NEUROIMAGING EVALUATION OF POST-STROKE ANGIOGENESIS AND NEUROPLASTICITY: A NARRATIVE REVIEW

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Abstract

Introduction

Angiogenesis and neuroplasticity are biologically based mechanism that mediate stroke recovery and are critical in restoring cerebral perfusion and restructuring neural pathways after injury. Current technology in neuroimaging, such as perfusion-weighted imaging (PWI), diffusion tensor imaging (DTI), functional MRI (fMRI), and transcranial Doppler (TCD), can be used to determine these restorative processes in vivo. However, it is not yet well understood to what degree traumatic brain injury (TBI) alters such regenerative pathways.

Material and Methods

A comprehensive literature search was conducted in PubMed, Scopus, and ScienceDirect, including both clinical and preclinical studies published between 1999 and 2024. Search terms included "stroke," "neuroplasticity," "angiogenesis," "traumatic brain injury," "MRI," "DTI," "fMRI," "PWI," and "cerebral perfusion." The studies were given priorities based on the inclusion of neuroimaging information pertinent to cerebral repair mechanisms post-stroke.

Results

The reviewed literature suggests that imaging markers of cerebral perfusion, white matter integrity, and functional connectivity are reliable measures of angiogenic and neuroplastic recovery following stroke. Patients with a history of TBI are often characterized by delayed or modified recovery patterns, which can be probably explained by chronic vascular impairment and impaired plastic capacity. Neuroimaging integration in post-stroke evaluation procedures aims to early detect unfavorable cases and develop more personalized rehabilitation plans.

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Conclusions

Neuroimaging is a powerful stroke recovery assessment modality. The need to identify risks with accuracy and provide a specific line of treatment amplifies its utility among patients with antecedent TBI. The entire dynamics between pre-existing brain injury and post-stroke repair mechanism is invaluable in promoting improved clinical outcomes.

Keywords: *Ischemic stroke, Angiogenesis, Neuroplasticity, Neuroimaging, Traumatic brain injury*

Rezumat

Introducere

Angiogeneza și neuroplasticitatea sunt mecanisme biologice fundamentale ce mediază recuperarea în urma unui accident vascular cerebral (AVC), fiind esențiale în restabilirea perfuziei cerebrale și în reorganizarea căilor neuronale. Tehnologiile moderne de neuroimagistică, precum RMN-ul de perfuzie (PWI), imagistica bazată pe rezonanța magnetica de difuzie (DTI), RMN-ul funcțional (fMRI) și Dopplerul transcranian (TCD), pot fi utilizate pentru a evalua aceste procese de regenerare. Cu toate acestea, impactul traumatismul cranio-cerebral (TCC) asupra acestor procese regenerative rămâne insuficient clarificat.

Cuvinte-cheie: *AVC ischemic, angiogeneză, neuroplasticitate, neuroimagistică, traumatism cranio-cerebral*

Introduction

Ischemic stroke continues to be one of the leading causes of prolonged debilitation[1]. Pathophysiology focuses on the disruption of cerebral blood flow, which leads to functional neurological deficits that often become permanent. Despite the belief that the adult brain has limited regenerative potential, recent research has shed light on two endogenous processes, angiogenesis and neuroplasticity, which are essential in post-stroke recovery[2,3].

The optimal level of oxygen and nutrient supply to damaged tissue are a result to angiogenesis, when new blood vessels develop secondary to ischemia. At the same time, neuroplasticity promotes adaption through the reinforcement of the existing connections, the formation of the new ones and recruitment of brain areas that have not been involved in the past to replace the lost functionality[5].

Neuroimaging technologies are invaluable tools in current clinical practice and research in evaluating brain regenerative capacity after stroke.

Perfusion-weighted imaging (PWI), arterial spin labeling (ASL), diffusion tensor imaging (DTI), functional MRI (fMRI), and transcranial Doppler (TCD) are the most common non-invasive techniques applied in the measurement of the cerebral blood flow, axonal integrity, and functional reorganization of cortical networks[7,8].

Despite these technological developments, recovery patterns following stroke are variable and a past history of traumatic brain injury (TBI) is a major covariate[9]. Optimal repair can be changed by previous TBI by decreasing vascular responsiveness, maintainimg chronic neuroinflammation, or by disrupting key structural connections. The remaining effects are capable of limiting both angiogenesis and neuroplasticity during the post-stroke phase[10]. Furthermore, it is still difficult to differantiate between chronic lesions, previous TBI and acute ischemic damage on neuroimaging[11].

The recent development of advanced neuroimaging modalities represent one of the most important tools in exploring the post-stroke angiogenesis and neuroplasticity. The occurance of prior history of traumatic brain injury (TBI) makes the interpretation and prognostic significance of these imaging measures difficult. Understanding of these interactions in detail therefore remains a very important factor in guiding individual rehabilitation and maximizing stroke recovery.

Objectives

The role of neuroimaging studies in comprehension of biological mechanism underlying facilitation of cerebral recovery after an ischemic stroke, particularly the complementary role of angiogenesis and neuroplasticity, will be discussed in the current narrative review[1,2]. These processes are necessary to reestablish cerebral perfusion and to enable functional reorganization after ischemic injury[3].

An additional objective is to explore the potential influence of a history of traumatic brain injury (TBI), normally related to long-term vascular changes and structural disruption on recovery patterns, as monitored using neuroimaging methods[4-6]. Even though stroke and TBI are usually examined separately, their overlap raises important clinical considerations that have not been fully explored[7].

This review outlines the molecular and physiological processes that underlie post-stroke angiogenesis and neuroplasticity, summarizes neuroimaging modalities that

are generally used to assess these regenerative processes, examines how a prior history of traumatic brain injury (TBI) may affect neuroimaging findings and post-stroke regenerative potential, and discusses the prognostic and therapeutic implications of imaging biomarkers to individualize rehabilitative interventions to patient profiles. By discussing these goals, these review will facilitate a more complete insight of post-stroke recovery process and demonstrate the importance of multimodal imaging in describing recovery patterns in patients with and without prior TBI.

Materials and Methods

This narrative review aims to synthesize and critically evaluate the available evidence related to neuroimaging-based evaluation of angiogenesis and neuroplasticity in patients with ischemic stroke and history of traumatic brain injury (TBI).

To systematic search was performed through PubMed, Scopus, and ScienceDirect, that resulted in articles published from January 1999 to March 2024.

Keywords used were combinations of the following: “stroke”, “ischemic stroke”, “angiogenesis”, “neuroplasticity”, “traumatic brain injury”, “MRI”, “diffusion tensor imaging”, “functional MRI”, “perfusion imaging”, “cerebral blood flow” and “transcranial Doppler.”

Stroke patients with a history of TBI showed reduced regional cerebral blood flow (rCBF) and cerebral perfusion reserve (CPR) as compared to stroke patients with no prior TBI along with inreased angiogenic biomarkers. Furthermore, such patients had more pronounced neurologic impairments and had more cogntice deficits. Taken together, these results indicate that previous TBI adversely affects post-ischemic angiogenesis and neuroloplasticity, which may affect the long-term recovery processes.

The inclusion criteria were the following:

1. Peer-reviewed articles published in English;
2. Clinical or preclinical focused on the treatment of ischemic stroke recovery and/or neuroregeneration;
3. Studies utilizing neuroimaging techniques to study the cerebral angiogenesis and/or neuroplasticity[9-11];
4. Studies that took into consideration the influence of previous TBI on stroke outcomes, imaging, or recovery patterns [12].

The exclusion criteria were the following:

1. Case reports, editorials, or narrative articles with no imaging data[18];
2. Studies that only focuses on hemorrhagic stroke or primary neurodegenerative disorders[19];
3. Articles that had limited imaging

methodology or outcome measures of recovery[20].

The current qualitative synthesis included ove 40 articles, namely clinical studies, neuroimaging studies, and translational works. The studies that used a more elaborate imaging techinique, such as perfusion-weighted imaging (PWI), arterial spin labeling (ASL), diffusion tensor imaging (DTI), and functional MRI (fMRI), to evaluate cerebral perfusion, structural connectivity, and functional cortical reorganization were given priority[21-25].

The protocols of the imaging studies and the clinical cohorts varied between studies, so they were not suitable to perform a formal meta-analysis. Thus, the results were narratively synthesized, with main imaging observations organized within two major areas: angiogenesis and neuroplasticity. It should be noted that the changing variables, especially a history of traumatic brain injury (TBI), were also systematically tested to determine the possible impact on the outcomes of recovery[26,27].

Neuroimaging Assessment of Angiogenesis

Whereas angiogenesis occurs at a microscopic level, a number of modern imaging enable assessment of its effects on cerebral perfusion in a non-invasive manner[21]. These have emerged as proxies of central importance in the assessment of vascular remodeling and microvascular recovery after stroke:

1. Perfusion-Weighted Imaging (PWI): A dynamic MRI sequencies which uses contrast agents to measure cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), and time-to-peak (TTP). Improvemets in CBV and normalization of MTT are commonly viewed as indirect markers of microvascular recovery[22,23].
2. Arterial Spin Labeling (ASL): A non-contrast MRI technique which magnetically labels arterial blood water so that CBF can be measured. ASL is especially adapted to repeated and longitudinal measuremens and is appropiate in research contexts, pediatric populations, and chronic stroke patients[24,25].
3. CT Perfusion (CTP): CTP is commonly used in acute stroke, and it can quickly estimate perfusiom mismatch and define infarct core and penumbra. Serial CTP scans can detect the changing perfusion patterns compatible with vascular remodeling, even though angiogenesis is not directly quantified[26].
4. Transcranial Doppler Ultrasound (TCD): Limited to the measurments of large basal artery flow velocities, TCD is capable of measuring hyperemia or hemodynamic changes after revascularization, which may correlate with downstream microvascular adaptation[27,28].
5. Susceptibility-Weighted Imaging (SWI): This imaging modality can be used to visualize angiogenic areas by increased venous prominence or microvascular proliferation. Yet, its specificity for angiogenesis detection is a topic of further research[29].

Clinical Significance and Limitations

Angiogenesis is a clinically relevant prognostic determiant in the context of stroke. It holds significant prognostic value. It has been demonstred that early restoration of cerebral perfusion is associated with better functional outcomes within 3 and 6 months of follow-up[28,29].

Still, direct measurement of angiogenesis is controversial, since current imaging biomar-

kers can only give indirect data. These imaging findings are usually complicated by disruption of the blood-brain barrier (BBB), cerebral edema, or pre-existing vascular damage due to prior traumatic brain injury (TBI), which can resemble angiogenic effects[30,31].

In addition, angiogenesis has a characteristic temporal course, appearing days to weeks following stroke, thus requiring imaging protocols tailored to this time window. It is expected that future progress will be made using integrated techniques involving a combination of structural, perfusion-based, and molecular imaging techniques to further characterize the extent and functional rsignificance of post-stroke angiogenic activity [32,33].

Post-Stroke Angiogenesis: Mechanisms and Imaging Correlates

In the case of ischemic stroke, angiogenesis has a key role in cerebral perfusion restoration after ischemic stroke. It is the formation of new capillaries out of the existing blood vessels that helps in metabolic recovery of the regions of penumbral tissue, which are hypoperfused but may be saved[34]. Hypoxia-inducible factors (HIFs), activate the expression of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and other pro-angiogenic cytokines[35,36]. The results of these paths activation are the proliferation of endothelial cells, basement membrane degradation, sprouting of capillaries, and groth of new functional microvasculature[37].

In acute and subacute stages of stroke, angiogenesis can stabilize penumbra and enhance perfusion, leading to improved outcomes[38]. Characteristics of angiogenis differs among patients, and can be influenced by their age, comorbidities, or pre-existing brain injury [39,40].

Neuroplasticity and Functional Reorganization after Stroke

The capacity of the brain to rearrange its structure, function, and neural connections following injury it is defined as neuroplasiticty. This compensatory mechanism is central to the recovery of sensorimotor, cognitive, and language functions, especially in case of early initiation of rehabilitation post-stroke [41,43].

Mechanisms of Post-Stroke Neuroplasticity

Neuroplasticity involves changes on many levels of the nervous system, including:

- Synaptic plasticity: Long-term potentiation (LTP) and long-term depression (LTD) improve synaptic transmission by reactivation of previously existing but underused pathways.
- Axonal sprouting: Existing neurons can send out new axonal projections into areas deprived of input particularly in the perilesional cortex[45].

- Cortical remapping: Functional compensation may be achieved by adjacent or contralateral brain areas taking over the task previously processed in the damaged area[46].
- Recruitment of latent networks: Latent circuits with little or no activity can be recruited to contribute to behavioral and cognitive recovery[47].

These neuroplastic responses are most noticeable in the subacute period, which occurs days to weeks after the stroke onset, when the brain is more responsive to the rehabilitation attempts and the ability to reorganize is increased[48].

Neuroimaging Assessment of Neuroplasticity

Neuroimaging techniques provide direct and indirect indicators on neural reorganization after stroke:

1. Diffusion Tensor Imaging (DTI): It is used to measure the white matter microstructure, especially through important tracts like the corticospinal tract (CST) and corpus callosum. Reduction in fractional anisotropy (FA) reflect damage to axonal integrity, whereas longitudinal increases in FA suggest remyelination or axonal realignment [49,50].
2. Functional MRI (fMRI): The fMRI detects blood-oxygen-level-dependent (BOLD) changes in functional activation. Early changes of ipsilesional to contralesional hemisphere activation in the motor domain are a frequent finding, whereas the normalization can often follow the successful motor recovery course[51,52].
3. Resting-State fMRI (rs-fMRI): It is a procedure that evaluates natural variability of the BOLD signals to identify functional connectivity. It is suggested that increased interemispheric syncrony has correlated postively with better motor and cognitive performance outcomes[53].
4. Electroencephalography (EEG) and Magnetoencephalography (MEG): Both of these methods have high temporal resolutions of dynamic neural activity. They are particularly useful in studies targeted on motor learning and neuroplastic adaptation in stroke rehabilitation[54].

Influencing Factors

The efficacy of neuroplastic responses following stroke depends on a number of related factors, including:

- The location and size of the lesion, which determine the degree of loss of function disruption and the presende of adjacent viable tissue;
- Time since the onset of stroke, because the capacity to reorganize is highest during the early subacute phase;
- The patient age and comorbidities, which can affect the neural stability and the chance of recovery;
- Exposure to early, intensive, and task-specific rehabilitation, as they are facilitating adaptive plasticity;
- Prior brain injury, such as traumatic brain injury (TBI), may result in fewer intact compensatory networks or leading to maladaptive plasticity patterns such as cortical hyperexcitability, abnormal connectivity, or spasticity[55-57].

Clinical Implications

Neuroimaging can be useful during stroke rehabilitation in the following ways:

- Individualized approach of planning rehabilitation, based on the profile of the neural reorganization;
- Tracking of progress of therapy over time using objective imaging parameters;
- Grading of recovery potential, which is

helpful in prognosis and care planning;
- Evaluation of new interventions, including non-invasive brain stimulation, robot-assisted therapy, and neuro-rehabilitation with virtual reality[58,59].

Neuroimaging biomarkers of plasticity are an interesting area of potential future application in clinical stroke care, which could enable more precise and individualized neurorehabilitation approaches[60].

Influence of Prior Traumatic Brain Injury on Stroke Recovery

Previous traumatic brain injury (TBI) may have a significantly impact on the recovery process after ischemic stroke. Despite being usually considered separate clinical entities, TBI and stroke have some common pathophysiological mechanisms, such as chronic neuroinflammation, axonal degeneration, and microvascular dysfunction, that can impair regeneration[61-63].

These changes have the potential to negatively affect angiogenesis and neuroplasticity in those with prior TBI, possibly leading to slower recovery or poor functional outcomes after stroke[64,65].

Vascular and Structural Impairment

Chronic neuropathological changes, including diffuse axonal injury (DAI), cerebral microbleeds, and disruption of the blood-brain barrier (BBB) are common in traumatic brain injury (TBI). These changes may affect cerebrovascular respomsiveness and reduce the brain abilty to respond to a second ischemic event witn an effective angiogenic response[66,67]. Moreover, perivascular fibrosis and gliosis may alter the local microenvironment which is essential for neovascularization [68]. In neuroimaging studies, it has been consistently found that a history of TBI is associated with:

- Decreased perfusion reserve, show by arterial spin labeling (ASL) or CT perfusion scans[69];
- Persistent injury of the white matter, as measured by reduced fractional anisotropy (FA) on diffusion tensor imaging (DTI)[70];
- Cortical thinning and regional atrophy, which may impair neuroplastic potential and decrease the ability for functional remapping[71].

All these factors add up to higher risks of infarct expansion, impaired recovery patterns, and severe long-term disability after ischemic stroke[72].

Functional Reorganization Limitations

TBI can impair brain ability to recruit compensatory networks or adjacent cortical areas, reducing the effectiveness of post-stroke rehabilitation. Studies using functional MRI studies have indicated that patients with

TBI and stroke tend to have less functional brain activation when performing a motor or cognition task[73].

In addition, chronic TBI can lead to maladaptive forms of plasticity, including excessive contralesional activation that compromises interhemispheric balance, or the persistence of non-functional circuits, which may interfere with recovery. These unusual reorganization patterns may reduce the overall success of neurorehabilitative inter-ventions unless addressed in a mechanism-specific, individualized manner [74,75].

Neuroimaging for Risk Stratification

Neuroimaging is essential in determining stroke patients who are at a high risk of poor outcomes[76].

Multimodal imaging has a number of advantages in this context, such as:

1. Distinguish acute ischemic damage from chronic TBI-related lesions[77];
2. Determine the integrity of post-structural connection via white matter[78];
3. Measure the hemodynamic reserve and identify perfusion mismatches, which can play a role in therapeutic windows[79];
4. Guide the design of individualized rehabilitation plans, including non-invasive brain stimulation and specific motor or cognitive therapies[80].

Identification of TBI-related waknesses enables clinicians to treat patients with more specific interventions, presenting the possibility of enhancing recovery despite biological limitations[81].

Neuroimaging Modalities in the Evaluation of Regenerative Processes

The assessment of post-stroke recovery has changes significantly with the introduction of multimodal neuroimaging techniques. These methods enable clinicians and researchers to go beyond the identification of structural damage and provide information about dynamic regenerative processes, like angiogenesis and neuroplasticity[82,83]. The different imaging modalities have specific benefits, providing a different way of looking at the different aspects of cerebral recovery.

1. Perfusion-Weighted Imaging (PWI) and Arterial Spin Labeling (ASL)

Perfusion-weighted imaging (PWI), commonly uses gadolinium-based contrast agents, to produce quantitative maps of cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT). These parameters give indirect but informative data on the processes of angiogenesis and reperfusion. During the subacute phase after stroke, increasing CBF and normalization of MTT can be used as an imaging manifestation of successful microvascular remodeling[84,85].

Arterial spin labeling (ASL) is a non-invasive alternative to the use of contrast agents , and specifically labels the blood as it flows into the brain. ASL is especially well adapted to longitudinal measurements, especially in pediatrics or renal impairment. It is able to identify gradual reperfusion patterns, which can be an indication of slow vascular adaptation or continued neovascularization[86].

2. Diffusion Tensor Imaging (DTI)

Diffusion tensor imaging (DTI) assesses diffusion of water molecules along axonal tracts, and offers important information about the structural integrity of white matter tracts. The main parameters that can indicate microstructural damage and recovery with time include fractional anisotropy (FA) and mean diffusivity (MD).

When applied to stroke rehabilitation, DTI has been applied to track:

- Degeneration or maintenance of the corticospinal tract, which is highly correlated to motor recovery;
- Integrity of the corpus callosum, which is relevant for bimanual coordination and interhemispheric communication;
- Dynamics of interhemispheric reorganization, especially the aspects of compensatory plasticity[87,88].

Longitudinal improvements in FA are usually taken as signs of neuroplastic repair and structural reorganization[89].

3. Functional MRI (fMRI)

The functional MRI (fMRI) is a task-based technique that quantifies changes in blood oxygenation level-dependent (BOLD) signals, as an indirect measure of neuronal activity. It has been routinely applied to study motor, language, and cognitive networks in cases of stroke. There is a typical pattern of recovery-related activation:

- Early contralesional compensation, whereby the unaffected brain areas temporarily take over the functions lost;
- Slow recovery in perilesional cortical regions, especially through specific training;
- Restoration of lateralized function, especially in patients who have a favorable outcome[90-91].

Resting-state fMRI (rs-fMRI), however, measures spontaneous low-frequency fluctuations in the BOLD signal to measure functional connectivity between brain networks. The impaired connectivity, particularly between homologous motor cortices, has been correlated with a poorer functional recovery. In contrast, a more balanced interhemisphericpattern has been shown to be a neuroimaging marker of successful post-stroke rehabilitation[92-93].

4. Transcranial Doppler Ultrasound (TCD)

Transcranial Doppler (TCD) ultrasound provides real-time measurment of cerebral blood flow velocities, giving a dynamic analysis of macrovascular status. It is useful in the post-stroke setting as a monitoring tool:

- Recanalization after thrombolysis;
- The dynamics of collateral flow, particularly with proximal arterial occlusion;
- Hemodynamic reserve, which is important in patients with chronic TBI or prior cerebrovascular disease[94].

In neuroregeneration, sustained high mean flow velocities during the recovery period can be a sign of angiogenic remodelling and increased vascular sensitivity [95].

5. Multimodal Integration and Emerging Tools

The integrated use of structural imaging (e.g., DTI), functional mapping (e.g., fMRI), and perfusion-based techniques (e.g., PWI, ASL)

give a wider perspective on the reparative potential of the brain after stroke. Such multimodal strategies provide a better analysis of both neurovascular and neuroplastic mechanism[97].

New technologies including machine learning, graph theoretical analysis, and connectomics are driving neuroimaging toward predictive neuroscience, where the ability to predict specific recovery pathways in individuals is increasingly accurate. In parallel, hybrid imaging modalities (such as PET-MRI) and molecular imaging techniques targeting specific biomarkers (e.g., VEGF-related angiogenesis) are being explored to directly visualize and quantify biological substrates of regeneration[98-99].

Discussion

Recovery after stroke is multidimensional and depends on the capacity of the brain to regain perfusion and reorganize neural networks [100]. This narrative review has highlighted how angiogenesis and neuroplasticity play key roles in post-stroke regeneration, and how modern neuroimaging techniques can be used to assess these processes across both clinicalally and in research studies[101].

The literature shows a common theme between angiogenesis and neuroplasticity. Vascular remodeling offers the metabolic support required for the reactivation of neural tissue, whereas neuronal activity promotes pro-angiogenic signaling, a reciprocal relationship commonly described as neuro-vascular unit[102]. To capture this dynamic relationship, imaging modalities viewing both structural and functional changes over time are needed[103].

Diffusion tensor imaging (DTI) and functional MRI (fMRI) provide important information regardig neuroplastic functions like cortico-spinal tract integrity and reorganization of large-scale network.

Simultaneously, perfusion-weighted imaging (PWI) and arterial spin labeling (ASL) can be used to longitudinally assess perfusion changes, serving as indirect markers of angiogenesis and microvascular repair [104-106]. Combined uses of these imaging strategies facilitate a more thorugh knowledge of regenerative capacity of the brain after stroke.

This review has also indicated the modifying role of prior traumatic brain injury (TBI), as this aspect has often been overlooked by most stroke researchers. A history of TBI may bring in:

- Microvascular instability, that can inhibit angiogenic responses;
- White matter disruption, restricting access to intact pathways to support plasticity;
- Chronic neuroinflammation, which may inhibit adaptive remodeling or induce maladaptive remodeling [107-108].

It is important to consider these additional variables when developing rehabilitation approaches and ensuring the best outcomes in stroke patients who have a history of TBI.

1. Interdependence of Angiogenesis and Neuroplasticity

There is growing awareness that angiogenesis and neuroplasticity are not independent processes, but rather they are interdependent elements of a coordinated neurovascular recovery network.

As new microvessels are created, they provide the required metabolic support that is needed to undergo synaptic remodeling and axonal growth, whereas active neuronal networks release trophic factors which support vascular proliferation[109,110]. Any disruption in one area can severely affect the

other making the need of an integrated evaluation necessary.

This mutual relationship is a strong argument in favor of multimodal imaging approaches that can trace both vascular and neural planes of post-stroke regeneration[111].

2. Neuroimaging: From Observation to Prediction

Modern neuroimaging has become far more than a descriptive tool. Perfusion-weighted imaging (PWI), arterial spin labeling (ASL), diffusion tensor imaging (DTI), and functional MRI (fMRI) are methods that can visualize anatomical and physiological changes as well as predictive models of recovery. The new evidence shows that functional outcomes are linked to specific imaging patterns:

- Increased fractional anisotropy (FA) of the corticospinal tract on DTI has been linked with better motor recovery[112];
- Recovery of interhemispheric connectivity on resting-state fMRI indicates positive cognitive outcomes[113];
- Improvement of perfusion normalization on ASL has been associated with improved language perfomance[114].

All these findings confirm the importance of neuroimaging as a biomarker-based tool that informs the intensity, type, and timing of neurorehabilitation interventions, and leads to the development of more individualized and effective recovery strategies[115].

3. Prior TBI: A Modifier Often Ignored

Traumatic brain injury (TBI) has a high prevalance, but it is underrepresented in stroke- based neuroimaging studies. The chronic sequelae of TBI, including micro-vascular rarefaction, diffuse axonal injury, and prolonged neuroinflammatory responses, may substantially modify the neural and vascular substrate on which the processes of stroke recovery rely[116].

To a neuroimaging perspective, previous TBI raises multiple diagnostic and interpretive issues:

- Chronic lesions can interfere with or reproduce acute ischemia[117];
- Disorganization of white matter may affect the reliability of prognostication through tractography[118];
- Changes in hemodynamics can complicate perfusion parameters to measure vascular recovery[119].

Moreover, maladaptive neuroplastic responses, are observed in some stroke patients with prior TBI, such as persistent contralesional overactivation, impaired hemispheric lateralization, or network disconnection[120].

They can be linked to lack of responsiveness to conventional neuro-rehabilitation. Early identification of such characteristics with the help of imaging can inform more intensive and tailored interventions, including

neuromodulatory therapies, or lead to reconsideration of strategies unlikely to be valuable[121].

4. Toward Precision Rehabilitation: The Role of Imaging

Recent trends of precision rehabilitation higlight the need of individualized, evidence-based, and dynamically adaptive therapy. Neuroimaging biomarkers form the key component of this paradigm shift, which can provide information to be used to plan individualized interventions. For instance:

- Patients with preserved corticospinal tract (CST) integrity have better chances of benefiting from task-specific motor training[122];
- Impaired connectivity in the default mode network can be an indicator of the need of specific cognitive rehabilitation;
- Areas with impaired perfusion may be a priority to vascular support therapies or neuroprotective interventions [123].

Even with its potenial, the use of imaging-derived measures in the standard clinical practice face numerous challenges, such as high costs, inconsitent access to advanced imaging options, absence of standard operating procedures, and specialized interpretative skills. However, the advancement in automated image processing, AI-based segmentation, and cloud-enabled analytics are inreasingly overcoming these obstacles[124]. Future research directions should focus on:

1. Standardizing neuroimaging biomarkers in stroke subtypes and populations;
2. Defining longitudinal imaging patterns in patients with both TBI and stroke history;
3. Formulating adaptive rehabilitation protocols, with real-time imaging feedback and personalized response profiles[125-127].

Conclusions

Recovery of cerebral activity after ischemic stroke is largely facilitated by the interdependence between angiogenesis and neuroplasticity[128]. These regenerative processes are needed to restore cerebral perfusion and rebuild functional neural circuits. Recent developments in neuroimaging technologies currently allow visualizing, as well as quantifying these processes in vivo, which will provide clinicians with the necessary tools to prognosticate, monitor the therapy, and develop personalized rehabilitation programs [129,130]. Previous history of traumatic brain injury (TBI) is a powerful, though frequently under-estimated, modifier of stroke recovery.

Microvascular dysfunction, destruction of white matter integrity, and impaired plasticity related to TBI can diminsh regenerative responses and limit functional outcomes. Multimodal neuroimaging is essential in identifying these vulnerabilities and risk-based therapeutic intervention[131]. The integration of quantitative imaging biomarkers into regular stroke care in the future may enable the development of precise rehabilitation and the ability to inividually adjust treatment plans based on patient response. Moreover, patients with TBI history must be inluded in neuroimaging-based stroke studies to ensure that new protocols developed are both factual and reflective of the clinical populations that are seen in practice[132].

In conclusion, advanced use of neuroimaging in angiogenesis and neuroplasticity is a promising direction of more personal, effective, and adaptive post-stroke intervention[133].

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