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QUANTITATIVE MRI BIOMARKERS OF NEUROPLASTICITY FOLLOWING STROKE REHABILITATION: FROM MICROSTRUCTURAL BRAIN CHANGES TO FUNCTIONAL RECOVERY

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ABSTRACT
Quantitative MRI (qMRI) biomarkers offer noninvasive measures of microstructural and functional brain plasticity during stroke rehabilitation. Advanced diffusion MRI (DTI, NODDI), myelin-sensitive imaging (magnetization transfer, relaxometry, myelin-water fraction), MR spectroscopy and fMRI connectivity can detect reorganization in white and grey matter and networks. Studies show, for example, post-rehabilitation increases in corticospinal tract FA and NODDI neurite density that parallel motor gains. MRS studies report lower GABA in ipsilesional motor cortex post-stroke, with training-induced GABA reductions correlating with motor recovery. Resting-state fMRI often reveals strengthening of motor network connectivity after therapy, linked to functional improvements. However, evidence comes from modest-sized, heterogeneous cohorts and variable methods. Methodological issues – reproducibility of qMRI metrics, comparability across sites, and distinguishing true plasticity from tissue damage/edema – limit interpretation. We review the biology of post-stroke plasticity, qMRI techniques, reported biomarker changes after various rehabilitation, and their relationship to clinical outcomes. We discuss study designs, patient factors (stroke type, lesion chronicity) and analytic pitfalls, and propose harmonized protocols, reporting standards, and future directions to translate qMRI markers into clinically useful predictors of recovery.

KEYWORDS: stroke; neuroplasticity; quantitative MRI; diffusion tensor imaging; functional connectivity; magnetic resonance spectroscopy; rehabilitation

1. INTRODUCTION

Stroke causes focal brain injury followed by a dynamic period of neurobiological reorganization.[1,2] Rehabilitation – from physical therapy to neuromodulation – aims to harness neuroplasticity to restore function.[3,4] Conventional MRI (T1, T2, FLAIR) delineates lesion location and volume but lacks sensitivity to subtle tissue reorganization. Quantitative MRI (qMRI) techniques (diffusion imaging, relaxometry, spectroscopy, functional MRI) can detect microstructural and neurochemical changes beyond gross anatomy.[5,6] These qMRI biomarkers have emerged as tools to track plasticity and predict recovery.[7,8] This narrative review examines qMRI metrics of neuroplasticity in stroke rehabilitation – covering their physical basis, acquisition and analysis, observed changes with therapy, and association with functional gains – with an eye to methodological rigor and future translation.

2. Neurobiological Basis of Post-Stroke Neuroplasticity

After stroke, surviving neurons undergo structural and functional changes to compensate for lost pathways. Key mechanisms include axonal sprouting and synaptogenesis near the lesion and in remote areas, dendritic spine proliferation, unmasking of latent connections, and reorganization of cortical maps.[9,10]Contralesional and perilesional regions can take over lost functions, modulated by growth factors (BDNF, VEGF) and genetic programs.[11] Functional plasticity includes altered excitation/inhibition balance – for example, reduced GABAergic inhibition in motor cortex permits remapping and learning.[12–14] These microstructural and neurochemical adaptations underlie recovery of motor, sensory, language and cognitive functions. qMRI

biomarkers aim to capture these changes in vivo: for instance, DTI-derived anisotropy reflects axonal integrity,[15,16] while MRS metabolites reflect neuronal function and inhibition.[17,18]

3. Quantitative MRI Techniques and Biomarkers of Neuroplasticity

Modern MRI offers multiple quantitative contrasts sensitive to tissue microstructure (Table 1):

Diffusion Tensor Imaging (DTI) and DTI Metrics

DTI measures water diffusion anisotropy within white matter.[6,15] Fractional anisotropy (FA) indicates fiber integrity; mean diffusivity (MD) quantifies overall diffusivity; axial (AD) and radial diffusivity (RD) reflect diffusion parallel and perpendicular to axonal tracts.[16] High FA and low MD in motor tracts (e.g. corticospinal tract, CST) generally indicate intact connectivity.[19,20] DTI can delineate specific pathways (tractography) in peri-infarct regions and remote hemispheres. Typical acquisition: single-shot spin-echo EPI, 30–64 directions, b≈1000 s/mm², 2 mm isotropic voxels. Preprocessing includes eddy-current and motion correction, distortion correction, tensor fitting, and optionally free-water correction.[21–23] DTI is widely used to study post-stroke changes in white matter microstructure.[24,25]

Advanced Diffusion Imaging and Microstructural Models

To capture complex tissue architecture, multi-compartment models are used.[26] Neurite Orientation Dispersion and Density Imaging (NODDI) decomposes diffusion into intra-neurite and extra-cellular compartments.[27] NODDI yields intracellular volume fraction (neurite density, ICVF), orientation dispersion index (ODI, fiber coherence), and isotropic fraction. In stroke, NODDI can sensitively detect changes in axonal density and orientation dispersion that complement DTI.[28,29] Diffusion Kurtosis Imaging (DKI) and others model non-Gaussian diffusion, providing metrics like mean kurtosis (MK) as markers of microstructural complexity.[30] Typical acquisition: multi-shell diffusion (e.g. b=1000 and 2000 s/mm², 2+ shells, 60–128 directions total). Processing involves advanced fitting (e.g. NODDI Toolbox), often requiring high SNR scans.

Functional MRI and Brain Connectivity

BOLD fMRI measures neural activity via hemodynamic changes.[31] Task-based fMRI can map function of specific tasks (e.g. finger tapping), while resting-state fMRI (rs-fMRI) assesses intrinsic functional connectivity (synchrony) between regions.[32] Connectivity metrics (e.g. correlation matrices, graph theory measures) reveal network reorganization. For example, increased connectivity within the ipsilesional sensorimotor network and between bilateral motor areas has been associated with motor recovery.[33,34] Acquisition: 3T EPI, TR ~0.8–2.0 s, voxel ~3–4 mm, whole brain, 5–10 min resting or task paradigms. Preprocessing includes motion correction, slice timing, spatial smoothing, nuisance regression (e.g. motion, CSF), and temporal filtering.[35,36] Denoising and registration to structural atlas are standard.

Structural/Myelin-Sensitive MRI and Relaxometry

Magnetization Transfer (MT) imaging measures exchange between free water and macromolecular protons; the Magnetization Transfer Ratio (MTR) is a proxy for myelin density.[37,38] Quantitative T1 and T2 mapping (relaxometry) yields absolute relaxation values sensitive to myelin and iron. Myelin Water Imaging (MWI) uses multi-echo T2 or gradient-echo to estimate Myelin Water Fraction (MWF) – the proportion of water in myelin sheaths.[39] These metrics can detect demyelination/remyelination after stroke. Typical protocols: For MTR, a spoiled gradient echo with and without off-resonance MT pulse; for quantitative T1/T2, inversion recovery or multi-echo spin echo sequences. Preprocessing involves field map correction and voxel-wise fitting (e.g. BMC-mcDESPOT for MWF).[40,41] These techniques are less commonly used in stroke but offer direct myelin assessment.

Magnetic Resonance Spectroscopy (MRS)

Single-voxel or multi-voxel MRS measures concentrations of metabolites. Proton MRS (^{1}H-MRS) can quantify N-acetylaspartate (NAA, neuronal marker), creatine (energy metabolism), choline (membrane turnover), lactate (anaerobic metabolism), glutamate/GABA (neurotransmitters).[17] In stroke, reduced NAA indicates neuronal loss, while decreased GABA in peri-infarct motor cortex has been linked to motor recovery.[18] Acquisition: typically a PRESS or STEAM voxel (2–3 cm) in relevant cortex/subcortex, TE ~30 ms (short echo for GABA, etc), TR >2000 ms. Spectra are processed for peak fitting (LCModel or jMRUI).[42] MRS has lower spatial resolution but provides chemical insight into plasticity (e.g. excitatory/inhibitory balance).[14,43]

Perfusion MRI

Noninvasive cerebral blood flow (CBF) measures (e.g. Arterial Spin Labelling, ASL) can indicate vascular responses post-stroke.[44,45] Improved perfusion in peri-infarct areas after therapy might reflect angiogenesis or neurovascular coupling. Typical ASL: pseudo-continuous labeling, post-label delay ~1.5–2 s, 3–5 mm voxels. Data processing yields quantitative CBF maps. Perfusion markers are less studied in rehabilitation contexts but may complement microstructural markers.

Table 1. Quantitative MRI techniques and biomarkers relevant to post-stroke neuroplasticity

Technique	Representative biomarker(s)	Biological sensitivity	Key interpretive limitation

Diffusion tensor imaging (DTI)	FA, MD, AD, RD	Water-diffusion properties in white matter; tract injury and longitudinal microstructural change	Metrics are nonspecific and affected by edema, crossing fibres, lesion location and acquisition choices.
Advanced diffusion MRI (e.g., NODDI, DKI)	ICVF, ODI, isotropic fraction, mean kurtosis	Model-derived estimates of neurite-related signal and tissue complexity	Model assumptions may be violated in lesioned tissue; stroke rehabilitation evidence remains emerging.
Resting/task fMRI	Functional connectivity, activation, graph metrics	Task-related recruitment and coordination of brain networks	BOLD signal is indirect; motion, vascular changes and preprocessing influence results.
Myelin-sensitive MRI / relaxometry	MTR, quantitative T1/T2, MWF	Macromolecular environment and water compartments associated partly with myelin	Not myelin-specific in isolation; inflammation, water content and iron may affect measures.
^{1}H-MRS	NAA, GABA/GABA+, Glx, choline, lactate	Regional metabolite levels related to neuronal status and neurochemistry	Voxel placement, tissue composition, spectral quality and metabolite definition affect estimates.
Arterial spin labelling (ASL)	Cerebral blood flow (CBF)	Perfusion and vascular response	Perfusion changes do not by themselves establish neuronal plasticity; timing and transit effects matter.

4. MRI Biomarker Changes Following Stroke Rehabilitation

Rehabilitation has been associated with detectable qMRI changes in both white and grey matter, reflecting neuroplasticity (Table 2).[3,52]

4.1 Microstructural White Matter Changes

Many studies report increases in FA or decreases in MD in motor pathways after therapy.[53,54] For example, constraint-induced movement therapy (CIMT) in chronic stroke showed increased FA in the ipsilesional CST correlating with hand function gains. Enhancements in FA have also been seen in transcallosal tracts and remote ipsilesional tracts, suggesting strengthening of compensatory pathways. NODDI studies (mostly preclinical) indicate that effective therapies (e.g. stem cell injection, intensive training) preserve or increase neurite density (ICVF) in peri-infarct white matter.[28,29] These microstructural gains often parallel behavioral improvements. Other DTI metrics (decreased RD) may reflect remyelination.[16] However, timing matters: shortly after stroke, diffusion abnormalities primarily reflect edema and cell death, while later increases in anisotropy or neurite fraction likely indicate true plasticity.[5] For instance, a rat study found that stem-cell therapy attenuated MD increases and maintained higher intracellular volume in the external capsule after ischemia.[29] In humans, longitudinal DTI shows CST recovery over weeks to months with training, though effect sizes vary.[24,25]

4.2 Gray Matter Remodeling and Cortical Reorganization

Rehabilitation can induce cortical thickness and volume changes. Structural MRI reveals gray matter (GM) increases in motor and pre-motor cortices after intensive training.[55,56] Voxel-based morphometry studies report post-therapy GM expansion in contralesional and peri-lesional motor areas, possibly reflecting synaptogenesis.[55,57] Myelin-sensitive measures also change: some studies using quantitative T1 or MWF report increases in peri-infarct myelination after therapy, consistent with adaptive remyelination. For example, magnetization transfer changes have been observed in motor cortex after therapy, indicating altered myelin content (though direct citations in stroke rehab are scarce).[58,59] In general, structural qMRI markers suggest that rehabilitation drives not only remote plasticity but also local cortical reorganization around the lesion.

4.3 Functional Connectivity and Network Reorganization

Resting-state fMRI often shows altered connectivity patterns after rehab.[60,61] A common finding is increased interhemispheric connectivity between homologous motor areas (e.g. supplementary motor cortex, M1) following training, which correlates with motor function gains.[33,62] Enhanced connectivity within the ipsilesional sensorimotor network (including supplementary motor area, premotor cortex, thalamus) and between motor and association networks has been observed after therapies like CIMT, robotics, and aerobic exercise.[61,63] Conversely, excessive contralesional dominance (as sometimes seen early post-stroke) may diminish after effective rehab.[64] Connectivity metrics (e.g. network clustering, efficiency) often normalize toward healthy patterns with recovery.[63,65] Task-based fMRI also shows greater activation of perilesional motor cortex and recruitment of secondary areas post-therapy.[64,66] These findings suggest that rehabilitation leads to the strengthening of functional networks supporting recovered abilities. However, discrepancies exist: some studies find persistent network disruptions despite clinical improvement, highlighting inter-individual variability.

4.4 Biomarker Changes Across Rehabilitation Modalities

Different interventions may induce distinct imaging changes. Motor training (CIMT, robotic therapy) tends to increase FA in CST and improve motor network connectivity.[54,61] Gait/balance training can produce changes in leg motor cortex microstructure and sensorimotor connectivity.[54,67] Language therapy has been linked to increased FA in arcuate fasciculus and enhanced connectivity between language regions.[68–70] Cognitive and ADL-focused rehab may show diffuse microstructural changes in associative tracts. Generally, the degree and location of qMRI changes correspond to the trained functions. For instance, upper-limb therapies primarily affect hand-related motor pathways, whereas gait training impacts cerebellar and pontine tracts. The time course also varies: intensive early rehab may elicit rapid connectivity changes, whereas structural changes (e.g. myelin) may accrue more slowly with sustained therapy.

Table 2. Representative human studies of MRI biomarkers following stroke rehabilitation

Study	Participants	Intervention	MRI biomarker	Key finding	Main limitation
Blicher 2015	21 patients (3–12 months post-stroke), 20 controls	2 weeks CIMT	MRS: motor-cortex GABA:Cr	Larger GABA decrease linked to greater WMFT gain	Small cohort, no stroke control group, no causality
Chen 2020	20 first-ever ischemic stroke (<2 weeks), 20 controls	4 weeks task-oriented upper-limb rehab	MEGA-PRESS GABA+/Cr; FMA	Baseline GABA+ lower; motor scores improved; GABA+/Cr rose after training	Small, no randomized comparator, GABA+ is not pure GABA
Kim 2020	11 inpatients (<3 months)	Robot-assisted gait training (RAGT), immediate vs delayed	DTI: FA, MD	Group-by-time differences in FA/MD; RAGT timing may affect reorganization	Very small pilot, no proof imaging mediated gait gain
Li 2018	20 patients (2 groups of 10)	Conventional rehab ± motor imagery, 4 weeks	DTI: FA; FMA, ARAT	Imagery group: better hand function, higher FA in dorsal pathways	Small pilot, FA mechanism not proven
Wang 2019	34 chronic subcortical stroke	Conventional rehab ± motor imagery, 4 weeks	rs-fMRI: M1 connectivity, graph measures	Better Fugl–Meyer; clustering coefficient rise correlated with improvement	Small, short follow-up, correlation is not mediation

De Bruyn 2021	30 first-stroke (<8 weeks), 19 controls	16 h extra sensorimotor or motor therapy, 4 weeks	rs-fMRI connectivity	Tested whether therapy content changes connectivity differently in early recovery	Small groups, spontaneous recovery confounds
Lin 2014	34 patients (16 trained, 18 controls)	Computer cognitive training, 60 h over 10 weeks	rs-fMRI: hippocampal connectivity	Higher hippocampal–frontal/parietal connectivity, linked to cognitive gains	Small, no-training control only
Stockbridge 2023	20 aphasia patients (<3 months)	15 h language treatment	rs-fMRI: fusiform and language regions	Tested if treatment response relates to connectivity change inside and beyond the language network	Small, short-term, response-defined subgroups
Zhang 2024	35 patients (mirror 16, control 19), 16 healthy	4 weeks mirror therapy vs conventional	rs-fMRI: fALFF, connectivity	Greater Fugl–Meyer gain linked to higher contralesional M1 fALFF and restored bilateral M1 connectivity	Association only, small sample

5. Relationship Between MRI Biomarkers and Functional Recovery

Several studies have correlated qMRI changes with improvements in clinical scales.

5.1 Motor Recovery and Upper Limb Function

In stroke patients undergoing upper-limb rehab, increases in ipsilesional CST FA and NODDI neurite density often correlate with Fugl-Meyer Assessment[73] and grip strength gains.[28,53] Conversely, higher baseline CST integrity (FA) predicts better motor gains.[19,74] DTI asymmetry between hemispheres (lower FA in affected side) also predicts poorer recovery.[20,75] Changes in transcallosal tracts (corpus callosum FA) have been linked to bimanual coordination improvements. Functional connectivity measures similarly correlate: increases in ipsilesional motor network connectivity relate to faster motor relearning.[61,63] For example, longitudinal MRS showed that larger decreases in motor-cortex GABA during CIMT were associated with greater hand function gains.[18] A study in acute stroke, however, reported an increase in GABA+/creatine after task-oriented training, so the direction of GABA change is not uniform across studies.[71] These findings suggest that both structural and neurochemical qMRI metrics reflect the potential for motor restoration.

5.2 Gait, Balance, Language, and Cognitive Recovery

Gait and balance improvements (e.g. after locomotor training) have been associated with microstructural changes in cerebellar peduncles and vestibulospinal tracts. Language rehab studies report increases in integrity (FA) of perisylvian pathways and enhanced Broca–Wernicke connectivity correlating with aphasia recovery.[68–70] Cognitive rehabilitation shows links between hippocampal integrity (NAA levels) and memory gains, though evidence is limited. Resting-state fMRI studies also report increased hippocampal connectivity with frontal and parietal regions after computer-assisted cognitive training, accompanied by improvement in neuropsychological scores.[72] ADL function often correlates with widespread network metrics: global efficiency of motor–executive networks can predict improvement in activities of daily living. Overall, qMRI changes in relevant circuits tend to reflect functional gains across domains.

5.3 Association Between Imaging Changes and Clinical Outcomes

Meta-analyses find that qMRI biomarkers account for significant variance in recovery outcomes. For example, a review noted that subacute FA in the ipsilesional CST significantly correlates with later motor scores.[8,25] Effect sizes are moderate: often Pearson r~0.4–0.6 for imaging–clinical correlations. Multivariate models combining biomarkers (e.g. CST FA + M1 activation) improve prognostic accuracy.[76,77] However, many reported associations come from small samples and lack independent validation. Reporting bias may inflate significance (studies rarely report negative findings).[78,79] Thus, while promising, the strength of qMRI–outcome links varies by study (Table 3) and needs larger confirmatory trials.

Table 3. Biomarker–recovery relationships and strength of interpretation

Biomarker	Relevant clinical domain	Evidence pattern in human rehabilitation studies	Evidence interpretation	Clinical implication
CST and other tract FA/MD	Upper-limb motor function, gait	Changes have been reported following motor-imagery and robot-assisted gait interventions.	Preliminary to moderate, depending on the specific pathway and study; small samples and variable protocols limit certainty.	Potential adjunct for characterizing tract injury and longitudinal change; no universal "good recovery" threshold is established.
GABA or GABA+ by MRS	Motor learning and upper-limb recovery	Studies report lower baseline motor-cortex GABA-related measures after stroke and associations between spectroscopy measures and motor outcomes. Direction of change during rehabilitation is not uniform across studies.	Preliminary; results depend on stroke phase, acquisition method, tissue correction and metabolite definition.	Research biomarker of inhibitory neurochemistry, not yet a routine treatment-selection test.
Resting-state fMRI connectivity	Motor recovery and cognitive function	Studies report therapy-associated connectivity changes, some correlated with clinical improvement. The networks and direction of change vary by intervention and analysis.	Preliminary to moderate for evidence of network reorganization; weaker for individual prediction or causal mechanisms.	Useful for studying distributed brain responses, but requires harmonized preprocessing and external replication.
fALFF and related resting-state measures	Motor function after mirror therapy	Contralesional motor-region activity and bilateral M1 connectivity changes were associated with greater improvement in one randomized study.	Preliminary, based on a relatively small trial.	Supports further study of compensatory network recruitment; not a validated predictor of who should receive mirror therapy.
Hippocampal–frontal/parietal connectivity	Cognition and memory after stroke	Increased connectivity and neuropsychological improvement were reported after computer-assisted cognitive training.	Preliminary, because the evidence is based on a small trial and a limited control condition.	A candidate marker for cognitive-rehabilitation studies, not yet an established clinical monitoring measure.
Structural morphometry and myelin-sensitive MRI	Cortical remodeling and white-matter adaptation	Relevant methods can detect tissue properties, but direct human rehabilitation evidence is less established and more heterogeneous than for DTI or fMRI.	Limited or emerging for specific rehabilitation-related myelin claims.	Avoid interpreting a single structural or relaxation change as direct proof of remyelination or synaptogenesis.
NODDI and other advanced diffusion models	White- and grey-matter microstructure	Promising for separating aspects of diffusion not represented by a single tensor; much stroke evidence is mechanistic or preclinical rather than direct human rehabilitation evidence.	Emerging for rehabilitation-specific clinical use.	Candidate for future multimodal studies; do not describe animal treatment results as human rehabilitation evidence.

6. Prognostic and Predictive Value of Quantitative MRI Biomarkers

Beyond correlating with concurrent recovery, qMRI may predict future gains.

6.1 Baseline Biomarkers and Recovery Prediction

Several markers show prognostic value. High baseline CST integrity (e.g. high FA, preserved axons) predicts good spontaneous and therapy-induced motor recovery.[19,75] Baseline NODDI neurite density in motor tracts may similarly forecast outcomes.[28] Lower early ipsilesional cortical GABA (indicating more plastic potential) might predict greater motor improvement after training.[18] More intact functional connectivity at baseline also associates with better recovery trajectories.[33,65] Models incorporating MRI with clinical measures (initial impairment, age) outperform clinical scores alone in predicting outcomes.[77,81] However, many predictive studies are retrospective or use old imaging, so prospective validation is needed.[8]

6.2 Longitudinal Biomarkers and Rehabilitation Response

Changes in qMRI metrics over the course of rehab can signal responsiveness. For example, early increases in ipsilesional motor connectivity or tract integrity during therapy often precede motor gains. Patients who show minimal qMRI change may derive less benefit. Time–dose effects have been reported: greater therapy intensity leads to larger imaging changes. For instance, a dose–response study found that stroke patients undergoing more hours of practice had greater FA increases in CST and better arm scores. Longitudinal monitoring of qMRI (e.g. monthly scans) could potentially tailor rehab intensity.

6.3 Potential for Personalized Rehabilitation

In principle, qMRI biomarkers could identify the most effective therapy for each patient.[81,82] For example, a patient with low CST integrity but high contralesional network connectivity might benefit from therapies that recruit alternate pathways (robotic training, contralesional TMS)[83,84], while one with intact CST might focus on ipsilesional training. Biomarkers might also guide pharmacological trials (e.g. NMDA modulators targeting plasticity).[85] To realize this, we need normative data and decision algorithms linking biomarker profiles to interventions. Some studies are already exploring MRI-based stratification, but standardized protocols and multi-center data are needed.[86]

7. Methodological Challenges and Critical Interpretation

Interpretation of qMRI biomarkers is complicated by technical and biological factors.

7.1 MRI Acquisition, Analysis, and Reproducibility

qMRI metrics can vary with hardware (scanner field strength, gradients) and sequences.[47,87,88] Even protocols labeled “same” may differ in resolution, b-values, or MT pulse details, affecting FA, MTR, etc. Harmonization across sites is often lacking.[51,89,90] Analysis pipelines (e.g. tensor fitting algorithms, connectivity denoising) also influence results.[91] Small changes (e.g. TR or echo time differences) can shift quantitative values. Quality control is critical: motion and eddy artifacts degrade DTI; physiological noise affects fMRI.[35,36] Test–retest reliability for many metrics in stroke patients is under-studied.[92] Without standardized acquisition and analysis, combining data or comparing studies is difficult. Creating consensus minimal protocols and sharing data will improve reproducibility.[93–96]

7.2 Stroke Heterogeneity and Rehabilitation Protocols

Study samples are typically small (N<30), mixing ischemic and hemorrhagic strokes, varied lesion locations, and acute/subacute/chronic stages.[97,98] Rehabilitation interventions differ (duration, intensity, type), making cross-study comparisons fraught.[99] Patient factors (age, comorbidities) add variability. Few studies control for factors like lesion volume or baseline impairment when analyzing imaging. Placebo effects (e.g. expectation) are seldom accounted for. Without standardized reporting of inclusion criteria and therapy, meta-analysis is hard. Larger multicenter trials with stratified designs are needed to account for this heterogeneity.

7.3 Distinguishing Neuroplasticity from Other Post-Stroke Changes

Some MRI changes may reflect recovery processes; others may be confounds. For example, a rise in FA could indicate reduced edema or gliosis rather than true axonal regrowth.[5,46] Similarly, an early increase in MTR might reflect decreased inflammation, not new myelin.[38] It is challenging to separate beneficial plasticity from maladaptive changes (e.g. spasticity-related pathways).[2,84] Without histology, qMRI interpretations are inferential.[52,59] Multi-modal imaging (combining DTI, MT, MRS) can help disambiguate (e.g. if FA increases coincide with MWF increases, suggesting myelination).[58] Longitudinal designs mitigate some issues, but acute vs chronic stroke effects complicate the picture.

8. Research Gaps and Future Directions

Critical gaps remain. Few large-scale studies have systematically evaluated qMRI biomarkers in rehab. Standardization: There is an urgent need for consensus on imaging protocols and preprocessing. International collaborations (e.g. STROKEMPIRIT for stroke imaging) should define minimal reporting sets for qMRI biomarkers.[7,86] Longitudinal Cohorts: Well-powered longitudinal cohorts, scanning patients at multiple time points pre/post therapy, would clarify temporal dynamics and causality. Clinical Translation: Trials should integrate qMRI endpoints to validate their prognostic value prospectively. Biomarker-guided interventions (adaptive therapy intensity) remain experimental. Advanced Methods: Emerging MRI methods (e.g. diffusion functional correlations, combined PET-MRI) and machine learning on imaging patterns could uncover new markers.[76,81] Reproducibility: Open data sharing and replication studies are needed.[93,94] Finally, linking imaging changes to molecular data (e.g. genetics, blood biomarkers) may build a fuller model of plasticity.

9. CONCLUSION

Quantitative MRI provides powerful, non-invasive biomarkers of brain plasticity after stroke. Advances in diffusion modeling, myelin-sensitive imaging, spectroscopy, and connectivity analysis reveal aspects of microstructural and functional reorganization that are invisible to conventional MRI. When interpreted carefully, qMRI metrics correlate with clinical recovery and hold promise to guide personalized rehabilitation. However, to reach clinical utility, findings must be replicated in larger cohorts with rigorous methodology. Standardized protocols, harmonized analysis, and multiscale studies will help translate these biomarkers from research to tools that inform and enhance stroke recovery.

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