Review Article

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Hearing loss and brain disorders: A review of multiple pathologies

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Abstract: Several causative factors are associated with hearing loss (HL) and brain disorders. However, there are many unidentified disease modifiers in these conditions. Our study summarised the most common brain disorders associated with HL and highlighted mechanisms of pathologies. We searched the literature for published articles on HL and brain disorders. Alzheimer’s disease/dementia, Parkinson’s disease, cognitive impairment, autism spectrum disorder, ataxia, epilepsy, stroke, and hypoxic-ischaemic encephalopathy majorly co-interact with HL. The estimated incidence rate was 113 per 10,000 person-years. Genetic, epigenetic, early life/neonatal stress, hypoxia, inflammation, nitric oxide infiltration, endoplasmic reticulum stress, and excess glutamate were the distinguished modifiers identified. Various mechanisms like adhesion molecules, transport proteins, hair cell apoptosis, and neurodegeneration have been implicated in these conditions and are serving as potential targets for therapies. To improve the quality of life of patients, these understandings will improve clinical diagnoses and management of HL and brain disorders.

Keywords: hearing loss, brain disorders, pathology, correlated risk factors

1 Introduction

Hearing loss (HL), deafness, or hearing impairment can be described as a total or partial inability to hear sounds. HL could be conductive, sensorineural, or mixed, depending on the parts of the auditory system being affected [1]. Globally, approximately 400 million people are diagnosed of HL [2,3] and millions of people suffered from one form of brain disorders. Environmental and genetic factors have been identified as the leading contributors. Syndromic HL is associated with numerous syndromes like Waardenburg syndrome, branchiootorenal syndrome, Usher syndrome, Pendred syndrome, keratitis-ichthyosis-deafness syndrome, and Alport syndrome [1,4]. Non-syndromic HL is a form of sensorineural HL that is not linked to a syndrome [5].

HL can cause several neurological and psychiatric complications that can reduce quality of life [6]. Some of the complications may include cognitive impairment, depression, dementia, and comorbidities like cardiovascular diseases and diabetes [4,7,8]. More so, the feelings of irritability, anxiety, and rage in patients with HL may emanate from undiagnosed brain disorders [2].

Physiologically, the brain is the true organ of hearing because the brain processes the sounds that are transmitted from the ears. Hearing is a complex process that requires connection between the peripheral and central auditory processing systems [9], this connectivity enables the sharing of aetiological factors. Impaired cochlear blood perfusion and microvascular damage in the ear can cause sensorineural HL, as well as certain brain disorders. This review aims to identify commonly associated brain disorders with sensorineural HL and explains the plausible mechanisms by which HL co-interacts with the brain disorders. The understanding of these multiple pathologies will contribute to the clinical management of patients.

2 Methods

2.1 Search method

We searched five electronic databases “PubMed, PubMed, Google Scholar, MEDLINE, and Embase” for published articles on HL and brain disorders between the years 2000 and 2021.
We used a combination of strings and MeSH terms (hearing loss) AND with OR (hearing impairment) AND with OR (deafness) AND with OR (brain) AND with OR (brain disorders) AND with OR (brain disease). The strings were adapted to each database entries.

2.1.1 Selection criteria

We prioritized the articles that have the searched terms in their title or abstract. Additionally, the articles that reported clinical, scientific, or technological findings on HL with brain disorders in humans were selected. The articles considered relevant had the following objectives:
1. Reported the incidence or clinical diagnoses of HL with brain disorders.
2. Evaluated the causative factors of HL with brain disorders.
3. Investigated novel potential targets for therapy in HL with brain disorders.

2.1.2 Extraction and data presentation

The full texts of the selected articles were downloaded to Zotero electronic reference manager for reference. We retrieved meta-data like demographics, the number of study participants and cases. We estimated the incidence rates as a measure of new cases/total, that is, the number of study participants considered at risk. The findings were summarized in Table 1. We provided a diagrammatic illustration to explain the underlying multiple pathologies and the mechanisms of HL co-interaction with brain disorder by using the biorender app (https://app.biorender.com/).

3 Results

The search engines gave an output of 39,454 articles, of which 8,531 articles were initially considered as relevant articles. They include case reports, reviews, short communications, letters to the editor, and original articles. However, after the filtering processes by using stringent criteria to select case reports, reviews, and original articles that presented meta-data or detailed information on the topic of HL with brain disorder only, we identified 71 important articles, of which 45 articles were original articles (Figure 1). The focus of the 45 articles was on molecular pathology, diagnosis, incidence, or genetics.

The results of our analyses showed that Alzheimer’s disease/dementia, Parkinson’s disease (PD), cognitive impairment, autism spectrum disorder, ataxia, epilepsy, hypoxic-ischaemic encephalopathy, and stroke have been reported to co-interact with HL (Table 1). The overall number of cases was 2,765 of 24,447 participants, and the estimated incidence rate was 0.113 per person-year or 113 per 10,000 person-years.

The demographic data derived from the studies imply that adult patients usually have Alzheimer’s disease, Parkinson’s disease, and cognitive impairment, whereas the infants and children had autism spectrum disorder (ASD), attention deficit hyperactivity disorder, and cerebral palsy with HL. Geographically, the studies were performed mainly in Europe and Asia. The researchers used different methods for diagnoses (Table 1), but generally the clinical presentations of the patients were similar. Likewise, the findings signified those complex mechanisms such as hereditary, acquired, or combination of factors including environmental and physical abnormalities in the causes of HL and brain disorders (Figure 2).

Furthermore, ten studies distinguished the roles of methylated genes and reported single nucleotide polymorphisms (SNPs), that overlap between HL and brain disorders (Table 2). We summarised, in Figure 3, the mechanisms involving the multiple pathologies of HL with brain disorders such as stress, inflammation, genetic factors, and environmental factors such as heavy metals, pesticides, bisphenol A; polybrominated diphenyl ethers; polychlorinated biphenyls; perfluorocarboxylic acids; and perfluoroctanesulfonate.

4 Discussion

Complex biological pathways and modifiers are involved in the onset of HL and brain disorders. The anatomical structures of the cochlea of the ear, and the brain show that the cochlea consists of hair cells that allow the neural conduction with the brain by the auditory nerves at the synapses [1,9,45–49]. The damage(s) to the auditory nerves, cortex, or thalamus is/are capable of inducing HL and brain disorders. We identified studies that showed that a bilateral lesion of the superior temporal gyrus and the thalamic nuclei of the brain caused HL, motor, sensory, and neuropsychological impairments [50,51]. Also, a haemorrhagic lesion in the right thalamus due to an aneurysm was linked to the aetiology of bilateral HL in children [52,53]. More so, cerebral palsy co-interacts with childhood HL [54].

The damages to the thalamus and the central auditory system can be caused by a stroke, head injury, brain
Table 1: Studies on brain disorders and hearing loss

| Type of diseases                        | Methods                                                                 | Major findings                                                                                                                                                        | Total number of cases | References |
|----------------------------------------|-------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|------------|
| Alzheimer’s disease (AD) and dementia  | Studies that performed PTA, ABR, and central auditory processing tests on participants diagnosed with dementia/AD. Patients were compared with control groups | There was a significant association between central auditory dysfunction and dementia/AD in the primary auditory cortex with evidence of abnormal blood glucose levels.                                      | 1,045                  | [10–14]    |
|                                        | Studies that performed longitudinal research on patients diagnosed with sensorineural HL and investigated association with dementia in participants | During the average 5 year follow-up period, the incidence rate of dementia in the sensorineural hearing loss (SNHL) cohort was 6.5 per 1,000 person-years compared with 5.09 per 10,000 person-years in the comparison group. HL was independently associated with a high incident rate of dementia in mild, moderate, and severe HL. | 17,523                 | [15–17]    |
| Parkinson’s disease (PD)               | Assessments of HL were evaluated in PD patients with audiometric testing, and a battery of central auditory processing tests | Compared to the control group, PD patients reported greater HL.                                                                                                       | 184                    | [18–24]    |
| Cognitive impairment                   | Patients diagnosed with HL were recruited for the study and completed the modified Mini-Mental State Examination, cognitive test, and linear mixed models for correlation | About one-sixth (15.7%) of the patients studied had cognitive decline; 10.1% had functional decline among individuals with HL. There was also an association with history of stroke.                                      | 5,445                  | [17,25–27] |
| Autism spectrum disorder (ASD)         | Audiological evaluation was performed using PTA tests in children diagnosed with autism | Mild-to-moderate HL was diagnosed in 7.9% and unilateral HL in 1.6%, profound bilateral HL was diagnosed in 3.5% of all cases.                                                                                           | 199                    | [28]       |
| Epilepsy and ataxia                    | A retrospective review of the detailed neurological and neuroradiological features were performed in nine children | All children presented with tonic–clonic seizures in infancy. Later, with non-progressive, cerebellar ataxia and profound HL.                                                                                           | 9 children, 1 adult    | [29,30]    |
| Hypoxic ischaemic encephalopathy (HLE) | Dual-stage hearing screening tests, including automated otoacoustic emissions and ABR tests, were performed in new-borns suspected to have developed HL | The study affirms a significant association between HL in term infants who have moderate/severe HLE with evidence of abnormal blood glucose and multi-organ dysfunction ($p = 0.006$). | 42                     | [31]       |
| Stroke                                 | Neurological and general examinations were performed, followed by audiogram and MRI screening | Acute stress was recognised and moderate sensorineural HL with the presence of bilateral temporal ischemic stroke lesions.                                                                                         | 1                      | [32]       |
tumours, or neurodegeneration [52,53]. These damages may lead to loss of auditory cortex, and may contribute to the down regulation of neural activities in the brain [55].

In essence, our study advocate for the use of advanced technology such as magnetic resonance imaging (MRI) in the diagnosis and early detection of HL and brain disorders. Furthermore, stress and inflammation contribute to the onset of HL and brain disorders. Stress has multiple effects that can be linked to the release of adrenaline and vasoconstrictors that may narrow blood flow into the tissues of inner ear [56]. Studies have shown a strong correlation (~32% of 9,756 participants) between HL and different types of daily stressors like occupational, poverty, long-term illness, lack of sleep, and higher burnout [57]. Also, the responses to stress via the hypothalamic-pituitary-adrenal (HPA) axis have been implicated in HL and various brain diseases [58]. The pathology may be linked to the release of cortisol and an imbalance of the N-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid receptors in the cochlea that can cause excess glutamate and glycine release, followed by excitotoxicity, and altered gene expression in the cochlea and the brain as described in Figure 2.

Stress can induce inflammation or hypoxia in the hair cell by affecting the epithelial cells in the brain to induce immune responses and cellular infiltration [46]. Stress-induced inflammation or hypoxia in the cochlea has been shown to be modulated by the macrophages [58].

**Figure 1:** Filtering processes and article selections in the study.

**Figure 2:** The description of intrinsic, extrinsic factors and disease modifiers underlying the pathologies of HL co-interactions with brain disorders.
| Methylated genes | Brain disorders | Proposed mechanisms | Associated SNPs/mutations | References |
|------------------|----------------|---------------------|--------------------------|------------|
| DNMT1            | Autism, cerebellar ataxia, Huntington disease | DNMT1 negatively impacts retrograde trafficking and autophagy | rs10418707, rs10423341, rs2116724, and rs759920 | [33–35] |
|                  | AD, and intellectual disability syndrome | Most of the mutations identified are predicted to disrupt the reading frame in a way that causes early translational termination and/or activates non-sense-mediated decay | Multiple mutations have been reported including the c.2314delG, c.2362C>T, c.5296C>A | [36–38] |
| NSD1             | AD, and intellectual disability syndrome | Enhanced nuclear H3K27me3 affects cell cycle and neuronal survival through reverse transcription mechanisms and complexes | Ser652 and Ser734 sites methylation | [39] |
| EZH2             | Ataxia | The addition of methyl groups to histone H3 lysine 9 linked to genomic imprinting, X-inactivation, and heterochromatin formation | | |
| EHMT1            | Intellectual disability, schizophrenia, and psychosis, autism, PD, and HD | The addition of methyl groups to histone H3 lysine 9 linked to genomic imprinting, X-inactivation, and heterochromatin formation | Multiple H3K9 dimethylation has been reported | [40] |
| KMT2D            | Kabuki syndrome (intellectual disability) and multiple malformations syndrome | Methylation leads to the truncation of C-terminal SET catalytic domain, likely resulting in the loss of enzymatic function | Multiple mutations have been reported including the p.Cys1430Arg and p.Cys1471Tyr | [41–43] |
| CHD7             | ASD and sleep disorder | Mechanisms not fully understood but were thought to control glia activation and causes hyperserotonemia | Multiple mutations have been reported in non-human subjects | [44] |
in English between the years 2020 and 2021. Also, we analysed articles that have free full text. Nonetheless, the significance of our study is in the identification of various brain disorders that are co-interacting with HL, and the raw incidence rate to expect per population. Our study gave an overview of diseases that may present clinically with HL. We emphasised genetics, epigenetic, damaged cortical/thalamus, stress, inflammation, and immune system dysfunction as primary contributors to the onset of HL and brain disorders. The identification of the multiple pathologies strengthen research ideas in this area and will promote healthcare awareness, contribute to target discoveries and novel treatments, as well as improve the diagnosis and care for people affected with HL and brain disorders.

### Abbreviations

- ASD: autism spectrum disorders
- HL: hearing loss
- HPA-axis: hypothalamic-pituitary-adrenal axis
- HLE: hypoxic ischaemic encephalopathy
- IHC: inner hair cells
- MRI: magnetic resonance imaging
- NO: nitric oxide
- NMDA: N-methyl-D-aspartate
- NSHL: non-syndromic hearing loss
- SGNs: spiral ganglion neurons
- AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid
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References

[1] Jensen EAH, Harmon ED, Smith W. Early identification of idiopathic sudden sensorineural hearing loss. Nurse Pract. 2017 Sep 21;42(9):30–6.

[2] GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019 May;18(5):459–80.

[3] Vos T, Abajobir AA, Abate KH, Abbafati C, Abbás KM, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet. 2017 Sep 16;390(10100):1211–59.

[4] Haile LM, Kamaven K, Briant PS, Orji AU, Steinmetz JD, Abdoll A, et al. Hearing loss prevalence and years lived with disability, 1990–2019: findings from the Global Burden of Disease Study 2019. The Lancet. 2021 Mar 13;397(10278):996–1009.

[5] Smith, RJ, Jones, MKN. Nonsyndromic hearing loss and deafness, DFNB1. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJ, Mirzaz G, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993. [cited 2021 Jul 2]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK12727/.

[6] Gardiner SA, Laing N, Mall S, Wonkam A. Perceptions of parents of children with hearing loss of genetic origin in South Africa. J Community Genet. 2019 Jul;10(3):325–33.

[7] Tabuchi S. Auditory dysfunction in patients with cerebrovascular disease. Sci World J. 2014 Oct 23;2014:e261824–8.

[8] Xipeng L, Ruiyu L, Meng L, Yanzhuo Z, Kaosan G, Liping W. Effects of diabetes on hearing and cochlear structures. J Otol. 2013 Dec 1;8(2):82–7.

[9] Appier JM, Goodrich LV. Connecting the ear to the brain: molecular mechanisms of auditory circuit assembly. Prog Neurobiol. 2011 Apr;93(4):488–508.

[10] Gates GA, Anderson ML, McCurry SM, Feneley MP, Larson EB. Central auditory dysfunction as a harbinger of Alzheimer dementia. Arch Otolaryngol Head Neck Surg. 2011 Apr;137(4):390–5.

[11] Gates GA, Beiser A, Rees TS, D'Agostino RB, Wolf PA. Central auditory dysfunction may precede the onset of clinical dementia in people with probable Alzheimer’s disease. J Am Geriatr Soc. 2002 Mar;50(3):482–8.

[12] Hung S-C, Liao K-F, Muo C-H, Lai S-W, Chang C-W, Hung H-C. Hearing loss is associated with risk of Alzheimer’s disease: a case-control study in older people. J Epidemiol. 2015 Aug 5;25(8):517–21.

[13] Idrizbegovic E, Hederstierna C, Dahlquist M, Rosenhall U. Short-term longitudinal study of central auditory function in Alzheimer’s disease and mild cognitive impairment. Dement Geriatr Cogn Disord Extra. 2013 Jan;3(1):468–71.

[14] Chiaraavalloti A, Fuccello E, Martorana A, Ricci M, Giacomini PG, Schillaci O, et al. Hearing and cognitive impairment: a functional evaluation of associative brain areas in patients affected by Alzheimer’s disease. Funct Neurol. 2019 Mar;34(1):15–20.

[15] Tai S-Y, Shen C-T, Wang L-F, Chien C-Y. Association of sudden sensorineural hearing loss with dementia: a nationwide cohort study. BMC Neurol. 2021 Feb 25;21(1):88.

[16] Lin FR, Metter EJ, O’Brien RJ, Resnick SM, Zonderman AB, Ferrucci L. Hearing loss and incident dementia. Arch Neurol. 2011 Feb;68(2):214–20.

[17] Lin FR, Yaffe K, Xue Q-L, Harris TB, Purchase-Helzner E, et al. Hearing loss and cognitive decline among older adults. JAMA Intern Med [Internet]. 2013 Feb 25 [cited 2021 Apr 22];173(4). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3869227/.

[18] Folmer RL, Vachhani JJ, Theodoroff SM, Ellinger R, Riggins A. Auditory processing abilities of parkinson’s disease patients. BioMed Res Int. 2017;2017:2618587.

[19] Guehl D, Burbaud P, Lorenzi C, Ramos C, Bioulac B, Semal C, Folmer RL, Vachhani JJ, Theodoro et al. Auditory temporal processing in Parkinson’s disease. Funct Neurol. 2019 Jul;35:1211–21.

[20] Hussein M, Koura R. Auditory and vestibular dysfunction in patients with Parkinson’s disease. Arch Neurol. 2019 Jul;35:1211–21.

[21] Lai S-W, Liao K-F, Lin C-L, Lin C-C, Sung F-C. Hearing loss may be a non-motor feature of Parkinson’s disease in older people in Taiwan. Eur J Neurol. 2014 May;21(5):752–7.

[22] Pisani V, Sisto R, Moleti A, Di Mauro R, Pisani A, Brusa L, et al. An investigation of hearing impairment in de-novo Parkinson’s disease patients: a preliminary study. Parkinsonism Relat Disord. 2015 Aug;21(8):987–91.
[23] Lewald J, Schirm SN, Schwarz M. Sound lateralization in Parkinson's disease. Cogn Brain Res. 2004 Nov;21(3):335–41.

[24] Vitale C, Marcelli V, Allocca R, Santangelo G, Riccardi P, Erro R, et al. Hearing impairment in Parkinson's disease: expanding the nonmotor phenotype. Mov Disord. 2012 Oct;27(12):1530–5.

[25] Lin MY, Gutierrez PR, Stone KL, Yaffe K, Ensrud KE, Fink HA, et al. Vision impairment and combined vision and hearing impairment predict cognitive and functional decline in older women. J Am Geriatr Soc. 2004 Dec;52(12):1996–2002.

[26] Bosmans J, Jorissen C, Saradalekshmi KR, Shilen N, Suresh PA, Banerjee M. Impaired hearing and vestibular decline on cognition in Alzheimer’s disease: a prospective longitudinal study protocol (Gehoor, Evenwicht en Cognitie, GECCO). BMJ Open. 2020 Sep 1;10(9):e039601.

[27] Kiely KM, Gopinath B, Mitchell P, Luszcz M, Anstey KJ. Cognitive, health, and sociodemographic predictors of lifelong decline in hearing acuity among older adults. J Gerontol A Biol Sci Med Sci. 2012 Sep;67(9):997–1003.

[28] Rosenhall U, Nordin V, Sandström A, Ahlsén G, Gillberg C. Autism and hearing loss. J Autism Dev Disord. 1999 Oct;29(5):349–57.

[29] Cross JH, Araor R, Heckemann RA, Gunry N, Chong K, Carr L, et al. Neurological features of epilepsy, ataxia, sensorineural deafness, tubulopathy syndrome. Dev Med Child Neurol. 2013 Sep;55(9):846–56.

[30] Lin C-Y, Kuo S-H. Cerebellar Ataxia and Hearing Impairment. JAMA Neurol. 2017 Feb 1;74(2):243.

[31] Fitzgerald MP, Reynolds A, Garvey CM, Norman G, King MD, Hayes BC. Hearing impairment and hypoxia ischaemic encephalopathy: Incidence and associated factors. Eur J Paediatr Neurol. 2019 Jan;23(1):81–6.

[32] Silva J, Sousa M, Mestre S, Nzwalo I, Nzwalo H. Cortical deafness of following bilateral temporal lobe stroke. J Stroke Cerebrovasc Dis. 2020 Jul 1;29(7):104827.

[33] Bayer C, Pitschelatow G, Hannemann N, Linde J, Reichard J, Pensold D, et al. DNA methyltransferase 1 (DNMT1) acts on neurodegeneration by modulating proteostasis-relevant intracellular processes. Int J Mol Sci. 2020 Jul 30;21(15):5420.

[34] Alex AM, Saradalekshmi KR, Shilen N, Suresh PA, Banerjee M. Genetic association of DNMT variants can play a critical role in defining the methylation patterns in autism. IUBMB Life. 2019 Jul;71(7):901–7.

[35] Hahn A, Pensold D, Bayer C, Tittelmeier J, González-Bermúdez L, Marx-Blümel L, et al. DNA methyltransferase 1 (DNMT1) function is implicated in the age-related loss of cortical interneurons. Front Cell Dev Biol [Internet]. 2020 [cited 2021 Jul 4];8. Available from: https://www.frontiersin.org/articles/10.3389/fcell.2020.00639/full.

[36] Choufani S, Cytnyraubm C, Chung BHY, Turinsky AL, Grafodatskaya D, Chen YA, et al. NSD1 mutations generate a genome-wide DNA methylation signature. Nat Commun. 2015 Dec 22;6:10207.

[37] Fallah MS, Szarics D, Robson CM, Eubanks JH. Impaired regulation of histone methylation and acetylation underlies specific neurodevelopmental disorders. Front Genet. 2021 Jan 8;11:613098.

[38] Altuna M, Urdañoz-Casado A, Sánchez-Ruiz de Gordo J, Zelaya MV, Labarga A, Lepesant JMI, et al. DNA methylation signature of human hippocampus in Alzheimer's disease is linked to neurogenesis. Clin Epigenetics. 2019 Jun 19;11(1):91.

[39] Li J, Hart RP, Mallimo EM, Swerdlow MR, Kusneov AW, Herrup K. EZH2-mediated H3K27 trimethylation mediates neurodegeneration in ataxia-telangiectasia. Nat Neurosci. 2013 Dec;16(12):1745–53.

[40] Adam MA, Isles AR. EHMT1/GLP: biochemical function and association with brain disorders. Epigenomes. 2017 Dec;1(3):15.

[41] Vallianatos CN, Iwase S. Disrupted intricacy of histone H3K4 methylation in neurodevelopmental disorders. Epigenomics. 2015;7(3):503–19.

[42] Cuvertino S, Hartill V, Colyer A, Garner T, Nair N, Al-Gazali L, et al. A restricted spectrum of missense KMT2D variants cause a multiple malformations disorder distinct from Kabuki syndrome. Genet Med. 2020 May;22(5):867–77.

[43] Shen E, Shulha H, Weng Z, Akbarian S. Regulation of histone H3K4 methylation in brain development and disease. Philos Trans R Soc Lond B Biol Sci. 2016 Sep 26;369(1652):20130514.

[44] Coll-Tané M, Gong NN, Beller SJ, van Renssen LV, Kurtz-Nelson EC, Szuperak M, et al. The CHD8/CHD7/Kismet family links blood-brain barrier glia and serotonin to ASD-associated sleep defects. Sci Adv. 2021 Jun;7(23):eabe2626.

[45] Bartlett EL. The organization and physiology of the auditory thalamus and its role in processing acoustic features important for speech perception. Brain Lang. 2013 Jul;126(1):29–48.

[46] Kurono Y, Lim DJ, Mogi G. Middle ear and Eustachian tube. Mucosal Immunol. 2005;1509–16.

[47] Moser T, Starr A. Auditory neuropathy – neural and synaptic mechanisms. Nat Rev Neurol. 2016 Mar;12(3):135–49.

[48] Fuchs PA. Time and intensity coding at the hair cell's ribbon synapse. J Physiol. 2005 Jul 1;566(Pt 1):7–12.

[49] Moser T, Neef A, Khimich D. Mechanisms underlying the temporal precision of sound coding at the inner hair cell ribbon synapse. J Physiol. 2006 Oct 1;576(Pt 1):55–62.

[50] Summers MJ. Neuropsychological consequences of right thalamic haemorrhage: case study and review. Brain Cogn. 2002 Oct;50(1):129–38.

[51] Schmahmann JD. Vascular syndromes of the thalamus. Stroke. 2003 Sep;34(9):2264–78.

[52] Agarwal N, Quinn JC, Zhu X, Mammis A. Neuroanatomical considerations of isolated hearing loss in thalamic hemorrhage. Int Discip Neurosurg. 2016 Dec 1;4:42–4.

[53] Lee J-H, Park S-S, Ahn J-Y, Heo J-H. Bilateral sudden hearing difficulty caused by bilateral thalamic infarction. J Clin Neurol Seoul Korea. 2017 Jan;13(1):107–8.

[54] Reid SM, Modak MB, Berkowitz RG, Reddihough DS. A population-based study and systematic review of hearing loss in children with cerebral palsy. Dev Med Child Neurol. 2011;53(11):1038–45.

[55] Shen Y, Ye B, Chen P, Wang Q, Fan C, Shu Y, et al. Cognitive decline, dementia, Alzheimer's disease and presbycusis: examination of the possible molecular mechanism. Front Neurosci [Internet]. 2018 [cited 2021 Jul 3];12:394. Available from: https://www.frontiersin.org/articles/10.3389/fnins.2018.00394/full.

[56] Alvarado JC, Fuentes-Santamaría V, Melgar-Rojas P, Valero ML, Gabaldón-Ull MC, Miller JM, et al. Synergistic effects of free radical scavengers and cochlear vasodilators: a new otoprotective strategy for age-related hearing loss. Front Aging
Neurosci [Internet]. 2015 [cited 2021 Jul 3];7:86. Available from: https://www.frontiersin.org/articles/10.3389/fnagi.2015.00086/full.

[57] Hasson D, Theorell T, Wallén MB, Leineweber C, Canlon B. Stress and prevalence of hearing problems in the Swedish working population. BMC Public Health. 2011 Feb 23;11(1):130.

[58] Szczepak AJ, Mazurek B. Neurobiology of stress-induced tinnitus. Curr Top Behav Neurosci. 2021 Feb 19;327–47.

[59] Levin SG, Godukhin OV. Modulating effect of cytokines on mechanisms of synaptic plasticity in the brain. Biochem Biokhimiia. 2017 Mar;82(3):264–74.

[60] Deng D, Wang W, Bao S. Diffusible tumor necrosis factor-alpha (TNF-α) promotes noise-induced parvalbumin-positive (PV+) Neuron loss and auditory processing impairments. Front Neurosci. 2020 Oct 12;14:573047.

[61] Dhukhwa A, Bhatta P, Sheth S, Korrapati K, Tieu C, Mamillapalli C, et al. Targeting inflammatory processes mediated by TRPVI and TNF-α for treating noise-induced hearing loss. Front Cell Neurosci [Internet]. 2019 [cited 2021 Jul 3];13:444. Available from: https://www.frontiersin.org/articles/10.3389/fncel.2019.00444/full.

[62] Cao X-J, Lin L, Sugden AU, Connors BW, Oertel D. Nitric oxide-mediated plasticity of interconnections between t-stellate cells of the ventral cochlear nucleus generate positive feedback and constitute a central gain control in the auditory system. J Neurosci. 2019 Jul 31;39(31):6095–107.

[63] Hockley A, Berger JJ, Smith PA, Palmer AR, Wallace MN. Nitric oxide regulates the firing rate of neuronal subtypes in the guinea pig ventral cochlear nucleus. Eur J Neurosci. 2020;51(4):963–83.

[64] Tripathi MK, Kartawy M, Amal H. The role of nitric oxide in brain disorders: autism spectrum disorder and other psychiatric, neurological, and neurodegenerative disorders. Redox Biol. 2020 Jul 1;34:101567.

[65] Mitchell BL, Thorp JS, Evans DM, Nyholt DR, Martin NG, Lupton MK. Exploring the genetic relationship between hearing impairment and Alzheimer’s disease. Alzheimers Dement Diagn Assess Dis Monit. 2020;12(1):e12108.

[66] Korver AMH, Smith RJH, Van Camp G, Schleiss MR, Bitner-Glindzicz MAK, Lustig LR, et al. Congenital hearing loss. Nat Rev Dis Primer. 2017 Jan 12;3:16094.

[67] Venkatesh MD, Moorchung N, Puri B. Genetics of nonsyndromic hearing loss. Med J Armed Forces India. 2015 Oct;71(4):363–8.

[68] Egilmez OK, Kalcioğlu MT. Genetics of nonsyndromic congenital hearing loss. Scientifica. 2016 Feb 18;2016:e7576064–9.

[69] Snoeckx RL, Huygen PLM, Feldmann D, Marlin S, Denoyelle F, Waligora J, et al. GJB2 mutations and degree of hearing loss: a multicenter study. Am J Hum Genet. 2005 Dec;77(6):945–57.

[70] Tishkoff SA, Reed FA, Friedlaender FR, Ehret C, Ranciaro A, Froment A, et al. The genetic structure and history of Africans and African Americans. Science. 2009 May 22;324(5930):1035–44.

[71] Layman WS, Zuo J. Epigenetic regulation in the inner ear and its potential roles in development, protection, and regeneration. Front Cell Neurosci. 2015 Jan 7;8:446.

[72] Nagalski A, Puuelles L, Dabrowski M, Wegierski T, Kuznicki J, Wisniewska MB. Molecular anatomy of the thalamic complex and the underlying transcription factors. Brain Struct Funct. 2016;221:2493–510.