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Opinion Paper

Modulating brain networks in space and time: Multi-locus transcranial magnetic stimulation

Heikki Sinisalo [a,1,*], Ilkka Rissanen [a,1], Olli-Pekka Kahilakoski [a], Victor H. Souza [a,b,d], Timo Tommila [a], Mikael Laine [a], Mikko Nyrhinen [a,c], Elena Ukharova [a], Ida Granö [a], Ana M. Soto [a], Renan H. Matsuda [a,d], Robin Rantala [a], Roberto Guidotti [e], Dubravko Kičić [a], Pantelis Lioumis [a,b], Tuomas Mutanen [a], Vittorio Pizzella [e,f], Laura Marzetti [e,f], Timo Roine [a], Matti Stenroos [a], Ulf Ziemann [g,h], Gian Luca Romani [f], Risto J. Ilmoniemi [a]

[a] Department of Neuroscience and Biomedical Engineering, Aalto University, Espoo, Finland
[b] BioMag Laboratory, HUS Medical Imaging Center, University of Helsinki, Aalto University, and Helsinki University Hospital, Helsinki, Finland
[c] AMI Centre, Aalto NeuroImaging, Aalto University School of Science, Espoo, Finland
[d] Department of Physics, Faculty of Philosophy Sciences and Letters of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil
[e] Department of Neuroscience, Imaging and Clinical Sciences, University G. d'Annunzio of Chieti-Pescara, Chieti, Italy
[f] Institute for Advanced Biomedical Technologies (ITAB), University G. d'Annunzio of Chieti-Pescara, Chieti, Italy
[g] Department of Neurology & Stroke, University of Tübingen, Tübingen, Germany
[h] Hertie-Institute for Clinical Brain Research, Tübingen, Germany

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1. Introduction

The healthy functioning of the human brain depends on the balanced interaction of its neuronal subsystems. In many serious disorders in which this balance is compromised, there is great need for remedy. Traditional methods, such as medication, psychotherapy, or surgery, often work but may be costly, unavailable, or have undesirable side effects. Transcranial magnetic stimulation (TMS) is a safe, non-invasive alternative, which is widely used for therapy with the capability of identifying biomarkers for various brain disorders. However, because of the form factor of the coils, conventional TMS has been limited to stimulating only one site (Kujirai et al., 1993; Massimini et al., 2005; Pascual-Leone et al., 1994), or maximally two or three distant locations (Arai et al., 2011; Ferbert et al., 1992; Hernandez-Pavon et al., 2023; Veniero et al., 2013), of the brain at a time, restricting its ability to modulate multiple nodes of spatially distributed brain networks.

Multi-locus transcranial magnetic stimulation (mTMS) is a groundbreaking technique in which a set of multiple coils, or a *coil array*, is used to enable the stimulation of different cortical target sites without moving the coils (Koponen et al., 2018; Navarro de Lara et al., 2021; Nieminen et al., 2022). The targeting is based on firing multiple coils simultaneously, with different pulse combinations stimulating different cortical locations. In practice, mTMS allows precise electronic shifting and re-orienting of focal electric fields with field patterns equivalent—but not limited—to those of conventional TMS coils (Nieminen et al., 2019; Souza et al., 2022). The stimulation can be aimed at any brain network nodes within the area determined by the coil array, with freely chosen time delays between pulses, down to less than a millisecond (Nieminen et al., 2019; Souza et al., 2021; Tugin et al., 2021). The operating principle of mTMS is illustrated in Fig. 1.

This technology makes it possible to define spatiotemporal pulse sequences able to excite multiple nodes of functional networks with any desired order and precise timing of the pulses, replacing the single-locus, predetermined stimulation paradigms of conventional TMS. Furthermore, we foresee a major paradigm shift in the possibility of controlling these spatiotemporal sequences with a closed-loop approach—a computer algorithm adjusting the treatment or study based on real-time feedback from electroencephalography (EEG), electromyography (EMG), or other recordings. We have already demonstrated such closed-loop paradigms with mTMS in experiments where an algorithm automatically optimizes the stimulation target on the cortex to maximize muscle or EEG responses (Tervo et al., 2020; 2022). These develop-

* Corresponding author at: Department of Neuroscience and Biomedical Engineering, Aalto University, Otakaari 3, 02150 Espoo, Finland.
E-mail address: heikki.sinisalo@aalto.fi (H. Sinisalo).
[1] Equal contribution.

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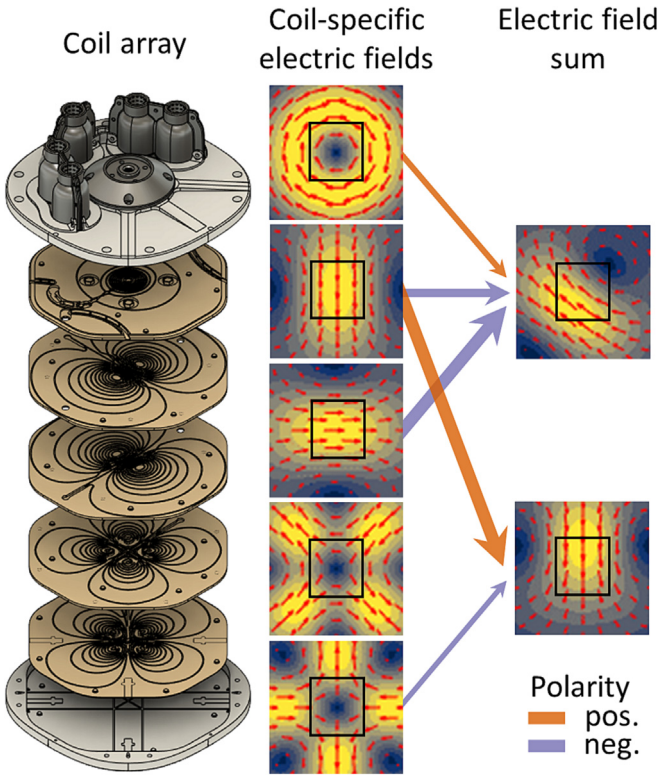

Fig. 1. Illustration of a multi-locus transcranial magnetic stimulation (mTMS) coil array, the field patterns of the individual coils, and how they can be combined to electrically manipulate the location and orientation of stimulation. The widths of the arrows indicating the coil contributions represent the relative strengths of their electric fields, with colors denoting polarity (orange for positive contribution, blue for negative). The black box indicates a region of interest under the coil array.

ments have been spearheaded by the European Research Council (ERC) Synergy-funded ConnectToBrain project, the ultimate goal of which is to realize closed-loop full-cortex mTMS stimulation guided by real-time EEG feedback (Ziemann et al., 2019).

In this article, we describe the working principles and potential applications of mTMS technology for stimulating brain networks, promising better treatments to neurological disorders and offering new opportunities for studying human brain function. The purpose of this article is to detail our vision of the future of this technology and its applications, offering a wider context for the development of specific hardware, software, and stimulation protocols for applying mTMS in research and clinical treatments.

2. mTMS and brain networks

Abundant evidence exists about structural and functional brain network alterations in various brain diseases, with pathological behavior rarely bound to a single cortical site (Cash et al., 2021; Fornito et al., 2015; Menon, 2011; Siddiqi et al., 2021, 2023; Siegel et al., 2022). Moreover, with the help of control theory, it has been shown that the brain as a state-space system is extremely difficult to control via single-site stimulation (Gu et al., 2015), further emphasizing the need for multi-site stimulation for therapeutic applications. Despite this, possibly due to technological limitations, therapeutic applications are still mostly focused on single-locus stimulation (Hett et al., 2021; Sciortino et al., 2021). Some studies have demonstrated superior treatment efficacy when two sites are stimulated (Fischer et al., 2017); for example, bilateral TMS has shown higher remission rates in treating older patients with treatment-resistant depression, compared to single-hemisphere TMS (Trevizol et al., 2019). However, the two brain sites are generally not stimulated concurrently, as conventional TMS coils are too bulky to fit close enough to each other for simultaneous stimulation.

With the capability of mTMS to rapidly shift the location and orientation of the induced electric field, we can select a set of connected cortical sites to stimulate near-simultaneously. This allows us to target brain networks with pulse combinations designed to facilitate or interfere with cross-site cortical activity (Nieminen et al., 2019; Souza et al., 2021; Tugin et al., 2021). For example, pulses could be aimed at two connected brain sites with a precise time delay coinciding with the natural propagation of signals from one target to the other. As connections between neurons firing together grow stronger (Bear et al., 2016; Hebb et al., 1949), concurrent multi-site stimulation could be used to, e.g., rehabilitate brain networks damaged by stroke. These possibilities are depicted

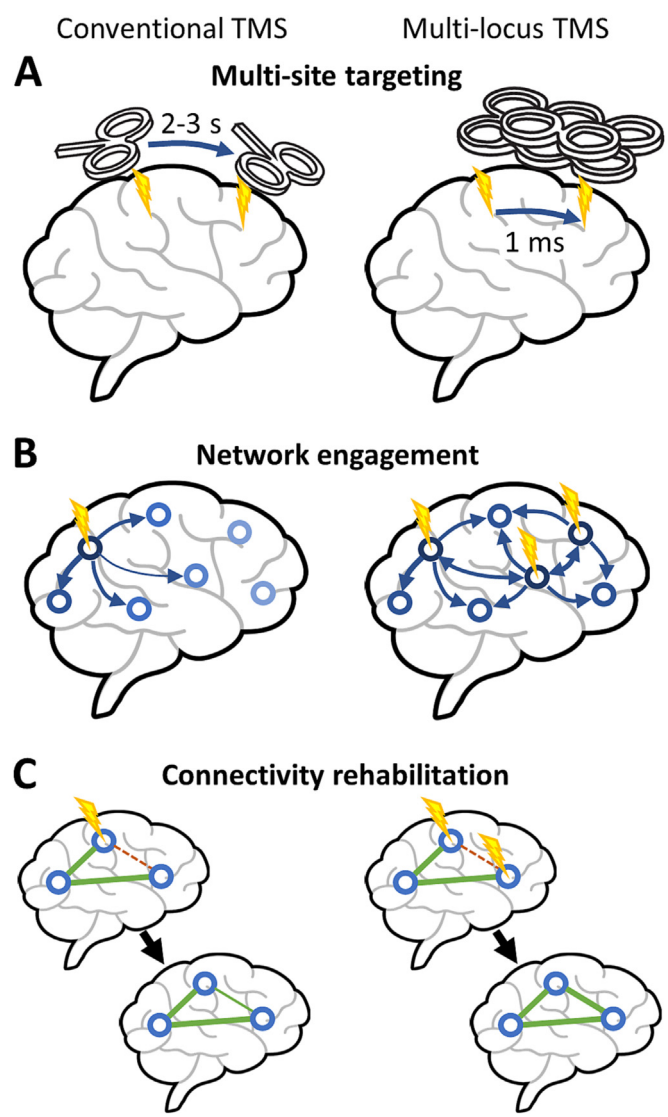

Fig. 2. Targeting of brain networks with multi-locus transcranial magnetic stimulation (mTMS). **A)** Concurrent stimulation of many brain sites is impossible with a conventional TMS device, as changing the stimulation target requires repositioning the coil, which typically takes seconds. With mTMS, the stimulation target can be electronically shifted in milliseconds. **B)** Stimulating one node of a brain network has a limited effect on network behavior. Rapid pulse sequences to multiple nodes at suitable intervals can modulate how cortical sites communicate with each other. **C)** Several brain disorders deteriorate critical communications between brain sites. One anticipated application of mTMS is to restore damaged connections with repeated concurrent pulses to connected sites. The thicknesses of the lines between nodes illustrate connection strengths.

in Fig. 2. We expect network-based mTMS therapies to allow development of new treatments in many network diseases and increase the efficacy of currently available treatments by enabling simultaneous stimulation of multiple relevant targets.

For the scientific and clinical communities to fully exploit the possibilities that mTMS enables, the technology must be conveniently accessible for research groups and hospitals. Modular design in hardware and software lowers the barrier of entry for adopting the technology by letting users start with a system featuring a small number of stimulation channels and expand to support larger coil arrays as needed. Modular design facilitates flexible research in other ways as well: building coil arrays separately from the power electronics enables swapping in specialized coil sets designed for particular stimulation modalities without the need to change anything else in the system. Modular software architecture allows any input signal to be used for controlling when and where to stimulate, enabling, for example, EEG-controlled closed-loop stimulation protocols or the use of novel readouts such as a video feed of the subject to control the stimulation.

3. Implementation of mTMS

3.1. Coil arrays

In mTMS, multiple separate coils with overlapping electric fields control how the brain is stimulated. The coil-specific electric fields can be summed together to generate a range of focal stimulation fields (Koponen et al., 2018). Importantly, the location, orientation and other features of these combination fields can be different from what any of the coils would produce alone. This allows, for example, smooth 360-degree rotation of the electric field orientation with a stack of only two coils (Pieramico et al., 2023; Souza et al., 2022). The range of possibilities increases with the number of coils: for example, a set of two coils can allow either rotating the induced electric field or shifting its locus on a straight line, but not both, whereas a set of five coils can allow shifting the target location in two dimensions, with arbitrary electric-field orientation (Nieminen et al., 2022).

Additional coils can increase the area in which the position and orientation of the field can be determined, or provide other features such as the ability to change the shape of the induced electric field. This design flexibility allows for the simultaneous targeting of nearby ipsilateral cortical nodes, going beyond the capabilities of conventional TMS devices, which can only stimulate one location at a time. As an example, while conventional technology allows for stimulation of the primary motor cortex, mTMS coil arrays can be designed to target the ipsilateral supplementary motor area, dorsal premotor cortex and primary motor cortex concurrently.

The freedom of designing coil arrays separately from the power electronics benefits mTMS in unique ways. While for conventional TMS changing the coil mainly changes the electric field profile, in mTMS, swapping a set of coils for another allows adjusting how the stimulation can be controlled. This enables great flexibility, even with electronics that support simultaneous use of only two coils. One two-coil array can be designed to allow rotation of the stimulation field, another can be designed to shift the locus of the field, and a third to allow altering focality while keeping the orientation and position fixed (Nurmi et al., 2021). With access to different coil arrays, even a simple two-channel mTMS platform enables research with any of these three different modalities of stimulation control.

While mTMS coil arrays offer great flexibility in stimulation, they are subject to certain practical considerations. A set comprising five or more coils is cumbersome for an operator to manually position on the scalp due to its size and weight. To ensure consistent cortical targeting throughout an experiment, collaborative robots can be used to position the coil array in the desired location and automatically compensate for head movements. Additionally, multi-coil setups are bound by the same limitations as any custom-designed single coil regarding electric field characteristics, including the depth of the induced electric field. Thus, mTMS cannot reach brain sites that cannot be reached with single-coil TMS. As it has been shown that direct, focal deep-brain stimulation is impossible with conventional TMS (Deng et al., 2014; Heller and van Hulsteyn, 1992), it is unattainable with mTMS as well.

A key challenge in mTMS coil array development is the increasing number of coils required to enable a wider range of electric field control. As the cortical field strength dramatically decreases with coil distance, the present approach of layering coils on top of each other (see Fig. 1a) becomes infeasible beyond the current state-of-the-art five-coil arrays. This could be addressed by fitting several smaller coils in each layer, or with overlapping windings using the empty space in adjacent layers to allow wires to cross over each other.

3.2. Electronics

The core of any TMS device is a power circuit capable of delivering strong current pulses through the coil winding. An mTMS device is essentially a set of centrally controlled, independently operating stimulators, each consisting of a power circuit and a high-voltage capacitor. Each of these so-called *channels* drives a single stimulation coil. As more channels become available, more versatile coil arrays will be possible. A more elaborate explanation of the current generation of mTMS electronics can be found in (Nieminen et al., 2022).

We envision a modular mTMS platform based on a system core with dedicated slots for channels, to which freely swappable stimulation units, each able to support a single coil, can be attached. A modular approach in the design of the mTMS system allows great flexibility, as the system can be expanded gradually to meet the growing needs. These needs can be, for instance, expanding the targeting region to both hemispheres or the capability to electrically adjust the shape of the induced electric field during stimulation sequences.

The mTMS electronics allow generating pulse combinations that induce a focal electric field at the desired location. To change the stimulation target within milliseconds, the pulse combination must be changed equally fast. To this end, an mTMS device exploits specialized power circuits and the high-frequency switching characteristics of modern semiconductors. This enables rapid changes in pulse waveforms while allowing their approximate shapes to be freely defined (Sinisalo et al., 2021; Sorkhabi et al., 2022). These adjustable waveforms have other benefits as well, such as optimizing them to minimize coil heating (Wang et al., 2022).

A major challenge in mTMS electronics is sustaining sufficient stimulation strength in new paradigms delivering stimuli to multiple locations at once at high repetition frequencies. In our state-of-the-art prototype, each channel requires to be recharged by the same—rather large—charging unit after each stimulation pulse: the larger the number of channels, the longer the minimum inter-pulse interval. Simply adding more charging units, while viable, greatly increases the bulk of the setup. Furthermore, the space taken by each individual channel increases with the desired maximum output. A thorough investigation of the specifications required is needed to optimize the power delivery and form factor of the device. As a modular mTMS system is architecturally quite complex, making the design robust but easily maintainable is yet another challenge.

3.3. Software

To make full use of the capabilities of mTMS, sophisticated real-time algorithms guiding the stimulation are required. To facilitate the stimulation of brain networks, it is essential to use group-derived or subject-specific prior information from other modalities, such as functional magnetic resonance imaging (MRI), diffusion MRI, EEG, or magnetoencephalography (MEG) (Antony et al., 2022; Cash et al., 2021; Luber et al., 2022). The software workflow should allow convenient, seamless integration and visualization of such priors, usually with neuronavigation software (Aydogan et al., 2023; Souza et al., 2018). In this way, these priors can both be used to drive the automated algorithms and complement the user with neurophysiological knowledge.

Using multimodal imaging requires the software to support multiple workflows. To achieve that, it is important to have a modular software design: functionality can be added based on the available setup and the requirements of the experiment. This is superior to a monolithic design, which cannot naturally extend to initially unplanned use cases, such as use of new algorithms or reading data from novel instruments. In modular design, a single bulky control program is replaced with small program components (Kahilakoski et al., 2021). These components perform specific functions, such as generating stimulation parameters or sending commands to the mTMS device.

In addition to the integration of priors, the software will process data from other modalities which can be acquired simultaneously with TMS, such as EEG, EMG, or other electrophysiological measurements. As an example, EEG data can be simultaneously used for multiple purposes in a closed-loop EEG–TMS experiment. In a stimulation paradigm in which the subject is exposed to visual stimuli, EEG can be used to trigger the presentation of the stimulus, as well as to determine when and where to stimulate. In modular design, it would be straightforward to add another readout device, controlled by another self-contained software component, to the measurement setup. Separate software modules could be responsible for preprocessing the streaming signals, real-time analysis of the EEG data, and sending the EEG-guided commands to the mTMS unit. Fig. 3 shows an example of how this interplay of software and hardware enables closed-loop mTMS stimulation. Making higher-level software components, such as algorithms guiding stimulation targeting based on electrophysiological responses, open source allows researchers from around the world to add new functionality as new instruments are developed and breakthroughs are made in understanding of brain function (Souza et al., 2018). Moreover, this helps to build a community that helps the software to be tested and maintained (Gleeson et al., 2017).

3.4. On the safety of mTMS

Due to the simultaneous use of multiple stacked coils to deliver pulses, mTMS involves certain unique safety considerations. The impulse noise and heat accumulation per pulse can be much higher than that of conventional TMS, necessitating stronger hearing pro-

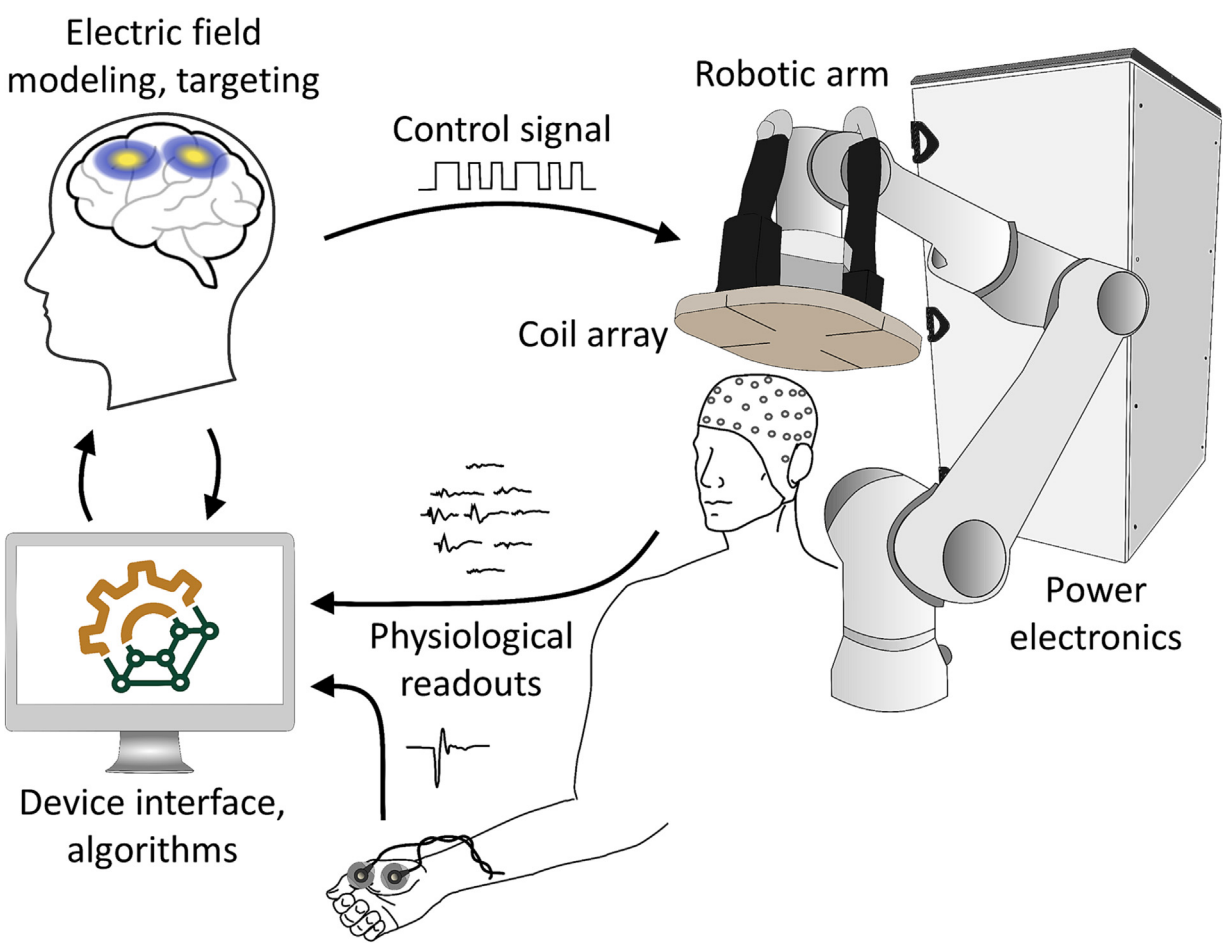

Fig. 3. A schematic diagram of a multi-locus transcranial magnetic stimulation (mTMS) system and its components. Software and hardware components cooperate to guide stimulation to desired targets, such as the individual nodes of a larger brain network. Software algorithms use readouts such as electroencephalography (EEG) and electromyography (EMG) to determine the desired site and timing of stimulation. Targeting algorithms utilize electric field modeling to determine the required mTMS pulse combinations to best reach the intended targets, while the robotic arm holds the coil array in place.

tection and careful tracking of coil array temperature. Coil designs (and pulse waveforms) optimized to minimize noise and heating can also be implemented (Koponen et al., 2021; Sánchez et al., 2017; Wang et al., 2022). Power electronics failures resulting in unintentional pulses may cause stronger adverse effects than in conventional TMS due to the possibility of firing several coils at maximum strength simultaneously, necessitating robust hardware and software design.

The capacity to stimulate multiple cortical sites at the same time, especially in an algorithmically controlled closed-loop paradigm, raises new questions on electric field dosage limits (Rossi et al., 2009, 2021). If the paradigm features no fixed frequency, intensity, or target sites, but rather determines these from real-time feedback, how should dosage be defined? When stimulating multiple sites, should the limit depend on the connectivity of the targeted regions? Could the limits be determined based on induced brain activity rather than induced electric field distributions? To ensure safety in machine-controlled multi-locus paradigms, appropriate dosage restrictions must be determined and integrated into the core software to prevent user-designed algorithms from going berserk and exposing the brain to excessive stimulation.

4. Novel applications

The ability to electronically control the location, orientation, timing, and intensity of the stimulation opens new possibilities for brain research and treatment. For instance, a common application of conventional TMS is pre-surgical mapping (Krieg, 2017; Lefaucheur and Picht, 2016; Picht et al., 2009; Vitikainen et al., 2009), which involves dense sampling of TMS-evoked responses within a cortical region of interest. mTMS allows creation of fully automatic and standardized mapping protocols, yielding more consistent and accurate priors for neurosurgical operations without user dependency. Similar procedures can be used to create personalized treatment protocols for brain disorders. For example, mTMS–EEG could be used to detect potential therapeutic targets for stroke patients, based on the local cortical reactivity patterns (Sarasso et al., 2020). While stimulation directly over the lesion does not produce TMS-evoked potentials, simple sleep-like evoked responses (Massimini et al., 2005) are observed in perilesional areas, where disrupted function can potentially be restored. Concurrent stimulation can be applied to such targets to strengthen surviving connections by having the neurons fire in synchrony (Bear et al., 2016; Hebb, 1949), a process currently utilized in corticocortical paired associative stimulation (ccPAS) protocols (Hernandez-Pavon et al., 2023). However, with conventional TMS the use of ccPAS is restricted to distant brain areas due to the size of the coils. This limitation is removed with mTMS, allowing the simultaneous activation of neighboring cortical targets with high precision.

Personalization of treatment approaches are further facilitated by closed-loop mTMS protocols. By steering mTMS based on the real-time responses from the patient, we can automatically find stimulation targets and paradigms that best elicit desired responses from individual subjects (Lioumis and Rosanova, 2022). For instance, the cortical hotspot and optimal stimulus orientation can be automatically optimized based on EMG and EEG feedback (Tervo et al., 2020, 2022). The utility of the real-time tracking of TMS–EEG responses does not stop at the spatial localization of the cortical target, but also allows timing of the stimulation according to properties of brain activity such as the phase of the oscillation (Rosanova et al., 2009). For instance, stimulation time-locked to the phase of the mu-rhythm in the motor cortex has been shown to produce long-term changes in corticospinal excitability (Zrenner et al., 2018), while the phase of the prefrontal alpha oscillation may govern the excitatory versus inhibitory effect of TMS in certain brain networks (Pantazatos et al., 2023).

A closed-loop approach also holds significant promise for improving paired-pulse treatment protocols such as ccPAS, the clinical effect of which depends on relative timing of the pulses (Arai et al, 2011; Hernandez-Pavon et al, 2023; Koganemaru et al, 2009), by optimizing the interstimulus interval based on immediate EEG or EMG feedback. Furthermore, real-time EEG measurements of distant cortical activity, i.e., large-scale brain states, can be taken into account to time stimulation to coincide with specific brain activity patterns of interest (Marzetti et al., 2024; Rösch et al., 2024). The ability of mTMS to target even adjacent cortical regions with millisecond precision based on real-time feedback opens myriad possibilities for closed-loop optimization of pulse sequences for excitation or inhibition of specific neural circuits for personalized network-based therapy.

With conventional TMS, the electric field spreads evenly around the locus, making it difficult, if not impossible, to avoid significant stimulation of neighboring sites. As the mTMS stimulation field is adjustable, we can shape the field to excite a particular region while avoiding a critical neighboring target. To benefit from this advancement, we need to be able to precisely localize the regions of interest. It can be done by integration of priors derived from various neuroimaging modalities, such as functional and diffusion MRI, positron emission tomography (PET), and MEG. The benefit of using functional MRI priors for target selection have been repeatedly demonstrated for the major depressive disorder (Cash et al., 2021; Siddiqi et al., 2023a, 2023b) and is already being implemented into clinical practice in novel rTMS protocols approved by the U.S. Food and Drug Administration (FDA) (Cole et al., 2022). And while mTMS technology does not allow direct focal activation of deep brain structures, precise spatiotemporal multi-site stimulation guided by tractography shows potential for strong indirect stimulation of subcortical nodes of a brain network—an unprecedented opportunity for treating conditions involving deeper structures (Chen et al., 2022; Luber et al., 2022; Palesi et al., 2015).

mTMS technology enables the development and testing of multitudes of treatment protocols that were previously unfeasible. As our ability to understand and identify brain networks and their states expands, the multilocus approach will allow us to detect exactly when and where to stimulate an individual in order to best facilitate a shift towards physiological brain states.

5. Concluding remarks

This concept paper, together with three other such publications (Marzetti et al., 2024; Rösch et al., 2024; Humaidan et al., 2024), highlights the direction of technical development in the ERC Synergy project ConnectToBrain. We aim to realize algorithm-driven closed-loop multi-locus TMS, capable of modulating brain networks via concurrent stimulation of the network nodes anywhere on the cortex. This paper describes the fundamental principles of mTMS and its application for brain network stimulation—a paradigm shift from the single-target approach of conventional TMS into connectivity-based methodology.

This revolutionary technology opens new avenues to visionary exploration of cortical networks, as well as enhanced, multi-site treatment protocols for the diversity of brain disorders. The capability to shift stimulation targets at millisecond scale enables versatile coupling to brain network activity, a feat unattainable with conventional TMS. Modular design facilitates development of specialized protocols for an expanding variety of use-cases, allowing hardware and software components designed for particular tasks to be seamlessly integrated to the system as required. Such proto-

cols could, e.g., algorithmically guide stimulation with real-time EEG feedback (Tervo et al., 2022; Zrenner et al., 2018) or with real-time computation of anatomical connections (Aydogan et al., 2023) for personalized treatment modalities. These advances are crucial steps towards our vision of algorithmically-controlled modulation of brain networks with TMS.

Conflict of interest

Risto J. Ilmoniemi is a patent holder for mTMS-related technology.

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