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Narrative Review

Olivocochlear System Neurobiology and Pathophysiology in Relation to Psychiatric Disorders: A Perspective

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Abstract

Recent research indicates an association between auditory efferent abnormalities and the core symptoms of several psychiatric disorders. Neurobiological and electroacoustic studies further implicate CNTNAP2 gene mutations in these efferent anomalies. The medial olivocochlear bundle (MOCB), originating from the periolivary region surrounding the medial superior olive, regulates outer hair cell activity and modulates basilar membrane motion, thereby influencing cochlear input transmission. Impaired neurotransmission along the MOCB or structural alterations of the medial superior olive may lead to efferent auditory dysfunctions that remain undetected by standard audiological assessments. This review explores these mechanisms in relation to auditory hallucinations, selective mutism, tinnitus, and autism spectrum disorder.

Keywords: Selective Mutism, Auditory Hallucination, Tinnitus, Hyperacusis

Introduction

More than seventy-five years have passed since the olivocochlear system was discovered and first described by Grant Litster Rasmussen in 1946.[1] The olivocochlear system consists of two anatomical subsystems: the medial bundle originates from the periolivary region around the medial superior olive, and the lateral bundle that originates from the lateral superior olive.[2] Because of the inability to record and measure activity of unmyelinated axons, a precise image of the lateral olivocochlear bundle function in humans still unavailable,[3] although some theories are established based on animal models. However, medial olivocochlear bundle (MOCB) has received the greatest research attention, and its mechanisms of function have been investigated since its discovery. As mentioned, the medial efferent system origin from the periolivary region, and make synapses with multipolar cells within the posteroventral cochlear nucleus on the contralateral side, the fibers, then, continue to run all the way to cochlea and innervate outer hair cells (OHCs).[2,4]

Electrophysiological and electroacoustic procedures facilitate the investigation of auditory efferent system functions, which are believed to enhance afferent pathway input in challenging hearing conditions, and protect against noise-induced hearing loss via medial olivocochlear projections to outer hair cells (OHCs) and supporting cells.[5] Efferent innervation to cochlea triggers hyperpolarization of OHCs by activating the calcium-activated potassium channels (SK2), which relax Prestin molecules and thereby amplify basilar membrane motion.[6] These voltage dependent length changes of OHCs have been confirmed as a protective mechanism in numerous animal studies, but have not yet been confirmed in humans.[3]

γ-aminobutyric acid (GABA) is an inhibitory neurotransmitter that has been found to be associated with auditory processing. The effects of GABA can be observed in both the brainstem and higher brain regions. For instance, decreased GABA levels in the inferior colliculus play a role in age-related alterations of neural circuits involved in auditory processing.[7] Furthermore, decreased levels of GABA leads to excessive release of acetylcholine from efferent terminals of the MOCB to the junction between efferent fibers and OHCs, resulting in hyperpolarization and changes in OHCs electromotility.[2] This alteration in OHC electromotility can suppress otoacoustic

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emissions (OAEs); therefore, abnormalities in the efferent auditory system can be indirectly assessed by testing OAE suppression. To that end, OAE suppression was investigated by researchers where the descending auditory system is thought to be implicated.

The crucial role of OHCs on transmission of auditory signals can be demonstrated by dysfunction in OHC electromotility, which is mediated by Prestin molecules. Children with rare heterozygous Prestin mutations are characterized by congenital or pre-lingual non-syndromic hearing loss with variable degrees of the impairment.[8,9] That indicates Prestin-mediated cochlear amplification in humans.

Indeed, OHCs are not the only terminal elements of the peripheral auditory efferent system, as supporting cells (SCs) also appear to have a relationship with medial olivocochlear neurons. A supporting cell gap junction-mediated efferent pathway has been proposed after the observation of MOCB nerve endings, postsynaptic acetylcholine receptors, and presynaptic vesicular acetylcholine transporters in and around the SCs area. This SC-Mediated efferent pathway is believed to enhance the effect of acetylcholine on OHCs electromotility.[5] In other words, medial olivocochlear fibers can modulate OHC motion, consequently, MOCB activity alters the amplitude of normal OHC output, namely the otoacoustic emissions (OAEs). Based on this, OAEs suppression is used to non-invasively and indirectly assess the strength of MOCB reflex.

MOCB reflex is one of the two major auditory efferent mechanisms, and is less well known than the second mechanism, the middle ear acoustic reflex, which is dominantly mediated by the stapedius muscle when a low frequency intense enough sound is presented to one or both ears.[10]

This perspective discusses the latest knowledge of the physiology and neurobiology of the olivocochlear system and its relationship to behavior, therefore proposes a hypothesis of decreased inhibition activity of the MOCB, which can lead to reduced suppression of auditory signals and justifies the core symptoms of many psychiatric disorders.

Olivocochlear System Dysfunction Effects on Behavior

Auditory Hallucinations

Auditory hallucinations are defined as the experience of auditory perceptions in the absence of corresponding external stimuli[11]. When these involve speech, they are referred to as auditory verbal hallucinations (AVH). Many conditions, medications and diseases can result in hallucinations, not only in psychotic contexts but also in the non-psychotic population, such as those with borderline personality disorder.[12,13] bipolar disorder, and major depressive disorder.[14] Since AVHs are among the most prevalent positive symptoms of schizophrenia,[15] they have been extensively studied in this population. Mainly, the literature suggests two potential etiologies of auditory hallucinations: misattribution of inner speech, and hyperexcitability of auditory cortex. However, the pathophysiology underlying the auditory features of schizophrenia remains under debate.

The inner speech model (self-directed speech) is a prominent psychological theory which had an extensive study for decades though it remains controversial and unreliable. It represents a complex cognitive mechanism that arises from both interoception and audition, reflected by measurable muscle activity occurring nonverbally in the speech musculature.[16] It is not completely clear how the inner speech relates to AVH, however, AVHs were considered as episodes of misattributed inner speech arising from self-monitoring abnormalities.[17]

In the inner speech model, the auditory cortices and the inferior frontal gyrus are thought to be involved in AVHs. To test this theory, researchers have used structural neuroimaging and measured regional cerebral blood flow during auditory hallucinations to identify which brain areas are specifically active. Positron emission tomography (PET) studies of language tasks support an association between increased activity in a network of cortical language areas and generation of auditory hallucinations,[18] which support the psychological concept of AVHs as a sound of inner speech.

In contrast, a recent systematic review and meta-analysis[19] found neither significant activity nor structural abnormalities at Broca's area or Heschl's gyrus during auditory verbal hallucinations in patients with schizophrenia, contrary to inner speech theory. Furthermore, no significant structural abnormalities were observed in the arcuate fasciculus when comparing hallucinators to non-hallucinators. Rather, the same meta-analysis found the left insular cortex to be both significantly active during AVHs, and to have

a significantly reduced grey matter volume in hallucinators compared to non-hallucinators.[19] However, the conclusions of published meta-analyses should be interpreted with caution. Most of the analyzed studies investigated cerebral activity during the hallucination episodes -specifically after participants began to perceive auditory hallucinations- which makes neuroimaging results suitable for confirming evident activity but not for excluding non-evident activity, given that neural activity changes may begin prior to the perception of auditory hallucination.

There has been growing neurobiological research on AVHs. Actually, studies investigating the neurobiological mechanisms of AVHs as a positive symptom of schizophrenia are far more common than studies examining AVHs themselves, regardless of population. Some studies revealed that excessive release of acetylcholine due to reduced GABA production, leads to hypersensitivity of OHCs micro-mechanisms in patients with schizophrenia. This may explain why these patients, compared to healthy controls, demonstrate significantly greater contralateral suppression of otoacoustic emissions -reflecting an increase in inhibitory effect of the efferent auditory pathway, particularly in the right ear.[20] The larger contralateral suppression in the right ear suggests functional asymmetry of the medial olivocochlear system in patients with schizophrenia.[21] In general, brain abnormalities in schizophrenia have been reported to be bilateral, but when unilateral, they are typically left-sided.[22]

There is strong evidence that schizophrenic patients- particularly those with auditory hallucinations- have anatomical asymmetry of the planum temporale.[23] Moreover, cortical thickness alterations have been confirmed in individuals with long-term schizophrenia, with cortical thinning reported in the right inferior frontal cortex, left lateral temporal cortex (including superior and middle temporal cortices), and right temporal pole.[24]

It can be suggested that different cognitive and neural mechanisms underlie auditory hallucinations. Several observations support this suggestion. First, AVH occur in the general population with a prevalence of 3-7%, and about 60% of adults reported to experience AVH do not have any mental disorder. This indicates that both patients and non-patients may experience AVH.[25] Second, some individuals exhibit varying degrees of direct and/or indirect control over their AVHs, such individuals are less likely to seek treatment even though they experience real psychosis.[26] Third, the persistence of AVHs in most cases of schizophrenia despite treatment with antipsychotics indicates the involvement of at least two neurotransmission systems in the emergence of AVHs, rather than a single dopaminergic effect (since the currently approved antipsychotics act primarily by blocking neuro-transmission at dopamine D2 receptors).[27,28] Moreover, antipsychotic agents currently used for schizophrenia fail to reverse the core negative symptoms and neurocognitive impairments[27], supporting the suggestion that both neurocognitive deficits and negative symptoms are primary intrinsic features of the underlying pathophysiology of schizophrenia, rather than an adverse side effect of treatment.[29]

Hence, the documented reduction in gray matter volume in several cortical regions of schizophrenic hallucinators is likely the main pathological substrate underlying both neurocognitive impairments and auditory hallucinations. These diverse neural mechanisms affect the auditory system in different ways, resulting in variations in the phenomenological features of auditory hallucinations and reflecting specific circuitry within brain structures and functions. and reflecting specific circuitry within brain structures and functions.

Selective Mutism

Selective mutism is a complex psychiatric disorder and one of the most challenging communicative disorders, with a general prevalence of 0.76% in both native and immigrant children[30] and a prevalence of 0.57% in native preschoolers.[31] Although slight differences exist across studies, all report a prevalence below 1%, indicating that only a small percentage of cases are detected. This low prevalence may partly explain the limited amount of published research on the neurobiological mechanisms underlying selective mutism. However, an increasing number of studies have focused on the behavioral patterns and behavioral treatments of SM.

Speech avoidance- the core behavior of SM- has been suggested to result from difficulty in processing incoming sounds during vocalization,[32] caused by reduced auditory efferent activity that prevents simultaneous sound processing and self-vocalization.[33]

However, auditory processing abnormalities are not necessarily comorbid with SM, as can be inferred from the literature.

A neurobiological model of Stress-Induced Cortisol Secretion has also suggested an elevated threshold of middle ear acoustic reflex caused by increased cortisol secretion in some individuals under social stress,[34] thereby contributing to the emergence of SM and social anxiety disorder.[32] Stress induced cortisol secretion is mediated by the Hypothalamic-Pituitary-Adrenal Axis (HPA), which is controlled by the medial parvocellular division of the hypothalamic paraventricular nucleus (PVN) and triggered by the release of cortico-tropin-releasing hormone (CRH).[35] CRH stimulates Corticotrophs in the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH) into the bloodstream[36] which in turn stimulates the zona fasciculata region of the adrenal glands to secrete cortisol in response to long-term stressors.

Researchers investigating the physiological mechanisms of cortisol, glucocorticoids, and mineralocorticoids on auditory perception and the acoustic reflex (an efferent mechanism) have widely used animal models. In humans, it has been possible to measure cortisol levels in the blood and observe their elevation in healthy subjects exposed to psychological stressors. These individuals also show increased middle ear reflex thresholds compared to their own acoustic reflex thresholds before stress exposure.[34] The neurobiological model may explain the high comorbidity of social anxiety in selectively mute children. Although selective mutism is not social anxiety disorder- or at least it has a unique component beside social phobia- this interpretation is supported by studies examining the prevalence of social anxiety disorder among children diagnosed with SM, where comorbid anxiety disorders, including social anxiety, are undiagnosable in approximately 20% of cases.[37]

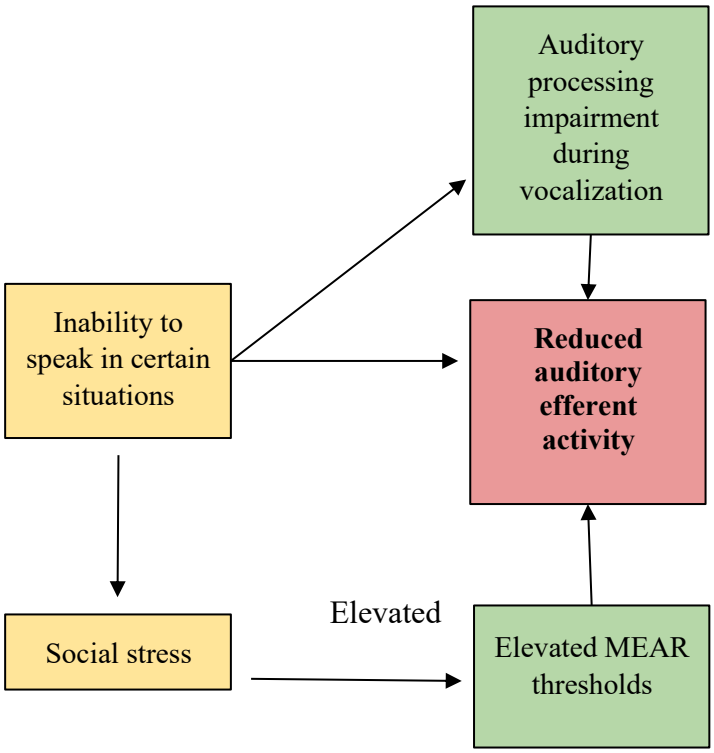

Figure 1. Cortisol Secretion as a Result of Stress will Elevate Thresholds of Middle Ear Reflex (MEAR) and Subsequently, Reduce Auditory Efferent Activity. The neurobiological model explains the high comorbidity between SM and anxiety disorders, specifically those in social settings as social anxiety disorder.

GABAergic inputs to the paraventricular nucleus (PVN) directly regulate the HPA axis. These inputs originate from both the forebrain and the hypothalamus and project to CRH-containing neurons.[38] Therefore, decreased GABA levels at forebrain regions and hypothalamus would increase the release of CRH, therefore, increase cortisol secretion. Interestingly, dysfunctional GABAergic neurotransmission in the

auditory cortex[39] along with reduced GABA levels in the inferior colliculus- including decreased numbers of GABA immunoreactive neurons, reduced glutamic acid decarboxylase activity, lower basal GABA levels and release, decreased $GABA_B$ receptor binding, as well as reduced numbers of presynaptic terminals- has been associated with poor speech discrimination and impaired auditory processing in presbycusis.[7] These findings may establish a relation between stress-induced cortisol secretion and processing deficits during vocalization in considerable proportion of patients with selective mutism.

GABAergic synapses and GABA transmission have been strongly proposed to be associated with the CNTNAP2 (also known as CASPER2) gene. The *Contactin-associated protein-like 2* (CNTNAP2) has been implicated in the severity of language delay in autism,[40] and its variants are associated with several complex disorders, including intellectual disability, dysarthria, language and speech delays, attention deficit hyperactivity disorder (ADHD), epilepsy, obsessive compulsive disorder[41] schizophrenia[42] as well as specific language impairment.[43] However, despite its association with many complex neurological disorders, the precise roles it plays in normal neurodevelopment remain inadequately understood.

The wide range of disorders for which the CNTNAP2 variants confer a genetic predisposition suggests a shared impairment in its functional contacts.[44] CNTNAP2 encodes the CASPR2 protein, a member of the neurexin superfamily of cell-adhesion molecules, which has been proposed to play several molecular roles related to development of the nervous system in mammals.[45] CNTNAP2 is expressed primarily in the cerebral cortex, with the highest expression in the second to fifth layers of temporal and frontal cortices. Furthermore, its expression has been detected in the thalamus, amygdala, and striatum.[44] Given that selective mutism (SM) is the disorder in question, studying the functional impairments resulting from CNTNAP2 mutations in affected individuals may help clarify the mechanisms underlying its core symptoms. The single-nucleotide polymorphism rs2710102, a variant of CNTNAP2, has been found to be associated with an increased risk of SM in family-based studies[46]. This same variation has also been suggested to contribute to subthreshold autistic traits.[47] Studies using animal models have shown that CASPR2 plays a role in the development and stability of GABAergic synapses.[48]

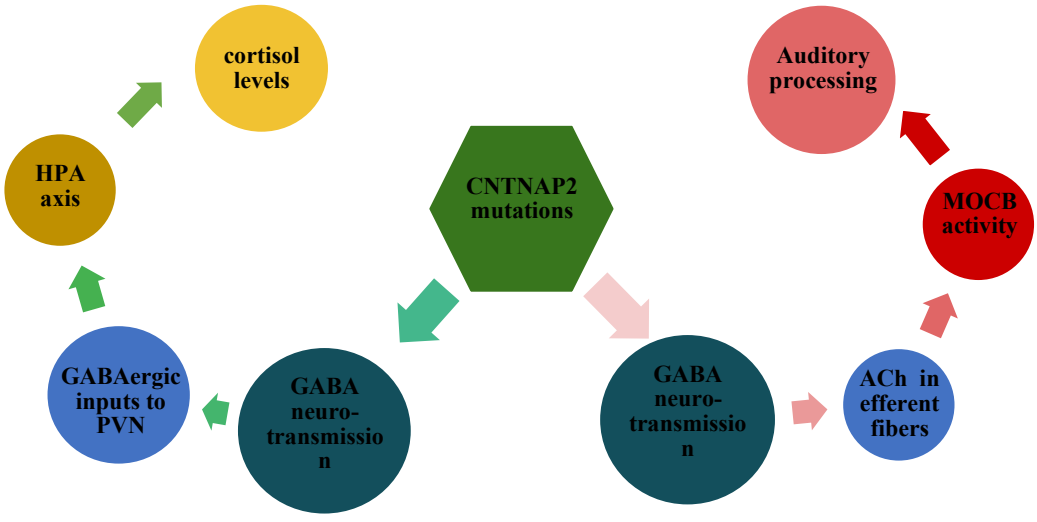

Figure 2. The Association between Auditory Processing Deficit Model and the Neurobiological Model of SM Etiology. This association justifies the difference in results of published studies, and explains that, theoretically, the two models are accurate and appropriate to each other.

We can better understand the role of typical CNTNAP2 expression in GABAergic transmission and function by examining CNTNAP2 knockout animal models. Such investigations have been conducted in various brain areas, including the medial geniculate nucleus,[49] visual cortex, and hippocampus, and have

revealed age-dependent inhibitory deficits, which indicates a developmental role for CNTNAP2 expression in the formation and maintenance of GABAergic synapses in the visual cortex.[50]

Behaviorally, CNTNAP2 mutant mice exhibit a dissociation in auditory processing abilities: impairments in temporal silent gap detection tasks, but, interestingly, enhanced pitch (frequency) discrimination.[49] However, generalizing conclusions of the published research requires caution, as current evidence cannot accurately or confidently predict the effect of CNTNAP2 expression on GABAergic transmission within the auditory pathway.

Individuals with auditory processing deficits exhibit higher left-ear suppression values compared to right-ear suppression values, in opposite of typical individuals where contralateral suppression values are higher in the right ear than in the left ear.[51] This difference between individuals with auditory processing disorders and healthy individuals in contralateral suppression values between left and right ears can be explained in two ways. First, individuals with auditory processing disorders and healthy individuals. Second, there may be a reduction in GABA levels and their inhibitory effect in the right hemisphere, resulting in elevated ACh levels and increased excitation of OHCs micromechanisms, which would elevate contralateral suppression values in the left ear. Theoretically, the second scenario is more likely, given the effect of the CNTNAP2 mutation on GABA synapses and transmission.

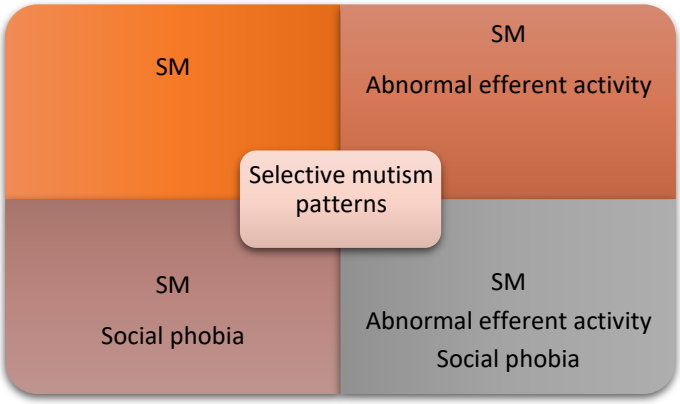

Figure 3. The Diversity of Comorbidity Patterns in Selective Mutism. Cases of SM exhibit inconsistent comorbidity of auditory efferent dysfunction and social phobia.

Based on the findings mentioned above, anomalies in the auditory efferent pathways (including MOCB activity) cannot be considered an etiology of SM, due to the lack of evidence and the inconsistency of the coexisting dysfunction shown in Figure 3. Instead, reduced activity of MOCB, cortisol levels elevation, and social phobia/anxiety should be viewed as comorbid conditions associated with SM, all originating from different variants of the CNTNAP2/CASPR2 gene. Taken together, SM cannot be considered an independent disorder, it is the outward symptom of multifaceted underlying pathophysiologies.

Hyperacusis in Autism Spectrum Disorders (ASD)

Many studies indicate a high prevalence of various forms of decreased sound tolerance among the autistic population. Zachary J Williams and his colleagues, in their meta-analysis, estimated that the lifetime prevalence of hyperacusis among individuals with ASD ranges between 50.37 and 69.76%.[52] Besides its effects on quality of life, the high prevalence of hyperacusis highlights the need to understand the underlying neurobiological mechanisms, and to develop targeted treatment strategies.

Salicylate, an anti-inflammatory compound known to induce hyperacusis, is frequently administered to animal models to elucidate its mechanisms of action. Two primary effects have been consistently observed in both human patients and experimental rodents following high-dose administration (>150 mg/kg): (1) an upregulation of corticosterone, the primary stress hormone, and (2) a suppression of distortion product otoacoustic emissions (DPOAEs).[53] Dysregulation of corticosterone, resulting from disturbances in the

hypothalamic-pituitary-adrenal (HPA) axis, may impair synaptic transmission at the junction between inner hair cells and auditory nerve fibers,[54] consequently reducing neural synchrony within the auditory nerve.[55] Notably, reduced auditory neural synchrony is also characteristic of autistic individuals, particularly during the processing low-level sound features.[56] Typically, diminished auditory neural synchrony compromises the temporal precision with which sound information is transmitted from the cochlea to the brainstem. A reduction in OAEs due to disrupted outer hair cell efferent activity may therefore be proposed as a downstream consequence of a disturbed afferent signal stream.

Autism spectrum disorder (ASD) is a neuro-developmental disorder characterized by varying degrees of difficulty in social interaction and communication, and it arises from heterogeneous etiologies.[57] ASD is commonly comorbid with hyperacusis- a disorder of loudness perception characterized by consistently exaggerated discomfort responses to sounds that are neither intrinsically threatening nor objectively loud.[58] Children with ASD often exhibit deficits across multiple sensory domains. However, in contrast to visual and proprioceptive abnormalities—whose frequency increases with autism severity—auditory sensory deficits remain relatively stable in frequency regardless of ASD severity.[59] Accordingly, auditory abnormalities may be considered a core feature of ASD rather than a secondary comorbidity, and may arise from pathological influences on brainstem nuclei. This interpretation is supported by auditory brainstem response (ABR) findings, which show prolonged latencies and atypical cortical responses to sound in newborns who were later diagnosed with autism.[60]

Abnormal ABR patterns can be explained by morphological abnormalities of superior olivary complex neurons, especially -and more prominently- those of the medial superior olive. Beside significant alterations in the orientation of its primary dendrites, the neurons comprising the medial superior olive are significantly smaller and more rounded than those observed in corresponding animal controls. In addition, fewer stellate and fusiform neurons, but many more round or oval neurons, have been reported in the medial superior olive. However, in the lateral superior olive, the number of neurons is preserved.[61] Such dysmorphologies of the medial superior olive have also been confirmed in humans[62] and significantly contribute to the hearing difficulties that are commonly observed in autistic population.[63] Nevertheless, the exact impact of these structural deficits on auditory functioning remains incompletely understood.

In parallel with those brainstem-level findings, increasing evidence also points to genetic factors that may contribute to broader neurodevelopmental vulnerabilities in ASD. For example, growing research supports a role for CNTNAP2 in neuroplasticity, as demonstrated by the brain disconnectivity observed in animal models carrying CNTNAP2 variants. This state of "disconnectivity" is considered a risk factor, rather than a direct cause, of autism.[64] It is also worth mentioning that CNTNAP2 variants have also been associated with selective mutism, various language deficits, language regression, and even stuttering.[65]

Electroacoustic assessments also provide evidence of functional abnormalities in individuals with ASD. Specifically, the strength of efferent inhibition has been shown to correlate with subjectively reported hyperacusis severity, with autistic children exhibiting severe hyperacusis demonstrating significantly reduced medial olivocochlear (MOC) suppression of transient evoked otoacoustic emissions (TEOAEs).[66] When considered alongside the previously reported morphological anomalies of MOC neurons in both humans and animal models, these observations suggest a reduction in MOC inhibitory function. Such a deficit likely intensifies cochlear amplifier gain, which is behaviorally expressed as hyperacusis.

Tinnitus

Tinnitus is a central neurological and auditory disorder with a high prevalence, diverse types, and multiple etiologies, but no universally effective cure. Many factors influence whether altered efferent auditory system function is involved in the emergence of tinnitus. Among the most influential are individuals' sound-tolerance levels,[67] the specific type of tinnitus, and the assessment methods used to evaluate the efferent system -particularly the medial olivocochlear (MOC) bundle -appear to be the most influential.

Given the heterogeneity of tinnitus and the substantial variability in individual experiences, it may be advantageous to examine more homogeneous patient

groups when investigating proposed mechanisms of tinnitus.[68] By reviewing the literature, two distinct populations can be identified: individuals with tinnitus who also exhibit hearing impairment, and individuals with tinnitus who demonstrate clinically normal hearing. To minimize bias when examining the latter group, this perspective considers only those studies that excluded participants with any past or present otological conditions, ototoxic exposure, or neurological pathology. Nevertheless, even among patients classified as having normal hearing, it is plausible that subtle hearing loss exists at frequencies above 8,000 Hz or that hearing was better prior to tinnitus onset.[69] Thus, future studies exploring the role of the efferent auditory system in tinnitus generation should carefully account for participants' hearing status, including the possibility of pre-tinnitus auditory decline.

When investigating tinnitus pathophysiology within the mentioned patient subgroups, it is important to recognize that several confounding factors can influence efferent auditory activity. Foremost among these is sound-level tolerance, which appears to be a critical factor underlying the variability in contralateral OAE suppression both across tinnitus studies and among participants within the same study. For example, greater contralateral suppression of distortion product otoacoustic emissions -indicating MOCB hyperactivity- has been reported in individuals with low uncomfortable loudness levels (UCLs) or low sound tolerance, regardless of whether they have tinnitus.[67] In contrast, although no differences in sound sensitivity were observed between individuals with bilateral tinnitus and controls, Cho et al. found that unilateral tinnitus patients with normal and symmetric hearing thresholds exhibit greater sound sensitivity than controls.[70] Additionally, patients with unilateral tinnitus demonstrate reduced TEOAE amplitudes in the affected ear.[71]

Documented clinical investigations revealed a rapid loss of presynaptic ribbons and postsynaptic terminals of Inner hair cells (IHCs) following acoustic overexposure. However, the disappearance of the somata occurs extremely slowly, indicating that damage does not affect IHCs directly or rapidly.[72] This phenomenon helps explain why behavioral hearing tests may yield normal results[70] despite patients reporting tinnitus and/or hyperacusis. Consequently, such patients are typically categorized as normal-hearing subjects.

Even minor changes in research methodology can influence measurements of contralateral OAE suppression. Moreover, each tinnitus trigger, whether sensory deprivation or acoustic overexposure, may engage distinct underlying mechanisms of tinnitus generation. For example, when examining contralateral OAE suppression in normal-hearing subjects before and after ten minutes of sensory deprivation, Tayade and Tucker reported no statistically significant differences in either total TEOAE amplitude or TEOAE suppression amplitude neither before nor after the silence period. Based on these findings, the authors suggested that brainstem structures, including the MOC bundle, may not play a role in tinnitus perception.[73]

The pathophysiology of tinnitus in patients with normal hearing is more complex than in those with hearing impairment. Because cochlear hearing loss commonly coexists with tinnitus, especially in cases of severe impairment,[74] a direct role of cochlear hair-cell loss in the emergence of tinnitus has been suggested. Cochlear hearing loss reduces the acoustic input to damaged or lost inner hair cells (IHCs). As a result, the efferent inhibition of outer hair cells (OHCs) in the corresponding region of the basilar membrane decreases in an attempt to enhance the amplitude of afferent acoustic input to the affected IHCs.[71] This compensatory mechanism may lead to undesirable basilar-membrane hyperactivity in otherwise normal epithelial regions. This occurs because OHCs receive diffuse efferent innervation, unlike IHCs, where each cell is innervated by a single specific afferent fiber, one efferent fiber typically branches to many OHCs. Consequently, tonal tinnitus may arise as a result of these compensatory changes following cellular loss in the cochlea.[69,71]

Many studies have investigated cortisol levels as indicators of hypothalamic–pituitary–adrenal (HPA) axis alterations in tinnitus patients, yet their findings vary widely. For example, one case–control study reported no significant difference in basal cortisol levels between tinnitus patients and healthy controls.[75] In contrast, another study demonstrated that cumulative cortisol secretion -measured using hair samples- is elevated in chronic tinnitus patients and increases in parallel with tinnitus loudness, suggesting that loud and distressing chronic tinnitus is associated with

substantial long-term alterations in HPA axis function.[76] Such inconsistencies across studies may be explained by several factors, most notably methodological differences. Cortisol measured in saliva or blood reflects short-term HPA axis activity, making these measures more susceptible to the influence of transient external factors unrelated to tinnitus itself.[77] In contrast, hair cortisol better reflects long-term systemic cortisol exposure, potentially offering greater sensitivity to chronic physiological changes associated with persistent tinnitus.

Chronic stress may also reduce phagocytic activity and cellular migration, thereby impairing the repair processes of the cochlear ganglion following injury.[78] These alterations may consequently compromise the brain's ability to process incoming auditory information, reflecting the potential impact of elevated cortisol levels on auditory processing. Such alterations could compromise the brain's ability to process incoming auditory information, reflecting the potential influence of elevated cortisol levels on auditory function. Stress-related disruptions within central auditory pathways may contribute to the development or exacerbation of tinnitus, as dysregulated neural activity and impaired auditory signal processing are key mechanisms implicated in tinnitus perception.

Despite these theoretical links, the current literature lacks investigations that directly examine central auditory processing under conditions of chronic stress using specialized assessments such as the dichotic listening test.

The involvement of HPA axis alterations or abnormal auditory efferent activity in tinnitus appears to depend on both the trigger and the severity of the condition. Chronic tinnitus often develops following acoustic overexposure and is more likely to be associated with long-term HPA axis alterations, whereas acute tinnitus more commonly arises after periods of acoustic deprivation. However, substantial potential for bias remains when comparing findings across studies conducted by different investigators and populations. Participants may be exposed to multiple triggers simultaneously. For example, in a study examining otoacoustic emission (OAE) suppression before and after short-term isolation in a soundproof room, participants may also have had frequent exposure to high-intensity sounds in their daily lives. In such cases, at least two triggers are present, and additional confounding variables may also act as triggers, complicating interpretation of the results.

Discussion

The aim of this perspective is to provide and analyze the latest knowledge of olivocochlear system neurobiology and pathophysiology, as well as investigate its relation with human behavior. To that end, four conditions were studied: Auditory hallucinations, selective mutism, hyperacusis in ASD, and tinnitus. It can be elicited that, each of the discussed disorders exhibit a specific type of auditory processing, sometimes with shared similarities among subjects with different disorders, supposed to be a consequence of the affected neurotransmission system and its mechanism of changing efferent pathway from cortex, through superior olivary complex, to cochlea.

One of the major challenges of studying olivocochlear system is the absence of precise assessment tool. To this review's date, three models were used to study olivocochlear system since its discovery: Electrical stimulation, surgical section, and otoacoustic emission testing. The problem with electrical stimulation and surgical section is the inability to specifically investigate the efferent neurons of the olivocochlear bundles, as well as the inability to apply those procedures to humans. However, in human subjects, the activity of efferent auditory system and MOCB can be assessed non-invasively by testing contralateral suppression of otoacoustic emission.[79] After all, OAE test still an indirect method of examination and is no more than global indicator for the auditory system function, and it also fails (as surgical section and electrical stimulation) to provide accurate measurement of olivocochlear structures. Being said, the main limitation for the study of efferent auditory system is the lack of sufficient and accurate method of examination.

It could be noticed through reviewing the literature a kind of deficits in GABAergic transmission and inhibitory deficits in animals' central nervous system after deletion of the autism-risk gene, CASPR2.[50] CNTNAP2 rs2710102 and rs7794745 are common variants of CASPR2 affecting indirectly the social performance,[80] in parallel, CNTNAP2 rs2710102 has been implicated with language expression ability, and for that is implicated in SM, and in language deficits in ASD population,[46] which indicates, to some extent, a shared neurobiology between ASD and SM.

Frequency selectivity is one of the OHCs functions[81], mediated by MOCB activity. Medial olive projections to OHCs in the contralateral cochlea regulate its micro-mechanism,[2,6] though, modulating perceived speech signal, a process underlying (at least partially) the concept of peripheral auditory processing. As not all documented selective mutism cases exhibited deviant efferent auditory activity (so auditory processing abnormality), future research should investigate whether those SM patients with aberrant efferent activity have more difficulties than the rest of SM population. And most importantly, if we should reconsider behavioral treatments of SM and dealing with it more like an auditory deficit.

For AVHs, there was much little published investigations of the MOCB functionality, nevertheless, the existent investigations till dated support the involvement of olivocochlear system in AVHs generation. Moreover, the inner speech model of interpreting auditory hallucinations seems to be no longer valid. Complex diverse cognitive and neural mechanisms underlie AVH, although there are some documented evidences on the functional anomalies of MOC system, we still lack enough research and adequate methodology to ensue and clarify deficits in efferent auditory pathways in general, and MOC system anomalies in particular.

The following table summarizes the efferent dysfunctions, neurobiological features, behaviors, and diagnostic criteria of each disorder:

Characteristics / Disorder	Core Efferent Dysfunction	Key Neurobiological Features	Behavioral Manifestation	Diagnostic Criteria
Auditory Hallucinations (Schizophrenia)	MOC hyperactivity / asymmetry (↑ OAE suppression, right ear bias)	Reduced GABA → excessive ACh release; cortical thinning; asymmetry of planum temporale	Perception of internally generated sounds as external (misattributed inner speech)	Functional right–left MOC asymmetry parallels hemispheric cortical abnormalities
Selective Mutism	Reduced efferent modulation during vocalization	CNTNAP2 variants → GABAergic deficits; elevated cortisol → raised middle ear reflex threshold	Speech avoidance, especially in social contexts	Dual mechanism: stress-induced efferent suppression + auditory feedback deficits
Hyperacusis as a comorbidity to ASD	Reduced MOC inhibition (↓ TEOAE suppression)	Dysmorphic medial superior olive neurons; reduced neural synchrony, disturbed OHCs activity	Sound hypersensitivity, exaggerated loudness perception	Structural brainstem anomalies relate MOC dysfunction to behavioral hypersensitivity
Tinnitus	Variable MOC dysfunction (hypo- or hyperactivity depending on etiology)	Cochlear synaptopathy; altered HPA activity; compensatory efferent changes post hair-cell loss	Phantom sound perception; often with hyperacusis	Mechanisms differ by subtype (hearing-loss vs. normal-hearing tinnitus)

Conclusion

This perspective explores the neurobiological and functional roles of the olivocochlear (OC) system, particularly the medial olivocochlear bundle (MOCB), and its potential involvement in the pathophysiology of several psychiatric and neurodevelopmental disorders. It integrates neurogenetic, neurophysiological, and behavioral findings to propose that abnormalities in the auditory efferent system -especially those linked to CNTNAP2 gene variants and GABAergic dysfunction- may underlie shared auditory and communicative symptoms across the discussed disorders.

Future Directions

The greatest limitation in current efferent auditory system research lies in the absence of precise, non-invasive methods to evaluate the medial and lateral olivocochlear bundles separately. Advancing imaging or electroacoustic technologies capable of isolating MOC and LOC activity in humans would significantly enhance our understanding of their functional contributions to both normal and pathological auditory processing.

Conflict of Interest

The authors declare no conflicts of interest.

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