

Assessing cortical excitability with electroencephalography: A pilot study with EEG-iTBS

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ABSTRACT

Background: Cortical excitability measures neural reactivity to stimuli, usually delivered via Transcranial Magnetic Stimulation (TMS). Excitation/inhibition balance (E/I) is the ongoing equilibrium between excitatory and inhibitory activity of neural circuits. According to some studies, E/I could be estimated in-vivo and non-invasively through the modeling of electroencephalography (EEG) signals and termed 'intrinsic excitability' measures. Several measures have been proposed (phase consistency in the gamma band, sample entropy, exponent of the power spectral density 1/f curve, E/I index extracted from detrend fluctuation analysis, and alpha power). Intermittent theta burst stimulation (iTBS) of the primary motor cortex (M1) is a non-invasive neuromodulation technique allowing controlled and focal enhancement of TMS cortical excitability and E/I of the stimulated hemisphere.

Objective: Investigating to what extent E/I estimates scale with TMS excitability and how they relate to each other.

Methods: M1 excitability (TMS) and several E/I estimates extracted from resting state EEG recordings were assessed before and after iTBS in a cohort of healthy subjects.

Results: Enhancement of TMS M1 excitability, as measured through motor-evoked potentials (MEPs), and phase consistency of the cortex in high gamma band correlated with each other. Other measures of E/I showed some expected results, but no correlation with TMS excitability measures or strong consistency with each other.

Conclusions: EEG E/I estimates offer an intriguing opportunity to map cortical excitability non-invasively, with high spatio-temporal resolution and with a stimulus independent approach. While different EEG E/I estimates may reflect the activity of diverse excitatory-inhibitory circuits, spatial phase synchrony in the gamma band is the measure that best captures excitability changes in the primary motor cortex.

1. Introduction

Cortical excitability is the predisposition of neuronal populations to

generate activity in response to various stimuli [1,2]. Cortical excitability is fine tuned across spatial and temporal dimensions, allows proper information integration and is impaired in nearly all

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neuropsychiatric conditions [3–8]. In the context of human studies, conventional assessment of excitability involves the application of Transcranial Magnetic Stimulation (TMS) and the measurement of elicited behavioural responses. TMS pulses interact with neurons spanning all cortical layers, yielding a response shaped by both excitatory and inhibitory neuronal inputs [9]. While TMS has established itself as a potent tool for the study of cortical excitability, it does come with inherent limitations. Firstly, TMS studies primarily focus on eloquent cortices (such as the primary motor cortex or primary visual cortex), where there are relatively easily measurable responses, i.e. muscular contractions or phosphenes. Secondly, when exploring non-eloquent cortices, concurrent neuroimaging measurements are necessary to measure the response to stimuli. Simultaneous TMS-Electroencephalography (TMS-EEG) [10,11], TMS-functional magnetic resonance imaging (TMS-fMRI) [12,13] and TMS-functional near-infrared spectroscopy (TMS-fNIRS) [14] are among the most common options [15], but the data acquisition process is long and difficult. Neuroimaging signals are affected by artifacts, and there is uncertainty on the extent to which neuroimaging metrics align with the classical definition of cortical excitability [14,16]. Thirdly, whether alone or in combination with neuroimaging, TMS pulses can only be administered at one specific site at a time, leading to a scattered spatial and temporal sampling. Fourthly, TMS pulses recruit a mixture of excitatory and inhibitory neurons in the human cortex [9,17], and multiple TMS protocols are needed to assess specific components of cerebral circuits (i.e. paired-pulse TMS, short-afferent inhibition, silent period, etc.).

In parallel with the development of concurrent TMS-neuroimaging approaches, there has been a remarkable development in the modeling and assessment of the equilibrium between excitatory and inhibitory activity of neural circuits, also known as Excitation/Inhibition balance (E/I). Since E/I proxies are not dependent on external stimulation, they have been termed ‘intrinsic excitability’ measures. The E/I is linked to the ongoing fluctuations of synaptic input ‘at rest’ and regulate the generation of field potentials [18].

Currently, modeling of electromagnetic (EEG or MEG) and hemodynamic (fMRI or fNIRS) brain signals are considered reliable approaches for the estimation of E/I [14,19–22]. For example, in the field of EEG and magnetoencephalography (MEG), E/I may be estimated using EEG phase synchronization [23–25], aperiodic component of the power spectrum [18,26], and entropy [27,28]; in the field of fMRI/fNIRS, E/I can be estimated from the amplitude, regularity, predictability and regional homogeneity of the hemodynamic activity [14,20,21,29].

Interestingly, the E/I is one of the strongest determinants of intrinsic cortical excitability (higher E/I relates to higher intrinsic excitability), and it can be measured independently from external stimuli [9,19], at high spatial and temporal resolution, and with better applicability and translational potential than TMS excitability alone [19,30–38].

Nevertheless, it remains to be understood if a relationship exists between E/I estimates (intrinsic excitability) and cortical excitability as measured from responses to TMS and to what extent different E/I estimates are related to each other.

Here we addressed this topic by performing EEG E/I estimates and TMS excitability measures before and after intermittent theta burst stimulation (iTBS) of the primary motor cortex. iTBS is a non-invasive neuromodulatory technique allowing controlled and focal enhancement of TMS cortical excitability and E/I of the target hemisphere [39–42].

We specifically focused on whether: 1) changes in excitability due to iTBS are linked to changes in E/I estimated with EEG, and 2) whether E/I estimates exhibit an expected modulation as reflected in behavioural outcomes (MEPs).

2. Material and methods

We enrolled 11 right-handed healthy adults at Campus Bio-Medico

University of Rome. Exclusion criteria were: present/past neuropsychiatric conditions, and medications acting on the central nervous system. All subjects underwent a resting state EEG and primary motor cortex TMS sessions to assess E/I and TMS excitability before and after iTBS of the left primary motor cortex (Fig. 1). All participants were asked to abstain from caffeine and alcohol in the two days before the study. This study was approved by the Ethics board of Campus Bio-Medico University of Rome and complied with the Declaration of Helsinki. All participants signed a written informed consent prior to participation. We additionally enrolled 7 participants that fulfilled the same inclusion criteria and underwent sham stimulation.

2.1. EEG recordings

EEG recordings were performed with a BrainAmp 32MRplus amplifier (BrainProducts GmbH, Germany) and 32 electrodes arranged on an elastic cap (<https://www.easycap.de>), with a sampling rate of 5 kHz. The reference was binaural, the ground was placed at the right arm, and electrode impedance was kept below 10 k Ω . EEG data was recorded for 5 min in a shielded room, with the subject comfortably lying down and with the eyes open.

2.2. Motor cortex excitability to TMS

Left primary motor cortex TMS excitability was measured by applying 15 single pulses of TMS and recording Motor Evoked Potentials from the right musculus opponens pollicis. TMS was performed with a Rapid Magstim Stimulator (Magstim Company, Dyfed, UK) and 70 mm eight-shaped coil. MEPs were recorded with surface electrodes positioned according to the standard tendon-belly montage, and connected to the bipolar headset of the BrainAmp 32MRplus amplifier. The Rapid Magstim delivers biphasic stimuli. The hotspot was searched with the TMS coil held approximately over the precentral region, with a 45° direction to the midline [43]. The resting motor threshold was defined as the stimulation intensity able to evoke MEPs in the target muscle >50 microV in 5 out of 10 stimuli [44]. The TMS intensity for single pulse TMS was set to 120 % of the Resting Motor Threshold.

iTBS was delivered over the left primary motor cortex with standard parameters [39,40]. The intensity was set to 80 % of the active motor threshold [45]. In details, iTBS consisted of short bursts of three TMS pulses delivered at 50Hz, repeated at 5Hz. A sequence of 10 bursts lasted 2 s and was repeated every 10 s (8 s break) for a total of 600 pulses and 190 s.

2.4. EEG data analysis

EEG data analysis was performed with the EEGLab toolbox [46], the Brainstorm toolbox [47] and custom code in Matlab (The Mathworks, Version 2022b).

For the preprocessing, we first applied a bandpass filter (1Hz–256Hz), a notch filter, and resampling to 1024Hz. Data were then visually inspected to remove segments affected by artifacts. Channels with excessive noise were interpolated using the spline method. Thereafter, we applied the `clean_rawdata` (https://github.com/scen/clean_rawdata) toolbox to remove sudden and brief artifacts and ICA (`runica`) to separate biological and artifactual EEG components. Artifactual IC component were automatically identified and rejected with the `ICLabel` toolbox [48], using default parameters. `ICLabel` was performed for pre- and post iTBS limited to eye and cardiac artifacts, keeping the same thresholds. The EEG cap was mounted and kept in place from the beginning to the end of the recording, to facilitate and make ICA cleaning more consistent over time. The cleaned EEG was then imported into Brainstorm. We considered a standard MRI template (ICBM 512) [49] and standard EEG positions. Sensor data were reconstructed onto the cortical surface with the minimum norm estimate [50]. We chose a simple head model with multiple spheres [32]. The noise

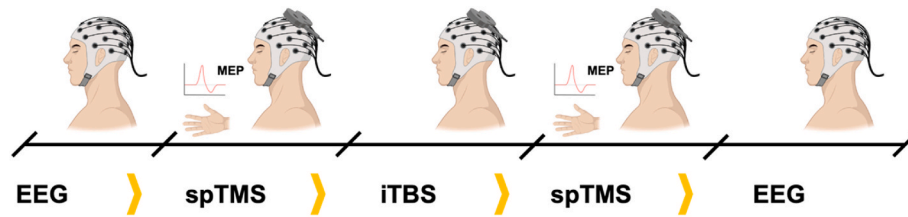


Fig. 1. Experimental design: EEG (5 min) and spTMS (15 pulses) were acquired before and after iTBS of the left motor cortex. E/I was estimated from EEG, applying several measures, whereas TMS excitability was measured as difference of MEP amplitude before and after iTBS. spTMS: single-pulse TMS, iTBS: intermittent theta burst stimulation. E/I: excitability/inhibition balance.

covariance matrix was computed based on the entire EEG signal. Estimates of E/I were computed in source space considering the Desikan-Killiany atlas [25,36,51,52].

2.5. E/I estimates

We focused on the following E/I estimates: a) Exc_ind; b) exponent of the aperiodic component of the Power Spectrum; c) Sample Entropy; d) Detrended Fluctuation Analysis based E/I index; e) alpha power.

- a) ‘Exc_ind’. This index was introduced and validated by Meisel et al. (2015). It corresponds to the mean spatial phase synchronization and, especially in high-gamma frequency bands, correlates well with cortical excitability as estimated via perturbational approaches and modulated via antiepileptic medications in epilepsy patients [23,24]. This E/I estimate roughly corresponds to the well-known phase locking value (PLV), broadly exploited in neuroscience and neurology [52–56], computed across space rather than time. We selected the high gamma band (55–95Hz), as recommended in previous studies [25];
- b) Exponent of the aperiodic component of the Power Spectrum. This estimate has been introduced recently by Voytek and collaborators [18,26]. In 2017 Gao et al. provided an elegant demonstration that E/I changes can be estimated from the power law exponent (slope) of the electrophysiological power spectrum [18]. Later on, the same group confirmed this concept with non-invasive and invasive recordings and developed a method to disentangle the periodic vs aperiodic component of the power spectrum and to estimate the exponent of the aperiodic component (FOOOF - fitting oscillations & one over f) [26]. We applied the FOOOF implementation available in the Brainstorm toolbox considering a frequency range between 10Hz and 40Hz [57], and extracted the exponent of the 1/f slope as E/I estimate. A flatter spectrum corresponds to a lower exponent and to higher intrinsic excitability, whereas a steeper spectrum corresponds to higher exponent and lower intrinsic excitability [26].
- c) Sample Entropy. Entropy measures have been linked to E/I. Lower entropy is linked to higher E/I, whereas higher entropy is linked to lower E/I [58,59]. Among the many available entropy measures, sample entropy is the most sensitive to E/I variations [27,28]. We computed Sample Entropy by including the code of Cannard [60] in the Brainstorm toolbox.
- d) Detrended Fluctuation Analysis (DFA) based E/I index. Another index of E/I can be extracted by applying DFA. This approach allows to investigate Long Term Temporal Correlations (LRTC), which are influenced by E/I. Higher values correspond to higher E/I. Recently, it has been demonstrated that this approach is sensitive to E/I alterations known to occur in Alzheimer Disease [61]. The computation of DFA-based E/I was performed in alpha band, following the method described in [61] and based on an adaptation for Brainstorm of the code available at https://github.com/annevanniferick/fEI_in_AD;
- e) Alpha band power is widely considered a marker of E/I, with higher alpha power corresponding to lower E/I [62]. Alpha power (8–12 Hz)

was computed with the Welch method available in Brainstorm, considering a window length of 1 s, and a window overlap ratio of 50 %.

2.6. Statistical approach

Left M1 TMS cortical excitability changes due to iTBS were estimated as POST-PRE MEPs amplitude difference. Similarly, whole cortex changes of E/I balance were computed as the delta (Post-Pre) of all E/I estimates. For some E/I estimates, lower values correspond to higher intrinsic excitability (see above). In order to have a comparable representation of the effects of iTBS on E/I, we computed the normalized differences, using t-values. POST-PRE was applied for ‘Exc_ind’ and ‘DFA-based E/I’. PRE-POST was used for all other measures. Hence, a positive delta always means an increase of E/I. Based on previous literature [39–42] we expect that iTBS increases E/I of the left M1 and left (stimulated) hemisphere. The relationship between excitability (TMS-based) and E/I (EEG-based) of the left M1 (Precentral gyrus of the Desikan Killiany atlas), we computed individual differences of each measure and applied the Spearman’s correlation coefficient. We additionally calculated the relationship between MEPs and intrinsic excitability measures before iTBS. In order to compare intrinsic excitability measures *per se*, we correlated the different measures with each other at baseline, as well as deltas. Furthermore, we have calculated correlations between correlation coefficients between intrinsic excitability measures and MEPs following Hittner, May and Silver (2003) [63].

3. Results

Exc_ind E/I increased consistently over the bilateral motor and premotor regions (Fig. 2, Panel A). Fig. 2 Panel B shows the map of Spearman’s correlation between TMS excitability changes estimated from MEPs’ amplitude (Panel C) and individual E/I differences. There is a definite positive correlation between the left sensorimotor region E/I increase and TMS excitability increase (the greater the increase in E/I, the greater the increase in iTBS-related excitability). The relationship is significant in the left M1 (Panel C and D, $Rho = 0.627$, $p = .019$). There was no significant correlation for the sham sample (Supplementary Fig. 1).

The results for all other E/I estimates are reported in Fig. 3. No other E/I index revealed a significant correlation between M1 E/I and TMS-evoked excitability changes. Specifically, Exponent ($\rho = -0.37$, $p = .26$), Sample Entropy ($\rho = -0.14$, $p = .69$), DFA base E/I ($\rho = 0.07$, $p = .84$) and Alpha Power ($\rho = -0.43$, $p = .19$). The iTBS-related variations showed an expected pattern, with increase of E/I in the left hemisphere and especially M1 for the Exponent of the PSD, Sample Entropy, and alpha power. Note that there was a reduction of E/I in the right hemisphere according to Exponent and DFA-based E/I. The effects of iTBS on the contralateral hemisphere have never been mapped. The TMS studies performed on M1 contralateral to the site of stimulation have provided conflicting results [40,42]. Alpha power was also higher in the right hemisphere in this respect. None of the measures showed a significant correlation with MEPs at baseline (Supplementary Table 1).

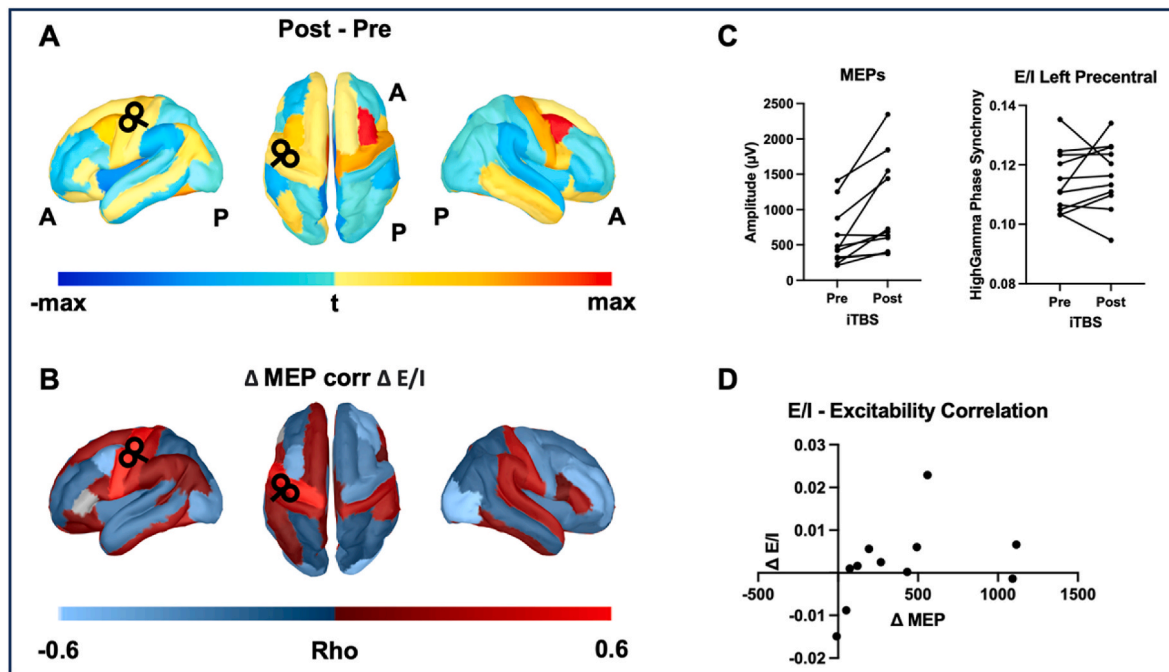


Fig. 2. Effects of iTBS on ‘Exc_ind’ extracted from EEG and cortical excitability extracted from TMS-MEPs. *Panel A* shows the normalized Post-iTBS – Pre-iTBS E/I difference. Note the increase in E/I in the bilateral precentral gyri, premotor cortex, left primary cortex and bilateral superior frontal cortex. *Panel B* Spearman’s Rho correlation between TMS excitability increase and E/I change, for all regions of the Desikan-Killiany atlas. Note a positive correlation in the left sensorimotor regions. *Panel C Left* Change in MEP amplitude, individual values across subjects. *Panel C Right* Change in E/I, individual values across subjects. *Panel D* Scatterplot of the correlation between E/I and excitability (MEP) changes for the left primary motor cortex (precentral gyrus), where iTBS was delivered (Rho = 0.627, $p = .019$).

Also, at baseline there was a significant negative correlation between Exponent and Entropy ($\rho = -0.79$, $p = .004$). None of the other measures did significantly correlate with each other. Correlation matrix between measures at baseline is depicted in [Supplementary Fig. 2](#). An additional correlation matrix between all deltas is depicted in [Supplementary Fig. 3](#). Correlations between correlation coefficients are shown in [Supplementary Table 2](#). The correlation of excitability index according to Meisel with MEPs was significantly distinct from the other measures besides DFA. The remaining correlations were not significantly distinct from each other.

4. Discussion

This study demonstrated for the first time that EEG-based E/I estimates can mirror excitability changes produced by iTBS on the motor cortex as evaluated by TMS. We also considered for the first time multiple EEG-based E/I estimates, demonstrating that the majority of them exhibits expected modulations due to external excitability tuning via iTBS.

4.1. Are changes in external excitability due to iTBS linked to changes in E/I estimated with EEG?

Previous studies demonstrated that iTBS induces an excitability increase in the stimulated M1 and a less consistent excitability decrease in the contralateral M1 [39–41,64]. Previous evidence also suggests that the increase in TMS excitability depends on the modulation of the E/I, through mechanisms that are specific to this neuromodulation technique [42,65]. In detail, iTBS increases the late I-waves that can be recorded at the cervical spine, suggesting the selective effect of iTBS on cortical interneurons producing these later components of the corticospinal volleys [66]. Single pulse TMS of the motor cortex, on the other hand, interacts with neurons spanning all cortical layers, recruiting both excitatory and inhibitory cortical circuits extending downstream to the neurons in the spinal cord [9]. Thus, spTMS MEPs are to be considered a

rough measure of cortical excitability and are unable to disentangle the effects of iTBS on specific intracortical excitation/inhibition circuits. Additionally, MEPs also reflect the excitability of the spinal cord that has not been selectively measured here. In spite of that, TMS of M1 and recording of MEPs remains the gold standard for non-invasive assessment of the excitability of the primary motor cortex. Furthermore, while iTBS mechanisms of action and effects have been characterized for M1 [42,64,66], it is unclear whether they also apply to other cerebral cortices, where the cytoarchitecture is different. Therefore, it is not surprising that a TMS-EEG study on the effects of dorso-lateral prefrontal cortex iTBS did not appreciate remarkable effects on cortical excitability as the increase of global mean field power, but only of E/I [67].

These are essentially the reasons why the relationship between TMS excitability and E/I was tested for the left M1, where iTBS was applied.

Among all measures tested here, only the Exc_ind showed a correlation with changes in excitability probed by TMS (Fig. 2). Meisel and collaborators developed this approach in 2015, suggesting that ongoing fluctuations of gamma phase synchrony are a proxy for intrinsic excitability [23]. They argue that neuronal transitions into stronger connectivity as reflected in increased phase synchrony might be underlying elevated excitability states [68,69]. In their studies, the global phase synchronization correlated with the amplitude of the cortical response following cortical stimulation, and with the presumed changes of intrinsic excitability linked to changes in antiepileptic medications [70] and awake time [23]. Our study extends previous findings in two relevant ways. Firstly, we demonstrate that this index is sensitive to enduring changes of excitability linked to neuromodulation and scales well with traditional excitability assessment via non-invasive TMS and recording of peripheral MEPs. Secondly, we provide insight into the spatial resolution of this measure. As the Exc_ind requires considering the phase synchrony across signals originating from spatially extended regions, it has an inherent limitation in terms of spatial resolution. In other words, it cannot be computed sensor-wise, or voxel-wise, or vertex-wise. Previously, the phase synchrony has therefore been mostly treated as a global property, reflecting global intrinsic excitability [23,

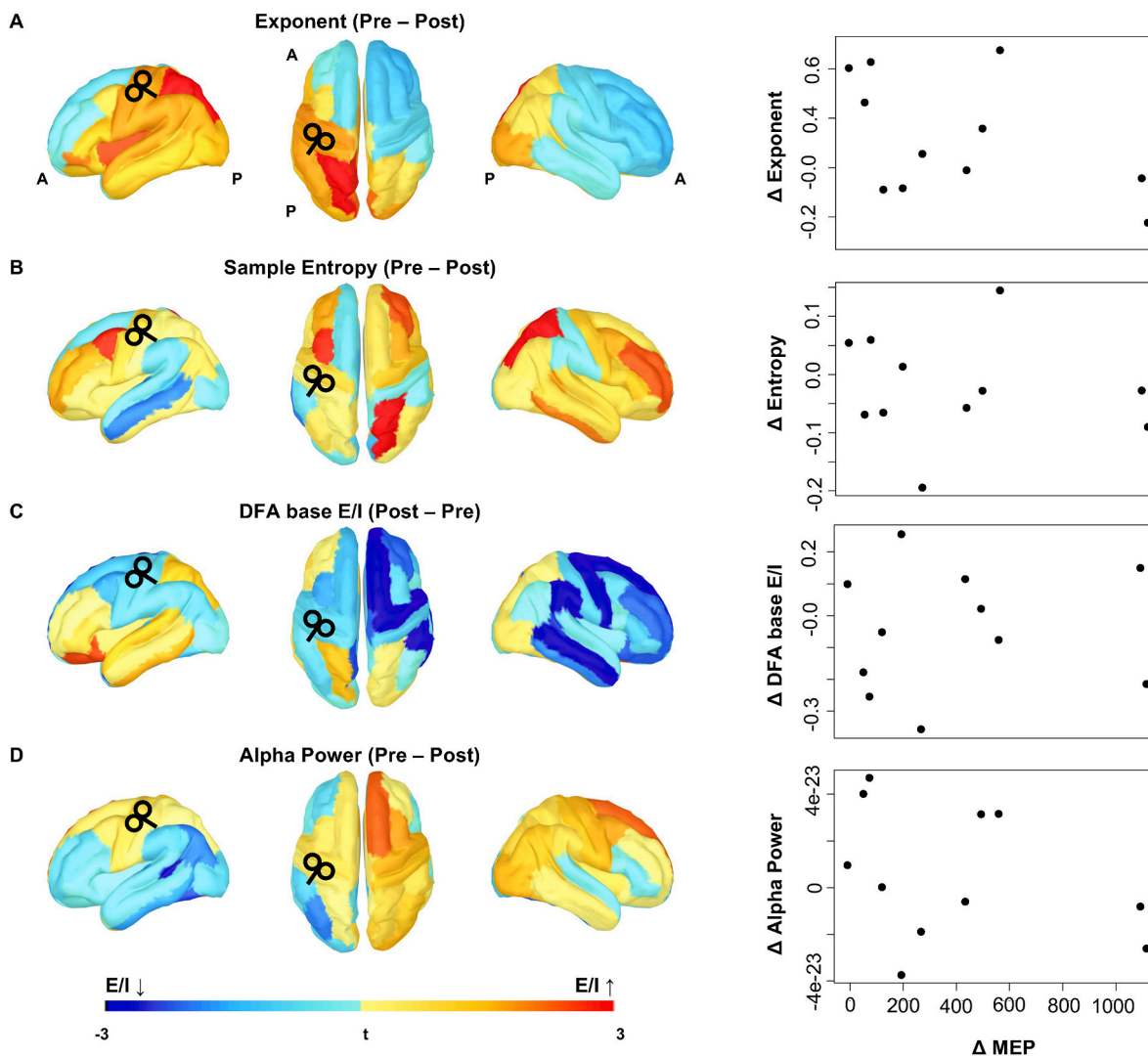


Fig. 3. Effects of iTBS on E/I estimates extracted from EEG. Each panel shows the E/I increase induced by iTBS as well as scatter plots between M1 extracted values and MEPs. Panel A: Exponent of the Power Spectral Density; Panel B: Sample Entropy; Panel C DFA-Based E/I; Panel D: Alpha power.

24,71]. We mapped intrinsic excitability changes due to auditory stimulation by applying the *Exc_ind* on spatially resolved time-series extracted from cortical reconstruction of 275 sensors MEG data and considering, in the same way as in this study, the Desikan-Killiany atlas [25]. The present work suggests that the *Exc_ind* has at least Desikan-Killiany spatial resolution, but further studies are needed to determine if a higher resolution could be achieved. We relied on the Desikan-Killiany atlas for all measures as EEG recordings were performed with 32 electrodes only. Nevertheless, the other measures of E/I are based on analysis of single time-series and can ensure higher spatial resolution, which is extremely important to achieve a non-invasive whole brain mapping of intrinsic cortical excitability, especially in clinical contexts.

Looking into the correlation between the different measures at baseline, only Entropy and Exponent show a strong negative correlation with each other, while deltas show a correlation between Alpha and Exponent. This finding suggests that the measures are distinct and might reflect different aspects of intrinsic excitability. Additionally, we could show that the relationship between intrinsic and extrinsic changes triggered by iTBS is distinct between the Meisel's Excitability Index and all other indices but DFA. Further, the other measures are not significantly different from each other in terms of their relationship with extrinsic excitability changes. Based on the observed significant change

in the Meisel index that is correlated with MEPs, this measure seems thus to most reflect changes that can also be measured with extrinsic excitability measures. The differences might be due to the different methods the respective measures were validated with including: altered consciousness (anesthesia), Alzheimer's disease and cognitive processing.

It remains to be unraveled whether the lack of significant relationship between changes in TMS cortical excitability and E/I for other E/I estimates could be due to the lower sensitivity of the other measures, the small sample size, or simply because other measures selectively assess particular aspects of E/I, which weight less in the global determination of TMS M1 excitability as suggested in the previous paragraph.

4.2. Do E/I estimates exhibit an expected modulation based on the known effects of iTBS?

Because of the known effects of iTBS (see above), it was reasonable to expect that EEG-derived E/I estimates would exhibit increases in intrinsic excitability especially in motor regions of the left hemisphere. All E/I estimates but DFA showed the expected pattern (Fig. 3). Differences across E/I estimates may be due to several reasons, intrinsic variability of the E/I estimate and sensitivity to different aspects of E/I.

The study of the exponent of the power spectrum as E/I estimate was motivated by the need to map E/I non-invasively and with high spatio-

temporal resolution [18,72]. The validation of this index is based on the definition of E/I as the property determining the ongoing fluctuations of local field potentials. While some specificity for cortical layers has been demonstrated [18], when applied to electromagnetic signals recorded non-invasively with EEG or magnetoencephalography, this index likely reflects E/I across all cortical layers and how it influences the fluctuations of post-synaptic excitatory and inhibitory potentials. In our study, the exponent-based E/I showed an expected increase around the left M1 and an expected decrease in the contralateral hemisphere. Nevertheless, no significant correlation with excitability as measured by MEPs was found.

The entropy and the DFA-based E/I estimations are measures based on the temporal regularity of the signal. Their validation as measures of E/I has been largely performed in relationship to changes in consciousness and effects of medications [27,28,59]. Therefore, entropy and DFA-based E/I should be considered as broad and rather unspecific measures of E/I, and the mechanisms sustaining their link to TMS excitability should be better ascertained. Here we demonstrated that sample entropy exhibited an expected pattern, whereas DFA-based E/I did not.

Alpha activity has been related to excitability patterns for a long time [62]. Here a role in conditioning the excitability is attributed to oscillations in specific frequency bands. This is therefore at the opposite of the exponent of the power spectrum, where E/I is inferred based on the spectral content of 'background' activity, after the removal of oscillations [26,73]. Higher alpha power in M1 at the time of stimulation corresponds to lower excitability, as probed by online TMS [74]. Here we show that alpha does indeed capture expected E/I changes induced by iTBS (Fig. 3). Alpha oscillations are generated by an interplay between cortex and thalamus [75], and their specificity for E/I components is difficult to ascertain. Interestingly, three of five measures (Exc_ind, sample entropy and alpha power) showed a larger E/I increase in the regions contralateral to the iTBS target, than in the left M1. This is in line with recent TMS-fMRI findings [12] and might reflect some compensatory mechanisms.

Overall, E/I estimates exhibited an expected modulation based on the known effects of iTBS, but also showed differences between each other, underlining that they could capture complementary aspects of the E/I.

4.3. Limitations

The main limitation of this study is the small sample size, which could be not sensitive enough to detect E/I modulations. However, both MEPs and the excitability index designed by Meisel et al. (2015) [23] are single subject measures by design and therefore to be considered as stable outcome measures. Moreover, there are no previous studies guiding on the sensitivity of various E/I estimates. Thus, this pilot study is a tool to inform follow up studies on healthy participants and patient populations in the future.

Another limitation is that we considered the effects of iTBS only. Other neuromodulatory protocols, such as inhibitory and excitatory repetitive TMS, paired associative stimulation, transcranial direct current stimulation (tDCS), do induce changes in brain excitability through the modulation of other intracortical circuits. In other words, our experimental design may not generalize to all externally manipulated excitability changes and different E/I estimates could be sensitive to modulation of different intracortical circuits.

The third limitation of the study is the low number of EEG channels. Nevertheless, in this pilot study we mostly focused on activity reconstructed in the left primary motor cortex, corresponding to the pre-central gyrus of the Desikan-Killiany atlas. Here we have sufficient coverage and sensitivity and confidence in the accuracy of the reconstruction.

The fourth limitation is that not all EEG/MEG potential E/I estimates have been considered in this study [76,77].

Finally, it has been discussed in previous literature that high-frequency oscillations are a product of muscle artifacts [78]. There is however evidence for high-frequency signals being reliably recorded by scalp electrodes [79]. The results of this study in gamma band are overall aligned with previous evidence from Meisel's group. In a recent study [25] we demonstrated that high gamma phase synchronization and spectral power in the same range were not significantly correlated, indicating that a potential influence of underlying muscle artifacts was not the main contributor of neural activity changes.

5. Conclusions

EEG-based E/I estimates depict some degree of expected modulation linked to iTBS stimulation. Remarkable differences were found across E/I estimates, possibly due to variable sensitivity to different aspects of E/I balance and activity of intracortical circuits.

Only the so-called Exc_ind, based on the spatial phase synchrony of the high-gamma band, was a reliable proxy of cortical excitability modulation linked to iTBS. Overall, the intrinsic estimation of cortical excitability from EEG-derived E/I index appears feasible. Further studies are needed for further characterization of the relationship between TMS excitability and E/I balance and to translate the full potential of E/I estimates as a tool to map intrinsic cortical excitability.

CRedit authorship contribution statement

Giovanni Pellegrino: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. **Anna-Lisa Schuler:** Conceptualization, Methodology, Software, Writing – review & editing. **Zhengchen Cai:** Conceptualization, Methodology, Software, Writing – review & editing. **Daniele Marinazzo:** Methodology, Software, Writing – review & editing. **Franca Tecchio:** Methodology, Writing – review & editing. **Lorenzo Ricci:** Data curation, Writing – review & editing. **Mario Tombini:** Data curation, Funding acquisition, Resources, Writing – review & editing. **Vincenzo Di Lazzaro:** Conceptualization, Funding acquisition, Methodology, Resources, Writing – review & editing. **Giovanni Assenza:** Data curation, Funding acquisition, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2024.01.004>.

References

- [1] Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol* 2015;126:1071–107. <https://doi.org/10.1016/j.clinph.2015.02.001>.

- [2] Siebner HR, Funke K, Aberna AS, Antal A, Bestmann S, Chen R, et al. Transcranial magnetic stimulation of the brain: what is stimulated? – a consensus and critical position paper. *Clin Neurophysiol* 2022;140:59–97. <https://doi.org/10.1016/j.clinph.2022.04.022>.
- [3] Di Lazzaro V, Pellegrino G, Di Pino G, Ranieri F, Lotti F, Florio L, et al. Human motor cortex functional changes in acute stroke: gender effects. *Front Neurosci* 2016;10. <https://doi.org/10.3389/fnins.2016.00010>.
- [4] Di Lazzaro V, Dileone M, Capone F, Pellegrino G, Ranieri F, Musumeci G, et al. Immediate and late modulation of interhemispheric imbalance with bilateral transcranial direct current stimulation in acute stroke. *Brain Stimul* 2014;7:841–8. <https://doi.org/10.1016/j.brs.2014.10.001>.
- [5] Lazzaro VD, Pellegrino G, Ranieri F, Florio L, Musumeci G, Caulo M, et al. Effects of repetitive TMS of the motor cortex on disease progression and on glutamate and GABA levels in ALS: a proof of principle study. *Brain Stimul: Basic, Translational, and Clinical Research in Neuromodulation* 2017;10:1003–5. <https://doi.org/10.1016/j.brs.2017.05.003>.
- [6] Landi D, Vollaro S, Pellegrino G, Mulas D, Ghazaryan A, Falato E, et al. Oral fingolimod reduces glutamate-mediated intracortical excitability in relapsing–remitting multiple sclerosis. *Clin Neurophysiol* 2015;126:165–9. <https://doi.org/10.1016/j.clinph.2014.05.031>.
- [7] Tombini M, Pellegrino G, Pasqualetti P, Assenza G, Benvenaga A, Fabrizio E, et al. Mobile phone emissions modulate brain excitability in patients with focal epilepsy. *Brain Stimul* 2013;6:448–54. <https://doi.org/10.1016/j.brs.2012.07.006>.
- [8] Di Pino G, Pellegrino G, Assenza G, Capone F, Ferreri F, Formica D, et al. Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. *Nat Rev Neurol* 2014;10:597–608. <https://doi.org/10.1038/nrneurol.2014.162>.
- [9] Di Lazzaro V, Ziemann U. The contribution of transcranial magnetic stimulation in the functional evaluation of microcircuits in human motor cortex. *Front Neural Circ* 2013;7. <https://doi.org/10.3389/fncir.2013.00018>.
- [10] Giambattistelli F, Tomasevic L, Pellegrino G, Porcaro C, Melgari JM, Rossini PM, et al. The spontaneous fluctuation of the excitability of a single node modulates the internodes connectivity: a TMS-EEG study: internode Connectivity Depends on Node Activity. *Hum Brain Mapp* 2014;35:1740–9. <https://doi.org/10.1002/hbm.22288>.
- [11] Tremblay S, Rogasch NC, Premoli I, Blumberger DM, Casarotto S, Chen R, et al. Clinical utility and prospective of TMS-EEG. *Clin Neurophysiol* 2019;130:802–44. <https://doi.org/10.1016/j.clinph.2019.01.001>.
- [12] Tik M, Woletz M, Schuler A-L, Vasileiadu M, Cash RFH, Zalesky A, et al. Acute TMS/fMRI response explains offline TMS network effects - an interleaved TMS-fMRI study. *Neuroimage* 2023;267:119833. <https://doi.org/10.1016/j.neuroimage.2022.119833>.
- [13] Mizutani-Tiebel Y, Tik M, Chang K-Y, Padberg F, Soldini A, Wilkinson Z, et al. Concurrent TMS-fMRI: technical challenges, developments, and overview of previous studies. *Front Psychiatr* 2022;13:825205. <https://doi.org/10.3389/fpsy.2022.825205>.
- [14] Cai Z, Pellegrino G, Spilkin A, Delaire E, Uji M, Abdallah C, et al. Hemodynamic correlates of fluctuations in neuronal excitability: a simultaneous Paired Associative Stimulation (PAS) and functional near infra-red spectroscopy (fNIRS) study. *Neuroimage: Report* 2022;2:100099. <https://doi.org/10.1016/j.ynirp.2022.100099>.
- [15] Bergmann TO, Karabanov A, Hartwigsen G, Thielscher A, Siebner HR. Combining non-invasive transcranial brain stimulation with neuroimaging and electrophysiology: current approaches and future perspectives. *Neuroimage* 2016;140:4–19. <https://doi.org/10.1016/j.neuroimage.2016.02.012>.
- [16] Conde V, Tomasevic L, Akopian I, Stanek K, Saturnino GB, Thielscher A, et al. The non-transcranial TMS-evoked potential is an inherent source of ambiguity in TMS-EEG studies. *Neuroimage* 2019;185:300–12. <https://doi.org/10.1016/j.neuroimage.2018.10.052>.
- [17] Hannah R, Rocchi L, Tremblay S, Wilson E, Rothwell JC. Pulse width biases the balance of excitation and inhibition recruited by transcranial magnetic stimulation. *Brain Stimul* 2020;13:536–8. <https://doi.org/10.1016/j.brs.2020.01.011>.
- [18] Gao R, Peterson EJ, Voytek B. Inferring synaptic excitation/inhibition balance from field potentials. *Neuroimage* 2017;158:70–8. <https://doi.org/10.1016/j.neuroimage.2017.06.078>.
- [19] Ahmad J, Ellis C, Leech R, Voytek B, Garces P, Jones E, et al. From mechanisms to markers: novel noninvasive EEG proxy markers of the neural excitation and inhibition system in humans. *Transl Psychiatry* 2022;12:1–12. <https://doi.org/10.1038/s41398-022-02218-z>.
- [20] Trakoshis S, Martínez-Cañada P, Rocchi F, Canella C, You W, Chakrabarti B, et al. Intrinsic excitation-inhibition imbalance affects medial prefrontal cortex differently in autistic men versus women. *Elife* 2020;9:e55684. <https://doi.org/10.7554/eLife.55684>.
- [21] Zou Q-H, Zhu C-Z, Yang Y, Zuo X-N, Long X-Y, Cao Q-J, et al. An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. *J Neurosci Methods* 2008;172:137–41. <https://doi.org/10.1016/j.jneumeth.2008.04.012>.
- [22] Zhang Z, Lu G, Zhong Y, Tan Q, Chen H, Liao W, et al. fMRI study of mesial temporal lobe epilepsy using amplitude of low-frequency fluctuation analysis. *Hum Brain Mapp* 2010;31:1851–61. <https://doi.org/10.1002/hbm.20982>.
- [23] Meisel C, Schulze-Bonhage A, Freestone D, Cook MJ, Achermann P, Plenz D. Intrinsic excitability measures track antiepileptic drug action and uncover increasing/decreasing excitability over the wake/sleep cycle. *Proc Natl Acad Sci U S A* 2015;112:14694–9. <https://doi.org/10.1073/pnas.1513716112>.
- [24] Meisel C, Plenz D, Schulze-Bonhage A, Reichmann H. Quantifying antiepileptic drug effects using intrinsic excitability measures. *Epilepsia* 2016;57:e210. <https://doi.org/10.1111/epi.13517>.
- [25] Schuler A-L, Brkić D, Ferrazzi G, Arcara G, Marinazzo D, Pellegrino G. Auditory white noise exposure results in intrinsic cortical excitability changes. *iScience* 2023;26. <https://doi.org/10.1016/j.isci.2023.107387>.
- [26] Donoghue T, Haller M, Peterson EJ, Varma P, Sebastian P, Gao R, et al. Parameterizing neural power spectra into periodic and aperiodic components. *Nat Neurosci* 2020;23:1655–65. <https://doi.org/10.1038/s41593-020-00744-x>.
- [27] Liang Z, Wang Y, Sun X, Li D, Voss LJ, Sleight JW, et al. EEG entropy measures in anesthesia. *Front Comput Neurosci* 2015;9.
- [28] Wei Q, Liu Q, Fan S-Z, Lu C-W, Lin T-Y, Abbod M, et al. Analysis of EEG via multivariate empirical mode decomposition for depth of anesthesia based on sample entropy. *Entropy* 2013;15:3458–70. <https://doi.org/10.3390/e15093458>.
- [29] Zang Y, Jiang T, Lu Y, He Y, Tian L. Regional homogeneity approach to fMRI data analysis. *Neuroimage* 2004;22:394–400. <https://doi.org/10.1016/j.neuroimage.2003.12.030>.
- [30] Pellegrino G, Machado A, von Ellenrieder N, Watanabe S, Hall JA, Lina J-M, et al. Hemodynamic response to interictal epileptiform discharges addressed by personalized EEG-fNIRS recordings. *Front Neurosci* 2016;10. <https://doi.org/10.3389/fnins.2016.00102>.
- [31] Pellegrino G, Hedrich T, Chowdhury R, Hall JA, Lina J-M, Dubeau F, et al. Source localization of the seizure onset zone from ictal EEG/MEG data: wMEM for ictal Source Imaging. *Hum Brain Mapp* 2016;37:2528–46. <https://doi.org/10.1002/hbm.23191>.
- [32] Pellegrino G, Hedrich T, Chowdhury RA, Hall JA, Dubeau F, Lina J-M, et al. Clinical yield of magnetoencephalography distributed source imaging in epilepsy: a comparison with equivalent current dipole method: distributed Magnetic Source Imaging in Epilepsy. *Hum Brain Mapp* 2018;39:218–31. <https://doi.org/10.1002/hbm.23837>.
- [33] Pellegrino G, Hedrich T, Porras-Bettancourt M, Lina J, Aydin Ü, Hall J, et al. Accuracy and spatial properties of distributed magnetic source imaging techniques in the investigation of focal epilepsy patients. *Hum Brain Mapp* 2020;41:3019–33. <https://doi.org/10.1002/hbm.24994>.
- [34] Chowdhury RA, Pellegrino G, Aydin Ü, Lina J-M, Dubeau F, Kobayashi E, et al. Reproducibility of EEG-MEG fusion source analysis of interictal spikes: relevance in presurgical evaluation of epilepsy. *Hum Brain Mapp* 2018;39:880–901. <https://doi.org/10.1002/hbm.23889>.
- [35] Hedrich T, Pellegrino G, Kobayashi E, Lina J-M, Grova C. Comparison of the spatial resolution of source imaging techniques in high-density EEG and MEG. *Neuroimage* 2017;157:531–44.
- [36] Schuler A-L, Ferrazzi G, Colenbier N, Arcara G, Piccione F, Ferreri F, et al. Auditory driven gamma-synchrony is associated with cortical thickness in widespread cortical areas. *Neuroimage* 2022;255:119175. <https://doi.org/10.1016/j.neuroimage.2022.119175>.
- [37] Machado A, Cai Z, Pellegrino G, Marcotte O, Vincent T, Lina J-M, et al. Optimal positioning of optodes on the scalp for personalized functional near-infrared spectroscopy investigations. *J Neurosci Methods* 2018;309:91–108. <https://doi.org/10.1016/j.jneumeth.2018.08.006>.
- [38] Pellegrino G, Arcara G, Cortese AM, Weis L, Di Tomasso S, Marioni G, et al. Cortical gamma-synchrony measured with magnetoencephalography is a marker of clinical status and predicts clinical outcome in stroke survivors. *Neuroimage: Clinical* 2019;24:102092. <https://doi.org/10.1016/j.nicl.2019.102092>.
- [39] Huang Y-Z, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron* 2005;45:201–6. <https://doi.org/10.1016/j.neuron.2004.12.033>.
- [40] Di Lazzaro V, Dileone M, Pilato F, Capone F, Musumeci G, Ranieri F, et al. Modulation of motor cortex neuronal networks by rTMS: comparison of local and remote effects of six different protocols of stimulation. *J Neurophysiol* 2011;105:2150–6. <https://doi.org/10.1152/jn.00781.2010>.
- [41] Suppa A, Huang Y-Z, Funke K, Ridding MC, Cheeran B, Di Lazzaro V, et al. Ten years of theta burst stimulation in humans: established knowledge, unknowns and prospects. *Brain Stimul* 2016;9:323–35. <https://doi.org/10.1016/j.brs.2016.01.006>.
- [42] Di Lazzaro V, Pilato F, Dileone M, Proffice P, Oliviero A, Mazzone P, et al. The physiological basis of the effects of intermittent theta burst stimulation of the human motor cortex. *J Physiol* 2008;586:3871–9. <https://doi.org/10.1113/jphysiol.2008.152736>.
- [43] Raffin E, Pellegrino G, Di Lazzaro V, Thielscher A, Siebner HR. Bringing transcranial mapping into shape: sulcus-aligned mapping captures motor somatotopy in human primary motor hand area. *Neuroimage* 2015;120:164–75. <https://doi.org/10.1016/j.neuroimage.2015.03.009>.
- [44] Mioli A, D'Alonzo M, Pellegrino G, Formica D, Di Pino G. Intermittent theta burst stimulation over ventral premotor cortex or inferior parietal lobule does not enhance the rubber hand illusion. *Front Neurosci* 2018;12.
- [45] Di Lazzaro V, Proffice P, Pilato F, Capone F, Ranieri F, Pasqualetti P, et al. Motor cortex plasticity predicts recovery in acute stroke. *Cerebr Cortex* 2010;20:1523–8. <https://doi.org/10.1093/cercor/bhp216>.
- [46] Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods* 2004;134:9–21. <https://doi.org/10.1016/j.jneumeth.2003.10.009>.
- [47] Tadel F, Baillet S, Mosher JC, Pantazis D, Leahy RM. Brainstorm: a user-friendly application for MEG/EEG analysis. *Comput Intell Neurosci* 2011;2011:1–13. <https://doi.org/10.1155/2011/879716>.
- [48] Pion-Tonachini L, Kreutz-Delgado K, Makeig S. ICLABEL: an automated electroencephalographic independent component classifier, dataset, and website. *Neuroimage* 2019;198:181–97. <https://doi.org/10.1016/j.neuroimage.2019.05.026>.
- [49] Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, et al. A probabilistic atlas and reference system for the human brain: international Consortium for Brain

- Mapping (ICBM). *Philos Trans R Soc Lond B Biol Sci* 2001;356:1293–322. <https://doi.org/10.1098/rstb.2001.0915>.
- [50] Hämäläinen MS, Ilmoniemi RJ. Interpreting magnetic fields of the brain: minimum norm estimates. *Med Biol Eng Comput* 1994;32:35–42. <https://doi.org/10.1007/BF02512476>.
- [51] Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 2006;31:968–80. <https://doi.org/10.1016/j.neuroimage.2006.01.021>.
- [52] Pellegrino G, Arcara G, Di Pino G, Turco C, Maran M, Weis L, et al. Transcranial direct current stimulation over the sensory-motor regions inhibits gamma synchrony. *Hum Brain Mapp* 2019;40:2736–46. <https://doi.org/10.1002/hbm.24556>.
- [53] Pellegrino G, Schuler A-L, Arcara G, Di Pino G, Piccione F, Kobayashi E. Resting state network connectivity is attenuated by fMRI acoustic noise. *Neuroimage* 2022;247:118791. <https://doi.org/10.1016/j.neuroimage.2021.118791>.
- [54] Pellegrino G, Mecarelli O, Pulitano P, Tombini M, Ricci L, Lanzone J, et al. Eslicarbazepine acetate modulates EEG activity and connectivity in focal epilepsy. *Front Neurol* 2018;9:1054. <https://doi.org/10.3389/fneur.2018.01054>.
- [55] Pinardi M, Schuler A-L, Arcara G, Ferreri F, Marinazzo D, Di Pino G, et al. Reduced connectivity of primary auditory and motor cortices during exposure to auditory white noise. *Neurosci Lett* 2023;804:137212. <https://doi.org/10.1016/j.neulet.2023.137212>.
- [56] Bruña R, Maestú F, Pereda E. Phase locking value revisited: teaching new tricks to an old dog. *J Neural Eng* 2018;15:056011. <https://doi.org/10.1088/1741-2552/aacfe4>.
- [57] Gerster M, Waterstraat G, Litvak V, Lehnertz K, Schnitzler A, Florin E, et al. Separating neural oscillations from aperiodic 1/f activity: challenges and recommendations. *Neuroinformatics* 2022;20:991–1012. <https://doi.org/10.1007/s12021-022-09581-8>.
- [58] Waschke L, Tune S, Obleser J. Local cortical desynchronization and pupil-linked arousal differentially shape brain states for optimal sensory performance. *eLife* n.d.;8:e51501. <https://doi.org/10.7554/eLife.51501>.
- [59] Sarasso S, Boly M, Napolitani M, Gosseries O, Charland-Verville V, Casarotto S, et al. Consciousness and complexity during unresponsiveness induced by propofol, xenon, and ketamine. *Curr Biol* 2015;25:3099–105. <https://doi.org/10.1016/j.cub.2015.10.014>.
- [60] Cannard C, Delorme A. An open-source EEGLAB plugin for computing entropy-based measures on MEEG signals. 2022. <https://doi.org/10.31234/osf.io/xwmyk>.
- [61] Van Nifterick AM, Mulder D, Duineveld DJ, Diachenko M, Scheltens P, Stam CJ, et al. Resting-state oscillations reveal disturbed excitation–inhibition ratio in Alzheimer’s disease patients. *Sci Rep* 2023;13:7419. <https://doi.org/10.1038/s41598-023-33973-8>.
- [62] Pellegrino G, Hedrich T, Sziklas V, Lina J, Grova C, Kobayashi E. How cerebral cortex protects itself from interictal spikes: the alpha/beta inhibition mechanism. *Hum Brain Mapp* 2021;42:3352–65. <https://doi.org/10.1002/hbm.25422>.
- [63] Hittner JB, May K, Silver NC. A Monte Carlo evaluation of tests for comparing dependent correlations. *J Gen Psychol* 2003;130:149–68. <https://doi.org/10.1080/00221300309601282>.
- [64] Suppa A, Ortu E, Zafar N, Deriu F, Paulus W, Berardelli A, et al. Theta burst stimulation induces after-effects on contralateral primary motor cortex excitability in humans: TBS and contralateral M1. *J Physiol* 2008;586:4489–500. <https://doi.org/10.1113/jphysiol.2008.156596>.
- [65] Cárdenas-Morales L, Nowak DA, Kammer T, Wolf RC, Schönfeldt-Lecuona C. Mechanisms and applications of theta-burst rTMS on the human motor cortex. *Brain Topogr* 2010;22:294–306. <https://doi.org/10.1007/s10548-009-0084-7>.
- [66] Di Lazzaro V, Profice P, Pilato F, Dileone M, Oliviero A, Ziemann U. The effects of motor cortex rTMS on corticospinal descending activity. *Clin Neurophysiol* 2010;121:464–73. <https://doi.org/10.1016/j.clinph.2009.11.007>.
- [67] Desforges M, Hadas I, Mihov B, Morin Y, Rochette Braün M, Lioumis P, et al. Dose-response of intermittent theta burst stimulation of the prefrontal cortex: a TMS-EEG study. *Clin Neurophysiol* 2022;136:158–72. <https://doi.org/10.1016/j.clinph.2021.12.018>.
- [68] Meisel C. Linking cortical network synchrony and excitability. *Commun Integr Biol* 2016;9:e1128598. <https://doi.org/10.1080/19420889.2015.1128598>.
- [69] Vasilieadi M, Schuler AL, Woletz M, Linhardt D, Windischberger C, Tik M. Functional connectivity explains how neuronavigated TMS of posterior temporal subregions differentially affect language processing. *Brain Stimul.* 2023;16(4):1062–71.
- [70] Ricci L, Assenza G, Pulitano P, Simonelli V, Vollero L, Lanzone J, et al. Measuring the effects of first antiepileptic medication in Temporal Lobe Epilepsy: predictive value of quantitative-EEG analysis. *Clin Neurophysiol* 2021;132:25–35. <https://doi.org/10.1016/j.clinph.2020.10.020>.
- [71] Manzouri F, Meisel C, Kunz L, Dimpelmann M, Stieglitz T, Schulze-Bonhage A. Low-frequency electrical stimulation reduces cortical excitability in the human brain. *Neuroimage Clin* 2021;31:102778. <https://doi.org/10.1016/j.nicl.2021.102778>.
- [72] Wilson LE, Da Silva Castanheira J, Baillet S. Time-resolved parameterization of aperiodic and periodic brain activity. *Elife* 2022;11:e77348. <https://doi.org/10.7554/eLife.77348>.
- [73] Romei V, Brodbeck V, Michel C, Amedi A, Pascual-Leone A, Thut G. Spontaneous fluctuations in posterior α -band EEG activity reflect variability in excitability of human visual areas. *Cerebr Cortex* 2008;18:2010. <https://doi.org/10.1093/cercor/bhm229>.
- [74] Sauseng P, Klimesch W, Gerloff C, Hummel FC. Spontaneous locally restricted EEG alpha activity determines cortical excitability in the motor cortex. *Neuropsychologia* 2009;47:284–8. <https://doi.org/10.1016/j.neuropsychologia.2008.07.021>.
- [75] Lopes da Silva F. EEG and MEG: relevance to neuroscience. *Neuron* 2013;80:1112–28. <https://doi.org/10.1016/j.neuron.2013.10.017>.
- [76] Pellegrino G, Tombini M, Curcio G, Campana C, Di Pino G, Assenza G, et al. Slow activity in focal epilepsy during sleep and wakefulness. *Clin EEG Neurosci* 2017;48:200–8. <https://doi.org/10.1177/1550059416652055>.
- [77] Tecchio F, Cottone C, Porcaro C, Cancelli A, Di Lazzaro V, Assenza G. Brain functional connectivity changes after transcranial direct current stimulation in epileptic patients. *Front Neural Circ* 2018;12.
- [78] Muthukumaraswamy SD, Carhart-Harris RL, Moran RJ, Brookes MJ, Williams TM, Ertzoe D, et al. Broadband cortical desynchronization underlies the human psychedelic state. *J Neurosci* 2013;33:15171–83. <https://doi.org/10.1523/JNEUROSCI.2063-13.2013>.
- [79] Gotman J. Oh surprise! Fast ripples on scalp EEG. *Clin Neurophysiol* 2018;129:1449–50. <https://doi.org/10.1016/j.clinph.2018.04.612>.