A Local Signature of LTP-Like Plasticity Induced by Repetitive Paired Associative Stimulation

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Abstract Repetitive paired associative stimulation (rPAS) repeatedly pairs electrical nerve stimulation (ENS) with transcranial magnetic stimulation (TMS) of the contralateral motor hand area (M1) at 5 Hz frequency. So far, there are only few studies concerning the effects of PAS on the modulation of EEG power. Hence, aim of the present study was to investigate rPAS long term after-effects on cortical excitability looking at EEG power spectra. In four experimental sessions, separated by 2 weeks interval, 12 awake subjects received rPAS of the right median nerve and left M1 at a fixed interval (ISI) of 25 ms (real condition), 5 Hz-TMS on left M1, 5 Hz-ENS, of the right median nerve, and rPAS with changing ISI (sham condition). We measured peak-to-peak MEP amplitude, evoked from the target muscle (right abductor pollicis brevis muscle) at rest and the absolute power (POW) in four frequency bands: α (8–12 Hz), β (13–30), θ (4–7) and δ (1–3), under rest conditions. All these parameters were evaluated in three detection blocks: baseline, immediately after and after 30′ from the end of the conditioning protocol. Real rPAS induced a long-lasting homotopic cortical excitability modulation, as indexed by MEP amplitude increase, that was paralleled by a long-lasting reduction of α/β-POW and by a widespread θ-δ-POW modulation. rPAS applied over the sensory-motor cortex induced an LTP-like plasticity, as indexed by a robust reduction in the α/β POW positively correlated with the MEP amplitude increase. $rPAS_{25ms}$ may be a useful tool for motor neurorehabilitation promoting a sensory-motor coupling within β oscillations.

Keywords Repetitive paired associative stimulation · Oscillatory activity · EEG power modulation · Long term potentiation · Associative plasticity

Introduction

Neuronal activity underlying sensory, motor and cognitive processes exhibit distinct oscillatory patterns that can be measured in humans by mean of electroencephalography (EEG) and magnetoelectroencephalography (MEG) (Calderone et al. 2014). However, the relationship between brain oscillations and cortical functions has remained elusive.

TMS enables direct rhythmic stimulation of the human brain at frequencies that characterize EEG or MEG signals (Miniussi and Thut 2010; Siebner and Ziemann 2010).

Therefore, protocols combining transcranial magnetic stimulation (TMS) and EEG represent a versatile method in studying the intra-and inter-cortical area dynamics related to brain cortical oscillations, in a real time manner thanks to the EEG high temporal resolution (George et al. 2002). Several pertubational approaches have been used to entrain brain oscillation activity such as repetitive TMS (rTMS), θ-burst stimulation and paired associative stimulation (PAS)

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(Rothwell 2011), and, more recently, transcranial direct current stimulation (Soekadar et al. 2014). This entrainment hypothesis posits that rhythmic TMS causes entrainment in direct interactions with the underlying brain oscillation (Thut et al. 2011).

Single and paired TMS can induce short-lasting brain oscillations (Paus et al. 2001; Manganotti et al. 2012), whilst repetitive methds can overall modulate oscillatory cortical activity possibly inducing long term after effects on cortical excitability (Fuggetta et al. 2008; Veniero et al. 2011; Fuggetta and Noh 2013; Thut et al. 2011; Miniussi and Thut 2010).

PAS repeatedly pairs electrical stimulation of a peripheral nerve with TMS of the contralateral sensory or motor cortex at a constant interstimulus interval (ISI) (Stefan et al. 2000; Wolters et al. 2003, 2005; Quartarone et al. 2006). Paralleling spike-time-dependent plasticity (STDP) in slice preparations, the ISI between the cortical magnetic stimulus (test stimulus, TS) and the peripheral one (conditioning stimulus, CS) plays a crucial role in defining the direction of the after-effects on corticospinal excitability (Dan and Poo 2004; Sjöström et al. 2008; Froemke et al. 2010).

Concerning classic PAS, if sensory input from median nerve stimulation reaches the primary motor area of the hand (M1-HAND) shortly prior to TMS, PAS potentiates regional cortical excitability. Conversely, if TMS precedes the arrival of sensory input to the cortex, PAS causes a suppression of cortical excitability. Since these after-effects are timing-dependent, long-lasting, input-specific (Stefan et al. 2000) and can be blocked by *N*-methyl-*d*-aspartate (NMDA) receptor antagonists (Stefan et al. 2002), PAS is likely to reflect LTP-like and LTD-like plasticity phenomena at system level.

PAS has been classically applied at low frequencies ($\leq$0.25 Hz), however compared to low-frequency PAS, high-frequency repetitive PAS (rPAS) has the advantage to use a low intensity of TMS stimulus (90 % active motor threshold-aMT) at a frequency of 5 Hz, which does not produce any descending corticospinal volley (Di Lazzaro et al. 1998). Therefore, whereas the LTP-like effects produced by rPAS may be considered purely cortical, some of the after effects of low-frequency PAS may be spinal in origin (Quartarone et al. 2006; Meunier et al. 2007).

To date, there are only few studies concerning the effects of PAS on the modulation of EEG spectrum and, in addition, all of them have mainly focused on the changes in EEG slow-wave activity during subsequent sleep (Huber et al. 2008; Thut and Pascual-Leone 2010). Therefore, aim of the present study was to investigate, during wakefulness, the after-effects of rPAS on EEGpow and on corticospinal excitability as indexed by the motor evoked potential (MEP) amplitude.

Methods

Subjects

Twelve healthy volunteers (five females), right-handed, mean age 28 $\pm$ 2 years, were enrolled in the study. All subjects were naïve for experimental protocols and unaware of its expected effects. The experiment was approved by the local Ethical Committee. All subjects gave their consent in written form. The subjects were seated on a comfortable reclining chair with adjustable headrest, with both arms outstretched in supination, parallel to each other and at right angles to the trunk, resting on a comfortable pillow. They were asked to stay in a relaxed state, throughout the whole experimental sessions. No subject reported side effects during or after the experimental sessions.

Design of the Experiment

Each subject underwent four conditioning protocol, separated by two-week interval. 1) real condition: rPAS protocol was delivered at a fixed interval of 25 ms ($rPAS_{25ms}$); 2) sham condition: rPAS at changing interval, ranging between 150 and 500 ms ($rPAS_{sham}$); 3) repetitive electrical stimulation (rENS): 5 Hz of right median nerve at wrist, given alone; 4) (rTMS): 5 Hz at 90 % aMT on the hot-spot of the right APB, given alone. The order of the sessions was random. We measured peak-to-peak MEP amplitude (mV), evoked from the target muscle (abductor pollicis brevis muscle, ABP, of right hand) at rest and the POW in four frequency bands: α (8–12 Hz), β (13–30), θ (4–7) and δ (1–3), under closed-eyes resting condition. All these parameters were evaluated in three detection blocks: baseline (T_{PRE}), immediately after (T_0) and 30′ (T_{30}) after the end of the conditioning protocol. Together APB, we also measured, in terms of topographic specificity, the MEP amplitude from the right hand abductor digiti minimi (ADM) muscle at T_{PRE}, T_0, and T_{30}.

Conditioning Protocol, Electrical and Magnetic Stimulation

In each session we delivered, continuously for two minutes and at frequency of 5 Hz, 600 pairs of stimuli. Each pair of stimuli was formed by a conditioning electrical stimulus (CS), applied on the right median nerve at the wrist, at 200 % of sensory threshold, and the magnetic one test (TS), issued after the CS, at 90 % of the aMT, applied on the hot-spot for the right APB. The intensity of the peripheral and transcranial stimuli were kept always below the threshold for the elicitation of muscle twitch and thus maintained throughout the experimental session; these

intensities were chosen in order to avoid any subcortical conditioning effect (Di Lazzaro et al. 1998), any spreading to the surrounding cortical areas (Takano et al. 2004) and re-afferent feedback depending by muscle contractions during the conditioning (Quartarone et al. 2006). The magnetic stimuli were delivered through a standard eight-shaped coil connected to a Magstim Rapid Stimulator (Magstim Company, Whitland, Dyfed, UK), with average diameters of the loops of the coil of 9 cm, with a biphasic-wave magnetic pulse, with an amplitude of about 300 μs. The coil was oriented backwards and laterally by 45° respect to the midline, approximately perpendicular to the central sulcus of the left hemisphere, on the optimal site on the scalp to get the wider MEP amplitude from the relaxed right APB (motor hot-spot). The current in the coil flowed, during the first phase of the stimulus, in the direction of the handle. Therefore, the current induced in the cortex took a posterior-anterior direction. We used this biphasic stimulus configuration and this coil orientation in order to ensure comparability with earlier studies on rPAS (Quartarone et al. 2005, 2006). The CS was applied to the right median nerve at the wrist, with the cathode proximally located and was delivered through a Digitimer D160 Stimulator (Digitimer, Welwyn Garden City, Herts, UK). The intensity of the stimulus, with square wave morphology, was individually set to twice the sensory threshold, with the stimulus duration of 500 μs. Concerning control experiments, we used the same set -up and the same means of stimulation. No EMG responses were evoked in the target muscles, regardless the ISI applied during both the rPAS induction protocol.

Recording Systems and Studied Parameters

EMG activity was recorded through Ag–AgCl surface electrodes applied to right APB and ADM using a classic muscle belly-tendon montage. Signals were amplified and filtered (from 32 Hz to 1 kHz) via a Digitimer D150 Amplifier (Digitimer Ltd., Welwyn Garden City, Herts, UK), and stored using a sampling frequency of 10 kHz on a personal computer for off-line analysis (SigAvg Software, Cambridge Electronic Design, Cambridge, UK). During the experiment, the EMG activity was continuously monitored with visual feedback (oscilloscope) and sound (speakers). We measured the peak-to-peak amplitude of 15 consecutive MEP from APB in resting state, obtained through magnetic monophasic stimuli delivered through a high-POW Magstim200 Stimulator (Magstim, Whitland, Dyfed, UK) connected to the same coil and using with the same position and orientation applied in the conditioning protocol; the rise time of the magnetic monophasic stimulus was about 100 μs with a to-zero of about 800 μs. The current flowed in handle direction during the rise-time of the magnetic field, then with a posterior-anterior direction. We applied an intensity of stimulation to obtain a MEP amplitude of ∼1 mV (∼120 % of rMT, rest motor threshold). Similar parameters were applied in recording from the ADM, in order to assess the effects in terms of topographic specificity. We preliminarily evaluated the rMT, defined as the smallest stimulus intensity able to evoke a peak-to-peak MEP of 50 μV in rest right APB, in at least five-out-ten consecutive tracks (Rossini et al. 1994), and the aMT defined as the stimulus intensity able to elicit a reproducible MEP of at least 200 μV in tonically activated right APB in at least five-out-ten consecutive tracks.

EEG was consecutively recorded for five minutes in rest conditions, in the same room where magnetic stimulation was delivered and in the same conditions described above. We used a standard pre-wired headset with 61 Ag–AgCl ring electrodes (FP1, FPz, FP2, AF7, AF3, AFz, AF4, AF8, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FCz, FC2, FC4, FC6, FT8, T7, C5, C3, C1, Cz, C2, C4, C6, T8, TP7, CP5, CP3, CPz, CP1, CP2, CP4, CP6, TP8, P7, P5, P3, P1, Pz, P2, P4, P6, P8, PO7, PO3, POz, PO4, PO8, O1, Oz, O2), as well as a ground-electrode and a reference-one, according to the International 10-20 System for EEG (Micromed, Mogliano Veneto, Italy). Signals were filtered with a bandwidth 0.3/70 Hz, with notch-filter, with a sampling frequency of 512 Hz (Micromed, Mogliano Veneto, Italy). The ground electrode was positioned over Fpz, while mastoids served as the active reference for all electrodes. Skin–electrode impedance was kept under 5 kΩ. The software used for data acquisition was a BrainQuick System (Micromed, Mogliano Veneto, Italy). Eye movements and blinks were detected through electro-oculogram (EOG) with additional electrodes on right peri-orbital region. Data were stored on a PC for offline analysis through a free license of EEGLAB toolbox (Delorme and Makeig 2004). Raw data were appropriately pre-processed and further elaborated in order to remove activities of artifactual nature and to isolate the components of neurophysiological interest. Each block of recorded EEG was divided into epochs of 1″ (300 epochs). For each epoch, time and frequency bands α (8–12 Hz), β (13–30 Hz), θ (4–7 Hz) and δ (1–3 Hz), we quantified the POW, applying a Fast Fourier Transform (FFT) (Hamming window, frequency resolution 1 Hz). The mean absolute band POW was obtained by averaging single POW values. The temporal percentage variations for the POW for each band and in six electrodes (F3, F4, C3, C4, P3, and P4) were calculated in analogy to the Pfurtscheller formula (Pfurtscheller and Lopes da Silva 1999).

Statistical Analysis

The effects of the conditioning protocols on the peak-to-peak MEP amplitude and on the POW, in each frequency

band, were evaluated by means of an analysis of variance for repeated measures (rmANOVA). In particular for the dependent variable MEP amplitude we applied a two-way rmANOVA with *time* (three levels: T_{PRE}, T_0, T_{30}) and *protocol* (four levels: $rPAS_{25ms}$, $rPAS_{sham}$, rTMS, and rENS) as within-subject factor. The peak-to-peak MEP amplitudes were compared by paired-sample *t*-tests. The effects in terms of topographic specificity were studied by an additional three-way rmANOVA with within-subjects factors *time* (T_{PRE}, T_0, T_{30}), *protocol* (four levels: $rPAS_{25ms}$, $rPAS_{sham}$, rTMS, and rENS), and muscle (APB, ADM). The Greenhouse-Geisser method was used if necessary to correct for non-sphericity. For POW we applied a three-way rmANOVA for each band of interest, with factors *protocol* (four levels: $rPAS_{25ms}$, $rPAS_{sham}$, rTMS, and rENS), *time* (three levels: T_{PRE}, T_0, T_{30}) and electrode (six levels: F3, F4, C3, C4, P3, and P4). The Huynh–Feldt correction factor ε was applied to compensate for the possible effects of non-sphericity in the compared measurements; this factor reduces the degrees of freedom of the F-test. In all conditions, the normal distribution of the data was evaluated with the Kolmogorov–Smirnov test (for all $p > 0.2$). Based on the significance of the F-value, to further investigate which electrodes supported the potentially significant three-way interactions, we tested a two-way interactions *protocol* × *time*. *Post-hoc* paired-sample *t*-tests were carried out to assess the significance of interactions, applying the Bonferroni correction for multiple comparisons. A p value < 0.05 was considered significant. All data are presented as mean ± se and as percent change compared to baseline. The correlations between MEP amplitude and POW modulation were performed through Pearson's correlation (significant for $p < 0.05$) for each band on the C3, that is the site of application of magnetic stimuli.

Results

Cortical Excitability

MEP amplitude percentual changes induced by each conditioning protocol ($rPAS_{25ms}$, $rPAS_{sham}$, rTMS, rENS) are shown in Fig. 1. The rmANOVA displayed a significant interaction *time* × *protocol* ($F_{(6,66)} = 42.5$, $p < 0.001$). Then, in order to assess *time* effects, separate ANOVA were carried out: there was a strong effect of *time* only in PAS_{25ms} ($F_{(2,22)} = 23.3$, $p < 0.001$). We obtained a significant increase in MEP amplitude at T_0 ($t_{(1,11)} = 5.65$ $p = 0.002$) and T_{30} ($t_{(1,11)} = 10.12$, $p < 0.001$) in comparison to baseline. Neither rTMS nor rENS produced significant changes of MEP amplitude (Fig. 1).

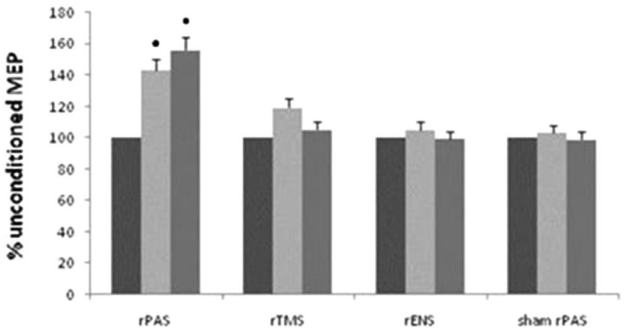


Fig. 1 Shows the conditioning protocols effects on MEP_{APB} amplitude. MEP amplitude increased significantly (the dot indicates the significant difference, $p < 0.05$) only after rPAS, at T_0 (*light gray*) and T_{30} (*middle gray*) in comparison to T_{PRE} (*dark gray*). The error bars refer to se

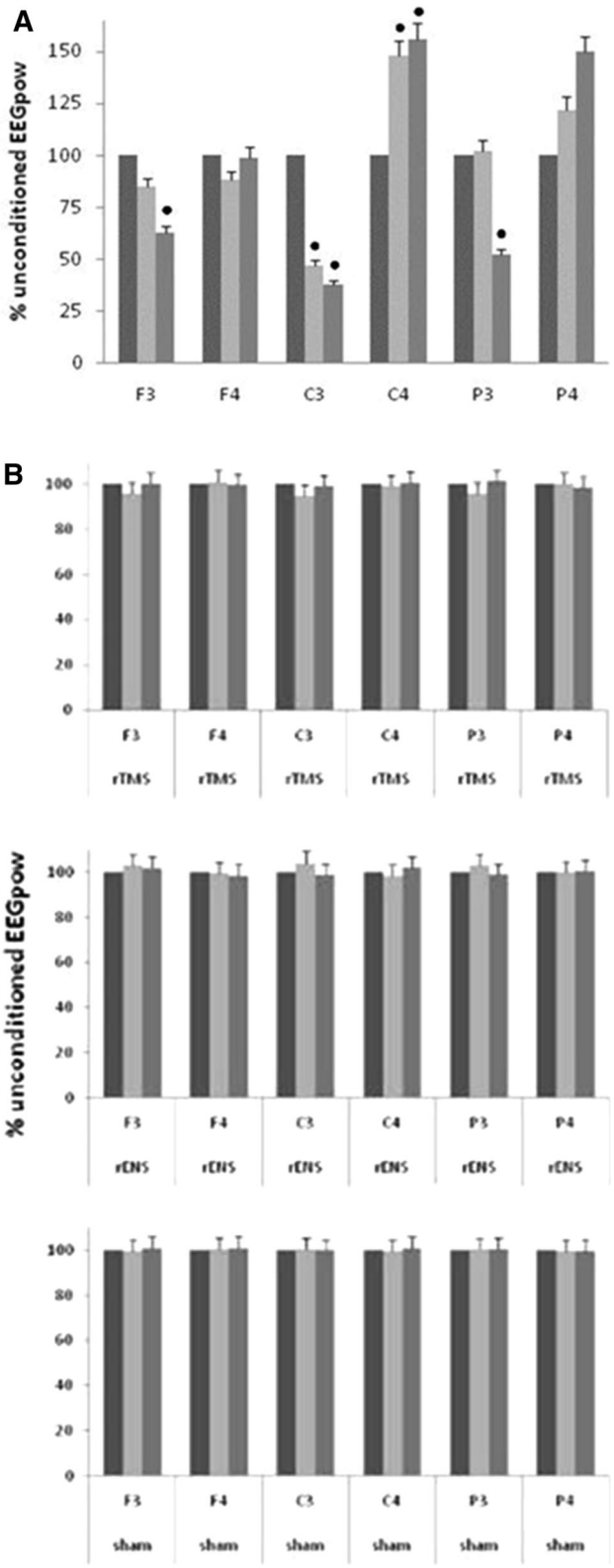
In control experiment we also recorded the MEP amplitude changes from right relaxed ADM muscle, in each subjects. rmANOVA showed a significant *muscle* × *time* × *protocol* ($F_{(6,66)} = 35.8$, $p < 0.001$). Specifically, post hoc *t*-tests showed that mean MEP_{APB} amplitudes were increased at T_0 ($p < 0.001$) and T_{30} ($p < 0.001$), but not in the ADM. Thus, no protocol had significant effects on MEP_{ADM} amplitude.

α Band

Average percentual changes of POW are shown in Fig. 2a. Statistical analysis showed a significant main interaction *protocol* × *electrode* × *time* ($F_{(30,330)} = 4.6$, $p < 0.001$) and *protocol* × *time* ($F_{(6,66)} = 6.3$, $p < 0.001$). POW after PAS_{25ms} showed a significant reduction in C3 inT_0 ($t_{(1,11)} = -3.4$, $p = 0.01$), and in T_{30} ($t_{(1,11)} = -4.7$, $p = 0.009$), in comparison to baseline, and an increase in C4 to baseline at T_0 ($t_{(1,11)} = 2.8$, $p = 0.02$) and T_{30} ($t_{(1,11)} = 3.1$, $p = 0.02$). In addition, POW reduction widespread from C3 to near ipsilateral electrodes P3 ($t_{(1,11)} = -2.3$, $p = 0.04$) and F3 ($t_{(1,11)} = -3.8$, $p = 0.01$) at T_{30}. No significant effects were detectable after PAS_{sham} (for all effects, interactions and comparisons, $p > 0.5$) (Fig. 2b). rTMS produced a wide, ipsilateral, and non-significant POW decrease (about − 4 %) at T_0, whereas rENS a slight non-significant increase (3 %). Both effects were short lasting, since they were absent at T_{30} (Fig. 2b).

β Band

Average percentual changes of POW are shown in Fig. 3a. Statistical analysis showed a significant interaction *protocol* × *region* × *time* ($F_{(30,330)} = 7.8$, $p < 0.001$) and *protocol* × *time* ($F_{(6,66)} = 8.6$, $p < 0.001$). POW data showed



◀**Fig. 2** **a** Displays the POW percent changes after $rPAS_{25ms}$ application in each electrode in α-band at T_0 (*light gray*) and T_{30} (*middle gray*) in comparison to baseline (*dark gray*). The dot indicates the significant difference ($p < 0.05$) between $T_{0,30}$ and T_{PRE}. α-POW modulation was firstly focal (decrease in C3, increase in C4), and then spread to F3 and P3 (both decrease) **b** displays the POW percent changes after the other three conditioning protocol in each electrode in α-bands, at T_0 (*light gray*) and T_{30} (*middle gray*), in comparison to baseline (*dark gray*). The error bars refer to se. No significant changes were detected

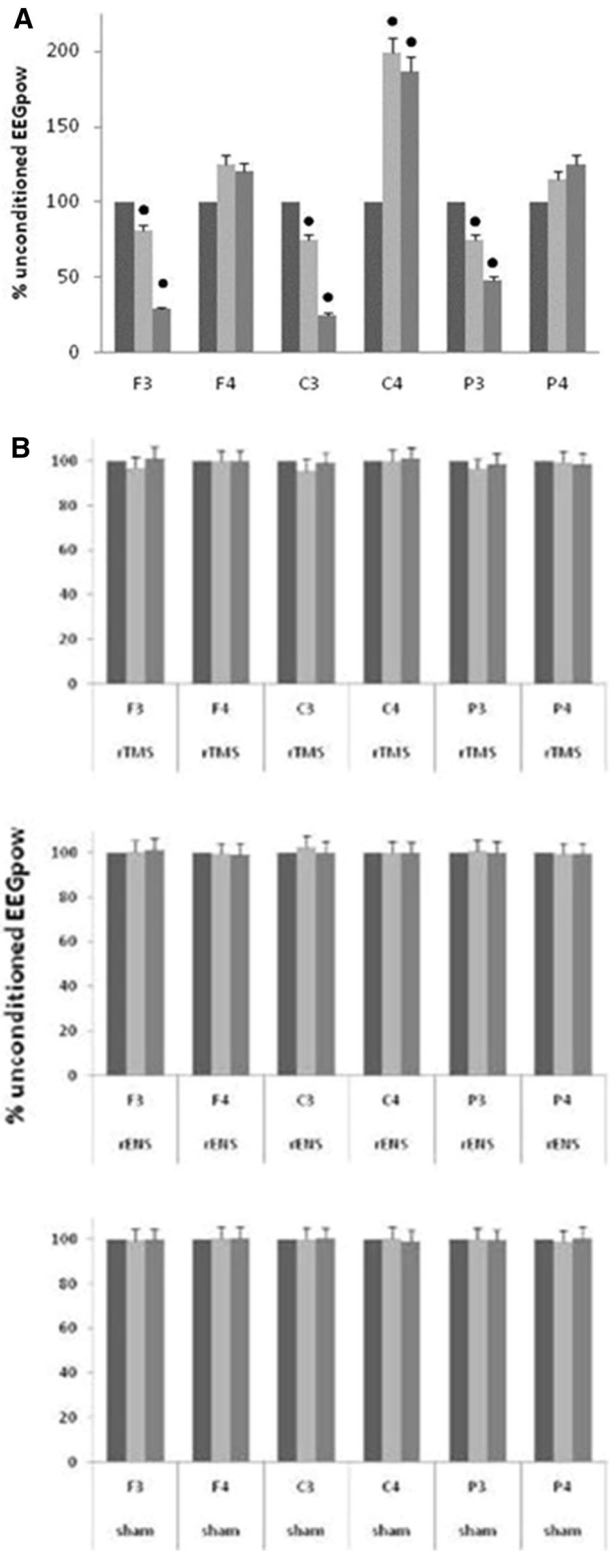
after PAS_{25ms} a diffuse hemispheric reduction in T_0 [C3 ($t_{(1,11)} = -3.02$, $p = 0.02$), F3($t_{(1,11)} = -3.1$, $p = 0.02$), P3 ($t_{(1,11)} = -2.2$, $p = 0.05$)] in comparison to baseline and in T_{30} to baseline [C3($t_{(1,11)} = -7.04$, $p = 0.004$); F3 ($t_{(1,11)} = -7.2$, $p = 0.004$); P3($t_{(1,11)} = -8.92$, $p < 0.001$)]. In C4 we observed a POW increase in T_0 ($t_{(1,11)} = 5.4$, $p < 0.001$) and T_{30} ($t_{(1,11)} = 4.8$, $p < 0.001$) to baseline. No significant effects were shown after PAS_{sham} (for all effects, interactions and comparisons, $p > 0.5$) (Fig. 3b). rTMS produced a focal (C3) and non-significant POW decrease (about − 2 %) at T_0, whereas rENS a slight non-significant increase (3 %). Both effects were short lasting, since they were absent at T_{30} (Fig. 3b).

θ Band

Average percentual changes of POW are shown in Fig. 4a. The statistical analysis showed a significant interaction *protocol* × *region* × *time* ($F_{(30,330)} = 4.9$, $p = 0.009$) and *protocol* × *time* ($F_{(6,66)} = 4.9$, $p = 0.001$). After PAS_{25ms}, we observed a hemispheric diffused short-lasting absolute POW reduction [F3 ($t_{(1,11)} = -2.55$, $p = 0.03$), C3 ($t_{(1,11)} = -3.4$, $p = 0.008$), P3 ($t_{(1,11)} = -2.3$, $p = 0.05$)], followed by an increase in T_{30} (C3 ($t_{(1,11)} = -3.4$, $p = 0.008$), F3 ($t_{(1,11)} = -3.4$, $p = 0.008$), P3 ($t_{(1,11)} = -2.4$, $p = 0.01$) in comparison to T_0. No significant effects were shown in the PAS_{sham} session (for all effects, interactions and comparisons, $p > 0.5$) (Fig. 4b). rTMS and rENS after-effects were similar to those observed in α/β-bands (Fig. 4b).

δ Band

Average percentual changes of POW are shown in Fig. 5a. The statistical analysis showed a significant interaction *protocol* × *region* × *time* ($F_{(30,330)} = 7.2$, $p < 0.001$), and *protocol* × *time* ($F_{(6,66)} = 3.2$, $p = 0.01$). The temporal variations after PAS_{25ms} were similar to that observed in θ band [T_0 to baseline: F3($t_{(1,11)} = -2.4$, $p = 0.04$), P3 ($t_{(1,11)} = -3.5$, $p = 0.007$), C3 ($t_{(1,11)} = -2.9$, $p = 0.02$). T_{30}–T_0: F3 ($t_{(1,11)} = -17.32$, $p < 0.001$), C3 ($t_{(1,11)} = -2.9$, p = 0.02), P3 ($t_{(1,11)} = -3.5$, $p = 0.007$)]. PAS_{sham} session did not produced significant effects (for all effects, interactions and comparisons, $p > 0.5$) (Fig. 5b). rTMS and rENS after-effects were similar to those observed in α/β-bands (Fig. 5b).



◀**Fig. 3** **a** Displays the POW percent changes after $rPAS_{25ms}$ application in each electrode in β-band at T_0 (*light gray*) and T_{30} (*middle gray*) in comparison to baseline (*dark gray*). β-POW was diffusely reduced ipsilaterally and increased in C4. The dot indicates the significant difference ($p < 0.05$) between $T_{0,30}$ and T_{PRE} **b** displays the POW percent changes after the other three conditioning protocol application in each electrode in β bands, at T_0 (*light gray*) and T_{30} (*middle gray*), in comparison to baseline (*dark gray*). The error bars refer to se

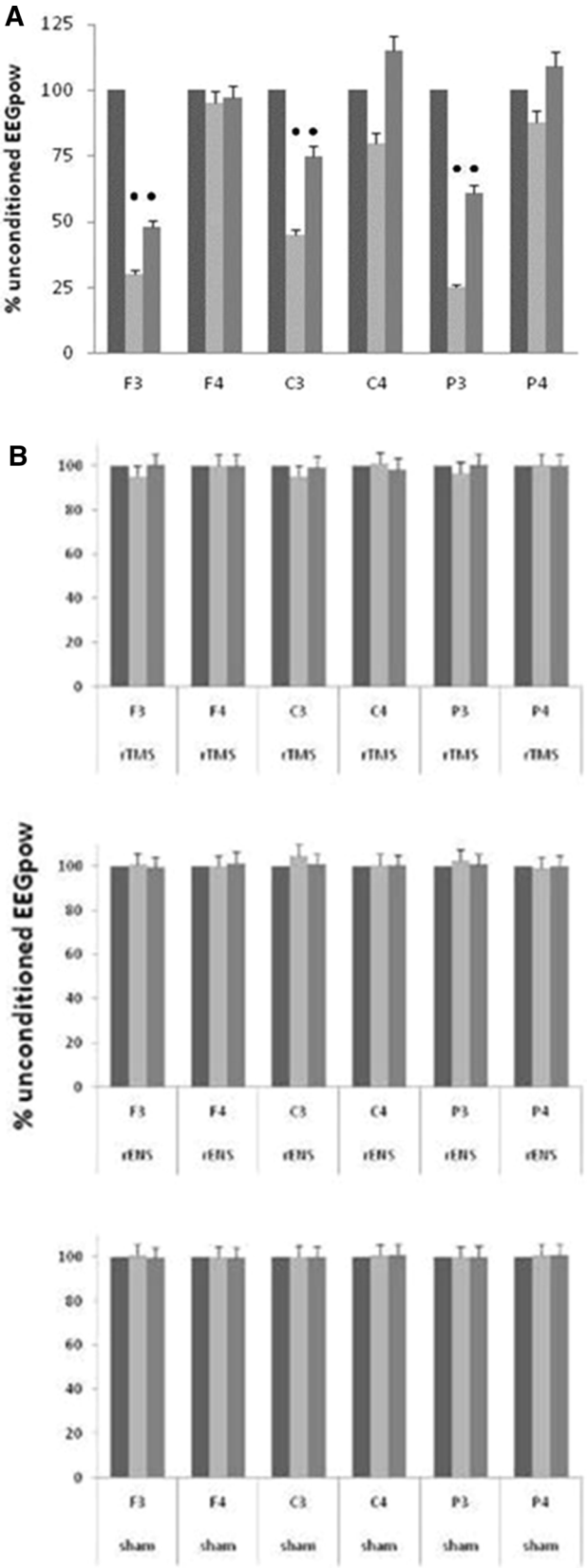
MEP-POW Correlations

After PAS application, we explored the correlation between MEP amplitude and POW changes in each band and time from C3, site of rPAS application and MEP induction. After $rPAS_{25ms}$ application we found in α-band a significant correlation between MEP amplitude increase and POW decrease [T_0 ($r = -0.843$, $p = 0.002$), T_{30} ($r = -0.860$, $p = 0.001$)], similarly to β-one (T_0, $r = -0.889$, $p = 0.001$; T_{30} ($r = -0.904$, $p < 0.001$)]. In correspondence of the highest values of MEP amplitude we found the lowest spectral POW ones. θ correlation values showed also a significant MEP amplitude-POW correlation in T_0 ($r = -0.924$, $p < 0.001$) and T_{30} ($r = 0.927$, $p < 0.001$).

Discussion

rPAS is a valuable non-invasive paradigm inducing regional LTP-like plasticity within the human sensory-motor cortex (Quartarone et al. 2006). In fact, only two minutes of sub-threshold 5 Hz-$rPAS_{25ms}$ induced a long-lasting increase in the excitability of the homotopic corticospinal output from the stimulated M1 (Quartarone et al. 2006). As an extension of this previous study, we demonstrated for the first time that changes in cortico-spinal excitability were paralleled by robust long-lasting effect on EEG power in many bands, below the stimulating TMS coil. More in detail, the rPAS protocol induced a long-lasting homotopic cortical excitability modulation, as indexed by MEP amplitude increase, that was paralleled by a long-lasting reduction of α/β POW and by a widespread hemispheric θ/δ bands POW decrease at first, and then increase. Both the high/low frequency bands-POW modulations were clearly correlated to MEP amplitude increase.

Indeed, our findings significantly differ from the high frequency rTMS synchronization after-effects on M1 brain oscillatory activity, reported in literature. In fact, high frequency rTMS has been shown to entrain cortical oscillatory activity with an α/β power increase during rTMS application, whose effects are relatively short-lasting (Fuggetta et al. 2008; Veniero et al. 2011). Other high frequency rTMS studies have shown a slow-frequency POW increase (Griskova et al. 2007), an α-event-related desynchronization (ERD) (Klimesch et al. 2003), and also effects on different bands-POW (Okamura et al. 2001). Notably, α and β bands are differently entrained by rTMS. In resting condition, the effects of rTMS over α-band are



◀**Fig. 4** **a** Displays the POW percent changes after $rPAS_{25ms}$ application in each electrode in θ-band at T_0 (*light gray*) and T_{30} (*middle gray*) in comparison to baseline (*dark gray*). θ-POW was diffusely reduced ipsilaterally at T_0 and then increased relatively at T_{30}. The dot indicates the significant difference ($p < 0.05$) between $T_{0,30}$ and T_{PRE} **b** displays the POW percent changes after the other three conditioning protocol application in each electrode in β bands, at T_0 (*light gray*) and T_{30} (*middle gray*), in comparison to baseline (*dark gray*). The error bars refer to se

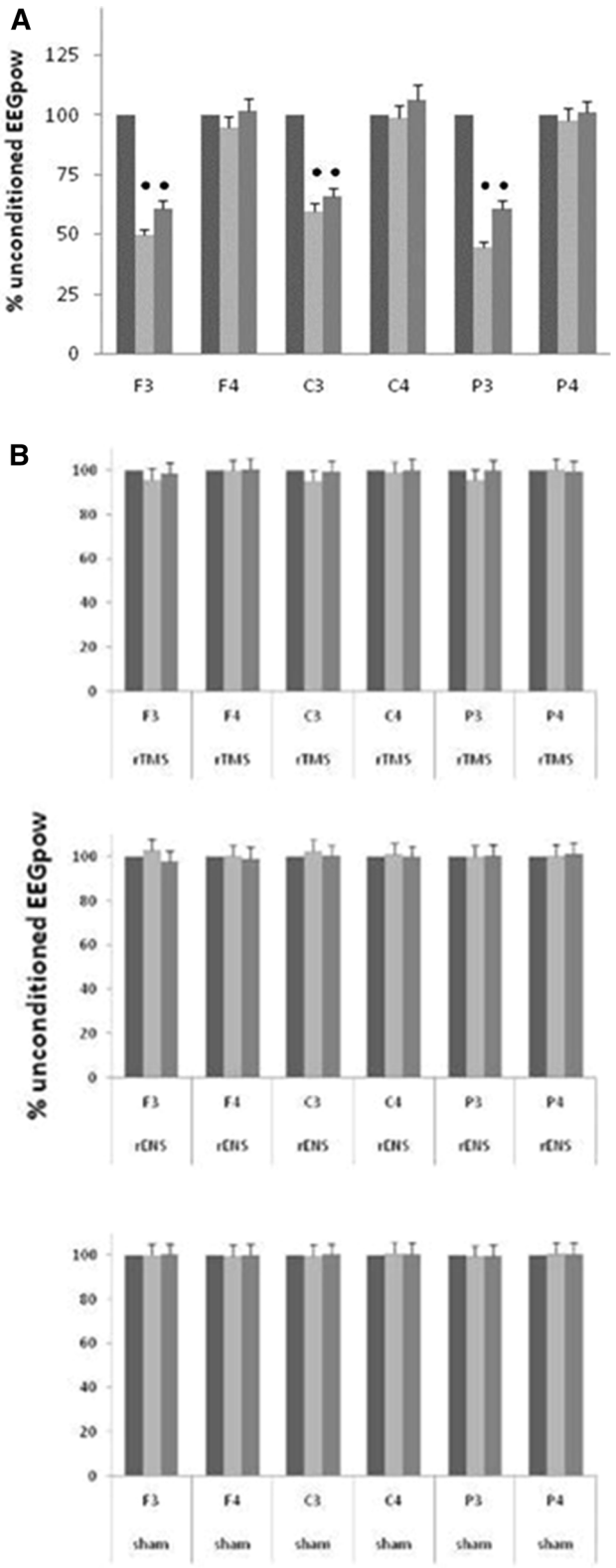
diffused and may outlast the stimulation train, according to either the stimuli number and intensity (Fuggetta et al. 2008; Veniero et al. 2011) or the general reactivity of sensory-motor cortex at rest (Fuggetta et al. 2005). On the other hand, β modulation is focal and short-lasting, since it is more related to MEP amplitude (i.e. to motor demand), than α-band (Veniero et al. 2011).

Concerning low-frequency oscillations (LFOs), a recent study on TMS event-related power (ERPow), showed a significant POW reduction after 5 Hz-rTMS, whereas 10 Hz frequency rose a synchronization (Fuggetta and Noh 2013).

It is likely that the discrepancies with previous works are mainly due to methodological differences related to the dual stimulation paradigm (rTMS + rENS) that is able to induce Hebbian associative plasticity at cortical level (Stefan et al. 2000; Quartarone et al. 2006).

Oscillatory Neuronal Substrate of rPAS-Induced Plasticity

Our rPAS protocol induced particular α/β-POW after-effects in terms of duration (long-lasting), direction (α/β reduction; θ/δ decrease at T_0, followed by increase at T_{30}), and regions involved (progressively diffuse in α, throughout diffuse in β, θ, and δ). The by-time growing POW after-effects could be related, in analogy to rTMS, to a progressively entrainment of the natural brain oscillations within sensory-motor cortex during rPAS application, likely due to a temporal summation of the effects induced by each single paired-pulses, able to bring to resonance the activity of a growing number (or the percentage) of neurons of the targeted sensory-motor network after rPAS application also. TMS probably activates intracortical fibers travelling 'horizontally' with respect to the cortical surface (Rothwell 1997), and peripheral electrical stimulation induces activity in cortico-petal (thalamo-cortical or cortico-cortical) 'vertical' fibers (Pons and Kaas 1985), that are the basic networks involved in associative plasticity. Differently from classic PAS, the rPAS induced cortico-spinal facilitation is paralleled by a selective loss of short-



◀**Fig. 5** **a** Displays the POW percent changes after $rPAS_{25ms}$ application in each electrode in δ band at T_0 (*light gray*) and T_{60} (*middle gray*) in comparison to baseline (*dark gray*). δ-POW was diffusely reduced ipsilaterally at T_0 and then increased relatively at T_{30}. The dot indicates the significant difference ($p < 0.05$) between $T_{0,30}$ and T_{PRE} **b** displays the POW percent changes after the other three conditioning protocol application in each electrode in δ bands, at T_0 (*light gray*) and T_{60} (*middle gray*), in comparison to baseline (*dark gray*). The error bars refer to se

latency afferent inhibition at an ISI of 25 ms (SAI_{25ms}) but not by a cortical silent period duration change (Quartarone et al. 2006).

SAI is controlled by muscarinic neurotransmission, since scopolamine (receptor-blockage) reduces the amount of SAI_{25ms} (Di Lazzaro et al. 2000), and by $GABA_A$ergic inhibition of acetylcholine release, since lorazepam modulate the magnitude of SAI_{25ms} (Vazquez and Baghdoyan 2003; Di Lazzaro et al. 2005). Therefore, it is conceivable that $rPAS_{25ms}$ reduced the amount of SAI_{25ms} through LTP-like effects on glutamatergic synaptic inputs reaching $GABA_A$ergic neurons that control the magnitude of SAI_{25ms}. This latter may in turn contribute to long lasting effect on corticospinal excitability. The lack of specific effects on intracortical inhibition may depend on different stimulation intensity/frequency in comparison to classic PAS. Hence, the involvement of glutamatergic and cholinergic networks, beyond GABAergic ones, may account for the rPAS after-effects direction.

Alternatively, it has been suggested that thalamus may have an important role in determining the direction and the topographic specificity of the effects of TMS stimuli (Groppa et al. 2013; Fuggetta and Noh 2013). A possible hypothesis is that a convergence of electric/magnetic stimuli at cortical and thalamic level, depending on the ISI applied, may have a modulatory direct/indirect effect on a thalamic pacemaker (Bestmann et al. 2004; Fuggetta et al. 2008, Veniero et al. 2011). The latter may in turn increase the sensory-motor areas reactivity, as expressed by the firstly focal α-POW reduction (on C3, where TMS stimuli were applied), and then diffused; α-modulation may in turn strength the motor output excitability, as indexed by the throughout diffused β-POW reduction. Similarly, the θ/δ-POW spread reduction may be also the results of a modulation within the thalamo–cortico–thalamic network (Fuggetta and Noh 2013).

As complementary finding, we observed that the effects of rPAS were not only confined to the sensorimotor regions underlying the TMS coil, but also extended to the contralateral sensorimotor cortex, although with the opposite sign (increase of α/β Pow). It is likely that trans-callosal inhibitory connections may also play a role (Ferbert et al. 1992), as suggested by functional magnetic resonance imaging studies, in which unilateral hand movements were associated with contralateral activation and ipsilateral deactivation (Allison et al. 2000). Our findings are also consistent with previous data showing that PAS effects on

EEG, as indexed by TEP, were not confined to the ipsilateral sensorimotor regions, but extended to the contralateral sensory-motor cortex, with opposite direction (Huber et al. 2008).

Nevertheless, a controversial problem is whether the oscillatory activity changes after our neuromodulation protocol are a simple rebound phenomenon to the synchronizing effect of repetitive paired-pulses application, or a direct entrainment after-effect on brain oscillations produced by STDP phenomena.

The first hypothesis seems unlikely since 5 Hz-rTMS protocol lacked of significant after-effects in analogy to (Fuggetta et al. 2008). Indeed, we observed only a small and diffuse α-POW and a focal β-POW reduction in the hemisphere of rTMS application, without significant MEP amplitude increase. It has been shown that subthreshold 5 Hz-rTMS can induce lasting changes in specific neuronal subpopulations in the human corticospinal motor system, depending on the intensity and duration of rTMS (Quartarone et al. 2005). Thus, the low number of stimuli we delivered (600) was probably not sufficient to induce any significant effect. Indeed, as indicated above the increase on POW described by (Fuggetta et al. 2005) is probably due to the higher intensity of stimulation employed (90 % aMT -our study- vs. 80/100 % rMT).

Similarly, the short lasting and weak synchronizing after-effect of rENS may be due to the limited number of stimuli (Sannita 2000). Moreover, previous studies have already demonstrated that more than 10 min of high-frequency rENS are required to consistently increase the corticospinal excitability (Ridding et al. 2000, 2001; Pyndt and Ridding 2004). Such increase has been proposed to be dependent on LTP-like phenomena (Ridding et al. 2000; Ridding and Uy 2003), and/or on a modulation of GABAergic interneurons (Kaelin-Lang et al. 2002), either at M1 or at dorsal premotor cortex level (Golaszewski et al. 2004; Wu et al. 2005). Furthermore, inhibitory intra-cortical circuits (e.g. SAI and LAI) may also be involved in such mechanism. Nevertheless, rENS has been shown to modulate spinal excitability (as suggested by H-reflex modulation), and then motor cortex excitability (Ridding et al. 2000; McKay et al. 2002). Hence the lack of significant effects on POW might also depend on the different way rENS and TMS act on motor neuronal pool.

Therefore, POW decrease was induced only by rTMS + rENS, since $rPAS_{sham}$ did not cause any significant effect.

A particular finding in our work concerns the clear MEP-POW correlations that have not clearly emerged in previous studies, maybe due to a weak recruiting effect of magnetic stimuli series on cortical oscillatory activity (Mäki and Ilmoniemi 2010), in comparison to higher frequencies (Veniero et al. 2011). On the other hand, EEG signals typically reflect the activity in a large cortical region, while cortical activity related to MEPs should be specific to the neurons controlling the target muscles and may be influenced by the spinal excitability. It is likely the rTMS combined with rENS may induce the emergence of the α/β-bands/MEP-amplitude correlation by boosting up LTP-like phenomena at sensory-motor cortex.

Another interesting finding consisted in the reduction of α/β-POW paralleled by a short-lasting widespread hemispheric decrease in θ/δ bands. Electrophysiological studies on animals have suggested that pyramidal neurons in the neocortex are able to sustain α/θ rhythmic firing activities (Silva et al. 1992). Hence, lower frequencies involvement in rPAS effects is not surprising. In addition, we found a significant biphasic MEP/θ-POW correlation (i.e. lower θ-POW with increased MEP amplitude at T_0, and higher θ-POW, compared to T_0 -but not T_{PRE}-, with increased MEP amplitude at T_{30}). Moreover, considering that this LFO is possibly related to $GABA_A$ receptors-mediated inhibitory neurotransmission within motor cortex (Manganotti et al. 2012), it is likely that a GABAergic disinhibition is required in order to trigger the subsequent LTP-like after-effects, indexed by α/β POW reduction. It is intriguing to note that the relative increase of θ/δ-POW at T_{30} may represent a widespread GABA-mediated homeostatic servo-mechanism, containing the spreading of the α/β oscillatory activity.

Potential Significance

Central α has been proposed to reflect the natural frequency of motor area at rest, as showed in in vitro studies (Castro-Alamancos 2000; Castro-Alamancos and Rigas 2002; Castro-Alamancos et al. 2007). Therefore, it is not surprising that rPAS would have affected the α-rhythm (Veniero et al. 2011).

Neural oscillations in the β-band are a defining signature of one of the most prominent networks in the primate nervous system: the somato-motor. These oscillations occur coherently throughout this network comprising the primary somatosensory (S1) and motor (M1) cortices (Brovelli et al. 2004; Witham and Baker 2007), premotor cortex (Ohara et al. 2001), basal ganglia (Jenkinson and Brown 2011), thalamus (Marsden et al. 2000; Paradiso et al. 2004), cerebellum (Aumann and Fetz 2004; Soteropoulos and Baker 2006), and even the spinal cord (Kilner et al. 2004; Baker 2007). In accordance with the anatomy of this network, these oscillations have traditionally been strictly associated with cortical control and monitoring of descending pathways (Baker 2007; Kilner et al. 2004; Salenius et al. 1997). However, recent evidences suggest that somatosensory demands, both in anticipation and

during the processing of tactile stimuli, also modulate β-oscillations throughout this network (van Ede and Maris 2013). It is worthy to remember that PAS, targeting the primary somatosensory cortex, led to excitability changes as indicated by analysis of the cortical somatosensory evoked potentials paralleled by an improvement of two-point discrimination performance (Tegenthoff et al. 2005). Future studies are needed to demonstrate a causality between these oscillatory signatures induced by rPAS and the relationship with relevant sensory-motor behaviors.

It has been proposed that the reorganization induced by afferent stimulation may have a therapeutic application for the rehabilitation of hand function (Conforto et al. 2002). Since 5 Hz-rPAS$_{25ms}$ is highly efficient in enhancing the excitability of the corticospinal output to the stimulated limb, it may be a useful tool for motor neurorehabilitation promoting a sensory-motor coupling within β-oscillations.

In conclusion, our findings about α/β-POW decrease may be hypothetically considered as a potential marker of a strengthened functional connectivity between sensory and motor areas, as expressed by sensory-motor areas activation (i.e. α/β-POW decrease), and by MEP amplitude increase. Further studies should be fostered in order to support our findings and better elucidate the mechanisms underlying such functional connectivity.

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