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To Treat or Not to Treat? Reflections on the Clinical Translation of Non-invasive Neuromodulation Therapy for Post-Stroke Upper Limb Recovery

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6 **To Treat or Not to Treat? A Point of View on the Clinical Translation of Non-invasive**
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8 **Neuromodulation Therapy for Post-Stroke Upper Limb Recovery**
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Clinical Translation of NIBS for Stroke

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Abstract

Despite more than two decades of research into non-invasive brain stimulation (NIBS) for post-stroke upper limb motor recovery, it has yet to become a routinely implemented intervention. Transcranial magnetic stimulation (TMS), for example, is FDA-approved for certain psychiatric conditions, but its role in neurorehabilitation remains uncertain.

Meanwhile, technological advances, such as disposable, portable electrochemical devices, are bringing NIBS closer to real-world use, although critical gaps in clinical translation persist.

This Point of View paper offers a timely commentary on key challenges and opportunities discussed during the 6th International Brain Stimulation Conference held in February 2025 in Kobe, Japan, with a focus on the clinical application of repetitive transcranial magnetic stimulation (rTMS) in post-stroke rehabilitation. We argue that the major barrier lies in the field's overreliance on standardized, one-size-fits-all protocols and its reluctance to embrace personalization in the pursuit of precision. During the conference, two research cultures were evident: the "Systematicists", who rely on conventional clinical trials, and the "Personalizers", who tailor NIBS protocols to individual patient characteristics. This dichotomy reflects a broader challenge: how can we reconcile the need for standardization with the demand for personalization in translational research? Traditional one-size-fits-all models, such as increasing ipsilesional or suppressing contralesional M1 excitability, often fall short in delivering consistent outcomes across diverse stroke survivors. We contend that future progress depends on moving beyond this dichotomy and developing structured models for precision rehabilitation.

Looking ahead, the future of NIBS may lie in patient-specific, biomarker-driven neuromodulatory protocols that incorporate deep phenotyping and brain state-dependent stimulation, such as closed-loop TMS guided by Hebbian plasticity principles. This approach

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3 recognizes that post-stroke recovering brain is a four-dimensional structure, shaped by space
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5 (length, width, and depth) and time, which contributes to substantial intra- and inter-
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7 individual variability, and therefore cannot be addressed with universal stimulation protocols.
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10 Understanding how NIBS interacts with each uniquely recovering brain is essential.
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12 Addressing this complexity remains a major challenge for designing rigorous clinical trials
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14 and moving the field closer to effective, personalized integration in stroke rehabilitation. By
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16 delineating key components of personalization and proposing pathways to test them, we aim
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18 to reframe the discussion from “if” NIBS works to “for whom, for what and why, for where
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20 and when, and how” it can facilitate clinically meaningful recovery.
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24 **Keywords:** Stroke, neurorehabilitation, motor recovery, motor restoration, neuromodulation,
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26 non-invasive brain stimulation, precision rehabilitation.
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To Treat or Not to Treat? A Point of View on the Clinical Translation of Non-invasive Neuromodulation Therapy for Post-Stroke Upper Limb Recovery

Introduction

The 6th International Brain Stimulation Conference, held in Kobe, Japan from 12 to 16 February 2025, opened with a plenary lecture by Prof. Marom Bikson, who introduced a printable, disposable electrochemical technology for neuromodulation that operates without electronic components, envisioning a future where non-invasive brain stimulation (NIBS) could be dispensed in pharmacies and carried in patients' pockets ¹. If a pill can alleviate depressive symptoms, why shouldn't a physician prescribe a portable, non-invasive, self-discharging adhesive band as an alternative? A similar principle could apply to neurorehabilitation, potentially enabling individuals with stroke to improve motor symptoms. Yet before imagining a future where NIBS is prescribed as routinely as pharmacotherapy, it is crucial to recognize that, despite over two decades of research ^{2,3}, NIBS has yet to become a standard component of patient care.

This point of view article reflects on the challenges and opportunities discussed at the conference regarding the clinical translation of NIBS for post-stroke upper limb recovery. In particular, the discussion centres on transcranial magnetic stimulation (TMS), which remains appealing due to its ability to directly modulate neuronal excitability in targeted cortical regions ⁴, but has recently drawn criticism because of inconsistent findings in randomized controlled trials (RCTs). The article examines why the clinical implementation of TMS has not yet achieved widespread clinical adoption and discusses potential steps to help bridge the gap between research and routine care. We argue that this gap reflects not only

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3 methodological challenges but also a deeper conceptual issue: the historical field's reliance
4 on standardized, one-size-fits-all protocols that fail to account for the heterogeneity of post-
5 stroke recovery. At the same time, advances in neuroimaging, electrophysiology, and
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8 computational modeling now provide unprecedented opportunities to move toward patient-
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12 specific, biomarker-driven neuromodulatory approaches.
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15 During the conference, two distinct approaches became evident. The "*Systematicists*" rely on
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17 conventional trials and standardized protocols designed to produce generalizable results
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19 across populations, whereas the "*Personalizers*" tailor stimulation protocols to individual
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21 patient characteristics, incorporating personal biological signatures to maximize the
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23 therapeutic effect. These two cultures have now reached a crossroads. The field must
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25 confront and reconcile what appears to be a contradiction: methodological rigor versus the
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27 heterogeneous and dynamic spectrum of post-stroke recovery. While both approaches
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29 advance the science of NIBS, we contend that the path to clinical translation depends on
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31 developing structured models of personalized precision.
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36 In this article, we therefore propose that meaningful clinical translation of NIBS will require
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38 creating practical models that operationalize personalization without abandoning the rigor of
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40 systematic research. We highlight emerging strategies to achieve this and most importantly,
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42 we propose that post-stroke recovering brain should be understood as four-dimensional
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44 structure shaped by space (length, width, and depth) together with time as the fourth
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46 dimension, which gives rise to unique individual variability. By reframing the discussion in
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48 this way, we aim to shift the central question from "if" NIBS works to "for whom, for what
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50 and why, for where and when, and how." it can facilitate clinically meaningful recovery in
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55 post-stroke rehabilitation.
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The problem

TMS is one of the most widely studied NIBS techniques. It modulates neuronal activity by delivering brief, high-intensity magnetic pulses through a coil positioned over the scalp.

These pulses induce electric currents in the underlying cortical tissue, leading to depolarization of neurons and modulation of cortical excitability. Delivering repetitive pulses (rTMS) can produce longer-lasting changes in brain activity. Specifically, high-frequency rTMS (≥ 5 Hz) typically increases cortical excitability, whereas low-frequency rTMS (≤ 1 Hz) reduces it, through synaptic mechanisms resembling the long-term potentiation (LTP) and long-term depression (LTD) ³.

In neuroscience research, rTMS has been extensively used in healthy adults to selectively and transiently modulate activity in specific brain regions, allowing researchers to infer causal links between neural circuits and behaviour. This approach, sometimes called a “lesion” method, typically uses low-frequency rTMS to inhibit cortical regions and assess the resulting behavioural effects, much like a temporary off-switch. For instance, rTMS helps reveal two distinct cortical pathways for human body perception, i.e. the fronto-parietal network for the upright body perception and the extrastriate body area (EBA) for the inverted body part processing ⁵.

In addition, TMS has been widely used to investigate the mechanisms and neural substrates underlying voluntary movement and motor learning by probing and modulating activity in specific cortical regions ⁶⁻⁹. These findings demonstrate that rTMS is a powerful experimental tool for investigating the functional architecture of the human brain and for inducing behavioural changes with potential therapeutic effects.

One of the most pressing challenges highlighted during the conference was the uncertain clinical impact of TMS in neurorehabilitation. Despite the fourteen oral presentations and

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3 fifteen posters on NIBS and post-stroke upper limb recovery, as well as extensive ongoing
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5 research beyond the conference, one question remains:
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8 **Is the evidence strong enough to justify integrating rTMS into everyday clinical**
9 **practice?**
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13 The application of rTMS in post-stroke motor rehabilitation has been primarily guided by the
14 interhemispheric rivalry model, which posits that a poor process of poststroke motor recovery
15 arises from a pathologically competitive neural circuit between the underactive ipsilesional
16 motor cortex and the overactive contralesional motor cortex developed after unilateral brain
17 damage ¹⁰. Consequently, two possible rTMS strategies have emerged: (1) excitatory
18 stimulation, such as high-frequency rTMS or intermittent theta burst stimulation (iTBS),
19 targeting the ipsilesional motor cortex to enhance cortical excitability; or (2) inhibitory
20 stimulation, such as low-frequency rTMS or continuous theta burst stimulation (cTBS),
21 applied to the contralesional hemisphere to reduce interhemispheric imbalance ¹¹. While this
22 model's mechanistic plausibility was supported by several early proof-of-concept studies ^{2,7},
23 meta-analyses of clinical RCTs consistently reveal substantial heterogeneity in recovery
24 outcomes in patients receiving different rTMS interventions ^{12,13}.
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42 The robust neuromodulatory effects of TMS on brain activity contrast with its variable
43 impact on clinical outcomes in post-stroke populations, leaving its future pathway for
44 translation and adoption unclear. While the U.S. Food and Drug Administration (FDA) has
45 approved rTMS for specific psychiatric conditions ^{14,15} its benefit and adoption in post-stroke
46 motor neurorehabilitation remain limited.
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54 While several conference sessions critically examined this translational gap, one particularly
55 salient example was the navigated inhibitory rTMS to contralesional hemisphere (NICHE)
56 multicentre RCT, which included 199 stroke participants, found no significant differences in
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3 upper limb function between the real and sham stimulation groups following therapy ¹⁶. An
4 extension of this study, the E-FIT multicentre RCT, replicated the NICHE stimulation
5 protocol but used a sham coil that matched the appearance of the active coil, without
6 delivering the weak electric field used in the NICHE. Unfortunately, the results were also
7 replicated, showing no significant additional clinical benefit ¹⁷. In response, the ongoing B-
8 STARS 2 multicentre RCT was introduced as another phase III trial designed to reassess all
9 these findings. This study employs cTBS and aims to enrol 454 participants randomized to
10 receive either sham or active cTBS. To date, 10 participants have been recruited ¹⁸.

11
12 A key challenge underscored during the session was the high interindividual variability in
13 response to NIBS. As Prof. Friedhelm Hummel emphasized, this variability may be
14 influenced by multiple factors, including lesion characteristics, time post-stroke, stimulation
15 parameters, and individual neurophysiological profiles. This heterogeneity complicates the
16 design of standardized protocols and may contribute to the inconsistent outcomes observed
17 across trials. Addressing this complexity is essential for optimizing treatment efficacy and
18 advancing clinical adoption ¹⁹.

19
20 Throughout the conference, in symposiums and poster sessions on rehabilitation, two distinct
21 research approaches emerged. The “*Systematicists*”, researchers conducting conventional
22 trials with methodological rigor where stimulation parameters are applied uniformly across
23 populations and groups, with limited or no stratification based on individual characteristics
24 ^{20,21}, in contrast to the “*Personalizers*”, those dissecting NIBS techniques, tailor interventions
25 to individual patient characteristics, for instance, targeting a high-excitability state of the
26 ipsilesional cortical activity that matches the neurophysiological profile of each stroke patient
27 ²². While both approaches are critical to advance the science and practice of NIBS, yet they
28 place scientists and clinicians at a critical crossroads. Together, these observations prompt a
29 fundamental question:
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3 **Given the variability in rTMS and other NIBS, is the field ready for large-scale phase**
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5 **III trials that can truly translate from bench to bedside?**
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8 There are key conceptual limitations in the prevailing clinical frameworks guiding rTMS.

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10 Although class A evidence supports the therapeutic efficacy of low-frequency (1 Hz) rTMS
11 over the contralesional motor cortex in post-acute motor stroke, effect sizes remain moderate.
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13 These findings stem from small studies ($n < 20$) with high intersubject variability and limited
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15 clinical impact. A major concern in the field relates to the theoretical mechanism of rTMS
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17 interventions, particularly the persistent reliance on a "one-concept" approach, the
18
19 assumption that simply increasing ipsilesional M1 excitability or suppressing contralesional
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21 M1 excitability, combined with rehabilitative therapy, will universally improve motor
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23 outcomes in stroke ²². This oversimplification overlooks the complex and diverse nature of
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25 post-stroke recovery processes.
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35 **The solution**
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38 In response to the challenges outlined above, ranging from variable clinical outcomes and
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40 patient heterogeneity to shortsighted theoretical frameworks, medicine is increasingly leaning
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42 toward precision approaches across evaluation, diagnosis, intervention, and monitoring.
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44 NIBS aspires to make a similar shift within neurorehabilitation. Precision rehabilitation in
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46 stroke has been defined as “applying the optimal type and dose of therapy at the ideal time to
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48 maximize return of function for individual patients” ²³. A growing body of research is
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50 examining this principle across the entire stroke continuum, from prediction of stroke events
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52 ²⁴ to the characterization of individual profiles (commonly referred as *deep phenotyping*) after
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54 stroke for stratification and management ²⁵, and to the design of optimized rehabilitation
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56 paradigms to these profiles ²⁶. Following this line, the same researchers who have pinpointed
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3 the limitations of current protocols are now advancing more individualized, technically
4 informed approaches to NIBS. Rather than pursuing universal protocols, the field is
5
6 beginning to prioritize customization based on brain-state specificity and biomarker-guided
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8 interventions. These strategies aim to address the variability that has hindered clinical
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10 translation and unlock the neuromodulatory potential of NIBS in facilitating motor recovery
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12 after stroke.
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17 To support this shift, translational research should adopt a patient-specific, parameter-
18 oriented approach, using personalized protocols based on deep phenotyping that integrates
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20 clinical, neuroimaging, and neurophysiological data ^{19,25}. Crucially, this level of
21
22 customization must account for the multiple variables that shape recovery within the
23
24 personalized space. These include lesion location and extent, corticospinal tract integrity,
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26 stroke onset and stage of recovery, comorbidities, medications, concurrent non-
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28 pharmacological interventions, and stimulation parameters, as well as variability both
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30 between patients (inter-individual) and within the same patient over time (intra-individual).
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32 Recognizing these variables as central inputs, rather than confounding factors, is essential for
33
34 developing clinically meaningful personalization neuromodulatory strategies. However, this
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36 level of individualization is complex to implement within standardized research designs,
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38 which require uniform interventions to ensure comparability and replicability.
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46 Because all of these variables cannot realistically be addressed at once, beyond both
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48 practicality and the scope of most RCTs, emergent approaches are being proposed
49
50 prioritizing specific factors as stepping stones toward personalization. Several projects
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52 presented at the conference illustrated this approach. For example, a promising avenue for
53
54 refining TMS application is targeting specific brain states, such as oscillation phases. For
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56 instance, the negative peak (trough) of sensorimotor mu oscillation is associated with LTP-
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58 like plasticity, while the positive peak is linked to LTD-like plasticity ²⁷. Repetitive state-
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3 dependent stimulation over a specific brain state would lead to a robust LTP/LTD plasticity
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6²⁸. An ongoing multicentre trial is evaluating personalized brain state-dependent rTMS in
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8 subacute motor stroke, comparing it to sham stimulation and conventional, non-brain state-
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10 dependent rTMS. EEG-TMS-based brain state-dependent stimulation could revolutionize
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12 NIBS by maximizing therapeutic plasticity effects²².
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15 Similarly, Prof. Sarah Hussain presented a real-time, machine learning-driven EEG-TMS
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17 system that modulates brain states with 86–95% accuracy to enhance residual corticospinal
18
19 tract function²⁹. Closed-loop stimulation represents a promising path for individualized
20
21 therapy and may lay the groundwork for future trials. Along these lines, Dr. Caroline
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23 Tscherpel emphasized concurrent TMS-EEG as a tool for personalized assessment of
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25 network pathology, aiming to optimize rehabilitation through biomarker-driven
26
27 neuromodulatory interventions³⁰.
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32 Particular attention should also be given to motor evoked potentials (MEPs), which have been
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34 shown to be predictive of early upper limb recovery. On top of the conventional MEP, a
35
36 novel MEP-derived threshold matrix framework has been proposed to examine peri-threshold
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38 corticomotor activation³¹.
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42 Overall, the field presents a mix of promising and inconsistent findings. The challenge
43
44 remains in translating neuromodulation into consistent and clinically meaningful outcomes,
45
46 and in identifying the therapeutic components required across the post-stroke recovery
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48 spectrum. The key may not lie in universal application, but in tailoring NIBS to individual
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50 brain states while monitoring recovery with reliable biomarkers. Yet brain state is only one
51
52 aspect of the broader personalized space of post-stroke recovery previously outlined earlier, a
53
54 crucial variable, but not the only one. To operationalize personalization, we propose framing
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3 the clinical translation of NIBS around four guiding model questions: for whom, for what and
4 why, for where and when, and how.
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8 “For whom” addresses the first axis of stratification: patient-specific biological and clinical
9 characteristics. These include lesion location, corticospinal tract integrity, comorbidities,
10 medications, and concurrent rehabilitation programs, to identify subgroups most likely to
11 benefit.
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18 “For what and why” refers to the selection of neuromodulation modality, whether rTMS,
19 transcranial direct current stimulation (tDCS), transcranial alternating current stimulation
20 (tACS), or other techniques, recognizing that each interacts differently with the injured brain.
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23 The “why” addresses the intended therapeutic mechanism of the stimulation, for example,
24 whether to excite, inhibit, or synchronize specific networks.
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30 “For where and when” highlight the importance of unique neuroanatomical and functional
31 brain structures that are not identical across individuals, owing to genetic factors and lifelong
32 exposure to environmental influences. These differences also manifest within the same
33 individual over time, particularly across the dynamic course of post-stroke recovery. The
34 dimension of when also encompasses both the recovery phase (acute, subacute, or chronic)
35 and temporal fluctuations in brain states. These time-sensitive windows, along with inter- and
36 intra-individual anatomical and functional variability, represent critical opportunities for
37 targeted neuromodulation to maximize neuroplasticity, as guided by EEG or neuroimaging
38 derived biomarkers.
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51 Finally, “how” concerns the optimization of stimulation parameters, such as frequency, for
52 instance, how many sessions are sufficient, whether tolerance develops over time, and
53 whether increasing intensity, such as the number of pulses or current (mA), can offset lower
54 frequency to accelerate results. It also includes considerations of how sessions should be
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3 sustained over time to ensure clinically practical outcomes, the use of standardized electrode
4 placements versus neuronavigation with or without neuroimaging, coil orientation, electrode
5 montage, priming strategies, or even combinations of stimulation modalities, all aimed at
6 fine-tuning therapeutic effects.
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13 Together, whether used in full or in part, the guiding questions of “for whom, for what and
14 why, for where and when, and how” offer a practical model for developing structured
15 approaches to post-stroke precision rehabilitation in NIBS.
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22 23 **Recommendations**

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26 While research continues to refine its understanding of NIBS and its most effective
27 implementation, clinical application has already begun. For instance, TMS is being used in
28 some rehabilitation clinics for post-stroke upper limb recovery, despite ongoing uncertainties
29 in outcomes and limitations in methodology. Although clinical guidelines have been
30 established and emerging data suggest its potential for therapeutic integration^{11,32,33},
31 delivering TMS without a clear understanding of when, how, and for whom it works risks
32 navigating uncertain ground.
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43 A more nuanced view of brain recovery goes beyond three-dimensional spatial structure
44 (length, width, and depth). The fourth dimension, the passage of time, shapes plasticity
45 through experience (Figure 1). Interindividual variability, then, can be viewed as an emergent
46 property of this temporal dimension, reflecting the unique ways each brain responds and
47 adapts.
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3 Variability is not merely a source of noise but may serve as a meaningful biomarker and a
4 pillar for personalization models: greater variability could reflect an unstable system, while
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6 reduced variance could be associated with consistent motor performance or reduced abnormal
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8 neural signals, which may indicate reacquired control. In neuromodulatory terms, the
9
10 potential effects of NIBS on variability warrant further exploration, particularly since it
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12 remains uncertain whether variability may increase following stimulation.
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17 Building on this, the recovery journey of each stroke survivor is inherently individual. Given
18
19 this multidimensional complexity, it is unlikely that a one-size-fits-all NIBS protocol will
20
21 yield optimal results across patients. Each unique brain interacts differently with the type of
22
23 NIBS technique and its stimulation parameters, such as duration, intensity, and electric field
24
25 distribution. As such, a systematic application of NIBS in neurorehabilitation may or may not
26
27 lead to therapeutic benefits. The true potential of NIBS likely resides in how it engages with
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29 this four-dimensional model of brain recovery. Understanding these dynamic interactions is
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31 essential before NIBS can realistically become available in pharmacies, ideally in the not-so-
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33 distant future ¹ though perhaps only in the more distant one if key uncertainties remain
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35 unresolved.
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41 This point of view article addresses these questions previously raised by proposing a four-
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43 dimensional model of post-stroke recovery of the brain for researchers to carefully consider
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45 when formulating hypotheses, and for clinicians when deciding whether to implement an
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47 rTMS or other NIBS-type protocol, or whether such an intervention is necessary at all, based
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49 on the current evidence and individual patient needs. In addition we propose a paradigm shift
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51 from protocol-centric to patient-centric neuromodulation through a guiding model structured
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53 around five core questions: "for whom," "for what and why," "for where and when," and
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55 "how."
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3 We suggest that personalization in NIBS should be operationalized through measurable,
4 stratifiable elements, which can be prioritized flexibly depending on the research or clinical
5 context. As a first step, patient stratification ("for whom") should focus on lesion type, stroke
6 phase of recovery and demographics variables like age, gender, ongoing treatments, pre-
7 existing medical conditions. This includes factors such as post-stroke depression, which is
8 often excluded in research criteria but highly prevalent, leading to underrepresentation in
9 study findings. Thus, it is important to measure physiological indicators, such as MEPs, and
10 structural measures, such as diffusion tensor imaging (DTI), to gain a clear picture of
11 corticospinal tract integrity. Even more importantly, these metrics should ideally be collected
12 longitudinally, before, during, and after the intervention, rather than cross-sectionally.
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27 Second, defining "what and why" requires selecting NIBS modalities. This includes a
28 rationale for choosing a specific form of TMS, or alternatives within transcranial electrical
29 stimulation (tES), based on feasibility and mechanistic alignment with the intended
30 outcomes. This process should be guided by the therapeutic aim, such as promoting
31 functional recovery in targeted anatomical regions or inhibiting maladaptive compensation
32 patterns.
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41 Third, "where and when" can be guided by individualized neuroimaging or EEG biomarkers
42 to determine accurate target site and timing. With access to a neurophysiological atlas that
43 integrates structural, functional, and temporal information, more precise decisions can be
44 made in both space and time to capitalize on neuroplastic windows.
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51 Finally, "how" involves adapting stimulation parameters and delivery methods in response to
52 individual biomarkers and feedback loops, in a continuously responsive and flexible manner
53 based on the patient's fluctuating neurophysiological profile.
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3 Acknowledging that RCTs are the gold standard and one of the highest levels in the evidence
4 pyramid, researchers should consider allowing more flexibility in trials using
5 neuromodulation, given the high variability in post-stroke recovery. For that reason, future
6 trials could adopt adaptive designs such as variable stimulation trials that allow parameter
7 adjustments during the intervention, N-of-1 studies that capture individual responses over
8 time, or stratified randomized controlled trials that isolate and evaluate specific components.
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Once these personalized elements are systematically accounted for, we advocate for the creation and use of shared data banks that allow for inter-study comparisons across stroke types and conditions. This approach moves from individual stratification to population-level interpretation, enabling both the construction of personalized profiles and their alignment with broader patterns in post-stroke recovery. Such efforts could facilitate the development of a core set of personalization metrics, such as MEPs or mu rhythm phase in EEG.

This point of view article was originally inspired by findings presented in the proceedings and by debates emerging during the panel sessions at the conference on stroke rehabilitation.

As such, some relevant information may not be included in this manuscript, but these proceedings fueled our reflection on the challenges that remain in translating non-invasive brain stimulation into clinical practice. We subsequently searched for additional published evidence to complement and expand upon the ideas developed in this article. Although the primary focus is on TMS, given its status as the most established NIBS technique and the substantial resources allocated to high-quality trials, other non-invasive brain stimulation methods were also presented during the conference (Table 1), such as tDCS, transcutaneous auricular vagus nerve stimulation (taVNS) and low-intensity focused ultrasound (LIFU).

INSERT TABLE 1 HERE

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3 Ongoing research beyond the conference continues to explore the combined use of multiple
4 NIBS approaches for post-stroke motor rehabilitation, such as pairing high-definition tDCS
5 (HD-tDCS) with electrical theta burst stimulation (eTBS). This strategy aims to integrate the
6 therapeutic advantages of both modalities, enhancing stimulation focality and practicality and
7 has shown encouraging results in sham-controlled study ³⁴.
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12 One notable recent contribution is the TRANSPORT2 study, a phase II multicentre
13 randomized controlled trial that investigated the effects of tDCS combined with one of the
14 most evidence-based interventions for motor recovery: modified constraint-induced
15 movement therapy (mCIMT). The trial enrolled 129 stroke survivors, between one and six
16 months post-stroke, who were randomized to receive sham stimulation, 2 mA, or 4 mA of bi-
17 hemispheric tDCS during the first 30 minutes of therapy, followed by 120 minutes of active
18 mCIMT per session, delivered over ten sessions within a two-week period. The results
19 showed no added benefit from tDCS ³⁵. Unfortunately, this well-designed study reflects the
20 findings of the multicentre TMS trials discussed earlier, raising further concern within the
21 scientific community about whether NIBS can ultimately provide a meaningful translational
22 clinical benefit in stroke rehabilitation.
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41 It is also worth noting that further preclinical studies using animal models focused on the
42 customization of NIBS for motor restoration may help address key uncertainties and support
43 the design of future phase III clinical trials in human stroke survivors. This is especially
44 important given the considerable difficulty, and, at times, the unrealistic nature of conducting
45 high-quality, evidence-based trials involving NIBS and other non-pharmacological therapies
46 in a robust manner, particularly in diverse stroke survivor populations.
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56 As the field advances, careful clinical translation grounded in individualized science will be
57 key to ensuring that NIBS delivers functional motor restoration in post-stroke upper limb
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3 rehabilitation. A major challenge ahead is designing protocols and clinical trials that can
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5 rigorously evaluate complex, personalized interventions, without narrowly restricting
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7 inclusion criteria. Stroke survivors often present with diverse comorbidities and varied
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9 recovery trajectories, which must be reflected in study populations to ensure clinical
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11 relevance. Embracing this heterogeneity aligns with the broader, emerging shift toward
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13 personalized, patient-centred medicine. Doing so will support a more comprehensive
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15 understanding of how NIBS interacts with real-world post-stroke recovery.
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42 During the preparation of this manuscript, the authors used BioRender.com to create figure 1.
43
44 The authors also used ChatGPT-4 to enhance readability and grammar. Plagiarism was
45
46 subsequently checked using iThenticate. After utilizing these tools, the authors thoroughly
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48 reviewed and edited the content as needed and take full responsibility for the final version of
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50 the published article.
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58 **Statements and Declarations**

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3 Not applicable
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9 **Ethical considerations**
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11 Ethical approval was not required
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18 **Consent to participate**
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20 Not applicable
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27 **Declaration of conflicting interest**
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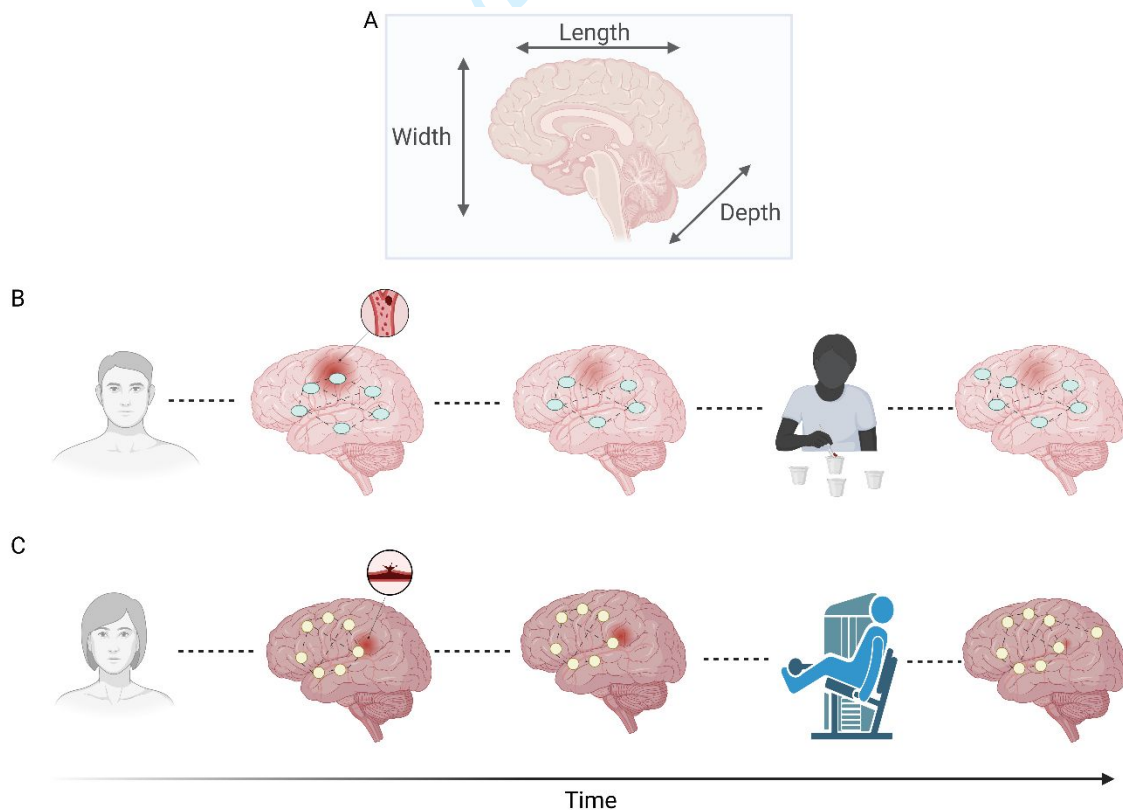
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3 **Figure 1.** The four-dimensional view of brain recovery. **(A)** Spatial dimensions of the brain
4 (length, width, and depth). **(B–C)** Two individuals (different gender and age) with distinct
5 brains who experience a stroke, each with different lesion locations and network changes.
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7 These panels illustrate how different post-stroke exposures, such as rehabilitation tailored to
8 current impairments, interact with evolving brain connectivity and lesion characteristics over
9
10 time. This progression highlights both interindividual variability in recovery trajectories and
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12 intraindividual variability when accounting for the passage of time. Both structural and
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14 functional changes can occur in the recovering brain, and each lesion in each brain is unique,
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16 as is its aftermath. In the stroke spectrum, if the central component is the person, then
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18 interventions should be designed to be central to the individual rather than to the stroke alone.
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Conference id	Presentation	Author	Title	Type of NIBS	DOI
PL02	Plenary lecture	Stagg, Charlotte	Targeted neuromodulation for motor control: breakthroughs in precision stimulation	tUS, TMS, tACS	10.1016/j.brs.2024.12.1156
PL05	Plenary lecture	Nudo, Randolph	Stimulation-induced neuroplasticity in sensorimotor networks	rTMS, PAS	NA
FS1G.4	Symposium	Schwab, Bettina	Imaging and modulation with theta-gamma tACS of an acceleration-dependent thumb movement task	TGP	10.1016/j.brs.2024.12.056
FS3F.1	Symposium	Ziemann, Ulf	Brain-state dependent TMS of motor cortex for treatment of motor deficits after stroke	rTMS	10.1016/j.brs.2024.12.168
FS3F.2	Symposium	Tscherpel, Caroline	The aim of an individual read-out of motor reorganization after stroke	TMS	10.1016/j.brs.2024.12.169
FS3F.5	Symposium	Shanks, Maxine et al.	A compositional neurophysiology biomarker for predicting stroke recovery and outcome	TMS	10.1016/j.brs.2024.12.172
FS3B.6	Symposium	Hays, Seth	Comparing invasive versus non-invasive VNS methods for enhancing recovery from stroke and post-traumatic stress disorder	VNS	10.1016/j.brs.2024.12.142
FS3F.7	Symposium	Khatri, Uttara et al.	Developing personalized brain state-dependent TMS to target residual corticospinal connections after stroke	TMS	10.1016/j.brs.2024.12.174
FS3F.8	Symposium	Sethi, Amit et al.	Transcranial random noise stimulation and functional-electrical stimulation-assisted task-specific practice to improve upper extremity function after moderate-to-severe stroke: a pilot randomized clinical trial	tRNS	10.1016/j.brs.2024.12.175
FS4C.1	Symposium	Mima, Tatsuya et al.	Efficacy of transcranial static magnetic field stimulation in improving upper limb function in subacute stroke patients	tSMS	10.1016/j.brs.2024.12.204
FS4F.5	Symposium	Hummel, Friedhelm C	Personalization of non-invasive brain stimulation to enhance the magnitude of recovery from stroke	NIBS	10.1016/j.brs.2024.12.232
FS4F.8	Symposium	Xu, Jing et al.	Abnormal premovement interhemispheric interactions are present in the chronic but not in the acute or subacute post-stroke periods	TMS	10.1016/j.brs.2024.12.235
FS4F.7	Symposium	Vink, Jord et al.	Implementation of rTMS treatment in post-stroke clinical rehabilitation	cTBS	10.1016/j.brs.2024.12.234
FS5G.7	Symposium	Merrick, Christina et al.	Kilohertz transcranial magnetic perturbation (kTMP): a new non-invasive method to modulate cortical excitability and behavior	kTMP	10.1016/j.brs.2024.12.295
P1.003	Poster	Safdar, Afifa et al.	A biomarker to target non-invasive brain stimulation in chronic stroke	iTBS	10.1016/j.brs.2024.12.442
P1.178	Poster	Nakamura, Ryota et al.	Effect of High-Frequency Repetitive Transcranial Magnetic Stimulation on very elderly Stroke Patients	HF-rTMS	10.1016/j.brs.2024.12.617

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3	P1.193	Poster	Lee, Seung Hyun et al	Resting-State Hemodynamic Changes and Upper Limb Function Improvement After High-Definition Transcranial Direct Current Stimulation in Stroke Patients: An fNIRS Pilot Study	HD-tDCS	10.1016/j.brs.2024.12.632
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6	P1.196	Poster	Hsu, Shih-Pin et al.	Bihemispheric transcranial direct current stimulation enhanced motor recovery and contralesional premotor cortical connectivity in subacute stroke patients who lacked corticospinal excitability	tDCS	10.1016/j.brs.2024.12.635
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9	P1.207	Poster	Yoo, Yeun Jie et al.	A multicenter, randomized controlled, double-blind, prospective trial to the safety and effectiveness of upper extremity function in patients with sub-acute and chronic stroke using personalized transcranial direct current stimulation	tDCS	10.1016/j.brs.2024.12.646
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13	P1.178	Poster	Nakamura, Ryota et al.	Effect of High-Frequency Repetitive Transcranial Magnetic Stimulation on very elderly Stroke Patients	HF-rTMS	10.1016/j.brs.2024.12.617
14						
15	P2.031	Poster	Lin, Rong-Jang et al.	The effect of transcutaneous auricular vagus nerve stimulation (taVNS) in stroke patients by Near infrared spectroscopy (NIRS)	taVNS	10.1016/j.brs.2024.12.708
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18	P2.091	Poster	Jean-Charles, Lamy et al.	Short-latency intracortical inhibition of the unaffected hemisphere as a predictor of motor recovery after stroke	TMS	10.1016/j.brs.2024.12.768
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20	P2.206	Poster	Kim, Taewon et al.	Transcranial focused ultrasound stimulation to lesional motor cortex is safe and enhances motor performance of the paretic hand in stroke patients	LIFU	10.1016/j.brs.2024.12.881
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23	P2.232	Poster	Sui, Youxin et al.	Task-based fMRI assessment of rTMS over the primary motor cortex in poststroke rehabilitation: a systematic review	rTMS	10.1016/j.brs.2024.12.906
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25	P3.089	Poster	Lin, Hung-Shih et al.	Comparison between motor evoked potentials elicited by 10 Hz and individual alpha frequency transcranial magnetic stimulation	rTMS	10.1016/j.brs.2024.12.1003
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27	P3.199	Poster	Narayan, Sunil et al.	Effect of Non-invasive Brain stimulation on Somatosensory Evoked potentials in Chronic Ischemic Stroke	tDCS and TMS	10.1016/j.brs.2024.12.1110
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29	P3.205	Poster	Verhoeff, Tessa et al.	The effect of contralesional cTBS treatment on motor function of the unaffected upper limb in recovering stroke patients. Results from the B-STARS trial	cTBS	10.1016/j.brs.2024.12.1116
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32	P3.219	Poster	Klomjai, Wanalee et al.	Effect of bi-hemispheric tDCS combined with physical therapy on interhemispheric inhibition and motor performance in sub-acute to chronic stroke	tDCS	10.1016/j.brs.2024.12.1129
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35	P3.223	Poster	Lee, Ho Seok et al.	Protocol for Efficacy of Personalized rTMS for Upper Extremity Motor Recovery in Subacute Stroke Patients	rTMS	10.1016/j.brs.2024.12.1133
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Table 1. Proceedings presented at the 6th International Brain Stimulation Conference related to non-invasive brain stimulation (NIBS) for post-stroke upper limb motor recovery. tUS – Transcranial Ultrasound Stimulation, TMS – Transcranial Magnetic Stimulation, tACS – Transcranial Alternating Current

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3 Stimulation, rTMS – Repetitive Transcranial Magnetic Stimulation, PAS – Paired Associative Stimulation, TGP – Theta-Gamma Phase-Amplitude Coupled
4 Stimulation, VNS – Vagus Nerve Stimulation, tRNS – Transcranial Random Noise Stimulation, tSMS – Transcranial Static Magnetic Field Stimulation,
5 NIBS – Non-Invasive Brain Stimulation, cTBS – Continuous Theta Burst Stimulation, kTMP – Kilohertz Transcranial Magnetic Perturbation, iTBS –
6 Intermittent Theta Burst Stimulation, HF-rTMS – High-Frequency Repetitive Transcranial Magnetic Stimulation, HD-tDCS – High-Definition Transcranial
7 Direct Current Stimulation, tDCS – Transcranial Direct Current Stimulation, taVNS – Transcutaneous Auricular Vagus Nerve Stimulation, LIFUS – Low-
8 Intensity Focused Ultrasound Stimulation.
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