ABR findings in Hidden Hearing loss: A systematic review

Suryakant yadav

19AUD038

The dissertation is submitted in part of the fulfillment for the degree of

Master of Science (Audiology) to University of Mysore.

Mysuru.

ALL INDIA INSTITUTE OF SPEECH & HEARING,

MANASAGANGOTHIRI, MYSURU, 570006

SEPTEMBER, 2021

Certificate

This is to certify this dissertation entitled "ABR findings in Hidden hearing loss – A systematic review" is a bonafide work in fulfillment for the degree of Master of Science (Audiology) of the student with registration no. 19AUD038. This has been carried out under the guidance of a faculty of this institute and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

Mysuru,

8-Sept-2021

Dr. M. Pushpavathi

Director
All India Institute of Speech and Hearing
Manasagangothiri
Mysuru- 570006

Certificate

This is to certify that this dissertation "ABR findings in Hidden hearing loss – A systematic review" has been prepared under my supervision and guidance. It is also certified that this has not been submitted earlier in other University for the award of any other Diploma or Degree.

Mysuru,

8-Sept-2021

Dr. Animesh Barman

Professor of Audiology,
Department of Audiology
All India Institute of speech and hearing,
Manasagangothiri,
Mysuru- 570006

Declaration

This dissertation entitled "ABR findings in Hidden hearing loss – A systematic review" is the result of my own study under the guidance of Dr. Animesh Barman, Professor in Audiology, Department of Audiology, All India Institute of Speech and Hearing, Mysuru, and has not been submitted earlier to any other University for the award of any Diploma or Degree.

Mysuru,

8-Sept-2021

Register No. 19AUD038

Dedication

I wholeheartedly dedicate this dissertation to my beloved father Late ***Mr. Shishupal Yadav****, whose love for me has no bounds; I wish we could have spent more time together. Although, he is no longer in this world, his memories will continue to regulate my life. Papa, I am just a reflection of your aura. I wish, someday I could become like you with same love and grace you hold for your family and friends. Love you and miss you a lot.*

To my mother, ***Mrs. Bhagwati Yadav****, the strength and the actual pillar of our family. I believe, it's her prayers that saves me from all the bad and put me in position to overcome all my difficulties. Maa, no words are enough to express the love I have for you and no words will be enough to justify, what you mean to me. So much to say yet no words would ever be enough. I just want to thank you for all times you gently picked me up, when I fell down.*

Acknowledgement

Foremost, I would like to express my heartfelt and sincere gratitude to my guide, ***Dr. Animesh Barman****, professor, Department of Audiology, All India Institute of Speech and Hearing, Mysuru, for his constant guidance and valuable suggestion throughout this dissertation. Thank you sir, for persistent help, patience and guidance, it's my absolute fortune that I got a chance to carry out my dissertation under your guidance.*

I would like to thank ***Dr. M. Pushpavathi****, Director, AIISH, Mysuru, for permitting me to carry out this dissertation.*

I extend my deep sense of gratitude to ***Debadatta sir****, whose words of motivation lead me to achieve my dreams. Sir, it couldn't have been possible to reach my goal if you would not have motivated me, not only through knowledge but through spirituality also. Thank you for believing in me before I believed in myself.*

I would like to thank my dissertation partners ***Sunny*** *and* ***Abhishek****, for support and suggestions throughout this journey. It was really a pleasure and fun working with you guys.*

Dear, ***Didi****, you have always been great to me. I am fortunate enough to get you as an elder sister. I always cherish our childhood memories. You are amazing, important and very special to me, and you will always be. Lots and lots of love from your younger brother.*

I will take this opportunity to thank my posting partners, ***Hasla****,* ***Anju*** *and* ***Kajol****, for making my clinical postings so wonderful and helping me out, constantly encouraging me throughout the course.* ***Haslu****, you are the best, thank you for being a ray of sunshine even on my darkest days, sometimes I just wonder what I would have done without you. Thank you for providing me with your valuable inputs to carry forward this dissertation.* ***Anjedi****, thank you for joining in my craziness, fun & laughter, you are one of a kind.* ***Kajo****, your kind and caring heart have meant so much to me, thank you for always putting smile on my face. I will always miss you guys.*

I would also like to thank my friend ***Trisha****, who introduced me this field. Without which I would not have came this long. Seven years passed away but still it feels like yesterday when we were about to leave school with thousands of memories.*

Khakha (Pappu) *and* ***Aman****, thank you for endless memories and all the fun at hostel and beyond. I will always cherish the craziest journey we had and all the good times.*

Hey ***polo****! A friend like you is a joy forever, I am so glad that I have you. May God bless you with lots of joy and happiness. Thank you !*

Special thanks to my BASLP-2015 batch brothers, ***Chandu****,* ***Vivek****,* ***Vinod****,* ***Jain bhai*** *and* ***Nagesh*** *for making my BASLP life memorable.* ***Chandu****, I have always missed you in this two years. You guys are the perfect example of what true friendship means.* ***Vivek****, thank you for always being there for me and our family. I am in debt to* ***Vinod****, for so much love and care.*

Shejal *and* ***Dipti*** *thanks a lot for bearing all my dramas ! You people always have made me feel like home with all your support and help. For all the good vibes, thank you so much...!*

It would be unfair if I forget to thank my Battle Ground squad for reviving me every time when I got shot. ***Bandhan****,* ***Aman****,* ***Sunny****,* ***Anirban****,* ***Abhishek****,* ***Samrendra****, Thanks for saying "I got supplies" whenever I have short of supplies, countering my stress and for providing moments of joy.*

How can I forget my favorite juniors? ***Harsha****,* ***shruti*** *and* ***shraddha*** *, thank you for all the love and respect I got from you, for making me believe in myself. May you achieve whatever you have dreamt for? I wish you luck for every step ahead in life. Rise and shine* !

Many thanks to my batchmates ***"renovators 2.0", my teachers*** *and all the people who were integral part of this journey and have directly or indirectly inspired me to do my best.*

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABR findings in Hidden Hearing loss: A systematic review

Chapter 1

Introduction

Auditory system is one of the most important sensory organs, which helps human being to be aware of the surroundings and connected with the environment. Auditory system consists of both peripheral and central auditory system and normal functioning of both peripheral and central auditory system is essential for effective and normal hearing. There are several tinny sensory cells in the inner ear and auditory neurons which helps to analyze the acoustic stimulus in terms of spectral and temporal component and help in hearing and understanding the meaning of the signals especially speech. Several factors can damage these tinny cells or auditory neurons and affect our hearing or perception of auditory signals. Auditory deprivation due to long term middle ear pathology can be a reason for losing out functional ability of the auditory neurons (Maruthy and Mannarukrishnaiah, 2008). However, there are several other reasons which can also affect the functioning of both sensory cells and auditory nerve like , exposure to noise (Kujawa and Liberman, 2009), exposure to loud music (Halevi-Katz, Yaakobi and Putter-Katz, 2015), usage of mobile phone (Velayutham, Govindasamy, Raman, and Prepageran, 2014), intake of ototoxic drugs (Musial-Bright, Fengler, Henze, and Hernáiz Driever, 2011), aging (Makary, Shin, Kujawa, Liberman, and Merchant, 2011), etc. Effect on sensory cells or auditory nerve can led to hearing loss or may not lead to hearing loss. It has been observed that up to 80% IHC loss may not even lead to elevation of audiometric threshold (Lobarinas Salvi and Ding, 2013).

Kujawa and Liberman, (2009) observed damage to the ribbon synapse between the inner hair cells and type I spiral ganglion nerve terminals due to over exposure of the noise in rodent

mice. However, there were no damage to the sensory hair cells and did not observe any effect on absolute hearing thresholds. This synaptopathy or loss of synapses within the auditory system has been termed as cochlear synaptopathy Schaette and mcalpine, (2011) termed this as 'hidden hearing loss' which was later supported by several authors and most commonly used term due to the hidden nature of this disorder as it doesn't express itself as the loss in absolute hearing sensitivity.

Subsequent studies in this area also suggest that this loss is attributing with the loss of low and medium spontaneous rate fiber instead of high spontaneous rate fibers i.e. The major destruction happens to the high threshold nerve fibers which are responsible for the processing of high intensity levels of sound (Furman, Kujawa, and Liberman, 2013). The absence of low spontaneous rate fibers leads to hearing difficulties in noisy situation because they may be more resistant to masking by the background noise which is below the threshold of this fibers as compare to low threshold i.e. High spontaneous rate fibers which gets activated by low level stimuli (Costalupes, 1985; Young and Barta, 1986). Sometimes tinnitus and hyperacusis can also be associated with this disorder as a symptom or can be as the coexisting phenomenon due to the increased gain and hyperactivity in the central auditory pathway (Hickox and Liberman, 2014; Schaette and mcalpine, 2011).

However, a recent research involving young individuals with and without tinnitus, matched for age, gender, and audiometric thresholds up to 14 KHz, did not suggested any association between ABR wave I amplitude and tinnitus (Schaette and mcalpine, 2011). Similar findings associated with cochlear synaptopathy are evident for the aging auditory system as well where the synaptic loss between the inner hair cells and spiral ganglion cells was observed in the CBA/caj mice in which the age related synaptic changes and neuronal

degenerations occurred without any exposure to high level noise (Sergeyenko, lall, libermann and kujawa, 2013). Ample evidence is present in the literature that suggests the presence of synaptopathy in humans (Bramhall, Konrad-Martin, mcmillan, and Griest, 2017; Hickox and Liberman, 2014; Liberman, Epstein, Cleveland, Wang, and Maison 2016; Stamper and Johnson, 2015a, 2015b). The loss of ribbon synapses with intact sensory hair cells leads to the assumption that this pathology can remain undetected for the individuals who have normal audiometric thresholds or normal findings in other subsequent clinical measures which are used to assess the functionality of auditory system. However, this cannot be the only case when the auditory system goes through the adequate insult leading to hair cell damage and hearing sensitivity which is being expressed through the audiometric threshold elevates and the damage to the auditory system can be clearly detected by test battery approach used for the assessment of hearing. This again can be consequence of overexposure to noise or presbycusis or other pathologies co existing with the hidden hearing loss. Although, it is a difficult task to assess the possibility of hidden hearing loss in the presence of other coexisting conditions. The reason behind this is due to manifestation of symptoms and the insensitivity of measures used to investigate the pathology. In such cases, the findings can be influenced by the existence of other conditions. However one can rule out the existence of hidden hearing loss with the help of histological investigation of temporal bones (Makary, Shin, Kujawa, Liberman, and Merchant, 2011; Wu, Liberman, Bennett, de Gruttola, O'Malley, and Liberman, 2019) but this cannot be possible with the living humans. To date, in our best knowledge there is no reliable or a gold standard measure available in the field of audiology to evaluate the possibility of hidden hearing loss but in many studies it has been noticed that a number of proxy measures or the combination of tests can be used to assess the presence of this disorder (Guest, Munro, Prendergast, Plack 2019; Prendergast et al.,

2019). However, ABR i.e. Auditory brainstem response has been administered often and findings suggests the reduction of wave I amplitude at suprathreshold levels (Kujawa and Liberman, 2009). Stamper and Johnson, (2015a, b) reported the first direct study of cochlear synaptopathy in humans, discovering that the amplitude of wave I of the ABR in response to high intensity stimuli correlated with noise exposure background. In the same study, for subjects with high noise exposure, wave I amplitude was reduced and wave V amplitude was either constant or enhanced in both animal and human participants. Some of the researchers presumed that the unchanged or increased wave V amplitude in this subjects could be an evidence of either central hyperactivity or reduced inhibition in response to reduced auditory nerve input which triggers the central gain mechanism resulting in more robust wave V (Bramhall, Konrad-Martin, mcmillan, and Griest, 2017; Schaette and mcalpine, 2011; Sergeyenko, Lall, Liberman, Kujawa 2013; Stamper and Johnson, 2015a). However, a few researchers have observed that ABR is not the sensitive measure for hidden hearing loss and it alone cannot help to conclude the diagnosis (Grinn, Wiseman, Baker, and Le Prell, 2017; Valderrama, Beach, Yeend, Sharma, Van Dun, and Dillon, 2018).

Many factors that can influence the sensitivity of ABR waves and latency are stimulus, transducer, gender, age etc (Don, Ponton, Eggermont, and Masuda 1994; Hecox and Galambos, 1974; Masuda and Ponton, 1993). However, ABR that helps in hearing evaluation is the essential clinical tool for audiologists and neurologists. It is clinically employed to estimate auditory sensitivity as well as to evaluate otoneurological abnormalities throughout the auditory nerve and auditory brain stem. Almost every study on the diagnosis of hidden hearing loss states the importance of test battery approach to evaluate the existence of this disorder in the auditory system and hence along with the wave I amplitude of ABR, there are other electrophysiological

measures available which holds the potential to aid in identification of this disorder. One of these measures is the envelope-following response (EFR), a persistent neural response to the envelope of an amplitude-modulated (AM) stimulus, though it is less often employed than the ABR. It is felt that low-spontaneous rate fibers have high synchronization to AM tones, thus it has been claimed that the EFR may have more contributions from low-SR fibers than the transient-evoked ABR (Shaheen, valero, and liberman, 2015). Hence, findings from various animal models indicate that EFR measures are quite sensitive to synaptopathy i.e. At high stimulus modulation rates of roughly 1 KHz, EFRs can help to detect the possibility of cochlear synaptopathy (Parthasarathy, Encina-Llamas, Shinn-Cunningham, Kujawa 2017.; Shaheen, valero, & liberman, 2015). The acoustic middle ear muscle reflex (MEMR), or involuntary contraction of the stapedius muscle in response to high-level sound stimuli, is relatively a recent addition to the battery of possible synaptopathy markers. Medium- and low-SR fibers can drive the afferent section of the reflex arc. According to Valero Hancock, Maison, and Liberman, (2018) MEMR measurements done on mice results in better sensitivity than wave I amplitude of ABR and also found that the sensitivity was increased when threshold was used instead of amplitude. In the same study it was also observed that the narrowband reflex elicitor is more effective than broadband reflex elicitor.

1.1 Need for the study

Clients having synaptopathy reports to the audiologist with the complain of tinnitus, hyperacusis and difficulty in understanding in noisy situation while their audiogram shows normal hearing, i.e., their thresholds remain well within <20dbhl in all audiometric test frequencies from 0.25 KHz to 8 KHz suggesting no damage to the auditory system(Guest, Munro, Prendergast, Howe, and Plack, 2017; Schaette and mcalpine, 2011; Stamper and

Johnson, 2015; Valderrama, Beach, Yeend, Sharma, Van Dun, and Dillon, 2018). In this case, audiologists should go further to evaluate the presence of 'hidden hearing loss' as this is the primary insult in the auditory system prior to the damage of hair cells which can lead to more evident hearing loss. Individuals with hidden hearing loss reported have to synaptic abnormality between the IHC and auditory nerve. Though they exhibit normal hearing, this type of abnormality likely to affect temporal processing of acoustic signal. Degraded temporal processing can severely affect speech perception especially in adverse listening conditions. Hence, early diagnosis of this disorder can lead to early intervention or at least precaution can be taken to slow down or to reduce the extent of damage occurring in the auditory system. Though the pure tone audiometry (PTA) is the "Gold standard test" in audiology but insensitive to detect the presence of hidden hearing loss. Not only PTA but also the other tests which are included in the usual test battery and performed by an audiologist to examine the integrity and functionality of auditory system, are not adequate for the diagnosis of this condition. It is very important to look for the measures that could identify and/or validate the diagnosis and can be added in the clinical test battery of this disorder. One of the most commonly used electrophysiological test is ABR and literature suggests that this could be a potential tool to diagnose hidden hearing loss. Thus, there is a need to gather information about its utility to identify hidden hearing loss based on systematic review.

1.2 Aim of the study

The study aimed to perform a systematic review of the ABR findings in hidden hearing loss.

1.3 Objectives of the study

The objectives of this systematic review are-

1. To identify the possible causes of Hidden hearing loss,
2. To identify the ABR parameters those are effective in identifying the Hidden hearing loss.
3. To examine the efficacy of using ABR in the identification of Hidden hearing loss.

1.4 Research questions

Research questions for this review are based on PICO/PECO framework i.e.-

Population - individual with hidden hearing loss,

Intervention/evaluation - Auditory brainstem response audiometry,

Comparison - With the other audiological tests available,

Outcome - Diagnosis of hidden hearing loss.

This review is an attempt to address the following questions-

1. What are the possible causes of hidden hearing loss?
2. Is ABR an effective tool to diagnose this disorder?
3. What are the ABR parameters that are effective in identifying the disorder?

Chapter 2

Methods

Scientific article from different sources focusing on hidden hearing loss or related articles will be gathered from the different sources to archive the objectives of the systematic review. Article collated from the different sources have been screened based on several criteria before arriving at the articles that have been considered for the systematic review. The details procedure for selection processes of the articles are given below.

2.1 Eligibility criteria

Eligibility criteria can be defined as inclusion and exclusion criteria based on which articles can be included and excluded in the systematic review. The inclusion and exclusion criteria for this systematic review are-

2.1.1 Inclusion criteria-

- Articles should be from a peer-reviewed journal.
- Articles should be a study including but not limited to the auditory brainstem response as a measure for identifying hidden hearing loss.
- Articles should include human participants of any age and gender.

2.1.2 Exclusion criteria-

- Articles, which includes animal participation.
- Articles, which are a single case study, case series, short communications, letter to the editor, systematic review.
- Articles including pathologies other than hidden hearing loss.

- Articles with low methodological quality (having higher risk of bias and high concern regarding the applicability in all domains, assessed through QUADAS-2 tool).
- Articles in languages other than English.

2.3 Information sources

Articles published from various peer-reviewed journals is searched in different databases like Pubmed central, J-GATE, science direct, and Google scholar. Hence, information or articles extracted from these four databases are only included in the systematic review.

2.4 Search strategy

Hidden hearing loss is also referred as cochlear synaptopathy by many authors and investigators due to which both the terms are included in the search process. Similarly, ABR has several synonyms that could be used across studies. Hence, different keywords for this measure were used while searching the data for this review. Search was initiated using Boolean operations such as AND/OR. The keywords used during the search process are:

Hidden hearing loss OR cochlear synaptopathy AND Auditory brainstem response OR Auditory evoked potential OR ABR OR BERA OR Brainstem evoked response audiometry. Filters available in different databases have been set to filter out or to reduce the occurrence of irrelevant articles.

2.4.1 The filters used in Pubmed central are under the below mention subheadings –

Species

As one of our inclusion criteria is “articles should include Human participants”, in the species section of Pubmed central “human” as a filter is used to filter out all the articles which doesn’t contain human participants.

Language

Language is an important characteristic when reviewing the articles as most of the readers considers English as a universal language; it has ability to conduct the information to the wider range of audience in comparison to other languages. Hence, “English” as in language filter is used to consider studies, which are only in English language.

Age

Age is an important factor when it comes to the interpretation of electrophysiological measures. As in children variability is more due to many factors such as head size, maturation of auditory system. In the age section, “Adults 19+ years” filter is used. One more reason to choose this age as a cutoff is because synaptopathy is more prevalent in adults.

Timeline

Since the evolution of cochlear synaptopathy is recently discovered, the timeline used for searching the articles is from January 2011 to February 2021.

2.4.2 The filters used in J-Gate are

Journal category

As we mentioned in our inclusion and exclusion criteria that the articles should be peer reviewed and a single case study, case series, short communications, letter to the editor,

systematic review will be excluded, the filter was set to consider only the Full text, Peer reviewed/ scholarly, professional and industry Journal articles.

Timeline

As mentioned above we are taking the 10 year timeline for our systematic review. The timeline was set to year – from January 2011 to February 2021.

In the database of science direct and Google scholar, only one filter option was available i.e. the year, which has been set from January 2011 to February 2021 along with the keywords and Boolean operators like the other databases mentioned.

2.5 Selection process

The selection of the articles included in the review is based whether they met the inclusion criteria mentioned in the eligibility criteria. Each article is screened keeping in mind the keywords for the review and inclusion and exclusion criteria. The article that does not fulfilled the inclusion criteria or which comes under the exclusion criteria mentioned, was excluded from the study. The selection process carried out by two authors independently followed by third author if any conflict of interest encountered. For data selection procedure, the articles were title screened in the first stage followed by abstract screening and then full text screening was done. Duplicate detection was done prior to title screening with the help of same software. After duplicate detection the remaining articles were title screened where relevant articles were shortlisted based on the title followed by the abstract screening. Again articles were shortlisted based on the abstract where articles fulfilling the inclusion criteria were selected for the full text screening whereas, the articles which didn't fulfilled the inclusion criteria or which comes under the exclusion criteria are excluded from the systematic review process.

2.6 Data collection process (extraction of articles)

The preliminary search was executed independently by two authors across all the electronic databases mentioned using Boolean operators and keywords, the results came from various databases are compiled together using a reference management system i.e. "Rayyan-intelligent systematic review". The articles from the Pubmed database was selected and downloaded in the form of text document, while the data from the science direct and J- gate databases was downloaded in the form of RIS file format which is developed by the research information systems. One more file format i.e. The ENW file which is developed by the Thomas reuters for Endnote citation manager was used to download the articles from the google scholar database and all the articles downloaded in different formats are uploaded in the reference management system mentioned above. After uploading the articles at a time in the reference management system further selection process was carried out starting with the duplicate detection and then screening of the title followed by abstract screening and full text screening as mentioned in the selection process. After finalizing the articles for the review, data from each study was collected with respect to the tests used for diagnosis of the Hidden hearing loss specifically auditory brainstem response, the criteria used for the diagnosis and the critical evaluation was done regarding the merits and demerits of the study included in the review.

2.7 Study risk of bias assessment

Risk of bias assessment was carried for selected studies using the Quality Assessment for Diagnostic Accuracy Studies (QUADAS-2) tool (Whiting et al., 2011). This tool assesses the following four domains:

1. *Patient selection*

2. *Index test*

3. *Reference standard*

4. *Flow and timing*

This 4 domains are assessed in terms of risk of bias and first 3 domains were assessed in terms of concern regarding applicability. The score were marked as ‘low’, ‘high’ and ‘unclear’ with respect to the risk of bias as well as concern regarding applicability. The tool consist of several signaling questions under each domain which can be answered as ‘yes’, meaning low risk of bias and concern regarding applicability where as if the signaling questions answered as ‘no’, it means there are high risk of bias and concern regarding applicability. However, if there are conflicts or in the case of uncertainty following inadequate information then it can be answered as ‘unclear’. Each included study is assessed for the risk of bias by two independent authors and in case of conflict; the third author has resolved it.

2.8 Synthesis of the results

Because of the heterogeneity of the included studies, the results of the literature review were synthesized using a narrative approach rather than a meta-analysis.

CHAPTER 3

Results

3.1 Search results-

The articles finalized based on the inclusion and exclusion criteria and based on the research question formulated according to the PICO/PECO framework. A total of 15,564 results were found among 4 databases out of which 1975 were deleted. The remaining 13,589 were articles went through the title screening stage. On the basis of title screening, 25 full text articles were finalized, while 13,564 articles are excluded because it does not fulfilled the inclusion criteria for this systematic review. Out of these 25 articles, 2 articles were excluded in the abstract screening stage and rest of the articles was shortlisted for full text screening. In full text screening procedure, 7 articles were excluded; the reason for the same has been given in table 1 and described in the discussion section. Hence, a total of 16 articles were finalized for the review. Details of the selection procedure are shown in **figure 3.1.**

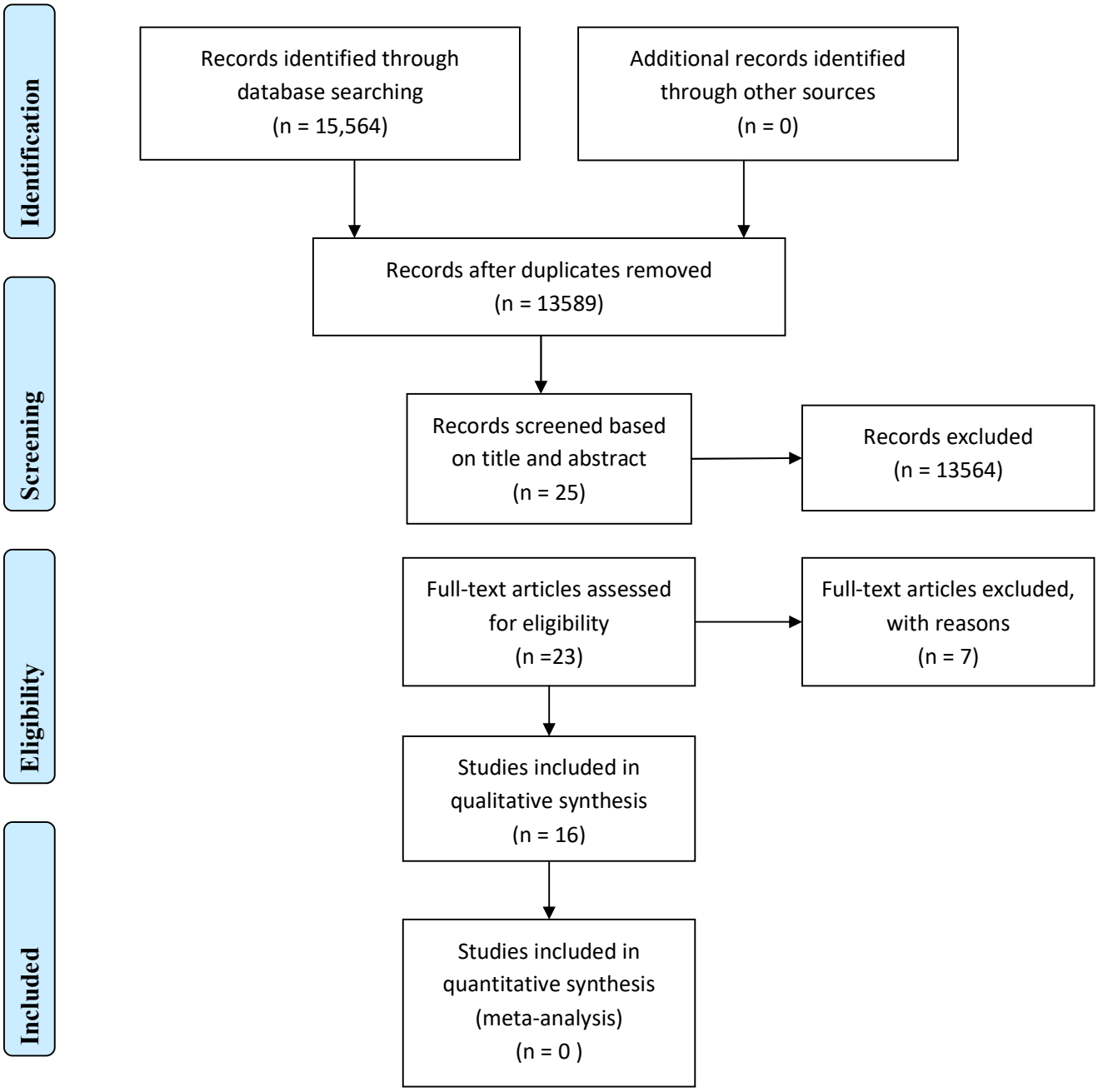


Figure 3.1: PRISMA flow diagram for representation of the items screened included and excluded in the systematic review.

Two article which are excluded in the abstract screening stage is Schaette and mcalpine, (2011) and Bramhall, (2019) because the former was a brief communication article and the later was a conference abstract, hence fulfilling one of our exclusion criteria. The seven articles, which are excluded in the full text screening stage, are the articles, which appear to be meeting the inclusion criteria, but are excluded due to the reason mentioned in the **Table 3.1.**

Table 3. 1: Reasons for exclusion of the articles from the review process.

Year & author	Title	Reason for exclusion
Guest, Munro, Prendergast, Howe and Plack, (2017)	Tinnitus with a normal audiogram: Relation to noise exposure but no evidence for cochlear synaptopathy	In this cohort study, there was no evidence of hidden hearing loss despite of wide range of noise exposure.
Ridley,Kopun, Neely, Gorga, and Rasetshwane, (2018)	Using thresholds in noise to identify hidden hearing loss in humans	Participants with sensorineural hearing loss, thresholds up to 66 dB HL were included in the study.
Carcagno and Plack, 2020	Effects of age on electrophysiological measures of cochlear synaptopathy in	Participants having high frequency hearing loss at 4 KHz were included in the study, also no selection criteria above 4 KHz frequency which can arise

	humans	the possibility of including high frequency hearing loss candidates in the study.
Guest, Munro, Pradergest. And Plack, (2019)	Reliability and interrelations of seven proxy measures of cochlear synaptopathy	The study assesses the reliability and inter-correlation between seven proxy measures of cochlear synaptopathy, without giving emphasis on diagnosis of the disorder.
Kamerer, Kopun, Fultz, Allen, Neely, and Rasetshwane, (2019)	Examining physiological and perceptual consequences of noise exposure	The inclusion of participants who have thresholds less than or equal to 65dbhl, which can include the possibility ofouter hair cell damage and its manifestation in the form of hearing loss.
Morimoto, Fujisaka, Okamoto, and Irino, (2019)	Rising-frequency chirp stimulus to effectively enhance wave-I amplitude of auditory brainstem response	The study assesses the potential of chirp stimulus in enhancing the wave I of ABR, without addressing the hidden hearing loss.
Kamerer, Aubuchon,Fultz, Kopun, Neely, and	The role of cognition in common measures of peripheral synaptopathy and hidden hearing loss	Inclusion of the participants with sensorineural hearing loss having thresholds up to 65 dBHL, which again arise the possibility of includes the participant with hearing loss due to outer hair cell damage.

Rasetshwane,(2019)		

3.2 Study characteristics

All 16 selected studies used the criteria of normal hearing sensitivity to identify the possibility of hidden hearing loss. However, the definition of normal hearing differs from article to article i.e. 3 articles included subjects having thresholds ≤15 dBHL (Bhatt and Wang, 2019; Mehraei et al., 2016; Washnik, Bhatt, Philips, Tucker and Richter, 2020) while 7 articles taken the subjects who had thresholds ≤20 dBHL (Bramhall, Konrad-Martin, mcmillan, and Griest, 2017; Bramhall, Konrad-Martin, and mcmillan, 2018; Couth et al., 2020; Grose, Buss, and Hall, 2017; Guest, Munro, Prendergast, Millman, and Plack, 2018; Megha et al., 2019; Suresh and Krishnan, 2020). Whereas other 2 studies used ≤25 dBHL as cut-off criteria for normal hearing sensitivity (Fulbright, Prell, Griffiths, and Lobarinas, 2017; Prendergast et al., 2019).

One of the study didn't define the normal hearing threshold in particular but have mentioned that participants with speech identification score of ≥70% has been included in the study(Dhrruvakumar, Shambhu, and Konadath, 2021). Rest of the studies have defined the normal hearing thresholds which differs according to the frequencies i.e. ≤20 dBHL at 0.5 to 4KHz, ≤30dBHL; 6 to 8KHz (Johannesen, Buzo, and Lopez-Poveda, 2019), ≤20 dBHL at 0.25 to 6KHz and near normal hearing sensitivity having threshold ≤25 dBHL at frequencies ≤2 KHz, ≤30 dBHL at 3 KHz, ≤35 dBHL at 4 KHz, ≤40 dBHL at 6 KHz (Valderrama, Beach, Yeend, Sharma,

vandun, and Dillonet al., 2018), ≤25 dBHL at frequencies ≤4 KHz, ≤35dBHL at 8KHz (Prendergast et al., 2017).All studies included young participants age ranging from 18 years to 40 years except 4 studies where the maximum age limit considered up to 68 years (Dhrruvakumar, Shambhu, and Konadath, 2021; Johannesen, Buzo, and Lopez-Poveda, 2019; Suresh and Krishnan, 2020; Valderrama, Beach, Yeend, Sharma, vandun, and Dillon, 2018). The summery of the articles which are included in the review process is given in the **Table 3.2.**

Table 3. 2: Summary of the research articles selected for systematic review

Year & Author	Title	Method	Results	Discussion & conclusion
Mehraei et al., (2016)	Auditory brainstem response latency in noise as a marker of cochlear synaptopathy	23 subjects were taken with mean age of 26.95 having normal thresholds in this cohort study. ABR was measured in quiet and in noise. To obtain wave V in quite condition; ABR was	In the presence of background noise increased wave V latency was observed from which the latency and masker level function was derived and calculated by linear fit, this latency shift varied over the	In the study there was a correlation between the growth of ABR wave I amplitude with stimulus level and masking noise latency shift but not with measures of cochlear function suggest that, relative change in ABR wave I amplitude with ABR wave V

		administered using 80 µsec clicks at 50-90 db peSPL in 10 db increments. While for measurement in noise clicks were presented at 80 dB peSPL with broadband noise from 42-82 db SPL in 10 dB steps. For wave I, click levels were varied from 60-100 dB peSPL in 10 db increments.	Normal hearing subjects from 0.0018 to 0.0464 ms/dB. Smaller wave V latency shift in noise was observed. Also Latency shift in noise did not correlated with latency shiftwith increasing stimulus level in quite. The relationship between wave I amplitude growth as increasing the level of stimulus and wave V latency shift in noise and quite was measured which revealed that the steeper the growth of wave I, the larger the latency shifts in	latency shift in noise can be used as a marker for cochlear synaptopathy as the absolute ABR peak amplitude and latency measurement can have inter-subject variability and can depend on various factors. The findings are in agreement with the fact that the loss of low spontaneous rate fibers affects both hearing in background noise as well as coding temporal information at supra-threshold level.

			noise however no correlation was observed between wave I amplitude growth and latency shift in quite.	
Bramhall Konrad-Martin, mcmillan, and Griest,(2017)	Auditory Brainstem Response Altered in Humans with Noise Exposure Despite Normal Outer Hair Cell Function	64 participants participated in the study with normal pure tone thresholds and DPOAES. History of noise exposure was taken through LENS-Q questionnaire and groups were divided accordingly. It includes 16 participants having significant history of noise exposure, 13 participants having less noise	Significant history of noise exposure group has smallest mean wave I amplitude while non-exposure group has highest. Wave III and V amplitudes are similar across all groups. Weak but significant effect of gender difference across wave I amplitude was observed.	The absence of any reduction in the wave III and V amplitude with reduction specifically in wave I amplitude is consistent with the findings observed in animal experiments and models of cochlear synaptopathy. This finding suggests synaptopathy can be rule out using wave I amplitude. However, no direct conclusion can be drawn without post mortem examination of temporal

		exposure, 12 participants with history of firearm use and 23 without firearm use. Tone burst ABR was administered at 1KHz, 3 KHz, 4 KHz, 6 KHz.		bone. As the wave I amplitude change could also indicate changes in OHC's function which can't be rule out through the DPOAE's or damage to IHC's or auditory nerve instead of Auditory nerve and IHC's synapses.
Fulbright, Prell, Griffiths, and Lobarinas, (2017)	Effects of Recreational Noise on Threshold and Suprathreshold Measures of Auditory Function	60 participants having 26 males with a mean age of 21.1 years and 34 females with a mean age of 20.4 years participated in this study. All the participants were exposed to noise at least for 1 year which was ascertain with the help of questionnaire used by	Noise exposure history was not significantly correlated with wave I amplitude for both the genders for click stimuli. High-risk TTS group has lower wave I amplitude for 4000 Hz tone burst with tiptrode placement but the difference is not statistically significant.	The present study did not find significant correlation between 1 year of noise exposure and wave I amplitude of ABR. According to author, it can be possible that deficit can be present in those individual who exposed to noise levels, which are louder, and for longer duration than for the participants, which are

		Spankovich(Spankovich, Le Prell, Lobarinas, Hood, 2017). ABR was administered for four click conditions i.e. At 4 suprathreshold levels of 70,80, 90, and 99 dBnHL and two tone burst condition i.e. at. 4000 Hz with tiptrode electrode and then with earlobe electrode at 90 dBnHL.		included in the study.
Grose,Buss, and Hall, (2017)	Loud Music Exposure and Cochlear Synaptopathy in	31 participants were recruited for experimental group having high noise exposure with mean age of 25 years, (21	Wave I amplitude was higher in control group in comparison to experimental group at both the levels while there was no	The experimental and control group were successfully differentiated based on ABR with the help of reduced wave I amplitude which is

	Young Adults: Isolated Auditory Brainstem Response Effects but No Perceptual Consequences	males) and 30 for control group having low noise exposure history with mean age of 23 years, (11 males). ABR was measured using click stimuli at levels of 95 and 105 dB ppeSPL.	change in the wave V amplitude at any level. Wave I to wave V ratio was also reduced in experimental group in comparison to control group at both the level tested.	consistent with the animal studies Kujawa and Liberman, 2015) and reduced wave I to V ratio in experimental group.
Prendergast et al., (2017)	Effects of noise exposure on young adults with normal audiograms I: Electrophysiology	126 participants were recruited in the study among them 75 were female with mean age of 22.9 years and rest were male having mean age of 23.3 years. Noise exposure history was taken using questionnaire "noise	Latencies of wave V and wave I to V inter-peak latency have significant correlation with the history of noise exposure that too for lower click stimuli level not for high level. However, amplitude did not have any correlation with noise exposure.	Positive correlation between wave I-V inter-peak interval and noise exposure is mainly due to the change in latency of wave V and also it is more evident for lower level clicks i.e. 80 db peSPL because noise exposure results in delayed response of low level clicks while not affecting

		exposure structured interview (NESI) (Lutman, Davis,and Furguson, 2008). The minimum level of daily noise exposure taken was 90dBA for 1 year. ABR was administered using 100 µsec. click stimuli for two levels i.e. 80 and 100 db peSPL.	In addition, there was no significant correlation between noise exposure and wave I:V amplitude ratio.	a faster response to the higher level click stimuli. According to the authors, in this study there is no evidence that the amplitude of electrophysiological measures are attenuated due to noise exposure. Hence, the ABR is either insensitive to cochlear synaptopathy in humans or the subjects included in this study doesn't have noise induced cochlear synaptopathy.
Guest, Munro, Prendergast, Millman, and Plack,(2018)	Impaired speech perception in noise with a normal audiogram: No	32 participants were taken as experimental group having spin impairment, all had history of noise exposure. 38	There was no difference between the groups with respect to the amplitude of ABR wave I and for wave I to wave V	Neither wave I/V ratio nor wave I amplitude was significantly reduced in participants with SPIN difficulties, which shows that either ABR offers

	evidence for cochlear synaptopathy and no relation to lifetime noise exposure	participants were taken as a control group with no auditory deficit. ABR was measured using filtered clicks at 102 dB peSPL.	amplitude ratio.	limited sensitivity to cochlear synaptopathy or the participants do not have cochlear synaptopathy despite of having SPIN impairment. According to authors, it can also be due to measurement variability from other sources or wave I amplitude is not that sensitive to the loss of low spontaneous rate fibers.
Bramhall, Konrad-Martin, and mcmillan, (2018)	Tinnitus and auditory perception after a history of noise exposure: Relationship to auditory brainstem	74 participants with normal hearing and normal DPOAE consist of 17 veterans (15 males) with significant history of noise exposure, 14 veterans (6 males) with less noise	14 veterans with high noise exposure history reported of tinnitus while 1 veteran with low noise exposure history complaint of having tinnitus. Individual with tinnitus had	Synaptopathy can result in tinnitus as a perceptual consequence. Although the result from this study revealed reduced wave I amplitude in individuals with tinnitus, which also results in reduction of wave I to V

	response measures	exposure, 27 non-veterans (7 males)controls with very limited noise exposure, and 16 non-veterans (7 males) with a history of firearm use. Noise exposure was estimated using LENS-Q questionnaire. History of tinnitus was also taken. ABR was administered using 4 KHz tone burst at 4 levels ranging from 80-110 dB p-peSPL in 10 db steps with tiptrode electrodes.	lower wave I amplitude as well as reduced wave I to wave V amplitude ratio in comparison to individuals who does not reported of tinnitus with greatest reduction at highest stimulus level but there was no correlation between the ABR wave V and wave III amplitudes and tinnitus.	ratio, the authors concluded that synaptopathy cannot be confirmed non-invasively because the cross-sectional nature of this study limits the comparison of within subjects ABR wave I amplitude, before and after the occurrence of tinnitus. It emphasizes the need of a prospective study of individuals exposed to high level of noise.
Valderrama, Beach, Yeend,	Effects of lifetime noise exposure on	74 participants took part in this study with mean age of	There was no correlation between lifetime noise exposure	This study shows a statistical negative association between life

Sharma, Van Dun, and Dillon, (2018)	the middle-age human auditory brainstem response, tinnitus and speech-in-noise intelligibility	43.36 out of which 37 were females. Noise exposure and tinnitus history was taken based on questionnaire adapted from the NOISE database (Beach, Gilliver and williams, 2013). ABR was administered using rarefaction clicks at 108.5 dB p-pSPL with mastoid and tiptrode electrode placement.	and amplitude ratio of wave I and V for mastoid placement however it was significant for the tiptrode electrode. Lower noise exposure history group showed higher amplitudes for the entire wave in ABR in comparison to higher noise exposure individuals. Wave I/V ratio was reduced in individuals with lower wave I amplitude i.e. For higher noise exposure group, delayed latency was also observed only for wave I. Tinnitus group also showed	time noise exposure and wave I amplitude of ABR at suprathreshold level using tiptrode as reference electrode. These findings are consistent with the main hypothesis of the study and hence led the author to conclude that the modest evidence of cochlear synaptopathy can be obtained through ABR and specifically, the amplitude of wave I can be used to diagnose this condition although large number of variables can affect it.

			reduced wave I/V amplitude ratio.	
Bhatt and Wang, (2019)	Evaluation of dichotic listening performance in normal-hearing, noise-exposed young females	Two groups were taken with 14 participants having high noise exposure background and 18 with low noise exposure background. Age range was 18-35 years. Noise exposure history was taken with the help of NEQ (noise exposure questionnaire) questionnaire (Johnson, cooper, stamper, and chertoff, 2017). Dichotic digits test was administered along with ABR.	There was no significant relationship between noise exposure background and ABR waves, nor for amplitude neither for latency with respect to wave I, III, V i.e. There was no significant difference between the high and low noise exposure background group. Subject with high noise exposure background however, have dichotic listening deficit without the loss of wave I	Noise exposure background doesn't have any correlation with ABR measure however deficit in Dichotic Digit Test revealed significant effect of noise exposure which could be detected prior to changes in ABR wave I. The explanation given by the author regarding the no difference in ABR findings between low noise exposure group and high noise exposure group could be because of the questionnaire used for calculating the extent of noise exposure. This

		Click stimulus was used for ABR measurement with alternating polarity at 11.1/sec and 71.1/sec i.e. Two stimulus rate conditions.	amplitude.	questionnaire evaluates the noise exposure of 1 year rather than lifetime exposure. Hence, it could be possible that some listeners may have been classified as low noise exposure group while they must have exposed to high level of noise in their lifetime and can already have synaptopathy.
Prendergast et al., (2019)	Effects of Age and Noise Exposure on Proxy Measures of Cochlear Synaptopathy	This study consists of 123 young participants with mean age of 23.11 years and 33 older participants with mean age of 44.81 years having normal audiometric threshold up to 4 KHz i.e. <25dB HL	There was no difference in ABR findings i.e. Amplitudes of wave I, V and I/V ratio, between the older and younger participants. Also between the noise exposures groups i.e. Low, medium and high noise	As the results showed no correlation between the noise exposure or age and ABR findings, despite of the fact that as the age increases, auditory system undergoes with more subtle changes like loss of synaptic connections (Viana et al., 2015; Wu,

		and <35 dB HL at 8 KHz..Noise exposure history was taken using structured interview “noise exposure structured interview (NESI) (Lutman, Davis, and Furguson, 2008) for noise exceeding 85dBA . ABR was administered using high pass filtered click stimuli at 100 dB peSPL.	exposure group, there was no correlation observed.	Liberman, Bennett, Gruttola, O'Malley, and Liberman, 2019). In addition, older listeners do have more lifetime noise exposure as compared to the younger age listeners. Hence, such findings led the author to conclude that there is potential lack of sensitivity of ABR in finding the subtle changes in auditory system due to aging or noise exposure such as cochlear synaptopathy.
Megha et al., (2019)	Narrow-band chirp and tone burst auditory brainstem response as an	40 adult male subjects were recruited for the study from a single work place. They were divided in to control group	Significant difference was not observed for wave V amplitude between both the groups in both stimulus conditions at all the	In this study, the significant difference observed in latency of low frequency stimulus could be due to abnormal functioning of the hair cells

	early indicator of synaptopathy in industrial workers exposed to occupational noise	(individuals who were not exposed to occupational noise) with mean age 23.5 years and experimental group (individuals exposed to occupational noise greater than 80 dBA for a duration of 8 hours per day) with means age 27.75 years. ABR was administered using tone burst and narrowband chirp stimuli at 500, 1000, 2000, and 4000 Hz at 80 dBnHL.	frequencies tested. However, there was significant difference between the groups for wave V latency for 500 Hz tone burst and 500, 1000, 2000 Hz narrowband chirp stimuli.	in the higher frequency, which might alter the signal conduction further along the basilar membrane to the frequency region coding low frequencies in individuals exposed to occupational noise. As stated by authors, the animal experiments shows the reduced ABR wave I as a marker of cochlear synaptopathy but it is difficult to obtain robustly in humans whereas wave V can be more robustly obtained than wave I in humans. Hence, the author concluded that the wave V could be better measure to identify cochlear

				synaptopathy and since the wave V amplitude does not revealed any differences in participants of this study, latency could be used to identify this disorder. In addition, among both the stimulus, narrow band chirp is more sensitive than tone burst stimuli.
Johannesen, Buzo, and Lopez-Poveda,(2019)	Evidence for age-related cochlear synaptopathy in humans unconnected to speech-in-noise intelligibility	94 participants (30 male) participated for the study having age range of 12-68 years. All are having normal hearing thresholds i.e. <20 dBHL at frequencies between 0.5 to 4 KHz and <30 dBHL	Slope of wave I (µV/dB) versus level function was determined. There were significant shallower slopes observed for increase in age while the difference was not significant for the effect of noise exposure,	Slope of wave I versus level function can be used to detect the changes in ABR findings due to cochlear synaptopathy as it is less rely on factors that can influence the amplitude of wave I for example head size, quality of electrode contact, sex,

	deficits	for frequencies 6 and 8 KHz. Noise exposure history was taken using questionnaire adapted from the NOISE database (Beach, Gilliver and williams, 2013). ABR was administered using rarefaction click stimuli for intensities 90, 95, 100, 105, 110 dB p-peSPL.	the results holds same for men and women both. To control the effect of elevated hearing thresholds due to age upon reduced ABR wave I, ABR wave I slopes are adjusted for the effect of 12 KHz thresholds by calculating the regression line between ABR slopes and 12 KHz thresholds, multiplying it with 12 KHz threshold and subtracting the product from ABR slopes. The adjusted ABR wave I was negatively correlated with the age but not	or audiometric thresholds. Whereas, slope is less affected by the subclinical cochlear dysfunction or outer hair cell dysfunction. However, cochlear synaptopathy significantly affect the slope. Hence, Shallower slope of ABR wave I can be an indicator of age related synaptopathy. However, it is difficult to differentiate between a loss of cochlear synapses (synaptopathy) and loss of auditory nerve fibers (deafferentation) in aged auditory system. According to author, click stimuli is insufficient in case where

			with the noise exposure.	the region affected is different from the region stimulated by click stimuli.
Suresh and Krishnan, (2020)	Search for Electrophysiological Indices of Hidden Hearing Loss in Humans: Click Auditory Brainstem Response Across Sound Levels and in Background Noise	Two experiments are carried out. For experiment 1: 28 participants were selected for both high-risk group (mean age = 21.28 years) and low risk group (mean age = 21.13 years). For experiment 2: 25 participants were selected for both the groups. Mean age for high-risk group was 21.28 years while for low risk group, it is 22.88 years. Groups are based on the	There was significant difference between the two groups in terms of inter-peak latencies where high-risk group exhibit larger I-III and I-V inter-peak latency than low risk group. The I-III inter-peak latency does not revealed any significant difference among the group. Reduced amplitude of wave I was observed in high risk group as compare to low risk group with no significant difference in	The smaller amplitude of wave I in high risk group at moderate and high stimulus levels consistent with the peripheral neural deficits whereas wave III and V amplitudes doesn't have any difference between the two groups suggest the operation of central compensatory gain mechanism with holds true for the wave V to I amplitude ratio also. Longer I-V and I-III inter-peak latencies suggest the conduction time delay between wave I generator and

		extent of noise exposure where the high-risk group consists of students who participated in marching band; the noise was measured informally during the practice session with the help of smart phone application, which revealed sound levels between 120-125 db SPL. ABR was administered using click stimuli at levels ranging from 30-90 dB nHL at 10 db steps in the first experiment and in second experiment click	response amplitude for wave III and V. Also larger V:I amplitude ratio was evident in high-risk group with the ratio greater at lowest stimulus level. Discriminant analysis was also performed, which shows that wave I was the most important variable to classify subjects into high and low risk groups. In the presence of noise, wave I amplitude reduction was smaller for high-risk group as compared to low risk group. The low risk group exhibit	other wave generators at more rostral sites (Moore, 1987a, 1987b). The amplitude reduction was smaller with increase in noise level for wave I in high risk group with no change in amplitude of wave V in both the groups suggests that the masking effect is less for high risk group, this can be due to reduction in low and mid spontaneous rate fibers which reduces the suppressive masking effect, specially at moderate level of masking noise. This differences between high and low risk group can be the consequence of cochlear

		stimuli at 70dB nHL was used in quite situation and also in the presence of broadband noise presented at 50, 60, and 70 dB SPL.	larger wave I amplitude only in quiet and 50 dB SPL noise condition. For high-risk group, the quite condition had greater amplitude than the three noise condition where in no significant difference was observed in amplitude between the noise conditions. There was no group difference evident for latency change of wave I and V, in the presence of noise.	synaptopathy which was evident with the help of ABR.
Washnik, Bhatt, Philips, Tucker &	Evaluation of cochlear activity in normal-hearing	75 participants are taken for the study with the age range of 18-30 years. The study	Weak negative significant relationship was observed between noise exposure	This study revealed a weak negative relation between the noise exposure background and amplitude of ABR

Richter, (2020)	musicians	consists of 25 non-musician students (23 females, 2 males), 25 brass major students (8 females, 17 males), and 25 voice major students (21 females, 4 males).Modified version of Noise exposure screening questionnaire developed by (Johnson, Cooper, Stamper, and Chertoff, 2017) was administered to estimate the noise exposure background. ABR was administered using click stimuli at 90, 75 and 60	background and wave I amplitude of ABR at 75 dBnHL, which was also evident for 90 dBnHL but only for females. After controlling the effect of gender, the wave I amplitude was not significantly different between the three groups. There was no statistical significant difference found for the wave III and V amplitude. The latencies of wave I, III and V were also not significantly different between the three groups taken.	wave I at 75 dBnHL. However, significant difference was observed in 90 dBnHL for females but not for males can be attributed to the fact that there are less number of male participants included in the study which can affect the statistical power for detecting the significant relationship between wave I and noise exposure back ground in male participants. According to author high variability in ABR, wave I amplitudes might be a factor for non-significant findings. One more plausible explanation given is the use

		dBnHL		of questionnaire to quantify noise exposure background, which only takes the exposure over the last one year. This can lead to the assumption that the low exposure background group may have high noise exposure in their lifetime and can already have synaptopathy. One more explanation given is that the humans may have high resistance towards the effect of synaptopathy. In conclusion, Cochlear synaptopathy cannot be solely attributed to this weak association hence it cannot be identified solely based on ABR

				findings. Among the groups, the unbalanced gender distribution affected the results in this study.
Couth et al., 2020	Investigating the effects of noise exposure on self-report, behavioral and electrophysiological indices of hearing damage in musicians with normal audiometric thresholds	76 musicians with age range of 18-26 years (36 male, 40 female)and 47 non musicians (21 male, 26 female) with age range of 18-27 years were taken for the study. Noise exposure history was taken with the help of structured interview "NESI" (Guest et al., 2018)according to which the group has been divided in to high and low noise	There was no significant correlation between wave I amplitude and growth with musicianship and noise exposure. As compared to non-musicians, there was significantly greater wave I:V ratio for musicians. This difference is due to slightly larger wave I amplitude for musician and slightly smaller wave V amplitudes in non-	However, there was no difference between high and low noise exposure group too except the increased ABR wave V latency, which is only evident in male participants. This finding suggests a delay propagation of action potential across auditory brainstem pathway but since the wave I latency and amplitude was unaffected, this finding seems unlikely. According to authors, it is difficult to ascertain the exact reason

		exposure group. ABR was administered using 100 µsec click stimuli at 60 and 80 dbnhl.	musicians; however, these differences are not significant. At 60 dBnHL the latency of wave I and V was delayed as compared to 80 dBnHL. For wave I latency the effect of musicianship and noise exposure was not significant whereas for wave V, there was a significant difference between the groups i.e. Higher noise exposure was associated with increased ABR wave V latency as compared to low noise exposure group. However, there	behind this finding. There can be number of possible explanation for this. The greater wave I to V ratio for musicians is driven by the slightly large wave I amplitude and slightly smaller wave V amplitude, which was not significant. According to the authors, young human adults can be less susceptible to noise induced cochlear synaptopathy. However, if cochlear synaptopathy is present in humans than it can be more related to the aging factor rather than noise induced synaptopathy. Additionally, there is large variability in human

			was no significant difference found for musicianship. There was also a significant difference in terms of inter-peak latencies where the high noise exposure group has larger inter-peak latencies than low noise exposure group participants.	participants as compared to animals where the variables can be control, also the extent of life-time noise exposure can be different i.e. It is much more irregular in humans and its difficult to monitor accurately across the life span. It can be possible that the measure used here in this study for calculating the extent of noise exposure may have provided insufficient information in terms of lifetime noise exposure. Hence, with findings of this study, the authors concluded that ABR is not related to lifetime noise exposure as the proxy

				measure of cochlear synaptopathy.
Dhrruvakumar, Shambhu, & Konadath, (2021)	Assessment of Hidden Hearing Loss in Individuals Exposed to Occupational Noise Using Cochlear, Neural, Temporal Functions and Quality of Life Measures	50 participants with age range of 25-45 years were included in the study. 25 individuals have noise exposure history of 75 dB (A) and the other 25 individuals do not have any history of noise exposure. ABR was administered using click and CE-Chirp stimuli at the level of 80dB nHL.	For clicked evoked ABR there was no significant difference found between two groups for wave V latencies. Whereas, prolonged latencies of wave V were observed in individuals with noise exposure for CE-Chirp stimulus.	In this study ABR, using CE-chirp was found to be more sensitive to identify the earlier cochlear changes like hidden hearing loss at brainstem level due to high exposure of noise than click ABR.. Prolonged latency of wave V in individuals with exposure of occupational noise suggest the changes in the basal region of cochlea affecting the nerve fibers which in turn affects the overall firing rate which results in increase in conduction timing hence prolonging the response generated for

				wave V. However, the authors did not talk about the wave I amplitude or latency measures which are the limitation of the study.

3.3 Quality Analysis:

Quality assessment was done using QUADAS-2 tool. Out of 16 selected studies, two studies got high risk of bias and 1 study got unclear under the patient selection domain while under index test domain all studies have low risk of bias. Under the reference standard domain 1 study got high risk of bias and 4 studies appears to be at high risk of bias. For applicability concern, in patient selection and index test domain, all studies got low concern for applicability. However, under reference standard domain 1 study got high concern for applicability and 1 study got the unclear concern for applicability. In flow and timing domain, all studies have low risk of bias. Results of the quality assessment through QUADAS-2 tool are summarized in Table 3 where score of "1" indicate low risk of bias, "2" indicates high risk of bias and "3" indicates unclear risk of bias.

Table 3. 3 Tabular presentation of quality analysis QUADAS- 2 results.

Study	Risk of bias				Applicability concern		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Mehraei et al., (2016)	1	1	3	1	1	1	3
Bramhall, Konrad-Martin, mcmillan, and Griest, (2017)	1	1	1	1	1	1	1
Fulbright, Le Prell, Griffiths, and Lobarinas, (2017)	1	1	1	1	1	1	1
Grose, Buss, and Hall, (2017)	1	1	1	1	1	1	1
Prendergast et al., (2017)	1	1	1	1	1	1	1
Guest, Munro, Prendergast, Millman, and Plack, (2018)	1	1	2	1	1	1	2
Bramhall, Konrad-Martin, and mcmillan, (2018)	1	1	1	1	1	1	1

Valderrama, Beach, Yeend, Sharma, Van Dun, and Dillon, (2018)	1	1	1	1	1	1	1
Bhatt and Wang, (2019)	1	1	1	1	1	1	1
Prendergast et al., (2019)	2	1	1	1	1	1	1
Megha et al., (2019)	1	1	1	1	1	1	1
Johannesen, Buzo, and Lopez-Poveda, (2019)	1	1	3	1	1	1	1
Suresh and Krishnan, (2020)	1	1	3	1	1	1	1
Washnik, Bhatt, Phillips, Tucker, and Richter, (2020)	2	1	1	1	1	1	1
Couth et al., (2020)	3	1	3	1	1	1	1
Dhrruvakumar, Shambhu, and Konadath, (2021)	1	1	1	1	1	1	1

*Low -1, High -2, Unclear -3

Figure 3. 2: Graphical representation of QUADAS-2 results depicting proportion of studies with low, high, and unclear for risk of bias assessment.

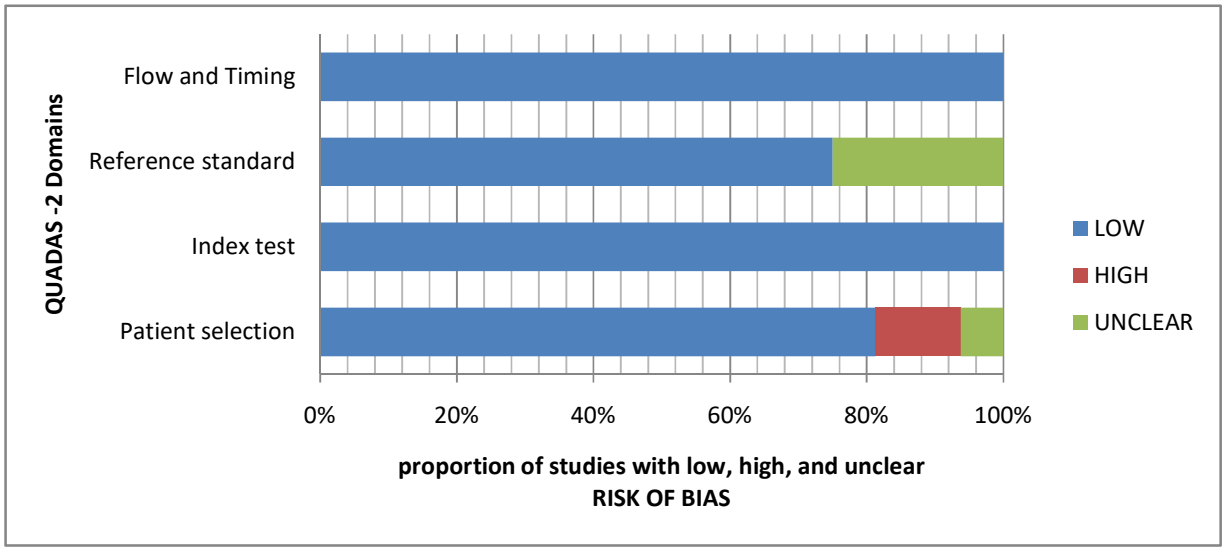
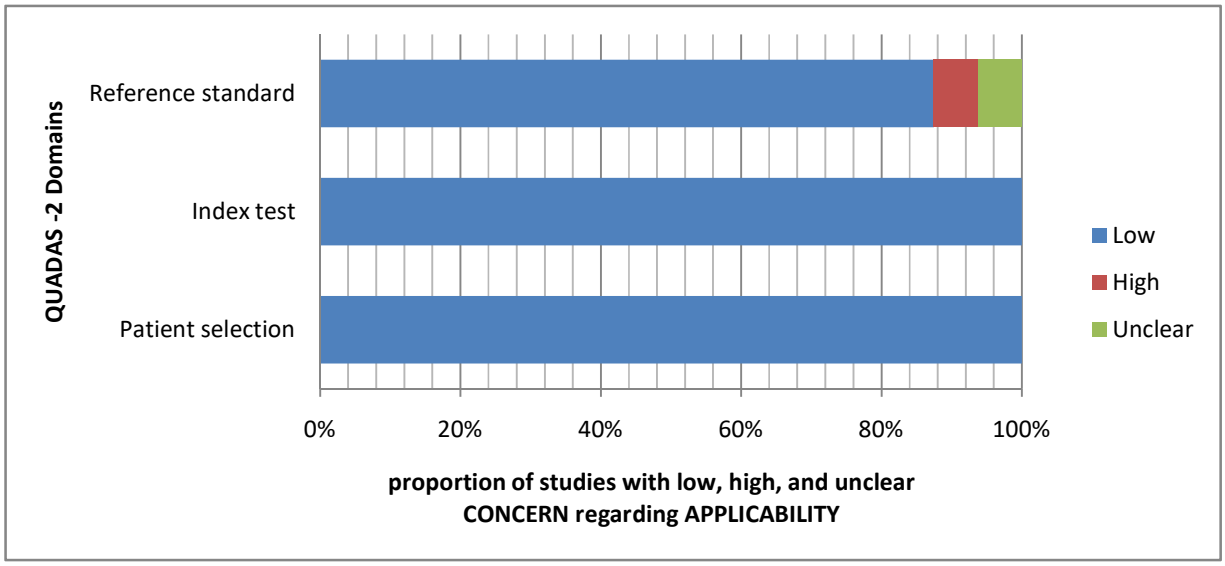


Figure 3. 3: Graphical representation of QUADAS-2 results depicting proportion of studies with low, high, and unclear for concern regarding applicability.



Out of the total studies included in this systematic review, **Figure 3.2** shows the proportion of studies with high, low and unclear risk of bias while **Figure 3.3** shows the proportion of studies with high, low and unclear concern regarding applicability. The results from the studies included in this systematic review were synthesized qualitatively to meet the aim and objectives of this study. The results are further discussed in the discussion chapter of this systematic review

Chapter 4

Discussion

The first objective of this systematic review was to identify the possible causes of hidden hearing loss. All 16 studies taken for the systematic review have given emphasis on the noise induced cochlear synaptopathy i.e. the subtle change in the auditory system more specifically in the synapses between the inner hair cells and spiral ganglion nerve fibers which is induced by the exposure of high level of noise. Out of this 16 studies, two studies have also put emphasis on the synaptopathy or hidden hearing loss caused due to the ageing of the auditory system (Johannesen, Buzo, Lopez-Poveda, 2019; Prendergast et al., 2019). The cochlear synaptopathy caused due to noise exposure has also been confirmed in the animal studies done by Kujawa and Liberman, (2009) where the noise exposure in mice leads to the peripheral auditory changes without affecting the standard audiometric threshold, altering the output of auditory nerve without hampering the outer hair cells. The same subset of findings has also been confirmed in another animal study where the rhesus monkey was taken as subject and exposed to high level of noise. As a result of this exposure the authors reported that there was a dramatic loss of synapses in the basal half of the cochlea whereas the hair cell loss was minimal (Valero,Burton,
Hauser, Hackett, Ramachandran, and Liberman, 2017). This type of auditory change can lead to impaired speech perception without hampering the detection of tonal signal (Marmel, Cortese, and Kluk, 2020) which results in undetectable nature of this disorder during the routine audiological assessments. These findings suggest that there are other structures in the mammalian auditory system which can also be affected by the noise or other hazards prior to the outer hair cells and the changes are quite subtle which cannot be confirmed with the routine audiological evaluation of hearing. It has its impact on the ribbon synapses between the auditory nerve and type I spiral ganglion nerve terminals which is the main cause for the alteration in the

response of the auditory nerve (Furman, Kujawa, and Liberman, 2013; Kujawa and Liberman, 2009). However some of the studies also revealed that lifetime noise exposure does not have any relation to cochlear synaptopathy (Marmel, Cortese, and Kluk, 2020). The same holds true for the age related cochlear synaptopathy also where a similar kind of synaptic loss has been observed between inner hair cells and spiral ganglion neurons (Sergeyenko, Lall, Liberman, and Kujawa, 2013). Many studies in the area of age related auditory changes had revealed that normal age-related loss of Inner hair cells, outer hair cells, spiral ganglion neurons, and cochlear synapses between outer hair cells and medial olivocochlear efferent fibers can be subject of this alteration independently (Fu et al., 2010; Kidd and Bao, 2012). Both the causes which are mentioned in studies included in this review has almost same pathophysiology behind it but the way it expresses itself in auditory system is different with respect to the mechanism and causal factor, which is different for noise induced cochlear synaptopathy and age related synaptopathy. There are two types of spiral ganglion afferent nerve fibers which carries auditory signal from hair cells to the central auditory system i.e. Type I and II spiral ganglion neurons. The type II spiral ganglion nerve fibers makes synapses with outer hair cells in cochlea, which is only about 5% of total spiral ganglion neurons. The type I spiral ganglion neurons which synapse with the inner hair cells, can be further divided into three functional groups based on their dynamic range and spontaneous rate fibers. High-spontaneous rate fibers of spiral ganglion nerve consist of 61% of all type I spiral ganglion neurons; have low thresholds and narrow dynamic range. Low spontaneous rate fiber consist of 16% of the fibers, have high thresholds and wide dynamic range, and remaining 23% are medium spontaneous rate fibers have both thresholds and dynamic ranges intermediate to high and low spontaneous rate fibers (Gelfand, 2004). Several anatomical differences are responsible for these differences in spontaneous rate and dynamic range. High

spontaneous rate fibers has more mitochondria, thicker axons, and synapses on the pillar side, while low and medium spontaneous rate fibers have fewer mitochondria, thinner axons, , and tend to synapse on the modiolar side of the IHC (Liberman, 1988). In addition, there are significant differences in the manner of synapses (Liberman, Wang, and Liberman, 2011). Each spiral ganglion neuron contacts only a single inner hair cell, but each inner hair cell is innervated by multiple type I spiral ganglion neurons. At pre-synaptic regions of this synapses, an electron dense ribbon is located which is generally surrounded by a disc of synaptic vesicles which contains glutamate (Fuchs, Glowatzki, and Moser, 2003a; Moser and Starr, 2016). The vibration induced by the sound deflects the stereocilia of inner hair cells which turns on or activate the mechanoelectric transduction channels, and the resulting influx of potassium (K+) cation generates a depolarizing receptor potential. This graded potential triggers the influx of calcium (Ca2+) ion through voltage-gated calcium channels at the pre-synaptic active regions of the ribbon synapse, driving glutamate release with the synaptic vesicle fusion (Fuchs, 2005).Studies have shown that glutamate in excess concentration can leads to synaptic loss between inner hair cells and spiral ganglion neurons (Wang and Green, 2011). Toxic concentrations of this neurotransmitter which is excitatory in nature, can lead to large sodium, potassium, and calcium ion influx into spiral ganglion neurons which can result in swelling, and ultimately breaching and rupturing the postsynaptic structures (Le Prell, Yamashita, Minami, Yamasoba, and Miller, 2007; Puel, Pujol, Tribillac, Ladrech, and Eybalin, 1994; Puel, Ruel, Gervais D'Aldin, and Pujol, 1998). Based on the manner in which ion channels in spiral ganglion neurons might be permeable to calcium, both T-type (transient activation) and L-type (long-lasting) calcium channels could contribute to this excess calcium following noise stress. This both the channels are responsible for selective conduction of calcium ions through cell membrane. The

investigations in this area have indicated T-type calcium channels as playing a key role in noise induced hearing loss (Bao et al., 2013; Kopecky, Liang, and Bao, 2014). Apart from increased calcium influx in postsynaptic terminals, noise exposure causes an increase in calcium in hair cells (Glowatzki, Grant, and Fuchs, 2008), which may contribute to further calcium release from intracellular storages. Excess calcium might cause not only excessive glutamate release, which could harm postsynaptic structures, but also activates the downstream calcium dependent pathways, which could trigger mitochondria-mediated cell death pathways (Oishi and Schacht, 2011). As a result, if a specific limit is reached, this can cause damage to the synapses, resulting in cochlear synaptopathy and, eventually, hair cell loss.

For age related cochlear synaptopathy, the plausible cause could be the degenerative changes in the cochlear microstructures that can happen due to ageing, which eventually reduces the number of synaptic terminal in old aged cochlea leading to cochlear synaptopathy (Parthasarathy and Kujawa, 2018). Numerous studies in animal models have been revealed that there can be imbalance excitatory and inhibitory effects of neurotransmitter in older age which plays an important role in degeneration process which in due course leads to glutamate excitotoxicity ultimately increasing the concentration of glutamate resulting in greater influx of ions, which in turn causes damage to synapses and eventually mitochondrial cell death (Chen, Jia, Ni, and Chen, 2019; Johannesen, Buzo, and Lopez-Poveda, 2019; Pujol et al., 1991; Rousset et al., 2020; Stamataki, Francis, Lehar, May, and Ryugo, 2006; Tadros et al., 2007). However, there are several studies other than what included in this systematic review which also shows that ototoxicity can be one of the possible cause of hidden hearing loss (Greguske, Llorens, and Pyott, 2021; Hinojosa and Lerner, 1987; Lobarinas, Salvi, and Ding, 2013a; Sone, Schachern, and Paparella, 1998).

The second objective of this study was to identify the ABR parameters those are effective in identifying the Hidden hearing loss. Out of 16 studies selected for this review, 14 studies have given emphasis on the wave I of the ABR which is consistent with the animal studies (Bhatt and Wang, 2019; Bramhall, Konrad-Martin, and mcmillan, 2018; Bramhall, Konrad-Martin, mcmillan, and Griest, 2017; Couth et al., 2020; Fulbright, Le Prell, Griffiths, and Lobarinas, 2017; Grose, Buss, and Hall, 2017; Guest, Munro, Prendergast, Millman, and Plack, 2018a; Johannesen, Buzo, and Lopez-Poveda, 2019; Mehraei et al., 2016; Prendergast et al., 2019, 2017; Suresh and Krishnan, 2020; Valderrama, Beach, Yeend, Sharma, Van Dun, and Dillon, 2018; Washnik, Bhatt, Phillips, Tucker, and Richter, 2020). Initial experiments done on the animal models has confirmed that the reduced amplitude of wave I in ABR is a significant marker for this condition (Kujawa and Liberman, 2009). Out of these 14 studies, 7 studies concluded that the wave I of ABR can be used as a marker of cochlear synaptopathy (Bramhall, Konrad-Martin, & mcmillan, 2017, 2018; Grose, Buss, & Hall, 2017; Johannesen, Buzo, & Lopez-Poveda, 2019; Mehraei et al., 2016; Prendergast et al., 2019; Suresh & Krishnan, 2020; Valderrama et al., 2018). However, there are number of variables that can alter the amplitude of wave I of ABR, like tissue resistance, age, gender and head size (Abadi et al., 2016; Dehan and Jerger, 1990; Don, Ponton, Eggermont, and Masuda, 1994). In fact apart from this individual difference there could also be involvement of some factor related to the protocol used to measure the wave I of the ABR specially in case of cochlear synaptopathy as according to the Don and Eggermont, (1978) there is large contribution of frequencies above 2 KHz in generation of wave I amplitude, while the amplitude of wave V is primarily generated by lower frequencies. In case of cochlear synaptopathy the response from the high frequency regions become important because the experiment done on animal models reports that the synaptopathy is more confined to the high

frequency region i.e. The more basal region of basilar membrane in cochlea (Kujawa and Liberman, 2009). Hence, it is very important to imply a protocol and parameters which can provide sufficient information from the basal region of the cochlea. ER-3A inserts are used in about 12 studies included in this systematic review(Bhatt and Wang, 2019; Bramhall, Konrad-Martin, and mcmillan, 2018; Bramhall, Konrad-Martin, mcmillan, and Griest, 2017; Couth et al., 2020; Fulbright, Le Prell, Griffiths, and Lobarinas, 2017; Grose, Buss, and Hall, 2017; Johannesen, Buzo, and Lopez-Poveda, 2019; Megha et al., 2019; Prendergast et al., 2017, 2019; Valderrama et al., 2018; Washnik, Bhatt, Phillips, Tucker, and Richter, 2020). One of the study (Mehraei et al., 2016) appear to be using ER-10C inserts which is a variation of ER-3A insert earphones having same frequency response while two of the studies (Dhrruvakumar, Shambhu, and Konadath, 2021b; Guest, Munro, Prendergast, Millman, and Plack, 2018a) failed to mention the transducer used which we think is a major drawback specially in case of synaptopathy where we are interested in response from the extended high frequency regions. However, if the synaptopathy occurs first at the most basal regions in humans also then these insert earphones might not be able to stimulate the basal region sufficiently which contributes in the generation of wave I because the frequency response of ER-3 earphones rolls off above 5 KHz. Out of this 12 studies, only 6 studies have concluded that the ABR can be a tool aiding in diagnosis of synaptopathy (Bramhall, Konrad-Martin, and mcmillan, 2018; Bramhall, Konrad-Martin, mcmillan, and Griest, 2017; Grose, Buss, and Hall, 2017; Johannesen, Buzo, and Lopez-Poveda, 2019; Megha et al., 2019; Valderrama, Beach, Yeend, Sharma, Van Dun, and Dillon, 2018). While this studies did not discussed about this factor except for Johannesen, Buzo, & Lopez-Poveda, (2019). In this study, they have mentioned that this could not be the factor which can influence the results, considering two reasons. First, they had used high level click stimulus of

90—110 db ppeSPL which is sufficient to ensure equal basilar membrane excitation for characteristic frequency up to ~10 KHz (Ruggero, Rich, Recio, Narayan, and Robles, 1997). Second, in animal experiments, the results showed that the synaptopathy often ranged till basal half of the cochlea (Kujawa and Liberman, 2009; Liberman & Liberman, 2015). In humans this will be correspond to the approximately 2 KHz region and this region is well within the frequency range of ER-3 insert earphones (Johannesen, Buzo, and Lopez-Poveda, 2019). However, if synaptopathy affected beyond this frequency and restricted only till those frequencies than it will be difficult to rule out such pathology with the help of ER-3A insert earphones. Suresh and Krishnan, (2020) considering this factor used the ER-2A insert earphones which has relatively flat frequency response till about 12-14 KHz (Elberling, Kristensen, and Don, 2012), which enable them to record the neural activity which contribute to wave I over an extended high frequency region in comparison to ER-3A earphones(M Don and Eggermont, 1978; Eggermont, 1979). The result from this study suggest that there was reduced wave I amplitude for high risk group (noise exposed) in comparison to low risk group and also in the presence of background noise which was varied in level, there was greater reduction in low risk group consistent with the hypothesis that low spontaneous rate fibers affected in noise induced synaptopathy.

.In this systematic review 6 studies (Bramhall, Konrad-Martin, and mcmillan, 2018; Bramhall, Konrad-Martin, mcmillan, and Griest, 2017; Fulbright, Le Prell, Griffiths, and Lobarinas, 2017; Grose, Buss, and Hall, 2017; Valderrama, Beach, Yeend, Sharma, Van Dun, and Dillon, 2018; Washnik, Bhatt, Phillips, Tucker, and Richter, 2020) used the tiptrode electrode which is being placed near the tympanic membrane inserted in to the ear canal tend to produce more robust wave I amplitude (Minaya and Atcherson, 2015) than the surface electrodes

used in the remaining studies. Near field electrodes generate the robust response with greater amplitude while the electrode which is far from the generating site tend to be picking responses but are smaller in amplitude while sometime the response from the generating site could be very small and weak and can be contaminated due to electrodes at far distance (Ghigo, Erwin, and Erwin, 1991)However there are studies which states that the tiptrode electrode placed near to the tympanic membrane is supposed to be nearer the generating site (Don and Eggermont, 1978; Rattay and Danner, 2014) generate only slightly improved in response amplitude (Fuchs, Glowatzki, and Moser, 2003b). This supports the findings from the studies included, where although tiptrode electrodes have been used but the results are not in agreement with the cochlear synaptopathy (Fulbright, Le Prell, Griffiths, and Lobarinas, 2017; Washnik, Bhatt, Phillips, Tucker, and Richter, 2020). However, some studies using tiptrode electrodes have found significant changes (Bramhall, Konrad-Martin, and mcmillan, 2018; Bramhall, Konrad-Martin, mcmillan, and Griest, 2017; Grose, Buss, and Hall, 2017; Valderrama, Beach, Yeend, Sharma, Dun, and Dillon, 2018).

Three types of stimulus used in different studies taken in this systematic review i.e. Click, tone burst and chirp stimulus. However most of the studies have used click stimuli (Bhatt and Wang, 2019; Couth et al., 2020; Fulbright, Le Prell, Griffiths, and Lobarinas, 2017; Grose, Buss, and Hall, 2017; Guest, Munro, Prendergast, Howe, and Plack, 2017b; Johannesen, Buzo, and Lopez-Poveda, 2019; Mehraei et al., 2016; Prendergast et al., 2017, 2019b; Suresh and Krishnan, 2020; Valderrama, Beach, Yeend, Sharma, Van Dun, and Dillon, 2018; Washnik, Bhatt, Phillips, Tucker, and Richter, 2020) because it covers wide frequency response especially high frequencies up to 4 KHz (Marttila and Karikoski, 2006). Utility of tone burst stimulus used in 4 studies (Bramhall, Konrad-Martin, and mcmillan, 2018; Bramhall, Konrad-Martin, mcmillan,

and Griest, 2017; Fulbright, Le Prell, Griffiths, and Lobarinas, 2017; Megha et al., 2019) have its own advantages mainly in terms of specificity of the regions in cochlea which is stimulated with the help this frequency specific stimuli. (Hurley, Hurley, and Berlin, 2005).However 1 of the studies (Fulbright, Le Prell, Griffiths, and Lobarinas, 2017) did not concluded the sensitivity of the tone burst stimuli in identification of cochlear synaptopathy while 3 studies (Bramhall, Konrad-Martin, and mcmillan, 2018; Bramhall, Konrad-Martin, mcmillan, and Griest, 2017; Megha et al., 2019) have shown to be effective using tone burst stimulus in which the study done on veterans by Bramhall, Konrad-Martin, and mcmillan, (2018) has a significant large effect of noise exposure at 4000 Hz tone burst stimuli given emphasis on wave I amplitude while the other study (Megha et al., 2019) has find significant increase in latency of wave V for the tone burst stimuli of 500 Hz but not for 1000 and 2000 Hz. One more study which has used 1, 3, 4 and 6 KHz tone burst and found significant reduced wave I amplitude in noise exposed participant at all four frequencies (Bramhall, Konrad-Martin, mcmillan, and Griest, 2017). The contrast findings between the studies of Bramhall, Konrad-Martin, and mcmillan, (2018) and Bramhall, Konrad-Martin, mcmillan, and Griest, (2017) has been supported with reference to the animal study done by Kujawa and Liberman, (2009) where the loss of synaptic ribbons was observed in CBA/caj mouse due to over exposure of noise evident in basal region confined to high frequencies and hence high frequencies are compromised in those subjects. However in study done by Bramhall, Konrad-Martin, mcmillan, and Griest, (2017) all tested frequencies are affected because the ABR administered in the participants was after months to years of noise exposure which can result in accelerating the age related synaptopathy and hence can be spread towards the low frequency end of the cochlea over time. While in study of Megha et al., (2019), the findings were justified by the study done by Sergeyenko, Lall, Charles Liberman, and

Kujawa, (2013) where similar result was observed i.e. Synaptic ribbon losses were initially larger at apical region of the cochlea when compared to base, but with increasing age, the synaptopathy moved towards the basal end spreading throughout the cochlea. One possibility stated by the author is that the surviving hair cells in the cochlea can be of very high frequency region which may be present but the functioning is abnormal (Liberman and Kiang, 1978; Salvi, Ahroon, Perry, Gunnarson, and Henderson, 1982) which can affect the further conduction of signal in the cochlea and because of that delay in latency is more evident in low frequency region. However, in that case the wave I and III of ABR could have also been affected which was not described in the study. The study only mentioned about the wave V of ABR which is not sufficient for the hypothesis and justification given by the author. Also if high frequency regions are the cause for the conduction delay than rest of the frequencies would also have some effect considering the fact that the ABR was administered in 4 frequencies i.e. 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. However, in the same study narrow band chirp was also used which showed a significant latency difference between control and experimental group at all tested frequencies except 4000 Hz.

The chirp stimulus has been used in 2 studies i.e. CE chirp was used in study by Dhrruvakumar, Shambhu, & Konadath, (2021) while in the study by Megha et al., (2019) narrowband chirp was used. Both the studies found that latency of wave V was increased in experimental group in comparison with the control group and concluded that chirp stimulus can be very useful and effective in identifying the cochlear synaptopathy rather than wave I as it is difficult to measure the wave I robustly across different stimulus levels. Also the chirp stimulus are designed in such a way that it can compensate for the conduction delay along the basilar membrane resulting in enhanced synchrony in nerve fibers and can provide a robust response (Telian, Kileny, Niparko, Kemink, and Graham, 1989).

All studies included in this systematic review have used the stimulus intensity at suprathreshold level. The rationale behind using this level is in agreement with the fact that low spontaneous rate fibers have high threshold which is the suspected group of fibers to be affected in cochlear synaptopathy (Kujawa and Liberman, 2009; L. D. Liberman, Wang, and Liberman, 2011; M. C. Liberman and Kiang, 1978; M. Charles Liberman, Epstein, Cleveland, Wang, and Maison, 2016). Hence, it is important to use an intensity level which can stimulate these fibers in order to gather information regarding the functioning of the same.

Masking noise was used in two of the studies included (Mehraei et al., 2016; Suresh and Krishnan, 2020) where in both the studies broadband noise was presented at different levels to evaluate the amount of masking taking place. In the study by Mehraei et al., (2016), they showed that wave V latency shift with increase in noise level was reduced in subjects with risk of cochlear synaptopathy, which was then correlated with the growth of wave I amplitude along with the stimulus level. They found that the listeners with steeper growth of wave I amplitude had large wave V latency shift whereas those with shallower growth reflected reduced latency shift with increase in background noise level. The authors suggested that there is a difference in desynchronization of auditory nerve fibers where for low spontaneous rate fibers have high thresholds (J. Costalupes, 1985; Young and Barta, 1998) while the high spontaneous rate fibers have low thresholds (M. Charles Liberman, 1978; W. S. Rhode, Geisler, and Kennedy, 1978). Hence as the noise level increases there relative contribution in masking is also increase while in case of cochlear synaptopathy which affects the low spontaneous rate fibers, the neural contribution from this fibers decreases resulting in reduced masking effects at high level of noise. In contrast to this study, another study which incorporated the masking phenomenon to identify its effect in synaptopathy i.e. Suresh & Krishnan, (2020) did not showed any difference

in latency measure. However, they showed that there was reduced effect of masking in their high risk group but this was in terms of wave I amplitude where the increasing level of masking noise showed reduced suppression effect on wave I amplitude. In the participants who were in high risk group, shallower reduction in wave I amplitude was observed in comparison to the low risk group individuals. The authors correlated these findings with the smaller amplitude of wave I in high risk group, which shows the reduced number of neural element, particularly medium and low spontaneous rate fibers (Delgutte, 1990; William S. Rhode, 1978) or the absence of suppression by the central component (Cai and Geisler, 1996b, 1996a; Delgutte, 1990; William S. Rhode, 1978). However, the contrary findings between these two studies had been addressed by Suresh & Krishnan, (2020),but with respect to mice experiment done in the same study by Mehraei et al., (2016). The author assumed that these contrary findings can be result of contribution from the more broader region of cochlea in their subjects which can minimize the latency difference among groups. This finding suggests that ABR when administered with making noise at varied levels can provide potential information about the cochlear synaptopathy.

The final objective of this systematic review is to identify the efficacy of using ABR in the identification of hidden hearing loss. Out of 16 studies taken for the systematic review, 9 of the studies (Bramhall, Konrad-Martin, and mcmillan, 2018; Bramhall, Konrad-Martin, mcmillan, and Griest, 2017; Dhrruvakumar, Shambhu, and Konadath, 2021; Grose, Buss, and Hall, 2017; Johannesen, Buzo, and Lopez-Poveda, 2019; Megha et al., 2019; Mehraei et al., 2016; Suresh and Krishnan, 2020; Valderrama, Beach, Yeend, Sharma, Van Dun, and Dillon, 2018) concluded that ABR can be a useful tool in the identification of hidden hearing loss. However, the results from the studies show that different parameters have been addressed in identification of this disorder. The details of the studies have been summarized in the summary table included in the

result section of this systematic review. Most of the studies showed Wave I is a potential ABR parameter to study effect of noise (Bramhall, Konrad-Martin, and mcmillan, 2018; Bramhall, Konrad-Martin, mcmillan, and Griest, 2017; Grose, Buss, and Hall, 2017; Johannesen, Buzo, and Lopez-Poveda, 2019; Mehraei et al., 2016; Suresh and Krishnan, 2020; Valderrama, Beach, Yeend, Sharma, Van Dun, and Dillon, 2018) which has been supported by the initial animal experiments done in this area (Kujawa & Liberman, 2009; M. C. Liberman, Epstein, Cleveland, Wang, & Maison, 2016; Lobarinas, Salvi, & Ding, 2013). However, some studies have also considered other parameters like, wave I to wave V amplitude ratio (Bramhall, Konrad-Martin, and mcmillan, 2018; Prendergast et al., 2019; Suresh and Krishnan, 2020), wave V latency shift in noise and growth function of wave I (Mehraei et al., 2016)with increasing the stimulus level. We found that the most promising parameter is the reduced amplitude of ABR wave I, along with the reduced amplitude ratio of wave I to V which is the product of smaller wave I amplitude, but no change or robustness of wave V amplitude due to the central gain mechanism (Schaette and mcalpine, 2011; Sergeyenko, Lall, Charles Liberman, and Kujawa, 2013) Some studies have shown that increased latency of wave V can be a potential parameter to identify the cochlear synaptopathy (Couth et al., 2020; Dhrruvakumar, Shambhu, and Konadath, 2021; Megha et al., 2019; Prendergast et al., 2017). However, in findings of Prendergast et al., (2017) increase in wave V latency in response to 80db click was not reflected when they increase the level of the stimulus, which does not fit the assumption of low spontaneous rate fibers model of cochlear synaptopathy. While in study done by Couth et al., (2020) increase in latency was seen only in males and because the wave I amplitude and latencies was unaffected author does not conclude it to the fact that delayed propagation of action potential should be a cause of this prolongation, taking cochlear synaptopathy in to consideration. However, if they could have

assess the prolongation of wave V in presence of multiple background noise (Mehraei et al., 2016) they could have find out the effect of noise exposure and neural conduction at different stages of auditory pathway. One more study which focused upon the latency of wave V is study done by Megha et al., (2019), however they only get this findings for tone burst of 500 Hz but not for 1000 and 2000 Hz, where she had discussed that this could be the consequence of abnormal functioning of hair cells at higher frequency region which is hampering the conduction of signal towards the apical sites. However, in our knowledge this could not be the reason because if the conduction is the reason then there should be delay also for the 1000 and 2000 Hz. Furthermore, the results described by the Dhrruvakumar, Shambhu, & Konadath, (2021) revealed that prolonged latency of wave V can be used to identify the hidden hearing loss, but their findings were only significant for the CE-chirp stimulus not for the click evoked responses which they have justify with the compromised neural conduction timing in noise exposed individuals (Pushpalatha and Konadath, 2016). However, compromised neural conduction time should also play role with click stimuli which has not been discussed in the study.

The effect of age related cochlear synaptopathy has also been discussed by some studies where in the study by Johannesen, Buzo, and Lopez-Poveda, (2019) slope of wave I (μV/dB) versus level function was determined. There was a shallower slopes observed for increase in age while the difference was not significant for the effect of noise exposure. However, contrary findings were observed by the Prendergast et al., (2019) where they did not find any significant effect of age and level noise exposure on the ABR findings.

Furthermore, there are studies which did not find that ABR is effective in identification of this pathology (Bhatt and Wang, 2019; Couth et al., 2020; Fulbright, Le Prell, Griffiths, and Lobarinas, 2017; Guest, Munro, Prendergast, Millman, and Plack, 2018b; Prendergast et al.,

2017, 2019b; Washnik, Bhatt, Phillips, Tucker, and Richter, 2020) , there are many reasons which can be responsible for these findings. One of the main reasons addressed in the studies is the use of noise exposure questionnaire to quantify the extent of exposure, which can give in adequate information leading to the uneven distribution of groups into high and low risk individuals (Bhatt and Wang, 2019; Bramhall, Konrad-Martin, and mcmillan, 2018; Bramhall, Konrad-Martin, mcmillan, and Griest, 2017; Fulbright, Le Prell, Griffiths, and Lobarinas, 2017; Valderrama, Beach, Yeend, Sharma, Van Dun, and Dillon, 2018; Washnik, Bhatt, Phillips, Tucker, and Richter, 2020). As some of the questionnaires used in the studies have used one year of noise exposure as a criteria to identify the groups in to low and high risk, there can be possibilities that the individuals have already had enough noise exposure in their life time which leads to cochlear synaptopathy. Despite of this fact, as they have low level of noise exposure in last one year they are assigned to the low risk group. This distribution can introduce bias in the results where there will not be any difference between two groups.

Same factor can be taken another way round that, does the cochlear synaptopathy exist in individuals included in the study i.e. does the exposure to noise is sufficient enough to cause synaptopathy in individuals taken for the study. As there are studies which had taken the noise exposure history through interview however, with the help to interview and questionnaire it is difficult to quantify the total noise exposure took place. Sometime subjects do not able to report the exact information while taking the history. This could be one of the factors which are responsible for the insignificant findings among the studies.

Another factor which can be taken in to account is, while the studies take references from the earlier animal experiments it is important to note that in animal experiments done by Kujawa & Liberman, (2009) there is little or no genetic variation, also there were no difference

in experiences in life prior to the experiment. Whereas, in human subjects there are genetic variations and different life style variation which can make an individual more or less vulnerable to this subtle changes. It is not know that whether there is equivalent susceptibility to loss of synapses across genders, across listeners with same age and across the lifetime. As this is in relation with the noise exposure we know that the concept of tough and tender ears has been considered in this context (Cody and Robertson, 1983). As studies focused more on the healthy and young individuals it can be possible that the synaptopathy does not have existed in those subjects or it can be present after an age achieved (Fernandez, Jeffers, Lall, Liberman, and Kujawa, 2015) which should be ruled out taking a vast age range subjects having noise exposure, prior to the outer hair cell loss due to presbycusis.

In the early work done in this area revealed that in mice the synaptopathic changes are irreversible. While in the experiments done in guinea pigs suggested that after an initial loss of synaptic ribbons, there was recovery which has been observed (Liu et al., 2012; Shi et al., 2013). However, this reversible change restores anatomically, but there function remains abnormal (Shi, Chang, Li, Aiken, Liu, and Wang, 2016; Song et al., 2016). These differences between the experiments done on animals suggest that there can be a difference in manifestation of cochlear synaptopathy in different species, hence it is very important to consider the fact that how cochlear synaptopathy may manifest itself in human auditory system.

Studies included in this systematic review also highlights having tinnitus is a good indicator of cochlear synaptopathy (Bramhall, Konrad-Martin, and mcmillan, 2018; Couth et al., 2020; Suresh and Krishnan, 2020; Valderrama, Beach, Yeend, Sharma, Van Dun, and Dillon, 2018). The results of this studies showed that the wave I of ABR is reduced individuals with tinnitus while the wave V latency was either robust or same and reduced wave I to V ratio, which

highlights the central compensation mechanism taking place where reduced input to the higher levels results in compensatory increase in neural activity to normalize input to the higher levels of ascending auditory pathways generating tinnitus as a consequence. This neuronal hyperactivity in cochlear synaptopathy results from the deafferentiation of low-SR fibers (Bramhall, Konrad-Martin, and mcmillan, 2018). Hence, cochlear synaptopathy can be identified with the help of ABR while combining it with the noise exposure history and symptoms like tinnitus with normal audiogram configuration can add more reliability in the ABR findings.

Chapter 5

Conclusion

The aim of this study was to perform a systematic review of the ABR findings in hidden hearing loss. Where articles were searched with the specific keywords in 4 databases i.e. Pubmed central, J-GATE, science direct, and Google scholar. The total number of articles found based on keywords are 15,564 in number out of which 1975 duplicates were deleted and remaining articles were screened based on title. After title screening stage 25 articles were finalized for abstract screening. In abstract screening stage 2 articles were excluded as they are fulfilling the exclusion criteria for systematic review. 23 articles went through the full text screening stage where 16 were finalized for the systematic review and 7 articles were excluded based on the specific reasons. The finalized articles are then synthesized qualitatively to meet the objectives of this study.

The first objective addressed in this systematic review was to identify the possible causes of hidden hearing loss. Most of the studies have highlighted the main cause of hidden hearing loss as overexposure to noise which they refer as noise induced synaptopathy. While, some of the studies have also concluded that neural changes due to age can be a cause for this disorder which is referred as age related cochlear synaptopathy. However, it is difficult to rule out the combine effect of age and noise exposure and just the effect of age. Both of this causes the alteration in ribbon synapses as mentioned by the studies. Hence, noise exposure history and age can be taken into consideration as a possible cause, while suspecting the cochlear synaptopathy in an individual.

With reference to the second objective that is to identify the ABR parameters those are effective in identifying the Hidden hearing loss. Most of the studies showed amplitude of wave I

and reduced wave I to V ratio as a potential parameter to identify this disorder. However, wave V latency has also been addressed by some studies but they are few in number. With the help of the studies taken in this systematic review we can conclude that the potential parameter is wave I amplitude and wave I to V amplitude ratio which can be achieved by implying appropriate protocol with click stimulus or chirp stimulus at suprathreshold levels. Tiptrode electrodes are more effective for the more robust response with filter setting of 100-3000 Hz to reduce low frequency artifacts and clearer response without high frequency clutters. ER-2 insert earphones should be used due to their increased contribution from the high frequency regions of the basilar membrane. Masking noise at varied levels can also be used to study the cochlear synaptopathy and its effect on wave I amplitude reduction and wave V latency shift which should be reduced in subjects with cochlear synaptopathy.

The third and last objective of this systematic review was to examine the efficacy of using ABR in the identification of Hidden hearing loss. As the findings from many studies in this systematic review suggests that synaptopathy can be identified with the help of ABR particularly if wave I amplitude or wave I to V amplitude ratio is compromised. In addition to this wave I amplitude reduction or wave V latency shift as a function of multiple noise levels at suprathreshold intensities in ABR recording can add on to the efficacy of this measure. But it is not clinically feasible to administer such a time consuming assessment protocol. However, one should not rely completely on the ABR for the diagnosis and test battery approach should be practiced to reach a conclusion for the diagnosis of this disorder. Appropriate case history should be taken which includes the noise exposure history and tinnitus. Since, many studies in this systematic review have mentioned that tinnitus can be related to cochlear synaptopathy. However, communication skill assessment in adverse condition may be better predictor for this

disorder than ABR waves as Guest, Munro, Prendergast, Millman, and Plack, (2018) and Bhatt and Wang, (2019) did not see any change in ABR but did report change in SPIN scores or Dichotic tests results.

5.1 Future directions-

To our best knowledge none of the studies have studied the relationship between noise exposure and cochlear synaptopathy over an extended period of time in humans. Hence, longitudinal studies are required to observe these subtle changes over the period of noise exposure to quantify the extent of noise exposure which can lead to hidden hearing loss. Furthermore, there is a lack of sensitivity in predicting the potential cause of this disorder when age and noise exposure both coexist in an auditory system. The challenge is more in diagnosis of senile auditory system who do not have normal audiometric function. A test battery or a protocol should be developed in this area to rule out the possible fiber group affected by the cochlear synaptopathy. In ABR studies, more high frequency tone burst should be used to evaluate the extended high frequency range and to distinguish which frequency region is most and first affected by this order. This could be compared in noise exposed and aging auditory system to know if the same frequencies or the different set of frequencies are affected among these disorders, also the effect of different types of noise and their manifestations as cochlear synaptopathy. At last, there is a need to develop an evidence based protocol for the assessment for this disorder as it can help in early identification and prevention.

5.2 Implications of the study

The implication of this systematic review are-

1. It throws light on possible reasons for cochlear synaptopathy.
2. It explores the pathophysiology responsible for the subtle changes in auditory system.

3. It also suggests the possibility of age related neural synaptopathy
4. Important ABR parameters that can be used to study or monitor the changes in cochlear synapse or Auditory nerve degeneration.
5. It gives the evidence for the future research.

References-

Abadi, S., PhD, Khanbabaee, G., MD, Sheibani, K., & MD. (2016). Auditory Brainstem Response Wave Amplitude Characteristics as a Diagnostic Tool in Children with Speech Delay with Unknown Causes. *Iranian Journal of Medical Sciences*, *41*(5), 415. /pmc/articles/PMC4967486/

Bao, J., Hungerford, M., Luxmore, R., Ding, D., Qiu, Z., Lei, D., Yang, A., Liang, R., & Ohlemiller, K. K. (2013). Prophylactic and therapeutic functions of drug combinations against noise-induced hearing loss. *Hearing Research*, *304*, 33–40. https://doi.org/10.1016/j.heares.2013.06.004

Beach, E. F., Gilliver, M., & Williams, W. (2013). The NOISE (Non-Occupational Incidents, Situations and Events) Database: A new research tool. *Http://Dx.Doi.Org/10.1080/11745398.2013.793157*, *16*(2), 149–159. https://doi.org/10.1080/11745398.2013.793157

Bhatt, I. S., & Wang, J. (2019). Evaluation of dichotic listening performance in normal-hearing, noise-exposed young females. *Hearing Research*, *380*, 10–21. https://doi.org/10.1016/j.heares.2019.05.008

Bramhall, N. (2019). Characterizing noise-induced hidden hearing loss in veterans. *The Journal of the Acoustical Society of America*, *145*(3), 1907. https://doi.org/10.1121/1.5101918

Bramhall, N. F., Konrad-Martin, D., & McMillan, G. P. (2018). Tinnitus and auditory perception after a history of noise exposure: Relationship to auditory brainstem response measures. *Ear and Hearing*, *39*(5), 881–894. https://doi.org/10.1097/AUD.0000000000000544

Bramhall, N. F., Konrad-Martin, D., McMillan, G. P., & Griest, S. E. (2017a). Auditory Brainstem Response Altered in Humans with Noise Exposure Despite Normal Outer Hair Cell Function. *Ear and Hearing*, *38*(1), e1–e12. https://doi.org/10.1097/AUD.0000000000000370

Bramhall, N. F., Konrad-Martin, D., McMillan, G. P., & Griest, S. E. (2017b). Auditory Brainstem Response Altered in Humans with Noise Exposure Despite Normal Outer Hair Cell Function. *Ear and Hearing*, *38*(1), e1–e12. https://doi.org/10.1097/AUD.0000000000000370

Cai, Y., & Geisler, C. D. (1996a). Suppression in auditory-nerve fibers of cats using low-side suppressors. I. Temporal aspects. *Hearing Research*, *96*(1–2), 94–112. https://doi.org/10.1016/0378-5955(96)00034-2

Cai, Y., & Geisler, C. D. (1996b). Suppression in auditory-nerve fibers of cats using low-side suppressors. II. Effect of spontaneous rates. *Hearing Research*, *96*(1–2), 113–125. https://doi.org/10.1016/0378-5955(96)00035-4

Carcagno, S., & Plack, C. J. (2020). Effects of age on electrophysiological measures of cochlear synaptopathy in humans. *Hearing Research*, *396*, 108068. https://doi.org/10.1016/j.heares.2020.108068

Chen, D., Jia, G., Ni, Y., & Chen, Y. (2019). Hidden hearing loss: current perspectives and potential therapies. *Journal of Bio-X Research*, *2*(2), 62–67. https://doi.org/10.1097/JBR.0000000000000035

Cody, A. R., & Robertson, D. (1983). Variability of noise-induced damage in the guinea pig

cochlea: Electrophysiological and morphological correlates after strictly controlled exposures. *Hearing Research*, *9*(1), 55–70. https://doi.org/10.1016/0378-5955(83)90134-X

Costalupes, J. (1985). Representation of tones in noise in the responses of auditory nerve fibers in cats. I. Comparison with detection thresholds. *Journal of Neuroscience*, *5*(12), 3261–3269. https://doi.org/10.1523/JNEUROSCI.05-12-03261.1985

Costalupes, J. A. (1985). Representation of tones in noise in the responses of auditory nerve fibers in cats. I. Comparison with detection thresholds. *Journal of Neuroscience*, *5*(12), 3261–3269. https://doi.org/10.1523/jneurosci.05-12-03261.1985

Couth, S., Prendergast, G., Guest, H., Munro, K. J., Moore, D. R., Plack, C. J., Ginsborg, J., & Dawes, P. (2020). Investigating the effects of noise exposure on self-report, behavioral and electrophysiological indices of hearing damage in musicians with normal audiometric thresholds. *Hearing Research*, *395*, 108021. https://doi.org/10.1016/j.heares.2020.108021

Dehan, C. P., & Jerger, J. (1990). Analysis of gender differences in the auditory brainstem response. *Laryngoscope*, *100*(1), 18–24. https://doi.org/10.1288/00005537-199001000-00005

Delgutte, B. (1990). Two-tone rate suppression in auditory-nerve fibers: Dependence on suppressor frequency and level. *Hearing Research*, *49*(1–3), 225–246. https://doi.org/10.1016/0378-5955(90)90106-Y

Dhrruvakumar, S., Shambhu, T., & Konadath, S. (2021a). Assessment of Hidden Hearing Loss in Individuals Exposed to Occupational Noise Using Cochlear, Neural, Temporal Functions and Quality of Life Measures. In *Indian Journal of Otolaryngology and Head and Neck*

Surgery. https://doi.org/10.1007/s12070-021-02373-7

Dhrruvakumar, S., Shambhu, T., & Konadath, S. (2021b). Assessment of Hidden Hearing Loss in Individuals Exposed to Occupational Noise Using Cochlear, Neural, Temporal Functions and Quality of Life Measures. *Indian Journal of Otolaryngology and Head and Neck Surgery*, 1–8. https://doi.org/10.1007/s12070-021-02373-7

Don, M, & Eggermont, J. J. (1978). Analysis of the click-evoked brainstem potentials in man using high-pass noise masking. *Journal of the Acoustical Society of America*, *63*(4), 1084–1092. https://doi.org/10.1121/1.381816

Don, Manuel, Ponton, C. W., Eggermont, J. J., & Masuda, A. (1994). Auditory brainstem response (ABR) peak amplitude variability reflects individual differences in cochlear response times. *Journal of the Acoustical Society of America*, *96*(6), 3476–3491. https://doi.org/10.1121/1.410608

Eggermont, J. J. (1979). Narrow-band AP latencies in normal and recruiting human ears. *Journal of the Acoustical Society of America*, *65*(2), 463–470. https://doi.org/10.1121/1.382345

Elberling, C., Kristensen, S. G. B., & Don, M. (2012). Auditory brainstem responses to chirps delivered by different insert earphones. *The Journal of the Acoustical Society of America*, *131*(3), 2091–2100. https://doi.org/10.1121/1.3677257

Epidemiological Evidence for the Effectiveness of the Noise at Work Regulations, RR669 | Request PDF. (n.d.). Retrieved August 16, 2021, from https://www.researchgate.net/publication/313214445_Epidemiological_Evidence_for_the_Effectiveness_of_the_Noise_at_Work_Regulations_RR669

Fernandez, K. A., Jeffers, P. W. C., Lall, K., Liberman, M. C., & Kujawa, S. G. (2015). Aging after noise exposure: Acceleration of cochlear synaptopathy in “recovered” ears. *Journal of Neuroscience*, *35*(19), 7509–7520. https://doi.org/10.1523/JNEUROSCI.5138-14.2015

Fu, B., Le Prell, C., Simmons, D., Lei, D., Schrader, A., Chen, A. B., & Bao, J. (2010). Age-related synaptic loss of the medial olivocochlear efferent innervation. *Molecular Neurodegeneration 2010 5:1*, *5*(1), 1–9. https://doi.org/10.1186/1750-1326-5-53

Fuchs, P.A., 2005. Time and intensity coding at the hair cell’s ribbon synapse. J. Physiol. 566, 7e12.

Fuchs, P. A., Glowatzki, E., & Moser, T. (2003). The afferent synapse of cochlear hair cells. In *Current Opinion in Neurobiology* (Vol. 13, Issue 4, pp. 452–458). Curr Opin Neurobiol. https://doi.org/10.1016/S0959-4388(03)00098-9

Fulbright, A. N. C., Le Prell, C. G., Griffiths, S. K., & Lobarinas, E. (2017). Effects of Recreational Noise on Threshold and Suprathreshold Measures of Auditory Function. In *Seminars in Hearing* (Vol. 38, Issue 4, pp. 298–318). https://doi.org/10.1055/s-0037-1606325

Furman, A. C., Kujawa, S. G., & Charles Liberman, M. (2013). Noise-induced cochlear neuropathy is selective for fibers with low spontaneous rates. *Journal of Neurophysiology*, *110*(3), 577–586. https://doi.org/10.1152/jn.00164.2013

Gelfand, S. A. (2004). Hearing: An introduction to psychological and physiological acoustics, fourth edition. *Hearing: An Introduction to Psychological and Physiological Acoustics, Fourth Edition*, 1–501.

Ghigo, J., Erwin, A. C., & Erwin, C. W. (1991). Near-field vs. far-field evoked potentials. *American Journal of EEG Technology*, *31*(2), 109–118. https://doi.org/10.1080/00029238.1991.11080362

Glowatzki, E., Grant, L., & Fuchs, P. (2008). Hair cell afferent synapses. In *Current Opinion in Neurobiology* (Vol. 18, Issue 4, pp. 389–395). Curr Opin Neurobiol. https://doi.org/10.1016/j.conb.2008.09.006

Greguske, E. A., Llorens, J., & Pyott, S. J. (2021). Assessment of cochlear toxicity in response to chronic 3,3′-iminodipropionitrile in mice reveals early and reversible functional loss that precedes overt histopathology. *Archives of Toxicology*, *95*(3), 1003–1021. https://doi.org/10.1007/s00204-020-02962-5

Grinn, S. K., Wiseman, K. B., Baker, J. A., & Le Prell, C. G. (2017). Hidden hearing loss? No effect of common recreational noise exposure on cochlear nerve response amplitude in humans. *Frontiers in Neuroscience*, *11*(SEP), 465. https://doi.org/10.3389/fnins.2017.00465

Grose, J. H., Buss, E., & Hall, J. W. (2017). Loud Music Exposure and Cochlear Synaptopathy in Young Adults: Isolated Auditory Brainstem Response Effects but No Perceptual Consequences. *Trends in Hearing*, *21*, 1–18. https://doi.org/10.1177/2331216517737417

Guest, H., Dewey, R. S., Plack, C. J., Couth, S., Prendergast, G., Bakay, W., & Hall, D. A. (2018). The Noise Exposure Structured Interview (NESI): An Instrument for theComprehensive Estimation of Lifetime Noise Exposure. *Trends in Hearing*, *22*. https://doi.org/10.1177/2331216518803213

Guest, H., Munro, K. J., Prendergast, G., Howe, S., & Plack, C. J. (2017a). Tinnitus with a

normal audiogram: Relation to noise exposure but no evidence for cochlear synaptopathy. *Hearing Research*, *344*, 265–274. https://doi.org/10.1016/j.heares.2016.12.002

Guest, H., Munro, K. J., Prendergast, G., Millman, R. E., & Plack, C. J. (2018). Impaired speech perception in noise with a normal audiogram: No evidence for cochlear synaptopathy and no relation to lifetime noise exposure. *Hearing Research*, *364*, 142–151. https://doi.org/10.1016/j.heares.2018.03.008

Guest, H., Munro, K. J., Prendergast, G., & Plack, C. J. (2019). Reliability and interrelations of seven proxy measures of cochlear synaptopathy. *Hearing Research*, *375*, 34–43. https://doi.org/10.1016/j.heares.2019.01.018

Halevi-Katz, D., Yaakobi, E., & Putter-Katz, H. (2015). Exposure to music and noise-induced hearing loss (NIHL) among professional pop/rock/jazz musicians. *Noise and Health*, *17*(76), 158–164. https://doi.org/10.4103/1463-1741.155848

Hecox, K., & Galambos, R. (1974). Brain Stem Auditory Evoked Responses in Human Infants and Adults. *Archives of Otolaryngology*, *99*(1), 30–33. https://doi.org/10.1001/archotol.1974.00780030034006

Hickox, A. E., & Liberman, M. C. (2014). Is noise-induced cochlear neuropathy key to the generation of hyperacusis or tinnitus? *Journal of Neurophysiology*, *111*(3), 552–564. https://doi.org/10.1152/jn.00184.2013

Hinojosa, R., & Lerner, S. A. (1987). Cochlear Neural Degeneration without Hair Cell Loss in Two Patients with Aminoglycoside Ototoxicity. *Journal of Infectious Diseases*, *156*(3), 449–455. https://doi.org/10.1093/infdis/156.3.449

Hurley, R. M., Hurley, A., & Berlin, C. I. (2005). Development of low-frequency tone burst versus the click auditory brainstem response. *Journal of the American Academy of Audiology*, *16*(2), 114–121. https://doi.org/10.3766/jaaa.16.2.6

Johannesen, P. T., Buzo, B. C., & Lopez-Poveda, E. A. (2019). Evidence for age-related cochlear synaptopathy in humans unconnected to speech-in-noise intelligibility deficits. *Hearing Research*, *374*, 35–48. https://doi.org/10.1016/j.heares.2019.01.017

Johnson, T. A., Cooper, S., Stamper, G. C., & Chertoff, M. (2017). Noise Exposure Questionnaire (NEQ): A Tool for Quantifying Annual Noise Exposure. *Journal of the American Academy of Audiology*, *28*(1), 14. https://doi.org/10.3766/JAAA.15070

Kamerer, A. M., Aubuchon, A., Fultz, S. E., Kopun, J. G., Neely, S. T., & Rasetshwane, D. M. (2019). The role of cognition in common measures of peripheral synaptopathy and hidden hearing loss. *American Journal of Audiology*, *28*(4), 843–856. https://doi.org/10.1044/2019_AJA-19-0063

Kamerer, A. M., Kopun, J. G., Fultz, S. E., Allen, C., Neely, S. T., & Rasetshwane, D. M. (2019). Examining physiological and perceptual consequences of noise exposure. *The Journal of the Acoustical Society of America*, *146*(5), 3947–3959. https://doi.org/10.1121/1.5132291

Kidd, A. R., & Bao, J. (2012). Recent advances in the study of age-related hearing loss: A mini-review. In *Gerontology* (Vol. 58, Issue 6, pp. 490–496). Karger Publishers. https://doi.org/10.1159/000338588

Kopecky, B. J., Liang, R., & Bao, J. (2014). T-type calcium channel blockers as neuroprotective

agents. In *Pflugers Archiv European Journal of Physiology* (Vol. 466, Issue 4, pp. 757–765). Pflugers Arch. https://doi.org/10.1007/s00424-014-1454-x

Kujawa, S. G., & Liberman, M. C. (2009). Adding insult to injury: Cochlear nerve degeneration after "temporary" noise-induced hearing loss. *Journal of Neuroscience*, *29*(45), 14077–14085. https://doi.org/10.1523/JNEUROSCI.2845-09.2009

Le Prell, C. G., Yamashita, D., Minami, S. B., Yamasoba, T., & Miller, J. M. (2007). Mechanisms of noise-induced hearing loss indicate multiple methods of prevention. *Hearing Research*, *226*(1–2), 22–43. https://doi.org/10.1016/j.heares.2006.10.006

Liberman, L. D., & Liberman, M. C. (2015). Dynamics of cochlear synaptopathy after acoustic overexposure. *JARO - Journal of the Association for Research in Otolaryngology*, *16*(2), 205–219. https://doi.org/10.1007/s10162-015-0510-3

Liberman, L. D., Wang, H., & Liberman, M. C. (2011). Opposing gradients of ribbon size and AMPA receptor expression underlie sensitivity differences among cochlear-nerve/hair-cell synapses. *Journal of Neuroscience*, *31*(3), 801–808. https://doi.org/10.1523/JNEUROSCI.3389-10.2011

Liberman, M. C., & Kiang, N. Y. S. (1978). Acoustic trauma in cats. Cochlear pathology and auditory-nerve activity. *Acta Oto-Laryngologica*, *86*(SUPPL.358). https://agris.fao.org/agris-search/search.do?recordID=SE7901291

Liberman, M. Charles. (1978). Auditory-nerve response from cats raised in a low-noise chamber. *Journal of the Acoustical Society of America*, *63*(2), 442–455. https://doi.org/10.1121/1.381736

Liberman, M. Charles. (1988). Physiology of cochlear efferent and afferent neurons: Direct comparisons in the same animal. *Hearing Research*, *34*(2), 179–191. https://doi.org/10.1016/0378-5955(88)90105-0

Liberman, M. Charles, Epstein, M. J., Cleveland, S. S., Wang, H., & Maison, S. F. (2016). Toward a differential diagnosis of hidden hearing loss in humans. *PLoS ONE*, *11*(9). https://doi.org/10.1371/journal.pone.0162726

Liu, L., Wang, H., Shi, L., Almuklass, A., He, T., Aiken, S., Bance, M., Yin, S., & Wang, J. (2012). Silent Damage of Noise on Cochlear Afferent Innervation in Guinea Pigs and the Impact on Temporal Processing. *PLoS ONE*, *7*(11), e49550. https://doi.org/10.1371/journal.pone.0049550

Viana, L. M., O'Malley, J. T., Burgess, B. J., Jones, D. D., Oliveira, C. A., Santos, F., Merchant, S. N., Liberman, L. D., & Liberman, M. C. (2015). Cochlear neuropathy in human presbycusis: Confocal analysis of hidden hearing loss in post-mortem tissue. *Hearing research*, *327*, 78–88. https://doi.org/10.1016/j.heares.2015.04.014

Lobarinas, E., Salvi, R., & Ding, D. (2013). Insensitivity of the audiogram to carboplatin induced inner hair cell loss in chinchillas. *Hearing Research*, *302*, 113–120. https://doi.org/10.1016/j.heares.2013.03.012

Makary, C. A., Shin, J., Kujawa, S. G., Liberman, M. C., & Merchant, S. N. (2011). Age-related primary cochlear neuronal degeneration in human temporal bones. *JARO - Journal of the Association for Research in Otolaryngology*, *12*(6), 711–717. https://doi.org/10.1007/s10162-011-0283-2

Marmel, F., Cortese, D., & Kluk, K. (2020). The ongoing search for cochlear synaptopathy in humans: Masked thresholds for brief tones in Threshold Equalizing Noise. *Hearing Research*, *392*, 107960. https://doi.org/10.1016/J.HEARES.2020.107960

Marttila, T. I., & Karikoski, J. O. (2006). Comparison between audiometric and ABR thresholds in children. Contradictory findings. *European Archives of Oto-Rhino-Laryngology*, *263*(5), 399–403. https://doi.org/10.1007/s00405-005-1019-x

Maruthy, S., & Mannarukrishnaiah, J. (2008). Effect of early onset otitis media on brainstem and cortical auditory processing. *Behavioral and Brain Functions*, *4*(1), 1–13. https://doi.org/10.1186/1744-9081-4-17

Masuda, A., & Ponton, C. W. (1993). Gender differences in cochlear response time: An explanation for gender amplitude differences in the unmasked auditory brain-stem response. *Journal of the Acoustical Society of America*, *94*(4), 2135–2148. https://doi.org/10.1121/1.407485

Megha, K. N., Divyashree, K. N., Lakshmi, A., Adithya, S., Keerthana, K. P., Pushpalatha, Z. V., & Konadath, S. (2019). Narrow-band chirp and tone burst auditory brainstem response as an early indicator of synaptopathy in industrial workers exposed to occupational noise. *Intractable and Rare Diseases Research*, *8*(3), 179–186. https://doi.org/10.5582/irdr.2019.01073

Mehraei, G., Hickox, A. E., Bharadwaj, H. M., Goldberg, H., Verhulst, S., Charles Liberman, M., & Shinn-Cunningham, B. G. (2016). Auditory brainstem response latency in noise as a marker of cochlear synaptopathy. *Journal of Neuroscience*, *36*(13), 3755–3764. https://doi.org/10.1523/JNEUROSCI.4460-15.2016

Minaya, C., & Atcherson, S. R. (2015). Simultaneous Extratympanic Electrocochleography and Auditory Brainstem Responses Revisited. *Audiology Research*, *5*(1), 1–4. https://doi.org/10.4081/AUDIORES.2015.105

Moore, J. K. (1987a). The human auditory brain stem: A comparative view. *Hearing Research*, *29*(1), 1–32. https://doi.org/10.1016/0378-5955(87)90202-4

Moore, J. K. (1987b). The human auditory brain stem as a generator of auditory evoked potentials. *Hearing Research*, *29*(1), 33–43. https://doi.org/10.1016/0378-5955(87)90203-6

Morimoto, T., Fujisaka, Y. ichi, Okamoto, Y., & Irino, T. (2019). Rising-frequency chirp stimulus to effectively enhance wave-I amplitude of auditory brainstem response. *Hearing Research*, *377*, 104–108. https://doi.org/10.1016/j.heares.2019.03.016

Moser, T., & Starr, A. (2016). Auditory neuropathy-neural and synaptic mechanisms. In *Nature Reviews Neurology* (Vol. 12, Issue 3, pp. 135–149). Nature Publishing Group. https://doi.org/10.1038/nrneurol.2016.10

Musial-Bright, L., Fengler, R., Henze, G., & Hernáiz Driever, P. (2011). Carboplatin and ototoxicity: Hearing loss rates among survivors of childhood medulloblastoma. *Child's Nervous System*, *27*(3), 407–413. https://doi.org/10.1007/s00381-010-1300-1

Oishi, N., & Schacht, J. (2011). Emerging treatments for noise-induced hearing loss. In *Expert Opinion on Emerging Drugs* (Vol. 16, Issue 2, pp. 235–245). Expert Opin Emerg Drugs. https://doi.org/10.1517/14728214.2011.552427

Parthasarathy, A., Encina-Llamas, G., Shinn-Cunningham, B., & Kujawa, S. G. (n.d.). *Temporal Processing Deficits due to Noise-Induced Synaptopathy Studied Using Envelope-Following*

Responses CONCLUSIONS.

Parthasarathy, A., & Kujawa, S. G. (2018). Synaptopathy in the Aging Cochlea: Characterizing Early-Neural Deficits in Auditory Temporal Envelope Processing. *Journal of Neuroscience*, *38*(32), 7108–7119. https://doi.org/10.1523/JNEUROSCI.3240-17.2018

Prendergast, G., Couth, S., Millman, R. E., Guest, H., Kluk, K., Munro, K. J., & Plack, C. J. (2019). Effects of Age and Noise Exposure on Proxy Measures of Cochlear Synaptopathy. *Trends in Hearing*, *23*. https://doi.org/10.1177/2331216519877301

Prendergast, G., Guest, H., Munro, K. J., Kluk, K., Léger, A., Hall, D. A., Heinz, M. G., & Plack, C. J. (2017). Effects of noise exposure on young adults with normal audiograms I: Electrophysiology. *Hearing Research*, *344*, 68–81. https://doi.org/10.1016/j.heares.2016.10.028

Puel, J. -L, Pujol, R., Tribillac, F., Ladrech, S., & Eybalin, M. (1994). Excitatory amino acid antagonists protect cochlear auditory neurons from excitotoxicity. *Journal of Comparative Neurology*, *341*(2), 241–256. https://doi.org/10.1002/cne.903410209

Puel, J. L., Ruel, J., Gervais D'Aldin, C., & Pujol, R. (1998). Excitotoxicity and repair of cochlear synapses after noise- trauma induced hearing loss. *NeuroReport*, *9*(9), 2109–2114. https://doi.org/10.1097/00001756-199806220-00037

Pujol, R., Rebillard, G., Puel, J. L., Lenoir, M., Eybalin, M., & Recasens, M. (1991). Glutamate neurotoxicity in the cochlea: A possible consequence of ischaemic or anoxic conditions occurring in ageing. *Acta Oto-Laryngologica*, *111*(S476), 32–36. https://doi.org/10.3109/00016489109127253

Pushpalatha, Z. V., & Konadath, S. (2016). Auditory brainstem responses for click and CE-chirp stimuli in individuals with and without occupational noise exposure. *Noise and Health*, *18*(84), 260–265. https://doi.org/10.4103/1463-1741.192477

Wu, P. Z., Liberman, L. D., Bennett, K., de Gruttola, V., O'Malley, J. T., & Liberman, M. C. (2019). Primary Neural Degeneration in the Human Cochlea: Evidence for Hidden Hearing Loss in the Aging Ear. *Neuroscience*, *407*, 8–20. https://doi.org/10.1016/j.neuroscience.2018.07.053

Rattay, F., & Danner, S. M. (2014). Peak I of the human auditory brainstem response results from the somatic regions of type I spiral ganglion cells: Evidence from computer modeling. *Hearing Research*, *315*(100), 67. https://doi.org/10.1016/J.HEARES.2014.07.001

Rhode, W. S., Geisler, C. D., & Kennedy, D. T. (1978). Auditory nerve fiber responses to wide-band noise and tone combinations. *Journal of Neurophysiology*, *41*(3), 692–704. https://doi.org/10.1152/jn.1978.41.3.692

Rhode, William S. (1978). Some observations on cochlear mechanics. *Journal of the Acoustical Society of America*, *64*(1), 158–176. https://doi.org/10.1121/1.381981

Ridley, C. L., Kopun, J. G., Neely, S. T., Gorga, M. P., & Rasetshwane, D. M. (2018). Using thresholds in noise to identify hidden hearing loss in humans. *Ear and Hearing*, *39*(5), 829–844. https://doi.org/10.1097/AUD.0000000000000543

Rousset, F., Nacher-Soler, G., Coelho, M., Ilmjarv, S., Kokje, V. B. C., Marteyn, A., Cambet, Y., Perny, M., Roccio, M., Jaquet, V., Senn, P., & Krause, K. H. (2020). Redox activation of excitatory pathways in auditory neurons as mechanism of age-related hearing loss. *Redox*

Biology, *30*, 101434. https://doi.org/10.1016/J.REDOX.2020.101434

Ruggero, M. A., Rich, N. C., Recio, A., Narayan, S. S., & Robles, L. (1997). Basilar-membrane responses to tones at the base of the chinchilla cochlea. *The Journal of the Acoustical Society of America*, *101*(4), 2151. https://doi.org/10.1121/1.418265

Salvi, R. J., Ahroon, W. A., Perry, J. W., Gunnarson, A. D., & Henderson, D. (1982). Comparison of psychophysical and evoked-potential tuning curves in the chinchilla. *American Journal of Otolaryngology--Head and Neck Medicine and Surgery*, *3*(6), 408–416. https://doi.org/10.1016/S0196-0709(82)80018-5

Schaette, R., & McAlpine, D. (2011). Tinnitus with a normal audiogram: Physiological evidence for hidden hearing loss and computational model. *Journal of Neuroscience*, *31*(38), 13452–13457. https://doi.org/10.1523/JNEUROSCI.2156-11.2011

Sergeyenko, Y., Lall, K., Charles Liberman, M., & Kujawa, S. G. (2013). Age-related cochlear synaptopathy: An early-onset contributor to auditory functional decline. *Journal of Neuroscience*, *33*(34), 13686–13694. https://doi.org/10.1523/JNEUROSCI.1783-13.2013

SG, Kujawa., & MC, Libermann. (2015). Synaptopathy in the noise-exposed and aging cochlea: Primary neural degeneration in acquired sensorineural hearing loss. *Hearing Research*, *330*(Pt B), 191–199. https://doi.org/10.1016/J.HEARES.2015.02.009

Shaheen, L. A., Valero, M. D., & Liberman, M. C. (2015). Towards a Diagnosis of Cochlear Neuropathy with Envelope Following Responses. *JARO - Journal of the Association for Research in Otolaryngology*, *16*(6), 727–745. https://doi.org/10.1007/s10162-015-0539-3

Shi, L., Chang, Y., Li, X., Aiken, S. J., Liu, L., & Wang, J. (2016). Coding deficits in noise-

induced hidden hearing loss may stem from incomplete repair of ribbon synapses in the cochlea. *Frontiers in Neuroscience*, *10*(MAY). https://doi.org/10.3389/fnins.2016.00231

Shi, L., Liu, L., He, T., Guo, X., Yu, Z., Yin, S., & Wang, J. (2013). Ribbon synapse plasticity in the cochleae of guinea pigs after noise-induced silent damage. *PLoS ONE*, *8*(12). https://doi.org/10.1371/journal.pone.0081566

Sone, M., Schachern, P. A., & Paparella, M. M. (1998). Loss of spiral ganglion cells as primary manifestation of aminoglycoside ototoxicity. *Hearing Research*, *115*(1–2), 217–223. https://doi.org/10.1016/S0378-5955(97)00191-3

Song, Q., Shen, P., Li, X., Shi, L., Liu, L., Wang, J., Yu, Z., Stephen, K., Aiken, S., Yin, S., & Wang, J. (2016). Coding deficits in hidden hearing loss induced by noise: The nature and impacts. *Scientific Reports*, *6*. https://doi.org/10.1038/srep25200

Spankovich, C., Le Prell, C. G., Lobarinas, E., & Hood, L. J. (2017). Noise history and auditory function in young adults with and without type 1 diabetes mellitus. *Ear and Hearing*, *38*(6), 724–735. https://doi.org/10.1097/AUD.0000000000000457

Stamataki, S., Francis, H. W., Lehar, M., May, B. J., & Ryugo, D. K. (2006). Synaptic alterations at inner hair cells precede spiral ganglion cell loss in aging C57BL/6J mice. *Hearing Research*, *221*(1–2), 104–118. https://doi.org/10.1016/J.HEARES.2006.07.014

Stamper, G. C., & Johnson, T. A. (2015a). Auditory function in normal-hearing, noise-exposed human ears. *Ear and Hearing*, *36*(2), 172–184. https://doi.org/10.1097/AUD.0000000000000107

Stamper, G. C., & Johnson, T. A. (2015b). Letter to the Editor: Examination of Potential Sex

Influences in Stamper, G. C., & Johnson, T. A. (2015). Auditory Function in Normal-Hearing, Noise-Exposed Human Ears, Ear Hear, 36, 172-184. In *Ear and Hearing* (Vol. 36, Issue 6, pp. 738–740). Lippincott Williams and Wilkins. https://doi.org/10.1097/AUD.0000000000000228

Suresh, C. H., & Krishnan, A. (2020). Search for Electrophysiological Indices of Hidden Hearing Loss in Humans: Click Auditory Brainstem Response Across Sound Levels and in Background Noise. *Ear and Hearing*, *42*(1), 53–67. https://doi.org/10.1097/AUD.0000000000000905

Tadros, S. F., D'Souza, M., Zettel, M. L., Zhu, X. X., Waxmonsky, N. C., & Frisina, R. D. (2007). Glutamate-related gene expression changes with age in the mouse auditory midbrain. *Brain Research*, *1127*(1), 1–9. https://doi.org/10.1016/J.BRAINRES.2006.09.081

Telian, S. A., Kileny, P. R., Niparko, J. K., Kemink, J. L., & Graham, M. D. (1989). Normal auditory brainstem response in patients with acoustic neuroma. *Laryngoscope*, *99*(1), 10–14. https://doi.org/10.1288/00005537-198901000-00003

Valderrama, J. T., Beach, E. F., Yeend, I., Sharma, M., Van Dun, B., & Dillon, H. (2018). Effects of lifetime noise exposure on the middle-age human auditory brainstem response, tinnitus and speech-in-noise intelligibility. *Hearing Research*, *365*, 36–48. https://doi.org/10.1016/j.heares.2018.06.003

Valero, M. D., Burton, J. A., Hauser, S. N., Hackett, T. A., Ramachandran, R., & Liberman, M. C. (2017). Noise-induced cochlear synaptopathy in rhesus monkeys (Macaca mulatta). *Hearing Research*, *353*, 213–223. https://doi.org/10.1016/j.heares.2017.07.003

Valero, Michelle D., Hancock, K. E., Maison, S. F., & Liberman, M. C. (2018). Effects of cochlear synaptopathy on middle-ear muscle reflexes in unanesthetized mice. *Hearing Research*, *363*, 109–118. https://doi.org/10.1016/j.heares.2018.03.012

Velayutham, P., Govindasamy, G. K., Raman, R., Prepageran, N., & Ng, K. H. (2014). High-Frequency Hearing Loss Among Mobile Phone Users. *Indian Journal of Otolaryngology and Head and Neck Surgery*, *66*(SUPPL.1), 169–172. https://doi.org/10.1007/s12070-011-0406-4

Wang, Q., & Green, S. H. (2011). Functional role of neurotrophin-3 in synapse regeneration by spiral ganglion neurons on inner hair cells after excitotoxic trauma in vitro. *Journal of Neuroscience*, *31*(21), 7938–7949. https://doi.org/10.1523/JNEUROSCI.1434-10.2011

Washnik, N. J., Bhatt, I. S., Phillips, S. L., Tucker, D., & Richter, S. (2020). Evaluation of cochlear activity in normal-hearing musicians. *Hearing Research*, *395*, 108027. https://doi.org/10.1016/j.heares.2020.108027

Whiting, P. F., Rutjes, A. W. S., Westwood, M. E., Mallett, S., Deeks, J. J., Reitsma, J. B., Leeflang, M. M. G., Sterne, J. A. C., & Bossuyt, P. M. M. (2011). Quadas-2: A revised tool for the quality assessment of diagnostic accuracy studies. *Annals of Internal Medicine*, *155*(8), 529–536. https://doi.org/10.7326/0003-4819-155-8-201110180-00009

Wu, P. Z., Liberman, L. D., Bennett, K., de Gruttola, V., O'Malley, J. T., & Liberman, M. C. (2019). Primary Neural Degeneration in the Human Cochlea: Evidence for Hidden Hearing Loss in the Aging Ear. *Neuroscience*, *407*, 8–20. https://doi.org/10.1016/j.neuroscience.2018.07.053

Young, E. D., & Barta, P. E. (1986). Rate responses of auditory nerve fibers to tones in noise near masked threshold. *Journal of the Acoustical Society of America*, *79*(2), 426–442. https://doi.org/10.1121/1.393530

Young, E. D., & Barta, P. E. (1998). Rate responses of auditory nerve fibers to tones in noise near masked threshold. *The Journal of the Acoustical Society of America*, *79*(2), 426. https://doi.org/10.1121/1.393530

Annexure-

QUADAS-2 tool: Risk of bias and applicability judgments

Domain 1: Patient selection	
A. Risk of bias	
Describe methods of patient selection:	
• **Was a consecutive or random sample of patients enrolled?**	Yes/No/Unclear
• **Was a case-control design avoided?**	Yes/No/Unclear
• **Did the study avoid inappropriate exclusions?**	Yes/No/Unclear
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR
B. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting):	
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 2: Index test(s) ***(if more than 1 index test was used, please complete for each test)***	
A. Risk of bias	
Describe the index test and how it was conducted and interpreted:	
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear
• **If a threshold was used, was it pre-specified?**	Yes/No/Unclear
Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR
B. Concerns regarding applicability	
Is there concern that the index test, its conduct, or interpretation differ from the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 3: Reference standard	
A. Risk of bias	
Describe the reference standard and how it was conducted and interpreted:	
• **Is the reference standard likely to correctly classify the**	Yes/No/Unclear

target condition?	
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR
B. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 4: Flow and timing	
A. Risk of bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): **Describe the time interval and any interventions between index test(s) and reference standard:**	
• **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/Unclear
• **Did all patients receive a reference standard?**	Yes/No/Unclear
• **Did patients receive the same reference standard?**	Yes/No/Unclear
• **Were all patients included in the analysis?**	Yes/No/Unclear
Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR