Brain Stimulation 12 (2019) 296–299

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

State-dependent brain stimulation: Power or phase?

Fatemeh Khademi, Vladislav Royter, Alireza Gharabaghi*

Division of Functional and Restorative Neurosurgery, and Tuebingen NeuroCampus, Eberhard Karls University Tuebingen, Germany

ARTICLE INFO

Article history:
Received 24 May 2018
Received in revised form
19 October 2018
Accepted 22 October 2018
Available online 26 October 2018

Keywords:
Corticospinal excitability
Gain modulation
Oscillatory power
Oscillatory phase
Transcranial magnetic stimulation

ABSTRACT

Background: Intrinsic motor cortex activity modifies corticospinal excitability (CSE) in accordance with both oscillatory power fluctuations and phase-specific modulation along the oscillatory beta cycle, particularly in the 16–17 Hz frequency bin.
Objective: To determine the magnitude of CSE and the relevance of stimulation timing for input gain mediated by either oscillatory power or phase.
Methods: We applied single-pulse transcranial magnetic stimulation (TMS) over the primary motor cortex of healthy subjects at rest during electroencephalography recordings. The corticospinal gain modulation was indexed by the amplitude variability of the induced motor-evoked potentials recorded from the forearm muscle.
Results: Low compared to high beta power led to a robust 40–70% CSE increase over a wide range of power values. By contrast, the phase modulation was critically dependent on the precise timing of the stimuli to the rising phase of the oscillatory beta cycle, but could then achieve CSE increases of 180%.
Conclusion: These findings can influence closed-loop, state-dependent stimulation in the context of neurorehabilitation.

Introduction

Intrinsic fluctuations of oscillatory activity reflect the current brain state, i.e., high and low oscillatory power indicate the inhibitory and excitatory state, respectively. They determine how the brain responds to external stimuli [1,2]. Furthermore, the motor cortex shows gain modulation along the oscillatory cycle. It adheres to a unimodal pattern of increased responsiveness and peaks at the rising phase of the oscillatory beta cycle [3]. This frequency- and phase-specific response modulation does not depend on oscillatory power fluctuations [3]. We therefore hypothesize that oscillatory power and phase vary in their influence on the magnitude of corticospinal excitability (CSE) as well as with regard to the temporal precision required for the input gain of stimulation-induced responses. To prove our hypothesis, data must be sampled in such a way as to enable us to make direct comparisons between different subgroups of power levels and phases. The findings will be relevant for brain state-dependent stimulation protocols which are attracting ever more attention. In particular, it remains unclear as to which physiological property of the intrinsic brain activity (i.e., power vs. phase) would be the most appropriate control signal for effective state-dependent interventions for robustly increasing corticospinal excitability. Moreover, we require clarification as to which temporal precision is required by these triggered stimulation systems to achieve the desired effects.

Materials and methods

We investigated 61 healthy, right-handed subjects (mean age, 24.32 ± 3.4 years, range 18–36 years, 38 females). All participants had given their written informed consent prior to participation in the study which was approved by the ethics committee of the Medical Faculty, University of Tuebingen. This was a secondary analysis of a previously reported dataset that had revealed frequency- and phase-specific gain modulation independent of the respective power fluctuations [3]. In this study, we analyzed the contributions of power and phase to the magnitude of CSE, and the relevance of the temporal precision of the applied stimuli for the input gain. Data acquisition and analysis were performed as recently described by our group, and are cited here accordingly [3]:

In brief, we used a TMS stimulator (MagVenture, Willich, Germany) with a biphasic current waveform connected to a figure-8 coil [4]. The stimulator was navigated with frameless stereotaxy

* Corresponding author. Division of Functional and Restorative Neurosurgery, Eberhard Karls University Tuebingen, Otfried-Mueller-Str.45, 72076, Tuebingen, Germany.
E-mail address: alireza.gharabaghi@uni-tuebingen.de (A. Gharabaghi).

https://doi.org/10.1016/j.brs.2018.10.015
1935-861X/

(Localite GmbH, SanktAugustin, Germany) based on a standard MNI dataset (ICBM152). The subjects relaxed in a reclining chair throughout the measurements and were instructed not to move during the stimulation periods, each of which lasted only a few minutes. During the intervention, the examiner monitored the EMG of the target muscle and provided verbal feedback. Following the intervention, artifact rejection (e.g., due to involuntary EMG activity) was performed on the basis of trial variance using a custom-written script. The hotspot of their left forearm muscles was determined in the right hemisphere as described previously [5,6]. The resting motor threshold (RMT) was determined using the relative frequency method, i.e., by detecting the minimum stimulus intensity that resulted in MEPs >50 μV in the peak-to-peak amplitude in at least 5 out of 10 consecutive trials [7]. This analysis focused on data acquired at near-motor threshold (100% RMT), since previous work had revealed that a robust frequency- and phase-specific gain modulation occurs at this intensity [3].

Electromyography (EMG)/electroencephalography (EEG) data were recorded at a sampling rate of 5 kHz after band-pass filtering (using an antialiasing filter) with cutoff frequencies at 0.16 Hz and 1 kHz. In a next step, data were downsampled to 1.1 kHz by the BrainAmp Amplifier [8,9]. The raw EEG and EMG signals were cut into epochs of ±1 s around the TMS pulse and detrended linearly. Following artifact rejection, the epochs with MEP amplitudes >50 μV were taken into account. In a follow-up analysis, MEP amplitudes >40 μV, >30 μV, or >20 μV were also considered, and confirmed the findings for >50 μV. The power spectrum was estimated using Fourier transformation with zero-padding. Epochs were given a length of 360 ms before the TMS onset [3]. The phase of the EEG/EMG rhythm was estimated in 1 Hz intervals preceding the TMS pulse. Epochs had a length of 2 cycles at the respective frequency and ended prior to the TMS artifact [3]. They were Fourier transformed to determine the phase at the respective frequency [10]. Since EEG/EMG power may differ across subjects, the absolute values could not be directly compared with each other. Normalization was thus necessary prior to group analysis. We therefore normalized the pre-TMS EEG/EMG power and MEP amplitude for each subject individually before group analysis. The MEP amplitude (and pre-TMS power accordingly) of each epoch was normalized for each subject with regard to the maximum MEP amplitude (power) across all epochs.

To quantify the respective effect of power and phase on the MEP increases observed, we applied a binning procedure with a 50% overlap of adjacent bins for the pre-TMS power and phase at the site of stimulation (C4 sensor) as described previously [3,10]. Specifically, we classified the epochs on the basis of the power of 16–17 Hz (which showed both the highest correlation coefficient between power and MEP and the highest phase-related modulation depth [3]) and binned them to provide four groups with 2, 4, 8, and 16 bins, respectively. In parallel, the 16 overlapping phase bins (estimated previously on the unit circle with centers equally spaced between -π and +π and a width of 45° [3]) were downsampled by merging the epochs of adjacent phase bins, yielding four groups with 2, 4, 8, and 16 bins, respectively. Finally, the corresponding power/phase groups were compared by estimating the MEP differences between the bins with the lowest/highest power and optimum/non-optimum phases, respectively. The optimum and non-optimum phases corresponded to the highest and lowest MEP amplitudes, respectively. This binning procedure therefore enabled us to draw direct comparisons between the different subgroups of power levels and phases. We could thus determine the impact of the stimulation timing on MEP increases in each binning resolution. Specifically, when 2 broad bins equivalent to a median split of all epochs were applied, we could compare the upper to the lower half of the samples; when 16 bins were applied, the most optimal phase could be compared to the least optimal phase opposite to it, or the highest beta power could be compared to the lowest beta power. We were thus able to explore the specificity of the power- and phase-dependent findings.

For our statistical analysis, MEP amplitude differences were tested by applying rmANOVAs with factors 'power' (2 levels: low, high) and 'bin resolution' (4 levels: 2, 4, 8, 16 bins), 'phase' (2 levels: rise, decline) and 'bin resolution' (4 levels: 2, 4, 8, 16 bins). Post-hoc tests were applied with a Bonferroni-corrected p-value of 0.0125.

Results

We observed a significant effect of bin resolution on power $F(3,103) = 24.129$ $p < 0.0001$ and phase $F(3,103) = 4.2$ $p = 0.017$. Post-hoc tests revealed that the beta power had a significant inverse relation with MEP amplitudes for different bins (for 2 bins $t(113) = 4.66$, $p < 0.0001$, unpaired *t*-test, Fig. 1A; for 16 bins $t(26) = 3.42$, $p = 0.0021$, unpaired *t*-test, Fig. 1B). This led to a robust 40–70% CSE amplitude increase across binning resolutions when stimuli were applied at low instead of high power levels (Fig. 1E). By contrast, the phase-modulation was critically dependent on the binning procedure (for 2 bins $t(113) = 0.51$, $p = 0.61$, unpaired *t*-test, Fig. 1C; for 16 bins $t(4) = 27.48$, $p = 0.0001$, unpaired *t*-test, Fig. 1D), indicating the importance of precisely timing the stimuli to specific phases of the oscillatory cycle. However, when phase specificity was achieved, a CSE increase of 180% could be attained (Fig. 1E) with an optimum phase in the rising flank of the oscillatory beta cycle (1.68Pi ± 0.17Pi after cosine fitting).

Discussion

Near-threshold stimulation enabled us to probe the differential influence of oscillatory power and phase on the magnitude of CSE: The lower the beta power (16–17 Hz), the higher the MEP amplitudes with an increase across the levels investigated. Deviations in power may account for 40–70% of MEP amplitude differences between inhibitory and excitatory states. This suggests that state-dependent stimulation, when triggered by low oscillatory beta power, may lead to a >20% improvement in the MEP magnitude in comparison to unspecific stimulation applied at an average power level. Notably, previous power-triggered stimulation achieved precisely this magnitude of robust CSE changes, which lasted beyond the intervention [11,12].

Notably, the binning procedure applied in this study resulted in different MEP sample sizes for different power bins. This may influence the mean MEP amplitude when grouped according to low and high pre-TMS EEG power (Fig. 1A/B). This means that, in EEG power groups with relatively higher sample sizes, i.e., in the 2 bin condition with a median split of all samples, there is a higher probability that they contain samples also applied at the optimal phase (see below). These samples will thereby disproportionally increase CSE, since power and phase influence the MEP amplitude independently of each other [3].

However, the present study suggests that phase-triggered stimulation may improve the input gain even further, albeit only when it is applied with a temporal precision of at least <8 ms at the rising flank of the beta oscillatory cycle investigated (16–17 Hz). The corresponding CSE increase was 180% higher than at the least optimal phase in the falling flank, i.e., opposite the most optimal phase. Importantly, if these stereotyped phase patterns of rhythmic synchronization in the underlying neuronal populations are to influence the response to probe stimulation, the latter must be weak [3]. Gain modulation was therefore revealed when stimuli were applied at near-threshold intensity only, i.e., at 100% RMT [3]. This stimulation intensity-dependent influence of alternating neuronal

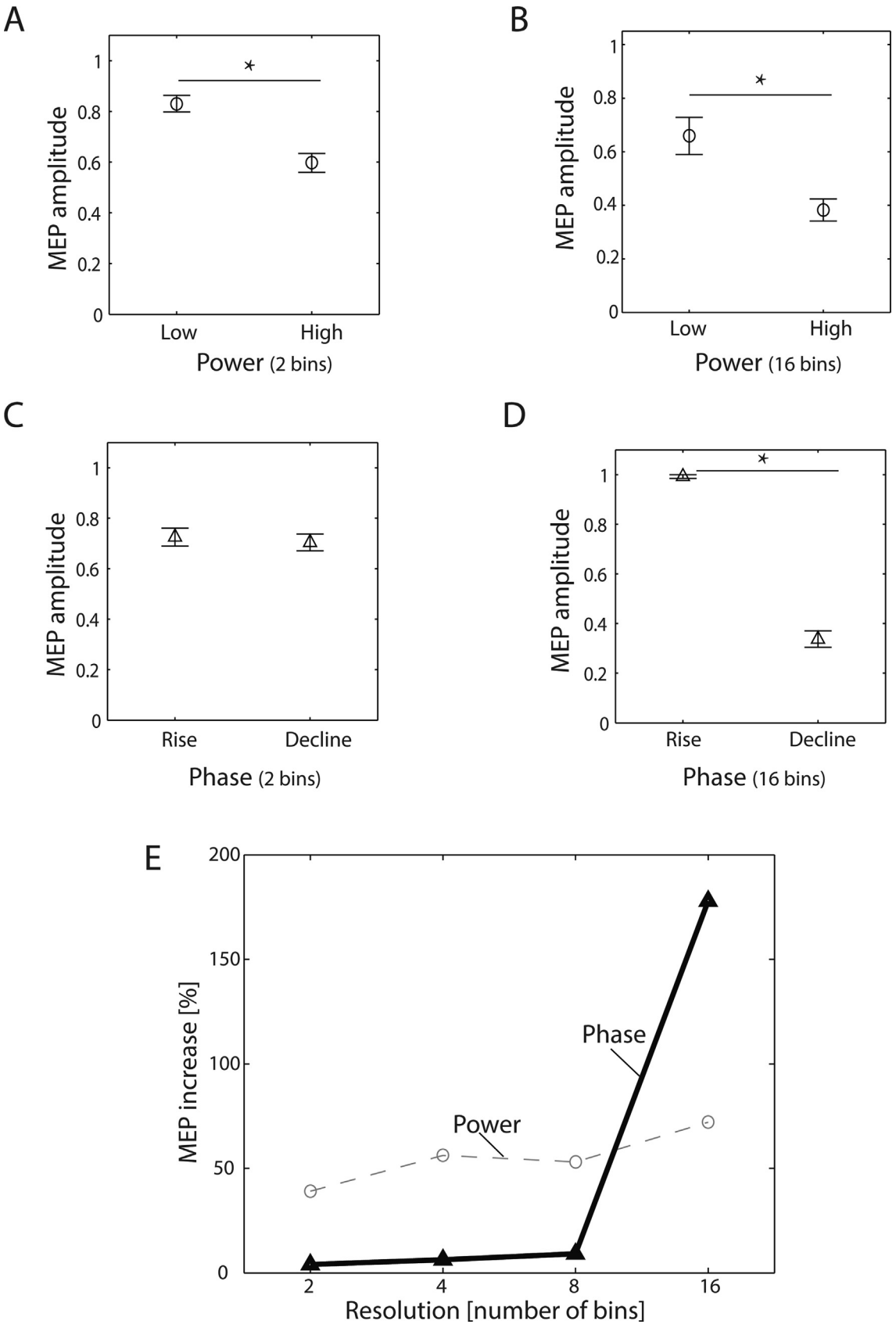

Fig. 1. State-dependent CSE increases by power versus phase. **A,** Average and standard error (vertical line) of the MEP amplitude grouped according to low and high pre-TMS EEG power (2 bin-resolution). The asterisk '*' represents the statistically significant difference between the mean of the compared groups ($p < 0.0001$). **B,** Same as **A** except for 16 bin-resolution ($p = 0.0021$). **C,** and **D,** Same as **A** and **B** except for pre-TMS phase, ($p = 0.61$ and $p = 0.0001$, respectively). **E,** Percentage of MEP amplitude increase related to the pre-TMS power (dashed gray line) and phase (solid black line) after binning at different resolutions (number of bins).

up and down states on CSE was recently confirmed by Schaworonkow and colleagues [13] when targeting the peak or trough of alpha oscillations (8–12 Hz). In their study, a subgroup of the examined subjects (8 out of 15) showed a state-dependent CSE modulation. The largest response variability and relative CSE changes were observed during low-intensity stimulation at 107% RMT. The corresponding CSE increase was 100% for the trough compared to the peak condition. On the basis of the present findings, the observed CSE gains may be increased even further by targeting a different frequency (beta vs. alpha) and/or phase (rising vs. through) and by achieving a higher precision of the applied stimulation than that reported [±55.67°].

However, since online phase estimations may not be able to synchronize pulsed stimulation with the required temporal precision to the intrinsic rhythms, the oscillatory activity may be artificially modulated by simultaneous exogenous stimulation. By combining alternating current stimulation with concurrently applied and temporally targeted [14–18], rhythmic [19] or burst [20] stimulation, we may be able to overcome this limitation. These findings may influence the timing of those state-dependent interventions informed by the instantaneous oscillatory beta-band that aim to restore post-stroke motor function [21–25].

Conflicts of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and that there has been no significant financial support for this work which could have influenced its outcome.

Author contributions

A.G. designed research; V.R. performed research; F.K. and A.G. analyzed data; F.K. and A.G. wrote the manuscript.

Acknowledgements

This work was supported by the Baden-Wuerttemberg Foundation [NEU005, NemoPlast]. F.K. and V.R. were supported by the Graduate Training Centre of Neuroscience & International Max Planck Research School, Graduate School of Neural Information Processing (F.K.) and Graduate School of Neural and Behavioral Sciences (V.R.), Tuebingen, Germany. A.G. was supported by grants from the German Federal Ministry of Education and Research [BMBF 13GW0119B, IMONAS; 13GW0214B, INSPIRATION; 13GW0270B, INAUDITAS]. The authors declare no competing financial interests.

References

[1] Salinas E, Thier P. Gain modulation: a major computational principle of the central nervous system. Neuron 2000;27(1):15–21.
[2] Chance FS, Abbott LF, Reyes AD. Gain modulation from background synaptic input. Neuron 2002;35(4):773–82.
[3] Khademi F, Royter V, Gharabaghi A. Distinct beta-band oscillatory circuits underlie corticospinal gain modulation. Cerebr Cortex 2018;28(4):1502–15.
[4] Mathew J, Kübler A, Bauer R, Gharabaghi A. Probing corticospinal recruitment patterns and functional synergies with transcranial magnetic stimulation. Front Cell Neurosci 2016;10:175.
[5] Kraus D, Gharabaghi A. Projecting navigated TMS sites on the gyral anatomy decreases inter-subject variability of cortical motor maps. Brain Stimul 2015;8(4):831–7.
[6] Kraus D, Gharabaghi A. Neuromuscular plasticity. disentangling stable and variable motor maps in the human sensorimotor cortex. Neural Plast 2016;2016:7365609.
[7] Groppa S, Oliviero A, Eisen A, Quartarone A, Cohen LG, Mall V, et al. Apractical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. Clin Neurophysiol 2012;123(5):858–82.
[8] Kraus D, Naros G, Bauer R, Leão MT, Ziemann U, Gharabaghi A. Brain-robot interface driven plasticity: distributed modulation of corticospinal excitability. Neuroimage 2016a;125:522–32.
[9] Royter V, Gharabaghi A. Brain state-dependent closed-loop modulation of paired associative stimulation controlled by sensorimotor desynchronization. Front Cell Neurosci 2016;10:115.
[10] van Elswijk G, Maij F, Schoffelen JM, Overeem S, Stegeman DF, Fries P. Corticospinal beta-band synchronization entails rhythmic gain modulation. J Neurosci 2010;30(12):4481–8.
[11] Kraus D, Naros G, Bauer R, Khademi F, Leão MT, Ziemann U, Gharabaghi A. Brain state-dependent transcranial magnetic closed-loop stimulation controlled by sensorimotor desynchronization induces robust increase of corticospinal excitability. Brain Stimul 2016b;9(3):415–24.
[12] Kraus D, Naros G, Guggenberger R, Leão MT, Ziemann U, Gharabaghi A. Recruitment of additional corticospinal pathways in the human brain with state-dependent paired associative stimulation. J Neurosci 2018;38(6):1396–407.
[13] Schaworonkow N, Triesch J, Ziemann U, Zrenner C. EEG-triggered TMS reveals stronger brain state-dependent modulation of motor evoked potentials at weaker stimulation intensities. Brain Stimul 2018;S1935–861X(18):30311–5.
[14] Guerra A, Pogosyan A, Nowak M, Tan H, Ferreri F, Di Lazzaro V, Brown P. Phase dependency of the human primary motor cortex and cholinergic inhibition cancelation during beta tACS. Cerebr Cortex 2016;26(10):3977–90.
[15] Nakazono H, Ogata K, Kuroda T, Tobimatsu S. Phase and frequency-dependent effects of transcranial alternating current stimulation on motor cortical excitability. PLoS One 2016;11(9), e0162521.
[16] Raco V, Bauer R, Tharsan S, Gharabaghi A. Combining TMS and tACS for closed-loop phase-dependent modulation of corticospinal excitability: a feasibility study. Front Cell Neurosci 2016;10:143.
[17] Raco V, Bauer R, Norim S, Gharabaghi A. Cumulative effects of single TMS pulses during beta-tACS are stimulation intensity-dependent. Brain Stimul 2017;10(6):1055–60.
[18] Schilberg L, Engelen T, Ten Oever S, Schuhmann T, de Gelder B, de Graaf TA, Sack AT. Phase of beta-frequency tACS over primary motor cortex modulates corticospinal excitability. Cortex 2018;103:142–52.
[19] Romei V, Bauer M, Brooks JL, Economides M, Penny W, Thut G, Driver J, Bestmann S. Causal evidence that intrinsic beta-frequency is relevant for enhanced signal propagation in the motor system as shown through rhythmic TMS. Neuroimage 2016;126:120–30.
[20] Khatoun A, Asamoah B, Mc Laughlin M. Simultaneously excitatory and inhibitory effects of transcranial alternating current stimulation revealed using elective pulse-train stimulation in the rat motor cortex. J Neurosci 2017;37(39):9389–402.
[21] Gharabaghi A, Kraus D, Leão MT, Spüler M, Walter A, Bogdan M, Rosenstiel W, Naros G, Ziemann U. Coupling brain-machine interfaces with cortical stimulation for brain-state dependent stimulation: enhancing motor cortex excitability for neurorehabilitation. Front Hum Neurosci 2014;8:122.
[22] Naros G, Gharabaghi A. Reinforcement learning of self-regulated β-oscillations for motor restoration in chronic stroke. Front Hum Neurosci 2015;9:391.
[23] Naros G, Naros I, Grimm F, Ziemann U, Gharabaghi A. Reinforcement learning of self-regulated sensorimotor β-oscillations improves motor performance. Neuroimage 2016;134:142–52.
[24] Naros G, Gharabaghi A. Physiological and behavioral effects of β-tACS on brain self-regulation in chronic stroke. Brain Stimul 2017;10(2):251–9.
[25] Belardinelli P, Laer L, Ortiz E, Braun C, Gharabaghi A. Plasticity of premotor cortico-muscular coherence in severely impaired stroke patients with hand paralysis. NeuroImage Clin 2017;14:726–33.