Med & Health Jun 2023; 18(1): 4-8 https://doi.org/10.17576/MH.2023.1801.02

EDITORIAL

Neuroplasticity of the Brain: An Uncharted Sea with Great potential?

SRIJIT D, SADHANA R

Department of Human & Clinical Anatomy, College of Medicine & Health Sciences, Sultan Qaboos University, Al Khoud, Muscat 123, Sultanate of Oman

The word 'plastic' is derived from the Latin word 'plasticus' which means molded or formed. Neuroplasticity is a process during which there is an adaptive structural and functional change in the brain in response to a stimulus. In simple terms, the nerve cells adjust to an altered environment. According to researchers, a better definition might be "the ability of the nervous system to change its activity in response to intrinsic or extrinsic stimuli by reorganizing its structure, functions, or connections" (Mateos-Aparicio & Rodríguez-Moreno 2019). In neural plasticity, or brain plasticity, the nervous system changes its activity with regard to structure, function, or connection in response to any extrinsic or intrinsic stimuli (Mateos-Aparicio & Rodríguez-Moreno 2019).

In an earlier concept by the famous neuroscientist Santiago Ramon y Cajal, it was suggested that the increase in the number of connections between neurons could augment the capacity of the brain (Jones 1994; DeFelipe 2006). Every neuron relays impulses through multiple synapses. A child's brain, as it grows, develops manifold synapses. It was reported that at birth, every neuron in the cerebral cortex has 2,500 synapses, and by the age of three, the child has approximately 15,000 synapses per neuron (Judith 2022).

The immense neuroplasticity of the human brain is evident in the complex processes governing its embryonic development. Each neuroprogenitor cell (NPC) lining the embryonic neural tube (neuroepithelium) at first undergoes symmetric mitotic divisions to form more NPCs, but in later stages it shows linear specificity, an asymmetric cell division to form an NPC and a neuron. Early neurons located in the ventricular zone (VZ) initially migrate to the deepest cortical region of the human neocortex. Neurons from this transient zone migrate more superficially to form the pre-plate (PP) neuron layer, which is further split into a marginal zone (MZ) and a sub-plate region (SP) by new superficially migrating neurons. The VZ, PP, MZ, and SP are all transient populations of neurons but are essential for the

Address for correspondence and reprint requests: : Dr. Srijit Das. Department of Human & Clinical Anatomy, College of Medicine & Health Sciences, Sultan Qaboos University. P.O. Box 35, Al-Khoud, Muscat 123, Sultanate of Oman. Tel: +968-24143546 E-mail: drsrijit@gmail.com

six cortical layers of the mature brain to form normally. These neurons eventually undergo apoptosis during the fetal period. Postnatally, the excessive synapses formed during this early neurogenesis, also regress, thus exhibiting not only immense neuroplasticity but different timelines as well (Stiles & Jernigan 2010). Thus, during the process of neurogenesis, the brain eliminates all connections that are rarely used (Judith 2022). However, despite this mass regression of neurons and their connections, the adult human brain retains a 100 billion neurons (Pakkenberg & Gundersen 1997) with approximately 60 trillion synapses, which enable the nervous system to perceive and make appropriate responses to both external and intrinsic stimuli, manifesting as our thoughts, memories, actions, and feelings (Stiles & Jernigan 2010). Given these surfeits of neuronal connections, the existence and potential of neuroplasticity in the human brain raises exciting possibilities for the future of neuro-regenerative medicine, following pathological processes that ravage the structure and hence function of the brain, which were hitherto considered irreversible brain damage.

The structural differentiation of neurons and their distinct synapses during development, results in the creation of distinct cortical structural and hence functional areas, another example of its immense neuroplasticity. These areas receive different inputs, have their own distinct connections with other brain areas, and govern different types of functional responses. This differentiation into sensory, motor, or other areas, is determined by different molecular signals such as *Emx2* and *Pax6*, two transcription factors expressed by the same genes that are essential for the early patterning of these areas (Bishop et al. 2002; Hamasaki et al. 2004; Bishop et al. 2000).

The interplay between these molecules determines whether an area is destined to function as a motor or sensory area. A higher concentration of Pax6, combined with low Emx2 expression in certain areas, determines the differentiation of the motor cortex, and a reverse concentration results in the differentiation of the visual cortex. Intermediate levels of both of these factors govern the differentiation of the sensory cortex. This raises the exciting possibility of selective neuronal regeneration by reactivating or blocking these transcription factors, which could then perhaps induce the NPCs to differentiate into a specific damaged functional area. Coup-TF1 and SP8 are other signaling molecules that are selectively expressed in specific areas of the developing brain and additionally control the differentiation of specific functional areas.

It was found that blocking the expression of these genes results in distinct alterations in the sensorimotor organization of the neocortex (O'Leary et al. 2007; O'Leary & Sahara 2008). Further differentiation of these functional areas continues in the later fetal and postnatal periods. Significantly, in the early postnatal period, the structural and functional identity of these basic brain areas remains adaptable and 'plastic', hence

is influenced by experiences, stimuli, and other inputs-thus, nurture can mold nature.

Could a brain then be compared to a computer? A computer has a distinct stored programme memory for its functions. On the other hand, the brain has neural pathways or connections that are reported to replicate those of another functional area. Hence, minor errors in development, or even temporary loss of function due to neuronal insult, can be easily rectified by rerouting signals along a different pathway (The Conversation 2016). This fact is further emphasized by the immense neuroplasticity and adaptability exhibited by the brain in cases of congenital anomalies of the brain or neural tube defects compatible with survival.

In adults, given the vulnerability of the brain to pathological processes, be it cerebrovascular accidents, (a hemorrhagic or an ischemic stroke), neurodegenerative disorders such as multiple sclerosis or Alzheimer's disease, tumors, or traumatic injuries, it becomes vital to attempt to restore the normal functioning of the brain as soon as possible, to avoid permanent disability. Hence the potential of neuroplasticity in enabling the establishment of new neuronal connections, thus facilitating the recovery of a damaged area in the brain, cannot be undermined. An interesting fact is that rigorous treatment following a stroke episode, helps to reverse the brain damage caused by inadequate blood supply and assists in restoring the functionality of damaged connections (The Conversation 2016). It cannot be forgotten that the brain needs oxygen and glucose for its metabolism. The ability of the brain to store metabolic nutrients is limited, and the cerebral blood flow is proportional to the metabolic rate (Karbowski 2011; Fregni & Pascual-Leone 2007). Reinforcement or repetitive activities in a patient, cause the adult brain to retain the memory of the new activity, but the recovery may depend upon the size of the damaged area, treatment, rehabilitation, and the age of the brain (The Conversation 2016). The extent of damage also depends on whether the stroke is ischemic or hemorrhagic.

Several strategies have been proposed by various researchers in order to enhance neuroplasticity. These include transcranial direct current stimulation (Fregni & Pascual-Leone 2007) deep brain stimulation (Johnson et al. 2008), functional electrical stimulation (Chen et al. 2006), aerobic exercise (Rhyu et al. 2010), brain derived neurotropic factor therapy (Tanaka et al. 2014), statins, erythropoietin therapy (Keswani et al. 2004), phosphodiesterase type 5 inhibitors (PDE-5 inhibitors) (Reierson et al. 2019), and vascular endothelial growth factor (VEGF) therapy (Zhang et al. 2000).

Studies on neurogenesis in the adult have revealed that this process occurs throughout life in all mammals, (Eriksson et al. 1998) but is restricted to specific areas in the human brain, under normal conditions, namely the dentate gyrus of the hippocampus and the subventricular zone of the lateral ventricle (SVZ). New neurons are continuously generated in the SVZ

and migrate to the olfactory bulb to function as interneurons (Gage 2000; Ming & Song 2011)

In Alzheimer's disease patients, where early degenerative changes are seen in the hippocampus and dentate gyrus, resulting in anterograde amnesia (recent memory loss), and subsequently gradually worsening to retrograde amnesia (long term memory deficit), new adult granule cells in the dentate gyrus offer an exciting possibility as a regenerative cure for such degenerative disorders.

Recent research focused on studying the regenerative capacity of neural precursor cells (NPCs) found in certain zones of the brain is gaining momentum. NPCs are being considered one of the best sources of 'stem cells' due to their capacity to produce specific CNS cells, including neurons, astrocytes, and oligodendrocytes (Gage 2000).

Studies on mouse cell lines, on the effects of an orexin receptor antagonist such as 20 µm of JNJ-10397049, in low concentration, on the behavior of NPCs revealed that it helped in increased differentiation of oligodendrocytes from the existing NPC population (Karami et al. 2022).

In demyelinating diseases like multiple sclerosis, sleep patterns are severely disrupted in these patients, with debilitating insomnia. The orexin-rich neurons in the hypothalamus and other regions regulate neurotransmitters involved in these cycles, such as serotonin, acetylcholine etc. An orexin antagonist drug like Suvorexant helps ameliorate insomnia in these patients, by promoting oligodendrocyte proliferation from NPCs, thus increasing their potential to re-generate myelin. It also has potential for other degenerative conditions like Alzheimer's disease. The ongoing studies further highlight the tremendous potential of neuroplasticity, even in the adult brain (Karami et al. 2022).

In conclusion, there is great potential to harness this property of neural plasticity following cerebral damage, to enable the brain to recover its compromised function. While a complete, rapid recovery is still a distant goal, with neural plasticity facilitation, a stroke patient may regain some measure of strength, power, and lost skills, and thus, develop confidence and become independent with the restoration of function. Neuroplasticity in the human brain is like an uncharted sea, with immense possibilities due to the inherent capacity of the human brain to adapt and reorganize itself, not only during development, but also following injury. Learning more about the phenomenal capacity of the human brain to adapt to situations hitherto deemed fatal, and acquiring the capability to harness its neuroplasticity, neurogenerative medicine will hopefully cross a new and exciting frontier in the near future.

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Received: 16 May 2023
Accepted: 17 May 2023