Neuroplasticity

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Neuroplasticity can be defined as the ability of the nervous system to modify its structure on the basis of different environmental changes and stimulation.

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1. Neuroplasticity: Definition and Mechanisms

Neural plasticity can be distinguished as structural and functional plasticity. The structural plasticity refers to modifications occurring in neurons' axons and dendrites in addition to renovation of these cells and synapses (neurogenesis and synaptogenesis). On the other hand, the functional plasticity comprehends the biochemical mechanisms behind synaptic efficacy [1]. This is a continuous remodeling process which allows short-term, medium-term, and long-term reshaping of the synaptic net, contributing to modifying or renewing its functions [2]. Thus, the brain's plasticity plays a pivotal role throughout the lifespan of the individual, from the critical period in early development—with the creation of new neural maps thanks to learning through sense stimulations—to adulthood and old age, when these circuits are stabilized. However, this neural reshaping may also be elicited by peripheral or central nervous system (CNS) lesions [3][4]. For example, after a peripheral nervous lesion or limb amputation, the corresponding cortical areas begin to receive signals from peripheral areas surrounding the damaged site. This has been documented in the primary motor cortex (M1) after a peripheral nerve lesion, causing the extension of nearby cortical areas in the M1 territory [5]. On the other hand, if a cortical lesion occurs, its function ends up being carried out by nearby cortical areas. Furthermore, animal experimentations showed how, after an M1 ischemic lesion, the use of specific training, such as constraint therapy applied to the limb involved, could enhance the reorganization of unharmed M1 portions [6]. Merzenich et al. demonstrated how the primary cortical sensory map in adult animals can go through a process of reorganization after various peripheral sensory perturbations. In particular, studies on monkeys showed how after the section of the median nerve, somatosensory representation of its innervation areas undergoes rapid reorganization. Moreover, the cortical areas near the ones of the median nerve expand at its expense, as seen for the cortical representations of the ulnar nerve [7][8]. In a study of Kaas et al. based on macaques that underwent upper limb deafferentation 12 years earlier, the stimulation of the animal's face produced activation of the area representing the deafferented limb, showing how there had been a reorganization of these two neighboring cortical areas [9].

1.1. Biological Basis of Neuroplasticity: Microscopic Aspects

The biological processes that underlie neuroplasticity take place at both the microscopic and macroscopic levels. Microscopic mechanisms include neurogenesis, synaptic activity modifications, reactivation of latent synaptic networks, and modulation of neural circuits mediated by glia and an extracellular matrix. During the early stages of development, the proliferation and differentiation of neurons and their structures (e.g., dendrites and axons), as well as their connections through synapses, take place [10]. Afterward, because of sense stimulation and experience, these networks are molded through apoptosis and the modification or regression of synaptic connections [11][12]. These structural changes may also take place after a brain injury, showing renovation in particular dendrites [13]. There is also evidence concerning the role of neurotrophins (NTs) in neural plasticity, mediating the differentiation and survival of neurons in synaptic transmission and reshaping [14][15]. In addition to neurogenesis, synaptic plasticity plays an important role in the brain's reorganization. It refers to the modulation of synaptic efficacy due to repetitive nerve impulses. Thus, this process is based on changing the stimulation from a presynaptic to postsynaptic cell, providing an increase or decrease in synaptic efficacy, named long-term potentiation (LTP) and long-term depression (LTD), respectively [16][3][17][18]. LTP originates from rapid presynaptic depolarization of the synapses, which activates NMDA-type glutamate receptors in the postsynaptic membrane, causing a rise in intracellular Ca^{++} levels. This induces the expression of AMPA-type glutamate receptors in the postsynaptic membrane, leading to an increase in synaptic strength. It also causes the release of brain-derived neuronal growth factor (BDNF) in neurons, which enhances LTP and enlarges the dendrites ([3][19] "AMPARs and synaptic plasticity: The last 25

years"). On the contrary, LTD comes from slow repetitive stimulation of the synapses, which causes a migration of AMPA receptors in the cytoplasm [17]. While LTP has a key role in learning and memorization, as seen in the hippocampus, both LTP and LTD seem to mediate the reorganization of neural networks in the sensory motor cortex [20]. In a review article, Sheperd et al. described how *ARC* gene expression is involved in the regulation of synaptic plasticity. In fact, it seems to control the neural output of excitatory neurons by facilitating LTD and by modulating the expression of AMPA glutamate receptors [21][22]. In a work by Pfeiffer, B. and Huber, K., it is explained how, in order to maintain LTP and LTD as functional synaptic changes in the cortical areas, it seems that local or dendritic specific protein synthesis is required [23]. Another kind of synaptic plasticity is represented by the conversion of silent synapses in active connections. The organization of cortical networks in functional areas is granted by the activity of inhibitor GABA interneurons, which stop the horizontal connections between different areas. Events such as sensory deprivation or learning may interrupt this kind of control, unleashing these latent connections and creating a sort of short-term plasticity [24][25]. A synapse's activity can also be directly influenced by neuroglia. This wide network, through the production of neurotransmitters and extracellular mediators, has the potential to improve synaptic transmission [26][27]. Moreover, glial cells can also communicate with each other by using gap junctions and intracellular messengers [28] to coordinate the activity of neural networks. Control of the neuronal activity is also accomplished by the extracellular matrix [29].

1.2. Biological Basis of Neuroplasticity: Macroscopic Aspects

Several mechanisms lead to functional reshaping at a macroscopic level. Macroscopic changes include cross-modal plasticity, a modality-specific brain area that is deprived of its usual sensory input and becomes responsive to the stimulation of other modalities. For example, the occipital cortex in visually impaired patients may be activated by sound changes [30]. Furthermore, a vicariation modality is possible, as the takeover of the function by areas not originally involved in the damaged performance that are remote from the site of the primary damage, known as diaschisis [31]. Other macroscopic mechanisms of plasticity are functional redundancies, or intrinsic reorganization of eloquent areas with multiple cortical representations of the same function within the same region. On the other hand, a reorganization within a functional network is another crucial pathway, as other regions belonging to the same functional network may be recruited: the perilesional areas first, and if still insufficient to the functional purpose, remote structures [4]. If the unimodal association areas are damaged, there is a rapid over-recruiting of new areas to sustain the impaired process based on an activation–hyperactivation pattern. These compensatory strategies were first described on the dorsolateral prefrontal or intraparietal cortices [32]. These mechanisms can also have a macroscopic impact on the volume of gray matter, as analyses revealed a region of increased gray matter in Broca's area in the left inferior frontal gyrus in musicians, and studies of the anatomical effects after environmental experience and training in humans demonstrated a cortical volumetric increase [33][34].

2. Neuroplasticity in the Auditory System

The initial idea of plasticity applied to the hearing system was that of a process starting once the inner ear starts functioning and then shaped by experience only during a critical period in early development. However, in the last few decades, several studies demonstrated how the auditory system remains capable of reorganizing itself in response to different auditory stimulations or sensory organ modifications. Thus, the auditory system has a plasticity potential which also continues in adulthood. This process may vary from short-term adaptation to long-term modification of neural circuits, as seen in the case of hearing loss. This may derive from the effect of different sensory inputs (bottom-up processes) or the influence of learning, attention, or doing specific tasks (top-down processes) [35][36][37].

2.1. Mechanisms of Auditory Plasticity

An example of auditory system plasticity is stimulus-specific adaptation (SAA), a process leading to a lower neuron response to repeated acoustic stimulation [38]. This has been demonstrated by presenting a series of identical stimuli interspersed with individual different ones, during which neurons showed adaptation to first stimuli while they continued responding to the second ones. Such findings suggest how SSA could be a sort of adaptation of the auditory cortex to acoustic stimuli in order to focus only on relevant ones [36]. Hearing system plasticity may also happen as a consequence of hearing loss so that it reorganizes itself after the injury. The first studies about this kind of plasticity were performed on animals and adult humans after cochlear injury, analyzing changes in a neuron's frequency sound selectivity and the remodeling of the corresponding area in cortical tonotopical map [36][39]. In fact, damage to hair cells in the cochlea or exposure to high-intensity sounds can result in the inability to discriminate precise sound frequencies. It has been noted that, after an injury, the portions of the auditory cortex surrounding the area which represented the damaged part of the cochlea expands at its expense [37][40]. The result is that a higher number of neurons focus on frequencies that are still heard. However, even if this plasticity may seem useful because it avoids losing frequency discrimination, it disrupts the

neural coding in the auditory cortex. In fact, the reorganization of the auditory system, which has the aim to continue hearing certain frequencies after an injury, does not help to recover from hearing loss [30][36]. On the contrary, it seems to be a maladaptive process, as it has been associated with tinnitus [36]. This may result from the fact that, after an injury, some neurons in the auditory cortex start responding to different frequencies, which could lead to inappropriate coding of certain frequency stimuli [35][41][42]. Patients suffering from these kinds of injuries can benefit from the use of cochlear implants. In particular, it has been noted how hearing recovery largely depends on the auditory system plasticity induced by these hearing aids [43]. The role of these implants is to make the patient hear certain sound frequencies again after a cochlear injury so that the neurons which used to respond to those frequencies can be stimulated again. After implantation in deaf adults due to cochlear injuries, sound frequency discrimination and thus speech understanding are gradually restored [44][45]. These implants' effects on the auditory cortex can be observed through magnetoencephalography (MEG). Pantev et al. reported increased evoked brain activity in the auditory cortexes of two deaf adults with implants, which related to the increase of neural activity in these areas due to the restored auditory stimuli [46]. It is important to consider that the beneficial effect of hearing aids depends on when they are implanted after the cochlear injury. We discussed above how, after an injury, auditory fields which were stimulated from that part of the damaged cochlea start responding to the frequencies of nearby neurons. This could lead to interference between these stimuli and those provided by hearing aids [35]. Moreover, the deprivation of this stimulation can also induce cross-modal plasticity of other sensory modalities at the expense of these auditory cortex areas [47]. The result is that these patients will not benefit from hearing aid stimulation, or at least these forms of plasticity can lead to a maladaptation if hearing aids are implanted late [48][49]. For this reason, in order to obtain the best result from hearing aids, it is important to consider early implantation after an injury [35][37].

Plasticity in the hearing system may also derive from the repetition of a specific pattern of tasks, consisting of focusing and discriminating specific auditory stimuli. This kind of training is known as perceptual learning. Most studies on this form of plasticity were based on training regarding sound frequency discrimination. During the training in animals, as the frequency identification improves, there is a progressive increase in the representation of those frequencies in the auditory cortex [50][51]. In humans, an example of perceptual learning is the one resulting from musical training, which influences the cortical processing of sound stimuli both in the auditory cortex and in the brainstem [52][53].

2.2. Biological Basis of Auditory Plasticity

Auditory plasticity develops at microscopic levels through different processes, including molecular and cellular mechanisms involved in cortex reorganization. Brain-derived neurotrophic factor (BDNF) plays a role in adult organization of the auditory cortex [54]. BDNF contributes to the maturation of GABAergic interneurons including parvalbumin (PV) interneurons, which contribute to regulating the onset and ending of critical periods and thus the plasticity potential [55]. In fact, a reduction of inhibitory transmission has the potential to re-open the plasticity window of the critical period [56]. This can be achieved through the loss of acoustic input at a juvenile age [57] or in adulthood [58]. Glutamate has also been found to have a role in auditory plasticity, as a block of NMDA receptors performed using ketamine reduces the amplitude and augments the latency of Mismatch Negativity (MMN). MMN is an evoked potential which occurs in response to an unexpected auditory stimulus, placed in a series of repetitive tones which differ from the latter. MMN is considered to be a measure of auditory plasticity, as it can be generated by the nervous system only if a memory trace of the repetitive tones has already been formed. In fact, the stimulus-specific adaptation (SSA) of auditory cortex neurons to these patterns seems to be necessary for MMN [59]. Microglia are also able to mediate cortical plasticity. These nonneural cells are activated after brain damage and act by removing neurons' debris after their death, but they are also active in non-injured brains through monitoring synaptic functions and playing a role in their maturation or elimination through fagocitation of axonal terminals and dendritic spines. In a study conducted on mice, Paolicelli et al. showed these roles of microglia on the synapses. In particular, the study was based on mice lacking Cx3cr1, a receptor for fractaline, a chemochine which guides microglia migration. These receptors are usually expressed on neurons through which they recall the microglia. During their development, mice brains lacking these receptors showed lowered synaptic pruning, which resulted in immature synapses [60][61]. Microglia activity may be induced by traumatic noise exposure [62]. Neurotransmitters have the potential to influence synaptic plasticity. Cholinergic projections to the auditory cortex can play a role in plasticity by inhibiting PV interneurons during the development ages in the critical period [63] and also in adulthood [64]. In an experiment on cats, McKenna et al. showed how, in the presence of ACh during a presentation of a series of different tones with different sound frequency stimuli, there was a facilitated response in the auditory cortex toward frequencies which differed from the neurons' "best frequency" [65]. Kilgard et al. demonstrated how a simultaneous electrical stimulation of an adult rat's basal forebrain (thus with consequent cholinergic cortical projections) and presentation of auditory stimuli with a precise frequency produced an expansion of the auditory cortex tuned on that frequency [66].

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