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Neuroplasticity and Recovery from Brain Injury: A Comprehensive Review of Current Research

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Abstract: ***"Traumatic Brain Injury (TBI)" is stimulating for both diagnosis and treatment. It consists of physiological or structural injuries in brain function along with external forces. These injuries may cause formation of gliotic scar, cellular death, and damage from inflammation and reactive oxygen. A lot of research attention has been given to external influencers to promote neuroplasticity with significant effects on neurologic injury treatment. A lot of these methods and existing studies are reviewed in this study. With advancements in neuroscience, an in - depth knowledge of the intricacy of interconnection in the brain and its capability to adapt to the environment is "promoting neurorehabilitation which augments the capacity of brain to adapt with neuroplastic change". This systematic review has been conducted to explore the benefits of innovative technologies used for neurorehabilitation of patients suffering from brain injury. There has been a rise in recognition and appreciation of neuroplasticity which has brought modern approaches to encourage neuro - recovery, which boosts stimulation and secretion of neutrophic factors. Some of the modern approaches are non - invasive stimulation, pharmacologic agents, task - based and aerobic exercise, mirror therapy, and improvement of sleep. Future studies are needed to build the foundation of therapeutic techniques and rehabilitation to promote natural healing of brain and functional results.***

Keywords: traumatic brain injury, TBI, neurorehabilitation, neuroplasticity, brain injury, neuroplastic change, neuro - recovery

1. Introduction

Neuronal plasticity or neuroplasticity is not uncommon in recent years. William James coined the term "neuroplasticity" in the year 1890 in his book titled "Principles of Psychology" when he mentioned "Plasticity" which means having a structure which is "weak enough to produce an influence, and strong enough not to produce all at the same time". Nervous tissue or organic matter is supposed to be endowed with great amount of plasticity (Warriach & Kleim, 2010; Kleim & Jones, 2008). The improved acceptance and understanding of the natural adaptability of the brain in its environment, along with shedding of limitations of localization, have increased the potential medicinal uses of plasticity to improve brain functions after injury (Stein & Hoffman, 2003).

The ability to map the brain regions electro - physiologically has helped this development and revealed the reorganization as per the training after and before injury (Nudo & Milliken, 1996; Nudo et al., 1996). There is also an improvement in understanding of complexity and interconnection of the brain with improved anatomical and functional testing as well as neural mapping (Fuchs & Flügge, 2014; Duffau, 2014; Grefkes & Fink, 2011). In addition, there has also been the clarification of the role played by dendritic sprouting, synapse, genetics, and neurotrophic agents. At the same time, it has enabled therapeutic interventions to improve neuroplasticity to provide better results after all kinds of brain injury.

These interventions consist of non - invasive stimulation, pharmacologic interventions, aerobic exercise, mirror therapy, sleep, and talk - based activities " (Clayton et al, 2016; Thieme et al., 2018; Carrillo - Mora et al., 2017; Al - Dughmi et al., 2017) ". These interventions are beneficial individually but they depend on smart rehabilitation to provide its benefits. Hence, any treatment provided must be the part of a comprehensive plan for rehabilitation.

1.1 Background

Neuroplasticity is the part of neuro - recovery, apart from the issue of secondary brain injury. The "central nervous system (CNS)" is highly capable to adapt and recover "secondary compensatory mechanisms" from injury. Neuroplasticity is the foundation of recovery, i. e., the ability of "neuronal circuits to make adaptive changes on both functional and structural level, ranging from cellular, synaptic, and molecular changes to more global changes in the network. Traditionally, the adult brain was supposed to be stagnant. " Neuroplasticity has always reflected the flows of scientific and philosophical beliefs over time.

As per Darwin's "Natural Selection" concept, humans must adapt to their environment and they are shaped this way due to the plastic nature of their brains. In the book titled "The Brain that Changes itself, " Norman Doidge presented the timeline in which nature's perception is changed from the "vast living organism" according to Socrates and ancient Greeks to "as a machine" by Galileo and "as history" which ultimately became the inspiration for Charles Darwin (Doidge, 2007). Hence, the perception and knowledge of humans about their body, especially brain, has changed from "something that can be trained like the bodies trained by gymnasts" according to Socrates to a pump or a machine as per Rene Descartes, a French philosopher (Doidge, 2007).

2. Literature Reviews

Villamar et al. (2012) conducted a study to review "non - invasive brain stimulation (NBS) " therapy to improve neuroplasticity after TBI. It is observed that the pathophysiological mechanisms after brain injury vary as per time and needs "varied interventions. Theoretically, with the neurophysiological effects of both "tDCS and TMS, " these tools may decline "cortical hyperexcitability" acutely followed by brain injury, modulate synaptic plasticity in the long term to prevent maladaptive effects,

and promote cortical consolidation and reorganization of learning in neural networks with behavioral and physical therapy. With human and animal studies, potential benefits of NBS are revealed in reducing the impact of injury and improving plastic changes to promote recovery and learning of function in lesioned neural tissue.

When it comes to treat stroke survivors, chronic functional deficits are the major challenge which affects daily living activities. Irrespective of major functional recovery in initial weeks after stroke, around half of survivors suffer from hemiparesis after 6 months of stroke, which is significant as motor recovery peaks after three to six months. Bundy & Nudo (2019) discussed recent advancements to improve knowledge in neuroplasticity after experimental models of TBI. First, they review the effects of rehabilitation and, secondly, they described functional relevance of specific reorganization patterns. At the end, they concluded preclinical evidence for various therapies to improve neuroplasticity in different levels of developments of clinical tests.

TBI induces behavioral and motor problems and cognitive impairments. Earlier evidences have found that transplantation of "neural stem cell (NSC) " could promote functional recovery from the brain but their mechanisms are supposed to be elucidated. Xiong et al. (2018) established TBI model with electromagnetic - controlled cortical impact device" in rats. The researchers observed improvement in "neurological functional improvement" in rats who got NSC transplanted, which was related to BDNF expression and upregulation of synaptophysin. With microassay analysis, it is observed that 14 genes like "Gsk3 - β and Wnt" were downregulated followed by BDNF knockdown.

D'Arcy et al. (2020) used "functional Magnetic Resonance Imaging (fMRI)" in a high - profile case study to track motor function improvements associated with neuroplasticity after rehabilitation for severe TBI. Improvements can be observed years after existing limits as observed in the findings. The researchers extended the investigation on functional imaging to characterize "neuromodulation impacts" on neuroplasticity to push the boundaries further. The findings of the study provided important insight to potential benefit of "non - invasive neuromodulation" to improve neuroplasticity to recover after perceived rehabilitation boundaries.

TBI is a significant cause of prolonged disability and death across the world. There is a lack of effective remedy till date for brain injury. Recombinant "tissue Plasminogen Activator (tPA)" is the best medication to treat acute ischemic stroke. Apart from its "thrombolytic impact", tPA is also the part of neuroplasticity in brain. However, tPA has extreme side effects when it is administered IV like brain hemorrhage and edema. Administered by "intranasal delivery" during subacute stage after brain injury, Meng et al. (2014) found that tPA has therapeutic benefits. Brain injured animals were cured intranasally with tPA or saline 7 days after injury. It is found that "subacute intranasal tPA treatment" improves brain neurogenesis, functional recovery, and spinal cord sprouting after brain injury.

2.1 Research Gap

Earlier, the studies on people who suffered "Traumatic Brain Injury (TBI)" observed that there was 8.5% prevalence of TBI in adults aged above 18 years (Silver et al, 2018). In 2010, TBI caused 2.5 million hospitalizations, visits to emergency department, and deaths, according to the "Centers for Disease Control and Prevention" and TBI was associated with "30% mortalities" (CDC, 2014). Despite having lack of studies, brain injury is a major concern as it has highest number of mortalities and cases (Adelson, 2014; Kraus et al., 1987). Given the compensation for "quality of life, rehabilitation, job loss, and home services along with medical expenses", the economic impact is hard to determine in case of brain injury. So, this study fills the most important research gap in this field by discussing various modern techniques for neuroplasticity and recovery because recent studies have yielded interesting results and findings.

2.2 Research Question

- What are the pros and cons of imaging modalities for neuroplasticity?
- What are the promising new therapies to enhance neuroplasticity?

2.3 Research Objectives

- To compare various scanning modalities for neuroplasticity after brain injury
- To discuss promising therapies to enhance neuroplasticity after traumatic brain injury

3. Research Methodology

3.1 Research Approach

The research approach for this study is systematic review of recent studies according to "Preferred Reporting Items for Systematic Reviews and Meta - Analysis (PRISMA) " guidelines (22) to fulfill the above research objectives.

3.2 Data Collection

Secondary data has been collected from Google Scholar, PubMed, and other databases with different keywords like "neuroplasticity", "traumatic brain injury", "neurorehabilitation", and "innovative approaches". For performing a complete search, references of articles selected have also been analysed.

3.3 Inclusion and Exclusion criteria

The inclusion criteria include articles and studies conducted on patients affected by severe or moderate traumatic brain injury, pilot studies, randomized clinical trials, and systematic reviews, studies published in English language and in a peer - reviewed journal. On the other hand, exclusion criteria consist of narrative reviews, retrospective studies, studies conducted on mild TBI cases, children and teens, and studies published in other languages.

4. Analysis of Study

4.1. Scanning Modalities for Neuroplasticity after Brain Injury

Until recently, "non - invasive neuroimaging" was not much effective to detect structural changes of white matter. The development of techniques has changed response detection after TBI, such as "functional MRI (fMRI), positron emission tomography (PET), transcranial magnetic stimulation (TMS), and diffusion tensor imaging (DTI) " (Table 1).

Table 1: Difference between Scanning Modalities for Neuroplasticity

Scanning Modality	Measuring "Neuronal Activity"	Pros	Cons
fMRI	Measures gluco - metabolism and oxygen consumption indirectly or BOLD signal	No radiation. Maximum 1 - 6mm spatial resolution and sound temporal resolution	Various factors affecting the data like blood flow, medication, and cerebral dominance
PET	Measures cerebral blood circulation indirectly	Up to 5 - 10 mm of spatial resolution	Invasive therapy, requires injecting or inhaling radioactive tracers.
TMS	Magnetic pulses used to boost or suppress cortical excitation	Non - invasive procedure which measures and stimulates response. Potential to compare after and before treatment	Limited efficacy and confined to motor cortex
DTI	Measures changes in white matter with water diffusion	Higher sensitivity to injury due to white matter as compared to CT/MRI. Capable to detect diffused axonal injury.	Limited accuracy to individual tracts of white matter.

4.1.1. Functional MRI (fMRI) and PET

fMRI and "Positron Emission Tomography (PET) " are the techniques which indirectly scan neuronal activity with metabolic and vascular changes, respectively, as signs of neuronal activity. PET consists of either injection or inhalation of radioactive tracers which combine in activated areas in the brain, making it more invasive therapy. PET depends upon the concept that cerebral blood circulation rises to neuronal activity areas. Then, changes in signal are mapped over the "MRI scan of the brain for anatomical correlation". Though around 5 to 10 mm of high spatial resolution is provided, PET has inferior temporal resolution because of time required to analyze blood flow (Belanger et al., 2007).

4.1.2. TMS

Electrical shock and magnetic fields are used by "Transcranial Magnetic Stimulation (TMS) " to arouse cortical areas of the brain. This noninvasive therapy is majorly used to activate plasticity of the brain in motor system. It consists of application of current over scalp opposite a "motor region and then activates electrographic response in specified muscles named "motor evoked potentials (MEP) (Rossini & Pauri, 2000).

4.1.3. DTI

DTI or "Diffusion Tensor Imaging" is highly sensitive to microscopic injury and is widely used to diagnose previous signs of TBI. It scans microstructure of white matter on the basis of vector maps made from diffusion of water molecules. Fiber tracts can be evaluated by algorithms which can analyze properties and can confer details on damage and orientation of fiber which cannot be detected with traditional MRI (Suskauer & Huisman, 2009; Arfanakis et al., 2002; Inglese et al., 2005). Considering the preliminary studies, it is found that DTI is capable to detect microscopic injury in moderate to extreme brain injury, while imaging on mild injury cases have not shown any major change in comparison to patients who were neurologically intact (Inglese et al., 2005).

In a nutshell, scanning modalities like PET, fMRI, and DTI are ideal for their potential use to monitor existing neuroplasticity. However, DTI has limited potential to track only individual tracts of white matter and its sensitivity is reduced with various white matter tracks degenerating or intersecting in injured or complex areas. Though prolonged improvement and neuroplasticity has not been monitored well after injury, training and stimulation improve long - lasting neural changes.

4.2 Promising Therapies to Enhance Neuroplasticity

TBI leads to both direct (injury of blood vessels and neurons) and indirect (inflammation, edema, and secondary ischemia) damages. By destroying "blood - brain barrier (BBB)", brain injury enables immune cells to trigger inflammatory responses by entering the injured area. It also activates astrocytes and microglia to release chemokines, inflammatory cytokines, and prostaglandins which further leads to rise in penetrability of blood - brain barrier (Galindo et al., 2011). There are several promising therapies still in early stages of development but they target processes like inflammation, neurogenesis, synaptic modeling, angiogenesis, and formation" (Table 2).

Table 2: Promising Therapies and their mechanisms

Therapies	Mechanism	Trials	Severity of injury	Pros	Cons
"Bone - marrow based mesenchymal stem cells (BM - MSCs)	Affects angiogenesis and neurogenesis; unclear to modify immune response and "ameliorate	Human and mouse	Different models	Affects microenvironment; poor immunogenicity; significant proliferative	Benefit is affected by age, stem cell delivery, and injury of the patient

	inflammatory response" post injury			rate	
"Neural stem cells (NSCs) "	Distinguish between astrocytes, neurons, and oligodendrocytes and integration on neural networks	Mouse	Several models	Responding to trophic factors and secretion; dedicated neural family	Potentially tumorigenic; avoids microenvironment of tumor; hard to preserve cells
"Umbilical cord - based mesenchymal stem cells (UC - MSCs) "	Similar to BM - MSCs	Limited trials on human and mouse	Diverse TBI models	Proliferatively higher rate than BM - MSCs; easy to obtain; immunomodulatory	Indistinct chromosomal or genetic makeup of cells
"Cyclosporin A (CsA) "	Affects permeability of "mitochondrial transition pore" and affects calcineurin	Human and mouse (Ph - II)	Moderate, mild, and severe brain injury	Controls lesion size and axonal injury	Lack of "long - term study"; studies rely on model of the injury; different benefits in motor outcomes.
Antioxidant therapy	Avoids forming reactive species of oxygen which can lead to death or neuronal damage	Limited clinical benefits achieved on human trials (Phase 1 and 2)	Severe	Decent safety	Big molecules with limited permeability in BBB

To understand neuroplasticity after "brain injury, it is worth considering the inferences of differences between human survivors of brain stroke and animal models. Either nonhuman primate or rodent models were used by most of the preclinical studies. Both primates and rodents have secondary and primary cortical motor areas and significant efforts are made to interpret structural and functional reorganization in secondary motor regions due to damaged primary motor regions. Rodents have two cortical regions linked to the skilled forelimb movements. The "caudal forelimb area (CFA) " is similar to "primate primary motor cortex (M1) " and borders the "primary somatosensory forelimb" region on the caudal border.

The "rostral forelimb area (RFA) " is secondary motor region which is placed more rostrally and has been known as premotor region on the basis of similarities in neuronal responses and connectivity related to premovement and movement planning (Neafsey & Sievert, 1982). Even though secondary premotor area plays a vital role for enabling rodents to grasp something with forepaw, nonhuman primates make better sample for human motor mechanism while enabling to produce more complex behaviors. The ability to conduct complex movements is promoted partly with several "segregated secondary motor areas" having "ventral premotor cortex (PMv) " and "dorsal premotor cortex", the cingulate motor regions and the supplemental motor region (Figure 1) (Rizzolatti et al., 1998) ".

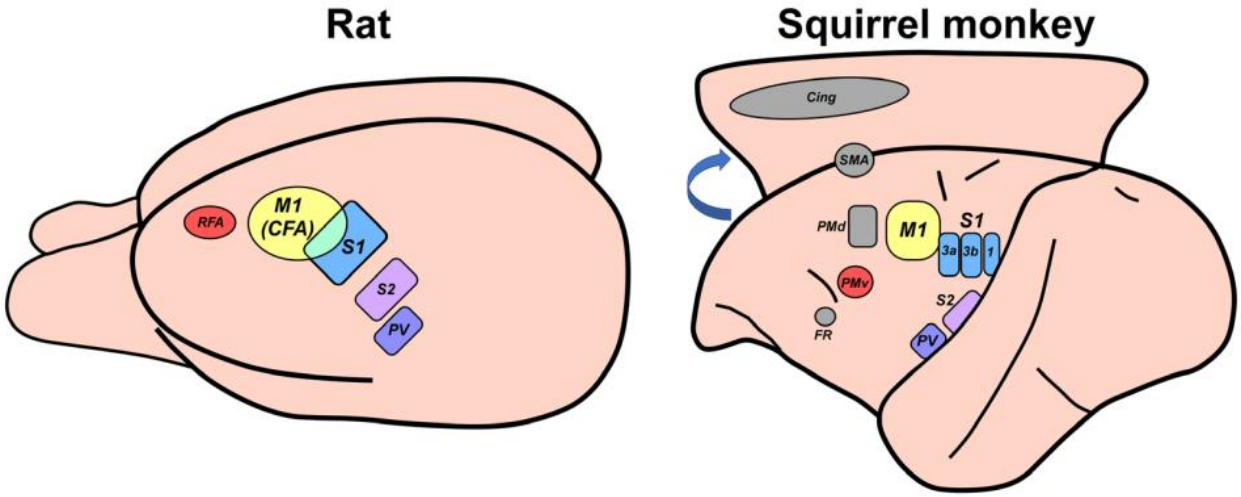

Figure 1: Organizing "Sensorimotor system"
Source- "(Rizzolatti et al., 1998) "

Figure 1 illustrates "sensorimotor system" of rat or rodent (to the left) and non - human primates like squirrel monkey (to the right). Both have various and diverse motor and sensory regions. The cortical system of rodent consists of "caudal forelimb area (CFA) " and "rostral forelimb area (RFA) ". Non - human primates have various premotor regions like "ventral and dorsal premotor cortices (PMv and PMd) ", "cingulate motor areas (Cing) " and "supplementary motor area (SMA) ". The cortical sensory areas of both nonhuman primate and rodent consist of "secondary somatosensory cortex (S2) " and "somatosensory cortex (S1) " as well as "parietal ventral area (PV) ". Even though the origin of corticospinal neurons is various regions, The PMv and M1 of "nonhuman primates" and RFA and CFA of rats have a high number of corticospinal neurons.

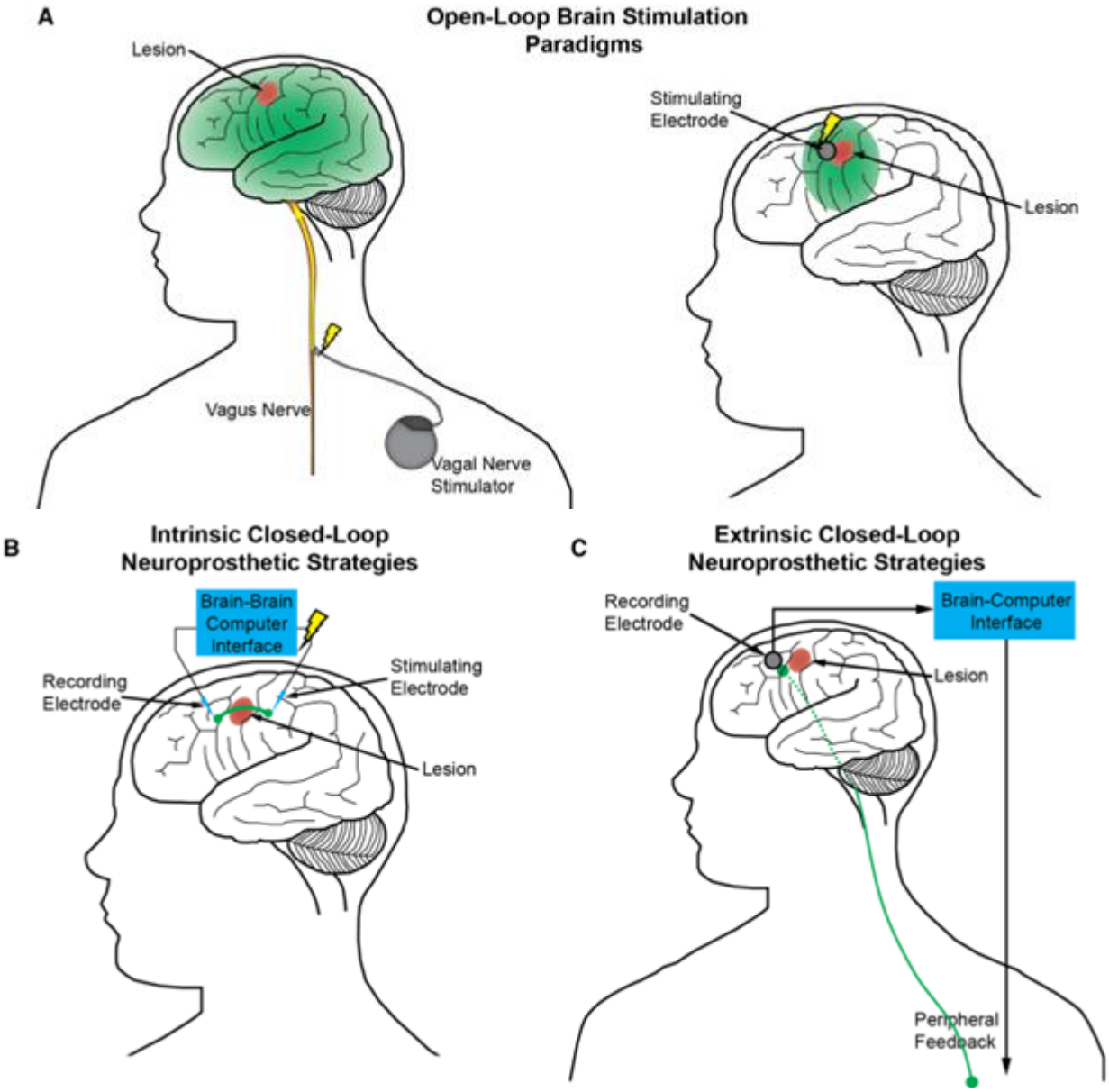

Figure 2: Promising technologies to stimulate neuroplasticity
Source: Bundy & Nudo (2019)

A lot of latest technologies are proposed to direct and promote neuroplasticity by Bundy & Nudo (2019). Neuroplasticity is enhanced nonspecifically by "open - loop interventions" to improve efficiency of rehabilitation by stimulating "direct cortical stimulation (right) " and "vagal nerve (left) " (Figure 2A). In Figure 2B, there are "closed - loop strategies" which enable plasticity in target paths either to boost "intrinsic cortico - cortical connections" or to promote descending output of motor from the "targeted motor region" (Figure 2C).

5. Results

Some of the valuable outputs are available from test models of TBI which can be useful to test the instruments of plasticity to promote retrieval of "motor function which has been damaged. Motor function recovery has been related to maintenance or rise in size of motor representations in both secondary motor regions and "perilesional parts of M1" in ipsilesional hemisphere across lesion models and species. In addition, the maturation and rise of synaptic connections in these regions come up with observed reorganization of the function. In addition, in test models, the observed reorganization is corresponding with studies related to humans which have observed that proper motor recovery is related to return to more common motor activity patterns (Ward & Brown, 2003).

Even though preclinical studies enable performing "well - controlled tests" with constant lesions, it is worth noting that the survivors of human stroke showed more different range of stroke regions which don't always respond well with the most widely used models of lesions (Edwardson et al., 2017). The extent and area of the lesion may especially be relevant about the role of varied motor regions, including "contra - lesional hemisphere in motor recovery" (Touvykine et al., 2016). In addition, since the change in this location of lesion will affect the success rate of therapies in patients, it will be vital to use different approaches for test animals along with small and large

lesions (Touvykine et al., 2016), cohorts of aged animals (Wang et al., 2016), subcortical lesion areas (Karthikeyan et al., 2019), and animals having comorbidities like the ones in human patients to test the systems of recovery related to possible therapies.

Testing subjects of ischemia and brain injury will also be important constantly to further growth of novel therapies designed to boost neuroplasticity. Even though recent studies have showed the potential of such approaches to boost motor function, further studies are important to improve knowledge of particular mechanisms in each intervention, helping to choose the right implementation for each approach and improve the chance of proper translation on clinical groups.

6. Conclusion

After TBI, recovery process is very slow. With increasing studies on neuroplasticity, the potential for recovery is no longer that forbidding. The actual mechanism is supposed to be unknown. However, a lot of circumstances are under the radar of research community. A lot of possible therapeutic opportunities are about to be explored to common changes related to neuroplasticity, from differential cellular proliferation and gene expression to the upregulation of proteins to modulation of inflammation and the adoption of immune cells to control the volume and size of damage". Future therapies might be beneficial to target various systems of recovery and combination of various pharmacological therapies and stem cell therapies is very important.

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