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REVIEW

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Neuroplasticity-targeted Intervention for Idiopathic Sudden Sensorineural Hearing Loss: A New Therapeutic Direction

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Abstract

Sudden sensorineural hearing loss (SSNHL) can be a frightening experience for patients, and practitioners have yet to arrive at a consensus with regard to the most appropriate course of treatment for this condition. This can be attributed primarily to a lack of understanding pertaining to the true etiopathogenesis of SSNHL. Given that the management of idiopathic SSNHL presents a challenge for clinicians and neuroscientists alike, research pertaining to SSNHL therapy may benefit from alternative approaches to this problem. This current review addresses the topic of therapeutic strategies for idiopathic SSNHL from the perspective of neuroplasticity. Assertions pertaining to the plausibility of this approach are based on a large body of evidence from animal experiments and recent studies on humans.

Keywords: acoustic; hearing loss; MEG; neuroplasticity; sound therapy

Sudden Sensorineural Hearing Loss

Sudden sensorineural hearing loss (SSNHL) is defined as a subjective sensation of rapid onset hearing impairment (i.e. occurring over a period less than 72 hours) that meets the following audiometric criteria: (1) a ≥30 dB decrease in hearing related to premorbid thresholds or (if premorbid audiometry is not available) opposite ear thresholds; and (2) at least 3 consecutive frequencies are affected [1].

SSNHL is an otologic condition first described in 1860 by Everberg, who reported a case of sudden deafness secondary to mumps [2]. SSNHL can be a frightening experience for patients, particularly those who depend on their hearing for their work, such as musicians, professional drivers, or athletes. Indeed, SSNHL can have a tremendous impact on one's quality of life, and has been correlated to an increased risk of adverse cognitive and functional outcomes. The number of new SSNHL cases is generally between 5 and 20 per 100,000 people per year; however, this figure is based on an 8-year prospective study on 225 patients, which was published in 1984 [3]. In 2004, a population-based cross-sectional study of SSNHL epidemiology in Germany reported that the incidence may be closer to 160 SSNHL cases per 100,000 people per year [4]. The higher number of SSNHL cases in the German study may be due to advances in screening and evaluation tools, which have enabled more definitive diagnoses of hearing-related diseases. Furthermore, the high incidence rate in the German study suggests that SSNHL is not a rare disease (as defined by the WHO and the European Union: less than 50 cases per 100,000 people) [4].

It has been estimated that, in Taiwan, there are approximately 2000 to 3000 new cases of SSNHL per year [5], whereas in the United States, there are approximately 4000 new cases of SSNHL per year [6]. Nonetheless, it is likely that these numbers have been underestimated, given that many patients spontaneously recover without receiving medical attention [7]. All cases of spontaneous recovery occur within the first 2 weeks following the onset of symptoms [1,6,8]. Reports on the likelihood of spontaneous recovery vary considerably (between 32% and 65%) [3,6,9]. Furthermore, spontaneous recovery has been shown to depend on several factors, including age, vestibular symptoms at onset, severity of hearing loss at presentation, and the amount of time that elapses between symptom onset and treatment [1]. SSNHL typically occurs in middle adulthood (43 to 53 years of age), and incidence increases with age [3,5,7]. Males and females are equally affected [7].

SSNHL can result from an abnormality of the cochlea, auditory nerve, or higher aspects of central auditory perception or processing [1], but the cochlea is thought to be most probable lesion site [10]. The underlying cause of SSNHL can only be identified in approximately 10% of cases; but in these cases, the most common causes have been found to be acoustic neuroma, stroke, and malignancy [11]. The remaining 90% of cases are idiopathic and presumptively attributed to vascular, infectious, immunologic, or multiple etiologies [1].

Treatment Modalities for Idiopathic SSNHL

The unclear etiology of SSNHL has led to the application of multiple therapy modalities, including systemic and intratympanic steroids, antiviral agents, anticoagulants, volume expanders, vasoactive substances, antioxidants, hyperbaric oxygen, anti-anxiety medication, diuretics (alone or in combination) [1], or observation alone [12]. Nonetheless, over the past three decades, a tapering course of corticosteroids (including prednisone, methylprednisolone, solumedrol, and dexamethasone) has been widely adopted as the principal treatment for idiopathic SSNHL [1]. The success rate of this treatment strategy is reported to be between 50 and 80% [7,13,14]. However, recent systematic reviews of randomized controlled trials determined that the use of corticosteroids in SSNHL treatment is an issue of some controversy; i.e., these findings are based on conflicting results from multiple studies [1,9,15-17], and other treatment options have not been validated by sufficiently rigorous randomized trials [1].

The primary challenges related to the management and treatment of SSNHL can be attributed to insufficient understanding of its etiopathoge-

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nesis. Indeed, in the absence of an underlying cause that is known and treatable, the management of idiopathic SSNHL presents a challenge to clinicians and neuroscientists alike. The fact is that (1) SSNHL has serious consequences and negatively impacts one's quality of life [1,18], and (2) no medication has proven effective in treating SSNHL [1]. Clearly, research into SSNHL therapy could benefit from new perspectives. This current review approaches the topic of therapeutic strategies for idiopathic SSNHL from the novel perspective of neuroplasticity. The biological plausibility of plastic therapeutic assumptions are based on a large body of evidence from animal experiments [19-23] and recent human studies [24,25].

Neuroplasticity

The word "plasticity" is derived from the Greek word "plastos", meaning molded [26]. Neuroplasticity or neural plasticity refers to the ability of the nervous system to reorganize its structure, function, and connections in response to environmental stimuli or demands [27]. The term "plasticity" was first introduced to the neurosciences in 1890 by American psychologist William James [28], who reported that nervous tissue appears to have an extraordinary degree of plasticity, and that, in living beings, the phenomenon of habit is due to plasticity [26,28]. When the concept of brain plasticity was first introduced, it challenged the belief that the structure of the brain is relatively unchangeable after a critical period during early childhood, which was the dominant belief among neuroscientists of the day. In 1904, Santiago Ramón y Cajal, a Spanish Nobel prize winner and the father of modern neuroscience published a book entitled "Textura del Sistema Nervioso", extended the notion of plasticity to the neural substrate by reporting that, when an individual acquires new skills, the brain changes by reinforcing preexisting connections and then forms new pathways [26]. By the middle of the 20th century, efforts to prove or disprove the concept of neuroplasticity led to innovative breakthroughs in experimental design, which became the cornerstones of neuroplasticity theory. In 1949, Canadian psychologist and father of neuropsychology Donald Olding Hebb proposed Hebbian theory, which posits that the brain exhibits synaptic plasticity during the learning process [29]. He made the following claims: "When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased." The Hebbian activity-dependent refinement model is commonly referred to as Hebb's Law and can be summarized as: "Cells that fire together, wire together." In brief, Hebb's Law posits that excitatory connections are formed between coactive presynaptic and postsynaptic cells. The Hebbian prediction that coactive inputs are stabilized was supported by evidence from a recent study by Munz, et al., who presented live observations of axonal structural plasticity directed by patterned visual stimuli in vivo [30]. Hebbian theory presented a significant early challenge to the conventional wisdom of fixed-brain theory. However, it was not until the late 1960s that Raisman introduced the term "neuronal plasticity" to describe a permanent plastic change that he observed in the neuropils of septal nuclei of adult rats in response to deafferentation. Decades of research has shown that the brain responds to various internal and external stimuli dynamically [31]. Moreover, recent studies have indicated that although neuroplasticity underlies a fundamental lifelong property of the nervous system, it is particularly common during the developmental stage and underlies the ability of children to learn quickly [26,27].

Neuroplasticity involves adaptive responses to conditions resulting in a behavioral gain, such as learning. Gaser and Schlaug used a voxel-by-voxel morphometric technique to compare professional musicians (keyboard players) with a matched group of amateur musicians and non-musicians [32]. They found that professional musicians had the largest volume of gray matter in the motor, auditory, and visual-spatial regions of the brain involved in playing music, followed by amateur musicians and non-musicians. A study by Woollett, et al. [33] revealed that the hippocampus, which plays a role in navigating large-scale spatial environments [34], of taxi drivers in London is larger than that of bus drivers. This finding may be explained by the fact that taxi drivers must navigate busy London traffic and typically use a different route every time they deal with a new customer; while bus drivers operate along a constrained set of routes. The authors concluded that neuropsychological and structural brain changes can occur after extensive mental effort. Finally, Pantev, et al. used functional magnetic source imaging (single dipole model) to measure cortical representations in highly skilled musicians. They found that training-induced functional reorganization extended farther across the sensory cortices of musicians than across that of control subjects who had never played an instrument. Findings from that study revealed that tonotopic representations can undergo dynamic changes, particularly after the training of skills [35]. Several other studies on humans and animals have also reported strong links between use-dependent structural adaptations in the brain and extensive training efforts [36-40].

Plasticity-promoting Interventions

Plastic change is an adaptive gain in function associated with the performance of a skill or the retention of a memory. It may occur during healthy development or during recovery from brain damage. For example, following a brain lesion, cortical reorganization may increase residual function or otherwise compensate for the loss of function, such that initial deficits in behavior, perceptual, and/or cognitive skills present signs of improvement over time [41]. The recovering, re-normalizing entity of neuroplasticity offers a promising intervention strategy for clinical applications. Specifically, neuroplasticity can be harnessed to achieve therapeutic gains by reversing maladaptive cortical reorganization [25-27,42-44]. Given that plasticity-promoting theory has been implicated in the alleviation of clinical disorders, several promising neuroplasticity-based interventions aimed at enhancing brain plasticity have been proposed. These include the principles of Hebbian learning [45], task-specific training [46], transcranial magnetic stimulation [47], deep brain stimulation [48], cognitive behavioral therapy [49], physical training [50], and neuropharmacotherapies that involve the molecular manipulation of cellular and synaptic pathways [27,51,52]. These interventions have been shown to promote clinical gains, improve behavioral outcomes, and increase brain plasticity. However, the extent of behavioral benefits conferred by plasticity-promoting interventions depends on the availability of sufficient residual neural capacity, rather than the type or duration of neurological insult [27,53,54].

Plasticity-preventing Interventions

Advances in the field of brain plasticity have led to the development of promising interventions for severe neurological conditions and disorders. These interventions promote adaptive neuroplastic changes to compensate for lost functions or to maximize remaining functions. Nonetheless, our understanding of the complexity and multidimensionality of neuroplasticity is incomplete. Some adaptive plastic changes are associated with behavioral gain (e.g. skill learning) or functional compensation (e.g. post-stroke recovery), whereas other forms of plasticity can induce maladaptive neuroplastic changes and negatively affect disease pathogenesis [25,27,41,55-57]. Notable examples of maladaptive cortical reorganization include focal hand dystonia [58], phantom limb pain [59], and tinnitus [60,61], which can have disastrous effects on one's quality of life [41]. Most strategies addressing the adverse consequences of plasticity involve prevention rather than promotion. Behavioral training has been shown to reduce or to reverse maladaptive cortical reorganization. Collectively, maladaptive plastic changes can have a strong influence over undesirable patterns of cortical activation [26]. Interventions aimed at moderating the effects of plasticity can also help to elucidate maladaptive cortical reorganization.

Neuroplasticity-targeted Interventions for Idiopathic SSNHL

As noted above, neuroplasticity can have positive as well as negative effects [41,61]. Nonetheless, the gain in functional recovery can be improved through the promotion of adaptive cortical reorganization or through the prevention of maladaptive plastic changes. In this regard, neuroplasticity-based interventions represent a promising therapeutic direction for the management of neurological disorders.

No medications have been proven successful in the treatment of SSNHL. Even steroids (the most commonly "standard" treatment option), lack evidence-based proof of efficacy [1]. Furthermore, many patients do not qualify as candidates for steroids due to the potentially severe side effects associated with this treatment, including the suppression of hypothalamic-pituitary-adrenal function, insomnia, weight gain, gastritis,

mood changes, hyperglycemia, hypertension, cataracts, opportunistic infections, osteoporosis, and osteonecrosis [1,62].

SSNHL can be a frightening incident causing embarrassment, frustration, anxiety, insecurity, loneliness, depression, and social isolation [1,63]. Treatment limitations and the potentially serious consequences of SSNHL highlight the need to explore new therapeutic strategies. Neuroplasticity-based interventions may represent a feasible approach.

Neuroplasticity-targeted Interventions in Animal Models

Neuropathogenic mechanisms underlying SSNHL were used in the development of a revolutionary approach to treatment based on neuroplasticity. In animal models, acoustic trauma has been shown to induce hearing loss via damage to the cochlea [64,65] and auditory nerve fibers [66,67]. The resulting decrease in the rates of firing (spontaneous and driven) in auditory nerve fibers can lead to central reorganization [22,23,68]. Researchers have also revealed that animals subjected to auditory stimulation following acoustic trauma are less affected by hearing loss and hair cell damage in the cochlea, compared to animals that are not subjected to post-traumatic acoustic stimulation [19,20,22]. One recent study reported that cats exposed to traumatizing noise presented changes in tonotopic organization in the primary auditory cortex, whereas the cortical tonotopic map of cats in a quiet environment presented no signs of reorganization [22]. These studies strongly indicate that changes in brain plasticity may be triggered by a decline in the spontaneous and driven firing rates in auditory nerve fibers following cochlear damage [22]. Using neuroplasticity-targeted interventions, therefore, acoustic energy delivered to ciliated cells in the cochlea is converted into electrical impulses that are transmitted to the auditory cortex through auditory nerves [24]. The form of rehabilitating mechanism of neuroplasticity-targeted interventions may (1) compensate for the loss of afferent neural inputs induced by deafferentation and (2) prevent maladaptive neuroplasticity, thereby enhancing the process of hearing recovery and facilitating hearing gain [24,25].

Neuroplasticity-targeted Interventions in Human Models

In recent functional magnetic resonance imaging (fMRI) studies on humans [69,70], using acoustic stimulation was shown to alter the auditory cortical response of patients suffering from sudden unilateral deafness. Immediate and protracted changes in auditory pathway functions have also been observed in studies on magnetoencephalography (MEG) [71-75]. These studies indicate that humans can undergo similar SSNHL-induced brain plasticity as that observed in animal studies. Li, et al. further observed altered hemispheric plastic asymmetry with a pattern of "healthy-side dominance" of N100 response (N100m in MEG) to tone burst stimulation in patients with early stage idiopathic SSNHL. Conversely, subjects with normal hearing showed "contralateral dominance" [10,75]. These initial observations of MEG hemispheric asymmetry can be interpreted as evidence of active compensation to facilitate the recovery of hearing.

In 2012, López-González, et al. published a study comparing the outcomes of 65 SSNHL patients treated with medication only (steroids, piracetam, or antioxidants) and 67 SSNHL patients treated with medication in conjunction with sound therapy (a combination of music and speech) [24]. Sound therapy was shown to greatly enhance the effectiveness of treatment on idiopathic SSNHL patients. Unfortunately, they analyzed audiometric outcomes without using neuroimaging methods, such as fMRI or MEG, thereby precluding the possibility of determining the extent of changes due to brain plasticity.

In 2014, Okamoto, et al. designed a modified form of sound therapy, referred to as "constraint-induced sound therapy (CIST)," for patients with idiopathic SSNHL [25]. CIST was designed in accordance with a well-established approach to neuro-rehabilitation, known as "constraint-induced movement therapy." This method has been shown to improve chronic motor deficit in patients with stroke. CIST includes two major components: (1) plugging the intact ear to ensure that the cochlea does not receive acoustic (mechanical) inputs, thereby preventing the transmission of afferent electrical neural impulses to the contralateral auditory cortex; (2) stimulating the affected ear with music (six hours per day) to prevent maladaptive auditory cortical plasticity on the healthy side. They also compared pure tone audiograms obtained from patients who underwent constraint-induced sound therapy combined with standard corticosteroid therapy (CIST+SCT, n=22) with those of patients who underwent standard corticosteroid therapy only (SCT, n=31). In that study, the hearing recovery of the CIST+SCT group far exceeded that of the SCT group. They also used MEG to analyze the neural activity of six patients from the CIST+SCT group, focusing on the following types of neural activity: N1m response (generated mainly in the belt and parabelt areas of the auditory cortex) [76] and the auditory steady state response (generated in the primary auditory cortex) [77]. They found that monaural stimulation induced contralateral dominance, which is indicative of normal hearing. This suggests that treatment with CIST+SCT reversed contralateral cortical maladaptive plastic changes induced by SSNHL [10,75]. Clearly, acoustic stimulation could play a significant role in neuroplasticity-targeted interventions for idiopathic SSNHL by preventing as well as reversing the adverse effects of maladaptive cortical plasticity. Nonetheless, the study by Okamoto, et al. suffered from important limitations. To begin with, only 6 of the 53 (11%) patients chose to undergo an MEG test, which may have resulted in a biased sample. These findings should therefore be validated in future research with a larger patient population. Second, audiometric data for the six patients who underwent MEG were not available. Thus, it may be premature to conclude that there is an association between hearing recovery and reversion of cortical reorganization.

The only studies on SSNHL interventions with acoustic stimulation were those of López-González, et al. [24] and Okamoto, et al. [25]. Thus far, all attempts to validate the postulated theory (i.e., that sound therapy may prevent or reverse SSNHL-induced maladaptive cortical reorganization) have failed [25]. Furthermore, all of the patients in these studies also underwent steroid treatment (which is the current first-line treatment); therefore, functional recovery cannot be attributed solely to sound therapy. At present, steroid therapy has a success rate of approximately 50% to 80% [14]. Furthermore, the large number of patients that undergo spontaneous recovery (32% to 65%) makes it very difficult to determine the degree to which acoustic stimulation actually improves hearing function [3,6,9].

Future Work

Evidence from animal models suggests that acoustic stimulation may interrupt the mechanisms that contribute to central reorganization, thereby helping to protect the auditory system from further damage. Indeed, the success achieved in animal models has encouraged scientists to employ similar strategies in the study of human with SSNHL. Although sound therapy has been applied on human subjects and we now have a far better understanding of the neuroplasticity-targeted interventions for idiopathic SSNHL, the theoretical hypothesis that sound therapy can improve SSNHL outcomes has not been tested in a sufficiently rigorous manner. Further evidence confirming the therapeutic effects of sound therapy on hearing protection is needed.

In the future, we hypothesize that hearing loss in patients with idiopathic SSNHL could be restored by boosting audio levels targeting specific frequencies while constraining the transmission of signals (at corresponding frequencies) to the unaffected ear. Evidence obtained in animal studies indicates that the mechanism underlying hearing restoration may involve the model of neuroplasticity-prevention [19,20,22].

Conclusions

This review introduced acoustic models aimed at elucidating the mechanisms underlying the process of hearing restoration induced by acoustic stimulation. The hypothesis of neuroplasticity-prevention states that hearing restoration may be in attempt to provide neurophysiological implications of neuroprotective acoustic training in patients with idiopathic SSNHL.

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