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Individualized treatment of cortical stroke: a perspective on open-loop, closed-loop and adaptive closed-loop brain state-dependent TMS

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1. Closing the loop on stroke therapy

Stroke is a leading cause of disability in adults (Feigin et al., 2022; Katan and Luft, 2018), affecting cognitive, language, or motor functions (Langhorne et al., 2011). Hence, validated rehabilitation to improve post-stroke recovery of motor functions is in great demand. We here argue that closed-loop transcranial magnetic stimulation (TMS) has potential in enhancing rehabilitation, and will highlight the distinction between non-adaptive closed-loop TMS, and adaptive closed-loop TMS. Briefly, non-adaptive closed-loop TMS aims at bringing a typical patient's brain state to a desired target state and overcome expected perturbations. Adaptive closed-loop TMS additionally offers the ability to adapt to individual patients and to unexpected perturbations (Åström and Wittenmark, 2013). We also discuss how leveraging state-of-the-art methods might support the implementation of these advanced TMS rehabilitation approaches in the near future.

2. Investigating stroke recovery with neuroimaging methods

Motor function is tightly choreographed by the cerebral motor network, comprising the primary motor cortex (M1), premotor cortex (PMC), supplementary motor area (SMA), the cerebellum, and subcortical areas such as the thalamus (Rehme and Grefkes, 2013). Stroke lesions in these areas do not only lead to a loss of function of the affected area but also disrupt healthy motor network functioning (Baldassarre et al., 2016; Carrera and Tononi, 2014; Grefkes and Fink, 2014; Rehme and Grefkes, 2013; Siegel et al., 2022). There is no one unique route of reorganization of the motor network after stroke to recover motor function (Di Pino et al., 2014; Grefkes and Fink, 2014). Instead, we face a very heterogeneous clinical population, where the path to recovery needs to be enhanced individually (Di Pino et al., 2014; Ziemann et al., 2019). Identifying prognostic biomarkers may be beneficial in selecting the individual therapeutic steps for motor recovery after stroke.

Potential biomarkers have been reported from different neuroimaging techniques: magnetic resonance imaging (MRI) helps identify brain areas that are involved in motor functions, and derived structural and functional connectivity analyses may help predict individual patient recovery (Grefkes and Fink, 2014; Stinear, 2017). Magneto-/electroencephalography (MEG/EEG), as neurophysiological methods, can furthermore represent brain activity at a millisecond scale, enabling the coordination of interventions with rapidly changing brain states.

Spontaneous EEG provides functional information characterized by activity in different frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (>30 Hz) (Keser et al., 2022). Moreover, the so-called sensorimotor rhythm refers to oscillations recorded over the sensorimotor cortex with peaks around 10 and 20 Hz (Hari, 2006). In this paper, we relate to the alpha range (8–12 Hz) over the Rolandic fissure when mentioning the mu-rhythm. Activity within frequency bands can be examined using quantitative EEG measures derived from power spectrum analysis, and the relation of power between different frequency bands (Finnigan and van Putten, 2013), or the functional connectivity (FC) between different brain areas (Keser et al., 2022). The latter is commonly calculated based on the coherence within given frequency bands between distant regions (Keser et al., 2022). In view of stroke as a network disruption, FC seems to be a promising tool to represent brain network changes that correspond to recovery. EEG can be combined with non-invasive brain stimulation (NIBS) techniques, such as TMS (Hernandez-Pavon et al., 2023; Kallioniemi and Daskalakis, 2022; Tremblay et al., 2019). Effective connectivity, as investigated by combining EEG and TMS has potential to be a prognostic tool for stroke recovery (Tecchio et al., 2023). TMS–EEG measures as predictive biomarkers have been reviewed recently (Keser et al., 2022).

3. Electrophysiological biomarkers in motor stroke

In the following section, biomarkers in motor stroke are reviewed with a focus on FC estimated from EEG-recorded data and frequency-based measures of EEG-power. Literature on acute, sub-acute, and chronic stages of stroke as well as different types of stroke (subcortical, cortical, ischemic, hemorrhagic) is considered. This overview covers only a small part of the available publications; readers are referred to the literature that includes more extensive reviews and more details (Finnigan and van Putten, 2013; Guggisberg et al., 2019; Keser et al., 2022; Milani et al., 2022; Ulanov and Shtyrov, 2022).

3.1 Functional connectivity

EEG-derived FC reflects temporal correlations of the neurophysiological activity of remote brain regions (Fingelkurts et al., 2005). There are several methods to calculate FC (Bastos and Schoffelen, 2016) and it can further be examined with regard to inter- or intra-hemispheric connectivity, which is of relevance in the approach of stroke as a network disorder. Importantly for application in real-time settings, FC can be computed on the single-trial level (Basti et al., 2022). Such FC metrics are not identical to the "traditional" trial-average FC metrics. It is therefore important to note that the field of FC is heterogeneous; results from one metric need not translate directly to other metrics. With this note of caution in mind, we will briefly review how EEG-derived FC relates to stroke:

There is evidence that the reorganization of the imbalance in FC between and within the hemispheres is related to motor recovery. Higher MEG-derived FC in the alpha band of the ipsilesional primary somatosensory cortex and prefrontal cortex to the whole brain was followed by better recovery, whereas reduced connectivity between contralesional sensorimotor areas and the whole brain appears to be beneficial for motor recovery (Westlake et al., 2012). In the sub-acute stage, lower inter-hemispheric connectivity between motor cortices in the alpha band was detected in stroke patients with poor motor functions as

compared to healthy controls, together with an opposite pattern in the theta band (Kawano et al., 2020). Calculation of the graph-theoretic weighted node degree, which reflects the number of connections from different areas, has revealed that the global weighted node degree between the ipsilesional motor cortex to other cortical areas correlates with motor improvement within the first weeks after stroke, specific to the beta frequency band (Nicolo et al., 2015). FC in the sensorimotor network, investigated in the beta band by normalized inter-hemispheric strength, showed that lower beta is positively associated with corticospinal tract integrity and upper extremity function (Pichiorri et al., 2018). Keser and colleagues (2022) summarize that motor recovery is correlated with restoration of inter-hemispheric activity with increased intra-hemispheric coherence in the ipsilesional motor network.

3.2 Power measures in different frequency bands

The brain symmetry index (BSI) in different frequency bands quantifies the similarity of spectral power in EEG in the two hemispheres (van Putten, 2007). BSI, the amount of power in different frequency bands as well as the ratios between bands, like the delta–alpha ratio (DAR) or the ratio of delta+theta power to alpha+beta power (DTABR), are further methods of so-called quantitative EEG to characterize brain activity (Kaiser, 2007).

Chronic stroke patients had higher BSI values in delta and theta bands in the ipsilesional hemisphere compared to healthy controls, the increased asymmetry being associated with poor motor outcome (Saes et al., 2019). In acute stroke patients, an increase in relative delta power was observed, while healthy controls had higher relative alpha power, which resulted in a higher DAR for the patients (Finnigan et al., 2016). Similarly, the DTABR was higher in stroke patients due to higher relative beta power in the healthy controls (Finnigan et al., 2016). In the sub-acute stage, DAR is positively correlated with the National Institute of Health Stroke Scale (NIHSS) 30 days after the stroke event (Kwah and Diong, 2014), which indicates that a greater amount of slower EEG components is associated

with more impairment (van Putten, 2007). Hence, reductions in delta power, DAR, DTABR or BSI during the acute ischemic stroke stage are associated with relatively better functional outcomes (Finnigan and van Putten, 2013).

Analyzing narrow bands in the frequency domain is often done without addressing the aperiodic part of the signal, which is reflected in the decay of the EEG signal in the power spectral density plots. Investigation of the steepness of the spectral exponent, which represents broad-band EEG slowing, showed that slowing was more present in the affected hemisphere of acute cortical stroke patients compared to healthy controls, and the difference between the hemispheres became less two months after stroke (Lanzone et al., 2022). This normalization further correlated with improvements on the NIHSS, which indicates that the scale-free dimension of EEG can also be utilized as a marker of stroke recovery (Lanzone et al., 2022).

4. Closed-loop TMS

TMS is a promising tool for motor stroke rehabilitation because of its ability to induce plastic changes in the cortex (Ziemann et al., 2008). However, TMS effects on the motor system suffer from inter- and intra-individual variability (Hamada et al., 2013). This is partially explained by the cortical neuronal dynamics and endogenous network activity at the time of the TMS pulse (Bergmann, 2018).

To address this variability, brain state-dependent stimulation protocols have been developed, in which the TMS pulses are delivered in a time window when a selected brain state occurs. In the motor system, the instantaneous phase and power of the mu-rhythm have been identified as suitable indicators of opportune time windows (Bergmann et al., 2019; Hussain et al., 2019, 2020; Karabanov et al., 2021; Sato et al., 2015; Schaworonkow et al., 2018; Thies et al., 2018; Wischnewski et al., 2022; Zrenner et al., 2018, 2023). Stimulating

only during a specific target state can increase the efficacy of plasticity induction by TMS (Baur et al., 2020; Zrenner et al., 2018).

Brain state-dependent stimulation can be performed in open- or closed-loop modes (Antony et al., 2022): In open-loop brain state-dependent stimulation, pulses are delivered when *a priori* defined target brain states are observed (Antony et al., 2022), e.g., at the trough of the sensorimotor mu-rhythm (Schaworonkow et al., 2018). However, the immediate or even long-term effect of the stimulation on the brain state is disregarded. In contrast, in closed-loop brain state-dependent stimulation, this very effect of the stimulation is taken into account by continuously adjusting the stimulation parameters such as the targeted brain state. More precisely, the achieved outcome of the stimulus is compared against the desired outcome, and the stimulation parameters are chosen based on this comparison. In non-adaptive closed-loop control, this mapping from the deviation of the actual and the desired outcome is fixed. In adaptive closed-loop control, it is continuously adjusted by an adaptation mechanism (Åström, 1983). Adaptive closed-loop brain state-dependent stimulation may be a critical addition in clinical settings, considering the very heterogeneous stroke population and the highly variable recovery paths which are influenced by the type, location, and size of the stroke lesion.

This paper aims to present a conceptual approach, illustrated by examples of experimental set-ups, on how EEG biomarkers in adaptive closed-loop experiments can be utilized to support motor recovery in stroke.

5. Strategy for TMS

Based on the aforementioned evidence on the association between EEG-based connectivity and activity measures with motor outcome, it is possible to partially predict clinical recovery from motor stroke using electrophysiological biomarkers. A straightforward strategy to translate this into a therapy is to use TMS to enhance the expression of EEG biomarkers that

177 are predictive of good recovery, and suppress those that are predictive of unfavorable
178 outcomes. This way, the balance within the brain, disrupted by the lesion, may be restored.
179 However, it is likely that varying lesion locations (cortical vs. subcortical vs. subtentorial)
180 affect the EEG signal in different ways and to different extents, limiting the biomarkers that
181 can reliably be detected, and that stimulation methods and protocols need to be adjusted
182 depending on the individual patient and path of recovery (Di Pino et al., 2014).

183 ### 5.1 Considerations on causality

184 We should note that a biomarker that correlates with recovery does not necessarily imply a
185 causal relationship with recovery. Nevertheless, experimentally testing the identified
186 (plausible) candidate biomarkers can reveal a causal relationship that may be used in therapy.
187 In a recent extensive review, Cassidy and colleagues investigated the complexity of
188 correlation and causation with regards to biomarkers based on FC in post-stroke recovery
189 (Cassidy et al., 2022). The authors utilize the Bradford Hill Criteria (Hill, 1965) to
190 demonstrate opportunities and challenges of connectivity biomarkers to predict post stroke
191 recovery (Cassidy et al., 2022).

192 In this context, TMS aiming to modulate an EEG biomarker of FC could provide the
193 strongest evidence that the biomarker causally supports post-stroke recovery.

194 ### 5.2 Closing the control loop

195 Here, we follow previous literature that suggested using control approaches, especially
196 closed-loop control, to achieve better TMS efficacy (Antony et al., 2022; Zrenner et al.,
197 2016). As we aim to modify the brain with TMS in a way that an EEG biomarker changes,
198 we must ask: what control can we exert by TMS? This question has two aspects: first, we
199 need to characterize the stimulation parameter space; second, we need to characterize how
200 TMS affects the biomarker of interest. For concreteness, cohesiveness, and illustration, we
201 use EEG-derived FC as the biomarker of interest, without loss of generality.

5.2.1 The stimulation parameter space

The stimulation parameter space includes obvious parameters, such as the properties of the induced electric field — its intensity, location of the highest field strength, and orientation. With conventional TMS coils, this is defined by the coil geometry, position, and 3D orientation (Deng et al., 2013; Opitz et al., 2011). With multi-coil transducers, the spatial distribution of the induced electric field on the cortical surface can be adjusted electronically, i.e., without physically moving the coils (Koponen et al., 2018; Nieminen et al., 2022; Nurmi et al., 2021; Souza et al., 2022). Such multi-locus (mTMS) systems enable optimizing the stimulation parameters with automated algorithms to achieve a target response on real-time EEG and electromyographic recordings (Tervo et al., 2020, 2022). Additionally, the waveform (mono- vs. biphasic) (Sommer et al., 2006) and duration (D'Ostilio et al., 2016) of the TMS pulse contribute directly to the dynamics of the induced electric field and the evoked brain response. Furthermore, the interval between consecutive TMS pulses (interstimulus interval, ISI) constitutes another important stimulation parameter (Hassanzahraee et al., 2019; Julkunen et al., 2012). TMS pulses can also be delivered in trains, such as theta burst stimulation (TBS) (Chung et al., 2015). In this case, the duration (e.g., 3 pulses) and internal frequency (e.g., 50 Hz) of the bursts, and the frequency at which bursts are delivered (e.g., 5 Hz), as well as the number of bursts delivered continuously or in series (e.g., continuous TBS vs. intermittent TBS; Chung et al., 2015; Huang et al., 2005; Suppa et al., 2016) expand the stimulation parameter space substantially. Less obviously, the state of the brain at the time of stimulation can be considered a stimulation parameter. By giving the subject a suitable task, such as motor exercises or motor imagery in the case of stroke patients, the effects of TMS may change because the motor network is already in an active state (Hashimoto and Rothwell, 1999). In principle, the task during which TMS is

applied could thus be used to improve the efficacy of TMS, though this “task dynamics loop” (Zrenner et al., 2016) will not be covered here.

TMS can also be triggered based on the spontaneous dynamics of the brain as observed with EEG — in brain state-dependent stimulation. The brain state at which a pulse is delivered thereby becomes another parameter of stimulation. For example, single pulses have previously been delivered at specific phases of the sensorimotor mu-rhythm when there was sufficient mu-band power (Schaworonkow et al., 2018). In such a case, the target frequency band, the power threshold, and the target phase are also among the crucial stimulation parameters. Clearly, the stimulation parameter space can be further expanded: for example, brain states based on EEG phase synchronicity patterns in distributed networks (Stefanou et al., 2018) or based on FC patterns may be identified and real-time inferences can be developed.

5.2.2 Effects of TMS on functional connectivity

The goal we consider here is to modify FC with TMS in stroke patients suffering from a cortical lesion. To achieve this, TMS needs to alter FC in specific connections and in a defined direction. Open-loop brain state-independent TBS of M1 modifies the magnitude and direction of resting-state FC depending on the TBS protocol. Whereas continuous TBS decreased alpha-band FC across the whole cortex and increased beta-band FC between bihemispheric anterior areas (Shafi et al., 2014), intermittent TBS increased alpha-band FC (Zhang and Fong, 2021). Cortico–cortical paired associative stimulation can specifically increase the high-beta FC along a target connection, by delivering paired pulses to the nodes at either end of the connection (Hooyman et al., 2022). The orientation of the induced electric field has also been demonstrated to affect FC measures (Pieramico et al., 2023). Thus, we find it plausible that TMS is a suitable method to introduce specific, well-defined FC changes in the motor network.

In the following, we will introduce both non-adaptive and adaptive closed-loop TMS focused on FC with toy examples. These examples cannot directly be run as experiments yet, but they will highlight which parts of the process are currently missing and need to be filled in, in order to actually run such experiments.

5.3 Non-adaptive closed-loop brain stimulation

The notion of closed-loop control comes from control engineering and theory, and is for example explained in detail in (Ogata, 2010). As has recently been highlighted, there is substantial conflation of the terms closed-loop and brain state-dependent stimulation in the field of TMS (Antony et al., 2022). The goal of closed-loop control is to control the system state — driving the system or its response to a desired state by changing the stimulation parameters based on the observed state. In the case of open-loop brain state-dependent stimulation (e.g., triggering TMS on the trough of the mu rhythm), we affect the system during a specific brain state with fixed or predefined parameters without updating them based on measured effects. Such an open-loop stimulation may still alter the brain state, but this effect is not taken into account in choosing the subsequent stimulation parameters.

In accordance with prior literature (Antony et al., 2022; Ogata, 2010; Thut et al., 2017), we subscribe to the following definition: In closed-loop TMS, the stimulation parameters are chosen based on the deviation of the observed brain-state from a reference, i.e., a target brain state, to steer the brain state towards the reference. Therefore, closed-loop TMS requires some predefined reference state and entails altering neuronal activity towards that reference (Thut et al., 2017).

This reference could be derived *a priori* from the literature and medical knowledge, but may, importantly, also be selected based on the individual medical needs of the patient. In non-adaptive closed-loop control, the mapping of the deviation of the actual brain-state from the reference to the stimulation parameters is static.

The non-adaptive closed-loop approach is detailed in Figure 1, with an illustrative example (note that the example is speculative, and not strictly derived from prior literature): let the reference state be a high FC between intra-hemispheric motor nodes (let those be SMA and M1). This reference is then compared (not necessarily by subtraction) with the actual brain state (e.g., low FC), yielding the deviation or error signal (e.g., "FC needs to be increased"). This deviation is mapped onto stimulation parameters that are suitable to drive the brain towards the reference state (e.g., intermittent TBS during low mu-power). This mapping is called the "controller", or control function (Figure 2, left panel). The stimulation parameters are then translated into the actual stimuli by an "actuator". The stimuli (e.g., 10 theta bursts) are delivered by the actuator to the brain—in control-engineering terms, they are the control input to the system under control. The brain's modified state in reaction to the stimulation (e.g., slightly increased FC) is then observed in the EEG signal, and again compared to the reference. Thereby, the loop is closed. If the control function is fixed, the closed-loop control is called non-adaptive.

The brain state at which we deliver a pulse can be considered a stimulation parameter. In that case, the real-time EEG processing system that infers the current brain state and delivers a pulse when the selected brain state occurs, is (part of) the actuator and a tool of the controller.

This example already highlights problems that need to be addressed when implementing a closed-loop TMS protocol. Most prominently, the mapping from the deviation of the actual brain state to the reference has to be chosen. In the simplest case, this mapping might be manually defined led by prior knowledge. However, it might be more feasible and flexible to infer it by machine learning: from simple linear regression to generalized linear models to deep-learning based approaches (Gebodh et al., 2023). A wide

array of tools can be used to learn the mapping from an open-loop dataset. Naturally, this requires a dataset that covers enough of the stimulation-parameter space.

Hitherto, the mapping from the error signal to the control input has been static — i.e., the parameters of the controller are fixed (Figure 1). While the stimulation parameters chosen for too high FC may in general be different from those chosen when the FC is too low, the stimulation parameters for a particular deviation will stay the same (Figure 2, left panel). That is, the closed-loop control is non-adaptive. If this controller is then applied to a patient for whom it does not fit, the protocol will fail. This motivates making the controller adaptive.

5.4 Adaptive closed-loop brain stimulation

In adaptive closed-loop brain stimulation, the mapping from deviation to stimulation parameters is adapted on-line by an adjustment mechanism that takes the relation of control input to the system and the system output into account (Åström, 1983). Hence, the mapping of the deviation from the reference to stimulation parameters is no longer static, but automatically adjusted.

The adaptive closed-loop brain stimulation approach is visualized in Figure 3, along with a speculative example showing how it may be added to the above-described example of non-adaptive closed-loop TMS. In this extended example, everything is the same from the initial deviation to the first 10 theta bursts delivered. But now, let the original controller be unfit to the patient: Instead of an increased FC (reduced deviation), we observe a further decreased FC (increased deviation). In this case, if the controller remained static, it would simply repeat the same inappropriate input, and would thus likely not achieve an increase in FC. This is where the adjustment mechanism comes into play: the relation of the system input (10 intermittent theta bursts at high intensity, during low mu-power) to the observed system output (lower intra-hemispheric FC) is now used to modify the controller's parameters.

Figure 2 (right panel) illustrates an adjustment mechanism limited to the mapping from the error signal to the targeted mu-band power, and ignores the other stimulation parameters for the sake of brevity and illustration. The control function (dark red dashed line) was fitted to prior data (calibration data; black dots) from representative patients. This might for example be done by linear regression.

Since the aim is to increase FC (i.e., $\Delta FC > 0$ in Figure 2), the original mapping tells us to target a low power state (see Figure 2, left panel, gray arrow). But as the system delivers stimuli during low mu-power, we observe a decrease in FC — the opposite of what we expected based on the calibration data. In the adaptive setting, we might, for example, replace the first five data points of the calibration dataset with the five data points observed so far from the deviant patient. Afterwards, the mapping is recomputed from the updated data by linear regression — yielding a different mapping (see Figure 2, right panel). In this example, the linear regression-based mapping would now recommend targeting an average or above-average mu-power to increase FC, which is more appropriate for the simulated atypical patient. That is, the controller's parameters are being adapted to the system under control. Note that in this example the parameters are frequently adjusted to the new patient. Generally, the controller does not have to be adjusted after each "step"; it can be updated more slowly (Åström and Wittenmark, 2013).

It should be evident already that there are many ways of implementing such an adaptive controller. Naturally, other methods than linear regression may be used to select the controller's parameters. Furthermore, in the given example, the controller never "explores", it always "exploits", and basically finds an improved mapping by luck and the convenience of the given constructed example. This could, for instance, be addressed by an epsilon-greedy policy or importance sampling (Sutton and Barto, 2018). These would allow the controller to

sample parts of the stimulation-parameter space that may not be of immediate interest for controlling the system, but still may be important for system identification.

6. Conclusion and future directions

In this paper, we have highlighted the possibility to approach closed-loop brain stimulation in an adaptive fashion when aiming for motor recovery in stroke patients. While the concept of adaptive closed-loop stimulation itself is not new, we extend it with the integration of electrophysiological biomarkers that can be bidirectionally modified by TMS. We do not claim that only adaptive closed-loop stimulation is effective in improving motor recovery in stroke patients. Instead, we seek to present and distinguish increasingly flexible approaches to be employed, where they may become necessary. These approaches can be implemented in a new fundamental way by novel algorithms for real-time data analysis, together with the mTMS technology and methodology that we are currently developing (Souza et al., 2023; Sinisalo et al., under review; Marzetti et al., under review; Humaidan et al., under review).

To establish therapeutic applications, dedicated research is needed. One apparent question is, which biomarkers are of interest and sufficiently reliable, how these biomarkers change over time after stroke and how they relate to recovery. Collecting and sharing suitable large datasets will help address these questions collaboratively. This becomes crucial to draw evidence-based conclusions, especially in the light of diverse connectivity measures. Longitudinal studies that include patients and follow recovery for several months, from acute to chronic stages, may help specify and customize biomarkers for different patient groups. Studies aiming for causal relation instead of simple correlation can uncover brain mechanisms that need to be targeted. Restoring the balance between and within the ipsi- and contralesional hemispheres might play an important role (Grefkes and Fink, 2014). Another important issue is the time after stroke when the stimulation is applied. Effectiveness and

therapy goals might be considerably different according to stroke stage, e.g., from prevention of maladaptive changes in the early stage to supporting neuroplasticity at later stages.

Developments on TMS technology that enable rapid and multi-site stimulation is crucial to modulate multiple nodes of a functional network. Recent advances in mTMS systems (de Lara et al., 2021; Koponen et al., 2018; Nieminen et al., 2022; Souza et al., 2022) enable one to adjust the stimulation parameters at a millisecond scale. This includes not only intensity, timing, and wave shapes of the pulses but also the cortical target loci and induced electric field orientation. These advanced systems could deliver the therapeutic stimulation at the optimal brain state, to multiple brain regions of the unbalanced motor network after stroke (Baldassarre et al., 2016; Grefkes and Fink, 2014; Rehme and Grefkes, 2013), thus allowing the adjustment of far more parameters than the presently available instrumentation. This approach would exploit the full potential of adaptive closed-loop algorithms, and may lead to more effective treatments of network disorders than when stimulation is delivered at a single cortical location.

If possible, neuroimaging methods such as functional or diffusion MRI can be combined with MEG/ EEG methods to add to the overall diagnostic findings and to enable more accurate mapping of the parameter space (Aydogan et al., 2023; Pieramico et al., 2023). This may be especially necessary in cases where the latter methods fail to represent brain activity accurately, such as focal, subcortical lesions (Finnigan and van Putten, 2013).

On the one hand, it is essential to define distinct characteristics of the selected biomarkers that need to be targeted with a certain protocol. To this aim, computational models might be employed to take into account the effects of focal lesion on the motor network (Aerts et al., 2016). Moreover, the framework of closed-loop brain stimulation needs to be translated into the clinical setting. Here the challenges relate to more practical issues. A closed-loop stimulation approach should be built in such a way that it can reliably be applied

in the clinical environment with regard to the available equipment of medical institutions. Also, human operators should retain control of the automated closed-loop applications.

Secondly, we want to highlight the importance of these medically trained human operators: the choice of the reference state (goal of therapy) should be informed by the needs of the patient, the structural and functional lesions in the patient's brain and associated motor impairments. This may eventually be supported or even completely done by autonomous systems, but likely will for now and a long time remain at least partially the domain of humans. This means that it is not necessary for clinical applications to have a fully autonomous system based on machine learning — partial automation can already be very useful for clinical practice. Even when high-level decisions remain the field of human operators, automated algorithms that select and adjust the stimulation parameters in real time serve a crucial role in minimizing user-dependent errors (Nieminen et al., 2022; Tervo et al., 2022), and are a first step towards higher levels of autonomy as has been achieved in surgical robotics (Attanasio et al., 2021).

Adaptive closed-loop brain stimulation holds the potential to address the heterogeneity of the clinical population and to enhance motor recovery in stroke patients. Finally, motor stroke is just one example of a brain network disorder, but many other frequent neurological and psychiatric diseases, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, depression, obsessive compulsive disorder, anxiety disorder, addiction or pain can be conceptualized as network disorders that can also be targeted by adaptive closed-loop brain stimulation in a highly individualized manner.

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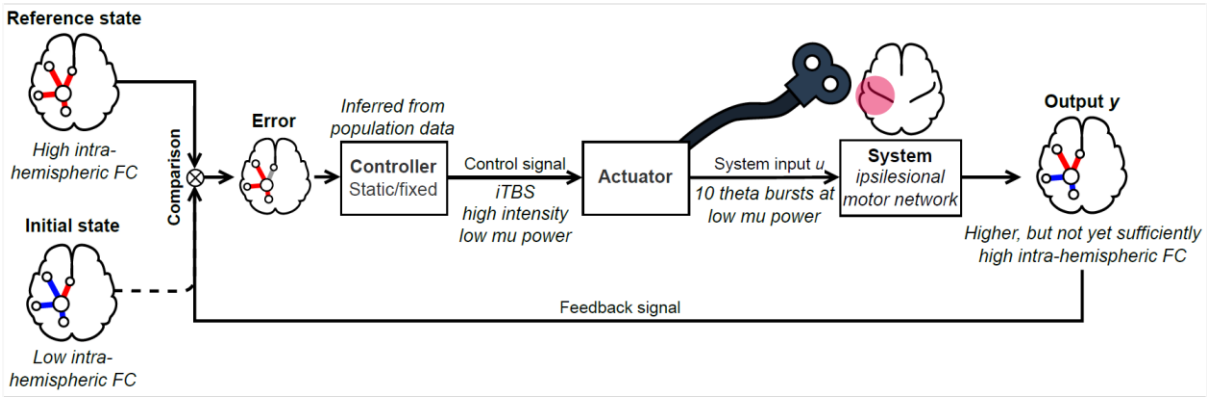
J.R. and D.E.V. contributed equally to the manuscript. D.E.V. created the figures, incorporating feedback from V.H.S.. All authors discussed the presented concept, made adjustments, revised the manuscript and approved its final version.

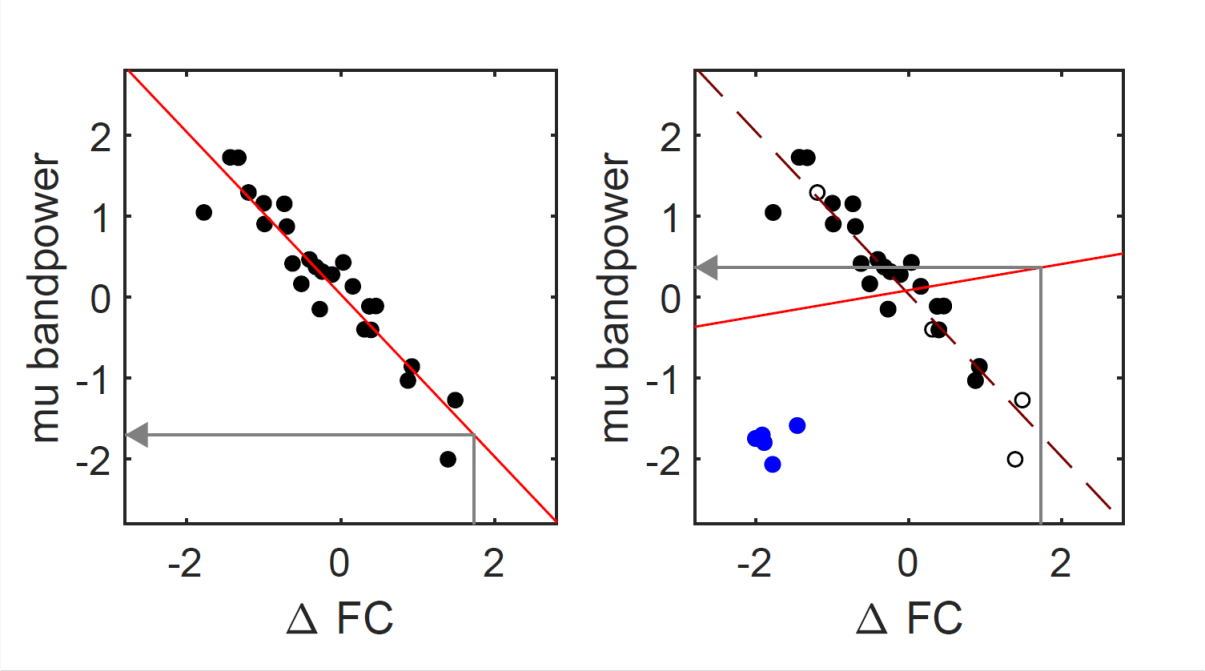
Declaration of competing interests

Risto J. Ilmoniemi is a patent holder for mTMS-related technology. All other authors declare no competing interests.

Figures



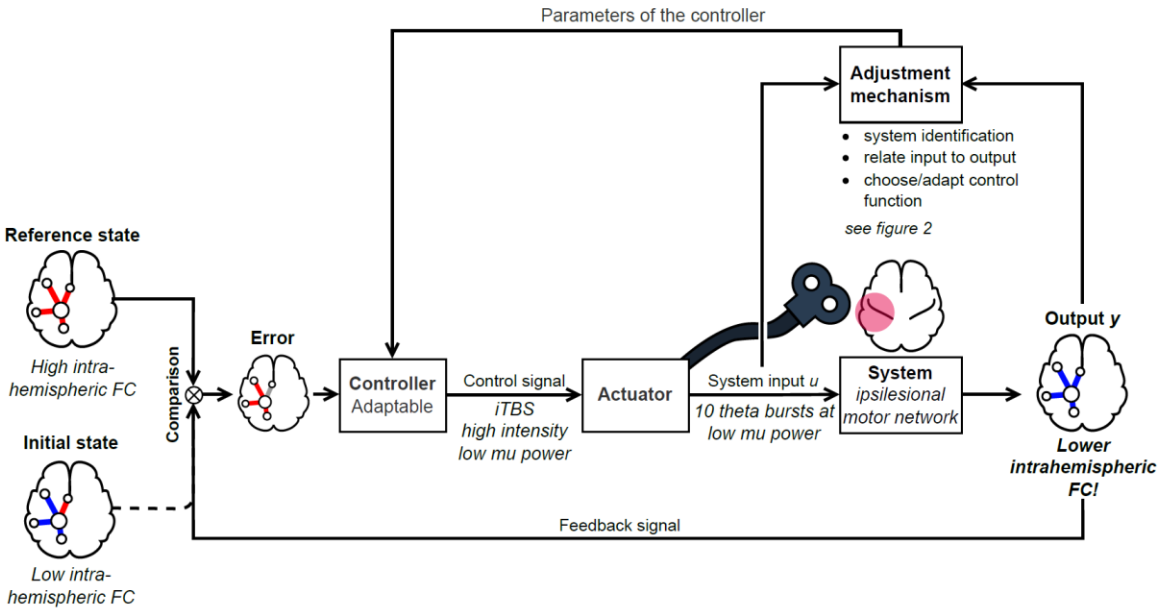
[CAPTION] FIGURE 1 Non-adaptive closed-loop control. General depiction of a non-adaptive closed-loop controller, with values from a speculative example for illustration: The reference (high intra-hemispheric functional connectivity (FC)) is compared to the initial system output (low intra-hemispheric FC), yielding the error signal ("FC needs to be increased"). The error signal is mapped onto the stimulation parameters by the controller (intermittent theta burst stimulation (iTBS), high intensity, low mu-power). The stimulation parameters are translated into the actual system input (10 theta bursts at low mu-power) by the actuator. The system (ipsilesional motor network of a motor stroke patient) then gives some output (increased, but low intra-hemispheric FC) in response to this input. The output is fed back to the comparison with the reference (closed-loop). Note that the controller's parameters are fixed/static (non-adaptive). *[END CAPTION]*



[CAPTION] FIGURE 2 Illustrative example of an adjustment mechanism (explanation see 4.4).

Left: the parameters of the controller (i.e., the mapping from error to control signal; red line) are inferred from a calibration dataset (black dots). The gray arrow in the left plot indicates how the desired change in functional connectivity (FC) ($\Delta FC > 0$) is mapped to the target low mu-power (see examples in 4.3 and 4.4, and Figures 1 and 3). Right: new observations (blue dots) sampled at this target band-power replace some of the calibration data (black circles), and the controller's parameters are re-inferred (red line). The updated controller thus will pick a different target mu-power to achieve the same change in FC (gray arrow).

All data here presented are fictional. *[END CAPTION]*



463

464 *[CAPTION] FIGURE* 3 Adaptive closed-loop control. General depiction of an adaptive
465 closed-loop controller: the reference is compared to the system output, yielding the error
466 signal. The error signal is mapped onto the stimulation parameters by the controller. The
467 stimulation parameters are translated into the actual system input by the actuator (intermittent
468 theta burst stimulationTBS (iTBS)). The system then gives some output in response to this
469 input. The output is fed back to the comparison with the reference (closed-loop). An
470 adjustment mechanism further relates system input/ stimulation parameters and output, and
471 on this basis can adjust the parameters of the controller, making it adaptive. The concrete,
472 illustrative values are nearly the same as in Figure 1, however, in this case, the result of the
473 stimulation is lower intra-hemispheric functional connectivity (FC), because the controller is
474 here applied to an unfit patient. The adjustment mechanism is illustrated in Figure 2. *[END*
475 *CAPTION]*

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