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LONG-RANGE TEMPORAL CORRELATIONS IN THE AMPLITUDE OF ALPHA OSCILLATIONS PREDICT AND REFLECT STRENGTH OF INTRACORTICAL FACILITATION: COMBINED TMS AND EEG STUDY

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Abstract—While variability of the motor responses to transcranial magnetic stimulation (TMS) is widely acknowledged, little is known about its central origin. One plausible explanation for such variability may relate to different neuronal states defining the reactivity of the cortex to TMS. In this study intrinsic spatio-temporal neuronal dynamics were estimated with Long-Range Temporal Correlations (LRTC) in order to predict the inter-individual differences in the strength of intra-cortical facilitation (ICF) and short-interval intracortical inhibition (SICI) produced by paired-pulse TMS (ppTMS) of the left primary motor cortex. LRTC in the alpha frequency range were assessed from multichannel electroencephalography (EEG) obtained at rest before and after the application of ppTMS protocols. For the EEG session, preceding TMS application, we showed a positive correlation across subjects between the strength of ICF and LRTC in the fronto-central and parietal areas. This in turn attests to the existence of subject-specific neuronal phenotypes defining the reactivity of the brain to ppTMS. In addition, we also showed that ICF was associated with the changes in neuronal dynamics in the EEG session after the application of the stimulation. This result provides a complementary evidence for the recent findings demonstrating that the cortical stimulation with sparse non-regular stimuli might have considerable long-lasting effects on the cortical activity. © 2016 Published by Elsevier Ltd on behalf of IBRO.

Key words: EEG, TMS, variability, neuronal oscillations, neuronal dynamics, motor cortex.

INTRODUCTION

A high variability of motor-evoked potentials (MEPs) to transcranial magnetic stimulation (TMS) is a widely recognized phenomenon and it is a subject of extensive research (Kiers et al., 1993; Ellaway et al., 1998; Livingston and Ingersoll, 2008; Rösler et al., 2008). One of the most likely explanations for this variability relates to changes in cortical excitability (Sauseng et al., 2009; Takemi et al., 2013; Keil et al., 2014; Kundu et al., 2014). A combination of TMS and electroencephalography (EEG) (Ilmoniemi et al., 1997; Nikulin et al., 2003; Lioumis et al., 2009) represents a particularly attractive approach for studying excitability since it directly relates cortical activity to motor responses. A quantification of the cortical activity on the basis of alpha oscillations (8–13 Hz) has a number of advantages given their presence in many individuals, susceptibility to experimental manipulations and high signal-to-noise ratio (SNR) (Palva et al., 2005; Palva and Palva, 2007; Klimesch, 2012; Frey et al., 2015). In line with these observations, previous TMS–EEG studies have shown that changes in cortical neuronal oscillations are indicative of the changes in cortical excitability reflected in MEPs (Sauseng et al., 2009; Takemi et al., 2013; Keil et al., 2014; Kundu et al., 2014) or in phosphenes (Romei et al., 2009; Dugué et al., 2011).

While abovementioned studies primarily used single-pulse TMS (spTMS) paradigms, in order to further elucidate the origin of TMS-responses variability across participants, we focused on the association of alpha oscillations at rest with the effects of paired-pulse TMS (ppTMS) phenomena including short-interval intracortical inhibition (SICI) and intra-cortical facilitation (ICF). We used relatively long time intervals of EEG recordings (~10 min) at rest, which allowed a quantification of subject-specific neuronal dynamics. The interest in the inter-individual analysis stems from the neuro-genetic studies showing high heritability of the amplitude of

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Abbreviations: APB, abductor pollicis brevis; DFA, detrended fluctuation analysis; EEG, electroencephalography; ICC, Intra-Class Correlation; ICF, intra-cortical facilitation; ISI, inter-stimulus-interval; LRTC, Long-Range Temporal Correlations; MEPs, motor-evoked potentials; ppTMS, paired-pulse TMS; RMT, resting motor threshold; SICI, short-interval intracortical inhibition; SNR, signal-to-noise ratio; spTMS, single-pulse TMS; TMS, transcranial magnetic stimulation.

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alpha oscillations (van Beijsterveldt and van Baal, 2002; Smit et al., 2006). Such heritability should also be manifested in high test–retest reproducibility of alpha oscillations' amplitude as has been shown previously (Gasser et al., 1985; Salinsky et al., 1991; Nikulin and Brismar, 2004). Interestingly, ppTMS phenomena are also subject-specific and demonstrate significant test–retest reliability, especially for SICI (Orth et al., 2003; Fleming et al., 2012; Hermsen et al., 2016). Moreover, ICF and SICI are known to depend on the ongoing status of the cortical excitability as demonstrated in pharmacological (Jung et al., 2004; Ziemann et al., 2015) and movement-related (Liepert et al., 1998; Muellbacher et al., 2000; Beck and Hallett, 2010) experiments. Therefore, given that the amplitude of alpha oscillations reflects cortical excitability, we hypothesized that it can also relate to subject-specific strength of ICF or SICI phenomena.

In addition to the commonly investigated amplitude of neuronal oscillations, we were particularly interested in the predictive value of their temporal dynamics for the effects of ppTMS. The dynamics of alpha oscillations were studied here with LRTC, which describe the decay of autocorrelation function (Kantelhardt et al., 2001; Blythe et al., 2014) and thus show how the neuronal activation at a given point in time depends on the history of the preceding neuronal events. Previous EEG/MEG research in humans has shown that LRTC are present in the amplitude dynamics of many neuronal oscillations including theta, alpha and beta frequency bands and may extend for tens of seconds (Linkenkaer-Hansen et al., 2001, 2004, 2007; Nikulin and Brismar, 2005; Montez et al., 2009; Palva et al., 2013; Smit et al., 2013). Moreover, the ubiquity of LRTC is also manifested through their presence in both cortical and subcortical structures (Hohlefeld et al., 2012).

Given the results presented above, we investigated the association of alpha oscillations with the strength of ICF and SICI and formulated the following two hypotheses. (1) Resting-state alpha oscillations before TMS sessions can predict the strength of ICF and SICI phenomena. (2) Prolonged TMS sessions with ppTMS protocols can affect the generation of alpha oscillations for a time period extending beyond the termination of stimulation. This second hypothesis was motivated by the fact that during the last few years long-lasting effect of the prolonged sessions with spTMS were reported (Julkunen et al., 2012; Pellicciari et al., 2015). Consequently we conjectured that by combining multichannel EEG with a novel sensitive method for the assessment of temporal neuronal dynamics (LRTC) we may detect changes in the neuronal activation due to ppTMS.

EXPERIMENTAL PROCEDURES

Participants

Seventeen healthy volunteers, 19–34 years of age (mean age 24.2 ± 4.4, six females) participated in the experiment after giving a written informed consent. All subjects were right-handed according to self-report. Subjects were screened for contraindications to TMS (Rossi et al., 2009) before the consenting process. Experiments were approved by the local Ethics Committee of the HSE, Moscow.

Coil positioning and threshold determination

A MagPro X100 (MagVenture) stimulator with MCF-B65 induction coil (75-mm wing radius) was used to produce biphasic TMS pulses. A frameless TMS navigation system (Localite TMS Navigator, Localite GmbH) was used for MRI-guided navigation allowing optimization and recording of the identified "hot spot" and ensuring consistent cortical target through the sequence of stimulations. The individual MR scans (T1 weighted; 1 mm thickness; sagittal orientation; acquisition matrix 256×256) were obtained with 1.5 T MRI scanner (Siemens Magnetom Avanto). Stimulation targeted the left primary motor cortex – the region of so-called "motor knob" (Yousry et al., 1997) at the motor representation of the right abductor pollicis brevis (APB) muscle. The final stimulation point was determined as the coil position with the strongest MEPs recorded from the APB. The resting motor threshold (RMT) for the given "hot spot" was determined as the minimal stimulator output evoking contralateral APB MEPs of minimum 50 μV in a resting muscle, in five out of 10 given stimuli (Rossini et al., 1999).

Protocol

After RMT determination, the first recording session was always 10-min rest EEG recording (Pre-TMS). During this and all other sessions, the subjects were sitting comfortably in a chair with elbows flexed at ~90°, prone hands. Participants were instructed to relax, keep eyes open while fixating on a small dot on the wall in front of them. Then three 10-min sessions of TMS of the APB "hotspot" in the left precentral gyrus followed. These sessions included: spTMS, ppTMS with an interstimulus-interval (ISI) of 2 ms for SICI and ppTMS with 12 ms ISI for ICF. ppTMS protocols, consisting of two stimuli, delivered sequentially on the same cortical area (Kujirai et al., 1993), are widely used to evaluate inhibitory/facilitatory processes (Bütefisch et al., 2008; Byblow et al., 2012; Lioumis et al., 2012; Du et al., 2014). In these paradigms the first conditioning stimulus (CS) modifies the response to the second test stimulus (TS). The effect of ppTMS depends on the intensity of both stimuli and on their ISI. Thus, ISIs of 1–5 ms lead to inhibitory effect - SICI, which involves GABA-A-ergic neurotransmission (Chen, 2004; Ziemann, 2004; Ziemann et al., 2015). Longer ISIs of 7–20 ms result in facilitatory phenomenon – ICF, which is believed to be distinct from SICI (Di Lazzaro et al., 2006; Rossini et al., 2015) and was shown to be mediated by glutamatergic drugs (Liepert et al., 1997; Ziemann et al., 2015).

The intensity of the spTMS pulses and test stimulus for SICI and ICF was 110% of RMT, the intensity of the conditioning stimulus for ICF and SICI was 90% of RMT. The interval between the consecutive pairs of TMS stimuli varied randomly between 4 and 10 s to prevent habituation (Ferreri et al., 2011). During each 10-min TMS sessions 100–120 trials were applied. Such

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design with separate spTMS, SICI and ICF TMS sessions was chosen because it is similar to what is often used for ppTMS investigation in healthy subjects (Ferreri et al., 2011) and patients (Lioumis et al., 2012; Mäkelä et al., 2015). After these three TMS sessions a second 10-min rest EEG session (Post-TMS) was recorded. Between all sessions there were 2–5 min breaks allowing subjects to relax.

EEG and EMG acquisition

The EEG/EMG data were recorded with BrainAmp amplifiers and BrainVision Recorder software (Brain Products GmbH, Munich, Germany). During the data acquisition the signals were band-pass filtered between 0.016 and 1000 Hz and digitized at a rate of 5000 Hz. For the EEG recordings we used 91-channel EEG cap (Ag/AgCl electrodes, Easycap GmbH, Herrsching, Germany). During the acquisition, EEG electrodes were referenced to the nasion, and the ground electrode was placed on the left cheekbone. Three electrooculographic (EOG) electrodes were placed above the nasion and below the outer canthi of the eyes (Schlögl et al., 2007).

MEPs during the three TMS protocols (SP, SICI, ICF) were obtained from the right APB using surface bipolar EMG, with Ag-AgCl electrodes in a belly–tendon montage.

Data analysis

MEP. For the offline processing, EMG signals were high-pass filtered at 10 Hz and additional notch filter was applied for the removal of 50-Hz power-line noise. Bad epochs, contaminated by the background EMG activity or electromechanical artifacts were removed (approximately 5%). We measured peak-to-peak amplitude of MEPs in the period of 20–50 ms after the TMS stimulus for three conditions (SP, SICI, ICF). The average amplitude across all epochs for a given subject and condition were used for the following statistical analysis. MEPs in SICI and ICF conditions were normalized by the MEPs in SP condition, thus providing a ratio between MEPs describing the strength of ppTMS. A statistical comparison for MEPs was performed with the *t*-tests.

EEG. EEG signals from the two resting sessions (before and after the application of TMS protocols) were band-pass filtered between 1 and 45 Hz (4th-order Butterworth filters (roll-off 80 dB/decade), and downsampled to 100-Hz sampling frequency. Visual inspection was performed in order to reject noisy channels (on average five channels were removed in each subject). Blink artifacts were removed with Fast ICA (Hyvarinen, 1999). The EEG data was re-referenced to a common average electrode.

Amplitude envelopes and detrended fluctuation analysis (DFA)

We used LRTC in order to quantify neuronal dynamics in the amplitude of alpha oscillations. Temporal correlation can be expressed in terms of the attenuation of autocorrelation function (Peng et al., 1995; Kantelhardt et al., 2001). While short-range temporal correlations are characterized by an exponential decay, LRTC follow a power law attenuation (Gisiger, 2001; Kantelhardt et al., 2001; Kello et al., 2010), implying that very remote parts of a process relate to the upcoming ones. In this study, we measure LRTC in the amplitude envelope of neuronal oscillations extracted around the individually determined peak frequency of alpha rhythm ±2 Hz. The peak frequency of the alpha oscillations was determined from a spectrum obtained through the averaging of spectra from all channels in a given subject. We specifically focused rather on alpha oscillations because: (1) they are known to reflect cortical excitability (Romei et al., 2008; Sauseng et al., 2009) and (2) they have high SNR thus making it less likely that the oscillations can be contaminated by scalp, neck and shoulder EMG. The amplitude of oscillations (obtained with Butterworth filter, 4th order) was extracted using analytic signal approach based on the Hilbert transform. For each subject, channel and rest session, we calculated corresponding mean amplitude envelope and LRTC scaling exponent.

In order to quantify LRTC, we use DFA (Peng et al., 1995; Kantelhardt et al., 2001). Note that LRTC refer to the correlation between different time points in EEG activity, not across different spatial locations.

Let $\boldsymbol{a}(t)$ be an instantaneous amplitude of oscillations extracted with the Hilbert transform for a given EEG channel and subject at time t. Next we calculate a cumulative sum of the signal:

$$Y(t) = \sum_{t=1}^{N} \boldsymbol{a}(t)$$

The integrated signal $Y(t)$, was then divided into non-overlapping windows of size τ with the window length varying from 5 to 50 s distributed equidistantly on a logarithmic scale. Altogether there were 30 window sizes in this time range. For each window size τ, the least-squares fitted line was computed and the ordinate of this line is denoted $Y_\tau(t)$. The integrated signal $Y(t)$ was then detrended in each window by subtracting $Y_\tau(t)$ and the variance was calculated as:

$$F^2(\tau) = \frac{1}{N}\sum_{t=1}^{N}[Y(t) - Y_\tau(t)]^2$$

where N is the number of samples in the window size τ. All $F^2(\tau)$ values for a given τ were then averaged and the square root was obtained leading to $F(\tau)$ value. The procedure of calculating $F(\tau)$ was repeated for all windows sizes τ. Usually the relationship between $F(\tau)$ and τ has a linear form in a double logarithmic coordinate system across many window-sizes τ. The slope of the least-squares line in this graph is called a scaling exponent and it quantifies LRTC. Scaling exponents in the 0.5–1 range indicate a presence of persistent temporal correlations, where larger fluctuations are likely to be followed by larger fluctuations. Uncorrelated signals (e.g. for white noise) have a scaling exponent 0.5.

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Further technical details on the use of DFA for the estimation of LRTC in EEG/MEG signals can be found in Hardstone et al. (2012). Apart from the calculation of LRTC, we also calculated a mean of the amplitude envelopes separately in Pre- and Post-TMS sessions. A calculation of the mean amplitude over long time interval is frequently used as a contrast to the dynamic measures capturing a temporal propagation of the signal.

Statistical analysis. Scaling exponents $\boldsymbol{\nu}$ and mean amplitude envelopes $\boldsymbol{a}$ between the two rest conditions (Pre-TMS and Post-TMS) were compared for each channel across subjects with non-parametric Wilcoxon signed-rank test correcting for multiple comparison with cluster statistics based on the permutation approaches (Maris and Oostenveld, 2007). In addition, in order to estimate reproducibility of LRTC and amplitude of oscillations between the two rest sessions in each EEG channel, Intra-Class Correlation (ICC) was calculated (McGraw and Wong, 1996). ICC is used for the assessment of reproducibility (test–retest reliability), which is relevant for us since we aimed at analyzing the reproducibility of amplitude and LRTC of neuronal oscillations in Pre- and Post-TMS sessions. Values of 1 and 0 would indicate complete and entirely absent reproducibility, respectively.

Correlation between LRTC, amplitude and strength of ICF and SICI. For each EEG channel we computed Spearman correlation across subjects between the scaling exponent $\boldsymbol{\nu}$ (or amplitude $\boldsymbol{a}$) obtained from the rest EEG sessions and ICF and SICI strength.

In order to compensate for the multiple statistical estimation of the correlations in different EEG channels, we used cluster statistics (Maris and Oostenveld, 2007).

All analysis steps were performed with scripts implemented in Matlab (The MathWorks Inc., Natick, Massachusetts, USA).

RESULTS

ICF and SICI effects

ppTMS with the ICF protocol resulted in the enhancement of MEPs amplitudes compared to MEPs amplitudes from SP session. This was statistically verified with the *t*-test comparing normalized MEPs against the unitary mean (ICF/SP mean ratio 2.28 ± 0.27; $P < 0.001$, Fig. 1). Likewise, SICI protocol resulted in the significant attenuation of MEPs compared to the SP session (SICI/SP mean ratio: 0.49 ± 0.07; $P < 0.001$, Fig. 1).

The amplitude of alpha oscillations

Fig. 2 shows a time course of the amplitude envelopes of alpha oscillations (8–13 Hz) in the electrode P3 in one representative subject in both rest sessions. Note the amplitude fluctuations at different time scales. Such intermittent patterns of amplitude fluctuations, varying in duration, represent a typical temporal structure of the signals with persistent LRTC. The overall strength of the signal was captured with the mean amplitude. On average the peak frequency of alpha oscillations was 9.8 ± 1.3 Hz.

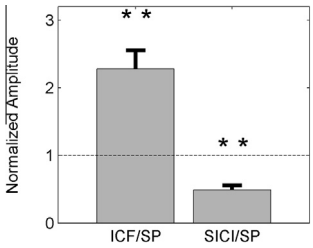

Fig. 1. Grand-average of normalized MEPs across subjects. The values are represented as mean + standard error of the mean (ICF = intra-cortical facilitation, SICI = short-interval cortical inhibition, SP = Single Pulse) ** indicates $P < 0.001$.

Fig. 3A shows an example of a spatial distribution of alpha-oscillations' amplitude in the representative subject in two rest sessions. The largest values were observed over occipito-parietal areas. In addition the figure shows in panel B spectra from all channels clearly displaying a prominent peak in the alpha frequency range. Fig. 3C demonstrates a grand average of the amplitudes across all subjects revealing again a spatial maximum over the posterior areas of the head. The topographies of the alpha oscillations were similar in the two resting sessions. This topographic similarity was further confirmed with the intra-class correlation, calculated across subjects (Fig. 3D), showing high and significant values for all electrodes, being particularly pronounced over the fronto-central and parietal areas. Importantly, we have not observed any significant differences in the amplitude of alpha oscillations between the two rest sessions.

LRTC in the amplitude dynamics of alpha oscillations

Amplitude dynamics of alpha oscillations have been reliably captured with DFA revealing a linear relationship between different time scales and corresponding fluctuations extending up to 50 s with the scaling exponents being on average 0.69 ± 0.01 (mean ± SEM). An example of the scaling behavior is presented in Fig. 4.

A topography of the scaling exponents in two rest sessions for a representative subject is presented in Fig. 5A. A grand-average topography across all subjects is presented in Fig. 5B. The topographic maxima of the scaling exponents were mostly over the frontal and centro-parietal areas. Compared to the amplitude of alpha oscillations, topographies of the scaling exponents were less reproducible across the two rest sessions, this being indicated by smaller values of ICC (Fig. 5C). Yet in many electrodes ICC values were significant thus suggesting a moderate reproducibility. Significant ICC values were absent in the occipital and left central areas (Fig. 5C). However, as in the case of the amplitude of alpha oscillations, the scaling exponents were not significantly different between the two rest sessions.

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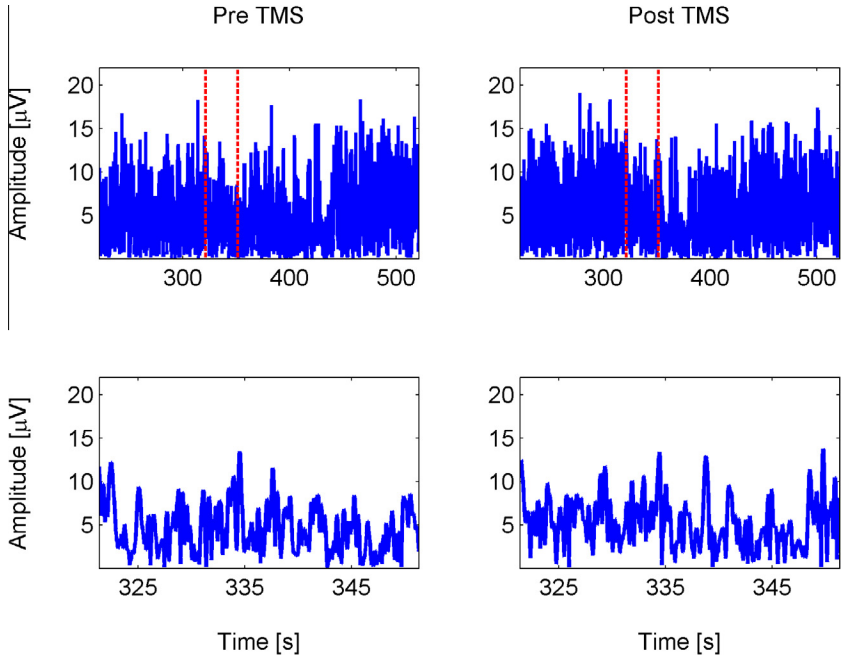

Fig. 2. An example of amplitude envelope dynamics. The amplitude envelope in the individual alpha frequency range (in this case: 9–13 Hz) for a representative subject (S7, channel P3) is presented for both rest sessions and different time scales. In the upper panels a larger interval of 300 s is displayed, and a shorter 30-s segment, marked by the red dotted lines, is extended in the lower panels. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

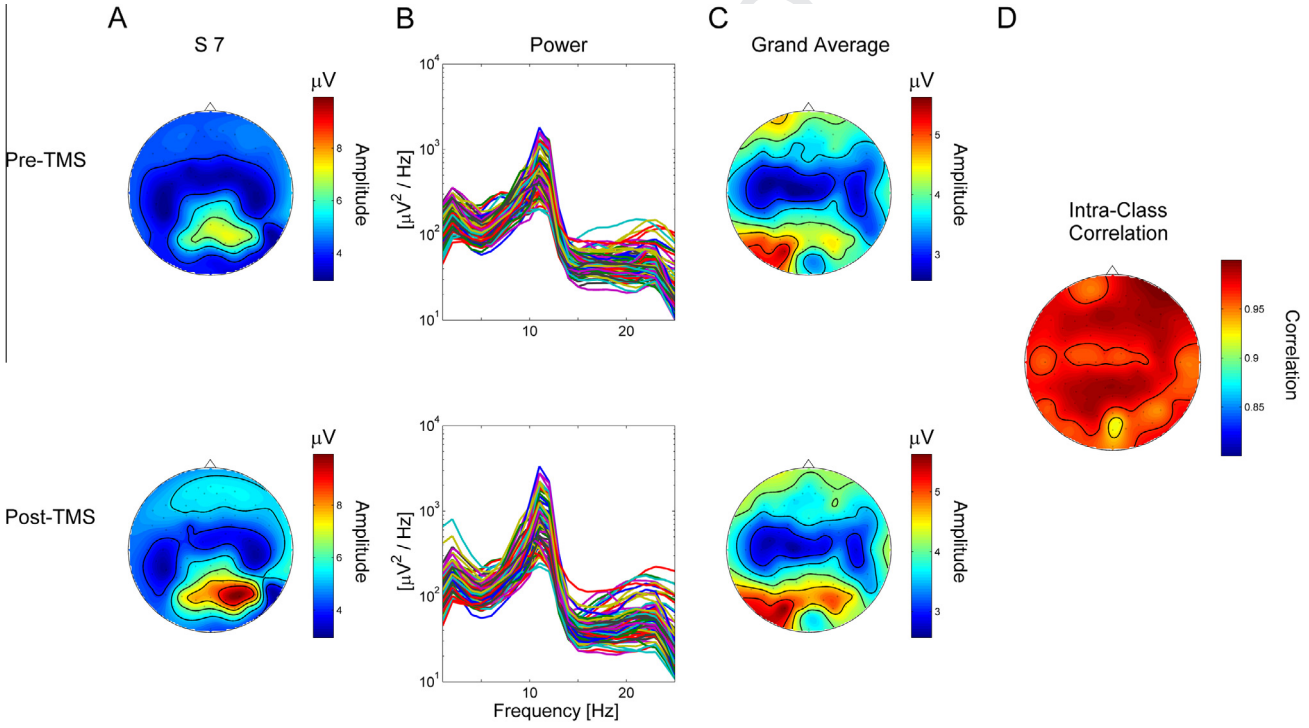

Fig. 3. The amplitude of alpha oscillations. (A) The topographies of the amplitude of alpha oscillations (9–13 Hz) for a representative subject (S7). (B) Corresponding spectra from all channels. (C) The grand-average of the amplitude topographies (across all subjects). The Pre-TMS and Post-TMS sessions are shown in the upper and lower panels, respectively. (D) The similarity between the two rest sessions across subjects is shown in terms of ICC (ICC values were significant for all channels, $P < 0.05$).

Prediction of ICF and SICI strength on the basis of amplitude and LRTC of alpha oscillations in Pre-TMS rest session

A prediction of ICF and SICI strength can in principle be achieved only with the Pre-TMS rest condition, before the application of TMS, since the parameters of the neuronal oscillations in the Post-TMS rest session might also reflect an effect of TMS.

The amplitude of alpha oscillations in the individually determined alpha range did not correlate significantly

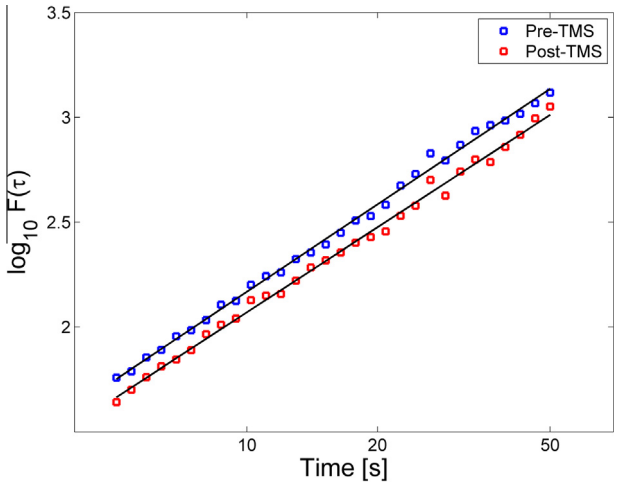

Fig. 4. An example of the DFA analysis for the amplitude envelope of alpha oscillations. Detrended fluctuations (S11, channel C6) are shown for both Pre-TMS (blue) and Post-TMS (red) sessions. Axes are in the logarithmic scale. The slope of the least-squares fitted lines (black) corresponds to the scaling exponent, $\nu = 0.69$ in Pre-TMS session to $\nu = 0.67$ in Post-TMS session. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

with the size of the normalized MEPs from the SICI or ICF protocols. At the same time, scaling exponents, characterizing LRTC of the alpha oscillations were positively correlated with the enhancement of MEPs during ICF. This correlation was observed in electrodes over fronto-central and parietal areas, as shown in Fig. 6, panel A. The cluster statistic indicated a significant Spearman correlation at the level $P < 0.05$. No significant correlation was found between the scaling exponents and SICI strength.

Effect of ppTMS on the neuronal dynamics in Post-TMS rest session

Although there were no significant differences in the strength of LRTC between Pre-TMS and Post-TMS sessions, we found that the strength of ICF was positively correlated with the scaling exponents of alpha oscillations in the Post-TMS session (Fig. 6B). Topographically this correlation, largely overlapping with the cluster identified in the Pre-TMS session, extended to the sensorimotor areas of both hemispheres. For SICI we did not find a significant correlation between the MEPs and the scaling exponents. Moreover, no significant correlations were found between the amplitude of alpha and the strength of ICF or SICI phenomena.

DISCUSSION

We showed that the temporal neuronal dynamics, manifested in the LRTC of alpha oscillations at rest, can predict the strength of ICF. Moreover, the application of ppTMS also changed LRTC in alpha oscillations at rest.

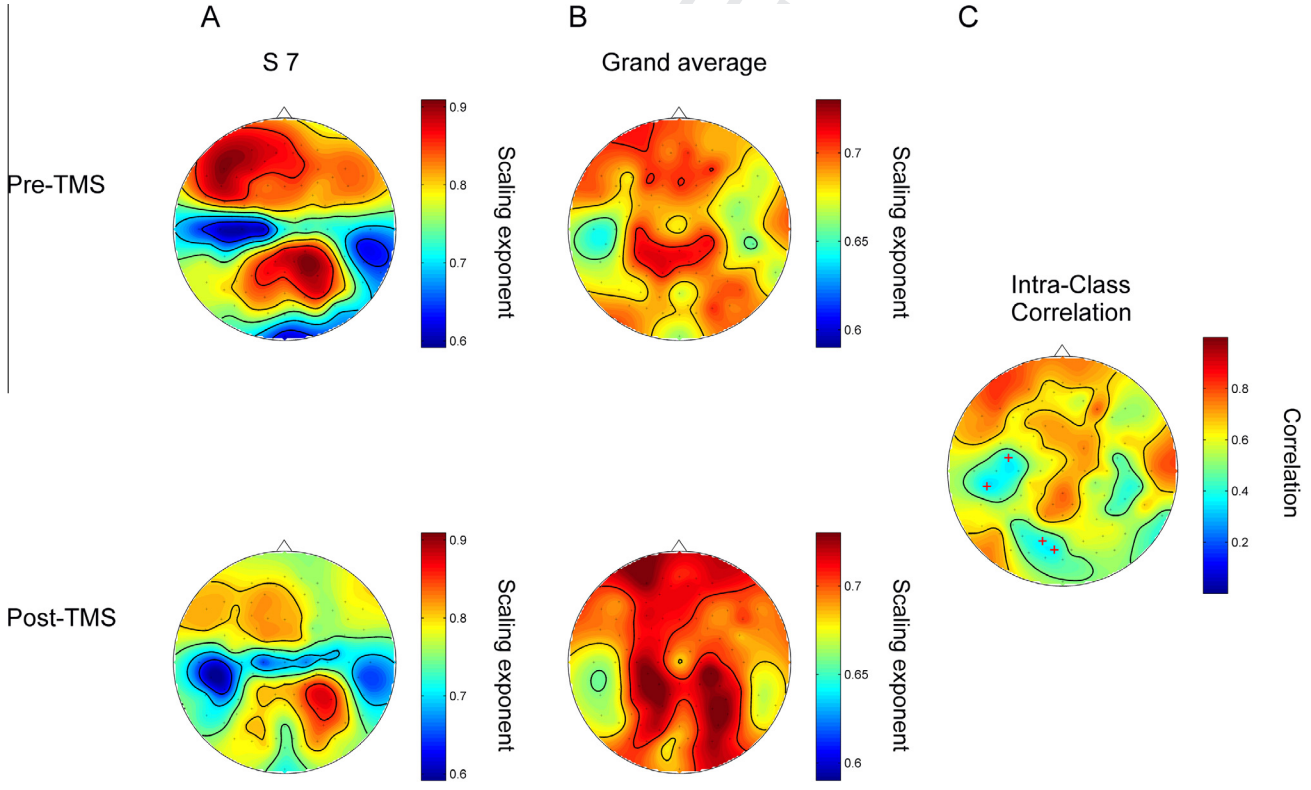

Fig. 5. LRTC of the amplitude envelopes of alpha oscillations. (A) The topographies of the scaling exponents of alpha oscillations for a representative subject (S11). (B) The grand-average of the scaling-exponent topographies (across all subjects). The Pre-TMS and Post-TMS sessions are shown in the upper and lower panels, respectively. (C) The similarity between the two rest sessions is shown in terms of ICC. ICC in all channels were significant ($P < 0.05$) apart from the channels highlighted with a red cross. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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In contrast, the amplitude of oscillations frequently used in many EEG studies had no association with the strength of ICF or SICI phenomena. Below we discuss the implications of these findings for the understanding of the cortical excitability in the context of TMS–EEG research.

Strength of SICI and ICF

On average MEPs were decreased by about 49% and increased by 120% during SICI and ICF protocols, respectively, in agreement with the values reported in the previous studies (Kujirai et al., 1993; Classen et al., 1998; Cohen et al., 1998; Du et al., 2014; Ito et al., 2015). There was a considerable variability in the strength of ICF and SICI phenomena across subjects. This variability is important for the present study since it provides a basis for determining its possible neural correlates associated with the amplitude or LRTC of the neuronal oscillations. Inter-subject variability in the strength of ppTMS phenomena was a topic of the previous research (Maeda et al., 2002; Orth et al., 2003; Fleming et al., 2012; Hermsen et al., 2016) investigating the reproducibility of subject-specific ICF and SICI strength. In these studies SICI showed the largest intra-subjects reproducibility. ICF/SICI ratio, so- called inhibition/facilitation profile, also demonstrated a high intra-subject reproducibility (Du et al., 2014). A reproducibility of ICF and SICI strength indicates that there might exist a relatively stable configuration of neural networks in each individual determining the reactivity to ppTMS, most likely reflecting complex cortical network interactions between interneurons and pyramidal cells (Lackmy-Vallee et al., 2012; Ziemann et al., 2014; Murase et al., 2015). Such intra-subject reproducibility is in a good agreement with the findings of ppTMS phenomena having genetic predisposition (Yi et al., 2013; Menzler et al., 2014). In the present study we showed that oscillatory dynamics, captured with LRTC, might serve as a correlate for the characterization of such subject-specific inhibition/facilitation profiles.

LRTC in the amplitude dynamics of alpha oscillations

We have primarily studied alpha oscillations as they allowed the most reliable estimation of the neuronal dynamics because of the high SNR. Our results provide an important outlook into the characterization of cortical excitability investigated by TMS–EEG.

The scaling exponents for alpha oscillations were on average $\nu = 0.69 \pm 0.1$, in agreement with the previous studies investigating LRTC in rest conditions with EEG/MEG (Nikulin and Brismar, 2004; Nikulin et al., 2012; Blythe et al., 2014). In the present study we could investigate LRTC only for the time intervals extending up to 50 s this being due to the limit imposed by the duration of the rest recordings. The presence of LRTC indicates that the remote parts the amplitude envelope of alpha oscillations are correlated and that this correlation attenuates slowly, according to a power-law. The presence of LRTC has been linked to the criticality phenomenon in neuronal networks (Linkenkaer-Hansen et al., 2001; Poil et al., 2012). The criticality implies that the system is at a metastable state which for the neuronal networks defines a delicate balance between excitation and inhibition (Beggs and Plenz, 2003; Poil et al., 2012; Shew and Plenz, 2013). Such balance is important for the proper functioning of the neuronal networks as demonstrated by the previous studies showing that the critical states are associated with the maximization of a dynamic range (Kinouchi and Copelli, 2006; Shew et al., 2009), information transfer and capacity in the brain (Shew et al., 2011).

LRTC of the Pre-TMS session predict strength of ICF

Scaling exponents of individual alpha oscillations were significantly and positively correlated with the strength of ICF (Fig. 6) in the Pre-TMS rest session. Since this session preceded application of ppTMS protocols, this result indicates that LRTC may define a subject-specific strength of ICF phenomenon. Given that LRTC in the alpha range show significant test–retest reliability across different days (Nikulin and Brismar, 2004) as well as high genetic heritability (Linkenkaer-Hansen et al., 2007) one can conclude that temporal correlations reflect a certain neuronal phenotype which is most likely shaped by the persistent individual anatomical and synaptic organization of the brain. The prediction of ICF strength was most pronounced for the cluster of electrodes covering fronto-central to occipito-parietal cortex. Although no definite conclusions can be made about the exact neuronal sources responsible for this prediction on the basis of the sensor-space data, a broad distribution of the electrodes, showing significant predictions, might indicate involvement of multiple cortical areas whose temporal dynamics at rest predict strength of ICF. In the present study we stimulated motor cortex, which is known to be tightly integrated in a larger sensorimotor network including SMA, pre-motor cortex and contralateral motor cortex (Bestmann et al., 2010; Kroeger et al., 2010; Rothwell, 2011). Therefore neuronal dynamics in these networks are likely to relate to the susceptibility of the motor cortex to TMS. A posterior part of the electrode cluster might reflect neuronal activity originating in the parietal cortical areas known to be associated with the alertness and arousal levels (Posner and Petersen, 1990; Petersen and Posner, 2012; Greene et al., 2014), the latter were also shown to affect susceptibility to TMS (Löfberg et al., 2014; Herring et al., 2015). ICF protocol includes a relatively long interval (12 ms) between conditioning and testing pulse and therefore ICF is likely to be based on many synaptic connections (Di Lazzaro et al., 2006; Di Lazzaro and Ziemann, 2013; Ziemann et al., 2015). Therefore ICF might reflect dynamics of larger neuronal networks than in the case of SICI. Such spatially distributed networks are also important for the generation of LRTC (Linkenkaer-Hansen et al., 2001; Poil et al., 2012). Consequently, ICF might be more prone to a long-range synaptic modulation than SICI. In line with this observation we indeed found predictive value of LRTC only for the strength of ICF.

While ICF relates to glutamatergic activity, it may reflect at the same time tales of GABA-A processes triggered by the conditioning stimulus (Cohen et al.,

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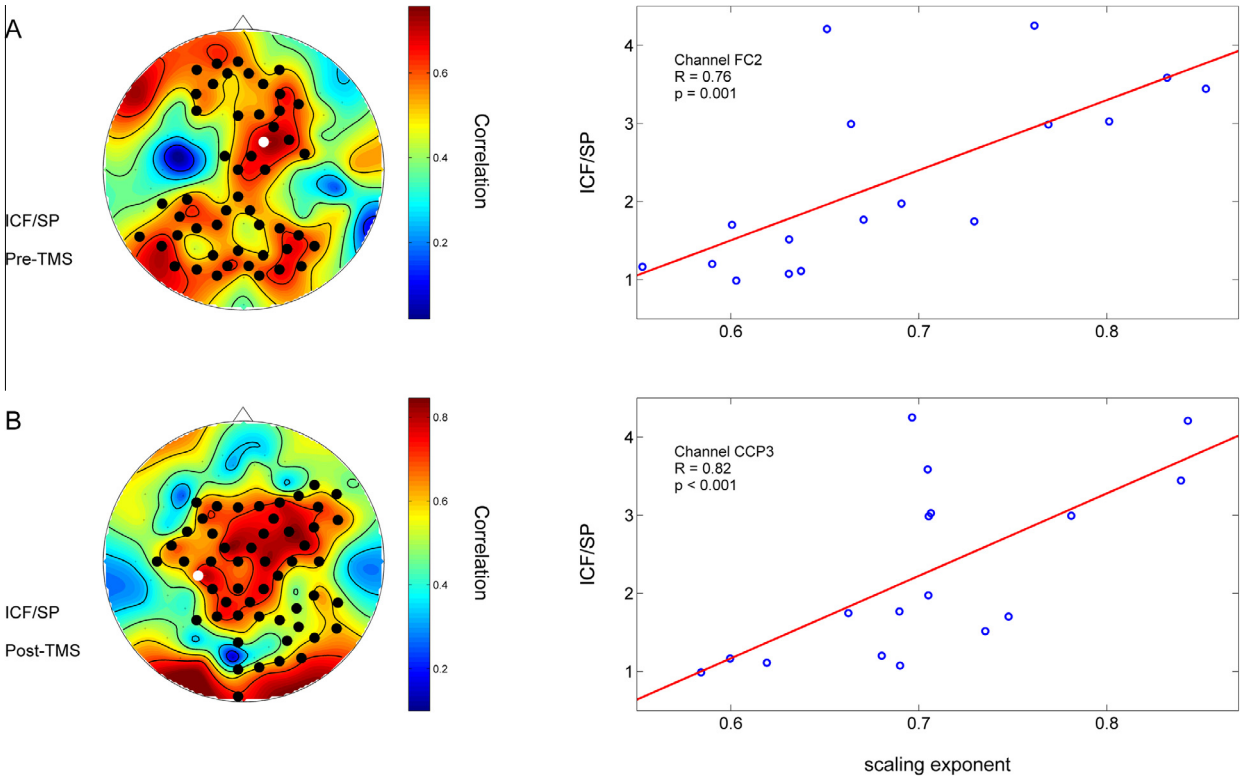

Fig. 6. Correlation between the scaling exponents and ICF/SP. The correlation between the strength of ICF and LRTC in pre-TMS session (A) and post-TMS session (B). Topographies show the strength of Spearman correlation for all channels. Black dots indicate channels belonging to a significant cluster ($P < 0.05$). The white dot indicates the channel from which the exemplified scatterplot is shown on the right side for the relationship between the scaling exponents and normalized MEPs in ICF. A correction for multiple comparisons was performed with the cluster statistics (see Methods).

1998; Chen, 2004; Ziemann et al., 2015). Such a complex combination of neurotransmitter effects along with the long latency of the testing pulse might provide an ample basis for ICF strength to reflect modulatory effects of other spatially distributed cortical areas.

Effects of ppTMS on LRTC

Surprisingly, despite the lack of a difference in the scaling exponents between the two rest sessions, we nonetheless found significant correlations between the scaling exponents and the strength of ICF phenomena. Naturally, the fact that the scaling exponents were not significantly different between the Pre- and Post-TMS conditions, does not mathematically preclude a correlation between the scaling exponents and the strength of ICF and SICI. Without the Pre-TMS rest session it would be difficult to conclude whether such correlations are due to the already existing correlation of Pre-TMS LRTC and the strength of ICF or whether LRTC indeed were affected by ppTMS.

The correlation of LRTC obtained in Post-TMS session with the strength of ICF showed considerably larger central distribution (Fig. 6B) compared to the topography obtained with pre-TMS LRTC (Fig. 6A). This difference in the correlation topographies thus clearly indicates that the effect of ICF on LRTC in the Post-TMS session cannot be reduced to the correlation of Pre-TMS LRTC and ICF strength. It is important to note that since we assessed neuronal dynamics directly with EEG, our findings most likely reflect cortical processes rather than the changes in the spinal cord, which might occur when the cortical excitability is assessed only with MEPs.

For many years repetitive TMS (Pascual-Leone et al., 1998; Tsuji and Rothwell, 2002; Wolters et al., 2005; Huber et al., 2008; Thut and Pascual-Leone, 2010), including patterned TMS like theta-burst (Huang and Rothwell, 2004) and some other TMS protocols with a regular order of stimuli (Cash et al., 2010, 2014) have been shown to have long-lasting neuromodulatory effects. However, recently some studies demonstrated cumulative effects of the prolonged protocols with spTMS both on the MEPs amplitudes (Julkunen et al., 2012; Pellicciari et al., 2015) and EEG dynamics (Stamoulis et al., 2011). These results thus echo our findings on long-lasting offline effect of the prolonged sessions of spTMS and ppTMS. Our results also agree with a recent study (Pellicciari et al., 2015), where a similar effect of the prolonged single-pulse TMS session on MEPs amplitudes was shown both for random and fixed intervals between the TMS pulses. However, the present work is the first demonstrating the long-lasting changes in the neuronal dynamics after prolonged ppTMS sessions.

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It might be that the long-lasting offline effect of ppTMS on LRTC was not due to the stimuli being paired but rather due to the fact that there was low-frequency (4–10 s) magnetic stimulation of the brain. Low-frequency stimulation at 0.2 Hz was shown to produce a reduction of cortical excitability (Ikeguchi et al., 2005) which in general agrees with the idea of low-frequency TMS (< 1 Hz) having inhibitory effects (for a review see Fitzgerald et al., 2006). Although the stimulation in the present study was not repetitive, its low-frequency nature might have reduced cortical excitability. A decrease in cortical excitability might prevent a rapid switching between the neuronal states thus leading to stronger LRTC. In addition, ppTMS with ICF protocol should lead to stronger activation of the cortex. Assuming that in our protocol stronger stimulation leads to stronger reduction of excitability, a positive correlation between the strength of ICF and LRTC would be expected (Fig. 6B).

Limitations of the study and future directions

One of the main limitations of the study was that TMS protocol was primarily designed to investigate a predictive value of neuronal dynamics for ppTMS effects and therefore, the protocols of ppTMS were used sequentially on the same day. This prediction is based on EEG being recorded before any TMS and thus does not reflect a combination of different stimulations. For Post-TMS effect, however, further research will be necessary to disentangle the influence of each TMS protocol on the neuronal dynamics. Given the presence of long-lasting effects on the intrinsic neuronal dynamics, it would be important to assess the role of the stimulation parameters and the duration of the post-stimulation effect in addition to the studied 10-min interval in the Post-TMS session.

CONCLUSIONS

We investigated cortical neuronal dynamics associated with ppTMS paradigms. In contrast to many previous TMS–EEG studies, using evoked responses or the mean amplitude of oscillations, we rather used a complex description of spatio-temporal neuronal dynamics captured with LRTC. With this measure, we showed that the strength of ICF can be predicted inter-individually from the rest recordings, which in turn attests to the existence of subject-specific neuronal phenotypes defining the reactivity of the brain to ppTMS. In addition, we showed that a combination of ppTMS and spTMS might affect neuronal dynamics recorded after the cessation of stimulation, this finding being in agreement with the emerging notion that not only repetitive TMS protocols but also the stimulation with sparse non-regular pulses might have considerable effect on the cortical dynamics.

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