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Abstract

Bilateral, profound-severe, congenital deafness causes widespread structural and functional changes of the auditory system. In humans, the consequences of these changes are extensive and often include detriments to language acquisition and auditory perception. Fortunately, early intervention methods, such as cochlear implantation, can significantly mitigate inevitable auditory deficiencies. This review begins by briefly addressing early stages of brain development and associated anatomical discrepancies observed in congenitally deaf subjects. Considering the deleterious effects of congenital deafness, neuroplasticity, the ability of the brain to rewire itself, is of paramount importance in reversing the auditory impairments. Hence, its incorporation into the methods required for successful auditory rehabilitation. Despite this phenomena, assistive devices such as the cochlear implant have shown a marked decrease in efficacy after a critical period has elapsed. Although the scientific community has made incredible gains in the understanding of neurogenesis and congenital deafness, additional research is required to concretize age-related limitations inherent in neural plasticity and provide further advances in congenital deafness intervention methods.

Introduction

Hearing loss is the third most common health problem in the United States. It is estimated that thirty million Americans struggle to hear. The disability is not only prevalent in America; it is estimated to affect 8.8 percent to 12.5 percent of the worldwide population (Burkey, 2015). The most common cause of this disability which affects approximately 2 out of every 1,000 children is sensorineural hearing loss (Sharma, Campbell, 2011). Sensorineural hearing loss is often caused by damage to the inner ear or as a result of non-functioning or missing sensory hair cells that normally operate within the cochlea. Without these cells, an individual is unable to detect and transmit auditory sound wave stimuli through the auditory nerve to the brain. As cortical development is contingent upon stimulus-driven learning, individuals born with sensorineural hearing loss are at risk for abnormal neurological development and brain connectivity needed for optimal auditory sensory function. In 1978, Dr. Graeme Clark introduced a revolutionary multi-channel cochlear implant that has developed into an incredibly effective and transformational neural prosthesis that allows severe and profoundly deaf individuals to achieve similar function to their unaffected peers. This device converts sound waves into patterns of electrical impulses that bypass the outer and middle ear, thereby directly stimulating Cranial Nerve VII fibers. The cranial nerve then carries the impulses to the brain, which converts and interprets these impulses as sound. Although different from typical acoustic stimulation, this electrical stimulation is able to mimic the coding of the cochlea and enable recipients to process speech and environmental stimuli (Hartmann, Kral, 2000).

As technology and implantation techniques improved in the 1990's, cochlear implant surgery gained FDA approval for use in younger subjects. As of 2010, approximately 80,000 of the 300,000 cochlear implant users worldwide were either infants or young children (Kral, O'Donoghue, 2010). Research studies quickly established that "when these children receive a cochlear implant at a relatively young age (for example, at 18 months) followed by intensive therapy, they tend to hear and speak better than those who received implants at an older age (fda.gov, 2017)." The success associated with such early cochlear implant intervention is often assumed to be related to a brain characteristic known as neuroplasticity. This fascinating neural capability allows neurons in the brain to compensate for injury or disease by restructuring and reorganizing neural pathways that affect function. It is the aim of the following analysis to explore the nature of age-related changes in neuroplasticity as they might specifically relate to the efficacy of cochlear implantation in subjects at various stages of development.

Methods

Critical analysis of the literature on age-related neuroplasticity in relation to cochlear implantation was conducted and compiled via access to the Touro College Library's online database, using PubMed and ProQuest search engines. In addition, Google Scholar was utilized in obtaining related research.

Discussion

Early Stages of Brain Development

Brain development begins around the eighteenth day after conception and continues into early adulthood. Approximately 2 weeks after conception, part of the ectoderm of the back of the embryo thickens and forms a neural plate. As the edges of this neural plate curl toward each other, eventual fusion occurs thereby forming the neural tube. The inner cells of this formation will comprise the central nervous system whereas the outer cells break away to create the autonomic nervous system. As the tube closes and matures, different areas become distinctive brain structures. In particular, the rostral end of the neural tube develops three interconnected chambers which become the three major parts of the brain: the

forebrain, midbrain, and the hindbrain (Carlson, Birkett, 2017). Any remaining cells will develop into the spinal cord. As the tube undergoes its metamorphosis, progenitor cells, descendants of stem cells, lead to the brain's multifaceted and sophisticated cellular network. Given the cerebral cortex's inside-out developmental pathway, the most recently formed neurons are more proximal to the cortical surface. The six layers of the cortex are formed by approximately 25 weeks after conception. The end of cortical development is observed when the progenitor cells receive a chemical signal which induces apoptosis. Once neurons have migrated to their proper locations, synaptogenesis occurs. The first synapses are usually detected around the 23rd week of gestation (Molliver et. al., 1973). Typically, synaptogenesis is followed by a gradual reduction of neurons known as pruning due to neural overabundance in the ventricular zones. Although this process occurs throughout an individual's lifespan, an initial explosion of synapse formations occurs during early brain development. Synaptic reduction is then significantly dependent on environmental exposure. Regions that are stimulated by these factors are strengthened and stabilized, whereas reduction occurs in synapses that are not sufficiently stimulated (Tierney, Nelson, 2009).

During the prenatal and early childhood years, the basic structure and functional capacity of the brain are formulated with refinement of neural networks persisting over time. Research suggests that brain development is hierarchical in nature. Higher level processes build on lower level processes. For example, language development depends on sensory and perceptual development. Infants are born with a brain wired for various types of experiences and abilities such as speech, language, and facial recognition. Newborns are initially programmed to perceive all languages, but with environmental experience, become focused and cognizant of their native language and lose the ability to perceive language that they are not exposed to. In this way, exposure drives subsequent learning (Kuhl, 2004). Research in 2004 supports the concept that healthy brain development requires adequate environmental exposure and that lack of these experiences could lead to underspecification and miswiring of brain circuits. This study found that children raised in Romanian institutions with a lack of stimulating experiences demonstrated underdeveloped brain and cognitive growth. Further research (Marshall et al., 2008) noted a critical time frame, suggesting that after age two the effects of decreased exposure on brain function worsen.

In early development, external stimulation is an important means through which significant neural connections and networks are created to facilitate behavioral growth and development. An absence of any one of the body's senses can have major implications on brain development. Animal studies have found that early deafness greatly affects auditory cortical development. Baker et al. (2010) performed a research study utilizing deaf cats to determine hearing loss related auditory brain stem pathology. Altricial animals, cats are born with closed ear canals that only open approximately 30 days after birth. The process of ear canal opening is the same in deaf and hearing cats; therefore, researchers hypothesized that abnormalities in the deaf cats would coincide with the development of hearing in typical-hearing cats. This would support the notion that lack of sound stimuli leads to pathological changes. Through the use of intracellular dyes, the Endbulb of Held in deaf white cats were examined. Large and complex synaptic endings, the Endbulbs of Held provide a coordinated release of neurotransmitters from presynaptic terminals onto the soma of bushy cells in the anteroventral cochlear nucleus (postsynaptic cell). They are considered to be centrally involved in the precise transmission of timing information from auditory stimuli. It was discovered at birth that the cochlea of the congenitally deaf white cats was void of abnormal morphology. The presence of a collapsed scala media and a degraded organ of corti appeared one week after birth. As time progressed, the deaf cats' endbulbs exhibited flattened and elongated postsynaptic densities (PSDs) and increased synaptic vesicle density. Cochlear abnormalities in cell synapses and circuitry as a byproduct of sound deprivation were exhibited. Human studies have subsequently arrived at similar findings. Using cortical auditory evoked potentials (CAEPs) with non-invasive EEGs on deaf children, these studies have found delayed or absent auditory responses supporting the theory that brain maturation is dependent on appropriate and adequate stimulation (Eggermont et al., 1997; Eggermont & Ponton, 2003).

Neuroplasticity and Developmental Periods

In addition to genetics, environmental factors also play an important role during the critical period of brain development. While genetics ostensibly play a larger and more significant role in prenatal development, environmental exposure is a key contributor to postnatal progression. Neural plasticity is the central nervous system's ability to attempt to support optimal performance by recovering functional abilities and enabling the body to adapt and learn in changing anatomical conditions. The nervous system's ability to reorganize its structure, connections, and functional abilities in response to intrinsic and extrinsic stimuli is complex. It can occur on a variety of levels from molecular to cellular during regular development and learning, or in response to disease or injury (Cramer et al., 2011). Plasticity of a brain region is affected by the area's peak synapse production.

This occurs at different times for various structures of the brain. For example, peak synaptogenesis for the visual and auditory cortices occurs between 4 and 12 months, whereas the prefrontal cortex that controls reasoning and planning increases more slowly and peaks at one year of age. The later the peak synapse production, the longer the area's plasticity (Goswami, 2004).

Neuroplasticity is an area of continuous research and hope in many clinical contexts. It is, for instance, widely researched in relation to stroke, trauma, and spinal cord injury. Associated studies have highlighted the brain's incredible ability to form representational maps with spontaneous intra-hemispheric and inter-hemispheric changes. For instance, when brain lesions of the left hemisphere damage important language centers, other areas in that hemisphere may be recruited for language function (Karbe et al., 1998b; Karbe et al., 1998a; Warburton et al., 1999). Moreover, in situations where severe impairment exists in the left hemisphere region, the right hemisphere appears to be capable of assuming some language functions (Warburton et al., 1999; Cramer et al., 2011).

The central nervous system's ability to adapt to pathology is affected by several parameters. One of the primary contributing factors is the age of onset, including critical developmental periods (Staudt, 2010). The greatest forms of neuroplasticity are available during early development. This is thought to relate to the overabundance of neuronal cells and synaptic connections present during early childhood which decrease through the pruning process with environmental exposure and aging. Additionally, other developmental events like inhibition and myelination can affect the developmental critical period. In the case of early neurological injury, research has found significant cross modal plasticity - the ability to reorganize and form new sensory maps and pathways. For example, successful changes in function from across brain hemispheres have led to highly successful behavioral advances for children (Cramer et al., 2011). Staudt's (2002) research supports this phenomenon showing that unlike adults, children demonstrate moderate to good right hemisphere control of language and movement following a significant injury to their dominant left hemisphere.

Data Defining Critical Periods for Cochlear Implantation

Adaptive plasticity and its relationship to age-dependent recovery of language is an active area of study. Research on children with a hemispherectomy showed a remarkable shift in motor and language function to the remaining hemisphere. Children under six years of age had the most significant level of reorganization (Chen et al., 2002b). Similar findings have been seen with congenitally deaf children. Cortical Auditory Evoked Potential (CAEP) testing - the time it takes for the brain to respond to auditory stimulation - was found to increase with age as a result of maturation and refinement of the central auditory pathways. These markers were tested in a variety of deaf children who received cochlear implants at different ages. In a study with a subject body of 245 congenitally deaf children with cochlear implants, researchers found that children implanted prior to 3.5 years of age had normal response times within 6 months of implant use. However, children whose initial stimulation occurred after age 7 demonstrated abnormal response times even after years of implant usage. Children who received cochlear implants between 3.5 and 7 years of age had variable responses (Sharma et al., 2002; Sharma & Campbell, 2011). These results have been supported by other studies utilizing PET scan brain imaging and behavioral measures. In addition, speech and language studies have demonstrated that children implanted under 3-4 years of age display significantly better speech and language skills as opposed to those children implanted at 6-7 years of age and older (Geers, 2006; Kirk et al., 2002). These results influenced the FDA to lower their age for approval of cochlear implantation for children to approximately 12 months.

Research reports that auditory cortex synaptogenesis begins in the first two months after birth with maximum density between 4 and 12 months followed by pruning (Goswami, 2004). This early synaptogenesis supports the need for early implantation and stimulation of the auditory nerve to allow maximal usage of the brain's regional plasticity and ability to learn to process auditory stimuli. Research has reinforced this theory. Electrical stimulation had a restorative effect on the Endbulb of Held synapse, and early electrical stimulation with a cochlear implant had significant positive results in congenitally deaf cats (Baker et al., 2010; Ryugo, 2015). Ryugo et al. (2005) reported decreased synaptic vesicle density and PSDs following cochlear implantation of congenitally deaf cats statistically similar to those of normal hearing cats. Auditory nerve activation at 3 months of age restored many key features of synaptic morphology, whereas less significant effects were seen at 6 months and on (Ryugo, 2015). With regard to humans, studies illustrate that those children who became deaf before the developmental onset of language and received early cochlear implant technology were successful in their acquisition of spoken language. However, those with late implantation displayed less benefit and ability to discriminate complex everyday sounds and speech (Svirsky, et al. 2004; McConkey, et al., 2004; Tong et al., 1988).

Cochlear Implant Considerations After Critical Periods

Early implantation, within the sensitive and critical period, is integral for speech and language development and necessary to avoid potentially deleterious re-organization of the cortex. Kral, 2007 found that in animal studies, the primary auditory cortex was partially or completely disconnected from the surrounding higher order cortex at the end of the sensitive period. This leaves the higher order auditory cortex at risk for recruitment from other sensory modalities. This has been seen in deaf adults where their visual processing may begin to take place in their auditory cortical areas. Although cross modal reorganization may allow for some enhanced processing, it could also result in significant deficits. For example, while deaf adults may have enhanced peripheral vision, they may suffer from severely impaired auditory processing and auditory-visual integration (Sharma & Campbell, 2011). Numerous studies have consistent data demonstrating notable improvement in speech perceptual skills in adolescents who received cochlear implants. However, adolescents with earlier implantation and shorter lengths of deafness exhibited significantly greater results in word and sentence testing. Children who were implanted after age 7 were found to demonstrate abnormal brain responses to auditory input and poorer language skills. Some relate these results to cortical plasticity where colonization of the auditory cortex occurs from other sensory modalities during critical periods of central nervous system development (Sharma et al., 2009; Zeitler et al., 2012). In post-lingual adults, studies relate that the duration of auditory deprivation has a negative impact on auditory performance with a cochlear implant, either due to cross modal plasticity or due to the limited capability of the superior temporal cortex (Anderson et al., 2017)

Cochlear Implant Benefits Before and After Critical Periods

Results from human studies report that uncorrected deafness results in fundamental change in the central auditory system so much so that benefit from a cochlear implant in later life is hindered. Adult recipients report cochlear implant benefits including increased environmental sound awareness, better quality of life, and increased psychological wellbeing. The area most variable is improvements in auditory speech perception. Specifically, the trajectory and rate of auditory performance vary across adult individuals (Anderson et al., 2017). Several abnormalities that arise in the auditory system include reduced number of spiral ganglion neurons, abnormal synaptic structure, ectopic projections in ascending pathways, and physiological alterations of auditory nerve responses in the cochlear nucleus. These affect synaptic transmission and result in decreased responsiveness in the inferior colliculus and auditory cortex. These fundamental changes inhibit older cochlear implant recipients from gaining true benefit. Although environmental sounds may be processed in adult recipients, language recognition is more difficult (Ryugo, 2015). Data from the Mayo Clinic's testing on 259 adults revealed that adult cochlear implant recipients had preoperative scores of 8% on tests of monosyllabic words and 7% on sentence recognition. After one year of implantation, these scores increased to 58% for word recognition and 75% for sentence recognition (Carlson, 2020). These results support the usefulness of cochlear implants in adulthood; however, when compared to the percentages and quality outcomes in children with early implantation they are markedly low.

Relevant Associated Neural Plasticity Research

For decades, scientists believed that neurogenesis was a process that existed in the brains of embryos and infants only to cease in adulthood. In the 1980's, this notion was challenged when researchers showed that neurogenesis occurs in the brains of certain adult animals. Further traction against the initial, misguided belief was made when signs of newly formed neurons in the adult human brain were observed. Alvarez-Buylla and colleagues studied the olfactory bulb in rodents and found continuous formation of new neurons. However, in humans the formation of new olfactory neurons occurs exclusively in infants. This dichotomy was also found in the frontal lobe where new neurons migrate during early childhood but cease migrating as age progresses (Pignatelli and Belluzzi, 2010). The most thorough study was done by Sorrells and colleagues on postmortem and postoperative hippocampal tissue from humans. The subjects ranged from fetuses at 14 gestational weeks to 77 years of age. Samples were stained with fluorescent marker antibodies to identify progenitor cells and young neurons. Definite signs of new neuronal formation in the hippocampus of infants and children were observed, whereas no such signs were exhibited in adult brains. Additionally, young neurons decreased in density as age level progressed (Sorrells et al., 2018).

In humans, it is theorized that neurogenesis occurs in the subgranular zone (SGZ) of the dentate gyrus of the hippocampus which maintains a neurogenic stem cell (NSC) niche. Some propose that the SGZ is an environment fit for NSC proliferation into granule cells from which migration to the granule cell layer occurs. Granular cells progress through the developmental

stages when specific protein markers are expressed, thereby revealing lineage specific cells in the neurogenic niche. This occurs before the cells integrate into the hippocampal circuitry and can influence the functions such as learning, memory, and spatio-motor performance (Kumar et al., 2019).

There is some research, albeit scarce and preliminary, that supports adult neurogenesis. One such study tested the brains of 5 cancer patients who had been injected with a chemical that incorporates into newly created DNA: Bromodeoxyuridine (BrdU). Traces of this chemical were found in the dentate gyrus of the hippocampus, thus supporting the theory that cells in this region are continuously dividing and creating new neurons (Eriksson et al., 1998). Another study also reported evidence of neurogenesis after identifying protein markers for various stages of neurogenesis in subjects 0 to 100 years of age (Knoth et al., 2010). In 2013, using carbon dating methods, Jonas Frisén's lab at the Karolinska Institute reported that up to 700 neurons are added each day to the dentate gyrus (Kumar et al., 2019). Although these are groundbreaking findings, many researchers question their validity. Asserting the possibility that BrdU can occasionally label dying cells instead of cells undergoing division, as well as the possibility that protein markers can accidentally label brain cells as glia instead of neurons, a body of researchers remains hesitant regarding claims of neurogenesis in adulthood. Nevertheless, the most robust study supporting adult human hippocampal neurogenesis was done by Boldrini and colleagues. Autopsying hippocampi of people ages 14 to 79, they found the production of intermediate neural progenitors, immature neurons, mature granule neurons, and glia to be similar between all age groups. Adhering to biological parameters and utilizing unbiased stereology, the researchers ensured that their samples were taken from healthy individuals (Boldrini et al., 2018). On the other hand, some studies have found results to be inconclusive. Kumar and colleagues used bioinformatic methods to study the differential expressions of neurogenesis signature markers in the hippocampi of prenatal to adult age subjects. Persistent but minimal hippocampal neurogenesis was observed. In addition, they initiated the criticism that newborn adult hippocampal cells could be glial cells (Kumar et al., 2019). The vast majority of research points to the stark difference between the human brains of infants and adults, with inadequate concrete knowledge and inconsistent evidence of adult neurogenesis. It is the hope of many scientists that future technology with the ability to provide imaging of new neuronal formation in the adult human brain will shed light on this debate.

Areas of Interest for Future Inquiry

Many factors limit the availability of research and tangible knowledge of adult neurogenesis, including sparse availability of ideal human brain tissue and limitations of study methods. A clearer understanding of the evidence surrounding adult human neurogenesis is crucial, as its presence or absence will have significant theoretical and practical effects on learning, age-related memory, pathology, and injury. Research and innovation are needed to produce safe investigatory methods to perform neurogenesis related research in living humans. Safe neuroimaging approaches to detect growth of newly formed cells in neurological niches and their integration into existing neural circuitry is needed. Possible stem cell methods of generating neural stem cells from the patient's own cells is another area of potential innovation.

Although the mechanisms of neurogenesis are not fully understood, there are a variety of avenues for further research and application. Some researchers have proposed a deeper investigation into the role of corticosteroids in reducing hippocampal neurogenesis. Others have suggested avenues related to trophic factors such as the brain derived neurotrophic factor, fibroblast growth factor, and epidermal growth factor, as well as the neurotransmitter serotonin, which have shown enhancement of neurogenesis. Additionally, studies have pointed to stress as the reason for increasing the production of glucocorticoids and decreasing trophic factors, thereby decreasing neurogenesis. On the other hand, environmental enrichment increases the secretion of trophic factors which, in turn, may facilitate neurogenesis (Kumar et al., 2019). These factors, along with further research, could conceivably be used as catalysts to promote adult neurogenesis and allow for greater recovery of learning and memory in the deaf population and beyond.

Limitations in conventional neuroimaging techniques to evaluate cortical plasticity pre- and post-implantation have hindered our ability to adequately study the effectiveness of cochlear implantation in the adult population. Given the application of powerful magnetic fields in MRI scanning, straightforward examination isn't feasible with the ostensible high-risk factor for the magnetic component of the cochlear implant. Surgically removing the magnet prior to MRI is risky and inconvenient. Removal would also impede auditory stimulation through the cochlear implant and would consequently distort the imaging of auditory cortical function. Unconventional neuroimaging techniques such as EEG and MEG are safe for cochlear implant users; however, they are unable to provide data about cortical processing of speech at the level of word identification and sentence comprehension.

In contrast, PET can be used to measure neural activity based on changes in cerebral blood flow and metabolism. Independent of electrical or magnetic cortical signaling, PET imaging allows for artefact free functional imaging in cochlear implant users. However, due to the use of a radioactive medium, testing repetition is limited and impedes on the adequate assessment of cortical changes that occur rapidly over a short period of time. The use of functional near infrared spectroscopy (fNIRS), a non-invasive optical imaging technique, is a possible area that, with further modifications, can be a promising means of data collection from cochlear implant recipients. This technique does not provide a direct measure of neuronal activation. Instead, it measures the consequential hemodynamic response seen in stimulus evoked changes in levels of oxygenated haemoglobin (HbO) and deoxygenated haemoglobin (HbR). Through the application of optodes, an optical sensor device with fiber-optic bundles, on the subject's scalp, the changes in HbO and HbR can be monitored and evaluated using a stimulus presentation paradigm. Although some limitations currently exist and further research is needed, multiple benefits of this technique include non-invasive and portable testing nature, high level of resilience to patient's head and body movement, and safe and flexible testing across a diverse population. Testing utilizing this technique has displayed an ability to measure cross-modal responses within the temporal lobes in cochlear implant recipients (Anderson et al., 2017).

Another area for further research is the therapeutic technique of speechreading prior to implantation. It is thought that speechreading in post-lingual deafness has the ability to maintain amodal linguistic functions and left hemisphere specialization for speech processing. Vision may facilitate the restoration of auditory function with modifications to the auditory cortex. This audio-visual synergy may enable adult cochlear implant users to capitalize on heightened levels of visual cortex activity to compensate for decreased auditory input from the implant. Consequently, sustainable close cooperation between the auditory and visual modality that post lingual deaf individuals can capitalize on during auditory rehabilitation is attainable. Evidence suggests that a synergy between modalities within the left temporal lobe may be a significant neural correlate in cochlear implant success (Anderson et al., 2017).

While cochlear implantation has opened a whole new world of hearing opportunities to the deaf population, the success rate is highly variable and still remains somewhat unpredictable. Although some basic markers for success are noted and understood, more sensitive prognostic tools are needed to accurately predict clinical outcomes. Growing research supports factors such as cortical plasticity within the temporal and temporo-occipital brain regions and synergistic relations between the auditory and visual modality and temporo-occipital interaction. Investigation on safe, sensitive, and thorough techniques to study brain changes pre- and post-implantation is an area of research that continues to expand.

Conclusion

Bypassing damaged peripheral structures, the multi-channel cochlear implant has provided profound to severe hearing-impaired individuals the ability to achieve similar auditory function to their unaffected peers. As anatomical and functional auditory integrity is of paramount importance, early cochlear implantation is a crucial determinant in the probability of a congenitally deaf individual attaining maximum auditory capacity. As supported by extensive data, implantation prior to the completion of the critical period plays an outsized role in neuroplasticity's ability to rewire one's neural circuitry while consequently preventing further recruitment of auditory cortical structures by other sensory modalities. As human sensory hair cells are incapable of regeneration, further research is needed to pursue avenues yet explored in the quest to further mitigate the deleterious side effects of congenital, early and late onset deafness.

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