INTRODUCTION

RATIONALE

Contralateral presentation of noise may interfere with the perception of sound, through the peripheral mechanism mediated via the olivocochlear efferent neurons, [1, 2] middle ear muscle system [3] and through the central masking mechanism. [4]

Efferent auditory fibers travel from the olivo-cochlear bundle at the level of the olivary complex in the brainstem through the vestibulo-cochlear (VIIIth) nerve to the cochlea. The medial olivo-cochlear (MOC) fibers terminate on the outer hair cells while the lateral olivo-cochlear fibers terminate on primary auditory neurons at the base of the inner hair cells. [5- 7] The influence of the MOC system on auditory pathway is measured by introducing an external suppressor stimulus and measuring its effect on otoacoustic emissions (OAEs). [7- 9]

Patients with auditory neuropathy (AN) characteristically show an abnormal olivo-cochlear reflex (OCR) measured by absence of contralateral suppression of OAEs. [7, 9] Authors suggest that the lack of this reflex is most likely related to a breakdown in the efferent portion of the reflex arc. [10]

For the auditory steady state response (ASSR), contralateral suppression was studied and found to exist in 40-Hz potential but was not found in 80-Hz potential in normal listeners. [11, 12] It is not evident that the neural substrate responsible for the suppression is the same for OAEs and ASSR or not. The hypothesis is that if the neural substrate for contralateral suppression is the same for OAEs and ASSR, then in AN, contralateral suppression of 40-Hz ASSR will be absent.

So, this study was designed to investigate the effects of contralateral suppression on 40-Hz and 80-Hz ASSR in those patients. There was no study done on patients with AN, till the date of writing, up to the knowledge of the authors..

REVIEW OF LITERATURE

Auditory neuropathy spectrum disorder:

The term auditory neuropathy/dys-synchrony (AN) had been used to describe a form of hearing impairment in which outer hair cell (OHC) function is normal but afferent and efferent neural conduction of the auditory pathway is disordered.[13,14]

In 1987, Soliman[15] described the pattern of the disease and named it after the commonest audiometric configuration "Low frequency sensori-neural hearing loss syndrome". Because low frequency configuration was not a constant finding, several terms have been suggested to describe the disorder according to its possible pathogenesis, most commonly; auditory neuropathy/ auditory dys-synchrony (AN/AD).[14]

It was precisely described in the mid-1990s by Starr et al, as a progressive sensorineural auditory disorder of variable configurations, ranging from mild to severe degree and it could be of normal auditory thresholds. The condition is typically characterized by poorer speech understanding than predicted from the degree of hearing loss, recordable otoacoustic emissions (OAEs) and/or cochlear microphonic (CM), absent or severely distorted Auditory Brainstem Response (ABR) and normal radiological assessment.[14,16,17]

Recently, the term auditory neuropathy was expanded to auditory neuropathy spectrum disorder (ANSD) to acknowledge the heterogeneous and multifaceted nature of this condition. [18]

Initially, ANSD in children was thought to be a rare form of sensorineural hearing loss (SNHL). In 2005, Rance suggested that ANSD occurs in 2.4% to 15% of pediatric cases those identified with permanent hearing loss. [19]However, a recent systematic review by Vlastarakos et al (2008) indicated that ANSD accounts for approximately 8% of the newly diagnosed cases of hearing loss in children each year. [20] On the other hand, the prevalence was 13.4% in egyptian children as stated by some authors in Al-Meniya and Al-Menoufiya universities.[21]

Etiology

The exact etiology of ANSD is still unknown, but in most cases it presents in conjunction with specific medical risk factors. These risk factors could be broadly categorized as neonatal insults, infectious processes, and genetic or syndromal conditions. The most commonly reported neonatal conditions that associated with ANSD are anoxia and hyperbilirubinemia. More than 50% of early onset ANSD cases presented thus far had shown one or both of these conditions in their neonatal histories. [19]

Infection-related causes of ANSD had been suggested in a small but significant number of the cases reported recently. Starr et al (2000) estimated that postviral infectious processes were involved in 10% of the 67 patients from their ANSD database.[22] Other studies had reported that mumps and meningitis can be associated with ANSD. [23]

That disorder also had been associated with Charcot-Marie-Tooth disease and other hereditary motor and sensory neuropathies. [24, 25] Other disorders thought to be associated with

ANSD included; Waardenburg syndrome, [26]Friedreich's ataxia, [27] mitochondrial disorder, [28] prematurity and major neonatal illnesses,[29] and infection or epilepsy of temporal lobe. [15]

Also, ANSD was reported in patients with mutation in otoferlin gene. This gene is a key calcium ion sensor involved in the Ca(2+)-triggered synaptic vesicle-plasma membrane fusion and in the control of neurotransmitter release at these output synapses. It interacts in a calcium-dependent manner to the presynaptic SNARE proteins at ribbon synapses of cochlear inner hair cells (IHCs) to trigger exocytosis of neurotransmitter. Also it is essential to synaptic exocytosis in immature outer hair cells (OHCs) and plays a role within the recycling of endosomes. [30] In a study that was done by Butiner et al (1999), they reported a genetic cause of ANSD that associated with hereditary sensori-motor peripheral neuropathy. The mode of inheritance was autosomal recessive and the genetic locus for the disorder was on the long arm of chromosome 8q24. [31]

However, in a survey that was done by Rance et al (1991), 3 out of 20 pediatric cases of ANSD, had no health concerns in their histories or evidence of permanent hearing loss of any kind in their immediate or extended families.[23] Moreover, Sininger and Oba (2001) run a survey on adult and pediatric cases, they found that ANSD occurred without associated risk factors in 27% of patients. [32]

Some researchers suggested that ANSD is a part of generalized neuropathy rather than isolated auditory nerve affection. These suggestions based on reported abnormalities either in peripheral nerve conduction studies, somatosensory evoked potentials or combined in many evoked potentials. [33,34]

Site of lesion

It may be difficult to locate the exact site of lesion in ANSD. Some possible sites of lesion include the cochlear inner hair cells(IHC), the synapse between the inner hair cells and type I auditory nerve fibers, spiral ganglion neurons, auditory nerve itself or any combination of the above sparing outer hair cells (OHCs),[23] evidenced by intact cochlear microphonic (CM) potentials and otoacoustic emissions (OAEs).[35]

Inner hair cells (IHCs) receive 95% of innervations of auditory nerve ganglion via type I cells, so they are more likely to be responsible for temporal synchronization of firing of action potential. [36] IHCs loss is a peripheral site of lesion that is consistent with absence of earliest ABR wave which is wave I, which represents the first action potential in the auditory nerve. [19]

In a study that was done by Salvi et al (1999), ANSD had been chemically induced in chinchillas treated with anti-neoplastic agent (carboplatin) that produce selective inner hair cell lesion. [37] ABR thresholds disruption in those animals was considered to be due to a diminution in response amplitude resulted from reduction of number of elements contributing to the volume conducted potential rather than from an increase in the firing threshold for the surviving elements, because single-unit response from inferior colliculus neurons showed normal response thresholds. As such, these findings suggest a mechanism whereby patients with ANSD could demonstrate normal or near normal behavioral hearing thresholds in conjunction with severely disordered evoked potential findings. [19]

The synapse between the cochlear inner hair cells and type 1 auditory nerve fibers also had been proposed as a mechanism that could produce ANSD pattern.[38]At the base of IHCs, there are anatomic structures involved in the storage and release of neurotransmitters. Disorders at this site may be pre-synaptic (involving the release of transmitters) or postsynaptic (affecting the ability of the receptor sites on the auditory nerve dendrite to respond these substances). [22]

Auditory nerve fiber could also be a site of lesion in ANSD, either by demyelination, axonal neuropathy or mixed. Demyelination has profound effects on ABR which is reliant on precise synchronous response of nerve fibers to the stimulus. Axonal damage can occur in isolation as a result of specific disease process or can occur in conjunction with or as a consequence of demyelinating conditions.[39] It reduces the number of neural elements- if it is isolated- but do not directly affect the conduction speed.[40]

Accurate differentiation between axonal and demyelinating neuropathies could be only made from a histological postmortem examination of temporal bone or the brainstem at the point of entry of the auditory nerve. Peripheral nerve studies can be done by taking a biopsy specimen of a small portion of another more accessible sensory nerve. For example, analysis of the sural nerve has been used in ANSD patients in this way.[31,41]

Pathology

One of the suggested underlying pathologies of ANSD is demylination. [14] Partial or complete loss of myelin affects the generation and propagation of action potentials within auditory nerve fibers. It results in an increase in membrane capacitance and a decrease in membrane resistance, leading to a delayed excitation, a reduction in the velocity of action potential propagation and an increase in conduction vulnerability. [42] Fibers that are demyelinated to different degrees conduct neural signals at different speeds, and the synchrony of discharges can be affected. Reduction in the temporal synchrony of demyelinized VIII nerve fibers leads to a significant reduction in amplitude. [19]

Although neurons that are not entirely myelinated are capable of conducting action potentials, they do so with prolonged refractory periods and an impaired ability to transmit high-frequency pulse trains. [42] As a result, repetitive activation of demyelinated fibers results in a progressive increase in the conduction time of the action potential and may lead to an intermittent or total block in their propagation (conduction block). [43]

For axonal neuropathy, the pathology leads to reduction in the amplitude of the whole nerve action potential and ABR rather than an increase in latency or a broadening of these potentials (as in the case for myelin related disorders). [19] The refractory periods of surviving elements also tend to be normal, allowing a reasonably unimpaired response to high-rate stimuli.[40]In summary, disruption or absence of ABR in this disorder is thought to be the result of either a disruption in the temporal integrity of the neural signal, or a reduction in the number of neural elements available to contribute to the response. [19]

Clinical picture

The age of onset of ANSD falls into two groups: those who were presented with symptoms in infancy, and those in whom the condition developed in adolescence or early adulthood. Starr et al (2000) reported that only one in four cases with ANSD are older than

10 years at onset of symptoms, and owed that to some affected patients lose their emissions over time, and as such, may not be recognizable as ANSD cases.[22] Also the physiologic test techniques required to identify the condition (ABRs, OAEs, CM) are more frequently used in screening and diagnostic programs in pediatric populations. [22]

Patients with ANSD may show different degrees of permanent or fluctuating hearing loss. The most characteristic feature is difficult speech understanding especially in noise or in difficult hearing situations.[14, 16, 44]

Basic audiological assessment

Patients with ANSD show variable degrees of unilateral or bilateral sensorineural hearing loss, ranging from slight to profound. Normal hearing thresholds are also had been reported. Low-frequency or flat audiograms are common if any degree of hearing loss exists. Nevertheless, a smaller percentage of patients display other audiometric configurations. [32]The finding of a low-frequency hearing loss in many of ANSD patients may be due to their impaired auditory processing of temporal information since the timing of auditory nerve discharge plays a role, particularly, in the encoding of low spectral acoustic signals.[14]

In most patients, speech discrimination scores are reduced dramatically, and are significantly poorer than would have been expected for sensorineural losses of equivalent degree. [14, 16, 19, 21, 32] Immittancemetry shows normal middle ear functions and elevated or absent middle-ear muscle reflexes (MEMRs) for both adults and children with ANSD, to both ipsilateral and contralateral stimulation. [19]

Electrophysiological assessment

The presence of OAEs associated with absent ABRs is pathognomonic of ANSD. Although in some advanced and over amplified cases, OAE recordings may be absent in up to one third of ANSD cases. [45] Some authors suggest that, loss of emissions could be part of the extension of the Otoferlin gene activity which first compromises the IHCs. [46] Consequently, depending on when the initial diagnosis is made, preserved OAEs and absent ABRs will not provide a final definition and diagnosis of ANSD. Berlin et al (1998) suggest that electrophysiological assessment consisting of separate responses to negative and to positive polarity clicks to differentiate cochlear and neural responses, must be conducted to distinguish between cases of commonly understood sensorineural hearing loss and cases of ANSD with absent OAEs. [47] In such cases, the presence of CMs becomes the determinant finding in the differential diagnosis of this condition. [13, 45, 48] In ANSD, contralateral suppression of OAEs is absent. [10]

The presence of CMs in Electro-cochleography (ECochG) is indicative of at least some degree of outer hair cell function and is therefore suggestive of neural transmission abnormality in ears with absent or disrupted ABRs.[14, 38, 47] Reports in the literature have shown that CMs in these patients are more prominent, having an abnormally increased amplitude. [29, 38, 47, 49] Starr et al (2001) hypothesized that CMs amplitude may be enhanced due to a change in the OHCs resting membrane potential.[49] This potential persist for up to 4 to 6 milliseconds after click stimulation contrary to what is found in normal subjects.[50]

In ANSD, ABRs are absent or grossly abnormal including wave I at maximum stimulus presentation levels regardless of behavioral hearing level. [14, 23, 32] In a recent study [51], ABR testing with air-conducted clicks at the limits of the equipment (90 dBnHL) indicated a possible wave I bilaterally; however, no responses were obtained to unmasked bone-conducted clicks (65 dBnHL) or air-conducted 500-Hz tone bursts (90 dBnHL). By reversing the polarity of the stimulus, the apparent wave I inverted in phase indicating CM response rather than the compound action potential of the VIIIth nerve [51], as Berlin et al (1998) stated that a cochlear microphonic (CM) response will invert with polarity inversion while a neural response will not. [47]

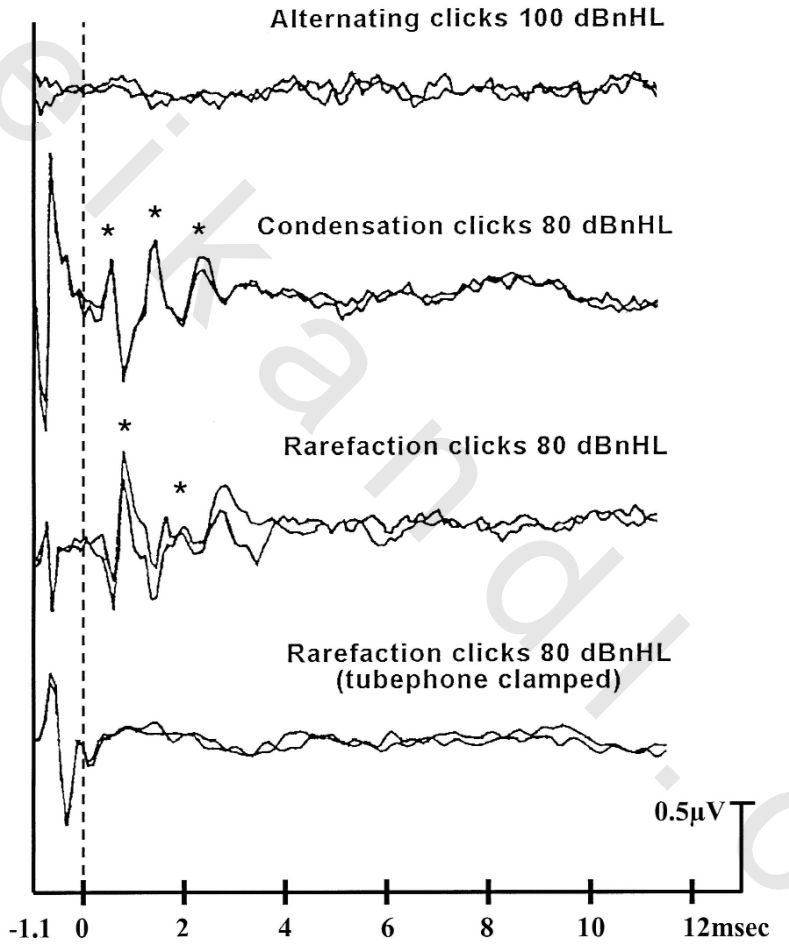

Figure (1): ABR recordings for a 3-year-old child with AN/AD type hearing loss.

The dotted line represents the point at which the stimulus reached the cochlea. The top tracings show no repeatable potentials to alternating clicks presented at 100 dBnHL. The middle tracing pairs show repeatable cochlear microphonic responses but absent brain stem response waveforms to unipolar stimuli at 80 dBnHL. The asterisks indicate the positive peaks in the cochlear microphonic waveform. The final tracings, in which only the stimulus artifact is evident, were obtained to Rarefaction clicks presented with the tube phone clamped. [19]

Middle latency response (MLR) is absent, indicating temporal affection. The late auditory evoked potentials showed recognizable N1 and P2 components. These were small and often slightly later than normal. There was also a recognizable P300 wave in response to a detected target stimulus. [14]

For Auditory Steady State Response (ASSR), dramatic differences have been reported between the auditory threshold results of behavioral audiometric tests and ASSR. Some studies have reported that PTAT results for all frequencies are better than ASSR, [52] whereas in other set of studies, these results have been observed to be poorer than ASSR results for most frequencies. [53] However, the discrepancy between the ASSR and PTAT results can be useful as an adjunct to the discrepancy between ABR and audiometric thresholds in the diagnosis of ANSD. [54]

Vestibular assessment

Vertigo and disequilibrium are rare complaints in patients with ANSD in spite of vestibular affection in the form of absent or reduced caloric response. [31] In a recent study,[34] vestibular affection was evaluated in 50 patients with ANSD by performing videonystagmography (VNG), rotation chair testing and dynamic posturography. Authors reported 44% of those patients had bilateral extensive peripheral vestibular lesion, even though only 18% had dizziness complaint. It is rare complaint because of slow rate vestibular degeneration and it is bilateral and symmetrical lesion that allow for central compensation.[55]

Psychophysical assessment

Reduced or absent masking level difference (MLD) and elevated auditory fusion thresholds in those patients are causes of temporal processing deficit that is responsible for poor speech discrimination scores. Pitch discrimination and Pitch pattern sequence tests also show abnormal results. [56,57]

Radiological assessment

Computerized tomography (CT) scan and magnetic resonance imaging (MRI) are normal in all patients with ANSD excluding any space occupying lesion. [14, 23]

Differential diagnosis

Patients with vestibular schwannoma (VS) that compress the VIII nerve without compromise of cochlear blood flow demonstrate many of the same auditory test results as the patients of ANSD. They could have normal otoacoustic emissions, [58] absent acoustic middle ear muscle reflexes, absent contralateral suppression of otoacoustic emissions, and disordered temporal processing manifested by a disproportionate loss of speech intelligibility relative to threshold change.

The most common audiometric pattern in patients with VS that differentiate it from ANSD is a high-frequency loss[59] due to peripheral position of fibers from the basilar end of the cochlea in VIII nerve rendering them particularly susceptible to the pressure effects from the tumor. [14]

Also, the most common ABR finding of VS is preservation of wave I with delay or attenuation of later waves. [60, 61] Wave I could be absent in VS patients accompanied with profound hearing loss if only the tumor compress the vascular supply of the cochlea

causing widespread ischemia and damage to the cochlea. In contrast in ANSD, all waves of ABR are absent or distorted even in least hearing impairment. [14] MRI (with gadolinium) is diagnostic in VS patients showing space occupying lesion, with normal finding in ANSD. Tinnitus and disequilibrium could be present in the VS cases rather than ANSD cases. [14]

Disorder of the brainstem portion of the auditory pathway sparing the VIII nerve shares most of the audiological features of ANSD since the cochlea is not involved. It can be distinguished from auditory nerve disorder by preservation of wave I which is generated by extracranial portion of auditory nerve. [14]

Treatment

The provision of hearing aids to patients (particularly children) with ANSD is currently a controversial issue. There are two main arguments against conventional amplification. The first relates to safety and the potential acoustic damage to cochlea especially outer hair cell function. The second concerns the inherent auditory pathway limitations in ANSD subjects and the likelihood that conventional amplification will simply produce a louder but equally distorted signal.[19]

This acoustic trauma occurs as the efferent suppression and acoustic reflex mechanisms that are thought to protect the cochlea from excessively loud sounds may be inactive in those patients. [14, 62, 63] It is recommended that OAEs be carefully monitored as a measure of OHCs health in the amplified ears, [64] or that hearing aids not be considered unless emissions have already disappeared. [50] OAEs amplitude reduction has been documented in children with high-powered amplification. [32] However, there have been a number of reports of emission presence at normal amplitudes after long-term aid use. [22, 23] Overall, no correlation had been established between hearing aid use and loss of OAEs. [19] Moreover, Starr et al (2000) and others presented results suggesting that the presence or absence of evoked OAEs is unrelated to either hearing threshold sensitivity or speech perception ability in affected patients.[22, 23, 45]

However, some authors have considered that amplification should not be used at all for children with ANSD, [65] or that if hearing aids are tried, they should only be fit monaurally and should be low-gain (provided intact emissions) to avoid acoustic trauma and wide dynamic range compression devices, even in subjects with severe-to-profound hearing loss. [64]

Berlin et al (2003) in summarizing their findings for 193 ANSD patients seen over a 20-year period, these authors have concluded that “while hearing aids improved detection thresholds, the long-term value of hearing aids in understanding speech is far poorer than predicted based on the audiogram and/or articulation index alone”. [66]

In its recent position statement, the Joint Committee on Infant Hearing (JCIH, 2007) recommended that "children with auditory neuropathy-type hearing loss undergo a trial with amplification and that decisions regarding continuing hearing aid use be guided by the benefits derived from amplification."[67]

Cochlear implantation might be of benefit to patients with ANSD. Patients who had cochlear implants and presented preoperatively with no speech discrimination ability, have

shown postoperatively significant perceptual benefits and have performed a range of speech discrimination tasks at levels consistent with their implanted sensorineural peers.[68- 71]

In addition to improved sound detection, authors proposed that electrical signals produced by cochlear implants stimulate the auditory pathway. That was evidenced by recording electrically evoked physiologic responses such as the compound action potential (CAP),[68, 69, 72, 73] and ABR. [69, 72, 74] That change represents either an improvement in the synchrony of neural firing or an increase in the number of contributing neural elements.[19]

Auditory steady state response

Auditory Steady State Response (ASSR) is a scalp-recorded auditory evoked potential that evaluates, among other aspects, neural synchrony, based on frequency or amplitude modulation of tones. The target potential is generated when a stimulus is presented in a stimulation/modulation rate rapid enough for the response to a given stimulus to overlap the response of the subsequent stimulus. This overlap causes a periodic frequency modulation response. [75, 76] The response itself is thought to be the superposition of MLRs and ABRs. [77]

Occasional reports of steady state responses to auditory stimuli recorded from the human scalp appeared in literature in the 1960s and in the 1970s by Geisler [78] and Campbell et al [79], respectively. However, the ASSR was first described in detail in (1981) by Galambos et al.[77] In his study, Galambos named "40 Hz event related potential" after the largest amplitude that recorded as an evoked response to a stimulus presented at a rate of 40/sec.[77]

Subsequent research in the mid- to late 1980s, identified that the 40 Hz response could not be reliably recorded in infants and young children as the peak amplitude of their ASSR occurred at rates of approximately 20 Hz, [80, 81] and the presence of the 40 Hz response was dependent upon subject state and could only be reliably recorded in awake subjects. [82- 84]

In 1991, Cohen et al proved that ASSR could be recorded in adults during various states of arousal when testing at higher modulation rates between 70 Hz and 100 Hz. [85] Pediatric studies recorded ASSR in infants either awake or sleep also at higher stimulation rates between 70 Hz and 100 Hz. [86- 88]

The ASSR test is most commonly used for estimating behavioral thresholds. It has been used in research to estimate residual hearing in pediatric candidates for cochlear implants, to confirm auditory thresholds, [89, 90] to draw comparisons between click-evoked auditory brainstem responses, ASSRs and behavioral thresholds,[91, 92] and to diagnose neonates who present evidence of ANSD. [23]

ASSR testing has advantages over click ABR. First, capability of introduction of multifrequency stimulation simultaneously (multiple ASSR), that is considered time saving approach.[93] Second, objective response detection technique provide ASSR testing with unbiased estimates of behavioral hearing thresholds due to its frequency domain statistical analysis approach, unlike the ABR, which requires human expert interpretation of time domain data. [94] Third, ASSR test evaluates residual hearing up to severe to profound

hearing loss ranges while ABR estimates up to severe hearing loss.[93] Lastly, frequency specificity and the ability to obtain higher output levels. [95]

Neural generators of ASSR:

ASSR can be generated by modulated stimulus over a wide range of modulation frequencies, and the physiological features vary considerably according to the modulation frequency. [76, 86]

Neural generators of the ASSR have been investigated using various types of neuro-imaging techniques including Brain Electrical Source Analysis (BESA) [96] magnetoencephalography(MEG),[97, 98] and functional magnetic resonance imaging (fMRI). [99] Studies also have been performed using patients with known lesions in the auditory cortex and/or midbrain regions of the auditory pathway,[100] and by conducting animal studies.[101, 102]

According to these results, authors suggested that when ASSRs are elicited by stimulus presented at rates less than 20 Hz, these responses are mainly generated by activity in the primary auditory cortex, [96, 101] when elicited by stimulus presented at rates between 20 and 60 Hz, the underlying neural generators are mainly located in the primary auditory cortex, auditory midbrain, and thalamus,[96, 97, 100, 101] and lastly, when elicited by stimulus presented at rates greater than 60 Hz, these responses are generated primarily by contributions from the superior olivary complex, inferior colliculus, and cochlear nucleus. [76, 96, 101, 103]

The results of these neural generator studies also demonstrated that ASSRs recorded at any of these stimulation/modulation rates, received contributions from multiple generators. However, recording parameters such as stimulus rate and electroencehalograhy (EEG) band pass filter settings can suppress contributions from certain underlying neural generators to the final averaged response.[93]

Characteristics of ASSR:

The ASSRs are typically elicited by amplitude-modulated (AM) and/or frequency-modulated (FM) stimuli. The stimuli are presented at a high rate enough to cause overlapping of the transient responses to successive stimuli. [104] The energy in the resultant response is at the modulation frequency and its harmonics, representing the synchronous discharge of auditory neurons in the brain stem, phase locked to the modulation frequency of the stimulus. [105]

The response is detected by using statistical measures of the response signal-to-noise ratio (SNR), typically either the amplitude of the response compared to background EEG noise or its phase variability. If the amplitude of the ASSR yields a significant SNR, a response is seemed to be present. No visual waveform identification is required. [104]

Types of stimuli:

Two primary terms are associated with ASSR, carrier frequency (CF) and modulation frequency (MF). The CF of the tonal stimulus is the test frequency of interest. The CF is associated with the region in the cochlea where the hair cells are activated in

response to the presentation of a stimulus. Typical CF tones used to record ASSR are 500, 1000, 2000, and 4000 Hz.[96,106]

The MF is the frequency at which the EEG activity is synchronized to fire. [93] It is derived by calculating the period (T) of the MF. (T = 1/f = 1 sec./ MF = 1000ms/ 100 Hz = 10 ms). In this example, a CF tone is presented with a 100 Hz MF. If the auditory nerve is intact and functioning normally, the VIIIth nerve fibers will synchronously fire at 10 ms intervals throughout the stimulus. [106]

There are several types of stimuli used to record ASSRs. These stimuli could be: broadband (non–frequency specific) stimuli and frequency-specific stimuli. [93]

Broadband stimuli encompass a range of frequencies and include clicks, noises, and chirps. In contrast, frequency-specific stimuli include filtered clicks, tone bursts, pure tones and band-limited chirps. [107]

The most common types of stimuli used in recording the ASSR are sinusoidal amplitude modulated tonal stimuli, frequency modulated tonal stimuli, mixed modulated tonal stimuli, and repeating sequence gated tonal stimuli.[93]

Amplitude modulated (AM) tone is stimulus that change in amplitude over a period of time, [76]the degree of change in the amplitude is referred to the depth of modulation and is reported as a percentage, with a larger number (90–100%) indicating a greater change in the amplitude of the response. [108]The acoustic spectra of AM shows energy at the carrier-frequency plus two side bands at frequencies equal to the carrier frequency plus/minus the modulation frequency. [95]

Frequency modulated (FM) tone is a stimulus in which only the frequency content of the stimulus changes over the duration of the tone. The change in the frequency of the tone is expressed as a percentage of the CF tone and these changes occur both above and below the CF. Frequency modulation looks at the maximum and minimum frequencies presented and how they relate to the CF. [109]

Mixed modulation (MM) tone is a stimulus that involves a combination of amplitude and frequency modulation.

Repeating sequence gated (RSG) tone. It includes various types of tonal stimuli such as linear-gated tones; cosine squared gated tones, and Blackman-gated tones. As the name implies, these RSG tones have a regular repeating pattern that can be combined to form either a single frequency tone or a multiple frequency tone. [93]

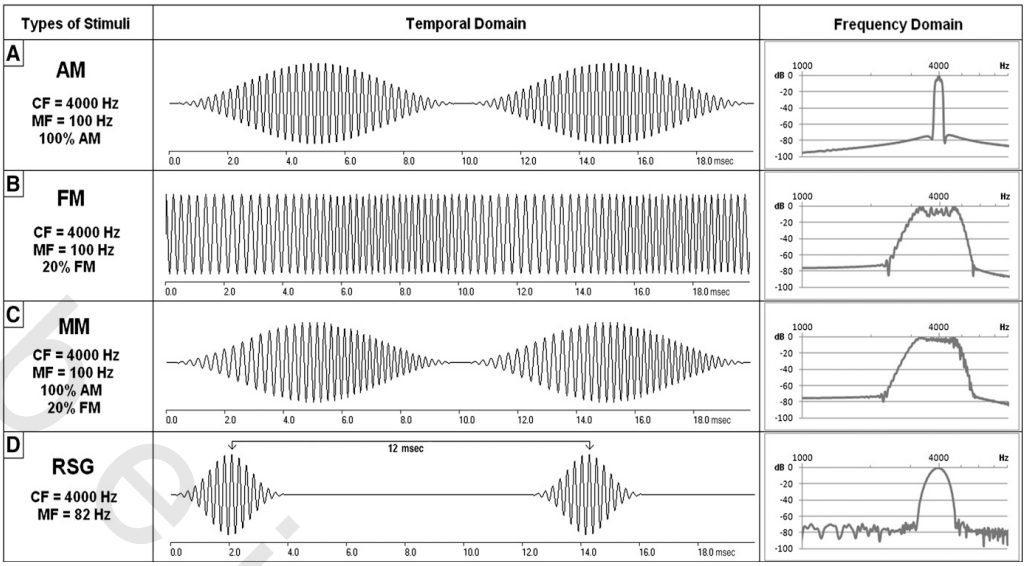

Figure (2): Most common types of stimuli used to elicit an ASSR response as seen in the temporal and frequency domains. (Modified and adapted from John and Purcell, 2008). [113]

The AM tone is the most frequency specific stimulus of these four types of stimuli. In contrast, the MM tone is the least frequency specific one; however, large response amplitudes are elicited with this type of stimulus. [110, 111] Dimitrijevic et al (2001) proposed that MM tone is affected by the phases of the AM and FM components, and this can alter the frequency spectra of the tone.[112]

When the AM and FM components are out-of-phase by 180 degree, the peak of the spectra will skew to the lower frequencies and potentially decrease the amplitude of the response. In contrast, when the AM and FM components are in-phase, reaching their maximum amplitude at the same time, the peak of the MM spectra will skew to the higher frequencies while increasing the amplitude of the response. [112]

Recently, John et al (2008) reported that the amplitudes of the ASSRs recorded to MM tones, within-phase AM and FM components, are approximately 20% larger than those recorded to either AM tones or FM tones and the responses still remain fairly frequency specific.[113]

Stimulation techniques:

Two primary stimulation techniques used to record the ASSR, a single frequency stimulation technique and a multi-frequency stimulation technique (multi-channel ASSR).[114] The single frequency stimulation technique presents one CF tone to one ear using one MF. The multi-frequency stimulation technique tests many CF tones presented simultaneously in either one or both ears (dichotic) with assigning a unique MF between 75 and 110 Hz to each of the CF tones.

In multi-frequency stimulation technique, the compound stimulus being delivered to the ear contains energy at each one of these CFs. These unique MFs are necessary for the

processing of the stimuli to remain independent through the auditory system and up to the brain. [93] With the multi-frequency stimulation technique, it is also possible to record the ASSR binaurally (dichotic) in approximately the same amount of time it would take to test one stimulus frequency in one ear using the single frequency stimulation technique(i.e., 8 different modulation rates).[115]

In the multiple technique, the possible interactions that may occur in the cochlea and/or brain among these stimuli at each of the carrier frequencies, must be considered. [93] Interactions as masking effects, suppression, and/or facilitation. [116]

Despite these concerns, several investigators had shown that ASSR amplitudes in normal hearing adults to the simultaneous presentation of four AM tones with MFs ranging between 70 and 110Hz to one and/or both ears at stimulus intensities at or below 60 dB SPL are not significantly different from ASSR amplitudes when each AM tone is presented alone. [108, 117- 119]

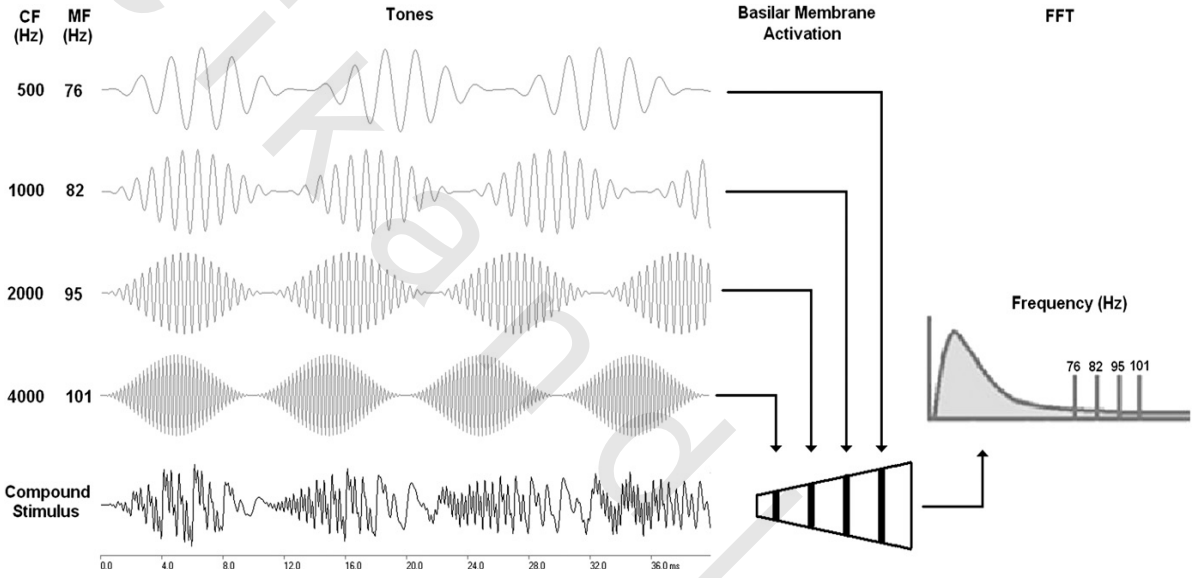

Figure (3): Multi-frequency stimulation technique

Displays how the four carrier tones are presented simultaneously and thus stimulate the frequency regions of the basilar membrane best tuned to these frequencies. The energy present at the MF can be seen in the FFT results. (Modified and adapted from John and Purcell, 2008). [113]

However, Dimitrijevic et al (2001) reported that 5 of their hearing-impaired subjects had more accurate ASSR threshold estimations for 2000 and 4000 Hz using the single frequency versus the multi frequency stimulation methods, thus suggesting that a possible masking effect was occurring in the multi-frequency test condition caused by inclusion of lower frequency stimuli (e.g., 500 or 1000Hz tones). [112]

Recently, Hatton and Stapells (2011) reported that the mean ASSR amplitudes for the monaural single frequency test condition were significantly larger than the response amplitudes for monaural multi-frequency and binaural multi-frequency conditions for 60 dB SPL stimulus, in 15 normal hearing infants. They suggested that the reductions in amplitude seen in the infants' multi-frequency test conditions are likely the result of the immaturity of neural development within the auditory brainstem.[120]

John et al (1998) provided several recommendations to avoid significant interactions effects when using the multi-frequency stimulation technique.[117] These recommendations include (1) MFs for the CF tones should be between 70 and 110 Hz, (2) CF tones need to be at least one octave apart in order to simultaneously present up to four tonal stimuli to one ear without significant loss in the amplitude of the ASSR, and (3) stimulus intensities of the CF tones need to be 60 dBSPL or less.

Analysis techniques:

Analysis of the ASSR is objective and relies on statistical methods, such as the F test, to predict the presence or absence of a response with a certain degree of statistical accuracy. [93] Two primary techniques are used to analyze the ASSR, and both methods initially require that the temporal waveform of the ASSR be converted into the frequency domain using Fast Fourier transform (FFT) analysis.

One technique used to analyze the ASSR relies on phase coherence values. Phase coherence (PC) is related to the signal (response)-to-noise (background EEG and myogenic) ratio and it is presented in squared (PC^2) value. [121]These PC^2 values range from 0.0 to 1.0 and are measured on a normalized scale. The closer the value is to 1.0, the higher the coherence value is, indicating that the amplitude of the response is significant and is distinguishable from the amplitude of the background noise. The amplitude and phase information, provided by the FFT results, is used to form a plot displayed in polar coordinates, commonly called a polar plot. The magnitude or amplitude of the response corresponds to the length of the vector, whereas the phase or time delay is indicated by vector angle. [93]

The pattern is considered **phase locked** representing significant neural response, if the PC value is close to 1.0, the vectors in the resultant polar plot are located primarily in one quadrant forming cluster of responses and that response is distinguishable from the EEG noise. This situation only occurs when the brain is responding or firing synchronously in response to the temporal information present in the stimulus. In contrast, it is considered **random response** representing undetectable true neural response if PC value is closer to 0.0 and the vectors are present in all four quadrants indicating dys-synchrony in the neural firing pattern.[93]

Another method of analyzing the ASSR uses a combination of the FFT results and the F-test, to statistically evaluate the presence or absence of a response to a certain CF tone presented at one stimulus intensity by providing a spectral view of the energy occurring at MFs in comparison to the energy present at the surrounding frequencies. If the amplitude of the response at the MF is significantly larger than the EEG energy at frequencies above and below the MF, then a response has been detected for the CF tone presented at that stimulus intensity. [93]

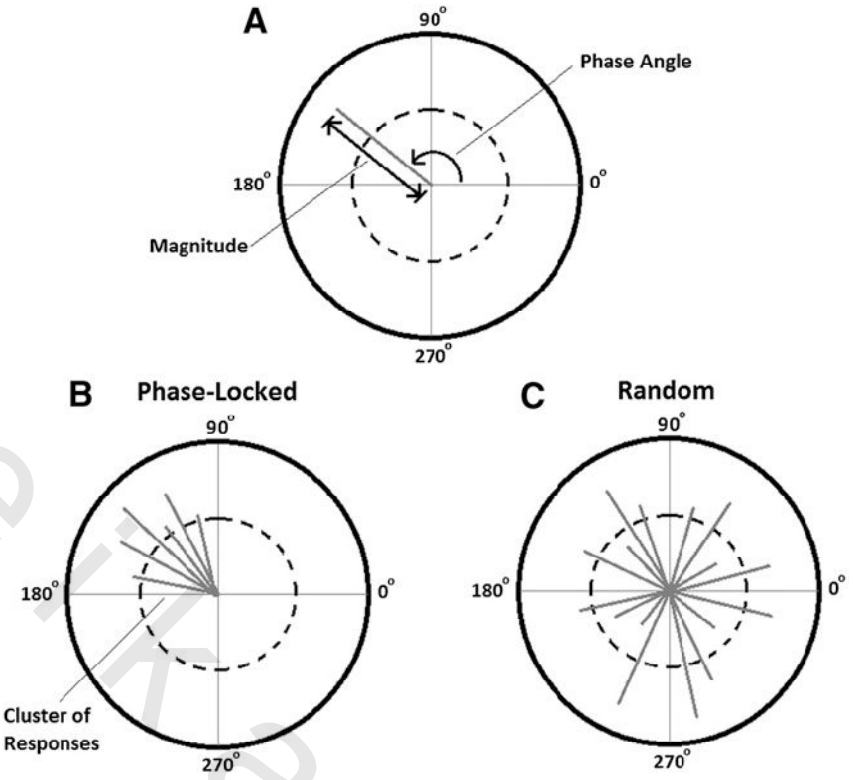

Figure (4): Polar plot

(A) An example of an EEG sample shown as a vector on a polar plot where the angle of the vector indicates phase information and the length of the vector indicates the magnitude of the response. (B) An example of a polar plot showing a response that is phase locked with all vectors in the same quadrant and a PC2 value of 0.9 indicating a high coherence value. (C) An example of an ASSR polar plot showing a response that is random due to the spread of the vectors across all four quadrants with a PC2 value of 0.1 indicating a low coherence value. [93]

40 Hz and 80 Hz modulation frequencies:

ASSR can be recorded for a large range of modulation frequencies, from 4 to 450 Hz.[122] Different stimulus rates result in ASSRs of different neural origins. The largest responses are obtained with stimulus modulation frequencies around 40-Hz and 80-Hz. [123]

Studies investigating the neural sources of the 40-Hz response concluded that this response has both brainstem and cortical generators (thalamus and primary auditory cortex.[96, 100, 124] Galambos et al (1981) record robust 40 Hz responses in awake subjects, especially in adults as their auditory cortices were fully mature and intact. Unfortunately, subsequent research showed the 40-Hz ASSR was decreased in sleeping subjects, [84, 85] and, more importantly, it is very difficult to record in infants,[80, 81] because their auditory cortices are not fully mature[93] and the peak amplitude of their ASSR occurred at rates of approximately 20 Hz. [80, 81]

However, some researchers demonstrated that ASSRs to stimuli presented with rates of 70- to 110-Hz—the brainstem ASSR—are easily recordable in sleeping infants.[88, 108, 115, 125] Recent studies investigating the neural sources of the 80-Hz ASSRs in humans and animals indicate that they originate primarily from brainstem structures. [102, 124, 126]

Although not yet confirmed, it is quite likely that the 80-Hz ASSRs are actually ABR waves V to rapidly presented stimuli.

Most studies using 40 Hz ASSR indicate that ASSR thresholds are within 10 to 20 dB of behavioral results. [76, 127] Furthermore, recent studies report that multiple 40 Hz ASSR thresholds are significantly closer to behavioral results compared to multiple 80 Hz ASSR. [127]

Levi et al (1993), found 80 Hz to be the optimal modulation rate to obtain clear ASSR in sleeping adults and infants. [128]Studies with neonates using these high modulation frequencies have shown that this evoked potential technique is a fast, reliable, and accurate automatic procedure suitable for mass screening. [87] These "high-rate" ASSRs, show equivalent latencies around 10 ms, supporting the theory of late brain stem generators. [85]

Estimation of hearing threshold:

It is believed that continuous AM-FM tones used for eliciting ASSRs may be more effective than transient stimulus in estimating hearing thresholds. First, continuous AM or AM/ FM tones produce sufficiently synchronized neural activity, unlike some transient AEPs. Second, frequency specificity of the stimulus allows the possibility of generating "evoked potential audiograms" that reflect the audiometric configuration of the subject.[129]

Third, behavioral detection thresholds for continuous modulated tones are typically within 1 to 2 dB of American National Standards Institute (ANSI) reference levels and are presented in the same units (dBHL). Brief stimuli, by contrast, require a correction factor (to compensate for their brevity), which creates the potential for calibration error. [129]

Fourth, continuous AM or AM/FM tones could be delivered up to maximum presentation levels for most test frequencies in the audiometric range as high as 120 dB HL, allowing for the possibility of assessment of hearing levels in the profound range. [130] By contrast, calibration corrections limit the maximum presentation levels available for tone burst testing to approximately 100 to 110 dB HL. [131]

ASSR thresholds have been shown to be highly correlated to behavioral thresholds in normal hearing adults and older children. [132- 134]Herdman and Stapells(2003) evaluated subjects with a range of hearing losses and configurations. Subjects having hearing losses that steeped by 30 dB or more between octaves had equally good correlations between ASSR and behavioral thresholds as subjects with shallower or flat losses. [135]

Artifactual ASSRs and Non-Auditory Responses:

One pitfall of using ASSR is demonstrated by the findings of spurious or artifactual responses, usually low frequency, to high intensity air-(at least 100 dBHL) and bone- (50 dBHL or higher) conduction stimuli in individuals with severe or profound hearing loss. [136- 138] Some of these artifactual ASSRs are now known to be due to high-amplitude stimulus artifact contaminating the recorded EEG, and aliasing to mimic physiologic responses. By changing the analog-to-digital (AD) rate; filtering the EEG and alternating the stimulus; thus removing any aliased energy, most of these artifactual ASSRs disappeared. [138]

In addition, there are physiologic but non-auditory ASSRs in individuals with severe or profound hearing loss have been recorded to 500 Hz and 100 Hz stimuli (no responses were seen at 2000 or 4000 Hz). [138] Small and Stapells (2004) found that even when using an appropriate AD rate, anti-aliasing filter, and alternated polarity stimuli, many of the deaf subjects still showed these responses.[138]Other studies using transient evoked potentials suggested that these responses might be vestibular in origin. [138- 140]

ASSRs in patients with ANSD:

ASSR had been compared to conventional behavioral audiometric thresholds in different populations; in normal-hearing individuals, and in individuals with different degrees of hearing loss. [52, 53, 115] In most of these studies the researchers were interested in using ASSR as a clinical tool for the estimation of audiometric thresholds at various frequencies. In general such studies had shown that ASSR is a suitable tool for assessing the hearing of patients who do not fully cooperate in behavioral audiometric tests, individuals with profound sensorineural hearing loss and for whom the application of other tests and methods such as ABR is not possible.[141]

In the case of ANSD, however, ASSR is clearly not suitable for the estimation of audiometric thresholds because of the substantial differences between PTAT and ASSR thresholds and the lack of correlation, between the two measures.[54, 142] Emara et al (2010) investigated ASSR thresholds in normal hearing subjects and patients with ANSD, they found that ASSRs had good predictive value for behavioral hearing thresholds in subjects with normal hearing; however they did not correlate with behavioral hearing thresholds in ANSD patients. [143]

The efferent (olivo-cochlear) pathway:

The olivo-cochlear pathway is a neural pathway which innervates the cochlear OHCs, comprised of efferent neurons that travel from the superior olivary complex in the brainstem to the cochlear outer hair cells playing an important role in the olivo-cochlear reflex (OCR). [144, 145]

There are two forms of olivocochlear efferent fibers, medial olivocochlear (MOC) and lateral olivocochlear (LOC) efferents. The majority are the thin unmyelinated fibers of the LOC system arising from the lateral superior olive and travel via the auditory nerve to the cochlea where they terminate in the nerve beneath the inner hair cells, receiving contributions from both sides of the brainstem. The majority of these fibers innervate the ipsilateral cochlea. Thick, myelinated neurons of the MOC pathway originate in the medial part of the superior olivary complex. A portion of fibers crosses the midline to the contralateral cochlea while others project to the ipsilateral cochlea, both via the vestibular nerves. [146]

Within the cochlea, the MOC fibers innervate the outer hair cells; this is referred to as the medial olivocochlear system (MOCS). The MOCS is innervated by ascending and descending neural pathways. Descending innervations arises from the inferior colliculus and auditory cortex of the same ear.[147, 148] Ascending innervations arises predominantly from the contralateral cochlea, crossing the brainstem from cochlear nucleus to the olivary complex.[149, 150]

Efferent stimulation can be activated by sound presented to the contralateral ear.[151] However, most studies of efferent stimulation had been performed by electrical stimulation of efferent axons and measurement of effects in the cochlea.[152] Contralateral acoustic stimulation (CAS) has been found to elicit similar effects to electrical stimulation of the MOCS.[153] Medial myelinated fibers have a lower threshold for extracellular current stimulation than do lateral unmyelinated fibers. Moreover, MOC axons travel nearer to the floor of the fourth ventricle where stimulating electrodes are usually placed. Sectioning of the olivocochlear bundle in the floor of 4th ventricle or in the inferior vestibular nerve abolished this contralateral suppression effect. [154, 155] Taken together, these observations imply that electrical stimulation activates medial but not lateral efferents. Thus, most efferent effects are attributed to the MOC system. [152]

Auditory suppression caused by efferent system stimulation either by contralateral sound or electric stimulation (in the floor of the fourth ventricle) activates contra- and ipsilateral axons of the MOC fibers to reduce the amplitude of the compound action potential produced by a brief acoustic stimulus. Moreover, basilar membrane motion is diminished by efferent activity. [156] These effects most likely result from an inhibition of the motor function of OHCs, which is required for sensitive IHCs responses, thus indicating that MOC activity reduces amplification causing auditory suppression in the form of elevation of hearing threshold (threshold shift). [156, 157]

Contralateral masking:

Auditory masking is a phenomenon in which the audibility of one sound (signal) is decreased by the presence of another sound (masker). According to the side where the masker is presented, it could be ipsilateral or contralateral. Under such masking conditions, the sensation thresholds for the signal sound are elevated and the amplitudes of the auditory evoked responses to the signal sound are usually reduced. “Masking” is known to occur at any level of the auditory pathway from the cochlea to the cortex. [2, 158, 159]

In 1924, Wegel and Lane proposed "two kinds of masking, *central* and *peripheral,* the former being generally relatively small and resulting from the conflict of sensations in the brain and the latter originating from overlapping of stimuli in the end organ".[160]

The major difference between ipsilateral and contralateral masking is the presence and absence, respectively, of direct interaction between signal stimuli and masking at the cochlear level. On the other hand, the contralateral masking phenomenon is often referred to as central masking, because the effect occurs beyond the ears; i.e., the brain is involved in the contralateral masking. [2] Contra lateral masking reflects the neural interactions between the two signals within the central nervous system. [4]

Central masking is one of the non- invasive methods of testing the medial olivocochlear bundle (MOCB) function that can be applied in human participants with normal auditory function. It has been hypothesized that central masking is mediated via the central nervous system and reflects an interaction of the masker and signal. [161] Based on the literature, this effect is mediated by the efferent pathways especially by MOCB. [161-163]

Contralateral masking of ASSR:

The effects of contralateral noise on ASSRs are known to depend on the modulation frequencies. [12,164, 165] Contralateral suppression was only observed in the 40-Hz ASSR[12, 164, 165, 166] and the 20-Hz ASSR [167] but not in the 80-Hz. [12] Considering that the 80-Hz ASSR is thought to mainly consist of signals originating from the brainstem,[102, 124, 126] it is supposed that contralateral noise might not so greatly affect the ASSR originating from the brainstem.[167]

On the other hand, contralateral noise suppression may be a phenomenon only observed in ASSRs originating from the auditory cortex. However, contralateral noise does not necessarily suppress other types of auditory cortical response such as N100, [165] so this phenomenon may be quite specific to cortical ASSRs, and is presumably related to the auditory processing of the modulation.

Contralateral suppression of OAEs is attributed to stimulation of the efferent system in the form of OCR that is mediated via MOC fibers. [7, 8, 9] Patients with ANSD show affected afferent and efferent regulation of the cochlea. [14] This is demonstrated by abnormal OCR, measured by absence of contralateral suppression of OAEs. [10]

If the neural substrate of the contralateral suppression of 40-Hz ASSR is the same as for emissions, as a result, patients with ANSD will show absent suppression of ASSRs as for emissions.

In the current study, the effect of contralateral masking of 40-Hz and 80-Hz ASSR in ANSD will be investigated. The goal of the research is to know, whether this evoked response is affected by the impaired efferent pathway or not.