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The role of neuronavigation in TMS–EEG studies: Current applications and future perspectives

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ABSTRACT

Transcranial magnetic stimulation combined with electroencephalography (TMS–EEG) allows measuring non-invasively the electrical response of the human cerebral cortex to a direct perturbation. Complementing TMS-EEG with a structural neuronavigation tool (nTMS–EEG) is key for accurately selecting cortical areas, targeting them, and adjusting the stimulation parameters based on some relevant anatomical priors. This step, together with the employment of visualization tools designed to perform a quality check of TMS-evoked potentials (TEPs) in real-time during TMS-EEG data acquisition, is pivotal for maximizing the impact of the TMS pulse on the cortex and in ensuring highly reproducible measurements within sessions and across subjects. Moreover, storing stimulation parameters in the neuronavigation system can help in replicating the stimulation parameters within and across experimental sessions and sharing them across research centers. Finally, the systematic employment of neuronavigation in TMS–EEG studies is also critical to standardize measurements in clinical populations in search for reliable diagnostic and prognostic TMS–EEG-based biomarkers for neurological and psychiatric disorders.

1. Introduction

Transcranial magnetic stimulation (TMS) was devised almost forty years ago to non-invasively activate the cerebral cortex in humans (Barker et al., 1985). TMS exploits the physical principle of electromagnetic induction, which was discovered by Faraday in 1831: a strong and short-lasting electric current that passes through a coil (primary circuit, i.e. the TMS coil) applied over the scalp generates a magnetic field (duration: about 0.1 ms; intensity: 1–2 Tesla); in turn, this pulsed magnetic field induces an electric field that depolarizes axonal membranes (secondary circuit) closest to the coil (Wagner et al., 2007), and leads them to fire action potentials (Mueller et al., 2014; Romero et al., 2019). In virtue of this chain of physical and neurophysiological events, targeting TMS on the primary motor cortex (M1) results in the generation of a synchronous volley of action potentials (Di Lazzaro et al., 2012) that is conducted down the corticospinal tract and hence evokes a motor evoked potential (MEP) that can be easily recorded by means of electromyography (EMG; Barker et al., 1985; Hallett, 2007).

At first, researchers in the TMS field were employing circular, non-focal coils and chose the M1 as the privileged target. The reasons for this choice were mainly two: 1) when combined with EMG (TMS–EMG), TMS provides an objective, measurable response of the corticospinal tract to the cortical stimulation, i.e., the MEP; 2) TMS does not necessarily require a neuronavigation system as the presence of MEPs clearly signal that the M1 and the corticospinal tract have been effectively stimulated. In fact, TMS on itself is blind to the undrelying anatomy of the cerebral cortex and targeting one specific cortical target is challenging.

Abbreviations: APB, Abductor Pollicis Brevis; AD, Alzheimer Disease; CST, Corticospinal Tract; DES, direct electrical stimulation; DLPFC, dorsolateral prefrontal cortex; dMRI, diffusion MRI; ECT, Electroconvulsive Therapy; EMG, electromyography; fMRI, Magnetic Resonance Imaging (fMRI); LIS, Locked-in syndrome; MCS, Minimally Conscious State; MEP, Motor Evoked Potential; mTMS, multi-locus TMS technology; M1, primary motor cortex; NREM, non-REM; nTMS-EEG, neuronavigated TMS-EEG; PCI, Perturbational Complexity Index; PD, Parkinson Disease; TEP, TMS-evoked potential; TMS-EMG, TMS combined with EMG; TMS-EEG, Transcranial Magnetic Stimulation combined with electroencephalography; rMT, resting motor threshold; rt-TEP, real-time TEP; UWS, Unresponsive Wakefulness Syndrome; VS, Vegetative State.

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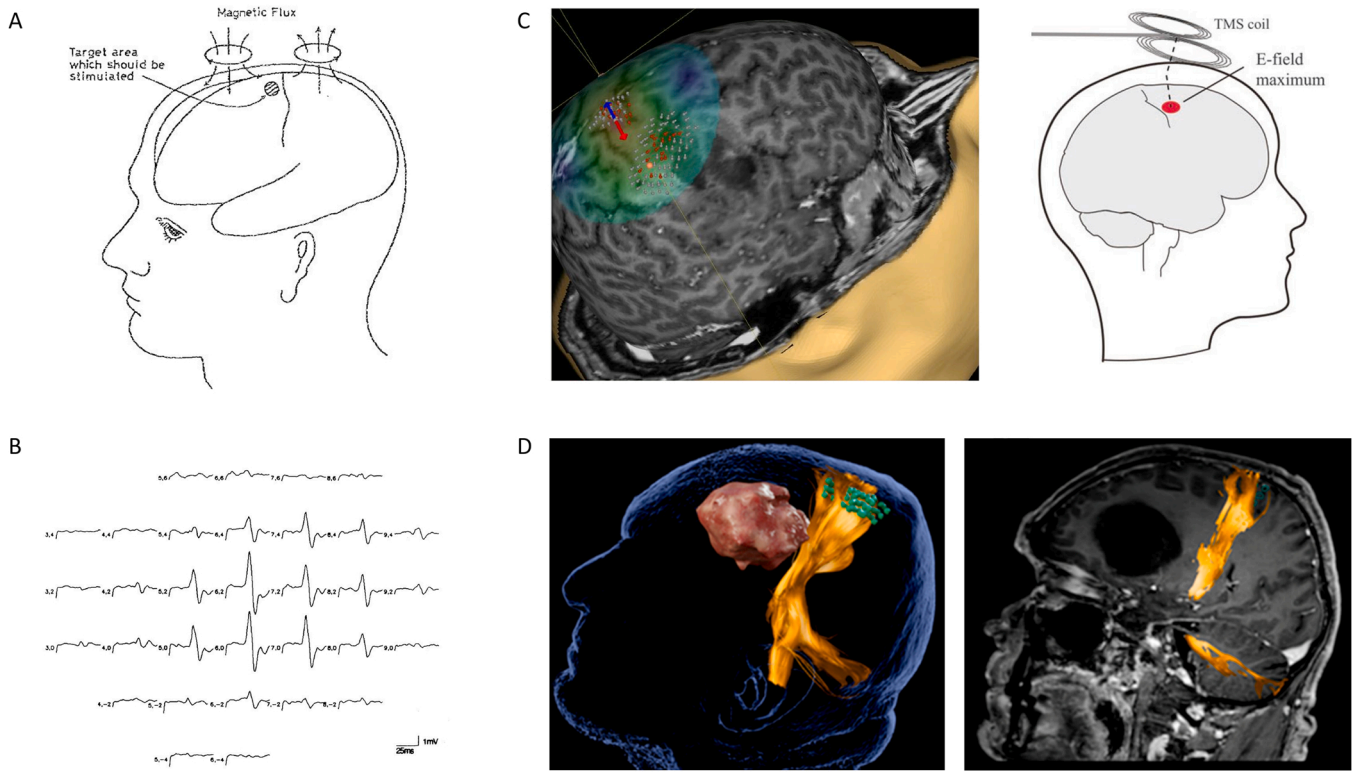

Fig. 1. Panel A. The principle of focal TMS, on which figure-of-eight TMS coils are constructed (reproduced from (Ueno et al., 1988)). Panel B: MEPs recorded from the left Abductor Pollicis Brevis (APB) after the stimulation of multiple scalp sites over the right motor cortex (reproduced from (Wilson et al., 1993)). Panel C (left). Example of visualization of the locations and orientations of the electric fields induced by TMS during a motor mapping protocol. The blue and red arrows indicate the main direction of the induced Efield. Note that red markers indicate effective stimulations (motor-positive in red) and that stimulations close to the midline were activating tibial muscle fibers, whereas more lateral stimulations were activating hand muscle fibers (reproduced from (Krieg et al., 2017)). Panel C (right). The principle of E-field navigation, which accounts for tissues conductivity boundaries and computes E-field maximum where TMS is supposed to be more effective (reproduced from (Hannula and Ilmoniemi, 2017)). Panel D (left). Tractography of the corticospinal tract (orange) based on an ROI constituted of motor-positive TMS targets (green). Panel D (right). Fusion of T1-weighted imaging and tractography results (axial plane). Note that the two pictures refer to an exemplary patient case (right-hemispheric glioma in a 56-year-old male patient) for illustration of CST reconstruction using tractography based on motor maps derived from motor mapping with nTMS (reproduced from (Sollmann et al., 2021)).

At later stages, figure-of-eight coils were introduced to induce more focal electric fields and hence more localized cortical activations (Ueno et al., 1988; Fig. 1, A). Since then, focal coils were employed to map M1 in both physiological and pathological conditions (Cohen et al., 1991; Wassermann et al., 1992; Wilson et al., 1993). In these studies, the coil was systematically moved at different scalp locations and MEPs were concurrently recorded to define the somatotopic cortical representations of single peripheral muscles, such as the thumb and other hand muscles, at the single-subject level (Fig. 1, B). However, even in the presence of measurable outputs, e.g., MEPs that clearly indicate the activation of a portion of M1 specifically controlling for hand muscles (hand motor hotspot or hand knob), knowledge about the anatomy of the individual cortical targets remained largely inaccurate. In addition, more than one stimulation site can result in the same output due to the overlapping of motor cortical representations for different muscles (Wassermann et al., 1992).

At the same time, cortical areas other than M1, such as the visual or associative cortices, were targeted. TMS over these cortical targets can interfere with both sensory processing (Amassian et al., 1998) and cognitive functions (Cowey and Walsh, 2001). More recently, TMS has been also combined with neuroimaging and electrophysiological techniques, such as functional Magnetic Resonance Imaging (fMRI) or electroencephalography (EEG), to objectively measure cortical responses to TMS, even in absence of motor outputs or sensory and cognitive modulations (Siebner et al., 2009). In particular, the combination of TMS with EEG (TMS-EEG) made it possible to measure the immediate electrical response of the human cerebral cortex to a non-invasive perturbation (Ilmoniemi et al., 1997). The availability of TMS focal coils that allowed to produce more focal activation of motor and non-motor cortical areas and, most importantly, the combination of TMS with other techniques, such as EEG, soon called for the implementation of neuronavigation systems to target cortical areas in a more accurate and reproducible way (Ruohonen and Karhu, 2010).

In this minireview, we will focus on the advantages of employing neuronavigation in TMS-EEG (nTMS-EEG) recordings, on the basic and clinical research applications that nTMS-EEG has made possible so far, and on the new prospects that it may bring in the near future by further developing new TMS paradigms, such as multi-locus TMS technology (mTMS; Koponen et al., 2018; Nieminen et al., 2021) and closed-loop approaches (Zrenner et al., 2018, 2016). The present review paper is not intended to be an exhaustive overview of the literature on nTMS–EEG, rather it focuses on studies that exemplify the importance of neuronavigation in ensuring reproducibility of TMS-EEG measurements and in promoting the standardization of experimental procedures.

2. Technical aspects of neuronavigation in TMS and TMS-EEG

2.1. Basic principles and applications of neuronavigation in TMS

Since its dawn, TMS has posed the problem of localizing the induced electric field on the cerebral cortex. The main method employed to infer the TMS cortical target in the absence of neuronavigation system exploits the functional specialization and the somatotopic organization of some cortical areas. Specifically, the method consists in finding the coil

position on the scalp that can elicit a consistent MEP for a specific muscle. Typically, this is a muscle of the thumb contralateral to the stimulated cortical area (Groppa et al., 2012; Rossi et al., 2021) and the intensity so defined is called resting motor threshold (rMT) for that specific muscle, i.e., the lower output of the TMS stimulator that is able to activate the muscle. It is worth mentioning here that a reference intensity as rMT has been of high value because the higher the intensity gets the larger the stimulated area becomes, thus specificity and precision decrease. Obviously, the search for the rMT not only leads to measuring corticospinal excitability, but also allows to indirectly localize the M1 in the absence of anatomical priors.

The scalp location where rMT is measured is also the reference site to stimulate cortical areas other than M1. In other words, the coil is translated over the scalp referring to the location where rMT was measured. For instance, the procedure to target the dorsolateral prefrontal cortex (DLPFC) involved first the localization of M1 and then the repositioning of the coil 5 cm, anterior to the "hand knob" (Pascual--Leone et al., 1996). However, the anatomy of the brain across subjects is highly variable (Amunts et al., 2000). As a result, targeting the same cortical area in different subjects solely relying on the localization of M1, is challenging (Ruohonen and Karhu, 2010). A different approach for placing the TMS coil on the scalp exploits the 10–20 EEG electrodes' positioning system. This approach is based on the assumption that across subjects there is a reliable overlapping between cortical areas and the scalp positions of the overlying EEG electrodes. Although this method can improve the reproducibility of TMS coil positioning across measurements and individuals (Walsh and Cowey, 2000), it does not compensate for the interindividual differences of the skull and cortical anatomy and may lead to target displacements of up to 20 mm (Herwig et al., 2003). Thus, targeting a cortical area other than M1, in the absence of any clue about the underlying cortical anatomy, could suffer from an even higher degree of inaccuracy due to the lack of any objective readout. Finally, the impact of the induced electric field on the cortex by the TMS pulse strongly depends on the scalp-to-cortex distance, which is also highly variable within the same brain and across individuals. Thus, controlling for this factor can further help in standardizing the experimental conditions within and across subjects.

To account for individual brain anatomy, commercial or open source neuronavigation systems (Souza et al., 2018) that can be coupled with TMS are now available. These neuronavigation tools typically rely on the co-registration between MRI-based 3-D modeling of individual head and brain images and the actual subject's head. For this purpose, an infrared camera locates a set of optical trackers that are placed on the TMS coil and on goggles/head-trackers that are worn by the subject (Hannula and Ilmoniemi, 2017; Ruohonen and Karhu, 2010). To align the 3-D MRI head model and the actual subject's head, landmarks that have been set on the MRIs are identified and selected manually on the head with a digitizing pen, which serves as a tracker tool. After this procedure, the coil, that is also provided with optical trackers, can be eventually visualized over the 3-D MRI head model and, most importantly, the site of stimulation over the cortex can be modelled and visualized as well. Interestingly, the association of TMS-EMG with neuronavigation enables mapping the motor cortex at a finer grain, resulting in identifying the cortical representation of several muscles, for example within the hand area only (Nazarova et al., 2021; Sollmann et al., 2021). Within a relatively small region of M1, some cortical targets will result in MEPs (motor-positive nTMS sites) and some others will not (motor-negative nTMS sites). Thus, motor cortical mapping through a neuronavigation system allows to identify the entire somatotopic organization of the M1 at the individual level (Fig. 1, C).

Different types of errors can affect neuronavigation systems: registration, localization, precision and repeatability (Souza et al., 2018). In the present context, it is worth noting that most of the neuronavigation systems localize the maximum of the TMS-induced electric field (maximum E-field) as the projection of the center of the coil on the cortical surface along a line perpendicular to the TMS coil surface (line navigation). However, when the coil is not perfectly tangential to the skull, line-navigation can be a further source of inaccuracy. For this reason, some commercially available neuronavigation systems for TMS have implemented an "E-field navigation", which takes into account the subject's head geometry (Hannula and Ilmoniemi, 2017). This improvement is particularly important for highly demanding clinical applications like the presurgical search for eloquent cortical areas. More specifically, navigation paved the way for the most crucial clinical application- from patients' safety point of view- so far like the presurgical mapping of the eloquent cortex (Bastos and Prabhu, 2017; Krieg et al., 2017; Picht et al., 2011, 2009; Vitikainen et al., 2009). nTMS is commonly used also in combination with diffusion-based MRI tractography in the motor functional mapping for the assessment of peri-Rolandic tumors and neoplastic lesions to control for the risk of injuring and distorting the pyramidal tract during the surgical resection. Presurgical, motor functional mapping by nTMS has shown to correlate well with intraoperative direct electrical stimulation (DES; Krieg et al., 2012; Picht et al., 2011; Tarapore et al., 2012; Vitikainen et al., 2009) and it has been associated with better patient outcomes (Krieg et al., 2014; Picht et al., 2016). Finally, low cost and relative ease of use contribute to the increasing application of this modality in preoperative planning (Bastos and Prabhu, 2017). In brief, during preoperative mapping, the TMS coil is moved and triggered to produce MEPs from the muscles under question inside and around the tumors and the eloquent cortex. The area of MEP generation gives an a priori idea to neurosurgeons to design the craniotomy, the mapping by DES and the final resection of tumor (Krieg et al., 2017). Besides providing useful knowledge about individual cortical anatomy for TMS targeting, the employment of a neuronavigated system usually allows the storage of the stimulation parameters (cortical target, coil orientation, the position of the induced electric field, etc. (Ilmoniemi et al., 1999). Interestingly, post-hoc use of stored neuronavigation data has again become relevant in support of neurosurgeons. The combination of nTMS motor cortical maps with diffusion MRI (dMRI) and fiber-tracking algorithms can provide a more exhaustive picture of the eloquent corticospinal pathways. For instance, using the motor-positive nTMS sites as seeding points for fiber-tracking allows the visualization of the corticospinal tract and helps the neurosurgeon in identifying the white matter network (Fig. 1, D).

On the other hand, storage of neuronavigation data is crucial in keeping the stimulation parameters constant throughout a single measurement and increases the reproducibility of subsequent measurements of the motor threshold and of the MEPs (Ruohonen and Karhu, 2010), i. e. in studies aimed at evaluating the effect of pharmacological or non-invasive brain stimulation treatments (e.g., rTMS and tDCS). Furthermore, TMS coil's accurate repositioning based on previously acquired information is fundamental in therapy sessions that are repeated daily, as in the application of rTMS in depression (Brunoni et al., 2017; Miron et al., 2021).

Finally, data stored in the neuronavigation systems can be integrated with Talairach based brain atlases, Montreal Neurological Institute (MNI) based brain atlases, and functional neuroimaging (Cash et al., 2021; Fox et al., 2013) for online or offline and positioning of the TMS coil based on standard anatomical or functional priors (Beam et al., 2009; Islam et al., 2019). Recently, it has been demonstrated that atlas-based targets can agree well with cortical areas defined by experts and can be easily overlaid in neuronavigation, thus can be a useful support in nTMS targeting (Reijonen et al., 2021). On the other hand, TMS coil targets on the cortical surface can be transformed into Talairach or MNI coordinates if and only if stimulation parameters were stored into the neuronavigation workstation.

2.2. The role of neuronavigation in TMS-EEG

As described in the previous section, the combination of TMS with EMG allows to measure the output of the corticospinal tract when M1 is

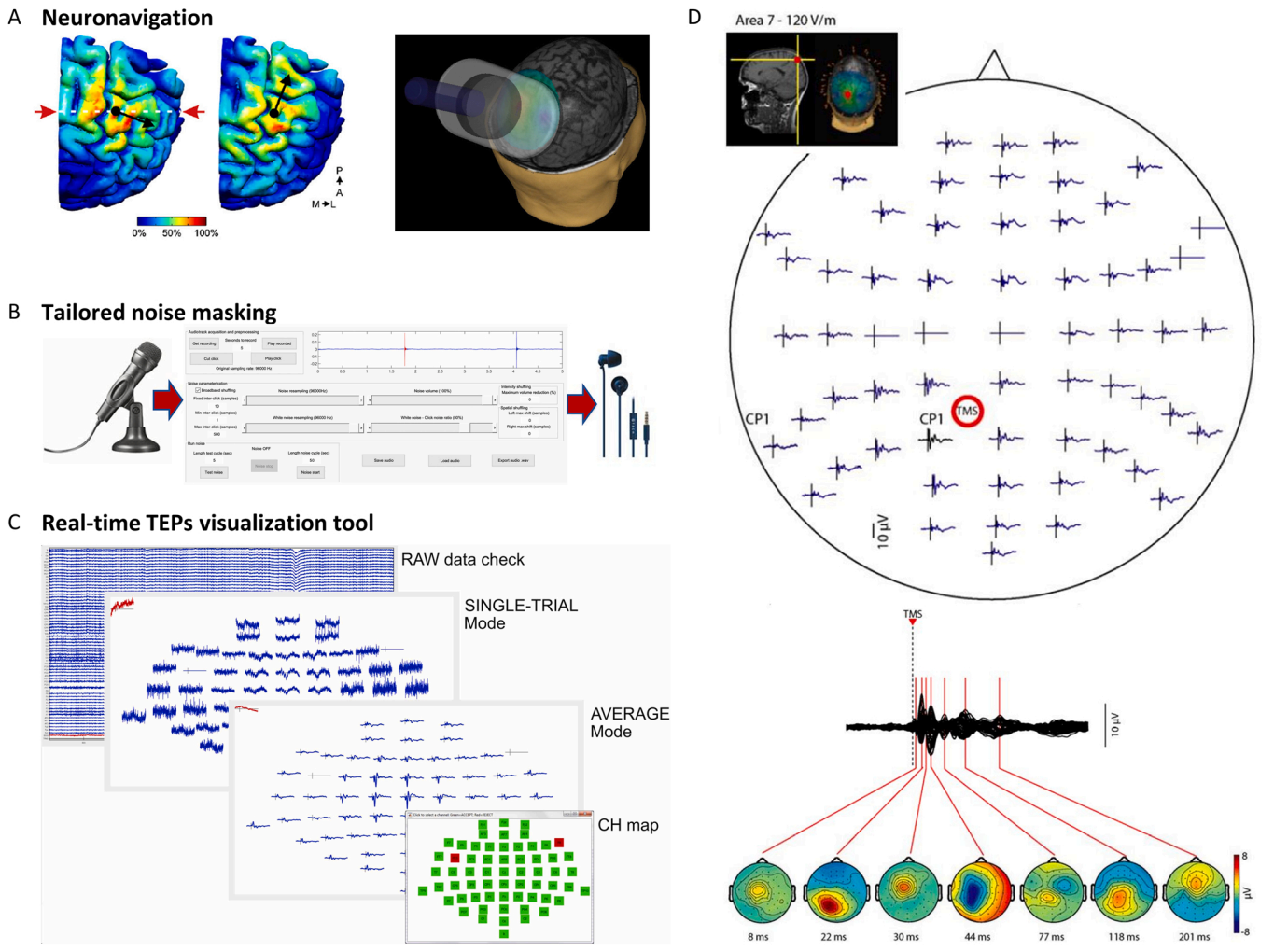

Fig. 2. Panel A left. 3-D modeling of the TMS-induced electric field (E-field) on the cortical cortex with the coil oriented along two different directions (reproduced from (Opitz et al., 2011)). Panel A right: a TMS coil and subject's head in the same virtual space to localize and estimate the E-field on the cortical mantle are pictured. Panel B: Screenshots from the software tool to generate an effective noise masking tailored both on the coil "click" and the subject's perception (TAAC; reproduced from (Russo et al., 2021)). Panel C: Screenshots from the software tool visualize the TEP in real-time during the acquisition (rt-TEP)(reproduced from (Casarotto et al., 2022)). Panel D: reports a screenshot from the neuronavigation system with the coil targeting the posterior parietal cortex and the display of all the EEG channels for a TEP obtained after the stimulation of that cortical area. Note that the TEP is characterized by larger components recorded at EEG channels close to the coil, which result in specific, asymmetric topographies at early and late latencies (reproduced from (Rosanova et al., 2009)).

targeted. Similarly, TMS–EEG allows measuring the electrical response of the targeted cortical area and the connected corticothalamic and corticocortical circuits. In this way, TMS-EEG can provide direct measures of cortical excitability for a given cortical area. However, contrary to TMS–EMG, which is restricted to M1, TMS-EEG can be applied virtually at any cortical area, including the associative cortices, which are covering a large part of the cortical mantle, underlie most of the high cognitive functions (Purves et al., 2001) and yet do not produce any motor output or sensory perception when targeted by single-pulse TMS.

When a conventional EEG amplifier is employed, the EEG response to TMS is covered by a large and long-lasting artifact caused by the intense electric field generated by the TMS pulse (Wagner et al., 2007). To cope with the TMS-induced electric artifact, at the end of 1990s, fully TMS-compatible EEG amplifiers were introduced with a sample-and-hold circuit (Ilmoniemi et al., 1997; Virtanen et al., 1999) that set the voltage value to a constant level during the TMS discharge. These amplifiers were able to recover after only 2 ms from the TMS pulse allowing recording very early (10 ms) TMS-evoked potentials (TEPs) under the coil (Ilmoniemi et al., 1997; Massimini et al., 2005; Paus et al., 1997). An alternative approach is based on the use of DC-amplifiers provided with a wide dynamic range and high sampling rates (≥5 KHz) that also allow to record TEPs with very short-lasting (5 ms) artifacts (Bonato et al., 2006; Casarotto et al., 2022).

Even when employing TMS-compatible EEG amplifiers, TEPs can still be contributed by spurious electrical responses due to biological activations other than cortical ones. A major confounder may be the high-amplitude biphasic early electrical deflection caused by the TMS-evoked activation of the scalp muscles under the coil (Mutanen et al., 2013). Second, the loud "click" (Nikouline et al., 1999) and the mechanical vibrations that follow the TMS coil discharge are systematically triggering auditory evoked potentials. Different approaches have been adopted to reduce or control for the contribution of these confounding factors. For instance, one can perform control measurements that employ TMS-sham conditions (Conde et al., 2019; Gordon et al., 2021) or can remove the evoked potentials due to muscle or auditory stimulations using off-line data preprocessing procedures (Mutanen et al., 2020; Rogasch et al., 2014; Ross et al., 2022).

An alternative approach relies both on the application of experimental procedures that are aimed at reducing or abolishing the confounding factors and on the employment of a visualization tool that allows performing TEPs quality check in real-time before and during data acquisition. On the one hand, TMS-evoked auditory evoked

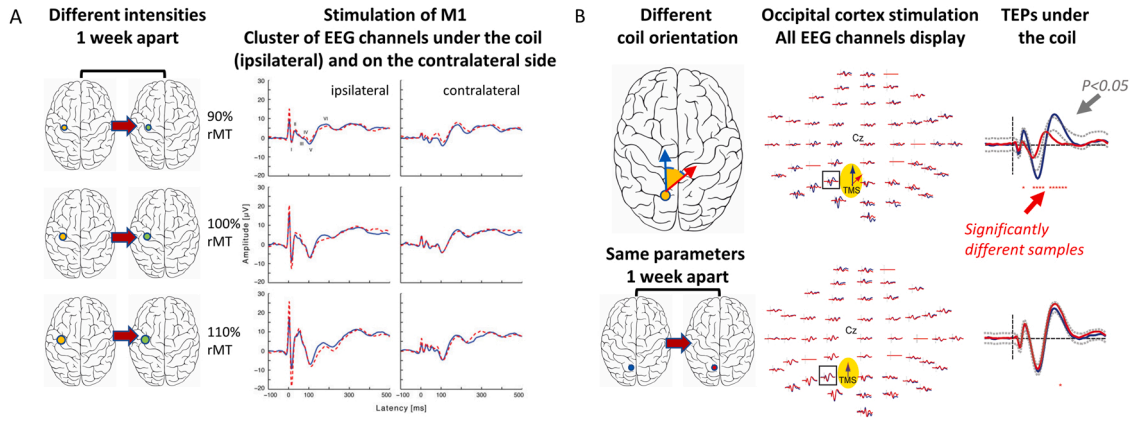

Fig. 3. Panel A: Grand average waveforms from 10 EEG electrodes under and around the coil in primary motor cortex (M1) stimulations with one week difference. Reproducibility is evident for 90%, 100% and 110% of rMT (reproduced by Lioumis et al., 2009). Different diameters of filled colored circles indicate different stimulation intensities. Dashed red traces represent the first recording, whereas blue solid traces represent the recording performed one week later. Panel B upper: Average responses from an electrode in the occipital cortex under the TMS coil after stimulating with two coil orientations of 60° difference, resulting in significant differences in the recorded signal (blue and red traces were recorded at 0° and 60° respectively). Panel B lower: Average responses from an electrode in the occipital cortex under the TMS coil after stimulating with exact same parameters but one week apart (blue and red traces represent the forst and the second recording respectively) (reproduced by Casarotto et al., 2010).

potentials can be effectively abolished by using a tool that generates a continuous masking noise that reproduces the time-varying spectral content of the coil "click" (Massimini et al., 2005; Russo et al., 2021; Fig. 2, B) and by interposing a foam layer between the TMS coil and the subject's scalp (ter Braack et al., 2015). In the same vein, scalp muscle artifacts can be reduced or abolished by appropriately rotating the TMS-coil (Casarotto et al., 2022; Mutanen et al., 2013; Tervo et al., 2022). On the other hand, Casarotto and colleagues have recently released a freely available software tool, called rt-TEP (Casarotto et al., 2022) that facilitates the recording of TEPs by providing an online readout of the immediate impact of the TMS pulse on the underlying cortical circuits. This software tool can be interfaced with different TMS-compatible EEG amplifiers and allows to display and check EEG data in raw mode, single-trial mode, and both in common and average reference mode (Fig. 2, C). Thanks to these modalities of EEG data visualization, not only the operator can check whether the procedures aimed at minimizing the confounding factors are effective, but it is also possible to maximize the impact of the TMS on the cortex (Belardinelli et al., 2019). Specifically, rt-TEP, but also any other equivalent visualization tool, can inform in real-time the operator about the presence of an auditory evoked potential or of a muscle artifact and guide them through the adjustment of noise masking tool or the stimulation parameters. Most important, rt-TEP visualization tools allow to fine-tune and optimize the stimulation parameters (coil rotation and stimulator output) in order to record TEPs with a good signal-to-noise ratio and characterized by scalp EEG topographies that are specific for the stimulated site (Casarotto et al., 2022).

Once a TMS-compatible EEG amplifier is employed (Ilmoniemi and Kičić, 2010; Rosanova et al., 2012) and the biological confounders due to the sensory co-stimulation are minimized or abolished, TEPs do reflect genuine cortical responses to TMS (Fig. 2, D) and the very early components of TEPs can be regarded as the immediate response of the cortical circuits underneath the coil and directly activated by the TMS pulse.

Hence, by carefully designing TMS–EEG measurements, the early TEP components are the direct cortical output after a TMS pulse. In this context, the combination of TMS–EEG with neuronavigation (nTMS–EEG) has two great advantages. First, the employment of a neuronavigation system can help maximize the impact of the TMS on the cortex, by choosing a target that results in brain responses larger than a given EEG end-point. Specifically, neuronavigation allows both targeting the maximum electric field on the convexity of the selected gyrus and avoiding sulci. In fact, stimulation within a sulcus may result in an increase of the scalp to cortex distance and a decrease of the effectiveness of the TMS pulse, the intensity of stimulation being the same. Thus, to compensate for such phenomena, the stimulator's output should be increased to reach either a given intensity of the induced electric field (expressed in volts/meter; V/m)or the desired minimum amplitude of the early TEP components. In this concern, a special case is represented by cortical lesions in neurological patients, which also must be avoided, and that will be treated below. In the same vein, neuronavigation allows choosing the coil orientation that maximizes the impact of the pulse on the cortical neurons (Fig. 2, A; Casarotto et al., 2022; Opitz et al., 2011). Second, nTMS–EEG is key in keeping the selected stimulation parameters constant within and across sessions in the case of longitudinal studies (Fig. 3; Casarotto et al., 2010; Lioumis et al., 2009). Notably, some neuronavigation systems may also consider the individual's head shape, coil position, and scalp-to-cortex distance, and tissues conductivity boundaries in real-time in order to estimate the electric field induced by TMS on the cortical surface (Fig. 1, C). In this case, TMS intensity can be adjusted according to the maximum electric field intensity estimated on the cortical surface, rather than relying on the individual motor threshold, or on the percentage of maximum stimulator output.

With most neuronavigation systems, the coordinates of the TMS coil are usually input to a virtual aiming device of the navigation software and can be used during the experiment to ensure stability of the position, angle, direction, and intensity of the stimulation. By using nTMS–EEG, Lioumis and colleagues (Fig. 3, A; Lioumis et al., 2009) showed the key role of neuronavigation for test-retest design studies that allow monitoring therapeutic effects (Ferrarelli and Phillips, 2021; Hui et al., 2019). In that study, not only it was demonstrated the reproducibility of TEP in two crucial targets for the treatment of neurological and psychiatric patients (M1 and DLPFC, respectively), but also that neuronavigation allows the placement of TMS coil perpendicular to the nearby located sulci, which results in delivering maximum E-field to the targeted cortical site (Ilmoniemi et al., 1999). That was shown by targeting the DLPFC, where this kind of placement resulted in maximum E-field induction and shorter and smaller artifacts than usually evoked in DLPFC (Lioumis et al., 2009). Almost at the same time, Casarotto and colleagues (Fig. 3, B; Casarotto et al., 2010) extended those results even further by showing that TEPs are sensitive to changes in the stimulation parameters and repeatable over time. In 2010, also Farzan and colleagues (Farzan et al., 2010), again with the utilization of neuronavigation,

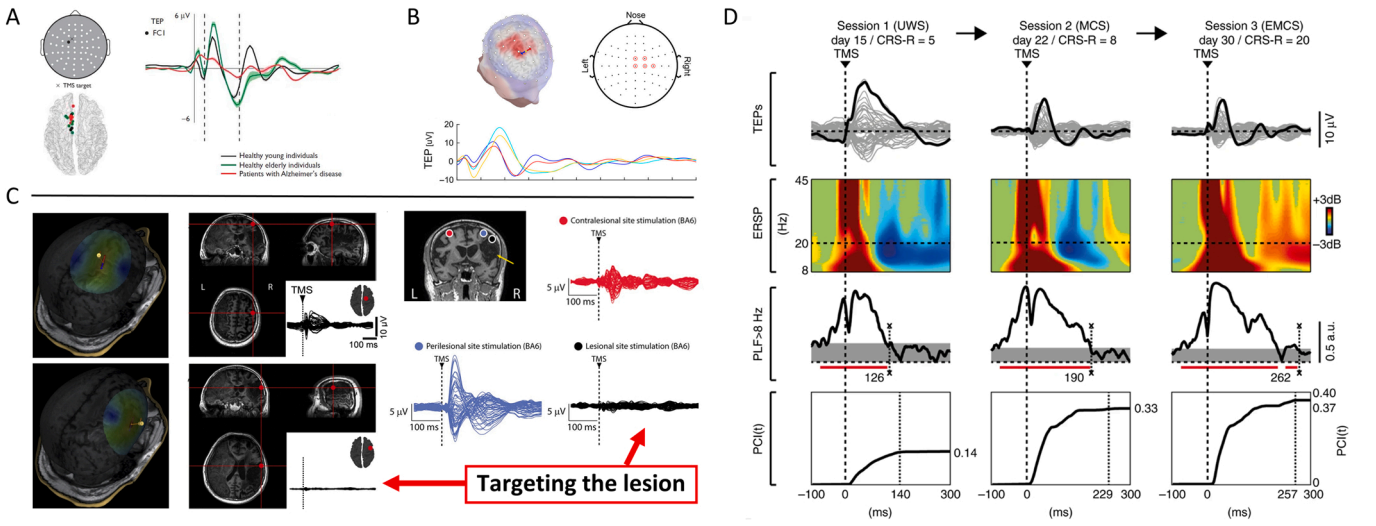

Fig. 4. Panel A: Cortical targets for three different populations, healthy young subjects, healthy elderly subjects, and patients with Alzheimer Disease (AD). Note that in the three populations the cortical targets are within the same cortical gyrus (left superior frontal gyrus) making the results comparable across the three populations, being the intensity of stimulation the same as estimated by the neuronavigation system (reproduced from (Casarotto et al., 2011)). Panel B: Cortical targets in a population of patients affected by Parkinson's Disease in which TEPs were recorded before and after L-Dopa administration. In this case, the neuronavigation system ensures that TEPs are comparable across patients and over time (reproduced from (Turco et al., 2018)). Panel C left: Two TEPs recorded in a severely VS/UWS brain-injured patient. Note that translating the TMS coil a couple of centimeters apart results in the absence of TEP due to the stimulation of a structural cortical lesion according to the information provided by the neuronavigation system (reproduced from (Gosseries et al., 2015)). Panel C right: Also targeting a lesion in a stroke patient results in the absence of TEP. Note that the stimulation of the perilesional area results in a TEP characterized by a sleep-like slow wave, whereas stimulating the homologous contralateral cortical area results in a TEP similar to the ones recorded in healthy controls (reproduced from (Sarasso et al., 2020)). Panel D: TEPs and derived measures collected longitudinally in a severely brain-injured patient during the clinical evolution. TMS-EEG measurements in this case can be compared because, thanks to the neuronavigation system, the same stimulation parameters were applied in the three time points (reproduced from (Rosanova et al., 2018)). TEP: TMS-evoked potential; FC1: EEG lead label; CRS-R: Coma Recovery Scale-revised; UWS: Unresponsive Wakefulness Syndrome; MCS: Minimally Conscious State; EMCS: Emergence from Minimally Conscious State; PCI: Perturbational Complexity System.

demonstrated the reproducibility and reliability of cortical inhibition indexes through the measures of long intracortical inhibition (LICI), which currently is tested as a potential biomarker for the treatment of suicidal ideation for major depressive disorder (MDD) patients (Daskalakis et al., 2008; Lioumis et al., 2018; Sun et al., 2016). Lately, one more reproducibility study was published and further stressed the notion about the importance of neuronavigation in recording reliable TEPs over time (Kerwin et al., 2018).

Importantly, nTMS–EEG allows targeting the same cortical area in different brain states. For instance, a neuronavigation system allowed to reliably keep track of changes of cortical excitability and TEPs waveforms between wakefulness and sleep (Massimini et al., 2007, 2005), between wakefulness and deep sedation or general anesthesia (Ferrarelli et al., 2010; Sarasso et al., 2015) and before and after neuromodulatory interventions (Esser et al., 2006; Pellicciari et al., 2013; Pisoni et al., 2018; Romero Lauro et al., 2014). In the same vein, the employment of a neuronavigation system allowed to study the oscillatory properties of the same cortical areas in different subjects (Fecchio et al., 2017; Ferrarelli et al., 2012; Rosanova et al., 2009).

Finally, the employment of a neuronavigation system is crucial for an accurate reconstruction of the cortical generators of TEPs. Indeed, the optical tracking system and the workstation of the neuronavigation system can be used respectively to digitize and store the coordinates of EEG electrodes with respect to the subject's scalp. For the latest overview of the full spectrum of TMS–EEG studies performed with or without neuronavigation see the recent review paper by Tremblay and other experts in the TMS, EEG field (Tremblay et al. (2019).

3. nTMS-EEG in brain disorders

3.1. Neurology

In recent years, nTMS–EEG has been largely employed as a research tool to study disorders of the central nervous system such as Alzheimer Disease (AD), Parkinson Disease (PD), epilepsy, Disorders of Consciousness (DOC) after severe brain injuries, and cerebral stroke.

Up to our knowledge, the first nTMS–EEG study in the neurology field was conducted by Julkunen and colleagues (2008) to measure cortical excitability in patients with Mild Cognitive Impairment (MCI), patients diagnosed with AD, and healthy controls (Julkunen et al., 2008). The authors observed a significant reduction of cortical excitability in AD patients compared to MCI patients and healthy controls. The neuronavigation system was used to localize the "hand knob" of the M1 cortex bilaterally and to optimally orient the coil relative to the target gyrus. Interestingly, although the actual intensity of TMS was set based on the rMT, the authors performed an offline statistical analysis of the TMS-induced electric field values for each cortical target, as estimated by the neuronavigation system. This analysis returned significantly lower values of TMS-induced electric fields in AD patients compared to MCI patients and healthy subjects suggesting that the cortex of AD patients was stimulated systematically at lower intensities and that this discrepancy could have contributed to the reported differences in cortical excitability (2008). Most importantly, this possible bias further highlights the need of neuronavigation to equalize the stimulation intensity and compensate for individual and systematic structural differences across different clinical populations, especially if areas other than the M1 are studied. In fact, in another study that measured cortical excitability in AD patients, young and elderly healthy controls using nTMS-EEG by targeting a premotor cortical area (Casarotto et al., 2011). To this aim, the neuronavigation system was employed to both targeting the left superior frontal gyrus in all study participants (Brodmann's areas BA6/8; Fig. 4, A) and to set the stimulation intensity at a TMS-induced electric field of 110 V/m, as estimated by the neuronavigation system, rather than at pre-set percentage of the individual rMT. The authors observed a significant reduction of cortical excitability in AD patients compared to healthy young and elderly control subjects,

thus confirming the findings of the previous study.

In the nTMS–EEG study by Casarotto and colleagues in AD patients (Casarotto et al., 2011), the use of the neuronavigation system was crucial to ensure reproducibility of stimulation parameters across study participants. Neuronavigation is equally important to keep constant the parameters of stimulation in the same subject/patient across different experimental conditions or over time. For instance, two studies have used nTMS-EEG to measure changes in cortical excitability before (meds-on) and after (meds-off) acute administration of levodopa in PD patients (Casarotto et al., 2019; Turco et al., 2018;Fig. 4, A and B). Both studies reported that levodopa intake results in a significant modulation of TEPs recorded after the stimulation of the supplementary motor area, with a larger effect on the hemisphere more affected by degeneration of basal ganglia due to PD. Casarotto and colleagues (Casarotto et al., 2019) also showed a circuit-specific effect as the levodopa induced excitability changes were restricted to the supplementary motor area, whereas when nTMS was targeted to the posterior parietal cortex, no significant effects were observed.

Besides neurodegenerative disorders, such as AD and PD, nTMS–EEG has been extensively used in DOC patients to better define the neural correlates of consciousness and to understand the mechanisms of loss and recovery of consciousness after severe brain injury. In a very early study, Rosanova and colleagues (Rosanova et al., 2012) performed nTMS–EEG measurements to identify the neural correlates of consciousness by evaluating cortical excitability and effective connectivity in 17 unresponsive patients either in Unresponsive Wakefulness Syndrome/Vegetative State (UWS/VS), Minimally Conscious State (MCS) and Locked-In Syndrome (LIS; Rosanova et al., 2012). They showed that in UWS patients, TEPs were characterized by a simple, positive-negative wave reflecting a breakdown of effective connectivity and resembling the one observed in unconscious healthy individuals during non-Rapid Eye Movement (NREM) sleep (Massimini et al., 2005), deep sedation (Ferrarelli et al., 2010), or anesthesia (Sarasso et al., 2015). On the contrary, MCS patients showed complex TEP activations involving cortical areas far from the stimulated one. Relevant to the present review are the longitudinal nTMS–EEG measurements performed in some of the acute DOC patients who spontaneously evolved from UWS/VS towards MCS and then emerged from MCS, thus recovering functional communication. This follow-up, which showed specific changes in cortical effective connectivity that preceded behavioral changes, necessarily relied on the employment of neuronavigation to keep the parameters of stimulation constant across measurement sessions occurring at different times (Fig. 4, D)(Rosanova et al., 2018). This study also pointed to the importance of neuronavigation in avoiding cortical lesions. Indeed, when TMS was delivered over cortical lesions, stimulation of the EEG response was absent. These results further highlight the importance of employing a neuronavigation system to target structurally intact cortical regions in brain-injured patients in order to obtain dependable results (Gosseries et al., 2015; Rosanova et al., 2012; Fig. 4, C). Importantly, the employment of neuronavigation also ensures the highest performance of a measure that captures the complexity of the cortical response to TMS, called Perturbational Complexity Index (PCI). PCI has been recently tested in discriminating between conscious and unconscious conditions (Casali et al., 2013; Casarotto et al., 2016; Sinitsyn et al., 2020; Rosanova et al., 2018). Specifically, TEPs were recorded, and PCI was computed in a benchmark population of 150 subjects composed of (i) healthy awake participants who were either able to report the presence of consciousness (wakefulness, REM sleep, and ketamine anesthesia) or unconscious (NREM sleep, anesthesia with Midazolam, Xenon and Propofol) and (ii) conscious patients with brain-injuries (stroke, LIS and emergence from MCS). A threshold for PCI values was then empirically estimated from this benchmark population and resulted in a sensitivity of 94.7% in detecting MCS patients. When PCI was computed in UWS patients, which is a homogeneous population in clinical terms, revealed a further categorization into three different subpopulations: a subpopulation of no-response patients (PCI=0; about 30%), a subpopulation of low-complexity patients (PCI<cut-off; about 50%) and a subpopulation of high complexity patients (PCI>cut-off; about 20%). In the future, this PCI-based categorization could help select different types of treatments for different patient groups, i.e., rehabilitation programs for high complexity patients or neuromodulation for low-complexity patients. In the present context, it is worth noting that when TMS is targeted over a cortical lesion, the EEG response to TMS is absent and results in PCI= 0 in an otherwise reactive cortex (Gosseries et al., 2020; Sarasso et al., 2020); Fig. 4, C). Thus, the use of neuronavigation is highly recommended in brain-injured patients in order to perform reliable mappings of the structurally preserved portions of the cortical mantle.

The employment of neuronavigation is particularly relevant also when TMS-EEG is used to study stroke patients with focal cortical lesions (Sarasso et al., 2020). As mentioned above, targeting the TMS over a cortical lesion, results in the absence of any significant EEG response to the stimulation, i.e., in the absence of any significant TEP components. On the contrary, when TMS is targeted on structurally preserved perilesional cortical areas a sleep-like, a positive-negative sleep-like EEG response to TMS is evoked (Fig. 4 C). Interestingly, the stimulation of a cortical area contralateral to the perilesional one results in a EEG response to TMS comparable to the ones recorded in healthy awake subjects (Fig. 4 C). Clearly, these results would have been more difficult to interpret in the absence of a neuronavigation system, which has provided the essential information to understand the spatial relationships between the maximum TMS-induced electric field over the cortex and the cortical area affected by the lesion.

3.2. *Psychiatry*

Psychiatric disorders diagnosis is based mostly on patients' subjective reports (van Os and Kapur, 2009). Objective biological markers are needed and very promising neurophysiological biomarkers can be derived from the EEG responses to TMS (Hui et al., 2019; Kallioniemi and Daskalakis, 2022; Sun et al., 2018, 2016). This is due to the great efficacy of TMS-EEG to probe local and global altered excitation-inhibition balance (Tremblay et al., 2019), which has shown to be altered in many mental disorders (Sohal and Rubenstein, 2019). Here, we will discuss the power of nTMS-EEG and its use in mood disorders and schizophrenia based on previously published reviews (Cao et al., 2021; Ferrarelli and Phillips, 2021; Kallioniemi and Daskalakis, 2022; Tremblay et al., 2019). We will mostly discuss some of the studies that utilized neuronavigation and made an impact in the field of biomarkers.

MDD and bipolar disorder (BD) are the most common psychiatric disorders. MDD, which is the leading cause of disability in the world (Friedrich, 2017), together with BD share similar neurophysiological features involving modulation of DLPFC activity (Arnsten and Rubia, 2012), as it has been shown in studies of TMS-induced modulation of cortical inhibition (Daskalakis et al., 2008; Kallioniemi and Daskalakis, 2022; Sun et al., 2016). Treating MDD and in general mood disorders is a great challenge. MDD is typically treated with antidepressant medication and cognitive-behavioral therapy. However, almost one-third of the patients are diagnosed as having medication-resistant depression (Souery et al., 2006), which leads to the prioritization of understanding the neurophysiological mechanisms of the mood disorder network, developing new strategies for therapeutic intervention targets in terms of rTMS and tracking or predicting treatment outcomes by means of nTMS-EEG.

Recently, a review paper listed all the studies that so far are utilizing indices based on TMS-EEG measurements as a biomarkers (Cao et al., 2021). Neuronavigation has been used to enhance the diagnostic, monitoring and predictive efficiency of the biomarkers in 10 out of 13 studies. For the non-navigated ones (due to time and technical limitations), one was predictive and two were monitoring. However, all these three (Noda et al., 2018; Sun et al., 2018, 2016) employed the Beam F3 method (Beam et al., 2009), which is a reverse co-registration from

specific stereotaxic coordinate on the standard MNI template brain (Fox et al., 2013).

To our knowledge, the first nTMS-EEG study in mood disorders was performed to measure cortical excitability in a small group of patients with MDD (Casarotto et al., 2013). The authors observed a significant increase of frontal cortical excitability after electroconvulsive therapy (ECT) as compared to baseline and suggested that nTMS–EEG can be applied for longitudinal monitoring of neuromodulation due to different therapeutic interventions. Neuronavigation allowed these authors to precisely stimulate the cortical target as selected on individual MR images, to estimate the intensity they needed to use in terms of the TMS-induced electric field on the cortical surface, and to repeat the same stimulation parameters between sessions. In an MDD clinical trial (Voineskos et al., 2019), the authors observed abnormalities in TEP deflections linked to inhibitory mechanisms (N-45 and N-100) suggesting an excitation/inhibition imbalance. Neuronavigation was utilized to choose the optimal DLPFC target for each individual based on their MRIs and Talairach coordinates. Furthermore, Hadas and colleagues (Hadas et al., 2019), demonstrated the hyperactive-hypoactive relationship between subgenual cingulate cortex and DLPFC in MDD patients, by employing effective connectivity indexes (Casali et al., 2013). Neuronavigation was not only used for locating the DLPFC accurately in each patient as performed in Voineskos et al. (2019), but also for source localization and effective connectivity purposes. In a recent study in young MDD patients (Dhami et al., 2021), N45 was associated with changes of depression symptoms due to TMS intervention. The authors claim that neuronavigation provided greater precision in targeting cortical regions of interest, as well as easing the test-retest design of the study. nTMS–EEG here showed once again its great potential as a predictor for treatment response.

In BD, Canali and colleagues investigated different neurophysiological markers during antidepressant treatment, such as sleep deprivation combined with light therapy (Canali et al., 2017, 2014). They observed lower amplitudes of the first evoked component (first TEP deflection) at the baseline in non-responders to the therapy, that did not reach after treatment the baseline levels of responders (Canali et al., 2014). They also showed that the main background frequencies in the premotor cortex were significantly lower to healthy volunteers, and they never changed after therapy (Canali et al., 2017). In both studies, neuronavigation was used in order to target the premotor cortex and to adjust the intensity in terms of V/m so that a reliable brain response is obtained, as it has been suggested in Belardinelli et al. (2019) and further explained in Casarotto et al., (2022).

In schizophrenia, antipsychotic drugs can reduce positive symptoms (i.e. hallucinations), but do not affect the so-called negative symptoms such as anhedonia and cognitive impairments (Hyman and Fenton, 2003). Thus, electrophysiological studies for discovering targets and developing new therapeutic interventions to deal with this wide range of symptoms are urgently needed. For this purpose, TMS-EEG studies in schizophrenia have focused on the excitation/inhibition balance, and their correlation mainly with cognitive deficits (Yizhar et al., 2011). Neuronavigation has been used so far in 11 out of 13 reported studies, while all the studies had a diagnostic purpose (Cao et al., 2021).

Ferrarelli and colleagues (Ferrarelli et al., 2019, 2015, 2008; Ferrarelli et al., 2012)) have extensively studied schizophrenic patients with nTMS–EEG. In their first study, they demonstrated decreased power TEPs oscillations in the gamma band after stimulating the prefrontal cortex (Ferrarelli et al., 2008). In their following studies (Ferrarelli et al., 2015; Ferrarelli et al., 2012)), they observed reduced values in cortical excitability and connectivity indexes in schizophrenic patients only in prefrontal areas and not in parietal areas and M1. In their last study, significantly reduced oscillatory activity at the beta/low gamma band in frontal motor areas was observed in schizophrenic patients at their first episode (Ferrarelli et al., 2019). Reduced gamma oscillatory activity was also demonstrated by (Farzan et al., 2010) in DLPFC. Neuronavigation ensured that a DLPFC site was stimulated where functional neurophysiological abnormalities have been demonstrated.

In all these works, nTMS-EEG was used to map the frontal and parietal lobes and, most importantly, to ensure a consistent selection and targeting of cortical areas within experimental sessions and across patients and clinical populations.

4. Open issues and outlook

4.1. Towards local threshold and hotspot based on the TMS–EEG responses

The use of neuronavigation in TMS–EEG studies has opened the way for reproducible and reliable positioning and repositioning of the coil (Casarotto et al., 2010; Kerwin et al., 2018; Lioumis et al., 2009). Recently it has been shown that TMS–EEG spatial resolution can be as high as 10 mm (Passera et al., 2022). Thus, cortical responses are very sensitive to slight changes of stimulation parameters (Casarotto et al., 2022; Casarotto et al., 2010; Tervo et al., 2022), and this fact has highlighted the unique potential of TMS–EEG as a mapping tool (Ferrarelli et al., 2012; Rosanova et al., 2009; Sarasso et al., 2020). Conde and colleagues emphasized how not carefully adjusting the stimulation intensity may result in multi-sensory stimulation and not in an effective stimulation of the cortical area under the coil (Conde et al., 2019). This conclusion leads to the necessity of neuronavigation and real-time EEG visualization tools for TMS–EEG mapping prior to the real recording sessions. Such a procedure can result in defining optimal targets, specific dosing for different cortical targets (Belardinelli et al., 2019; Casarotto et al., 2022) and a quality check before the actual recording.

Neuronavigation combined with a real-time EEG visualization tool will allow the TMS–EEG user to map the whole cortical area under investigation and find the most reactive cortical site by means of TEPs, in a similar manner as the M1 hotspot is defined by the MEPs. At the same time, the mapping by nTMS–EEG will result in areas without or with minimum possible contamination from muscle artifacts that usually mask the early responses, which are considered markers of cortical reactivity (Casarotto et al., 2016; Casarotto et al., 2022); this is a very important EEG-based information to determine the cortical target and the stimulation parameters. In this way, a local cortical nTMS–EEG--based hotspot can be identified. Then, the responses can be modulated by different intensities and the optimal stimulation parameters can be selected. By optimal stimulation parameters, we mean here those that: a) guarantees the early deflections (N15-P30 or earlier than 50 ms) to be over a threshold that the investigator may set (e.g., 6–10 μV) with a good signal-to-noise ratio, b) evokes higher early responses than later ones that may include multisensory responses and c) does not evoke muscle and decay artifacts, e) evokes clean cortical ipsilateral responses larger than the analogous contralateral ones. However, there are cases in which avoiding is challenging artifacts, and the underlying cortical site may be the ideal one for therapeutic interventions. Still, nTMS–EEG can be applied by using real-time TEPs visualization tools (Casarotto et al., 2022), real-time tools for artifact rejection (Makkonen et al., 2021) and automatic algorithms (Tervo et al., 2022).

Adjusting the coil position, orientation and intensity for each individual based on nTMS–EEG prior to any measurement may enhance the power of this tool in defining optimal targets for therapeutic interventions and biomarkers, due to the fact that the recorded TEPs may include cleaner, stronger and thus more specific and reliable brain signal. A limitation though of the described procedure is that it may require neurophysiology experts as users, which is logistically demanding especially in big clinical trials; therefore, future efforts may need to focus on real-time EEG read-out and analysis of responses (Casarotto et al., 2022; Tervo et al., 2022) fed in a closed-loop manner into the multi-locus technology driven by E-field guided neuronavigation (Nieminen et al., 2021). This kind of automatic approach may be proved to reduce the user-dependent induced variability in

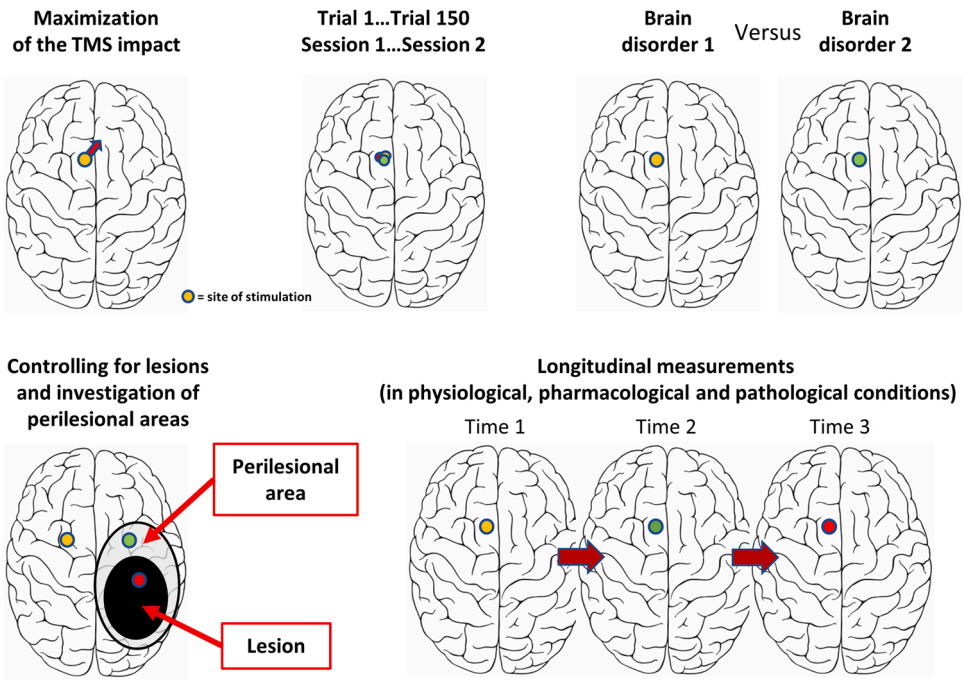

Fig. 5. Schematic representations of the key roles the neuronavigation plays for TMS-EEG measurements. Colored filled circles indicate the stimulated cortical sites. Different colors for the filled circles indicate different stimulation trials or sessions. The red arrow indicates the direction of the TMS-induced electric field.

TMS-EEG studies.

4.2. Stimulation based on off-line and real-time tractography

Very often, TMS–EEG has to be performed over anatomically defined areas. Nevertheless, neuronavigation still allows the optimization of stimulation parameters even in such conditions. This procedure can lead to the collection of good quality data, even thought mapping and data quality check prior to recording were not performed (Harquel et al., 2016; Raffin et al., 2020). Moreover, neuronavigation also allows the fusion of information from other modalities like tractography, which highlights the structural connectivity between neighboring or distant cortical areas, or the MEG/fMRI that can provide functional connectivity information.

Very importantly, maximum TMS-induced electric field on the cortex can be used as a seed in diffusion MRI-based tractography, and then TMS–EEG can be performed over nodes of the highlighted network or stimulate the cortical projections of the fibers that connect different nodes of the same network as it is done for presurgical motor cortical mapping (Sollmann et al., 2021). Structural connectivity guided mapping can be crucial in characterizing from the neurophysiological viewpoint different brain networks. Such a need becomes even more profound while technology allows the performance of real-time tractography (Aydogan and Shi, 2021). When nTMS–EEG will be equipped with these tools it could in real-time follow the white matter connections between two cortical nodes and allow potentially identifying neurophysiological signatures of structural connectivity.

4.3. Automatization with mTMS

New multi-locus technology, with coils that electronically rotate the orientation of the TMS-induced electric field (rotational coils; Nieminen et al., 2019; Souza et al., 2022), have already demonstrated how TMS can be performed automatically, tackling also the variability induced by individual users. Casarotto and colleagues and Tervo and colleagues have recently demonstrated how optimal coil orientation can be achieved in areas outside M1 manually and automatically respectively (Casarotto et al., 2022; Tervo et al., 2022). 5-channel mTMS technology (Nieminen et al., 2021) already allows electronic shift of the locus both in location and in orientation, therefore more complete reliable automatic high-resolution TMS–EEG mapping will be available in the following years in addition to or in combination with the current robotically guided neuronavigated systems (Giuffre et al., 2021; Harquel et al., 2016; Passera et al., 2022; Raffin et al., 2020).

Previously, robotized TMS–EEG has demonstrated that it can effectively map the electrophysiological properties of different cortical regions (Harquel et al., 2016), by using neurophysiological responses to local perturbations. Recently, the same group demonstrated new EEG markers to identify regions with different cytoarchitectonics (Raffin et al., 2020). These recent advances in probing cortical excitability can be provided with real-time TEPs visualization tools and streamed out for closed-loop EEG-triggered TMS automated purposes.

Automatic mapping of whole areas (Raffin et al., 2020) can serve for optimizing targets both for biomarker purposes and rTMS targets for therapeutic interventions. New technology of real-time artifact-rejection (Makkonen et al., 2021) combined with real-time visualization tools (Casarotto et al., 2022) optimization algorithms (Tervo et al., 2022, 2020) may result in automatic solutions for research and clinical applications. However, clinical trials will decide, whether defining the target based on EEG, or anatomically, or on a combination of neurophysiological and neuroimaging features, is more efficient.

5. Conclusive remarks

TMS-EEG is a valuable technique to study non-invasively the human brain in health and pathological conditions (Tremblay et al., 2019). However, the lack of standard methods and procedures still prevent its translation from bench to bedside (Julkunen et al., 2022) and hence into an reliable clinical tool. Towards this aim, the systematic application of a neuronavigation system is a crucial step. Indeed, nTMS–EEG is key for targeting, titrating stimulation parameters, optimizing stimulation impact and increasing repeatability within and across sessions, healthy subjects, and patients affected by brain disorders. Thus, together with tools allowing the visualization of TEPs in real-time, neuronavigation

contributes to collect reliable and reproducible TMS-EEG data. This aspect is fundamental in designing and conducting studies on healthy and clinical populations.

The experimental conditions in which neuronavigation plays a key role in TMS-EEG can be summarized as follows (Fig. 5):

a) Together with a visualization tool for real-time quality-check of TEPs, neuronavigation allows:

i) searching for an optimal target that maximizes the impact of the TMS on the cortex and minimizes the artifacts and confounders.

ii) further standardizing the experimental condition across subjects.

iii) titrating and assessing the stimulation intensity based on anatomical a-priori, such as cortical geometry and scalp-to-cortex distance, rather than rMT, no matter which is the stimulated area.

b) Neuronavigation allows monitoring the coil positioning throughout a single session and across sessions, thus reducing the variability of the TMS-EEG responses due to the coil holding and stimulation parameters. This is important for evaluating the neurophysiological effects of pharmacological treatments and non-pharmacological interventions in clinical trials.

c) Neuronavigation helps standardize TMS-EEG stimulation parameters across populations. This is crucial to make reliable comparisons between healthy controls and patients or patients affected by different brain disorders.

d) Neuronavigation is highly recommended when TMS–EEG measurements are performed in brain-injured patients to both avoid brain lesions and to study the cortical reactivity in the perilesional areas.

e) Neuronavigation is mandatory in longitudinal studies based on repeated TMS–EEG measurements, and changes of cortical excitability need to be monitored in different physiological states, before, during and after pharmacological interventions, and in pathological conditions.

Declaration of Competing Interest

Pantelis Lioumis has been a consultant for Nexstim Plc., for motor and speech mapping purposes and also for TMS-EEG hands-on.

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