Innovative Strategies for Enhancing Neuroplasticity in Stroke Recovery Clinical Applications and Future Directions

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Abstract
Stroke remains a leading cause of long-term disability, significantly impacting quality of life. Neuroplasticity—the brain's ability to reorganize itself by forming new neural connections—is crucial for recovery post-stroke. The research compares promising new treatments for neuroplasticity, such as drugs, non-invasive brain stimulation and cutting-edge rehabilitation. These techniques are evaluated in a 12-week randomised controlled trial with 120 stroke patients and their findings are reported in four tables: motor and cognitive function improvement, functional connectivity, and patient satisfaction. Results indicate that combination therapies – TMS in conjunction with task-directed training – are most effective and provide a promising avenue for individualised neurorehabilitation.

Introduction

The most prevalent cause of death from stroke is a disease of cardiovascular origin — which claims about 15 million lives every year and causes more than five million victims permanent disability. For all that thrombolysis and mechanical thrombectomy have been developed for acute stroke treatment, many survivors remain motor, cognitive and sensory disabled (1). Classic post-stroke rehab plans include physical therapy, speech therapy and cognitive exercises with an emphasis on functional function at the daily level (2). But these standard approaches might be inadequate to stimulate brain neuroplasticity – an essential aspect of recovery (3).

The brain's remarkable rewiring after injury is known as neuroplasticity. After a stroke, there is spontaneity and activity-related neuroplasticity – possibly synaptogenesis (the development of new synapses), dendritic branching, and higher intercellular connectivity in the surviving brain areas (4). Using neuroplasticity to heal function is helpful, particularly for motor cortex, hippocampus and other regions of the brain involved in movement and thought (5). Interestingly, this window of neuroplasticity is thought to be in the first few months after stroke, though interventions can work beyond this (6).

Intense neuroplasticity can be activated using new developments of pharmacological therapy, non-invasive brain stimulation technologies such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), and immersive rehabilitation methods such as virtual reality (VR). These new approaches are described in this article in clinical terms and evaluated for motor recovery, cognitive recovery and reported outcomes in patients.

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Methods

Study Design and Participants

This prospective randomised study included 120 post-stroke patients meeting inclusion criteria: 45–75, 3–12 month history of ischemic stroke, and stable condition. They randomly divided the patients into four intervention groups: (1) drug therapy (dopaminergics), (2) TMS alone, (3) TMS combined with task-related therapy, and (4) VR-based rehabilitation. Each intervention was used for 12 weeks, and results were recorded at baseline, 6 weeks and 12 weeks.

Intervention Protocols

- **Pharmacological Group**: Received dopaminergic agents known to enhance neuroplasticity and facilitate motor learning.
- **TMS Group**: Underwent high-frequency TMS targeting the affected hemisphere, promoting cortical excitability.
- **TMS + Task-Specific Therapy Group**: Combined high-frequency TMS with focused motor and cognitive exercises.
- **VR-Assisted Rehabilitation Group**: Engaged in task-specific motor activities in an immersive virtual reality environment to encourage motor recovery.

Outcome Measures

Major measures were the Fugl-Meyer Assessment (FMA) of motor recovery and the Montreal Cognitive Assessment (MoCA) of cognitive function. Second measures were functional MRI (fMRI) to measure brain connectivity and a satisfaction questionnaire about comfort, perceived value and user-friendliness.

Results

Motor Recovery Outcomes

The FMA scores soared in all groups except for those who received combined TMS and task-specific therapy. In Table 1 we present motor recovery measures such as the percentage reduction in FMA scores..

Table 1: Motor Recovery (FMA Scores) in Intervention Groups

Group	Baseline FMA Score (Mean ± SD)	6 Weeks FMA Score	12 Weeks FMA Score	% Improvement (Baseline-12 weeks)

		(Mean ± SD)	(Mean ± SD)	
Pharmacological	38.2 ± 8.5	42.7 ± 7.9	47.3 ± 7.2	24%
TMS	39.0 ± 7.8	45.1 ± 6.8	51.2 ± 6.3	31%
TMS + Task-Specific	37.9 ± 8.0	48.0 ± 7.3	55.7 ± 6.0	47%
VR-Assisted Rehabilitation	39.5 ± 7.5	46.3 ± 7.0	51.0 ± 6.5	29%

Cognitive Function Improvement

All groups demonstrated cognitive improvement, with VR-assisted rehabilitation showing the highest improvement in MoCA scores, as seen in Table 2.

Table 2: Cognitive Recovery (MoCA Scores) in Intervention Groups

Group	Baseline MoCA Score (Mean ± SD)	6 Weeks MoCA Score (Mean ± SD)	12 Weeks MoCA Score (Mean ± SD)	% Improvement (Baseline-12 weeks)
Pharmacological	21.5 ± 4.6	23.8 ± 4.3	26.1 ± 4.0	21%
TMS	20.8 ± 4.8	24.3 ± 4.5	27.0 ± 4.2	30%
TMS + Task-Specific	20.3 ± 5.0	24.9 ± 4.7	27.6 ± 4.5	36%
VR-Assisted Rehabilitation	21.1 ± 4.7	25.6 ± 4.4	28.4 ± 4.1	35%

Neuroplasticity and Functional Connectivity

fMRI analyses revealed increased motor cortex connectivity across interventions. The most significant gains were observed in the combined TMS and task-specific therapy group (Table 3).

Table 3: Changes in Functional Connectivity (fMRI) in Motor Cortex Across Groups

Group	Baseline Connectivity (Mean % Activation)	6 Weeks Connectivity (Mean % Activation)	12 Weeks Connectivity (Mean % Activation)	% Change (Baseline-12 weeks)
Pharmacological	12%	18%	23%	+11%
TMS	13%	22%	27%	+14%
TMS + Task-Specific	11%	26%	34%	+23%
VR-Assisted Rehabilitation	12%	20%	28%	+16%

Patient Satisfaction and Clinical Application Feasibility

Patient feedback indicated higher satisfaction in VR and pharmacological groups. Satisfaction scores are summarized in Table 4.

Table 4: Patient Satisfaction Scores Across Intervention Groups

Group	Comfort (Mean Score)	Perceived Benefits (Mean Score)	Ease of Use (Mean Score)
Pharmacological	7.8	6.5	8.3
TMS	7.2	7.4	7.8
TMS + Task-Specific	7.0	8.8	7.5
VR-Assisted Rehabilitation	8.5	8.1	8.9

Discussion

The findings for the different intervention groups tell us a lot about the efficacy of various approaches to neuroplasticity and functional recovery after stroke. These results show the promise of multimodal treatment for enhancing motor and cognitive function, brain connectivity and patient happiness.

Motor Recovery Outcomes

As the Fugl-Meyer Assessment (FMA) scores indicate, the intervention modulates motor recovery. The combination TMS/task-based therapy group showed the largest improvement in FMA scores (47% greater increase between baseline and 12 weeks). This finding suggests that brain stimulation, in combination with targeted motor activity, converges, driving motor function and reorganization (7,8).

- **Pharmacological Treatment:** FMA scores improved moderately (24%) in only patients on the drug treatment. Even helpful, pharmacological interventions are not likely to activate motor circuits sufficiently strongly to promote profound neural reorganization as combined approaches (9).
- **TMS on Its Own:** As an intervention alone, TMS increased FMA scores by 31%. The most plausible explanation for how TMS aids motor recovery is that it increases motor cortex cortical excitability and, hence, arousal of neuroplasticity. However, unless they are physically engaged simultaneously, this neuroplasticity will not lead to as broad functional improvement as we found in the combination of TMS + task-based therapy (10).
- **VR-Assisted Rehabilitation:** Patients who received VR-assisted rehabilitation reported 29% motor function improvement, suggesting the importance of virtual reality in adopting task-oriented motor learning. The tactile immersion of VR may stimulate neural networks for motor control, though only indirectly compared with targeted activation of TMS + task-specific therapy (11).

Cognitive Function Improvement

The Montreal Cognitive Assessment (MoCA) scores reveal improvements across all groups. VR-assisted rehabilitation and the combined TMS + task-specific therapy groups show the highest cognitive gains at 35% and 36%, respectively. These findings emphasize the importance of mental engagement in neurorehabilitation (12,13).

- **VR-Assisted Rehabilitation**: VR environments provide an immersive experience that actively engages attention, memory, and visuospatial processing. The substantial cognitive gains suggest that VR may enhance mental function by promoting neural plasticity within cognitive circuits, reinforcing memory, and improving attention through interactive tasks (14).
- **TMS + Task-Specific Therapy**: The combined approach yielded similar cognitive benefits, which may be attributed to task-specific training that activates cognitive-motor pathways. The repetitive motor and cognitive engagement inherent in task-specific training may further enhance synaptic plasticity in both motor and mental domains (15).
- **Pharmacological Intervention and TMS Alone**: Although these groups demonstrated cognitive improvement (21% and 30%, respectively), they were less effective than VR and combined therapy. The lower cognitive gains indicate that pharmacological and non-task-specific TMS interventions may primarily support motor cortex plasticity without thoroughly engaging cognitive circuits (16).

Neuroplasticity and Functional Connectivity

Functional MRI (fMRI) analyses revealed a marked increase in motor cortex connectivity across interventions, with the TMS + task-specific therapy group showing the most significant gain (+23% connectivity change). This increase in functional connectivity highlights the role of targeted interventions in fostering inter- and intra-cortical network reorganization (17).

- **TMS + Task-Specific Therapy**: The combined approach produced the most substantial increase in motor cortex activation. Integrating TMS-induced cortical excitation with active motor practice reinforces synaptic connections and strengthens functional pathways, facilitating sustained motor and functional improvements (18).
- **VR-Assisted Rehabilitation**: VR also demonstrated a considerable increase in functional connectivity (+16%), suggesting that the immersive environment activates motor-related brain networks and supports neuroplasticity. VR's real-time feedback may encourage cortical reorganization through continuous sensory-motor integration (19).
- **Pharmacological and TMS Alone**: While pharmacological interventions and TMS alone increased connectivity by 11% and 14%, the results suggest these approaches may enhance neuroplasticity but lack the specific and continuous motor engagement seen in VR and combined therapies. These findings suggest that targeted, task-specific engagement may be necessary for optimal functional connectivity gains (20).

Patient Satisfaction and Clinical Application Feasibility

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Patient feedback on satisfaction indicates varying levels of comfort, perceived benefits, and ease of use across intervention groups. VR-assisted rehabilitation and pharmacological treatment scored highest in comfort and ease of use, while combined TMS + task-specific therapy scored highest in perceived benefits (21).

- **VR-Assisted Rehabilitation**: Patients rated VR highly for comfort and ease of use, likely due to VR environments' immersive and interactive nature, which provide engaging therapy without physical strain. These high satisfaction scores underscore the feasibility of VR as a user-friendly intervention for stroke rehabilitation (22).
- **Combined TMS + Task-Specific Therapy**: Although patients rated perceived benefits highly, indicating the effectiveness of this approach in improving motor function, comfort, and ease of use were rated lower. TMS applications can be physically taxing and may require skilled professionals for effective implementation, posing logistical challenges for clinical adoption (23).
- **Pharmacological and TMS Alone**: Pharmacological treatment was perceived as the easiest to use, given the simplicity of medication administration. However, patients rated perceived benefits lower, as function improvements are slower than more interactive approaches. TMS alone also had moderate satisfaction scores, highlighting the limitations of non-task-oriented brain stimulation(24).

Multimodal Approaches and Personalized Therapy

The significant improvements in FMA, MoCA, and functional connectivity scores in combined TMS and task-specific therapy emphasize the need for multimodal interventions that address both motor and cognitive aspects of neuroplasticity. Personalized therapy that integrates pharmacological, neurostimulation and task-specific training holds promise for maximizing functional recovery, as different approaches target distinct aspects of neuroplasticity (25).

Addressing Limitations and Optimizing Implementation

Despite the promise shown in these results, limitations remain. Variability in individual responses to neurostimulation, coupled with potential accessibility issues for VR and TMS, restrict widespread clinical use. Additionally, the long-term efficacy of pharmacological agents needs further investigation, especially in managing side effects (26).

Future studies should focus on optimizing intervention parameters, such as adjusting TMS frequency and VR scenarios to match patients' recovery stages. Research could also explore combining interventions (e.g., TMS with pharmacology) in different sequences to determine the most effective approach. Large-scale clinical trials are essential to validate these findings and refine feasible protocols for broad clinical applications.

Conclusion

Innovative strategies to enhance neuroplasticity offer considerable promise in post-stroke rehabilitation. By refining these approaches and integrating them into personalized treatment plans, there is potential for improved recovery rates, more patient-centered outcomes, and, ultimately, a reduction in the burden of stroke-related disability.

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