

ABSTRACT

The Auditory Brainstem Response: History and Future in Medicine

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The Auditory Brainstem Response (ABR) is a neurophysiological test used to assess the functionality of the central auditory pathway, which includes structures from the auditory nerve to the rostral brainstem. The ABR provides a reading that measures hearing ability based on the electrical output from the different structures along the pathway. The waveforms in the results show the strength of the response and the time it takes for the auditory signal to travel between structures. Deviations in ABR output point to central auditory pathway dysfunction. These deviations can be used to diagnose sensorineural hearing loss due to diseases, lesions, and tumors at various points within this system. The objective of this thesis is to discuss the history of the ABR and the various ways in which this procedure has been used in the medical field. The discussion will cover a variety of medical uses, with a particular focus on the implementation of the ABR in a universal hearing screening for newborns and the benefits it provides by allowing for early detection and intervention for children with hearing loss.

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THE AUDITORY BRAINSTEM RESPONSE: HISTORY AND FUTURE IN
MEDICINE

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CHAPTER ONE

Introduction and Overview of the Auditory Brainstem Response

The brain is a complex and intricately formed part of the human body. It enables people to perform a multitude of diverse actions daily. The brain is the command center of the body, analyzing and synthesizing sensory information to make and carry out decisions. One of these senses which is vital to the normal sensory experience is hearing. Auditory signals allow people to orient themselves in the world, to become aware of possible threats, and to communicate with others. The auditory pathway in humans encompasses both peripheral and central structures. The peripheral structures cause sounds in the form of waves to transform into neural signals that can be processed by the brain. The central structures in the brain process and carry the electrical signals to the main auditory analysis center, the auditory cortex. Here, the information is deciphered and used for the various functions for which humans require sound.

At each major structure along the internal portion of the auditory pathway, there is an increase in electrical activity when the information reaches that structure and is passed along. This activity, generated deep within the brain, can be measured with electrodes attached to the scalp. The scalp-recorded activity is referred to as auditory evoked potentials, or auditory evoked responses. The earliest part of this activity reflects electrical activity in the brainstem and is called the Auditory Brainstem Response or ABR. The ABR appears as 6-7 waves or components. By measuring the ABR, it is possible to detect potential diseases or defects in the auditory pathway, including cochlear damage, brain tumors, and neural diseases like multiple sclerosis. Also, because

the different waves comprising the ABR are attributable to different structures of the pathway, it may be possible to determine the location of the problem. The methods of measuring and using the ABR have changed over the years as research has broadened understanding of how to interpret the output.

The ABR is a powerful tool in measuring brain function, and it has been employed in many areas of medicine, including neurosurgery, audiology, and diagnosis of brainstem lesions caused by disease. The ABR is capable of both detection and diagnosis of several major brainstem maladies and can be used as an affordable test in working to discover the nature of the problem. One of the most actively studied areas for decades has been the use of the ABR in pediatrics, especially with neonates. Historically, many instances of congenital structural or functional deficits in the peripheral auditory system or in the brainstem were not diagnosed until the affected individuals were several years old. This sometimes led to a delay in language development and socialization. Research with the ABR has made it possible to detect some of these problems in the first week of life. As a consequence, there is a movement towards using the ABR as a universal screening procedure for all children to test for auditory function and possibly other medical issues. ABR recordings can be used to find auditory threshold and normal waveform patterns. By screening early, children can be treated sooner and given the chance to develop and live with normal brain functions.

It is useful to begin with a brief summary of neuroscience concepts that will be used later in this thesis.

Nerves

The brain is made up of millions of nerve cells, or neurons, which receive, process, and send information through electrical signals. The basic parts of a neuron include the soma, dendrites, and axons. The soma is the cell body of the neuron, containing the nucleus and other organelles. The dendrites are branching extensions from the soma that receive signals from other neurons. The axons are long extensions from the soma that send signals to other neurons. Adjacent to the axon on the soma is the axon hillock, the main integration center for electrical signals.

Action potentials

Neurons receive many signals from other cells. These signals can be either excitatory or inhibitory depending on which signaling molecules and protein receptors are used. Excitatory signals activate a traveling electric response from the neuron, while inhibitory signals prevent this response. When an excitatory signal is received, sodium (Na^+), which is in higher concentrations outside the cell, rushes inward and causes depolarization - raising the charge inside the neuron. If the charge is raised to the threshold potential, then the nerve will produce an electrical signal, called an action potential. After the generation of the action potential, potassium (K^+) ions leave the cell and bring membrane potential back down to resting. The action potential travels from the axon hillock down the axon as the membrane is depolarized at different points along the path. In the brain, axons are covered in myelin, a fatty substance used to increase the speed at which the signal travels down the neuron. The electrical signal is able to jump from point to point and move down the axon to the synapse without decreasing in strength. When potassium is exiting the cell, there is actually an overshoot of the resting

potential and the cell is hyperpolarized briefly. This hyperpolarization prevents another signal from being sent until the cell is again at resting potential. This brief interval is called the refractory period, and it limits the rate of nerve firing.

Synapses

The point at which the axon of one neuron connects to another neuron is called a synapse. The axon terminal contains vesicles, bubbles formed by a phospholipid membrane, filled with signaling molecules called neurotransmitters. When an action potential reaches the axon terminal, the membrane depolarization causes the vesicles to bind to the membrane of the terminal and release the neurotransmitters into the space between the axon and the dendrite. The neurotransmitters go across the synapse and bind to chemical receptors on the postsynaptic membrane. Neurotransmitter bonding causes ions to enter the dendrite and create an electrical signal in the postsynaptic cell that can continue to propagate throughout that neuron.

Brain

The millions of neurons that form the brain create a complex web of connections allowing information to travel to the correct integrating and analysis points before being sent back to the appropriate destination to carry out the desired action. The brain is made of grey matter and white matter – grey matter is comprised of neuron bodies, while white matter is made of the myelinated axons. The human brain can be divided into six major parts: medulla, pons, cerebellum, midbrain, diencephalon, and cerebrum, moving in a caudal to rostral direction. The medulla, pons, and midbrain make up what is called the brainstem. The brainstem contains major tracts of the central nervous system that carry

sensory and motor information between the cerebral cortex and spinal cord; it is also the origin and target for many descending and ascending signals. The brainstem and cerebellum comprise the hindbrain, while the diencephalon and cerebrum – cortex – comprise the forebrain. The cerebrum is the largest portion of the human brain, and it is split into two cerebral hemispheres. The hemispheres are divided into four lobes – frontal, parietal, temporal, and occipital, moving posteriorly – each holding many different cortical functions, including sight, hearing, language, and decision-making.

Auditory Pathway

The auditory system is made up of two major sections: the peripheral and central auditory systems. Together they function to funnel, transduce, propagate, and analyze auditory stimuli.

Peripheral auditory system

The peripheral auditory system includes the outer, middle, and inner ear (see Figure 1). The outer ear contains the pinna, external auditory meatus, and tympanic membrane (Goldstein, 2007). The pinna is the external structure that sticks out from each side of the head. Sound travels through the external ear and into the external auditory meatus, or auditory canal, which funnels the sound waves inward toward the tympanic membrane, or ear drum. The middle ear consists of an air-filled space behind the ear drum containing three small bones: malleus, incus, and stapes. The bones vibrate when the tympanic membrane is struck by sound waves in order to carry the signal to the inner ear. The inner ear includes the cochlea and vestibular apparatus (Goldstein, 2007). The cochlea is a fluid-filled structure that converts the mechanical signal to a nerve impulse.

The stapes from the middle ear strikes the oval window on the cochlea, creating waves in the inner fluid. These waves cause the basilar membrane and Organ of Corti inside the cochlea to vibrate, and the cilia on the hair cells of the Organ of Corti transduce the signal into a chemical signal sent to the auditory cranial nerve. The cochlea has a tonotopic organization – high frequency sounds stimulate the cells at the basal end of the Organ of Corti and low frequency sounds stimulate the apical end (Biacabe, Chevallier, Avan, & Bonfils, 2001). The travelling wave created by an auditory stimulus travels slowly along the cochlea from base to apex; thus, high frequency-sounds are sensed before low-frequency sounds (Biacabe et al., 2001).

Central auditory system

The central auditory system begins with the eighth cranial nerve, also known as the vestibulocochlear or auditory nerve, and ends at the auditory cortex in the brain (see Figure 2). This system consists of a complex web of connections between many different parts of the brain that sends and analyzes the information sent from the peripheral auditory system. The major structures in the central auditory system include the auditory nerve, cochlear nucleus (CN), superior olivary nucleus (SOC), inferior colliculus (IC), lateral lemniscus (LL), medial geniculate body of the thalamus (MGB), and auditory cortex (Dorfman, 1983). The spiral ganglion connects the peripheral and central auditory systems (Biacabe et al., 2001). The bipolar cells of the spiral ganglion form the afferent – sensory – innervation to the inner ear and the auditory portion of the vestibulocochlear nerve. The tonotopic organization of the cochlea is maintained by placing the low frequency fibers in the center and the high frequency fibers in the peripheral parts of the

nerve. The auditory nerve travels through the internal auditory meatus to the ipsilateral cochlear nucleus in the brainstem (Biacabe et al., 2001).

The cochlear nucleus is located on the dorsolateral side of the brainstem and is cochleotopic, maintaining the basic organization of the cochlea. It is split into three major divisions: anteroventral cochlear nucleus (AVCN), posteroventral cochlear nucleus (PVCN), and dorsal cochlear nucleus (DCN) (Biacabe et al., 2001). Fibers leave the cochlear nucleus through one of three acoustic striae and connect to the superior olivary complex. The superior olivary complex (SOC) is made up of three nuclei – lateral superior olive (LSO), medial superior olive (MSO), and medial nucleus of the trapezoid body (MNTB) – surrounded by the periolivary nuclei (Biacabe et al., 2001). The SOC projects bilaterally to the nucleus of the lateral lemniscus and contralaterally to the inferior colliculus. The LL is a large tract of axons coursing from the SOC to the IC, and it contains both ipsilateral and contralateral connections. The IC are connected by the commissure of the inferior colliculus, and send bilateral ascending projections to the medial geniculate body of the thalamus (MGB) (Achor & Starr, 1980). Each MGB sends its ascending output to the ipsilateral auditory cortex where the signal undergoes sensory processing. These major ascending pathways are coupled with modulatory descending pathways including one from the cortex to the cochlear hair cells (Achor & Starr, 1980). Overall, the central auditory pathway is extremely complex and interconnected with excitatory and inhibitory projections to shape the auditory input.

Auditory Brainstem Response

The auditory brainstem response is an evoked potential created by the electrical responses of the structures of the auditory pathway and recorded using electrodes placed

on the scalp. The resulting output is a series of waves that occur within 10 milliseconds of the stimulus presentation. The positive vertex waves – those pointing upwards – are numbered I to VII, and each one generally corresponds to a specific point of activity along the central auditory pathway (see Figure 3). There has been some disagreement about which brain structures generate which waves, but one of the more common interpretations ascribes Wave I to the cochlea and distal portion of the auditory nerve, Wave II to the central portion of the auditory nerve, Wave III to the cochlear nucleus, Wave IV to the superior olivary nucleus, and Wave V to the lateral lemniscus (Boston & Møller, 1983). Although they are not commonly used clinically, it is thought that Waves VI and VII are attributed to the inferior colliculus (Boston & Møller, 1983). A more recent study connects Wave I with the spiral ganglion cells of the cochlea, Wave II with the cochlear nucleus, Wave III with the cochlear nucleus and contralateral SOC, Wave IV to the SOC, and Wave V to the lateral lemniscus and inferior colliculus (Biacabe et al., 2001). In this model Waves VI and VII are attributed to the MGB of the thalamus. Because of the immense amount of interconnectivity between the structures of the auditory pathway, the waveforms actually have several different structures contributing to each summed response. This complexity can lead to some overlap in which structures are associated with each wave.

The waves are measured by electrodes placed on the skull; for experimental purposes in animals, electrodes are surgically inserted into the brain to detect internal impulses and compare them to those picked up externally. For more clinical uses, the electrodes are generally placed on the vertex of the skull and the mastoid or the ear (pinna) ipsilateral to the stimulus (Nuwer, 1998). The signal used also affects the

waveforms produced by the ABR; the type of stimulus, the intensity, and the rate all have an influence on the auditory potential. The stimuli are presented through an earphone-transducer apparatus and the electrodes record the signals ipsilaterally. The sounds generally used in measuring the ABR are pure tones or click sounds (Boston & Møller, 1983). Both of these types of sound elicit a large number of neurons firing simultaneously, thus producing a larger response. Short bursts of sound are used to minimize stimulus residual effects on the signals picked up by the electrodes. Increasing or decreasing stimulus intensity produces a similar effect in peak amplitude. The change in intensity affects waves I-IV most prominently, while wave V is more robust. This robustness comes from the integrity of the lateral lemniscus from which wave V originates. Though individual nuclei may form slightly differently in each person, the large number of axons that form the LL cause the signal generated by this area to remain strong.

The rate of stimulus presentation also has an effect on the ABR. When the rate is increased to about 15-20 stimuli per second, the latencies and amplitudes of the peaks decrease (Boston & Møller, 1983). As with intensity changes, changing the rate affects wave V less than the other waves. Thus, for individual peak identification, rates of 10-15 stimuli per second are used, and for threshold testing where only wave V is necessary to measure, higher rates can be used (Boston & Møller, 1983).

The waves are able to be interpreted because of their consistency across subjects. The waveforms are extremely reproducible between subjects, especially waveforms I, III, and V (Boston & Møller, 1983). The waves are interpreted based on amplitude (peak to trough), latency (the time between the stimulus presentation and a particular peak),

interpeak latency (the time between peaks), and interaural latency (the difference in wave V latency between ears) (Nuwer, 1998). The particular waves that are analyzed are the vertex-positive peaks; there are negative peaks as well, but those are not as clinically useful.

When testing for different auditory parameters, different characteristics of the ABR are emphasized. When the ABR is used to test hearing acuity, the stimulus needs to be at an intensity that creates a barely-detectable response. Because wave V is the most robust and is seen at the lowest intensity, it is the wave of choice to determine auditory threshold (Boston & Møller, 1983). When the ABR is used to test auditory system integrity, the latencies of the different peaks are analyzed, as well as waveform changes. When a click sound is used, the high-frequency cells at the basal end of the cochlea provide the largest response (Boston & Møller, 1983). Because patients with sensorineural hearing loss tend to see the most damage in the cells at the basal end of the cochlea, it is easy to see a change in the ABR (Boston & Møller, 1983). If these cells are damaged, the cells located more apically become responsible for producing the neural response. The extra time required to reach those cells increases the latencies of the waves. Using absolute latencies can therefore detect cochlear damage. Interwave latency, on the other hand, is largely independent of stimulus intensity and cochlear deficiency effects (Boston & Møller, 1983). It can be used to detect central auditory system deficiencies.

In order to read the waveforms efficiently, it is necessary to eliminate the background noise that comes from the spontaneous EEG generated by cortical structures, the ABR itself, muscle activity that occurs in muscles of the head and neck following the

stimulus, electrical interference from lab equipment, and stimulus artifact (Boston & Møller, 1983). Background noise is reduced through averaging and filtering. Generally, between 1000 and 4000 stimuli are used in averaging to form a distinct ABR waveform. Digital averaging excludes individual responses with amplitudes significantly higher than that of the ABR; the background noise is at mV levels, while the ABR is in μV (Boston & Møller, 1983). The noisiness of the ABR is diminished by comparing a control response recorded just before the stimulus to the response recorded after the stimulus (Boston & Møller, 1983). By controlling for all of the outside noise, it is possible to achieve a fairly clear result in which all waveforms are visible.

In order to move forward with technology, it is important to know the beginnings of the work. To this end, the next topic covered is the humble origin of the ABR and some important advances that have led it to be in such wide use today.

CHAPTER TWO

History and Advances of the ABR

Scientists have been studying the brain for several hundred years and these brilliant minds have now created insightful and reliable ways of viewing it. Today, there are many different techniques and procedures used to visualize the structure and function of the brain, including Computer Axial Tomography (CAT), Positron Emission Tomography (PET), and Magnetic Resonance Imaging (MRI) scans. These particular procedures use X-rays, radioactive tracers, and powerful magnets, respectively, to create detailed images of the brain; certain scans can even be used to determine which parts of the brain are working during different tasks. These tests and others have helped broaden the available knowledge about how the brain works.

The Auditory Brainstem Response is an innovative test that has grown considerably in use since its origin. Because new experiments on the auditory brainstem response were done without the same communication abilities available today, many scientists who worked with this technique called it by a different name. To this day, no one has agreed on an official name that will take precedence over the others. Thus, there are now many names to describe this response and the test that measures it, including Auditory Brainstem Response, Brainstem Auditory Response, Auditory Evoked Potential, and Brainstem Auditory Evoked Potential. Whatever the name used to describe it, the general technique and results related to this event provide reliable and clinically useful information on the central auditory pathway.

First used in 1970 by D. L. Jewett, the ABR technique has been changed and tailored toward different uses over the years to include more efficient delivery of signals, more complex signals, and automated analysis. The understanding of the pathway and function behind the response has also increased with growing numbers of experiments. In 1960, Geisler published his work on cortical responses, in which the first waveform found from the ABR was found (Geisler, 1960). Because of its greater strength, wave 5 is the most likely candidate for the waveform found in this study. Sohmer and Feinmesser found cochlear responses and full ABR responses from the scalp in 1970. That same year, Jewett and his students published their findings on the ABR in cats and also from the human scalp (Jewett, 1994).

The first outputs could only be recorded directly from the brainstem because the signal was not strong enough to reach the scalp in a readable form. The advent of an averaging machine allowed the ABR to be performed noninvasively. By presenting many stimuli in succession and averaging the responses, the background noise is cancelled out, and the actual response generated by the brainstem structures of the auditory pathway can be seen. Through signal averaging, latencies were shown to be the same measured from the round window of the cochlea and on the scalp (Jewett, 1994). Thus, Jewett concluded that it is possible to record the electrical potentials from the scalp and maintain the integrity of the signal using averaging (Jewett, 1994). Jewett and Williston continued to record ABRs from the scalp and determined that the technique is reliable between subjects (Jewett, 1994). Around this same time, Moushegian discovered the frequency-following response (FFR) that occurs using sine waves at a higher rate of presentation instead of click stimulus (Skoe & Kraws, 2010). The FFR describes a more

sustained response that varies depending on the frequency of the stimulus, and it is not used as often in a clinical setting.

Originally, common scientific thought was that each positive wave of the output was attributable to a single structure along the track. A couple of key studies by Achor and Starr (1980) helped to change this view. Achor and Starr inserted electrodes into the brains of cats and measured the electrical responses both intra- and extra-cranially. The results of this experiment showed that the waves were much more complex than previously thought; most of the waves are in fact made up of the responses of several structures at different points along the pathway. Within the next few years, many researchers began to focus on which structures were generating each wave. Three of those at the forefront were A. Møller, Jannetta, and M. Møller, who did a number of studies using intracranial electrodes to clarify the generators for the different waves of the ABR (1982, and Møller & Jannetta, 1982). Studies in which the brainstem was lesioned to discover the function of each structure also became popular (Starr & Hamilton, 1976, and Achor & Starr, 1980).

As new data such as this was revealed, people came up with different physiological models to try to explain the anatomical and functional layout of the central auditory pathway (Boston & Møller, 1983). The major model used before Achor and Starr's insight was a linear model that envisioned the signal traveling in a straight line from ear to cortex, with each structure eliciting a wave response. After that came the empirical model, a three-dimensional model, a fixed dipole model, and a multiple dipole model (Boston and Møller, 1983). All of the later models took into account the fact that the structures of the auditory pathway have many connections that allow signals to

decussate – travel from one hemisphere of the brain to the other – and to pass both forward and backward along the track. The dipole models relate to the electrical dipoles created when signals are generated by the brainstem structures and sent through the pathway. The multiple dipole model is likely to be the most accurate in describing the auditory pathway anatomically, but the methods used to record this information are not as sensitive to waveform changes, rendering the procedure less useful for clinical purposes (Boston & Møller, 1983).

A more recent trend in ABR research has been to use complex stimuli to more closely mirror the sounds that people hear in everyday life and see how the brain responds in normal situations. These complex stimuli include a wide variety of noises from syllables and words to music and phrases (Skoe & Kraus, 2012). Greenberg was one of the first to use complex stimuli in testing auditory brainstem responses in 1980, and he discovered that the ABR encodes information specific to the stimuli presented (Skoe & Kraus, 2012). The information is so specific that cABRs with words as stimuli can be understood as those words when the response is converted from a neural signal into an audio signal (Skoe & Kraus, 2012). The cABR is unique from the normal ABR because it measures responses to both short stimuli – clicks or consonants – and sustained stimuli – tones or vowels – within the same output. cABRs are presented and recorded in the same way as click ABRs, but the analysis involves slightly different techniques because of the more complex output. Peak latency and amplitude are analyzed, as well as change in latency over time, cross correlation between two signals, and other wave characteristics (Skoe & Kraus, 2012).

The work that has been done in studying the cABR shows the technique to be an objective and non-invasive way of measuring auditory function (Skoe & Kraus, 2012). The studies have also revealed that the way the subcortical structures of the auditory pathway process stimuli is affected and can even be changed by cognitive processes including language and music. In this way, cABRs can be used clinically to measure more complex auditory function in the brainstem. They are useful as biological markers of auditory pathway maturation and predictors of outcome in auditory training. There is also a link between cABRs and higher-level language processing, including speech perception and reading (Skoe & Kraus, 2012). The cABR could be used to identify auditory deficits at an early age in development that could lead to language or learning disorders later in life.

Another recent advance in ABR technology is the automated auditory brainstem response, or AABR. The AABR reads the same response as a conventional ABR, but unlike the conventional form, it can be administered by someone with no audiological training (van Straaten, 1999). First made possible by Mason at the Queen's Medical Center in England, the AABR is programmed to automatically measure the electrical responses to the 35 dB signal emitted in order to determine the presence or absence of an auditory brainstem response (1988). It measures the ratio of response signals to background noise to decide if the response is strong enough to "pass" or "fail." The AABR can discriminate between "response plus noise," and "no response," or just pure noise. This technique was found to be at or near 100% sensitive for ABR presence with a specificity of about 97% (van Straaten, 1999). Sensitivity refers to the percentage of those affected who are correctly identified as such, and specificity refers to the

percentage of those correctly identified as healthy. Thus, the AABR has both high sensitivity and specificity, making it an effective technique. The AABR is a great screening tool for both neonates and normal infants due to its low cost, ease of use, and short duration of testing. Recent changes have made the AABR even quicker to use; although it is still longer than the Transient Evoked Otoacoustic Emissions test with which it is often paired for screening, the time to administer the AABR has been cut to make it even more practical for universal screening purposes (Konukseven et al, 2012).

All of the advances made in the technique and understanding of the ABR have made the procedure extremely useful in many different clinical areas. The ABR has found its way into detection and diagnosis of not only hearing disorders, but also a plethora of other brain-related maladies.

CHAPTER THREE

Clinical Applications of the ABR

Since its refinement, the auditory brainstem response has found use in many different areas of medicine. Some of its more common uses are investigating possible cases of multiple sclerosis, guiding prognosis in post-traumatic and anoxic-ischemic coma in the ICU, diagnosing the presence of structural lesions on the brainstem, and monitoring brainstem function intraoperatively during surgical removal of acoustic neuromas. Irregularities in the waveforms and their latencies can indicate disease, damage, or loss of function in the brainstem or other auditory structures. Although the ABR is not foolproof in its diagnosis, it is a helpful tool in determining if there is indeed a brainstem abnormality. The ABR can also be used clinically as a hearing assessment to test peripheral as well as central auditory function. This paper will discuss the clinical use of the ABR in multiple sclerosis, brainstem lesions, acoustic neuromas – tumors, intraoperative monitoring, coma, brain death, CPR efficiency, and hearing assessments.

Multiple Sclerosis

In patients with multiple sclerosis, the nerves making up the brain undergo demyelination, meaning that the myelin sheaths wrapped around the axons are damaged (Zieve & Jasmin, 2011). Demyelination prevents efficient nerve signaling and therefore interrupts normal brain function. Multiple sclerosis patients undergo episodes of abnormal nerve activity, manifesting as muscle spasms, tremors, numbness, and fatigue, alternating with bouts of remission (Zieve & Jasmin, 2011)). The symptoms vary

depending on the location of demyelination within the brain. Although the auditory sensory pathway is not one of the areas that usually shows clinical symptoms of MS, abnormal tests here are signs of multifocal involvement (Dorfman, 1983). The ABR is one tool that can help to identify the presence and potentially general location of demyelination in the brain stem. The ABR is abnormal in approximately 40% of patients who have MS but exhibit no signs of brainstem impairment (Nuwer, 1997). Though it is not a common symptom of MS, acute hearing loss may occur due to demyelination in the distal tract of the auditory nerve (Bergamaschi, Romani, Zappoli, Versino, & Cosi, 1997). Demyelination of the auditory pathway is characterized by changes in interwave latencies and wave amplitudes. Longer interwave latencies indicate a longer amount of time needed for the auditory signal to pass between structures. Demyelination of the neurons connecting the structures in the pathway causes an increase in interwave latencies because the lack of myelin forces the signal to travel more slowly down the axon. Diminished wave amplitudes can indicate the level of damage due to demyelination at the structures involved in the auditory pathway. Understandably, the ABR is more likely to be abnormal in cases where MS shows clinical symptoms, but it can also be used to detect silent lesions in patients who do not show symptoms of brainstem involvement (Walsh, Kane, & Butler, 2005).

Brainstem Lesions

The ABR has been shown to provide information about the presence and general location of brainstem lesions. Although it can be difficult to determine a specific location using this technique because the waves are formed by the combined responses of several different structures, it is possible to use the waveforms to indicate the general area of the

lesion along the rostral-caudal axis of the brainstem. In fact, the ABR results were shown to overlap with MRI results on side and site of brainstem lesions over half the time (Wedekind, Hesselmann, Klug, 2002). Both results were also proportional in abnormality to the severity of the lesion (Wedekind et al., 2002). In patients with lesions to the brainstem caused by trauma, the ABR is remarkably helpful in determining auditory function. Patients who experience hearing loss due to severe trauma may not be able to communicate their deficit and may find it difficult to participate in behavioral auditory tests. The ABR can be used in this situation because direct cooperativity is not required during the test to achieve accurate results (Lew et al., 2004). Despite its great use in determining auditory function, it is not always reliable to use the ABR results to determine the type or cause of the lesion as there can be many different kinds of auditory pathway dysfunctions that can affect similar areas of the electrical response. The ABR is best used to determine functionality of the auditory pathway, and can be used broadly to find damage due to disease, injuries caused by trauma, or tumors located on the brainstem.

Acoustic Neuroma

Acoustic neuromas, also referred to as vestibular schwannomas (VS), are slow-growing tumors that grow on the vestibulocochlear nerve (NIH, 2013). Although they are benign, they can do significant damage to brain structures and important cranial nerves as they grow larger. For example, VS growth can compress the acoustic nerve and associated blood vessels, slowing or inhibiting auditory signal conduction (Morlet, Dubreuil, Duclaux, & Ferber-Viart, 2003). Therefore, it is important to be able to determine if an acoustic neuroma is present and remove it as soon as possible. Recently,

the MRI has become the technique of choice in screening for VS because of its greater sensitivity to smaller tumors. MRIs use magnets and radio waves to form a detailed image of the brain and other nearby nervous tissue. The images created are extremely helpful in providing a visual representation of the brain and the size and location of the tumor; however, the MRI is much more expensive – around \$4000 – than the ABR – approximately \$350 (Walsh et al., 2005).

Despite the major cost differential, the ABR remains a good screening tool for the presence of VS. The ABR is almost always abnormal in patients who have acoustic neuromas on the auditory nerve. In fact, studies have shown the ABR to be extremely sensitive to these tumors; “ABR retains 93.4% sensitivity for detecting VS of any size (as expected, the sensitivity increases slightly to 95.6% for larger tumors and decreases slightly to 85.8% for smaller tumors)” (Koors, Thacker, & Coelho, 2012). The abnormal ABR due to an acoustic neuroma manifests as a longer interpeak latency between peaks I and III (Walsh et al., 2005). This increased latency is reasonably specific for a VS in patients with unilateral hearing loss (Walsh et al., 2005). Patients may also present with increased peak I and II latencies or absent responses in that time period. A severely diminished ABR, especially around wave III, is indicative of severe auditory nerve compression and adhesion to the nerve by the tumor (Matthies & Samii, 1997). Although it cannot be recommended to completely replace the MRI with ABR for diagnosing VS, the ABR remains a useful tool in lower risk patients to reduce cost and still maintain reliable diagnostic capability.

Intraoperative Monitoring

The ABR can be used during brain surgery to ensure that the surgeon does not disrupt normal brainstem functions throughout the procedure. The goal of neurophysiological intraoperative monitoring is to prevent damage to neural structures that may be harmed during the procedure. Monitoring detects neural changes due to neural injury or mechanical pressure caused by incorrect placement of the surgical instruments. Common procedures that benefit from using the ABR are: acoustic neuroma surgery, vestibular nerve section to relieve vertigo, brainstem tumor removal, and brainstem aneurysm clipping (Bhattacharyya, 2013). The technique is fairly resistant to anesthetic effects unlike EEGs that measure spontaneous cortical activity, so ABRs can be used as good indicators of maintained brain function throughout surgery (Walsh et al., 2005).

During the surgery, waveforms I, III, and V are the most clinically important (Oh et al, 2012). Decreased amplitudes of waves I and V, increased interpeak latencies of waves I-III, III-V, and I-V, increased peak latencies, and high interaural latency differences – differences between ears – are considered to be potentially concerning changes (Oh et al, 2012). Because it is the most robust, wave V amplitude is usually the wave that is watched most closely. The surgeon is usually alerted when wave V latency changes by 0.5 msec or more (Youssef & Downes, 2009). Although all aforementioned changes are important shifts to recognize, maintenance of waves I and V are the most clinically relevant in correlating to higher postoperative auditory preservation. Their presence before and throughout surgery is a reliable predictor of better hearing preservation after the procedure (Oh et al, 2012). They are not, however, good predictors

of the severity of any deficits that may occur due to changes of the waveforms during surgery (Oh et al, 2012). Individual changes in these waves caused by the operation cannot be used clinically to predict the type of damage caused or its full extent, but they still alert the surgeon to potentially harmful movements made throughout the surgery.

Although individual wave variations may not provide accurate predictions of hearing capabilities after surgery, the overall brainstem auditory evoked potential wave pattern does correlate with postoperative auditory function. Bischoff, Romstöck, Fahlbusch, Buchfelder, and Strauss found four identifiable intraoperative ABR patterns during vestibular schwannoma surgery: stable Auditory Brainstem Response, abrupt loss, irreversible progressive loss, and reversible loss (2008). Each of these patterns was significantly correlated with a certain outcome for the patients. All patients in the study with stable ABR showed preservation of hearing ability, and all patients with abrupt loss or irreversible progressive loss of ABR lost hearing completely. Those with reversible ABR loss had the possibility of recovering auditory function with treatment; in this case, a vasoactive treatment was employed. Bischoff et al. conclude that abrupt or irreversible progressive loss is most likely caused by additional mechanical injury to nerve fibers, and reversible loss by disturbed microcirculation of the auditory nerve (2008).

Interestingly, during surgery, the ABR stimuli are delivered to the patient through a foam plug insert that is attached to a plastic tube and secured inside the auditory canal. This technique is used to prevent the stimulus device from being removed from the ear during the operation. Using this setup also allows for the medical personnel to employ several different monitoring techniques at the same time, including the ABR, electrocochleography, and auditory nerve action potentials (Youssef et al, 2009). The

latter two techniques are different ways of monitoring auditory nerve function specifically. Combining these three monitoring methods allows for quick and accurate feedback on the various areas impacted by surgery involving the auditory pathway. As the facial nerve is physically close to the auditory nerve at the level of the brainstem, monitoring facial nerve function through electromyography (EMG) is also beneficial in intraoperative monitoring during acoustic neuroma removal (Youssef et al, 2009).

ABR latencies can be affected by changes in patients' homeostasis, including core body temperature, intracranial pressure, and arterial oxygen, so it is important to monitor these vital signs to obtain a reliable ABR result (Oh et al., 2012)). In order to perform the technique successfully, a preoperative ABR must be taken as a baseline, followed by a second recording after sedated to determine the unique effects of anesthetics (Youssef & Downes, 2009). During the operation, anesthetics are kept steady, so any other changes in the ABR are attributed to surgical events. Another consideration for using the ABR intraoperatively is that the recordings must be summed and averaged in order to obtain a reliable reading. Recording and averaging responses to 4000 stimuli usually takes around two minutes. This feature creates lag time between the delivery of the signal and the readable output. The delay can be anywhere from several seconds to a couple minutes (Oh et al., 2012). Obviously, this delay presents some issues in trying to monitor which actions produce specific changes. When direct readings are used, the delay can be diminished to 5-15 seconds, showing the potential for improvement (Oh et al., 2012).

The ABR can also be used preoperatively to determine whether hearing is likely to be preserved, especially during procedures removing tumors on or close to the auditory structures (Morlet et al, 2003). Severe ABR disruption seen before the operation is an

accurate indicator of a poor prognosis for hearing preservation (Walsh, 2005). Patients who have waves I, III, and V present are much more likely to retain hearing ability than those who have only one of those waves (Oh et al, 2012). By monitoring the changes that occur during the surgery, it is possible to reduce the likelihood of causing irreversible brain injury. Using the ABR allows surgeons to make corrections before any extreme changes occur in the brainstem and auditory nerve and to reliably predict the outcomes of surgery involving these important areas.

Coma

For use in coma patients, ABR cannot give information about cortical function, but it can give a prognosis relating to brainstem function preservation. It is thus a good tool used in conjunction with the EEG, which measures cortical activity. In providing prognosis, an abnormal ABR is linked to an unfavorable outcome in almost all cases, while a normal ABR is not reliably associated with a favorable outcome (Guerit et al., 2009). Balogh, Wedekind, and Klug suggest that this association only holds true for waves I-V (2001). They posit that wave VI is a more reliable indicator of prognosis for coma patients. According to their study, wave VI abnormality is highly specific for an unfavorable outcome in coma patients. Furthermore, wave VI is shown to be present in all healthy patients when the ABR stimulus is presented at a high intensity and optimum signal-to-noise ratio (Balogh et al, 2001). Although the specific location of the wave VI generator is debated – some say inferior colliculus while others say medial geniculate nucleus of the thalamus – it is certainly rostral to the generator of wave V, the lateral lemniscus. Their study showed that an abnormal ABR wave VI, even in the presence of normal waves I-V, is an accurate predictor of an unfavorable prognosis.

“Owing to their low intra- and inter-individual latency variability, short-latency and middle-latency EP are particularly sensitive to a decrease in sub-cortical conduction velocity. It is important to note that an increase in inter-peak latency (IPL) without peak distortion most often corresponds only to, usually reversible, brain-stem dysfunction as a consequence of drugs, metabolic disturbances, or hypothermia. By contrast, abnormalities of the V/I amplitude ratio may correspond to a true brainstem (midbrain) dysfunction” (Guerit et al, 2009). Increases only in peak latency, especially at the earlier peaks, can be attributed to peripheral dysfunction or temporary environmental strain. In this case, restoring the patient to homeostasis should bring the ABR reading back to normal. However, when the wave amplitudes are changed, it is more likely that a certain brainstem structure is damaged or otherwise not working correctly (Guerit et al, 2009).

According to several clinical studies, ABR abnormalities are generally not directly caused by anoxic events – cardiac arrest and stroke – because of the resilience of the pons, so any distortion in waves III-V show significant brainstem damage (Guerit et al, 2009). Therefore, “absence of waves III to V after both anoxic-ischemic cardiac arrest and traumatic brain injury is almost invariably associated with death or survival in a persistent vegetative state” (Guerit et al, 2009). Several studies have shown that ABR have better prognostic ability for unfavorable outcomes than favorable outcomes in patients with severe stroke in areas that put pressure on the brainstem. A decrease in amplitude or complete absence of wave V was significantly correlated with unfavorable outcome in a study by Su et al. (2010). The ABR’s prognostic capability for patients with severe stroke was 83.0-84.9% in the 100 cases studied (Su et al., 2010).

Complete abolition of the whole ABR following trauma or ischemic attacks must be interpreted with caution, however, because the cochlea and auditory nerve are particularly sensitive to these kinds of disruption (Guerit et al., 2009). Therefore, the absence of wave I does not necessarily point to complete brainstem failure, but instead could show only significant peripheral damage. At this stage, it is up to the clinician to do more tests to confirm the findings. Although the ABR is fairly resistant to ischemic events, as with all tissues of the body, lack of oxygen to the brain for an extended period of time can lead to permanent damage. With this damage, the ABR would also be negatively affected. Hata et al. found in gerbils that an ischemic event affecting the brain causes the ABR to disappear (1998). For brief events lasting only five minutes, the ABR waveforms returned to normal after the ischemia ended. However, for longer events lasting 10 to 30 minutes, the waveforms never completely recovered to their normal state (Hata et al., 1998).

Because of its resilience during anoxic events, the ABR is more useful in determining prognoses for coma patients whose condition is due to trauma. Normal results are good indicators of awakening and a positive neurological outcome. The ABR can also rule out brainstem injury in patients whose coma is due to unknown causes. Waveforms are generally normal in cases due to “metabolic disorders, intoxications, and bihemispheric cerebral dysfunction,” thus narrowing the possibilities for the cause (Guerit et al, 2009).

Brain Death

Similarly, the ABR can be used as a tool for determining brain death in patients who have undergone trauma or are in a coma. Many countries define brain death as the

complete and irreversible loss of all brain function – both cortical and brainstem (Waters, French, & Burt, 2004). There is no single way to confirm brain death, but using neurological tools can give a prognosis of the likelihood of present or future brain function. The loss of EEG recording shows loss of cortical function; this loss was once considered to be the definition of brain death because it is impossible for a person to function normally without the use of his or her cerebral cortex. However, when using techniques that measure brainstem function, it is possible to detect continuing neural signals from these structures even though cortical function has ceased. Thus, the use of the ABR and other evoked potential procedures, including visual or somatosensory tests, can show continued brainstem function in a person in which brain death is possible. The loss of all waves on the ABR shows complete loss of central auditory function, and can thus be used as part of a group of confirmatory tests to determine brain death. The use of the ABR on its own is not conclusive for brain death because other brainstem damage or disease can cause the loss of ABR recording without causing brain death (Waters et al., 2004). It is neither necessary nor sufficient to have loss of an auditory brainstem response to prove brain death, but it can be a telling sign when used in conjunction with other techniques.

CPR Efficiency

Along that same line of use, a study by Reid, Mullins, and Iyer has brought up the potential for employing the ABR in determining CPR efficiency (1997). The purpose of CPR is to continue blood flow to the brain when the heart stops, but improper technique does not provide this help and can actually contribute to further brain damage. This study found a particular wave on the ABR that can be used to determine if CPR is being done

correctly and the likelihood of the patient's survival and potential neurological capabilities. If the ABR is applied in time, the wave latency shift occurs early enough to allow for successful intervention if the CPR provided is not sufficiently effective (Reid et al., 1998). More research is needed to confirm the utility of the ABR in this capacity.

Hearing Assessments

Hearing assessments are needed throughout people's lives to ensure that everything is working correctly at all points along the auditory pathway. Hearing is tested with a screening test in newborns, in general testing for senior citizens, and in diagnostic testing for patients with symptoms of sensory impairment. The auditory process can be separated into three parts: sound conduction, transduction of sound waves into neural signals, and neural processing and analysis (Ptok, 2011). The hearing assessments test for impairments of these three areas. Impairments of conduction involve dysfunction in moving the sound waves from the environment to the inner ear. Impairments of transduction involve defects in sensation and transformation of the mechanical wave to an electrical signal where the cochlear cilia activate the auditory nerve. Finally, impairments of processing involve retrocochlear and central auditory defects in signal transmission and perception of stimuli (Ptok, 2011). Using the ABR, it is possible to test both peripheral and central auditory function. Wave I disruption signifies cochlear or auditory nerve dysfunction, and later waves signify brainstem dysfunction. Determining the general location of the problem allows the physician to choose the best treatment.

The Auditory Brainstem Response is used in many different clinical capacities, but one of the most common is as part of a screen for auditory deficits in neonates.

CHAPTER FOUR

The ABR as a Universal Screening Tool for Neonates

Hearing is an important part of people's everyday lives. However, it is easy to overlook a hearing deficit in young children, as they have not yet gained the ability to say that they cannot hear well, and may not even know that their sensory experience is not normal. Hearing impairments are also one of the more common congenital disorders. "The estimated prevalence of moderate, severe and profound permanent bilateral hearing impairment varies from 1 to 1.4/1000 newborns" (Verhaert, Willems, Van Kerschaver, & Desloovere, 2008). When newborns with monaural impairments are included, this number jumps to 1 to 6 per 1000 newborns (American Speech-Language-Hearing Association). At this level of prevalence, congenital hearing impairments are found at much higher levels than other conditions that have mandated neonatal screening. For example, phenylketonuria (PKU), a condition in which infants are born lacking the ability to break down the amino acid phenylalanine which leads to mental retardation, is found in only 1 in 10,000 neonates (Centers for Disease Control and Prevention, 2012).

Despite the relative commonality, hearing impairments may not be easy to detect behaviorally at a young age. An auditory deficit may simply be interpreted as slower development while the child is young, manifesting in behaviors such as not speaking much, having limited vocabulary, and not paying attention to others without having direct attention first (Centers for Disease Control and Prevention, 2012). Once it is determined that there is a sensory impairment at a general check-up, it may be too late to restore

normal auditory function. These lasting effects can make it more difficult to interact normally with their surroundings.

This impact is seen most clearly in areas of language and speech. Children pick up language from a young age, but there is a window of time called the critical period in which children are most susceptible to learning language. After this window has closed, it is extremely difficult to gain a normal mastery of language. The critical period for language ends at around seven years of age, but children acquire preference to the specific sounds related to the language they learn by six months. These sounds are called phonemes, and each language has different phonemes related to the way that letters and words are pronounced when spoken in native tongue. By six months, infants can no longer distinguish between phonemes of different languages than their own. Thus, similar to the difficulty in becoming fluent in a second language if it is not heard during development, children who are not exposed to normal forms of language during that critical period have to overcome a huge obstacle in using any language at all. Hearing impairment is one way that learning normal language is impeded. Thus, the earlier that a deficit is found, the greater the chance there is to intervene and provide the child with a normal hearing experience. Through the use of neonatal screening, auditory dysfunction is discovered much earlier than waiting for behavioral signs to exhibit in the child, and more can be done to allow that child to develop normal hearing and language capabilities.

Although it would be ideal to test all newborns for all diseases and conditions to make sure that no child with a congenital abnormality would get through the screening process without diagnosis, it is not practical economically or temporally. It would take a great deal of time and money to perform dozens of tests on every child, so only broad

tests for conditions with high-prevalence in the population are done universally. These universal tests create smaller groups who are at higher-risk for specific conditions than the general population. Performing the more specific tests within these groups makes the tests more useful and allows the tests to have higher specificity for the conditions. This greater specificity within the high-prevalence group means that the test will catch more of the children who have that particular condition, and that the test is more helpful in providing a diagnosis. The prevalence of congenital hearing loss provides good reason for including testing for this condition in a universal neonatal screen, which is now the case. Additionally, improvements that have been made in the ABR make it an invaluable resource in both universal screening and more in depth diagnosis of auditory function in neonates.

Most infants born in a hospital today undergo a group of universal screening tests that check for normalcy, including a blood test, a hearing screening, and a heart screening (Centers for Disease Control and Prevention, 2012). The blood test is used to check for different conditions like PKU, sickle cell disease, and hypothyroidism. The Universal Newborn Hearing Screening (UNHS) is generally done in two parts. The first part, recommended to be done no later than one month of age, is a cursory test that is easily passed with normal hearing (Centers for Disease Control and Prevention, 2012). The second part is done if the child does not pass the general test, and it involves more in depth testing of the auditory pathway. The full hearing test can include the ABR, Otoacoustic Emissions that test inner ear function, and Behavioral Audiometry Evaluation that tests the child's voluntary response to sounds. This second test is recommended to be done as soon as possible, but no later than three months of age

(Centers for Disease Control and Prevention, 2012). Those who pass this test are determined to have normal hearing or mild hearing loss – no greater than 35dB (Ptok, 2011). Those identified by these tests as having hearing deficit are categorized in terms of the severity of the loss. Hearing loss severity is determined based on the criteria of the BIAP – Bureau International d’AudioPhonologie (Ghirri et al., 2011). Mild impairment is considered to be between 21 and 40 dB of hearing loss, medium is between 41 and 70 dB, severe between 71 and 90 dB, and profound over 91 dB. To provide a reference, a whisper is normally about 15 to 25 dB, a normal speaking voice is about 65 to 70 dB, and the pain threshold falls at about 130 dB.

The UNHS is an important part of the screening process that can make a significant difference in the life of a newborn by finding hearing deficits as early as possible. Because of the magnitude of the effects of hearing impairments on a child, the UNHS should be mandatory in all hospitals before allowing the newborn to leave. Most states in the United States have mandated the UNHS at some level, some even requiring follow-up testing to monitor those who present with auditory deficits. Not all states require this screening, however. Though all states have implemented the UNHS, some only require that the screening be available in hospitals, but not that it be performed in all cases. In the United States, states in which the UNHS is mandatory have 95% of newborns screened, whereas states in which it is optional only have 26% screened (Ghirri et al., 2011).

Although some people may argue that their child does not need to undergo screening because there is no family history of hearing deficits and the baby does not have any other risk factors, the lack of risk factors does not preclude a child from

developing hearing impairments. Children with risk factors are almost ten times more likely to have a hearing deficit than the general population; however, approximately half of all children with hearing impairments do not exhibit any risk factors (Ghirri et al., 2011). If all children are not screened, many auditory deficits will go undiagnosed until much later when behavioral signs begin to show and it is significantly more difficult to intervene with satisfactory results. With the UNHS, diagnosis and the beginning of treatment are, on average, 24 months earlier than in children with hearing impairments who did not undergo screening (Ptok, 2011). Studies on speech comprehension show a large benefit in using UNHS, and children who had undergone UNHS show a trend toward better development of expressive speech.

Though the Universal Newborn Hearing Screening is gaining support across the United States and even around the world, this screen is not necessarily complete. Based on the previous position of the Joint Committee on Infant Hearing (JCIH), only sensory and conductive deficits were recognized (2007). These deficits are related to the function of the middle and inner ear, but did not take into account any central auditory pathway structures. Thus, the UNHS in most states recommends the use of Transient Otoacoustic Emissions to test cochlear and middle ear function, and behavioral testing to measure overall auditory function. TOAEs measure the sound created by the vibrations of the outer hair cells on the cochlea. These sounds echo back into the middle ear and are measure with a probe that is inserted into the ear. Despite their usefulness in detecting peripheral auditory deficits, neither TOAEs nor behavioral testing detect brainstem impairments. In addition, behavioral testing especially is prone to missing mild hearing loss. Based on this discovery, the JCIH recently updated their position to include neural

deficits in the recognized categories of auditory impairments, and they now recommend the use of the Automated ABR to screen newborns in the Neonatal Intensive Care Unit (NICU) (2007). Though the JCIH specifies newborns in the NICU because of the high risk of deficits associated with this group, because of its accuracy, ease of use, and low cost, adding the AABR to the universal screen for all newborns would allow for early detection and treatment of even more children with congenital auditory impairment.

By including the ABR as a screen for newborns, hearing impairments can be discovered early, and children can receive treatment that allows them to have a normal hearing experience. A study in Belgium showed that the ABR allowed for an earlier diagnosis and intervention for auditory dysfunction than behavioral tests (Verhaert et al., 2008). The early intervention allowed 85.4% of the children who presented with moderate, severe, or profound hearing impairment without any additional disabilities to enter mainstream education (Verhaert et al., 2008). By providing the children with hearing aids, cochlear implants, and other devices, many were able to gain normal language capabilities or have minimal delays. Nearly 80% of the children in this study who received cochlear implants and did not have any additional impairments were in mainstream education (Verhaert et al., 2008). Understandably, those who had more severe hearing impairment were not as likely as those with mild impairment to avoid a delay in learning language, but even this group showed improvement with early aid. The study also supports earlier intervention delivering better results. “Children implanted before the age of 18 months reached a higher expressive language level (NNST, RTOS), than those implanted between 24 and 30 months. Analyzing the expressive vocabulary of the early-implanted children, 25% had a score within normal range at age 4” (Verhaert et

al., 2008). Thus, early screening using the ABR allows for early detection and intervention that can greatly benefit children with auditory deficits.

It is interesting to note that ABR results for newborns are different from those for adults. “Whereas in adults waveforms normally occur within 10 ms after a click stimulus presented at high intensities (70–90dB normal hearing level), the first appearance of ABRs at 27 to 29 weeks of conceptional age shows smaller amplitude and longer latencies and requires stronger stimuli and slower rates of stimulus presentation” (Guzzetta, Conti, & Murcuri, 2011). This difference is due to the level of maturation of the auditory pathway. In newborns, the myelination of axons has not yet been completed, leading to the greater amount of time needed for the signal to pass between structures. The layer of myelin around the axons will continue to thicken up until about a year after birth (Sininger, Abdala, & Cone-Wesson, 1997). Similarly, the structures are not yet fully developed, causing the smaller amplitude of the waveforms. Although the cochlea is mature at birth, the child’s brainstem auditory pathway does not function at a level comparable to an adult’s until approximately two or three years of age (Sininger et al., 1997). Physiologically, the immaturity of the auditory structures means that the correct neurons do not yet fire together and they send signals more diffusely than only to their correct target. Due to the immaturity of the structures, the newborn is also less sensitive to sounds than an adult. In the ABR, this decreased sensitivity manifests as a higher threshold – as much as a 20 dB difference between infant and adult for higher frequencies (Sininger et al., 1997).

During development of the central nervous system, neurons send their axons out to travel to the target area at which they will synapse. The axons are guided by different

signaling molecules that attract the leading end in the correct direction and repel it from the wrong directions (Squire et al., 2008). These signaling molecules guide the axons and their branches to the general target area where they will form synapses with other cells. The synapses that are made and kept at this point are based on genetic directions. However, during the critical period for sensory pathway formation, the synapses are affected by the specific experiences of the child (Squire et al., 2008). Based on the sounds that the child encounters, the synapses that are used will be strengthened, and those that are not used will be lost. Because the brain is shaped by environment, it is important for children to have rich auditory experiences to ensure correct development. Without these experiences, the auditory pathway will not function correctly, due to aberrant or weak synaptic connections.

Because the nervous system is still developing at birth, it is important to have infants retested fairly frequently, especially if the hearing tests come back positive for auditory impairment. Even those whose results are negative for hearing impairment at the time of the screening should continue to monitor hearing ability as the children grow. False negatives do occur occasionally, so retesting during this key stage of development can help to catch any possible abnormalities and begin correction as soon as possible. Retesting can also find progressive or late-onset deafness that begins to manifest after the initial screen. These hearing impairments account for about 20-30% of hearing loss in infants (Ghirri et al., 2011). It is also possible for a positive result on the test to be shown as a false positive due to transient disorders in neonates. Some neonates may express a middle ear disorder that goes into remission before the follow up occurs, thus appearing as a false positive. However, the number of false positives due to continuing

development in the infants is not large enough to offset the benefit of catching auditory impairments as early as possible. With the advances in technology and operator training, it is possible to be close to 100% accurate with a specificity of 97-98% (Ghirri et al., 2011). These numbers mean that practically all infants with a hearing impairment above 40 dB will be diagnosed using the screening tests, and only 2-3% of the infants screened will be false positives. Those who are diagnosed with false positives will be retested and most will be identified as having normal auditory function.

It is especially important to test for normal auditory function in infants at risk for brain damage. Infants at risk include “those with a family history of hearing loss, in utero and neonatal brain hypoxic–ischaemic events and infections, craniofacial anomalies, severe hyperbilirubinaemia, and dysmorphic features suggestive of a syndrome associated with hearing disorders” (Guzzetta et al, 2011). As some of the risk factors for early brain damage overlap with risk factors for hearing dysfunction, it is more common for children with brain damage to also have auditory impairments. When used in conjunction with TOAEs (transient evoked otoacoustic emissions), the ABR is a useful tool in determining the presence and general location of any auditory pathway damage (Vatovec et al., 2001). TOAEs are good indicators of inner ear, or conductive, hearing impairments, and they provide quick results. Quick results are important because parents and physicians want to be able to intervene for correction as soon as possible, if it is necessary. TOAEs are limited to the cochlea, however, so combining the otoacoustic emission results with the ABR results can give an idea of the functionality of the majority of the internal auditory pathway (Vatovec et al, 2001). Because of the higher prevalence in at risk infants, it is prudent to err on the side of including children without deficits in

the group that receives follow-up treatment rather than clearing a child who has auditory impairment. Using a lower decibel range for detecting deficits will lead to more false positives, but it will also prevent true positives from slipping through the test unnoticed.

Because of their higher risk in having auditory dysfunction, it is particularly important for infants who graduate from the NICU – Neonatal Intensive Care Unit – to receive follow-up tests. Due to their congenital impairments and treatments that they must undergo while in the hospital, neonates in the NICU are as high as 10 to 20 times more likely to have sensorineural hearing impairments than those not in the NICU (Meyer et al., 1999). Not only that, but infants in the NICU are also at higher risk for developing delayed-onset or progressive sensorineural hearing loss. Conditions including severe respiratory failure and Persistent Pulmonary Hypertension of the Newborn, as well as ototoxic medications such as aminoglycosides used on NICU patients, have been linked to delayed-onset, progressive sensorineural hearing loss (Meyer et al., 1999). The later onset or delayed increase in severity of the impairment might be missed by the initial hearing screening, and would therefore require follow-up screens to find delayed presentations and monitor changes. An American committee of experts has even recommended that newborns with specific risk factors, including spending time in the NICU, should be monitored and examined regularly for three years in order to catch any changes that may occur over the course of initial development (Ptok, 2011).

Although many of the hearing impairments discovered using acoustic screening are due to genetic disorders or diseases caught in utero, some can be caused by perinatal complications. As seen in a recent study by Jiang, Chen, and Wilkinson, pre-term babies born at 33-36 weeks gestation who encounter complications and require time in the

NICU are at higher risk for auditory dysfunction (2012). Jiang and his associates used the Auditory Brainstem Response to test the central auditory function of late pre-term babies both in and out of the NICU. Using the non-NICU infants as a control group, the researchers determined that the perinatal problems can have a negative effect on the auditory pathway. In particular, they found that these NICU babies have an increased wave V latency and increased I-V and III-V interwave latencies. These results suggest that the complications have the greatest effect on the most central portion of the auditory pathway - the brainstem (Jiang et al., 2012).

Recent studies have found that the brain has matured enough by the third trimester to elicit an auditory brainstem potential. At this point in development there is already extensive myelination of the central auditory pathway, from the auditory nerve up to the MGB of the thalamus (Guzzetta et al, 2011). Although the results do not have the same pattern as those in adults, it is possible to test for brain function at this early stage using the ABR. Thus far, these tests have been done on pre-term infants between 27 and 29 weeks of gestational age, and they have been proven as reliable screening tools even at such a young age. In keeping with the idea of discovering and diagnosing auditory pathway abnormalities as soon as possible, it would be helpful to have a sensitive hearing screen for children in utero. It is a bit of a stretch considering that the ABR signal is not currently strong enough to be read without electrodes directly touching the scalp; however, it is a goal to keep in mind as medical technology continues to progress.

In the meantime, the multitude of studies supporting the use of the ABR along with other neurophysiological tests to screen newborns for auditory deficits is continually growing. Based on their findings, it would be prudent to nationally, and even

internationally, mandate a universal hearing screen for neonates that includes the Automated ABR. The AABR and TOAE provide reliable initial screening results that detect hearing dysfunction much earlier than behavioral tests, allowing for quicker intervention. In addition, including the AABR allows detection of a broader range of deficits by catching those whose deficit is neural. The full ABR can then be used to provide more detailed information that can lead to a diagnosis and treatment. Providing treatment early maximizes the benefit that the treatment will provide to the child's auditory function. The effects of treatment are much broader than simply having better hearing capability. Children with early treatment have better skills in language, learning, and social interaction. In conclusion, the ABR is an invaluable tool in the detection and diagnosis of auditory deficits, especially in neonates. A universally mandated hearing screening for newborns that includes the Auditory Brainstem Response is the next obvious step in working to minimize the effects of congenital hearing deficits for children all across the United States and all over the world.

SUMMARY AND CONCLUSIONS

The Auditory Brainstem Response is a neurophysiological test with remarkable diversity in its uses. The waveforms generated by the various structures along the central auditory pathway provide a great deal of insight into the functionality of the brainstem and hearing capability. What began as intracranial recordings in cats to discover how the brain processes sounds has found a broad spectrum of applications throughout the medical field. The ABR provides significant information relating to detection and diagnosis of damage in the brainstem due to lesions, tumors, diseases, coma, and congenital deficits. It also gives reliable prognosis for surgeries affecting the central auditory pathway and is part of a group of methods used to monitor brainstem and auditory nerve function during the operation. Most commonly, the ABR is used for hearing assessments, especially in neonates. Making the ABR part of a universal hearing screen could decrease the number of children with undiagnosed hearing deficits as well as increase quality of life in children who are able to receive treatment at an earlier stage because of the early detection.

In conclusion, the Auditory Brainstem Response has come a long way since 1970, and its utility only continues to grow.

APPENDIX

APPENDIX

Figures

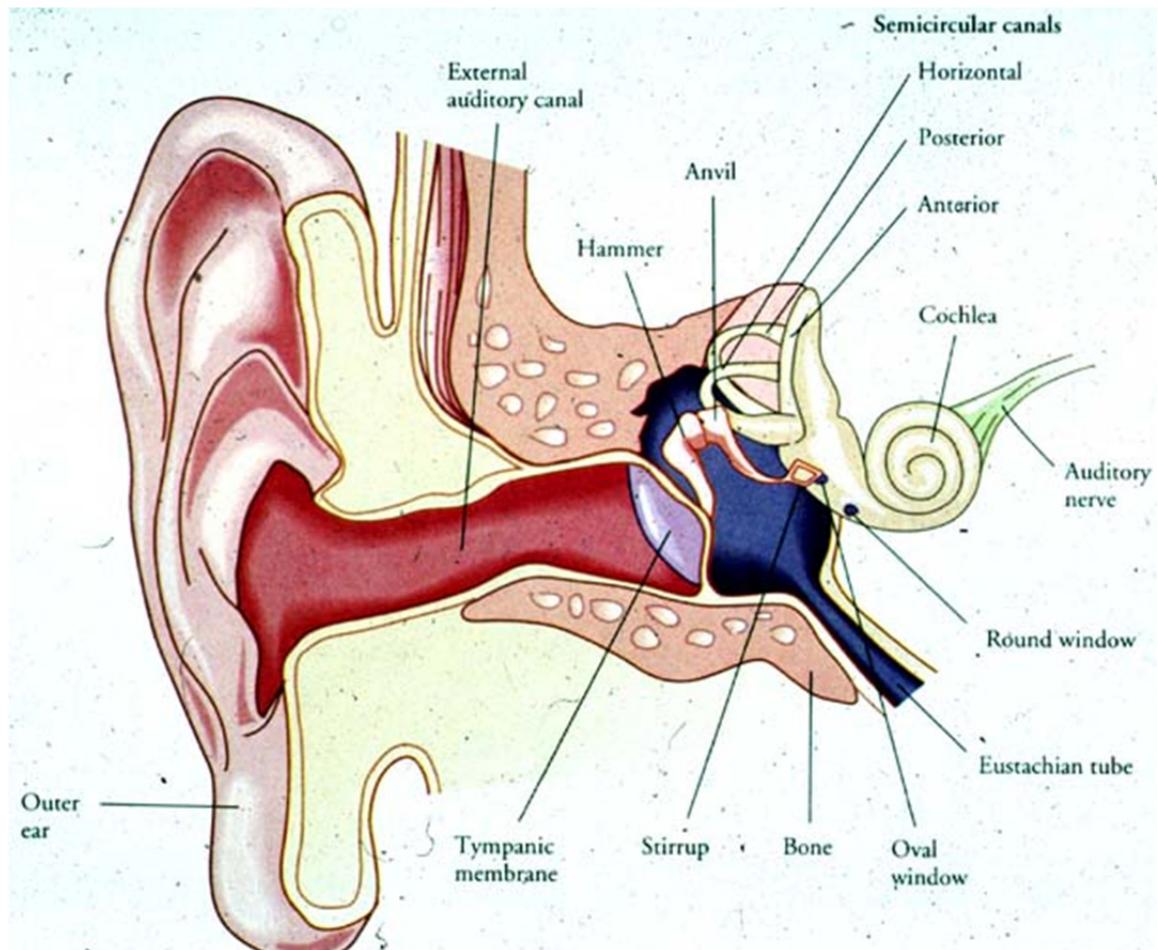


Figure 1. The peripheral auditory pathway.

Adapted from "Auditory System," by University of Texas,
<http://homepage.psy.utexas.edu/homepage/Group/GonzalezLimaLAB/Psy332BehavNeuro/AuditorySystem/large/auditory1.jpg>

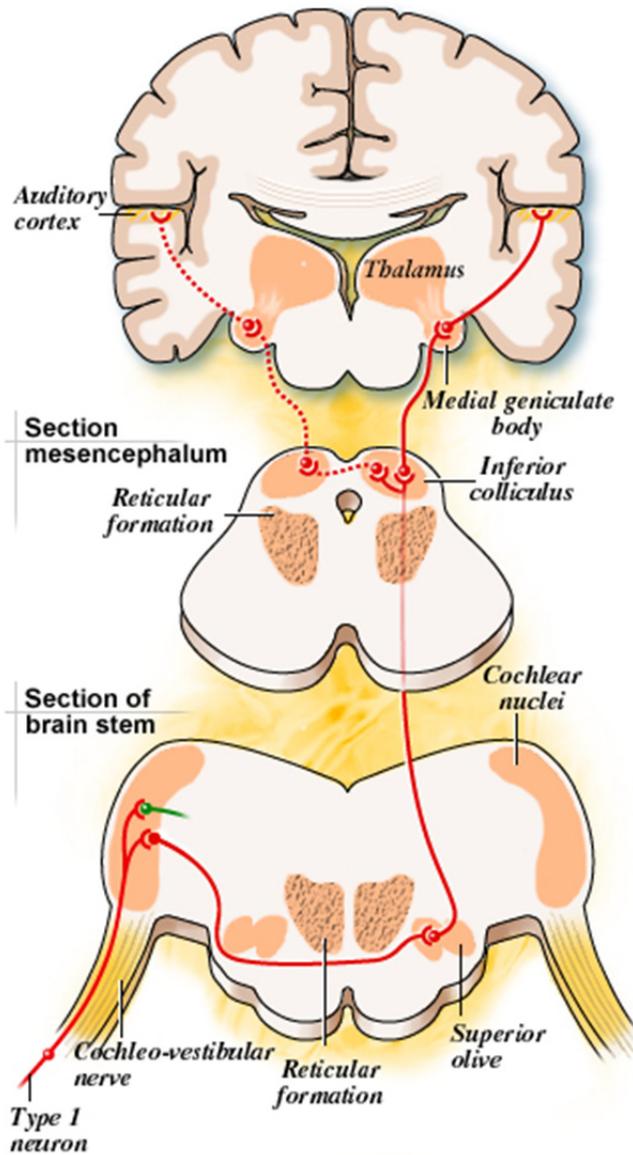


Figure 2. The central auditory pathway – simplified. An auditory signal generally moves down the vestibulocochlear nerve to the cochlear nucleus (CN), then it travels up the brainstem to the superior olivary complex (SOC), inferior colliculus (IC), medial geniculate nucleus of the thalamus (MGN), and ends at the auditory cortex.

Adapted from “Audition for Linguists,” by R. Port, 2007,
<http://www.cs.indiana.edu/~port/teach/641/auditory.path.jpg>

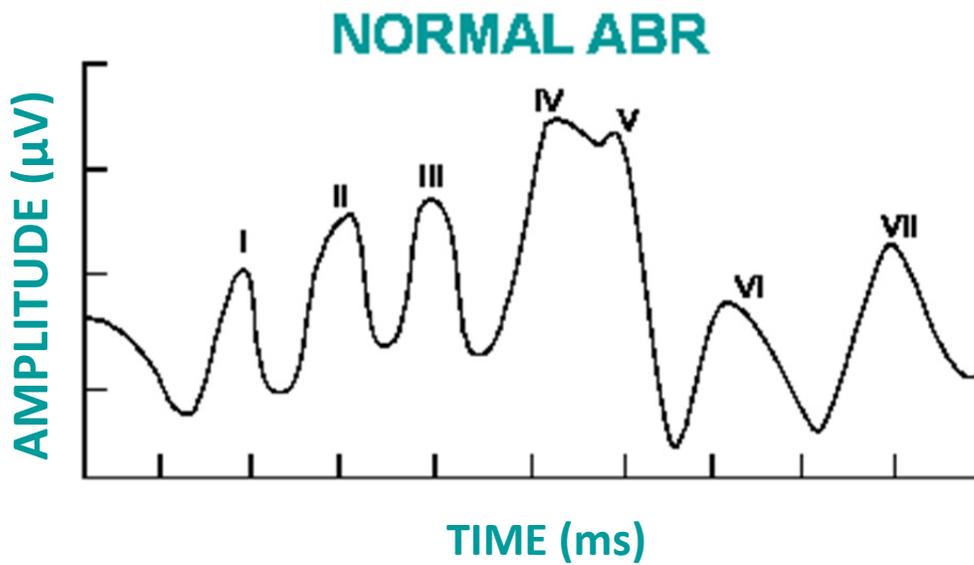


Figure 3. Auditory Brainstem Response waveform.

Adapted from “All about hearing loss: hearing tests to expect as your child grows,” by Boys Town National Research Hospital,
<http://www.babyhearing.org/images/HearingAmp/HearLoss/abr-normal.gif>

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