Neuromodulation for Rehabilitation: Restoring Functions One Synapse at a Time

Zekai Qiang

The University of Sheffield

zqiang1@sheffield.ac.uk

Introduction

One early afternoon during my clinical rotation at a tertiary centre, I had the opportunity to accompany a patient, who is in her 50s, for a repetitive transcranial magnetic stimulation (rTMS) session. She had recently undergone a craniotomy for resection of a low-grade glioma. While the surgery was uneventful, on the second day after return to the ward, she developed sudden right-sided hemiplegia and worsening aphasia. Radiology subsequently revealed a venous infarction in the left frontal-parietal region. The rTMS session was intense and involved four blocks of 15-minute intervals. During each block, she was asked to perform motor tasks against resistance and to name objects shown in pictograms. The therapy was delivered with high-frequency stimulation at 10 Hz to the motor and speech function regions of the affected left hemisphere and lower, but 1 Hz frequency stimulation to the unaffected right hemisphere.

The patient focused intently on the tasks, while the leading physician, guided the session, explained each task with clarity and offered words of encouragement continuously. Meanwhile, the resident and I stood beside the patient, assisted by holding the bulky stimulation coil and its cables, and monitored the alignment on the navigation displays. When the session concluded, we wheeled the patient back to her room. Her children gathered and hugged her in excitement while she appeared visibly fatigued. The physician provided words of hope and encouragement as we said our goodbyes. This was my first introduction to the world of neuromodulation technologies in rehabilitation medicine - as the repetitive magnetic pulses from the TMS coils passed through the skull, generating electrical currents that could potentially alter physiological activities in the underlying cortex. I was captivated by the idea of directly intervening in the neural substrates to correct dysfunctional outputs. This experience

sparked my curiosity to explore into the potential of these technologies and their opportunities for further development.

Neuromodulation involves applying electrical stimulation to specific cortical structures or circuits within the human nervous system to adjust and normalise aberrant neural behaviours caused by disease processes.(1) In addition to rTMS, which was initially discovered by Barker and colleagues in Sheffield (2), other non-invasive techniques include transcranial direct current stimulation (tDCS) and transauricular vagus nerve stimulation have demonstrated potential in promoting functional restoration. These techniques are being investigated for a range of conditions, including multiple sclerosis (3), traumatic brain injury (4), stroke (5) and spinal cord injury (6). Whereas invasive techniques such as deep brain stimulation (DBS) have been established therapies for movement disorders such as essential tremor and Parkinson's disease.(7) Emerging technologies, including brain-computer interfaces (BCIs), are also being developed with the potential to offer enhanced and personalised therapeutic outcomes. This essay aims to explore the current applications of neuromodulation technologies in rehabilitation, critically review existing literature, and identify opportunities, challenges, and pathways for future advancements.

Functional Recovery via Non-invasive Neuromodulation

Motor Rehabilitation

Neuroimaging studies reveal that stroke disrupts the motor control network, causing interhemispheric imbalances with disinhibition of the contra-lesional hemisphere and reduced connectivity in the ipsi-lesional hemisphere.(8) Patients with greater connectivity between the

contra-lesional motor cortex and the paretic limb often show more functional impairment and corticospinal tract damage.(9) These changes in connectivity and neuroplasticity, which start early after a stroke and persist into the chronic phase, impact motor recovery.(8, 10) Thus, neuromodulation techniques are introduced to address these maladaptive changes. High-frequency stimulation (>5 Hz) is thought to enhance cortical excitability, while low-frequency stimulation (≤1 Hz) reduces it, potentially influencing synaptic plasticity through long-term potentiation and depression processes.(11)

Studies on non-invasive neurostimulation for stroke re-ambulation shows promise. A systematic review of eight randomised controlled trials found that transcranial neurostimulation significantly improved lower limb function, gait, balance, and walking speed.(12) The benefits appear to be dose-dependent, with more significant recovery associated with longer or more frequent sessions.(12-14) Additionally, improvements appear agnostic to times since stroke-onset, stimulation device configurations, and protocols.(14, 15) However, the long-term sustainability of these benefits remains unclear, as most studies only tracked outcomes for up to one month post-treatment. While some studies also demonstrated improved force production in paretic limbs, only two of the 23 studies in the meta-analysis focused on lower limb strength, suggesting these positive effects should be interpreted cautiously.(16)

In contrast, long-term benefits from neurostimulation for upper limb dyskinesia recovery have been demonstrated.(13) However, its effectiveness decreases over time after injury, with patients beyond six months showing the least improvement. This suggests that early intervention, when the brain's plasticity is heightened and more receptive to stimuli, may be more beneficial.(17) Ongoing debate persists about how lesion location, stimulation sites and parameters affect rehabilitation outcomes. For example, high-frequency stimulation of the ipsi-

lesional primary motor cortex (PMC) improves movement kinematics only in patients with subcortical injury, but not those with cortical involvement.(18) Additionally, low-frequency stimulation of the contra-lesional PMC enhances dexterity in patients with infarction in the dominant hemisphere but not in those in the non-dominant hemisphere.(19) Indeed, the cortical representation, connectivity, and functional organisation of motor control networks for upper limb volitional movements are intricate, requiring precise cortical refinement and lateralisation.(20) These complexities highlight the necessity for deeper understanding into the network pathophysiology in brain injury and to optimise neuromodulation protocols tailored to specific lesion locations.

Combining neuromodulation with interventions such as constraint-induced movement therapy and robot-assisted therapy, however, has led to significant improvements in upper limb dexterity, even in chronic stroke patients.(21) This indicates that enhancing neural network connectivity coupled with effective behavioural and contextual stimulation is crucial, as both motor learning and cortical stimulation induce similar, persistent changes in the local excitability of lesioned and contra-lesional motor cortices.(22) Moreover, brain stimulation can enhance cortical excitability before motor training, optimising rehabilitation and resulting in more lasting functional gains. A better mechanistic understanding of each stimulation approach and motor skill acquisition is vital for refining their combined use and developing more effective rehabilitation strategies.

Speech Rehabilitation

In speech rehabilitation, low-frequency rTMS to the right Broca's area for 20 to 40 minutes daily over 10 to 15 days has improved naming, repetition, and speech fluency, but not

comprehension.(23) These gains are typically observed stable for up to 12 months after treatment, supporting the notion that stroke-induced disruption of transcallosal disinhibition increases activation in the right hemisphere, impeding full language recovery.(23, 24) While rTMS effectively promotes neural plasticity in chronic aphasia, the benefits are again found more pronounced during the subacute phase, where factors including reperfusion, diaschisis resolution, and functional reorganisation enhance language network plasticity.(25)

However, current research on stimulating posterior language regions for receptive aphasia rehabilitation is limited. One study found that a single session of theta burst stimulation (rTMS bursts of 50 Hz over the ipsi-lesional Wernicke's area) demonstrated a temporary improvement in auditory comprehension in 13 chronic stroke patients, although with effects observable only at 1 and 5 minutes post-stimulation and fading by 40 minutes.(26) This opens questions for repeated sessions and larger patient samples to prolong and capture the benefits. Additionally, a randomised controlled trial indicated that low frequency rTMS inhibiting the right posterior temporal gyrus significantly improved auditory comprehension and repetition in right-handed chronic stroke patients, though long-term effects were not assessed beyond 15 days.(27)

Effects of these techniques appear variable based on stimulation methods and target sites. For example, tDCS, where a constant low-level electrical current is delivered through scalp electrodes, significantly improved verbal comprehension when applied to the right superior temporal areas in subacute stroke, compared to over the left homologous areas.(28) This suggests that suppressing the non-lesional hemisphere with tDCS may be more effective than exciting the lesioned hemisphere. Similarly, combined language training with tDCS of the right Wernicke's area improved spontaneous speech and word-picture matching in an elderly patient with receptive aphasia.(29) Evidently, significant variability in stimulation techniques,

protocols, and targets exist, potentially inducing differential neural mechanisms, with no consensus on the optimal approach. Further high-quality investigations are necessary to provide clarity on these issues.

Accumulating evidence supports the dual-stream model of language function, linking speech comprehension to the ventral stream, which involves the lateral temporal lobe extending to the posterior-inferior frontal gyrus via the uncinate fasciculus.(30, 31) In contrast, the dorsal stream handles auditory-to-articulation processing and is organised in the left hemisphere's frontal areas and the temporal-parietal junction. This model emphasises the importance of cortical connections and complex interactions between these networks, moving beyond the simpler Wernicke-Lichtheim Model. It remains unclear how the current non-invasive neurostimulation techniques engage these broader neurolinguistic networks. Understanding how neuromodulation paradigms affect brain connectives is essential for advancing technologies in line with the latest knowledge of functional cortical networks. This understanding will allow for the creation of more refined and intuitive rehabilitation strategies, leading to better functional outcomes.

Visual Rehabilitation

In visual rehabilitation, neuromodulation is often combined with visual training exercises like eye movement and attention tasks. For instance, stimulation to the lesional occipital cortex in 14 subacute stroke patients for 10 sessions significantly improved detection accuracy compared to visual training alone.(32) However, these studies have limitations, such as lacking long-term follow-up and potential baseline confounding factors, including individual differences in lesion topography or visual attention, which could affect recovery. The open-label design of current

research makes it unclear whether improvements are due to neurostimulation or the visual training. Therefore, double-blinded, placebo-controlled trials with larger samples are needed for more definitive conclusions.

In chronic stroke patients, longer stimulation protocols were needed and yielded less pronounced visual improvements, indicating that early intervention remains a critical consideration.(33) However, improvements in visual function were inconsistent: while detection accuracy improved early in training, gains in visual field only appeared after training completion. Additionally, these visual field gains did not extend to other areas of visual performance, such as contrast sensitivity or reading ability.(34) This indicates that the current methods effectively target specific tasks but may not enhance broader visual functions that could potentially be important for daily activities. This highlights the need for future research to optimise the duration, type, and location of neurostimulation to enhance the overall effectiveness and applicability of visual rehabilitation strategies.

Emerging Developments and Outlook

Network-based Rehabilitation

Understanding the brain as a system where functions emerge from dynamic interactions between different cortical regions has increased the focus on targeting specific networks with neuromodulatory interventions. While current methods offer high spatial precision, they struggle to engage multiple network nodes simultaneously.(35) Novel approaches, such as paired associative stimulation, deliver electrical pulses to correlated cortical nodes to induce spike-timing-dependent plasticity and modulate inter-network connectivity.(36, 37) Multi-

channel transcranial stimulation systems have been experimented, aiming to facilitate broader network-based neuromodulation, but face challenges such as sophisticated stimulation parameters, unclear targets and protocols, undefined mechanisms of action, and a lack of patient-specific considerations.(35)

BCIs, in contrast, provide a top-down rehabilitation approach that promotes individual-specific neural circuit reorganisation.(38) Learning to control neuroprosthetics induces widespread cortical network modifications, including global changes that rapidly reduce motor errors and local adjustments that improve movement efficiency.(39, 40) Such BCI may utilise decoder algorithms to process neural activity, link neural patterns to intended behaviour, and generate signals that drive effectors. These effectors then act as neurofeedback, entraining individuals with limb weakness to enhance ipsi-lesional mu-rhythm activation and strengthen ipsi-lesional sensorimotor networks.(41, 42) Furthermore, more invasive approaches, such as DBS of the cerebellar dentate nucleus, have shown safety and feasibility in promoting functional reorganisation of the ipsi-lesional cerebello-thalamo-cortical pathway in chronic upper limb impairments.(43) These surgical neuromodulation options offer the potential for continuous, at-home, or demand-based rehabilitation.

Towards Intelligent, Personalised Neuromodulation

While early studies show non-invasive neurostimulation holds promise for enhancing functional rehabilitation, these often yield modest effects in randomised controlled trials and meta-analyses.(44) There is also significant variability in cortical responses, with fewer than 50% of participants experiencing the expected neural circuitry plasticity.(45, 46) This highlights the need for optimising stimulation protocols on an individual basis. Brain-state

dependent stimulation, which uses cortical features from techniques such as electroencephalography (EEG) to tailor stimulation protocols, could reduce variability and improve outcomes. For example, delivering low-frequency rTMS during phases of sensorimotor mu-oscillation that correspond to high excitability states has been shown to potentiate corticospinal plasticity and enhance motor learning. These neurophysiology-informed neuromodulation approaches could lead to more personalised interventions and drive the development of wearable devices for home use, reducing fatigue for both patients and providers, ultimately improving adherence to rehabilitation protocols.(47-49)

Machine learning methods, which can extract salient representations from spatiotemporally resolved neural data through iterative training and self-optimisation, have also been implemented.(50, 51) These techniques further enhance the individual specificity of extracted neural features across patients with various brain lesions. Using a vast feature space extracted from EEG data, including power spectral densities and phase coherences, a suite of logistic regression, random forest, and support vector machine classifiers demonstrated an average 73% accuracy in decoding motor excitability.(52) This demonstrates the potential for developing closed-loop neuromodulation using EEG features and artificial intelligence (AI) to improve the efficacy of personalised rehabilitation approaches.(53) Furthermore, advances in deep learning, which utilises layered artificial neural networks, hold promise for automatically acquiring hierarchical representations from extensive neurophysiological datasets, thereby streamlining feature extraction and simplifying pre-processing steps.(54)

Ethics of Neuromodulation

As neuromodulation technologies continue to evolve and expand into broader clinical applications, several ethical concerns require careful consideration. The high hardware and operative cost of these systems limits their access, potentially creating a "digital divide" that disproportionately affects elderly populations, individuals in lower socioeconomic groups, and those in regions with limited healthcare infrastructure.(55) This raises significant questions about equity in access to these potentially transformative technologies. It is essential that the development and deployment of these interventions include efforts to make them accessible to a wide range of patients, rather than restricting them to those who can afford them or live in areas where such treatments are available.

Advancements in neuromodulation technologies also necessitate robust regulatory frameworks and ethical oversight to ensure responsible use.(56, 57) This includes developing clear clinical guidelines, monitoring long-term effects, and adhering to ethical research protocols. The rapid innovation in this field challenges existing regulations, which need to adapt to address unique ethical issues, such as the misuse of technologies for cognitive enhancement or memory improvement.(58) Such misuse could intensify inequalities and create new forms of discrimination, giving unfair advantages in education and employment. Additionally, the potential for coercion, such as pressure on individuals to undergo enhancements for increased productivity, raises concerns about undermining personal autonomy and informed consent. As integrated artificial intelligence technologies continue to develop, legal frameworks must also adapt to address the complexities they introduce, including issues related to data privacy, informed consent, and neural data ownership.

Conclusions

In conclusion, neuromodulation interventions hold significant promise for enhancing rehabilitation across a range of functions, including movement, communication, and sensory processing. However, to fully realise their potential, a deeper mechanistic understanding of network-based rehabilitative approaches is essential. As the field evolves, integrating advances in high-dimensional neurophysiology and artificial intelligence, while addressing the ethical considerations will be pivotal. These developments should lead the way for more personalised and dynamically optimised stimulation protocols, ultimately allowing more effective and tailored rehabilitation strategies that significantly enhances functional recovery outcomes.

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