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THE TRUTH ABOUT BRAIN CELLS: IS ADULT NEUROGENESIS POSSIBLE?

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ABSTRACT

Background and Objective:

Brain cells regeneration involves renewal and repair of neurons and other cells in the brain, with restoration of their functions. Although this phenomenon was thought to end in early childhood, research has proven that adult neurogenesis is highly possible with some limitations. Regeneration of axons in the central nervous system is very slow and more complicated than neuronal regeneration, especially regeneration of peripheral nerves. Brain cell regeneration in the adult brain can help in recovery of damaged brain cells and correct cellular and brain tissue dysfunction that are commonly seen in some neurological disorders such as Stroke, Traumatic Brain Injury and some neurodegenerative diseases like, Dementia, Alzheimer's disease etc. Adult brain cells regeneration is a complex process that occurs in specific areas of the adult brain such as the Hippocampus and Ventricular zone and involves the formation of new neuronal cells from neural stem cells (Neurogenesis), as well as the formation of new neural connections (Neuroplasticity). This study investigates the processes involved in brain cell regeneration, the intersecting relationships between neurogenesis, neuroplasticity and therapeutic treatment of neurological disorders and the hope for better approaches to the permanent treatment of some neurodegenerative disorders.

METHODS:

This study was conducted with the review of literature from PubMed and Google Scholar along with a worldwide online survey with Google forms and questionnaires.

RESULTS:

There were 525 participants in this study.79% neurologists/neurosurgeons took part in the study. 85.7% had heard of neuroplasticity and neurogenesis before. 86.1% agreed that brain cells can regenerate. 97.1% said neurons while 91.6% said glial cells are capable of regeneration after brain injury. 36% agreed that brain cell regeneration can occur after TBI. 36.4% agreed that brain cells regeneration can occur after stroke. 96.4% agreed for neuronal stem cell implantation, 61.1% agreed for gene therapy and 60% for endogenous regeneration as the most effective method of maximising neuronal regeneration in the brain. Most agreed that the hippocampus and subventricular zone are common sites of brain cells regeneration.

CONCLUSIONS:

Resource analysis and the study concluded that adult neurogenesis is possible but it may take years for the brain cells to regenerate and repair. Further research is needed to investigate adult neurogenesis.

KEY WORDS: Regeneration, Neurogenesis, Neuroplasticity, Neurodegenerative diseases, Neurological disorders.

INTRODUCTION

Adult neurogenesis is a hotly debated and controversial topic among neuroscientists.[1] Brain cell regeneration is a complex process that involves the formation of neurons, axons, glial cells and synapses. Neurons and neuroglial cells are formed from the neural tube. The single cell layer of the neural tube multiplies to form the Marginal cell layer, Mantle layer and Marginal layer. The mantle layer and marginal cell layer gives rise to neurons and neuroglial cells, while neuroblasts from the mantle layer form the axon and dendrites, while germinal cells from the ependymal cell layer form the neuroblasts and neuroglial cells.[2] Permanent cells such as neurons and cardiac myocytes have limited regenerative and proliferating capacities in the cell cycle. Injuries to permanent cells/tissues result in

scarring.[3] During brain injury, the connection between neurons, known as Synapses, is altered.

Until a few decades ago, scientists believed that neurogenesis was limited or restricted to embryonic period and early childhood. This belief was based on the hypothesis that mature neurons do not undergo cell division. Recent studies have proven that adult neurogenesis is possible, with few limitations. Adult neurogenesis occurs in specific areas of the brain such as the Hippocampus and Subventricular zone through proliferation of neural stem cells. It also occurs in the olfactory bulb, hypothalamus and amygdala. Recent studies have shown that adult neurogenesis can probably occur in the cerebral cortex. Cells in the hippocampus studied through Carbon-14 dating have proven that neurogenesis can occur in the hippocampus, without the loss of any of its vital functions. However, neurogenesis in the hippocampus declines with aging.[4]

Some neurotrophic growth factors and neurotransmitters such as Gamma-amino butyric acid (GABA), Glutamate, Serotonin and Dopamine have been shown to be associated with adult neurogenesis. There is also a strong link between nutrition and adult neurogenesis. Neural stem cells have the potential to proliferate, substitute for lost tissues, survive and integrate into existing neural networks when a brain cell or tissue is damaged which may progress to the structural and functional recovery of the damaged brain cells or tissues. A dysfunction in any part of the brain or nervous system, due to problems in the formation of new brain cells and inability to establish proper neural networks may result in neurological disorders such as Stroke, Alzheimer's disease, Parkinson's disease etc. Over one billion people suffer from neurological disorders with over 6.8 million resulting deaths annually.

Knowledge of the processes and limitations of permanent cell regeneration and repair, neurogenesis and neuroplasticity may help reshape the future of neurological disorders following accidents, trauma or degeneration due to aging. This research investigates how these methods can help improvement and approaches to therapeutic/treatment strategies. With extensive knowledge and practical approaches, there is hope in the breakthrough in future neuroscience/neurology that may lead to the complete treatment of central nervous system degenerative disorders, stroke and traumatic brain injury.

METHODS

Data was collected from five hundred and twenty five experts and students in the field of neurology and neurosurgery all over the world through a random sampling technique via an online survey using Google forms and questionnaires.

RESULTS

The results of the survey are shown in the following figures:

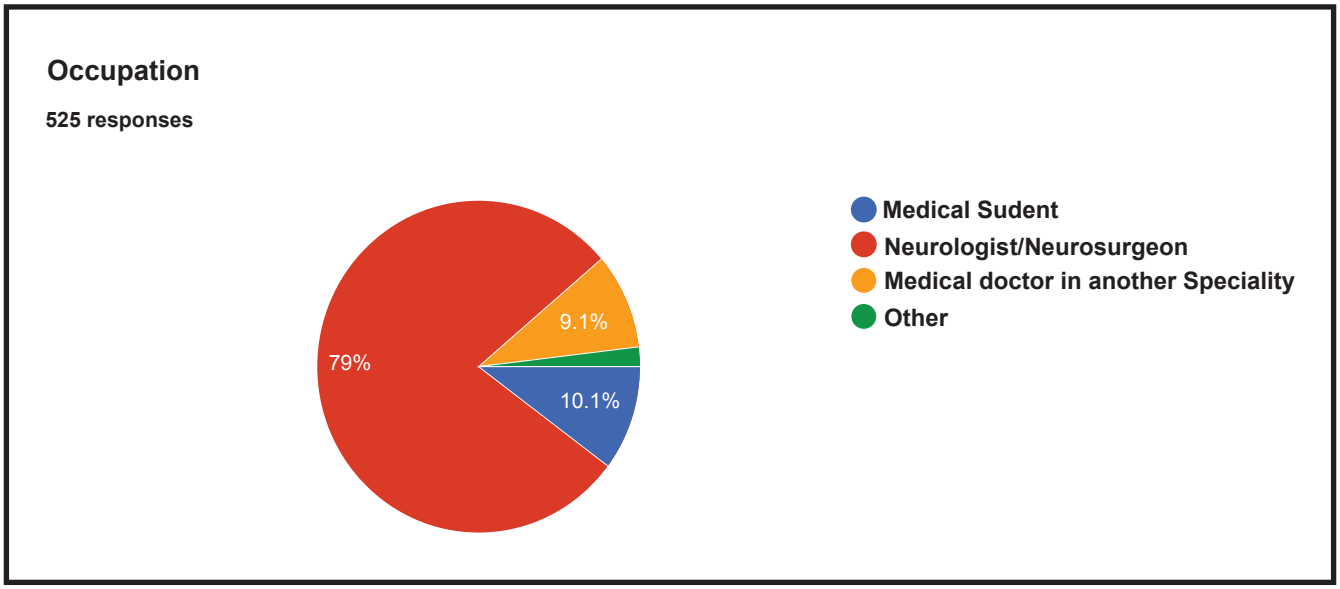

FIGURE 1: OCCUPATION OF PARTICIPANTS

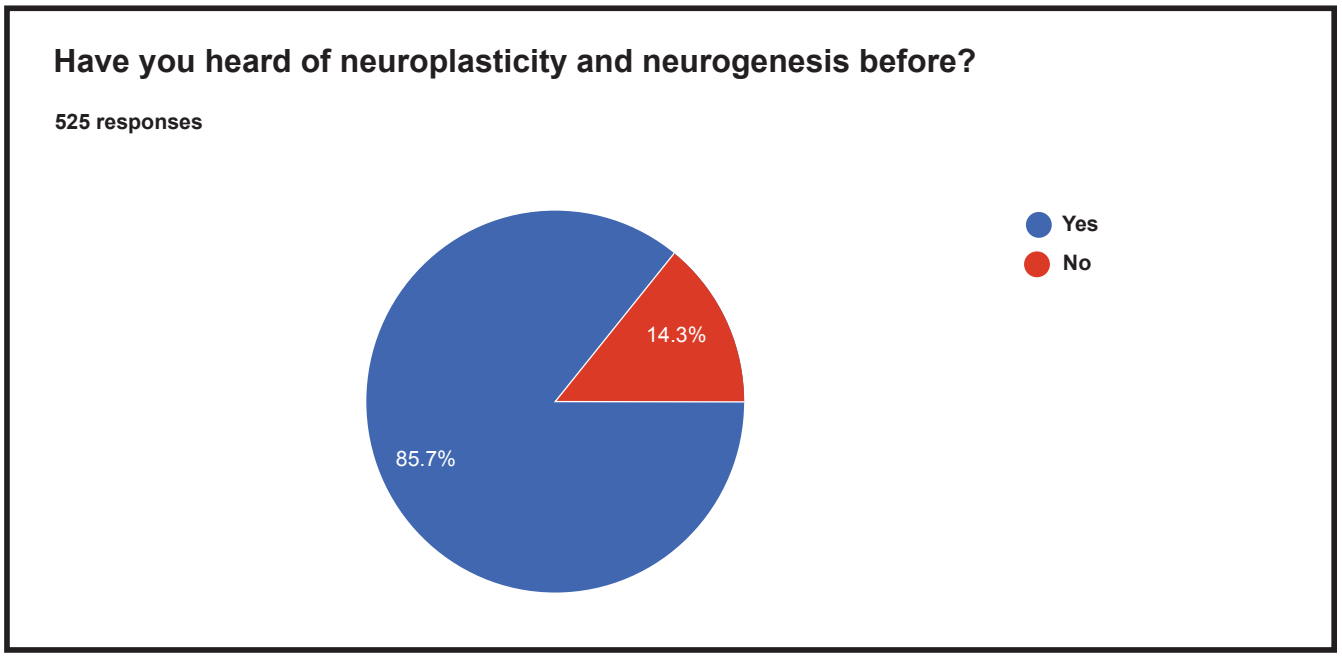

FIGURE 2: RESULTS OF KNOWLEDGE ABOUT NEUROPLASTICITY AND NEUROGENESIS

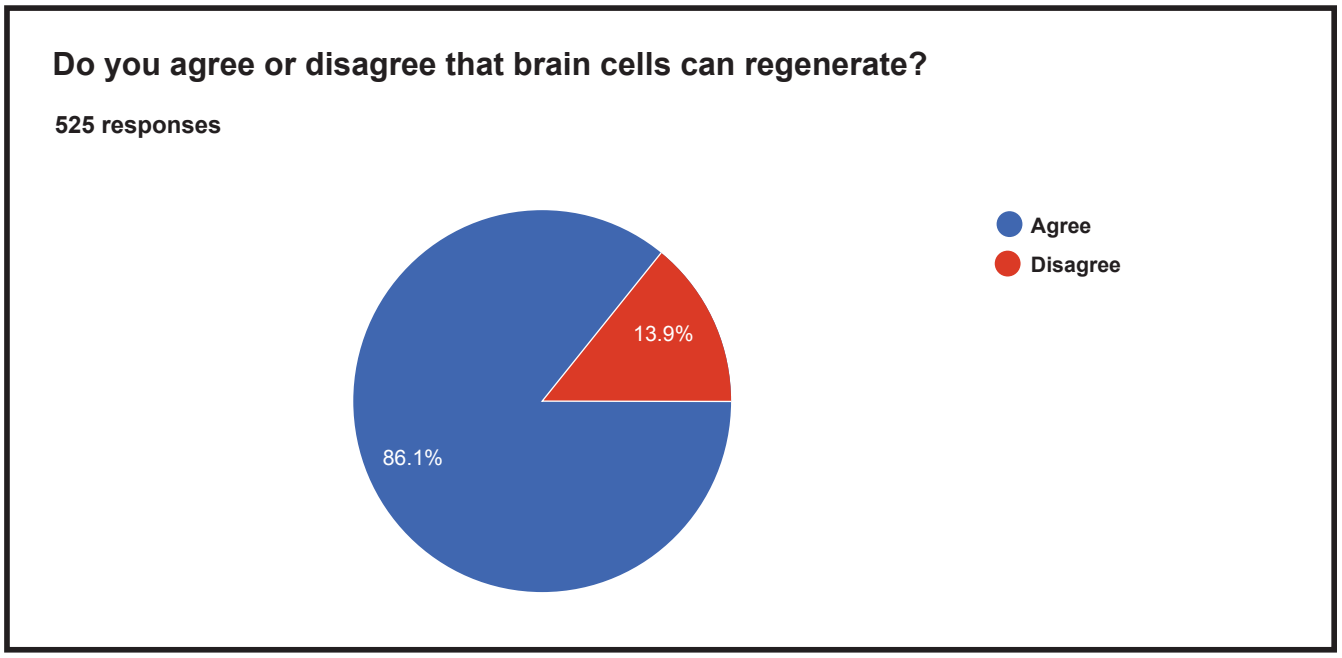

FIGURE 3: RESULTS OF AGREEMENT AND DISAGREEMENT OF REGENERATION OF BRAIN CELLS

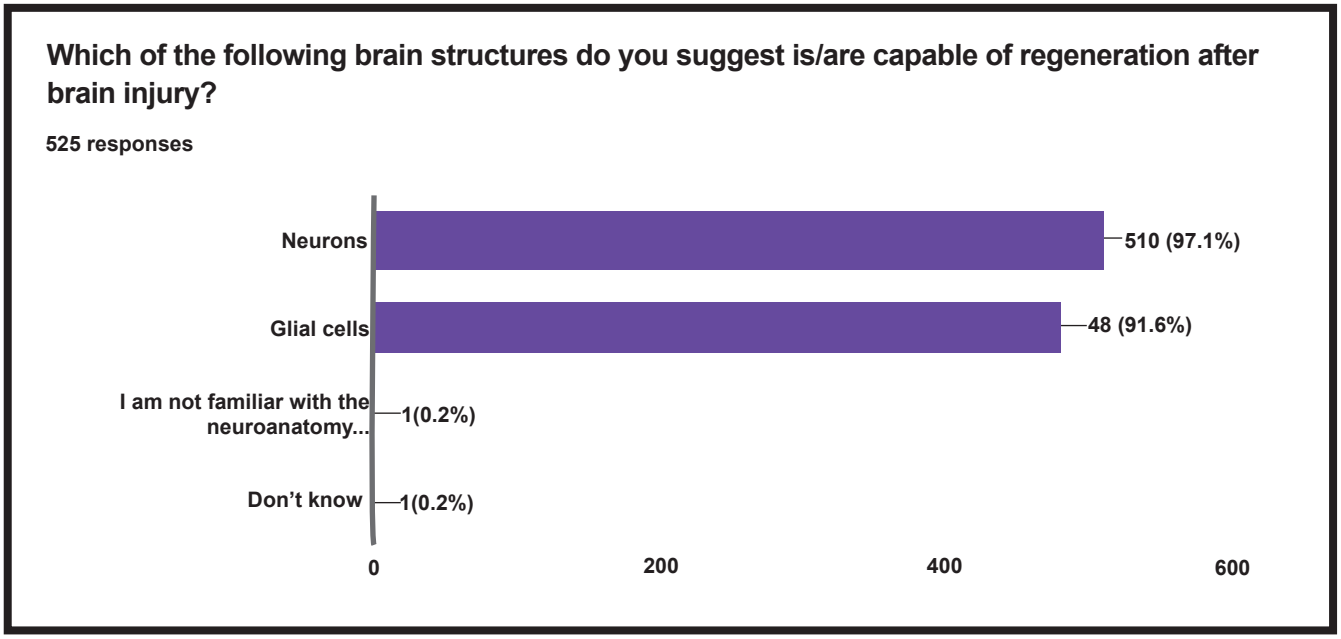

FIGURE 4: BRAIN STRUCTURES CAPABLE OF REGENERATION AFTER INJURY

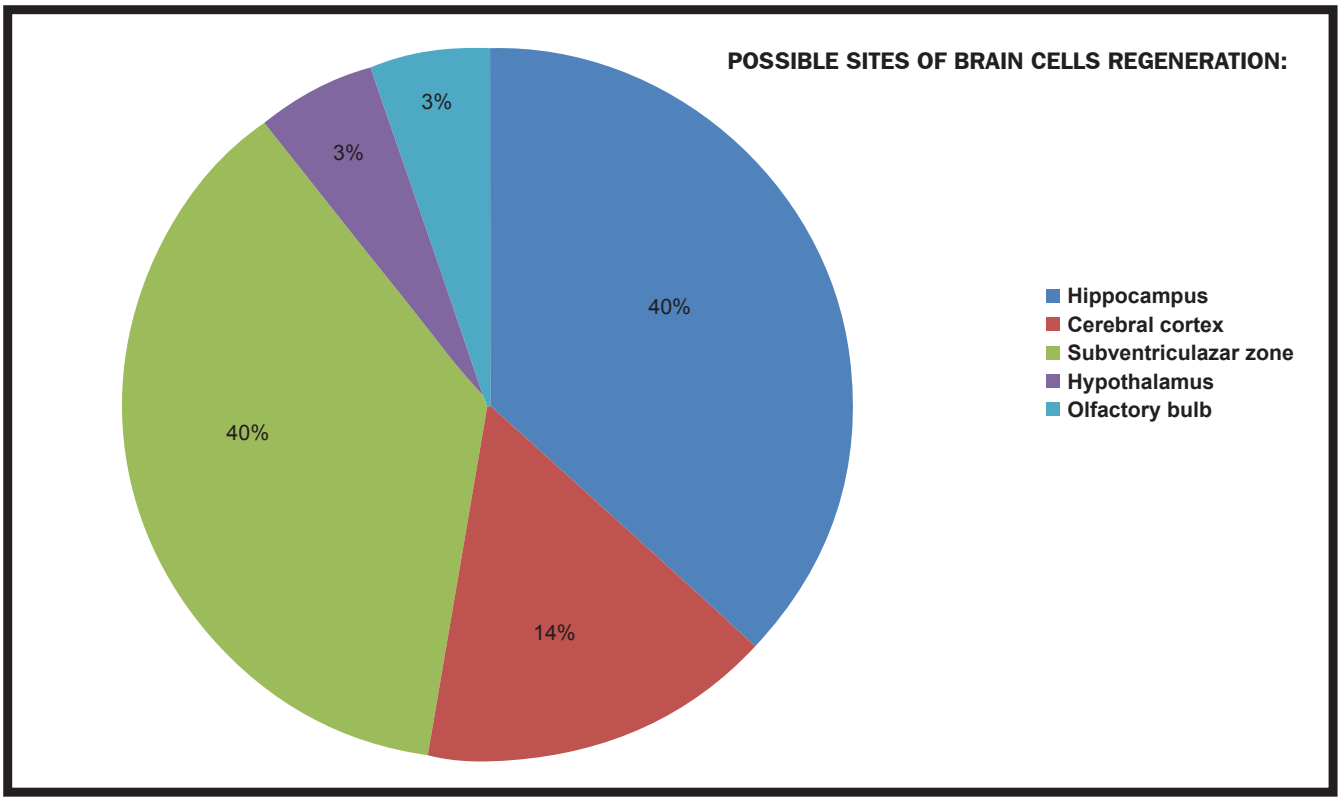

FIGURE 5: POSSIBLE SITES OF BRAIN CELLS REGENERATION

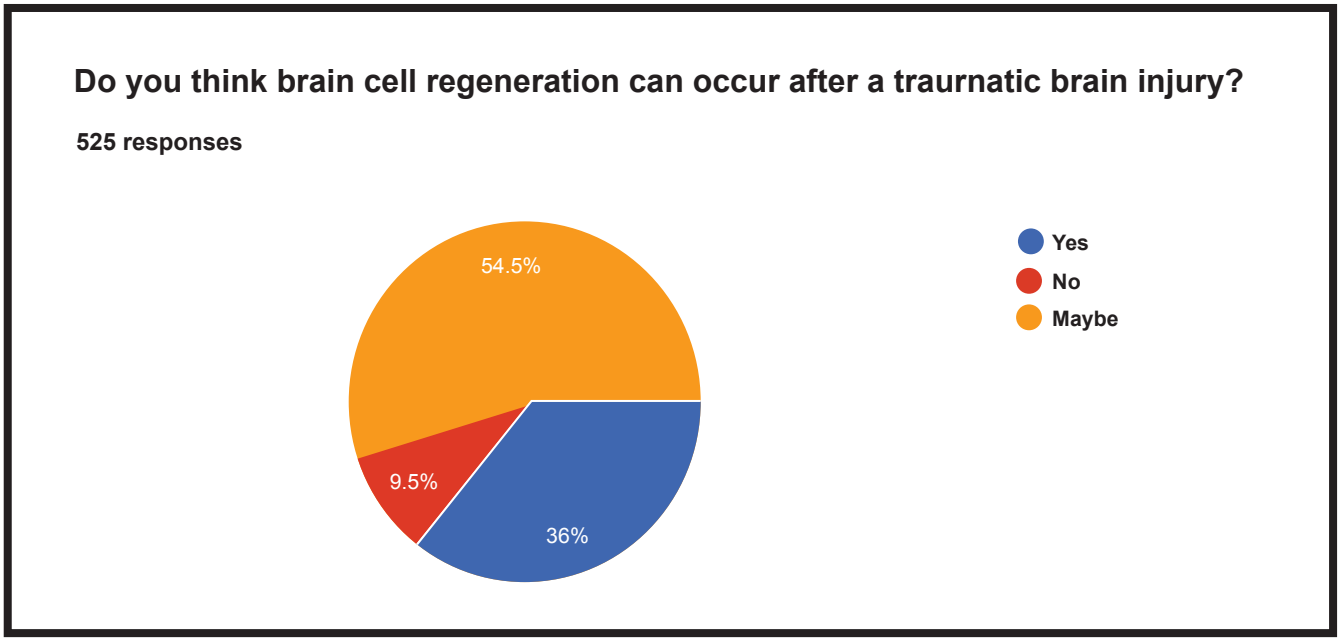

FIGURE 6: BRAIN CELLS REGENERATION AFTER TBI

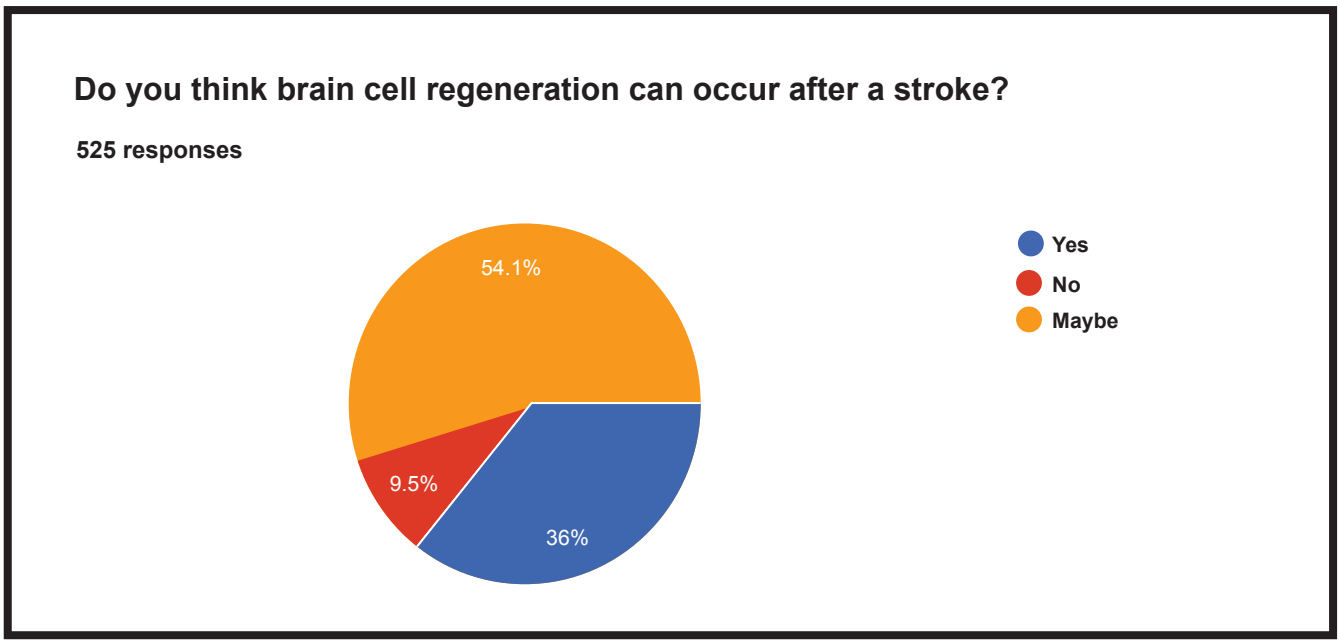

FIGURE 7: BRAIN CELLS REGENERATION AFTER STROKE

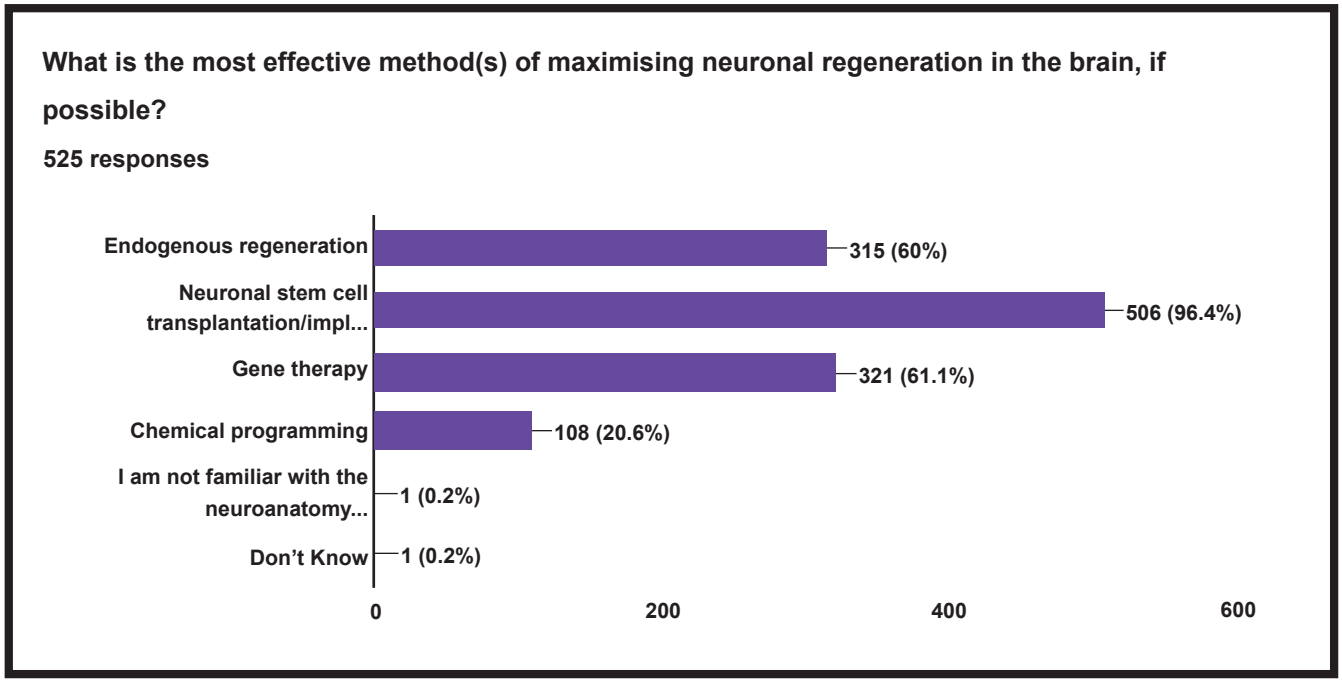

FIGURE 8: MOST EFFECTIVE METHOD(S) OF MAXIMISING NEURONAL REGENERATION IN THE BRAIN

According to this survey, 79% of neurologists/neurosurgeons were involved in the study. 85.7% had heard of neuroplasticity and neurogenesis before. 86.1% agreed that brain cells can regenerate. 97.1% said neurons while 91.6% said glial cells are capable of regeneration after brain injury. 36% agreed that brain cell regeneration can occur after TBI. 36.4% agreed that brain cells regeneration can occur after stroke. 96.4% agreed for neuronal stem cell implantation, 61.1% agreed for gene therapy and 60% agreed for endogenous regeneration as the most effective method of maximising neuronal regeneration in the brain. Most agreed that the hippocampus and subventricular zone are common sites of brain cells regeneration. The results of the online survey show that there is hope for regeneration of brain cells after brain injury. Several factors such as good nutrition and brain exercises can help stimulate the connection and strength of neuron synapses. Factors such as age, excessive alcohol consumption, smoking, stress, anxiety, overthinking, lack of sleep and exposures to carcinogens and free radicals may impair adult neurogenesis.

LITERATURE REVIEW AND DISCUSSION:

Adult neurogenesis is a multi-step process in which neurons are produced from dividing adult neural stem cells and then migrate to join existing neuronal circuits. Any of these changes limit neurogenesis and degrade brain function, resulting in cognitive impairment and neurodegenerative disorders.[5] For decades, several contrasting studies on neuronal regeneration have led to the disapproval of the fundamental principle of neuroscience that stemmed the idea that neurogenesis can only occur in the prenatal phase of human development. Until the late 20th century, it was believed that adult neurogenesis was almost impossible as the brain cells had limited capacity to regenerate, leading to a leap breakthrough in research studies on comparative ante mortem and post mortem normal and damaged brain cells. A review of some published articles was carried out on PubMed and Google Scholar. Searched articles related to the keywords of this study with no date restrictions were reviewed.

Josef Altman had a significant impact on the scientific community's understanding of neural plasticity in recent decades. Altman's results paved the way for an entire branch of neuroscience research dedicated to examining the adult brain's ability to generate new neurons, which had previously been thought impossible.[6] Autolysis, brain edema in some cases and inability to differentiate between the gray and white

matter are commonly seen in normal post-mortem CT scans of the brain. The subventricular zone and olfactory bulb are the most common areas used for experiments on neuroplasticity on brain cells not affected by stroke, traumatic brain injury or degenerative diseases. The ability to extract, grow, and transplant stem cells has given rise to a new specialty of medicine known as regenerative medicine.3 Neuronal regeneration is believed to be more complicated than glial cells regeneration in response to brain injury. Glial cells in response to brain injury can undergo cell division and multiplication, otherwise known as hyperplasia at site of injury or around damaged brain cells to form scars from further injury and block the growth and signal transmission/transduction between neurons.

A research study by University of California, San Diego School Of Medicine published on the 15th April, 2020 in Nature's Issue suggested that during brain injury, adult brain cells may regress back to its embryonic stage, which makes the injured brain cells capable of stumping, axonal sprouting and forming new connections for repair purposes. Attempts at repair are being made by chemically reprogramming glial cells into neurons by using a series of about nine small molecules but the results have not been satisfactory.[7] Grafted neural stem cells from the subventricular zone or dentate gyrus of the hippocampus in the adult human brain can promote repair after brain injury in some cases. The neurons spread out their axons to injury sites and form new connections. This may help to restore lost cognitive or motor functions.

Basic fibroblast growth factor (FGF2), Hepatocyte growth factor (HGF), Ciliary neurotrophic factor (CNTF), Sonic hedgehog (SHH), Galectin-1, Notch-1 and Noggin are some of the factors responsible for regulating the Wnt niche signalling and Bone Morphogenic proteins (BMPs) of neural stem cells in the dentate gyrus of the hippocampus and subventricular zone in the brain. Repairing central nervous system damage, especially brain damage can be tasking and difficult, but it is not impossible. During the regeneration and repair of damaged glial and neuronal cells, endogenous neural stem cells and pro-regenerative molecules are believed to play important roles. Several factors need to be present for successful regeneration to occur. They include:

1. Minimal separation of cut ends and connection of two ends of the crushed neuron.
2. The endoneurial sheath must be present, because a loss in the endoneurial sheath will promote degeneration.
3. Absence of tissue scar formation and infections.2

REGENERATION AND REPAIR AFTER A STROKE:

Stroke is a cerebrovascular accident (CVA) or an acute neurologic deficit which may be global or focal in origin. Any acute neurologic deficit which persists for more than 24 hours is known as Transient Ischemic Attack (TIA) or complete stroke. Stroke may result from ischemic or hemorrhagic vascular lesions. Stroke caused by ischemia occurs in about 80% of stroke cases, while hemorrhagic stroke occurs in about 20%. Of stroke cases. Stroke resulting from embolism, hypoxia, ischemia or infarction is categorized under obstructive vascular lesions, which may be global or focal, whereas, stroke resulting from rupture of the vessels in the central nervous system as a result of external factors such as Hypertension, Aneurysm or vascular malformations are categorized as hemorrhagic stroke. The clinical manifestations of stroke depend on the affected location in the brain, which may be rapidly resolved or lead to progressive partial or permanent disabilities. Stroke is the leading cause of neurologic morbidity and mortality also occur in the young and older people aged 60 years and over.

Adult neurogenesis after stroke is difficult as regrowing axons from stumps may be very slow and recovery after a stroke may last from some months to years. On microscopy, dead brain cells caused by hypoxia after a stroke reveal an avascular crater-like cavity in the brain with no axons or neurons. Neurons, astrocytes and oligodendrocytes are the commonly affected brain cells during a cerebrovascular accident. The loss of axons and neurons accounts for the functional long term or lifelong disabilities after a stroke.3,[8]

Some experiments suggest that neurogenesis can occur in stroke patients in the striatum and cerebral cortex, and more neural stem progenitor cells are generated in the subventricular zone for endogenous regeneration and repair, in response to brain injury.6 Rehabilitation after a stroke is encouraged to reduce the severity of impairments caused by hypoxia during the stroke, but absolute regeneration and repair may be almost impossible.

REGENERATION AND REPAIR AFTER TRAUMATIC BRAIN INJURY (TBI):

The most common cause of Traumatic Brain Injury (TBI) is Road Traffic Accidents. Other causes include: A heavy blow or hitting the head with a heavy object such as a heavy metal, stabbing and gunshot injuries to the area of the brain. TBI encompasses different neurological lesions such as: Brain contusion, subarachnoid

hemorrhage, epidural hematoma, subdural hematoma, Intraventricular hemorrhage and skull fractures.[9] The influence of plasticity in the context of a young, damaged brain is less well understood.[10] In response to brain injury, neural stem cells have regenerative and repair mechanisms which have not been fully understood. Endogenous regeneration, neuronal stem cell transplantation, gene therapy and chemical programming are some of the effective methods of promoting the regeneration and repair of damaged brain cells, especially in adults.[11]

FUTURE OF NEURODEGENERATIVE DISEASES:

Neurodegenerative diseases are the disorders that affect the central nervous system. They commonly affect the motor neurons, peripheral nerves, cerebral cortex, cerebellar cortex and spinal cord. The causes of neurodegenerative diseases are not well-defined, but can be interlinked with loss of neurons, accumulation of proteins that are resistant to breakdown (proteolysis) and gradual changes in the tracts in the nervous system especially in the gray matter, and sometimes, the white matter.[12]

The most common neurodegenerative disease in aged people is Alzheimer's disease. The cause of Alzheimer's disease has been associated with Apolipoprotein E4 as a major risk factor, while Apolipoprotein E2 is believed to have the least effect on its onset, accumulation of amyloid, tau protein, neuritic plaques, neurofibrillary tangles and degeneration of granules present in the vacuoles of the nervous system. Other neurodegenerative diseases include: Parkinson's disease, Pick's disease, Friedrich ataxia, Spinocerebellar ataxia, Ataxia telangiectasia, Corticobasal degeneration, Muscle atrophy, Amyotrophic lateral sclerosis and many more.[2] Loss or degeneration of the myelin sheaths in the central nervous system can result in a neurodegenerative autoimmune disease known as Multiple Sclerosis.Alzheimer's, Parkinson's, Lewy body, and Huntington's illnesses may share a common basic principle that connects them to psychiatric disorders like depression, which aren't considered 'neurodegenerative' in the traditional sense.[13]

The hippocampus is one of the brain regions that is most damaged by neurodegeneration and functional deterioration even in what is still considered "normal aging". Plasticity is the foundation for the brain's ability to adapt to changes throughout time. The discovery of adult hippocampal neurogenesis has added a whole new dimension to research on structural plasticity in the adult and aging hippocampus.[14]

It is believed that the knowledge of neurogenesis and neuroplasticity can help neurologists and scientific researchers in the field of neurology to find non-surgical treatments for these neurodegenerative diseases in the nearest future, thereby improving the rate of brain repair and healing in the affected patients.[15] Factors that stimulate or inhibit adult neurogenesis may be used in manipulating therapeutic approaches in reversing the damage associated with some neurodegenerative diseases. Because of the brain's complex anatomical, histological, and functional architecture, the use of neural stem cells in brain regeneration implies that cellular replacement alone cannot lead to efficient restoration of function.[16] Several studies carried out on neuronal regeneration, gene therapy and chemical programming in the treatment of these neurological disorders have not been successful as expected, but further experiments and tests are being carried out to replace lost neurons, repair accumulation of abnormal constituents and alter changes in the tracts in the nervous system to restore it back to normal.

CONCLUSIONS

Resource analysis and the conducted survey shows that adult neurogenesis is possible, although it is not time-limited and it may take years for the brain cells regeneration and repair to occur. In conclusion, with the provision of a conducive environment, during brain cells or tissue damage, the brain can trigger signals for regeneration and repair through the formation of neurons, slowing down the disease processes and linking of neural networks. Further research, however, is needed to properly investigate how to manipulate adult neurogenesis for a short time-frame and slow inflammatory processes triggered during cell or tissue damage.

REFERENCES

1. Kumar A, Pareek V, Faiq MA, Ghosh SK, Kumari C. Adult neurogenesis in humans: a review of basic concepts, history, current research, and clinical implications. Innovations in Clinical Neuroscience. 2019 May 1;16(5-6):30.
2. Pritha SB, Lakshmi R, Shyamkishore K; Inderbir Singh's Textbook of Human Neuroanatomy. New Delhi, India: Jaypee Brothers Medical Publishers (P) Ltd. c2014; 9th ed; pp. 52-54.
3. Robbins and Cotran Pathologic Basis of Disease. Philadelphia, USA: Elsevier Saunders. c2015, 9th ed, p.28.
4. Enciu AM, Nicolescu MI, Manole CG, Mureşanu DF, Popescu LM, Popescu BO. Neuroregeneration in neurodegenerative disorders. BMC neurology. 2011 Dec;11(1):1-7.

5. Ribeiro FF, Xapelli S. An Overview of Adult Neurogenesis. Adv Exp Med Biol. 2021;1331:77-94. doi:10.1007/978-3-030-74046-7_7
6. Owji S, Shoja MM. The History of Discovery of Adult Neurogenesis. Clin Anat. 2020;33(1):41-55. doi:10.1002/ca.23447
7. Poplawski GHD, Kawaguchi R, Van Niekerk E, Lu P, Mehta N, Canete P, et al. Injured adult neurons regress to an embryonic transcriptional growth state. Nature. 2020;581(7806):77-82.
8. Lindvall O, Kokaia Z. Neurogenesis following stroke affecting the adult brain. Cold Spring Harbor perspectives in biology. 2015 Nov 1;7(11):a019034.
9. Su YS, Veeravagu A, Grant G. Neuroplasticity after traumatic brain injury. Translational research in traumatic brain injury. 2016.
10. Anderson V, Spencer-Smith M, Wood A. Do children really recover better? Neurobehavioural plasticity after early brain insult. Brain. 2011 Aug 1;134(8):2197-221.
11. Ludwig PE, Thankam FG, Patil AA, Chamczuk AJ, Agrawal DK. Brain injury and neural stem cells. Neural Regeneration Research. 2018 Jan;13(1):7.
12. Ngwenya LB, Danzer SC. Impact of traumatic brain injury on neurogenesis. Frontiers in neuroscience. 2019:1014.
13. Steiner B, Wolf S, Kempermann G. Adult neurogenesis and neurodegenerative disease. Regen Med. 2006;1(1):15-28. doi:10.2217/17460751.1.1.15
14. Klempin F, Kempermann G. Adult hippocampal neurogenesis and aging. Eur Arch Psychiatry Clin Neurosci. 2007;257(5):271-280. doi:10.1007/s00406-007-0731-5
15. Abdipranoto A, Wu S, Stayte S, Vissel B. The role of neurogenesis in neurodegenerative diseases and its implications for therapeutic development. CNS NeurolDisord Drug Targets. 2008;7(2):187-210. doi:10.2174/187152708784083858
16. Quadrato G, Elnaggar MY, Di Giovanni S. Adult neurogenesis in brain repair: cellular plasticity vs. cellular replacement. Frontiers in Neuroscience. 2014 Feb 12;8:17.

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Ekene Nnagha; data collection, data analysis, manuscript writing, manuscript review
Queean- Halen Egbai; data collection, data analysis, manuscript writing, manuscript review
AhteshamKhizar; concept, data analysis, manuscript review