.
Ansari and Rangasayee (2015a)	20 adults (ages 18-25 years, mean = 21.3) Divided into normal hearing or hearing impaired. Hindi speakers, right handed.	40 ms Hindi /da/ created per standard /da/ presented at 65 dB SL, alternating polarities at 11.1 Hz, Vertical montage Bandpass filtered: 100 to 3000 Hz 4000 trials	Can an appropriate Hindi /da/ be created to elicit the speech ABR?	The onset responses for normal hearing adults were statistically different from individuals with hearing loss. Sustained measures were not reported.
Ansari and Rangasayee (2015b)	50 adults (ages 18-25 years, mean = 21.3) Hindi speakers, right handed, hearing thresholds ≤25 dB HL	40 ms Hindi /da/ As above	What does the Hindi /da/ evoked speech ABR look like for typical adults?	Onset and sustained components of the speech ABR to a Hindi /da/ are comparable to those detailed in western reports.

Appendix One. Table of Studies Using the 40ms /da/ Stimulus Continued

Authors (Year of Publication)	Subjects	Speech ABR Collection Protocol	Research Question(s)	Conclusions
Archana et al. (2015)	13 adults (ages 18-65) Moderate flat level of SNHL.	40 ms /da/ (not described) presented at 60 to 90 dBnHL,	What does the latency-intensity function of the speech ABR look like in adults with a moderate level of SNHL hearing loss?	The onset response of the speech ABR is better suited to exploring recruitment than using click or tone ABR, as the L-I function slope is steeper. No analysis of sustained measures presented.
Lehmann et al. (2015)	Groups 1: 10 congenital amusic adults (7 females) Group 2: 11 matched adults (10 females)	Standard /da/ presented at 70 dB SPL, alternating polarities at 11.1 Hz. Vertical montage 6000 trials	Are impairments in musical abilities visible in the speech ABR?	Fine-grained processing of sound differs from the normal range in people with congenial amusia. There is a decrease in spectral encoding and slower onset responses.
Mishra et al. (2015)	Group 1: 12 adults (ages 18-26; 5 women). Group 2: 12 adults (ages 18-26; 5 women) no acoustic reflexes. All with normal hearing	40 ms /da/ not described, rarefaction poliarity at 10.9 Hz Bandpass filtered: 100 to 3000 Hz 6000 trials	What does the speech ABR look like in people with normal hearing but absent acoustic reflexes?	No differences found between the two groups.

Appendix One. Table of Studies Using the 40ms /da/ Stimulus Continued

Authors (Year of Publication)	Subjects	Speech ABR Collection Protocol	Research Question(s)	Conclusions
Skoe et al. (2015a)	586 people (ages 0.25-72.4 years) Normal hearing.	Standard /da/ presented at 80 dB SPL, alternating polarities at 10.9 Hz. Vertical montage Bandpass filtered: 100 to 2000 Hz 6000 trials	What does the speech ABR look like across different age groups?	Developmental changes occur up to around age 11 years, changes also start to occur after age 50 years.
Uppunda et al. (2015)	15 adults (ages 17-25 years; 8 women) Normal hearing.	Standard /da/ presented at 80 dB SPL, alternating polarities at 7.1 Hz. Vertical montage Bandpass filtered: 30 to 3000 Hz 6000 trials	What are the characteristics of the binaural interaction component (BIC)for the speech ABR?	The BIC can be reliably recorded using the speech ABR. The onset BIC was present in all recordings but the BIC for the FFR was only present in ~75% of subjects.
Ansari and Rangasayee (2016)	Group 1: 25 adults (ages 18-25, mean = 20.9; 11 women) Normal hearing thresholds Group 2: 10 adults (ages 18-25, mean = 21.3; 4 women). Flat, mild level of SNHL .	Hindi 40 ms /da/, presented at 65 dB SL, alternating polarity at 11.1 Hz. Vertical montage Bandpass filtered: 100 to 3000 Hz 4000 trials	Can a corpus of Hindi syllables be created to elicit the speech ABR and is thera a difference for people with and without hearing loss?	The onset responses for normal hearing adults were statistically different from individuals with hearing loss. Sustained measures were not reported.

Appendix One. Table of Studies Using the 40ms /da/ Stimulus Continued

Authors (Year of Publication)	Subjects	Speech ABR Collection Protocol	Research Question(s)	Conclusions
Lagacé et al. (2016)	43 adults (ages 18-30 years) French speaking, normal hearing thresholds.	40 ms /da/ not described, presented at 60 dB HL.	Is there a link between speech ABR and words-in- noise (WIN) recognition?	Increase in the latency,decrease in the amplitude of the onset response when presented in noise. There was no apparent link between the WIN scores and the speech ABR results.
Zakaria et al. (2016)	Group 1: 15 Chinese adults (ages 21-25 yrs, mean = 23.1; 0 women) Group 2: 15 Malay adults (ages 21-25 years, mean = 22.3; 0 women) Right handed, normal hearing.	Standard /da/ presented through headphones (?), at 80 dB nHL, at 10.9 Hz Vertical montage Bandpass filtered: 100 to 1500 Hz 3584 trials	Is the speech ABR influenced by ethnicity?	No differences were found between Malay and Chinese adults for onset, sustained and offset responses for Malay and Chinese subjects. There were differences between reported results for Caucasian subjects.
Kumar et al. (2017)	Group 1: 15 adults (ages 18-25 years, mean = 23.3) Rock musicians with normal hearing. Group 2: 15 adults (ages 18-25 years, mean = 24.8) Normal hearing.	Standard /da/ presented at 80 dB SPL, rarefaction polarity at 10.9 Hz. Vertical montage Bandpass filtered: 100 to 3000 Hz 6000 trials	What does the speech ABR look like for rock musicians compared to non musicians?	Rock musicians had significant earlier latencies of the onset response and higher amplitude of encoding of F0 than non musicians.

Appendix One. Table of Studies Using the 40ms /da/ Stimulus Continued

Authors (Year of Publication)	Subjects	Speech ABR Collection Protocol	Research Question(s)	Conclusions
Skoe et al. (2017)	32 adults (ages 18-30 years, mean = 21) Monolingual American English speaker, normal hearing.	Standard /da/ presented at 80 dB SPL, alternating polarities at 10.9 Hz. Vertical montage Bandpass filtered: 100 to 2000 Hz 6000 artefact-free trials	Is the ABR linked to reading ability in adults?	Reading ability in adulthood related to ABR Wave V latency (click and speech evoked ABR).
Jalaei et al. (2017)	29 Malay adults (ages 19-30 years, 15 women). Right handed, normal hearing.	Standard /da/ presented at 80 dB SPL, alternating polarities at 10.3 Hz. Vertical montage Bandpass filtered: 100 to 2000 Hz 6000 trials	Is there a difference in the speech ABR between men and women and can this be accounted for by head size?	Differences were found between the transient but not the sustained components of the speech ABR. These differences could only partially be accounted for by head size.
Sanju et al. (2017a)	Group 1: 15 Healthy Indian people (ages 15-25 years). Group 2: 15 Healthy Indian people (ages 40-60 years) Normal hearing to 4000Hz. Sex not stated.	40 ms /da/ presented through earphones at 80 dB SPL, rarefaction polarity at 10.9 Hz. Vertical montage Bandpass filtered: 100 to 2000 Hz 6000 trials	Is there a difference in the speech ABR between young and middle aged people?	Wave V was later in the middle aged people. Encoding of F1 and F2 was less robust in the middle aged people. There are some differences in speech encoding between young and middle aged people, with middle aged people having poor encoding of certain features.

Appendix One. Table of Studies Using the 40ms /da/ Stimulus Continued

Authors (Year of Publication)	Subjects	Speech ABR Collection Protocol	Research Question(s)	Conclusions
Sanju et al. (2017b)	Group 1: 11 Healthy Indian adults (ages 40-55 years). Group 2: 11 Indian adults with a diagnosis of diabetes mellitus type II (ages 40-55 years) Mean age for total population tested 48.27 years. Right handed, normal hearing. Sex not stated.	40 ms /da/ presented through earphones at 80 dB SPL, rarefaction polarity at 10.9 Hz. Vertical montage Bandpass filtered: 100 to 2000 Hz 6000 trials	Is there a difference in the speech ABR between healthy adults and those with diabetes mellitus type II?	No differences were found between right and left ears, so data collapsed. All waves of the speech ABR were found to be significantly delayed in latency for adults with diabetes mellitus type II, compared to the healthy adult control group.

Appendix Two. Treatment as Usual in Ritson Clinic (Abbreviated)

This applies to admissions for alcohol detox only.

On admission:-

- Breathalysed and oral fluid drug screen taken. If suspicion of recent drug use / intoxication instant dip drug screen done
- Observations (P, BP, T) & MUST (weight)
- Nurse clerking
- Doctor clerking – includes MSE and full physical
- Offered BBV screening if relevant
- Bloods – U&E, LFT including GGT, glucose, FBC, clotting. B12/folate if indicated. If very underweight Mg, Phosphate, Ca (on days 1 and 4 of stay)
- Doctor writes up usual medication

Then started on Chlordiazepoxide (occasionally Oxazepam if liver function bad, approximately equivalent). WAIT until BAC coming down and starting to withdraw (but not too long)

If significant withdrawal, start Day Zero – 30mg Chlordiazepoxide qds plus 10-30mg PRN (up to 240mg total). This may need repeating.

Then use yellow pre-printed reducing schedule Days 1-6.

Acamprosate offered for neuroprotection (2 weeks from admission).

Offer im/iv Pabrinex unless particularly well-nourished (always offer this). Give iv if no muscle, preferred by patient or serious concerns. Routinely change this to oral thiamine 300mg daily after 3 days – unless ongoing symptoms such as confusion when parenteral should be continued.

Dose: 1 pair daily for 3 days for prophylaxis

2 pairs bd for up to 5 days (rarely more) if treatment

Other medication routinely prescribed includes metoclopramide (oral or im), loperamide, paracetamol (and REH symptomatic relief). Rectal diazepam is also prescribed in case of seizure.

Occasionally carbamazepine is used if very high risk seizures (previous history, concomitant benzodiazepine use). This may be started on admission or in week prior.

If a patient is prescribed opioids or benzos as replacement therapy, these will be continued (amnesty form signed if unsupervised)

Haloperidol is prescribed only if develop DTs (very rare)

Other medical or psychiatric problems are managed as appropriate. Unless impossible, changes in psychotropic medication will not be made until about 3 weeks sober (in community)

Patients are offered disulfiram and/or one of the anti-craving agents. They will be given written information as well as advice unless problems reading.

- **Disulfiram** (licensed) 200mg daily, supervised, and can be taken Mon, Wed, Fri (400mg, 400mg, 600mg). Dose may be increased if previously drunk on it and no reaction. If side effects, or significant neuropathy, may use 100mg daily.

Contra-indications – severely abnormal LFTs / jaundice; cardiac disease (recent, may need ECG); neuropathy (should be warned). If on antihypertensives, discuss and record increased danger of reaction (sign disclaimer).

- **Acamprosate** (licensed) 666mg tds. Started any time after arrival. Not used if previously ineffective / severe liver disease (rare)
- **Naltrexone** (licensed recently) 50mg daily. Possibly more effective at reducing heavy drinking, so used more in out-patients. Contra-indicated if moderately abnormal LFTs, or if taking any opioid-containing medications
- **Baclofen** (unlicensed) starting dose 5-10mg tds. Generally offered 3rd line, but may be requested by patients, or suggested by community staff if anxiety thought to be a major relapse issue. Timing – currently trying to delay this for 4 weeks (not always possible)

Duration of most admissions is 7-10 days if uncomplicated, more if required.

Rebecca Lawrence

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Appendix Three. Table of ABR and Alcohol Studies

Authors (Year of Publication)	Participants	Click ABR Collection Protocol	Research Question(s)	Conclusions
Stockard et al. (1976)	2 male patients with CPM. Patient 1: 51 years old, 33 year history of alcohol dependency Patient 2: 48 years old, 30 year history of alcohol dependency Hearing status not described.	0.1 msec click at 60 dB SL (or higher), presented at 10 Hz through headphones. Vertical montage Bandpass filtered: 100 to 3000 Hz 6000-12000 artefact-free trials	Can the click ABR be used to aid the diagnosis of CPM?	ABRs were recorded serially and it was found that there was slowed conduction velocity in the ascending pontine auditory pathway (increased interpeak latency for I-V, outside normal limits). It is possible to monitor the progress of demyelination or remyelination to aid with prognosis.
Squires et al. (1978)	6 adult males (age not stated), classified as social drinkers. Normal hearing stated but not tested.	0.5 msec click at 55 and 75 dB above threshold for normal hearing, presented at 10 Hz through headphones. Vertical montage Bandpass filtered: 100 to 3000 Hz 4096 trials	What are the acute effects of alcohol on the ABR?	No effect seen on wave I, but increases in latencies for waves II through V. However, latencies remained within normal limits.

Appendix Three. Table of ABR and Alcohol Studies Continued.

Authors (Year of Publication)	Participants	Click ABR Collection Protocol	Research Question(s)	Conclusions
Chu and Squires (1980)	52 patients with ADS (ages 20-75 years, mean = 47; 13 women) 26 patients had one neurological complication and 18 had more than one. Less than severe level of bilateral loss.	0.1 msec click at 65, 75 and/or 85 dB above threshold for normal hearing, presented at 10 Hz through headphones. Vertical montage Bandpass filtered: 150 to 3000 Hz 4000 trials	What is the prevalence of brainstem abnormalities* in people with ADS? *Increased I-V interval only	Nearly half had abnormal interpeak interval for I-V. 12% of patients with no neurological complications had abnormal ABRs. The prevalence increased with increasing number of neurological complications. All patients with three or more complications had abnormal responses.
Rosenhamer and Silfverskiöld (1980)	13 patients with ADS and slow tremor (ages 33-59 years, mean = 47.5; sex not stated). 7 had normal hearing and 6 had a mild-moderate, high frequency hearing loss. 10 healthy adults (ages 40-63 years) with normal hearing.	0.125 msec click at 60 or 80 dB SL (or higher), presented at 20 Hz through headphones. Vertical montage Bandpass filtered: 180 to 4500 Hz 4000 trials	Can the ABR* be used in conjunction with the presence of slow tremour to provide objective evidence of lesions? *Increased I-V interval only	Compared to healthy age matched controls, the group had longer wave I-V interpeak intervals. Ten patients had I-V intervals outside normal limits. Wave I was within normal limits. The ABR can be used to detect lesions in other systems alongside those found in the motor system.

Appendix Three. Table of ABR and Alcohol Studies Continued.

Authors (Year of Publication)	Participants	Click ABR Collection Protocol	Research Question(s)	Conclusions
Yufe et al. (1980)	Case study of 49 year old woman with ADS. Unable to perform PTA, ARTs present at 1 and 2 KHz bilaterally.	0.083 msec click at 90 dB nHL presented at 10 Hz through headphones. Vertical montage Bandpass filtered: 100 to 3000 Hz 8000 trials	Are the results of CT scan and ABR in agreement in the diagnosis of CPM?	Normal ABR for waves I-III bilaterally, no waves detected after III. CT scan found an area of decreased density at the area of the pons. ABR results and CT scan results in agreement.
Begleiter et al. (1981)	17 patients with ADS (age 38 ±2.1 years, all male). Dependent drinking history of 6-16 years. 17 age and education matched healthy males. Hearing status not described.	0.5 msec click at 70 dB above threshold for normal hearing, presented at 10 Hz through headphones. Vertical montage Bandpass filtered: 100 to 2000 Hz 2000 trials	What does the ABR look like in people with ADS but no overt clinical signs?	There were significant differences in the ABRs between the ADS group and the healthy controls, apart from wave I. There is increased neural transmission time in the brainstem of people with ADS.
Chu et al. (1982)	66 patients with ADS (mean age 44.8 years, 15 women). 17 had no neurological complications. Dependent drinking history of 6-50 years. Threshold ABR to check hearing, those with moderate to severe levels of loss excluded.	0.1 msec click at 65-85 dB nHL, presented at 11 Hz through headphones. Vertical montage Bandpass filtered: 100 to 3000 Hz 4000 trials	Do ABR results correlate with other data for people with ADS?	Incidence of abnormal ABRs =41% (increased wave I-V interval), often unilateral. When no neurological signs, 12% of ABRs abnormal. Increase in the incidence of abnormal ABRs with increasing number of neurological complications. CT scan results correlated with the ABR results.

Appendix Three. Table of ABR and Alcohol Studies Continued.

Authors (Year of Publication)	Participants	Click ABR Collection Protocol	Research Question(s)	Conclusions
Church and Williams (1982)	9 adult males (ages 22-34), classified as social drinkers. Screened for normal hearing.	0.1 msec, rarefaction click at 60 dB nHL presented at 10 Hz through headphones. Vertical montage Bandpass filtered: 100 to 3000 Hz 4096 trials	What are the acute effects of dose and time of alcohol administration on the ABR?	Statistically significant changes in latencies of wave V over time. Higher alcohol does resulted in longer latency and longer lasting latency shifts. Ethanol has a depressive effect on sensory pathways.
Reilly et al. (1983)	33 patients with ADS (age and sex not reported). 28 healthy controls. Hearing status not described.	Positive polarity clicks, at 70dB- 103dB SL Vertical montage Bandpass filtered: 150 to 3000 Hz 2048 trials	Does the ABR for people with ADS differ from healthy control and does it change over a period of abstinence?	No differences found in the ABR between the healthy controls and patients with ADS, except for visual inspection of morphology. Morphology had returned to normal after 3 weeks of abstinence.
Sztencel et al. (1983)	Case study of 28 year old man with ADS, admitted to hospital with suspected CPM. Severe level of hearing loss in left ear but no hearing testing performed.	Click presented at 80 dB, alternating polarity and presented at 10 Hz. Vertical montage Bandpass filtered: 32 to 3000 Hz	Are the results of CT scan and ABR in agreement in the diagnosis of CPM?	Increased wave I-V interpeak interval which returned to within normal after 32 weeks. Serial CT scans over the same time period showed regression of a hypodense pontine lesion. CT scan and ABR results were complementary methods of confirming CPM. ABR results more closely followed the clinical recovery.

Appendix Three. Table of ABR and Alcohol Studies Continued.

Authors (Year of Publication)	Participants	Click ABR Collection Protocol	Research Question(s)	Conclusions
Chan et al. (1985)	56 male patients with ADS (ages 25-63 years), of which 24 had evidence of cerebellar degeneration. Dependent drinking history of 10-30 years. 25 patients with WKS (ages 42-70, 4 women). Dependent drinking history of 10-35 years. 77 healthy adults (ages 18-69 years, 40 women). PTA performed and all hearing thresholds ≤20 dB HL.	0.1 msec, rarefaction click at 65-75 dB SL, presented at 12 Hz through headphones. Vertical montage Bandpass filtered: 100 to 3200 Hz 2000 trials	What is the incidence and nature of ABR abnormalities in people with ADS, with or without WKS.	Increased I-V interval in all patient groups. 13% of patients with ADS but neurological signs had abnormal ABRs. 25% of patients with ADS and cerebellar degeneration had abnormal ABRs. 48% of people with ADS and WKS had abnormal ABRs. Wave I-III interval was prolonged in 32% of patients with WKS but only in 6% of patients with ADS but no WKS. A prolongation of wave I-III may be a marker for WKS.
Chu (1985)	45 people with ADS (13 had been abstinent for 2-10 years) (ages 20-79, male to female ratio of 3:1) Dependent drinking history of 7-50 years. Threshold ABR performed to evaluate hearing.	0.1 msec condensation, click at 65-85 dB nHL, presented at 11 Hz through headphones. Vertical montage Bandpass filtered: 100 to 3000 Hz 4000 trials	Do ABR results correlate with CT scan results?	53% had abnormal ABRs. 31% of abstainers had abnormal ABRs. Those with abnormal ABRs had more instances of cerebral or cerebellar atrophies on CT scan. People with abnormal ABRs had increased size of brainstem cisterns.

Appendix Three. Table of ABR and Alcohol Studies Continued.

Authors (Year of Publication)	Participants	Click ABR Collection Protocol	Research Question(s)	Conclusions
Pfister et al. (1985)	4 patients with alcohol related CPM.	No Description	Can the click ABR be used to aid the diagnosis of CPM?	The authors state that the ABR results were normal but that the form of CPM was mild.
Hammond et al. (1986)	25 patients with WKS (ages 42-70 years, 4 women). Dependent drinking history of 10-35 years. 20 patients with MS (ages 18-45 years, 11 women) 77 healthy controls (ages 18-69 years, 40 women). PTA performed, all subjects had normal hearing.	0.1 msec clicks, at 65dB SL, alternating polarity at 12Hz. Vertical montage Bandpass filtered: 100 to 3200 Hz 2000 trials	Does using condensation or rarefaction stimuli have an effect on the ABR in people with WKS or MS?	40-48% of patients with WKS had ABR abnormalities, usually in the I-III interpeak interval. 50% of MS patients had ABR abnormalities, usually in the III-V interpeak interval. Diagnosis of abnormalities may be present on one polarity click e.g. rarefaction and not the other.
Mossuto et al. (1986)	Case study of 53 year old male with ADS, admitted to hospital with suspected CPM. Hearing status not reported.	Not reported	Are ABRs useful in diagnosis of CPM?	ABR recorded 41/2 months after initial admission. Increased interpeak intervals found for Waves III-V and I-V, bilaterally. Same result on recording after a further two weeks. ABR results are abnormal in CPM.

Appendix Three. Table of ABR and Alcohol Studies Continued.

Authors (Year of Publication)	Participants	Click ABR Collection Protocol	Research Question(s)	Conclusions
Chu and Yang (1987)	41 patients with ADS & liver disease. 17: minimally abnormal liver function tests, 11: liver disease but no hepatic encephalopathy (HE), 9: liver disease and grade 1/2 HE, 4 had liver disease and grade 3/4 HE. 18 healthy control participants. Hearing status not reported.	0.1 msec rarefaction, click at 60-80 dB SL, presented at 10 Hz. Vertical montage Bandpass filtered: 100 to 3500 Hz 2000 trials	What clinical factors influence the ABR in people with ADS?	Interpeak latencies for people with ADS were delayed but mean value was still within normal limits. Significant difference found in the absolute latencies for waves III and V. There was no difference between the groups. Hepatic failure does not affect the ABR.
Lille et al. (1987)	11 males with ADS (mean age =36 years). Average dependent drinking history of 11 years. 20 healthy ages matched males as a control group. Hearing status not reported.	0.1 msec clicks, at 20dB SL, alternating polarity at 11.1Hz. Vertical montage Bandpass filtered: 30 to 3000 Hz 2000 trials	What is the effect of chronic alcohol intake and short term abstinence on the ABR?	Abnormal I-V interpeak intervals in 2 (18%) individuals who also had nystagmus-clinical sign of brainstem dysfunction.
Nickel and Riedel (1987)	29 male patients with KS (mean age =50 years) 30 healthy, control male participants (mean age =31 years) PTA found normal thresholds between 0 and 2000Hz.	0.1 msec clicks, at 70dB HL, alternating polarity at 20 Hz. Vertical montage Bandpass filtered: 100 to 3000 Hz 2000 trials	Is the ABR useful in identifying subclinical deficits in brainstem function?	Increased interpeak latencies form peak II onwards for the patient group. There is value in looking at wave I-VI in this group.

Appendix Three. Table of ABR and Alcohol Studies Continued.

Authors (Year of Publication)	Participants	Click ABR Collection Protocol	Research Question(s)	Conclusions
Spitzer and Newman (1987)	14 people with ADS (ages 25-49 years). Dependent drinking history of 6-32 years. PTA performed and normal for age. 14 healthy controls (ages 23-34 years).	Alternating polarity click at 70 dB SL, presented at 11.3 or 31.3 Hz. Vertical montage Bandpass filtered: 150 to 3000 Hz 2000-4000 trials	What are the ABRs of newly detoxified people with ADS?	There were no significant differences between the ABRs from patients with ADS and healthy controls. The morphology of waveforms in patients with ADS was poorer.
Lille et al. (1988)	26 patient with ADS (mean age =35 years, 1 woman). Average dependent drinking history of 35 years. 13 patients exposed to lead 9 patients exposed to mercury 20 healthy male controls (mean age = 37 years) Hearing status not reported.	0.1 msec clicks, at 60dB SL, alternating polarity at 11.1Hz. Vertical montage Bandpass filtered: 30 to 3000 Hz 4000 trials	What are the effects of lead and mercury on ABRs?	Only one abnormality (increased I-V interpeak interval) found in one patient who had been exposed to lead and was a chronic, heavy drinker.
Erkulwater and Condon (1989)	2 males with Wernicke's Disease. Case 1, age 55 and 36 year drinking history. Case 2, age 57. Hearing tests unable to be performed due to unreliable responses.	0.1 msec clicks, at 90-103dB, alternating polarity at 15.1Hz. Vertical montage Bandpass filtered: 100 to 1500 Hz 2000-4000 trials	How does the ABR change over time during recovery from Wernickes Disease?	Initially only wave I identifiable, waves II-V emerged during the following 3 weeks and absolute latencies became gradually shorter. The ABR returned to within normal for case 1 but not for case 2.

Appendix Three. Table of ABR and Alcohol Studies Continued.

Authors (Year of Publication)	Participants	Click ABR Collection Protocol	Research Question(s)	Conclusions
Diaz et al. (1990)	15 patients with ADS (ages 23-51 years, 2 women). Average dependent drinking history of 8 years. Abstinent for at least 3 days. 15 healthy, age and sex matched controls. Thresholds <65dbSPL	0.1 msec clicks, at 70dB SL, alternating polarity at 11.3Hz. Vertical montage Bandpass filtered: 150 to 3000 Hz 2000 trials	What are the ABRs of people with ADS who are abstinent?	Wave V latencies were significantly later in the patient with ADS. III-V and I-V interpeak intervals were also prolonged but values within normal range.
Meinck et al. (1990)	44 male patients with ADS (ages 37 ± 9 years). Dependent drinking history of 1-25 years) 40 unmatched healthy controls (ages 32 ± 10 years, 23 women). Hearing status not reported.	0.1 msec clicks, at 90dB SL, alternating polarity at 11.3Hz. Vertical montage Bandpass filtered: 100 to 3000 Hz 2000 trials	What are the effects of ADS on the ABR?	Latencies of waves I, III and V and interpeak intervals I-V were significantly prolonged in the patient group. 18 patients (45%) had delayed ABR components. There are subclinical disturbances in afferent information processing in patients with ADS.
Menger and Jörg (1990)	42 patients with alcohol related CPM/EPM (ages 29-83, 17 women). Hearing status not reported	Not reported	Are ABRs useful in diagnosis of CPM?	ABR findings were abnormal in 22 (52%) patients. There was no clear pattern of abnormality.

Appendix Three. Table of ABR and Alcohol Studies Continued.

Authors (Year of Publication)	Participants	Click ABR Collection Protocol	Research Question(s)	Conclusions
Cadaveira et al. (1991)	32 patients with ADS (ages 23-57 years, sex not reported). Dependent drinking history of 8-30 years). 32 healthy age and sex matched controls. Hearing status not reported.	0.1 msec clicks, at 110dBpeSPL, alternating polarity at 10Hz. Vertical montage Bandpass filtered: 200 to 3000 Hz 2000 trials	What are the effects of ADS on the ABR?	Latencies of waves V and interpeak intervals III-V and I-V were significantly prolonged in the patient group. 18 patients (56%) had abnormal ABRs.
Haas and Nickel (1991)	22 patients with WE, 28 patients with delirium tremens. 30 healthy controls. Hearing status not reported.	Clicks, at 70 dB HL, alternating polarity at 20Hz. Vertical montage Bandpass filtered: 100 to 3000 Hz 2000 trials	Can the ABR be used to aid early diagnosis of WE?	Significant difference in interpeak intervals of I-III and I-V were found between healthy adults and those with WE. Interpeak interval I-V was greatest in those with WE but those with delirium tremens also had a significantly prolonged interval compared to healthy controls. The ABR can aid early diagnosis of WE.

Appendix Three. Table of ABR and Alcohol Studies Continued.

Authors (Year of Publication)	Participants	Click ABR Collection Protocol	Research Question(s)	Conclusions
Cadaveria et al. (1992)	32 male patients with ADS (ages 23-57). Dependent drinking history of >8 years. 32 age and sex matched healthy controls. Hearing status not reported.	0.1 msec clicks, at 110dBpeSPL, alternating polarity at 10Hz. Vertical montage Bandpass filtered: 200 to 3000 Hz 2000 trials	What are the effects of age on the ABR of people with ADS?	The patients had significantly longer Wave V latencies and increased III-V and I-V intervals compared to the controls. There was no effect of age on the ABRs. 15 patients (47%) had abnormal ABRs.
Worner and Lechtenberg (1992)	203 patients with ADS (ages 36.0 ±11.01 years for women and 41.6 0 ±10.01 years for men, 70 women).Average dependent drinking history >20 years. Hearing status not reported.	Not reported	Are there differences in the ABRs for men and women with ADS?	Although the women had shorter latencies than men, all results were within normal limits.

Appendix Three. Table of ABR and Alcohol Studies Continued.

Authors (Year of Publication)	Participants	Click ABR Collection Protocol	Research Question(s)	Conclusions
Cadaveria et al. (1994)	34 male patients with ADS (ages 23-56 years). Dependent drinking history of ≥8 years. 12 remained abstinent for 1 year. 34 age and sex matched controls. Hearing status not reported.	0.1 msec clicks, at 110dBpeSPL, alternating polarity at 10Hz. Vertical montage Bandpass filtered: 200 to 3000 Hz 2000 trials	Does the ABR in people with ADS change over a one year period of abstinence?	Patients had significantly longer Wave V latencies and increased III-V and I-V intervals compared to the controls. There was a significant reduction in these latencies after a year, with most differences between 5 and 12 months. Wave V still remained later in patients than for controls. Of the 12 patients that underwent longitudinal testing 2 (17%) had abnormal ABRs after 12 months. There was no effect of age on the ABRs.
Kuruoglu et al. (1996)	40 male patients with ADS (mean age= 37.5 years). Average dependent drinking history of 17.4 years. 10 healthy age matched controls Hearing status not reported.	Stimulus presented at 60dB SL, at 10Hz. Vertical montage Bandpass filtered: 100 to 5000 Hz 4000 trials	Do ABR results correlate with CT scan results?	Waves III and V as well as interpeak intervals I-III, III-V and I-V were significantly prolonged in patients. 17.5% of patients had abnormal ABRs. There was no correlation between CT scan findings and ABR results.

Appendix Three. Table of ABR and Alcohol Studies Continued.

Authors (Year of Publication)	Participants	Click ABR Collection Protocol	Research Question(s)	Conclusions
Nicolás et al. (1997)	40 male patients with ADS (mean age=42.6 ±9.1). Average dependent drinking history of 26.4 ±8.2 years. 20 age and sex matched healthy controls. Hearing status not reported.	0.1 msec clicks, at 90 dBpeSPL, rarefaction polarity at 11.7Hz. Vertical montage Bandpass filtered: 150 to 3000 Hz 1000 trials	Is brain impairment related to ethanol intake?	Waves I, III and V as well as interpeak intervals I-III, III-V and I-V were significantly prolonged in patients. 7 patients (17.5%) had an abnormal wave V. Presence of abnormalities was related to the total lifetime dose of ethanol.
Niedzielska et al. (2001)	30 patients with ADS (ages 26-55 years, mean =43.6 years). Dependent drinking history of 5-30 years. Abstinent for 1-9 months. PTA performed, to allow for correction for presbyacusis.	0.125 msec clicks, at 90 db nHL, at 30Hz.	Is there evidence of hearing dysfunction in people with ADS?	Wave I prolonged in 28 ears, wave III prolonged in 50 ears and V prolonged in 54 ears.Interpeak intervals I-III, III-V and I-V were significantly prolonged in patients. I-V was prolonged in 41 ears. There is evidence of hearing dysfunction in people with ADS.

Appendix Three. Table of ABR and Alcohol Studies Continued.

Authors (Year of Publication)	Participants	Click ABR Collection Protocol	Research Question(s)	Conclusions
Mochizuki et al. (2003)	9 male patients with alcohol related CPM (ages 34-65 years). Dependent drinking history of 1 to 39 years. 14 male patients with ADS (mean age= 50.3 years) 14 healthy male controls (mean age= 50.4 years). Hearing status not reported.	Click presented at 90dB. Vertical montage Bandpass filtered: 50 to 3000 Hz 2000 trials	How do the ABRs of people with CPM differ from those with ADS and healthy controls?	The I-III interpeak intervals were significantly prolonged in patients with CPM compared to both those with ADS and healthy controls.
Smith and Riechelmann (2004)	19 male patients with high risk/dangerous alcohol consumption (ages 40-69 years). 19 males patients with low risk/risky alcohol consumption (ages 35-68 years). PTA assessed and patients had normal hearing for age.	Clicks, at 90 dB SPL above threshold, alternating polarity at 20Hz. Vertical montage Bandpass filtered: 100 to 1500 Hz 2000 trials	Does cumulative lifelong alcohol consumption alter the ABR?	Patients with a high risk/dangerous drinking profile had significantly longer latencies of peaks III and V, as well as prolonged interpeak intervals for I-III and I-V compared to those with a low risk/risky drinking profile. ABR peak laetncies increase nonlinearly with increased cumulative, lifelong alcohol consumption.

Appendix Three. Table of ABR and Alcohol Studies Continued.

Authors (Year of Publication)	Participants	Click ABR Collection Protocol	Research Question(s)	Conclusions
Verma et al. (2006)	20 patients with ADS (mean age = 44.65 years). Average dependent drinking history = 11.85 years. 20 social drinkers (mean age = 47.60 years) 20 lifetime abstainers (mean age = 45.20 years) PTA performed	Pure tone clicks (?), at 85 and 100 dB, at 11Hz. Bandpass filtered: 150 to 3000 Hz 4000 trials	Is there evidence of hearing dysfunction in people with ADS?	Waves II and V, and the interpeak interval I-V were prolonged in the patients with ADS. 8 patients (40%) had abnormal ABRs. Patients had a statistically significant high frequency hearing loss compared to the control groups.

Appendix Four. History Form

Date completed. . . . . .

by……..(Audiologist)

PERSONAL DETAILS	
Study ID Number	
Date of Birth	
Age	
Occupation	
HEARING AND EARS	
Do you think you have difficulty hearing in either ear?	yes / no
IF YES: When did you first notice the loss?	
Was the loss sudden or gradual?	sudden / gradual
Is it getting worse?	yes / no
Which ear(s) is/are affected?	right / both / left
IF BOTH: which ear is worse	right / left
What concerns you most about your present problem?	
How does your family react?	
Do you have noises in your head or ears?	yes / no
IF YES: which ear(s)	right / both / left
When did the noises start?	
Was the start of the noise	sudden / gradual
Is it getting worse	yes / no
Describe the noise, eg: whistling, etc	
Does the noise throb like your pulse?	
Does anything make it better?	
Does anything make it worse?	
Does it affect your sleep?	yes / no

Appendix Four. History Form Continued

Have you ever had: Ear ache? Discharge from ears? Perforated ear-drum? Other form of ear disorder, if so what? Your ears syringed for removal of wax? IF Yes: Did it cause any trouble with your ears or hearing & what trouble?	Right Left □ □ □ □ □ □ □ □ yes / no
What treatment or other help have you been given for hearing, tinnitus, or other ear disorder? Operations? Hearing aids Specify type(s)? Tablets or medicines (type and dosage)?	 Right - Left - Right - Left -
Other help or treatment?	
HEARING AIDS?	
Do you wear hearing aids?	yes / no
When you were first supplied with a hearing aid?	
Do you wear 1 or 2 aids? If you only have 1, which side is the aid worn on?	1 □ 2 □ right □ left □

Appendix Four. History Form Continued

What type of aids are they?	RIGHT - bodyworn / behind the ear / radio aid / spectacle aid / bone conduction aid LEFT - bodyworn / behind the ear / radio aid / spectacle aid / bone conduction aid
What is the make & model (if known)?	RIGHT – LEFT -
Do you seem to hear better when wearing the aids?	yes / no
Are you happy with your hearing aids & earmoulds?	yes / no
If no, what are you not happy about?	
BALANCE	
Do you suffer from giddiness, dizziness or unsteadiness? If Yes: When did the giddiness start?	yes / no
How long do the attacks last?	
How often do they occur?	
Do they incapacitate you?	yes / no
Do you vomit during the attacks?	yes / no
Is the giddiness started by head or body movements, a particular body position or social situation?	yes / no
Have you had any treatment for vertigo?	yes / no
Any other comments on the giddiness?	

Appendix Four. History Form Continued

GENERAL HISTORY QUESTIONS	
Have you had any of the following illnesses? (what age and any effects on hearing and/or balance?)	Measles? Meningitis? Mumps?
Have you ever had any other serious illness or operation (other than ear operations)? If yes, what?	yes / no
Are you presently receiving treatment involving any medicine or tablets? If yes, what?	yes / no
Have you ever been exposed to noise at work If yes: what kind of noise? How much?	yes / no
Have you ever been exposed to the noise of guns Any noticeable temporary or permanent effects after exposure to gunfire noise (eg : dull hearing/ ringing in the ears)?	yes / no
Have you ever been exposed to any other loud noises, bomb blasts, explosions, etc, which seemed to have some permanent or temporary effect on your hearing (specify)?	yes / no
Have you ever been knocked unconscious or received a serious head injury?	yes / no

Appendix Four. History Form Continued

Are you waiting to see any other specialist? IF YES: who and for what?	yes / no
Is there anyone in your family with a hearing loss, giddiness, or noises in the ears? IF YES: give details?	yes / no
Have you or other members of your family ever had:	Allergies (eg: hayfever, asthma,eczema etc.)? Tuberculosis (TB)? Diabetes? High Blood Pressure? Thyroid disorder? Nervous or psychiatric illness? Travel sickness? Migraine? Kidney disorder? Eyesight disorder? Heart disease? Fits?
Have you had any of the following treatments in the past?	Quinine or other drugs for malaria? Antibiotics by injection other than penicillin? Diuretics (to make you pass more water)? Aspirin in large or regular doses? Any drugs producing dizziness or ringing in the ears?

Appendix Four. History Form Continued

Do you smoke?	yes / no
Would you consider yourself to be a musician or have musical training? If yes, when and for how long?	yes / no
Is English your first language? Are you fluent in any other languages?	yes / no
What is your highest level of education/qualification?	
Are you Right or Left Handed?	
Do you have any other problems that you would like to mention? (e.g.: learning, physical disabilities or emotional problems)	

Appendix Five. NHS Ethical Approval

Part of the research infrastructure for Wales funded by the National Institute for Social Care and Health Research, Welsh Government.
Yn rhan o seilwaith ymchwil Cymru a ariannir gan y Sefydliad Cenedlaethol ar gyfer Ymchwil Gofal Cymdeithasol ac Iechyd, Llywodraeth Cymru

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Mrs Christine Johnson
Speech and Hearing Sciences
Queen Margaret University
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EH21 6UU

19 January 2015

Dear Mrs Johnson

Study title: **Does the measurement of auditory brainstem responses (ABRs) in people with alcohol dependence syndrome, provide a useful means to document neurological change and monitor the beneficial impact of abstinence?**
REC reference: **15/WA/0019**
IRAS project ID: **156480**

Thank you for your email of 17 December 2014. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 3 December 2014.

Documents received

The documents received were as follows:

Document	*Version*	*Date*
GP Letter	2	16 January 2015
Participant consent form	2	16 January 2015
Participant information sheet	2	16 January 2015
Research protocol (inc. monitoring form)	2	16 January 2015

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	**Version**	**Date**
Covering letter on headed paper	1	07 January 2015
Evidence of Sponsor insurance or indemnity	1	14 August 2014
GP Letter	2	16 January 2015

IRAS Checklist XML		07 January 2015
Non-validated questionnaire [Hearing History Questionnaire]	1	02 June 2014
J White CV	1	17 December 2014
J Gill CV	1	
Participant consent form	2	16 January 2015
Participant information sheet	2	16 January 2015
REC Application Form	1	07 January 2015
Research protocol (inc. monitoring form)	2	16 January 2015
Summary CV for Chief Investigator C Johnson	1	
Summary CV for supervisor J Watson CV	1	
Flowchart of protocol	1	02 June 2014

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

15/WA/0019 **Please quote this number on all correspondence**

Yours sincerely

Sue Byng

Ms Sue Byng
REC Manager

CC: *Karen Haggart, NHS Lothian*