RELATIONSHIP BETWEEN SYNAPTOPATHY AND TINNITUS – A SYSTEMATIC REVIEW

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CERTIFICATE

This is to certify that this dissertation entitled "**Relationship between synaptopathy and tinnitus – a systemic review**" is a bonafide work submitted as a part for the fulfilment for the degree of Master of Science (Audiology) of the student with Registration Number: 19AUD03. This has been carried out under the guidance of the faculty of this institute and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

Mysore

Septmeber 2021

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CERTIFICATE

This is to certify that this dissertation entitled "**Relationship between synaptopathy and tinnitus – a systemic review**" has been prepared under my supervision and guidance. It is also being certified that this dissertation has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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DECLARATION

This is to certify that this dissertation entitled "**Relationship between synaptopathy and tinnitus – a systemic review**" is the result of my own study under the guidance of Dr. Prashanth Prabhu P., Assistant Professor in Audiology, Department of Audiology, All India Institute of Speech and Hearing, Mysore and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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Abstract

Tinnitus is the most common health problem seen in all age groups. It is usually present with hearing loss. But recent studies have shown that tinnitus is present among individuals with normal audiometric thresholds. The cause which is highlighted in recent studies for tinnitus among normal-hearing individuals is cochlear synaptopathy. Therefore, a comprehensive measure is required to identify and diagnose early so that many individuals will benefit through early detection and intervention of cochlear synaptopathy. The aim was to systematically review the articles related to hidden hearing loss and cochlear synaptopathy. Initially, a review search was conducted in different databases. This resulted in 122 topic-related articles. Among these, fifteen articles met the inclusion and exclusion criteria that were included for the study. The quality and potential risk associated with each article were evaluated using the Newcastle-Ottawa Scale (NOS). Review of the literature focused on physiological, behavioural and electrophysiological tests to diagnose cochlear synaptopathy. The study revealed that extended high frequency is a good measure in identifying hidden hearing loss. The reason which is mentioned for the same is vascular damage in the basal cochlear region. OAEs are also a good tool, but ambiguous results were reported. Reduced amplitudes of OAEs are due to dysfunctional OHC, but on the other hand, if the OAE amplitudes are not reduced, then the cause reported is damage in the higher auditory structures or at the IHC. ECochG has a very good implication in detecting cochlear synaptopathy. Damaged IHC would lead to the increased summating potential altering SP/AP ratio leading to hidden hearing loss. This review provides the relationship between cochlear synaptopathy and tinnitus in individuals with normal hearing. Extended high-frequency audiometry and ECochG are good tools for measuring cochlear synaptopathy. The leading cause that is described in the literature for hidden hearing loss is damage in IHC or basal cochlear region.

Keywords: Tinnitus, synaptopathy, hidden hearing lo

Chapter 1

Introduction

The perception of sound without any auditory signal is most commonly defined as tinnitus (Nicolas-Puel et al., 2002; Sanchez et al., 2005), affecting approximately 10-15% of adults worldwide (Eggermont & Roberts, 2015). Early in the 1980s, Shulman (1981) gave the first classification of tinnitus as otologic and neurotologic. This differentiation is based on the results of cochlear-vestibular testing obtained during the neurotologic examination. The other simplest form of classification of tinnitus is subjective and objective tinnitus. The auditory sensation of perception of sound only by a patient is called subjective tinnitus, whereas if both the patient and the examiner can perceive, it's termed objective tinnitus (Heller,2003). This is a vital difference because objective tinnitus is identified with the site of origin of tinnitus. This kind of tinnitus is also recognized as vibratory or extrinsic tinnitus or pseudo-tinnitus. Subjective tinnitus is otherwise called "tinnitus aurium" and "nonauditory tinnitus." (Heller, 2003)

Goodhill (1950) gave a classification system, which was divided into three types (1) noise which was heard within the head or within in the ear. (2) vibratory versus nonvibratory tinnitus, and (3) type of noise heard and ability to manage with tinnitus. Nodar (1996) published a new edition of the tinnitus classification system. Mnemonics were extracted to aid classify tinnitus: ABC was A for aurium, which indicates tinnitus in one ear, B for binaural indicating tinnitus in both ears, or cerebral tinnitus centered in the head; and C-CLAP for the cause of the tinnitus, composition, i.e., patient description of the tinnitus, loudness which is reported by the patient after administration of subjective scale or loudness matching tests, an annoyance which is obtained from questionnaires and pitch obtained again with the help of pitch matching tests on the audiometer (Nodar, 1996).

Another important classification is that between pulsatile and non-pulsatile tinnitus. The patient's description of the sound quality that they perceive determines the tinnitus (Heller, 2003). Tinnitus is a most common and distinct type of disorder of the hearing system, and its prevalence is reported to be approximately 10-15% of the population (Thabet, 2009; Schaette & Mcalpine, 2011). The prevalence studies revealed that tinnitus among the general older population was reported to be between 12% to 49% (Seidman & Jacobson, 1996). Recent researches have shown that among 1–2% of the population, tinnitus symptoms reduce the quality of life, which reduces socialization, causes depression and even suicidal tendencies (Schaette & Mcalpine, 2011).

A study By Michikawa et al. (2010) on Japanese aged 65 years or older reported that approximately one in five had tinnitus. The tinnitus also increases with increasing age and appears maximum at 60-69 years (Shargorodsky et al., 2010). These results are also supported by Thirunavukkarasu and Geetha (2013), which was on the Indian population, where they concluded that the prevalence of tinnitus in individuals who are 60 years and above with otological problems is 16.81%.

Also, studies are conducted to know the prevalence of adults with tinnitus and normal hearing thresholds, which was reported to be approximately 15% (Henry et al., 2005; Roberts et al., 2008). Around 8% of individuals with tinnitus have been reported to have normal pure tone audiometric thresholds (Barnea et al., 1990; Sanchez et al., 2005). Other researches have shown 20-40% of the tinnitus individuals with normal pure tone audiometric thresholds (Henry et al.,2008; Mitchell et al., 1993). These results were also supported by Xiong et al. (2019), reporting 1/3 of tinnitus patients having normal or near-normal hearing thresholds (≤25 dB HL).

Tinnitus claims to be a symptom of many conditions rather than a disease. Approximately 85% of adults with chronic tinnitus show hearing loss depicted on the audiogram (Henry et., 2005). The causes of tinnitus can be explained at the external ear, middle ear, and inner ear levels. The level of external ear causes includes impacted cerumen, otitis externa. The middle ear mainly includes otitis media, otosclerosis and at the level of the inner ear includes noise-induced hearing loss (Langguth et al., 2013), presbycusis, Meniere's disease, ototoxicity (Han et al., 2009). Neurologic origin is also seen for tinnitus. Few causes include head injury (Langguth et al., 2013), whiplash, multiple sclerosis, vestibular schwannoma, and other cerebellopontine-angle tumors. Sequelae of many infections, mainly Lyme disease, meningitis, syphilis, can also cause tinnitus. Mandible or maxilla joints, especially temporomandibular joint dysfunction and other dental-related disorders, can also lead to tinnitus (Han et al., 2009).

Hidden hearing loss or cochlear synaptopathy, defined as inner hair cell synapse damage besides normal hearing, could also cause tinnitus (Kujawa & Liberman, 2009). Several studies report on the relationship between hidden hearing loss and tinnitus. Studies are pointing out chronic tinnitus besides normal hearing (Henry et al., 2005). The cause in these is reported to be cochlear synaptopathy and dead regions of the cochlea, which leads to tinnitus generation without any evidence of hearing loss (Kara et al., 2020). Gault et al. (2018) reported that cochlear synaptopathy at the level of the auditory brainstem is responsible for the generation of tinnitus-related activities. Also, studies report loud music is the most common trigger of tinnitus, does not usually cause permanent threshold shift but leads to severe tinnitus (Szibor et al., 2018).

Tinnitus occurs with changes in either the cochlea or the central nervous system (Moller, 2003). Loss of outer hair cells integrity and atrophy of the stria vascularis are the common pathophysiology in patients with presbycusis with tinnitus (Terao et al., 2011). Generally, the observed pathophysiology leading to tinnitus is the dysfunction of the hair cells or fibers of the auditory nerve caused by acoustic trauma or ototoxicity. Here central gain takes place, which is the increase in gain to compensate for the reduced auditory input from the cochlea (Galazyuk et al., 2012). Central nervous system changes are detected morphologically (Moller et al., 2012) and physiologically (Willott & Lu, 1982), besides damage to hair cells due to overexposure to noise. Auditory deprivation may cause a reduction of neural plasticity at the level of CNS, which results in physiological changes causing tinnitus. Kaltenbatch & Afman (2000) reported that tinnitus caused by noise exposure results from increased hyperactivity in the dorsal cochlear nucleus because of loud noise exposure. The input to the neurons continues to remain stimulated even in the absence of a tone.

Modern understanding of tinnitus was considerably advanced by the publication of the Jastreboff Neurophysiological Model, which shows the relation between abnormally increased hyperactivity within the auditory pathways and a mechanism of hyperexcitability is implied. This hyperactivity evokes the limbic system (emotional) and autonomic nervous system (arousal reactions) to that sound (Jasterboff et al., 1994). The outcome that the limbic system is more active for any sound stimulation in some individuals with tinnitus supports the findings that the nonclassical auditory system is involved in tinnitus (Lockwood et al., 1998).

Studies also put forth the pathophysiology of tinnitus relating to cochlear synaptopathy. Cochlear synaptopathy has been indicated as possible pathophysiology among patients with normal audiometric thresholds and tinnitus (Shim et al., 2017).

After the noise exposure, presynaptic ribbons and postsynaptic terminals remain affected, despite the complete recovery of the hair cell function (Kujawa & Liberman, 2009).

1.2 Need for the study

Many studies explain the importance and findings of behavioral and electrophysiological tests for examining the hearing thresholds in individuals with tinnitus. Kara et al. (2020) carried few tests on normal-hearing individuals with tinnitus to diagnose hidden hearing loss (cochlear synaptopathy). They reported abnormal speech perception in the presence of noise and cochlear dead regions. They reported a possible hidden hearing loss in individuals suffering from tinnitus.

Shim et al. (2017) reported that auditory brainstem response (ABR) data in individuals with tinnitus did not show the presence of hidden hearing loss. However, reduced sound tolerance was written in these patients. Liberman et al. (2016) concluded evidence of increased SP/AP ratio in tinnitus patients with a normal audiogram. Middle Ear Muscle Reflex measurement can also be used to detect hidden hearing loss in individuals with tinnitus (Wojtczak et al., 2017).

Thus, there are many studies that account for the presence of a hidden hearing loss in individuals with tinnitus.

It is essential to have better comprehension about hidden hearing loss to control further damage to the auditory system and know about the early diagnosis so that patients will be helped for early detection and intervention of cochlear synaptopathy. And therefore, there is a requirement for conducting a systemic review to understand the strength of the relationship between tinnitus and hidden hearing loss.

1.3 Aim of the study

A systematic review aims to understand the relationship between hidden hearing loss/synaptopathy and tinnitus.

1.4 Objectives of the study

- Screening of articles relevant to the study from significant databases
- Compilation of these articles through appropriate data extraction
- Evaluation of the quality of the studies selected
- Interpretation to understand if there is a relation between hidden hearing loss/synaptopathy and tinnitus

Chapter 2
Methods

A systematic search was conducted within the following electronic databases: Google Scholar, Shodhganga, PubMed for English language articles published in peer-reviewed journals. Screening of the articles in the above-mentioned databases was done till August 2020. A comprehensive list of search terms was used. These keywords included "cochlear synaptopathy," "hidden hearing loss," and "tinnitus" used with the appropriate Boolean operators. The study criteria included population included in the study were adults (>18-45 years), studies published in peer-reviewed journals, publications in English, observational studies that highlight the relation between tinnitus Synaptopathy/hidden hearing loss. All the articles not meeting the above-mentioned inclusion criteria were excluded from the study. In addition, the exclusion criteria include studies based on animal models and articles that are not in English. PRISMA guidelines (Moher, Liberati, Tetzlaff & Altman, 2009) provided in figure 2.1 were used to screen the articles. Title and abstract screening were conducted to identify the relevant observational studies for full-text review, as per the inclusion and exclusion criteria.

This is also registered for the systematic review in PROSPERO (CRD42020212762).

The full texts of all eligible articles were obtained and reviewed. The data obtained from selected papers were organized in a table that included: bibliographic information, the number of patients included, method, outcome, and merits/drawbacks of the study to identify synaptopathy/hidden hearing loss in each included study.

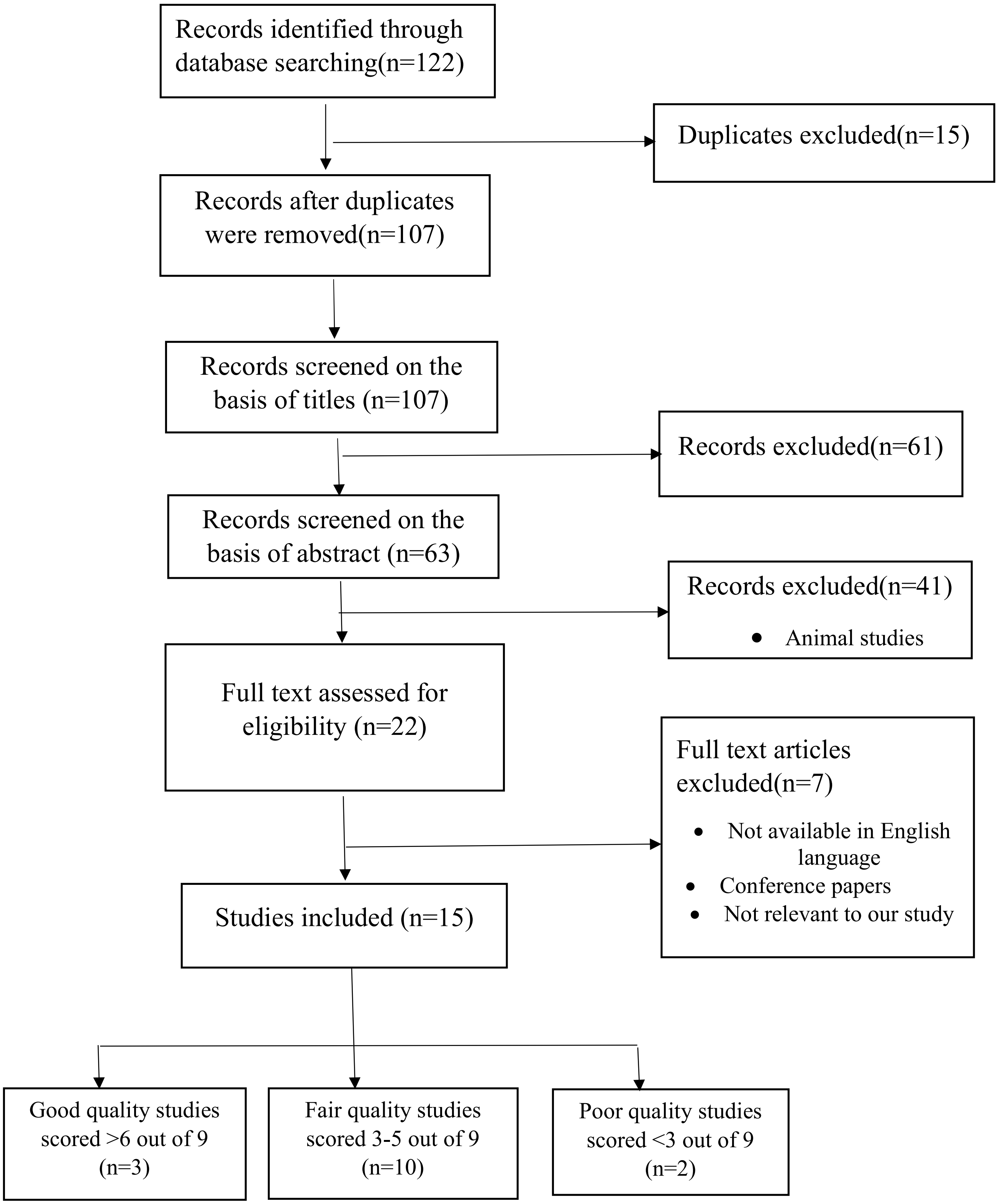


Figure 2.1: Prisma Flowchart for Selection of the articles

A total of 122 articles were identified using database searches, which excluded 15 duplicates. A total of 63 articles were selected for the title and abstract screening. From those, 22 articles were selected for full-text screening. Eighteen articles that met the inclusion criteria were selected for the study. The selection process was validated by inter-judge selection and discussion of disputes.

A comparison of each study was made for the strength and quality of the study with the questionnaire tool The Newcastle-Ottawa Scale (NOS) developed by Wells et al. (2000).

Chapter 3

Results

3.1 Selection of articles

A total of 122 articles were identified using database searches, which excluded 15 duplicates. A total of 107 and 63 articles were selected for the title and abstract screening, respectively. From those, 22 articles were selected for full-text screening. Fifteen articles that met the inclusion criteria were selected for the study. The summarized content of the included research is provided in the table below. The selection process was validated by inter-judge selection and discussion of disputes. The detailed PRISMA flow diagram for the selection of studies is in Figure 2.1.

3.2 Summary of the selected articles:

Summary of the selected articles is provided in terms of objectives of the study, population type, method used, results, and discussion of the study along with few advantages and disadvantages are listed in table 3.1.

3.3 Quality Analysis of the selected articles:

The Newcastle-Ottawa Scale (NOS) checklist was used for the analysis of the selected studies. A cohort part of the questionnaire was used for the quality assessment. It has eight questions to analyze the article. All most of all articles demonstrated the outcome of interest at the beginning of the study. Also, all articles had good inclusion and exclusion criteria for the exposed and non-exposed cohorts. Most of the studies lacked information on record linkage and also on follow-up. All the studies had shown acceptable results, had good implications, and were in line with the other earlier published studies. Hence no articles were removed for final qualitative data analysis. The results of the quality analysis administered on the selected articles are shown in table 3.2.

Table 3.1

Summary of the selected articles

Study	Research Design	Research question	Population type	Method	Results and Discussion	Advantages and disadvantages
Kara et al (2020)	Convenience sampling	The study aimed to identify the functions of different cochlear structures among individuals with or without tinnitus through electrophysiological tets.	• 13 Participants without tinnitus in control group. • 6 Participants in the study group who reported tinnitus aged between 21 and 59 years.	• Audiometric thresholds from 125 Hz to 16000 Hz • Transient evoked otoacoustic emissions (TEOAEs), distortion product otoacoustic emissions (DPOAEs), at 1.4, 2, 2.8, and 4 kHz • Threshold equalizing noise (TEN) test at 500, 1000, 2000, and 4000 Hz frequencies.	• Hearing thresholds between 6K to 16K Hz was increased among study group compare to control group. • DPOAE and TEOAE responses were normal in each group. This finding supports that the outer hair cell (OHC) were functioning normally in study group. • Study revealed dead regions in 75% among study group which indicates inner hair cells (IHC) damage.	Advantages: • Evidence of SP/AP ratio through ECochG and TEN test on normal hearing individuals with tinnitus are shown. Disadvantages: • Sample size considered in the study is less to generalize the results. • Left ear results shows that there is no significant difference in SP/AP ratio • Justification with supporting articles is not given for SPIN results. • These differences between the ears are

				• ECochG • SPIN	• Increased SP/AP ratio in the study group. • Decreased SPIN scores in study group This could be the possible cause of hidden hearing loss.	not explained in the study.
Guest, Munro, Plack (2019)	Quota sampling	The study aimed to find relation between Middle Ear Muscle Reflex (MEMR) threshold and presence of tinnitus, between MEMR threshold and Speech in noise (SPIN)	70 participants (including 19 with tinnitus) aged between 18–39 was recruited.	• Pure-tone air-conduction audiometric thresholds at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz. • MEMR thresholds at 1, 2, and 4 kHz • Speech in noise (SPIN)	• The results revealed absence of relation between MEMR threshold and the presence of tinnitus, SPiN, and noise exposure. This provides no evidence for synaptopathy in the population studied.	Advantages: • Sample size considered was large. • Different tests are considered for the evaluation of tinnitus. • Study population was compared with Age and sex matched controls. Disadvantages: • Conclusion of the study is not clear.

		and MEMR threshold and self-report noise exposure.				• Sample size of tinnitus individuals were less • Lax criteria are used for inclusion and exclusion. • Type of noise exposure by participants is not mentioned.
Shim, Kim, Yoon (2017)	Quota sampling	The aim of the study was to reconfirm the "hidden hearing loss" theory through a within-subject comparison of wave I and wave V amplitudes and to verify uncomfortable loudness level (UCL).	• 43 unilateral tinnitus patients 19 (aged 28.58±10.88 years) males, 24 (aged 37.58±14.38 years) females. • 18 age- and sex-matched control participants were also enrolled.	• Auditory brainstem responses (ABR) Uncomfortable (UCL) with 500 Hz and 3000 Hz pure tones.	• The ABR data do not represent meaningful evidence supporting the hypothesis of "hidden hearing loss", although several TEs showed extremely high V/I amplitude ratios implying increased central gains. • Reduced sound level tolerance in both TEs and NTEs reflects increased central gain consequent on hidden synaptopathy that was subsequently balanced between the	Advantages: • Sample size considered for the study was large. • Explanation of the results are well mentioned with the help of figures. • New evidence towards the SLT and central gain in normal was depicted here. Disadvantages: • They have reported that meaningful evidence to support the "hidden hearing loss" was not identified. • The side of the lesion was not reported in the

					ears by lateral olivocochlear efferent. • The selective loss of auditory nerve fibers and synapse can be correlated with cochlear synaptopathy.	study with reduced UCL scores. .
Schaette and McAlpine (2011)	Convenience and purposive sampling	The aim of the study was to establish evidence for central gain in presence of decreased neuronal activity.	Thirty-three female subjects, fifteen with tinnitus (mean age 36.3 ± 2.6 years) and eighteen controls (mean age 33.2 ±1.9 years) participated in the study.	Auditory brainstem responses	• Reduced amplitude of ABR wave I in subjects with tinnitus. • This is because of the homeostatic plasticity which is reported in the study. This overcomes the neuronal activity deprivation by increasing or decreasing the excitatory and inhibitory synapses responses.	Advantages: • Derived band ABR measurements are shown. • Results Indicate the pathophysiology of homeostatic plasticity. • Age and sex matched control subjects are recruited for the study. Disadvantages: • Test results cannot be generalized across different age groups as

						it is focused on only one age group. • Reason stated for not carrying the test on males is unclear.
Xiong et al (2019)	Convenience and Quota sampling	The study aimed to find the hearing loss in tinnitus patients with normal audiograms which is missed by standard pure tine audiometry (PTA).	106 tinnitus subjects (58 males and 48 females, 17-83 years old, mean age = 41.9) with unilateral tinnitus and normal or near normal audiograms were recruited for the study.	• Tinnitus pitch, loudness and residual inhibition (RI) • Precision pure tone audiometry (P-PTA) were tested in 1/24 octave band • DPOAE test	• The P-PTA test is a useful test in identifying cochlear lesions that could be missed by conventional PTA. • 22% of tinnitus patients had normal DPOAEs with notched hearing loss. Results of the same study revealed that notch which was found may be induced by lesions in IHCs or postsynaptic structures. This could be the possible cause for tinnitus in normal hearing individuals.	Advantages: • Sample size considered is large. • Importance of P-PTA is shown in the study • Explanation of the results are well mentioned with the help of figures. • The former factors had led to increase in number of patients with positive residual inhibition. • Using fine frequency step in tinnitus pitch match, the successful matching rate increased. Disadvantages:

						• Statistics is not clearly mentioned • Tough P-PTA is a very reliable tool, the inclusion of the same test into routine audiological evaluation is very time consuming. • High frequency audiometry is not caried out because of which hearing loss above 8 kHz might be missed. Age range considered for the study is too wide where presbycusis component was not eliminated.
Szibor et al, (2017)	Convenience and Quota sampling	The aim of this study was to record clinical and psychophysical characteristics of music	• Participants recruited were 71 males and 33 females with an age ranging from 14 to 62 years	• Pure tone-audiometry from 125 Hz to 12.0 kHz. • Pitch and loudness matching.	• Music can cause an acoustic trauma, various degrees of hearing dysfunction and tinnitus. • Damage to cochlear high-threshold afferent fibers	Advantages: • Sample size considered was large. • Extended high frequency was included for threshold estimation.

		induced hearing loss (MIHD) from individuals after a single trial of acoustic overstimulation from music.	(average ± SD 31.3 ± 9.3)	• Tinnitus handicap inventory (THI). • Tinnitus loudness and annoyance using the visual analogue scale (VAS)	(synapses) causes the tinnitus. • This shows the evidence of cochlear synaptopathy.	• Strict exclusion and inclusion criteria were defined. • Subjective test was involved and was correlated with VAS. • Good graphical representation of the results. Disadvantages: • Age range considered was very wide i.e., till 62 years in which presbycusis component may also alter the results. • Evidence for the results is not clearly mentioned. • Intensity, type and duration of music exposure is not mentioned in the study.

Marmel, Cortese and Kluk (2020)	Quote sampling	This study aimed to advance towards a clinical diagnostic method for detection of cochlear synaptopathy.	• Participants with unilateral or bilateral non-pulsatile tinnitus lasting more than 5 min at least once a week for more than 6 months. • 36 participants (18 in both control and study group) • The mean age was 38 ± 3.0 years for the control group and 39 ± 3.5 years for the experimental group	• Noise Exposure Structured Interview (NESI) • Pure-tone air-conduction audiometric thresholds at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz. • DPOAEs were recorded from 2 to 10 kHz • Measurement of masked thresholds for tones in TEN. •	• Masked thresholds for brief tones in TEN were similar for tinnitus sufferers and controls. • This study failed in identifying cochlear synaptopathy in humans through brief tone masked audiometry. • All had DPOAEs present for at least 2 of the tested frequencies. Only few in both the group had presence of DPOAEs at higher frequencies.	Advantages: • Life time noise exposure was considered as factor. • Cochlear synaptopathy was discussed under different factors. Disadvantages: • Very lax criteria were defined for normal threshold. • Lifetime noise exposure was determined with open ended questions wherein subjects may mis out relevant information and accuracy of the obtained information will be questionable. • These findings do not support the study's rationale that brief-tone masked audiometry could help in detecting cochlear

						synaptopathy in humans
Epp, Verhey, Schaette (2012)	Purposive sampling	To test the relation between just-noticeable intensity differences (intensity JNDs) for pure tones measured in normal hearing listeners reporting tinnitus and in control participants without tinnitus.	• 14 participants in control group, mean age 26 ±2 year and 11 participants who reported tinnitus in tinnitus group, mean age 38 ±4 year.	• Masked thresholds and JND at frequencies 1000, 2450, and 6000 Hz • Hearing thresholds from 125–8000 Hz • Tinnitus pitch and loudness matching was done.	• There is no difference between 1000 Hz and 2500 Hz tone for JND intensity at 30,50- & 70-dB SPL. • But for 6000 Hz frequency there was mid-level hump seen at 50 dB SPL because of deafferentation of high-threshold auditory nerve (AN) fibers. This hypothesis explains the tinnitus with normal hearing.	Advantages: • This study led us to a new understanding of tinnitus with normal hearing i.e., deafferentation of AV fibers could underlie tinnitus with a normal audiogram • Inclusion of psychoacoustic parameters in the study. Disadvantages: • More studies are not quoted to strengthen the results. • Sample size was small.

						• Inclusion and exclusion criteria are not clearly mentioned.
Lefeuvre et al, 2019	Purposive sampling	The aim of the study was to validate a protocol for correct diagnosis of hidden hearing loss associated with tinnitus and to optimise the characterisation of the tinnitus in order to improve the treatment of these patients.	• Sixty-six patients with unilateral or bilateral chronic tinnitus (more than 6 months) of high-frequency sound ringing type and tone-like were included over a 2-year period. 24 participants were recruited for control groups.	• PTA at 500, 1000, 2000 and 4000 Hz. • Pitch, loudness, masking and residual inhibition. • THI and a VAS test.	• The results demonstrate that the high-definition audiogram provides better characterisation of tinnitus testing than the classically used test and should be used to improve treatment guidance.	Advantages: • The protocol presented in this study allows audiologists to obtain the precise information on hearing loss and tinnitus characteristics to improve tinnitus treatment with hearing aids. • Results are well represented through graphs. • Sample size considered is large Disadvantages: • Clinically not practical to adopt the protocol as its time consuming.

						• Rationale for results is not mentioned in the discussion.
Wojtczak, Beim, Oxenham (2017)	Convenience sampling	The aim of this study was to investigate the relationship between the presence of tinnitus and the strength of the middle-ear-muscle reflex (MEMR) in humans with normal and near-normal hearing.	18 individuals in study group with tinnitus (12 male, 6 female) aged 46 years (range: 25-63 years)	• PTA at frequencies from 250 Hz to 8 kHz. • The wideband measure of MEMR. •	• Results revealed significantly weaker MEMR in humans with tinnitus related to excessive noise exposure but with clinically normal or near normal hearing than in control group. • The reason that they give is diffuse loss of synaptic IHC/AN connections. This can be correlated for the reason behind cochlear synaptopathy.	Advantages: • Results are discussed with strong studies. • Provides information of MEMER as a good clinical tool for identification of cochlear synaptopathy. Disadvantages: Sample size considered was less

Fabijanska et al., (2012)	Quota sampling	To evaluate DPOAEs and extended high-frequency (EHF) thresholds among control group and in patients with normal hearing sensitivity reporting unilateral tinnitus.	• 70 patients in study group,14 to 40 years • 60 years ranging from 14 to 60 years in control group	• Extended high frequency Audiometry • DPOAE •	• Increased thresholds in EHF were seen among tinnitus patients. • DPOAE levels in tinnitus ears were decreased than those in ears of non-tinnitus subjects, suggesting that subclinical cochlear impairment. • The reason that authors discuss is that OHC impairment in the most basal region. • This could be the possible reason for cochlear synaptopathy.	Advantages: • Sample size is large. Disadvantages: • Synaptopathy is not high lightened in the study.
Sanchez 1 et al., (2016)	Convenience sampling	To evaluate the prevalence of tinnitus and reduced SLT among adolescents, which could	• 170 participants aged between 14 to 17.	• Loudness discomfort levels • PTA from 205 to 16 kHz • TEOAE's and DPOAE's	• Reduced SLT in adolescents with tinnitus. • Reduced OAE'S both DPOAE's and TEOAE's at higher frequencies.	Advantages: • Sample size is good • Participants are young adults where the application lies to greater extent. Disadvantages:

		forecast increased risk for hearing difficulties in later years.			One of the reasons that is mentioned for justification is that loss of ribbon synapses which also explains the hidden hearing loss.	• Clear results with justifications are not mentioned for OAE's test results. • Questionnaire used isn't mentioned in the article. No specific exclusion criteria is mentioned.
Guest, Munro, Prenderg ast, Howe, Plack (2016)	Quota sampling	The study aimed to determine tinnitus with normal audiogram (TNA) is associated with greater lifetime noise exposure, temporal coding deficits, relations between electrophysio logical	• 20 participants aged 25.7 ± 1.3 in the study group. • 20 participants in the control group with mean age 25.5 ± 1.3 were recruited for the study.	• Pure tone audiometry from 250 to 8 K Hz • Auditory brainstem Response. • Envelope following response (EFR)	• ABR and EFR didn't provide any evidence to identify cochlear synaptopathy in humans. • Tinnitus may be the result of subclinical damage due to excessive noise exposure.	Advantages: • Inclusion of Envelope following response test • Different aims are investigated Disadvantages: • Noise exposure history was taken in a structured interview in which most of the information might be missed. • Estimation of noise level and duration

		measures of synaptopathy				was not measured with relevant tools.
Liberman, Epstein, Cleveland, Wang, Maison (2016)	Purposive sampling	Aim of the study was to identify "hidden hearing loss" which is widespread in young adults with normal audiometric thresholds, especially those who abuse their ears regularly.	• Participants were aged between 18 & 41 years.	• PTA from 250 to 16 K Hz • Word recognition test • DPOAE's • Electrocochleography	• High risk group showed elevated thresholds above 8 K Hz of audiometric frequencies. • Poor speech scores with competing signal and reduced speech recognition in the noisy environment among high-risk group. • Increased SP/ap ration among high-risk group. Basal-turn hair cell damage is the reason that is justified in the article for cochlear synaptopathy for	Advantages: • Results are clearly mentioned with justifications. • Inclusion of speech and electrophysiological test into identify cochlear synaptopathy. Disadvantages: • High and low risk groups are not defined clearly • Number of participants are not mentioned • DPOAE results are not discussed.

					increased thresholds at higher frequencies. • Also, this study supports researches concluding the damage to the IHC which accounts for cochlear synaptopathy	
Paul, Bruce, Roberts (2016)	Convenience sampling	Aim of the study was to investigate the low-SR fiber synaptopathy accounting for individual differences in temporal coding ability in young adults with normal audiometric thresholds, and to explain the presence of	• 24 participants in control group aged between 18-28 years mean age 19.5 • 13 participants in the study group aged between 18-39 years mean age 23.2	• Amplitude modulation detection • Envelope following measures (EFR)	• AM encoding was poorer overall in tinnitus subjects. • Reduced EFR among study group. • Inhibition and increased gain in central auditory pathways after deafferentation are the justification given for the synaptopathy	Advantages: • Detailed explanation for results. • Involvement of EFR and AM to identify synaptic changes. Disadvantages: • Typological error in the method section.

		chronic tinnitus by a greater degree of synaptopathy				

3.3 Quality Analysis of the selected articles:

The Newcastle-Ottawa Scale (NOS) checklist was used for the analysis of the selected studies. The cohort part of the questionnaire was used for the quality assessment. It has eight questions to analyze the article. All most of the articles demonstrated the outcome of interest at the beginning of the study. Also, all articles had good inclusion and exclusion criteria for the exposed and non-exposed cohorts. Most of the studies lacked information on record linkage and also on follow-up. All the studies showed acceptable results, had good implications, and were in line with the earlier published studies. Hence, no articles were removed for final qualitative data analysis. The results of the quality analysis administered on the selected articles are shown in table 3.2

Table: 3.2

Quality analysis of the selected articles

Author	Year	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Control for important factor or additional factor	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total quality scores
Kara et al	2020	*		*	*	*				4
Guest, Munro, Plack	2019				*	*				2
Shim, Kim, Yoon	2017			*	*	*				3
Schaette and McAlpine	2011	*	*	*	*	*				5
Xiong et al	2019	*		*	*	*				5

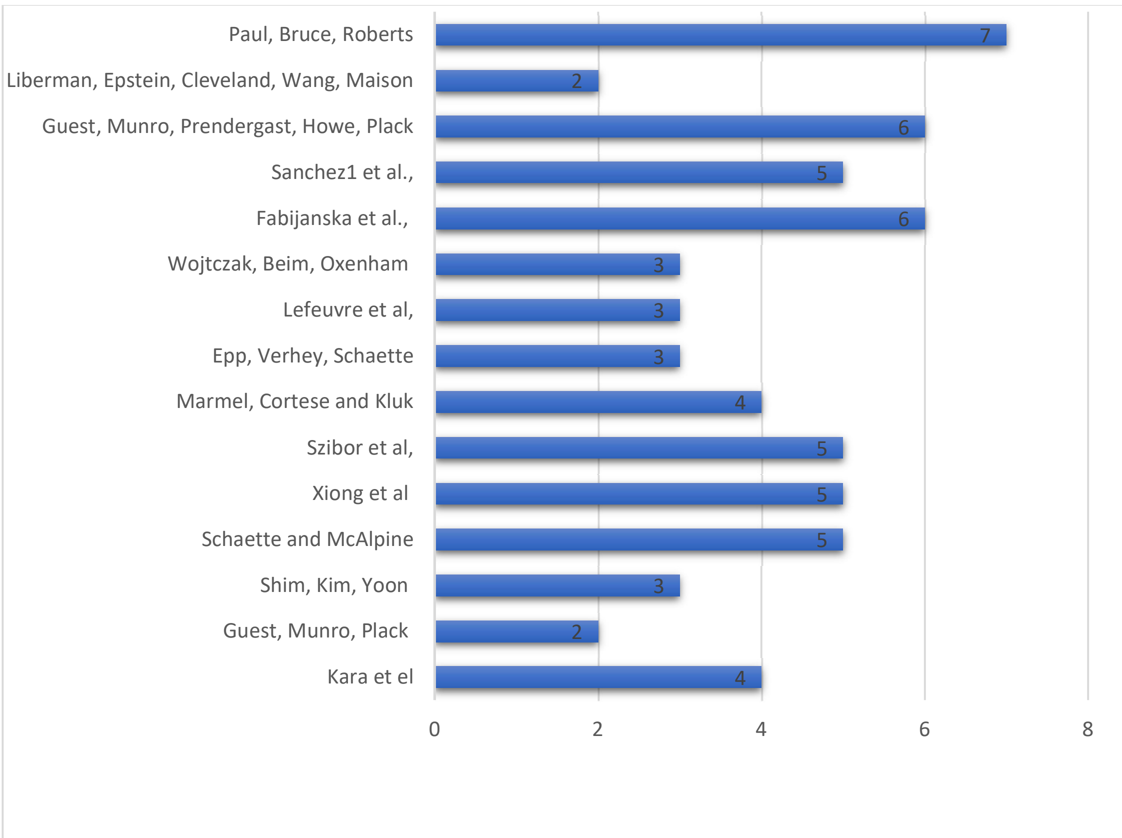
Author	Year	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Control for important factor or additional factor	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total quality scores
Szibor et al,	2017	*		*	*	**				5
Marmel, Cortese and Kluk	2020	*	*		*	*				4
Epp, Verhey, Schaette	2012			*	*	*				3
Lefeuvre et al,	2019			*	*	*				3
Wojtczak, Beim, Oxenham	2017	*			*	*				3
Fabijanska et al.,	2012	*	*	*	*	**				6

Author	Year	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Control for important factor or additional factor	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total quality scores
Sanchez1 et al.,	2016	*	*	*	*	*				5
Guest, Munro, Prendergast, Howe, Plack	2016	*	*	*	*	**				6
Lieberman, Epstein, Cleveland, Wang, Maison	2016	*				*				2
Paul, Bruce, Roberts	2016	*	*	*	*	**			*	7

The summary of the results in terms of scores obtained from the Newcastle-Ottawa Scale (NOS) checklist for different domains is shown in the figure 3.1.

Figure:3.1

Graphical representation of quality judgement of the selected articles.



Chapter 4

Discussion

4.1 Puretone and other behavioral measures:

From their study, Kara et al. (2020) concluded that hearing thresholds between 6k to 16k Hz were increased among the study group compared to the control group. Fabijanska et al. (2021) concluded from their study that increased EHF thresholds among tinnitus patients had normal audiometric thresholds. These results were also supported by Liberman et al. (2016). They reported that the high-risk group had elevated thresholds above 8 k Hz of audiometric frequencies and poor speech recognition scores. Xiong et al. (2019) reported from their study that P-PTA is very useful in detecting hidden hearing loss. They showed that 46% of individuals who claim to have normal hearing had a notch in the P-PTA.

Elevation of thresholds at higher frequencies was identified through extended high frequencies. Possible reasons could be predisposing vascular damage in the basal cochlear region (Dhrruvakumar et al., 2021). It is also reported that extended high-frequency thresholds were affected earlier than conventional audiological in hidden hearing loss. The study by Morgan et al. (2021) reported that hidden cochlear damage in high-frequency hearing loss is present in patients with tinnitus.

Other behavioral tests like TEN, JND, and SPIN were also assessed in several studies. Kara et al. (2020), from their study, revealed dead regions with TEN tests in 75% among the study group. But research conducted by Marmel et al. (2020) did not give any evidence for synaptopathy with the TEN tests. TEN tests were conducted by Thabet et al. (2009). They found that dead regions were found in 15% of individuals. They provide dysfunctional IHCs/and or neurons termed deafferentation as the cause for the dead regions (Gilles et al., 2013; Thabet, 2009b).

Other studies which used JND (Epp et al., 2012) revealed no correlation between hidden hearing loss and synaptopathy. SPIN was used by Kara et al. (2020) and concluded that scores were reduced in the study group. However, Guest et al. (2019) reported no correlation between SPIN and other electrophysiological tests among the study and control group. These findings were also supported by (Bramhall et al., 2018).

All studies related to EHF audiometry and TEN tests scored fair in quality judgment tasks, indicating that both tests can be a good tool for investigating the hidden hearing loss. JND study also showed relevant results, but further research is required in this area to substantiate the same. SPIN studies showed ambiguous results with a fair and poor score, so extensive research is essential for the test to implicate clinically.

4.2 Physiological measures:

The study by Kara et al. (2020) concluded that DPOAEs and TEOAEs were normal among both study and control groups. This result was also supported by Xiong et al. (2019) where they showed that 22% of tinnitus individuals with normal audiometric thresholds had DPOAEs and TEOAEs. Liberman et al. (2016) also reported DPOAEs and TEOAEs at all tested frequencies without significant amplitude difference among control and study group. In contrast, other studies report a decrease in DPOAE and TEOAE amplitude or absence of the response in the tinnitus group (Fabijanska et al., 2012; T. G. Sanchez et al., 2016).

In most studies, researchers have found that TEOAEs and DPOAEs are absent or reduced in tinnitus patients with normal hearing thresholds. (Granjeiro et al., 2008; Zhou et al., 2011). For instance, Granjeiro et al. (2008) examined the prevalence of TEOAE and DPOAE test results among tinnitus individuals with and without hearing loss. They concluded that tinnitus with normal hearing had a more significant percentage of abnormal TEOAE and DPOAE results than the non-tinnitus normal-hearing control group. Damaged or dysfunctional OHC is the prediction of the possible cause for the decreased DPOAE results.

The reason that is justified for the reduced DPOAE amplitudes is OHC impairment may also be contributed by other subclinical pathologies, like loss of high-threshold spiral ganglion cells, which results in tinnitus (Fabijanska et al., 2012). Another possible reason that is mentioned in the studies is that the damaged basal region of the cochlea may, to some extent, contribute to DPOAEs measured at lower frequencies (Arnold et al., 1999)

For most of the studies, the quality judgment of these articles scored fair and indicated that DPOAEs and TEOAEs are excellent tools for assessing hidden hearing loss. But one study by Liberman et al. (2016) had a poor-quality rating.

Other studies which used MEMR showed ambiguous results. The survey by Guest et al. (2019). revealed no relation between the MEMR threshold and the presence of tinnitus. Wojtczak et al. (2017) concluded significantly weaker MEMR in tinnitus individuals with clinically normal or near-normal hearing who had excessive noise exposure than in the control group. Hence, further detailed investigations with MEMR test to identify the relation between cochlear synaptopathy and tinnitus has to be carried out. These articles scored poor and fair in the quality judgment task, respectively. Hence, it indicates that further extensive research is needed in this field.

A study on mice found a significantly weaker MEMR in noise-exposed mice with cochlear synaptopathy (Valero et al., 2016). The justification given for the results is that pure OHC damage does not affect the MEMR results because, besides this, OHC damage studies have shown dips in auditory nerve FTCs. At the same time, the dynamic range (typically 20–30 dB) and maximum discharge rate remain unchanged (M. Liberman et al., 1978).

OHC impairment in tinnitus individuals with normal audiograms is not so severe. Those other kinds of cochlear damage, like IHC damage or AN fiber deafferentation, are more responsible for the tinnitus perception (Tan et al., 2013). The study by Weisz et al. (2016) also concludes that tinnitus is due to severe inner-hair cell damage. There is an increase in the central gain due to the presumed deafferentation of AN fibers at the level of the brainstem. This suggests a potential mechanism for the generation of tinnitus (Schaette & McAlpine, 2011).

4.3 Electrophysiological measures:

Studies that were reviewed included tests like ECochG, ABR, and EFR. Increased SP/AP ratio among individuals with tinnitus and normal audiogram was reported (Eyyup Kara et al., 2020; M. C. Liberman et al., 2016). ECochG is a helpful tool for measuring cochlear synaptopathy caused by age or noise-related changes in the auditory system (Kujawa & Liberman, 2015). The cause which is stated in the studies for increased SP/AP ratio is IHC damage which contributes to cochlear synaptopathy (E Kara et al., n.d.). Liberman et al. (2016) stated that increased SP is the main cause for cochlear synaptopathy.

But with the ABR test, ambiguous results were found. The study by Schaette & McAlpine (2011) reported reduced amplitude of ABR wave I in subjects with tinnitus. Other studies concluded no difference in wave I and waved V amplitude, the amplitude ratio of wave V/I, and latencies of the wave V & I (Guest, Munro, Prendergast, et al., 2017; Shim et al., 2017a).

The reason that is claimed for the reduced amplitude of ABR wave I is the diffuse loss of inner hair cells in the tinnitus subjects (Gu et al., 2017). Other studies report about the reduction of the excitatory response of ANFs via the lateral olivocochlear efferent, which terminates on their endings (Shore et al., 2003).

Contrarily other researchers say no difference in ABR wave amplitude among tinnitus with normal hearing and controls (normal hearing) because the site of lesion of hidden hearing loss is at the level of the primary auditory nerve, and generation is likely connected to a homeostatic response of neurons of the brainstem (H et al., 2013).

The study by Guest et al. (2017) concluded that EFR provided no evidence for cochlear synaptopathy. On the other hand, Paul et al. (2017) showed reduced EFR results among tinnitus with normal audiogram individuals. Guest et al. (2017). they are reported from their study that there is a correlation between EFR results and tinnitus in individuals with normal hearing. The reason that is justified for the same is the poor selection of stimulus factors. Contrarily other studies found a reduction in EFR response in tinnitus individuals, as EFR records response from IHC to IC anywhere the lesion in the auditory pathway is detected (Bharadwaj et al., 2014) also because EFR is more focused on detecting lesions of higher auditory structures than hair cells (Shaheen et al., 2015).

Quality judgment of articles where ECochG was used scores fair (Kara at al., 2020) and poor (Liberman et al., 2016) results. ABR articles had fair and good scores, though quite good scores are achieved in quality judgment task further assessment is requires for the implication of the test into clinical practice. Both the articles of EFR score good on quality judgment tasks, but as the results are further ambiguous, research is required to establish the efficacy of the test.

Extended high frequency is a good measure in identifying hidden hearing loss, as seen in the review of the literature. The reason mentioned is vascular damage in the basal cochlear region. OAEs are also a good tool, but ambiguous results are seen.

Reduced amplitudes of OAEs are due to dysfunctional OHC, but on the other hand, if the OAE amplitudes are not reduced, then the cause reported is damage in the higher auditory structures or at the IHC. ECochG has a very good implication in detecting cochlear synaptopathy. Damaged IHC would lead to the increased SP altering SP/AP ratio leading to hidden hearing loss.

Chapter 5

Summary and Conclusions

A systematic review aims to understand the relationship between hidden hearing loss/synaptopathy and tinnitus.

Screening of the articles in the Google Scholar, Shodhganga, PubMed databases was done till August 2020. A comprehensive list of search terms such as "cochlear synaptopathy," "hidden hearing loss," and "tinnitus" was used with the appropriate Boolean operators. Appropriate inclusion and exclusion criteria were followed. PRISMA guidelines (Moher, Liberati, Tetzlaff & Altman, 2009) was used to screen the articles. Title and abstract screening were conducted to identify the relevant observational studies for full-text review, as per the inclusion and exclusion criteria. The data obtained from selected papers were organized in a table.

A total of 122 articles were identified using database searches. Eighteen articles that met the inclusion criteria were selected for the study. A comparison of each study was made for the strength and quality of the study with the questionnaire tool The Newcastle-Ottawa Scale (NOS) developed by Wells et al. (2000).
Summary of the selected articles is provided in terms of objectives of the study, population type, method used, results and discussion of the study, and few advantages and disadvantages.

The Newcastle-Ottawa Scale (NOS) checklist was used for the analysis of the selected studies. The cohort part of the questionnaire was used for the quality assessment. All most the articles demonstrated the outcome of interest at the beginning of the study. Also, all articles had good inclusion and exclusion criteria for exposed and non-exposed cohort. All the studies had shown acceptable results, had good implications and were in line with the other earlier published studies. Hence no articles were removed for final qualitative data analysis.

5.5 Implications

- This review provides the relationship between cochlear synaptopathy and tinnitus in individuals with normal hearing.
- Extended high-frequency audiometry and ECochG are good tools for measuring cochlear synaptopathy, which can be incorporated in clinics for detecting hidden hearing loss.
- The main cause that is described in the literature for the hidden hearing loss is damage in IHC or basal cochlear region.

5.4 Future directions:

- Further studies can also look into carrying out Meta-analysis.

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