EJN fens European Journal of Neuroscience

*European Journal of Neuroscience, Vol. 31, pp. 770–778, 2010* doi:10.1111/j.1460-9568.2010.07100.x

COGNITIVE NEUROSCIENCE

# Endogenous control of waking brain rhythms induces neuroplasticity in humans

Tomas Ros,[1] Moniek A. M. Munneke,[2] Diane Ruge,[3] John H. Gruzelier[1] and John C. Rothwell[3]
[1]Department of Psychology, Goldsmiths, University of London, Lewisham Way, New Cross, London, SE14 6NW, UK
[2]Department of Clinical Neurophysiology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
[3]Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, London, UK

*Keywords*: brain–computer interface (BCI), electroencephalogram (EEG), neurofeedback, neuroplasticity, primary motor cortex (M1), transcranial magnetic stimulation (TMS)

## Abstract

This study explores the possibility of noninvasively inducing long-term changes in human corticomotor excitability by means of a brain–computer interface, which enables users to exert internal control over the cortical rhythms recorded from the scalp. We demonstrate that self-regulation of electroencephalogram rhythms in quietly sitting, naive humans significantly affects the subsequent corticomotor response to transcranial magnetic stimulation, producing durable and correlated changes in neurotransmission. Specifically, we show that the intrinsic suppression of alpha cortical rhythms can in itself produce robust increases in corticospinal excitability and decreases in intracortical inhibition of up to 150%, which last for at least 20 min. Our observations may have important implications for therapies of brain disorders associated with abnormal cortical rhythms, and support the use of electroencephalogram-based neurofeedback as a noninvasive tool for establishing a causal link between rhythmic cortical activities and their functions.

## Introduction

Brain oscillations have thus far been implicated in many 'ongoing' functions such as binding and attention (Buzsáki & Draguhn, 2004; Fries *et al.*, 2008; Schroeder & Lakatos, 2009); however, less direct evidence exists on the long-term effects of their entrainment and possible role in brain plasticity (Steriade & Timofeev, 2003). Today's brain stimulation devices, including transcranial magnetic stimulation (TMS) and direct-current stimulation, are noninvasive and enable the accurate study of neuroplasticity in the intact human brain. The added hope is that their joint use with electroencephalogram (EEG) registration will further elucidate the functions of neuronal oscillations.

The present study, which combines TMS and EEG, is the first to additionally exploit a brain–computer interface (BCI) in order to manipulate brain rhythms endogenously (Fetz, 2007). A BCI allows real-time information of brain activity to be fed-back to a user by means of a computer in a closed 'neurofeedback' loop (NFB), enabling endogenous control and natural operation of brain oscillations across cortical networks *in vivo* (Nowlis & Kamiya, 1970; Delorme & Makeig, 2003). Crucially, brain stimulation investigations to date have induced plasticity by magnetic or electric fields that are by definition exogenous and artificial. Such patterns and the driving forces they produce may not necessarily be intrinsic to the brain. Moreover, the inherent problem faced by many behavioural manipulations of the EEG is the difficulty of dissociating stimulus-dependent vs. stimulus-independent oscillations. During NFB subjects are exposed to the same visual feedback stimuli, and hence their entrained EEG differences may be considered as resulting minimally from external factors, and instead represent the modulation of internal or 'background' brain state(s). Finally, we also investigated the relationship between TMS measures and full-band EEG (Vanhatalo *et al.*, 2005), which here includes very fast oscillations (> 100 Hz), as well as slow direct currents (DCs). To the best of our knowledge, specific changes in these two latter EEG measures have not been previously explored in TMS–EEG studies (Thut & Miniussi, 2009).

Although neuroplasticity appears to be active through diverse cellular processes (Nelson & Turrigiano, 2008) in the central nervous system, in TMS methodology it is operationally defined as a significant and lasting change in the motor-evoked potential (MEP), whose amplitude is representative of the strength of neurotransmission from motor cortex to muscle, evoked by a magnetic pulse. We therefore investigated whether both pronounced and persistent oscillatory patterns expressed during NFB would be associated with tangible and long-lasting (plastic) changes in MEPs elicited by TMS of primary motor cortex. A growing body of evidence (Lazzaro *et al.*, 2008) indicates that MEPs evoked by single TMS pulses best reflect the overall responsiveness of the corticospinal pathway, or corticospinal excitability (CSE), whereas those originating from paired pulses enable the discrimination of intracortical transynaptic mechanisms, such as those pertaining to short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF). Our hypothesis was that

*Correspondence*: Dr T. Ros, as above.
E-mail: t.ros@gold.ac.uk

*Received 18 September 2009, revised 11 November 2009, accepted 11 December 2009*

NFB-induced alpha (8–12 Hz) rhythm desynchronization, generally considered a marker of cortical activation (Neuper *et al.*, 2006), might produce a durable enhancement in corticospinal excitability, given that previous studies have found an inverse association between spontaneous alpha synchronization and MEP amplitude (Romei *et al.*, 2008; Sauseng *et al.*, 2009). In contrast, low beta (12–15 Hz) synchronization, which has been associated with cortical deactivation (Oishi *et al.*, 2007) and motor inhibition (Sterman, 1996), might produce an opposite pattern.

## Materials and methods

### *Study design*

Twenty-four healthy participants (12 women, 12 men, 31 ± 5 years, all right-handed) were randomly allocated to two protocol groups for a single 30-min NFB session: alpha desynchronization ($n$ = 12) or low beta synchronization ($n$ = 12). All participants were naive to the neurofeedback protocols used in this study. Experimental procedures were approved by the NHHN/ION research ethics committee, and were in accordance with the Declaration of Helsinki, and no adverse effects were reported by the participants during the study.

### *NFB apparatus and procedure*

EEG signals were recorded using a NeXus-10 DC-coupled EEG amplifier using a 24-bit A-D converter (MindMedia, Roermond-Herten, the Netherlands) capable of full-band EEG recording, and NFB training was carried out with Biotrace+ software on an Intel DualCore computer with a 15-inch screen. The EEG used for recording and feedback was sampled at 256 Hz with an Ag/Cl scalp electrode placed above the right first dorsal interosseous (FDI) muscle cortical representation/'hot spot' (approx. C3), which was referenced to the contralateral mastoid. The scalp area was carefully scrubbed with NuPrep abrasive gel, followed by application of Ten20 electrode paste. The ground electrode was placed on the right arm. For the purpose of online NFB training, the EEG signal was infinite impulse response (IIR) bandpass filtered to extract alpha (8–12 Hz) and low beta (12–15) amplitudes ($\mu$V peak-to-peak) with an epoch size of 0.5 s. Likewise, EEG was passively co-registered at the left FDI motor cortical representation (approx. C4) referenced to its contralateral mastoid. In order to analyse data offline, IIR digital filtered (Butterworth 3rd order) EEG amplitude data of each bandwidth [DC, delta (1–4 Hz), theta (4–7 Hz), alpha (8–12 Hz), low beta (12–15 Hz), beta (15–25 Hz), high beta (25–40 Hz), low gamma (40–60 Hz) and high gamma (60–120 Hz)] were then exported at 32 samples/s. In addition, offline fast Fourier transform of raw (256 Hz) data was used to calculate and export the mean frequency for each bandwidth (except for DC) at 32 samples/s. All sampled data were subject to offline voltage-threshold artefacting for ocular, head movement and muscle contamination, whereby outlying data points with amplitudes of > 3 SD were rejected using histogram analysis of each bandwidth. All means were then computed for the 3-min epochs each defined as a 'period'. Periods 0 and 11 consisted of pre- and post-(feedback-free) resting EEG measurements in the eyes open condition. Periods 1–10 consisted of visual feedback training.

### *NFB training procedures*

The first resting baseline was recorded during a 3-min eyes open EEG recording at rest just before the start of feedback, and the second 3-min EEG just after the end of training. During feedback, the ALPHA group aimed to suppress absolute alpha (8–12 Hz) amplitude while the BETA group aimed to elevate absolute low beta amplitude (12–15 Hz). Subjects were given no explicit instructions or mental strategies by the experimenter on how to achieve control over their EEG, but were told to be guided by the visual feedback process. This consisted of a clearly visible bar graph on the left-hand side of the screen whose height was proportional and fluctuated according to the real-time amplitude of the relevant scalp EEG rhythm. Participants were told to try and learn to maintain the level of the bar graph for as long as possible either above (in case of low beta) or below (in case of alpha) a set threshold. This threshold was automatically computed and set to be either 30% of the time above or below the initial 3-min mean baseline alpha or low beta amplitude, respectively. The dynamic of several visual games could thus be influenced depending on the volitional control of the EEG amplitude and whether the 'reward' threshold condition was met. For example, in a game called 'Puzzles', moving puzzles automatically assembled to form an image but this process would momentarily stop when the reward threshold was not met during feedback. All other games were based on a similar 'start/stop' scenario, and included the 'Mazeman', 'Space Invaders', 'Mandala' and 'Bugs' games, which are part of the Biotrace+ software (MindMedia). Both NFB protocols used the same series of displays and games, which were given in a random order for approx. 6 min each. For the low beta protocol a supplementary inhibition (40–60 Hz) that temporarily stopped the game was used to ensure low beta reward was not driven by muscle artefacts. Right (FDI) and left (FDI) hand electromyographic (EMG) activity was monitored via the EMG amplifier used to record the TMS MEPs.

### *Neurofeedback data analyses*

Offline analysis of NFB training efficacy for each subject was defined by a training coefficient, or the Pearson correlation between the period number (0–10, baseline = 0) and the average EEG amplitude ($\mu$V, peak-to-peak) of that period. This had a range of −1 (relative decrease) to +1 (relative increase). Hence for subjects in the ALPHA and BETA groups successful training was indicated by more negative or positive coefficients, respectively. Additionally, the normalized training EEG change for each subject was estimated by the ratio of the average EEG amplitude for each of the ten training periods and the first baseline EEG, and designated as training EEG change (for that period). Likewise, the normalized change in the baseline EEG amplitude was expressed by the ratio of the second divided by the first baseline, and designated as resting EEG change.

### *Transcranial magnetic stimulation (TMS) apparatus and procedure*

The course of the experiment is shown in Fig. 1, which was used to test the impact of NFB training on corticomotor measures of CSE, SICI and ICF. TMS parameters (CSE, SICI, and ICF) were measured before ($T_0$) and twice after NFB ($T_1$ and $T_2$). In random order, 78 TMS responses were measured, which required approximately 6 min per hemisphere. We evaluated the TMS parameters of both hemispheres, first left (trained) and then right (untrained) hemisphere, to investigate hemispheric effects of NFB. The $T_1$ measurements were performed about 3–15 min after NFB training, and $T_2$ after 15–27 min. Well-established standard TMS paradigms were used to measure the corticospinal and intracortical parameters (Lazzaro *et al.*, 2008). All measurements were carried out with two monophasic Magstim 200 magnetic stimulators (Magstim, Whitland, UK), which


FIG. 1. Schema showing time-line of the experiment. Before and twice after neurofeedback training (NFB), motor-evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS) were recorded during 6-min blocks of time periods $T_0$, $T_1$ and $T_2$ from the hand muscles (FDI, first dorsal interosseous) corresponding to the trained left and untrained right hemisphere corticospinal projections.

were connected with a 'Y-cable' to a 70-mm figure-of-eight coil. We determined the 'hot spot' of the FDI muscles for each hemisphere separately. The coil was placed flat on the skull with the handle pointing backward and rotated about 45° away from the midline. Resting motor threshold (RMT) intensity was defined as the lowest stimulator output intensity capable of inducing MEPs of at least 50 $\mu$V peak-to-peak amplitude in the FDI muscle in at least half of 10 trials. Active motor threshold was defined as the intensity needed to evoke an MEP of about 200 $\mu$V during a 5–10% maximum voluntary contraction. CSE was quantified by the amplitude of the MEP elicited by a single test TMS pulse. The test pulse intensity was set to yield an average MEP amplitude of 1 mV at baseline ($T_0$), and was kept constant throughout the experiment. SICI and ICF were evaluated using the paired pulse protocol developed by Kujirai *et al.* (1993). In random trials the test pulse was preceded by a subthreshold conditioning pulse (80% active motor threshold) with an interstimulus interval (ISI) of 3, 10 or 12 ms. The test response was suppressed (SICI) at ISI = 3 ms, whereas facilitation occurred at ISI = 10 and 12 ms (ICF = mean of both time points). A run consisted of 78 stimuli given at approximately 0.25 Hz. Forty-eight paired-pulse (12 for each ISI) and 30 single-pulse MEPs were recorded. Single-pulse MEP amplitudes were normalized as $T_1$ divided by $T_0$ and $T_2$ divided by $T_0$. For SICI and ICF the amplitude of the conditioned response was expressed as a percentage of the amplitude of the test response alone. Ratios $< 1$ indicate inhibition, whereas ratios $> 1$ indicate facilitation.

### *EMG measures and analysis*

Surface EMG recordings were made using a belly-tendon montage with Ag/AgCl-plated surface electrodes (9 mm diameter). Raw EMG signal was amplified and filtered using Digitimer D150 amplifiers (Digitimer Ltd, Welwyn Garden City, Herts., UK), with a time constant of 3 ms and a low-pass filter of 3 kHz. Signals were recorded via a CED 1401 laboratory interface (Cambridge Electronic Design Ltd, Cambridge, UK) and stored on a PC for later analysis using a sampling rate of 5 kHz.

### *Statistical analyses*

All statistical procedures were two-tailed with significance set at $\alpha = 0.05$. Protocol group EEG differences were examined with a GROUP × PERIODS (2 × 11) repeated-measures ANOVA, from period 0 (baseline) to period 10. Within-group EEG was assessed by a one-way ANOVA with PERIODS as a repeated-measures factor; *post hoc* Dunnett's test was used to detect significant changes from the baseline rest period. TMS measures of CSE, SICI and ICF for each hemisphere were subjected to a GROUP × TIME (2 × 3) repeated-measures ANOVA; Greenhouse–Geisser correction was used where necessary. Subsequent to reliable main effects, planned comparisons were conducted via Bonferroni corrected *t*-tests for long-term (> 20 min) changes after NFB ($T_0$–$T_2$). A regression analysis was performed between normalized EEG (% baseline) vs. normalized TMS parameters (% baseline), as well as between training and resting EEG (% baseline). With regards to the weighted least squares (WLS) regression analysis, the reciprocal variance of the relevant training period amplitude (32 samples/s) was used as each subject's weighting factor. Statistical analyses and structural equation modelling were respectively carried out with SPSS 15.0 and Amos v7.0 (SPSS Inc., Chicago, IL, USA). For structural equation modelling we used maximum-likelihood estimation as well as bootstrapping (2000 samples, with a 95% bias-corrected confidence level). The final indirect model was also verified by an automatic specification search in the software. Chi-square (column minima) and baseline fit measures (e.g. normed fit index) were used to estimate relative goodness-of-fit, along with parsimony measures (e.g. parsimonious normed fit index).

## Results

### *NFB is associated with significant changes in EEG amplitude during training*

ALPHA and BETA protocol subjects attempted to respectively decrease their alpha or increase their low beta EEG amplitudes, recorded from left motor cortex during a 30-min NFB training session; for the sake of analysis, this session was subdivided into ten equal segments of 3 min each, called 'periods'. A feedback-free, eyes-open, resting baseline was also recorded for 3 min (period 0) before the start and after the end of NFB. A repeated-measures one-way ANOVA on the ALPHA group revealed that alpha amplitude in the trained hemisphere decreased significantly ($F_{10,110} = 2.7$, $P < 0.05$) from baseline (9.08) to period 10 (8.50), with a largest decrease at 15–18 min, or period 6 (7.93, $t_{11} = 4.0$, $P < 0.01$). As seen in Fig. 2A, for the trained hemisphere, *post-hoc* Dunnett's test comparisons with the baseline period revealed a significant reduction ($P < 0.05$) for all periods except periods 2, 8 and 10. Interestingly, high gamma mean frequency (60–120 Hz) was inversely correlated with alpha amplitude during training ($r = -0.25$, $P < 0.01$). Within-subject amplitude correlations between theta, alpha, low beta and high beta during NFB were consistently positive within a statistically significant range of $0.5 < r < 0.9$ ($P < 0.01$). No reliable associations were detected between oscillatory EEG bands and DC shifts, although the latter exhibited a negative correlation with period number ($r = -0.31$, $P < 0.01$). In contrast, as seen in Fig. 2B, one-way ANOVA for the BETA group trained hemisphere showed no consistent change in low beta ($F_{10,110} = 1.7$, n.s.) or other EEG amplitudes.

In conclusion, NFB led to a sustained reduction in the amplitude of alpha but not beta rhythms in naive subjects. These effects were

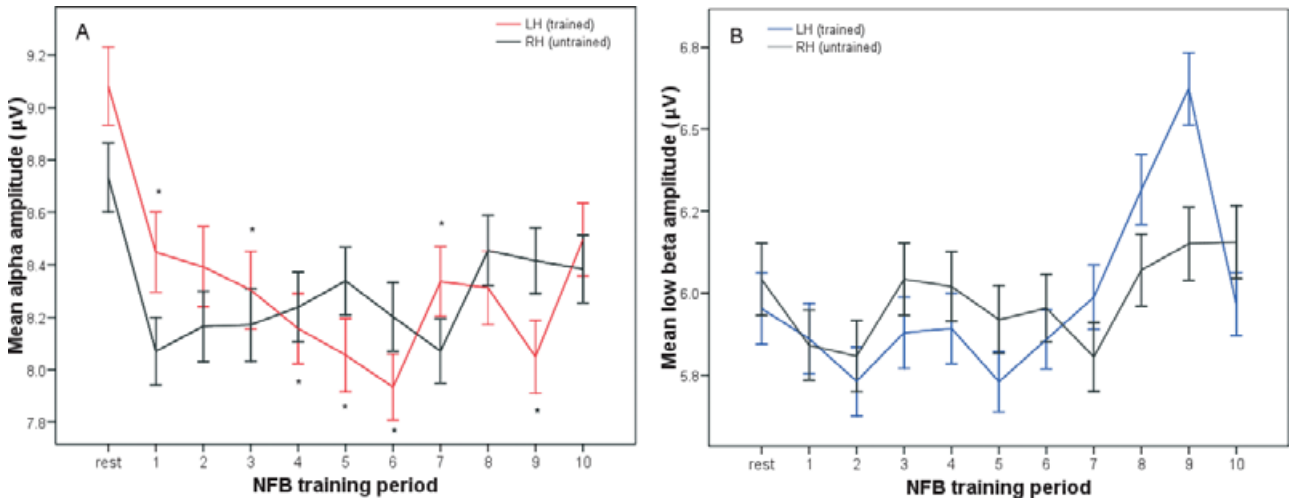


FIG. 2. Time-course of mean training EEG amplitudes for (A) ALPHA and (B) BETA groups, during a session of neurofeedback training (NFB). Each session began with a 3-min baseline at rest, followed by 30-min of EEG feedback training (periods 1–10) from the left hemisphere (LH). Right hemisphere (RH) amplitudes are also shown for the untrained hemisphere. Periods significantly different from baseline are indicated with an asterisk. Error bars represent SEM.

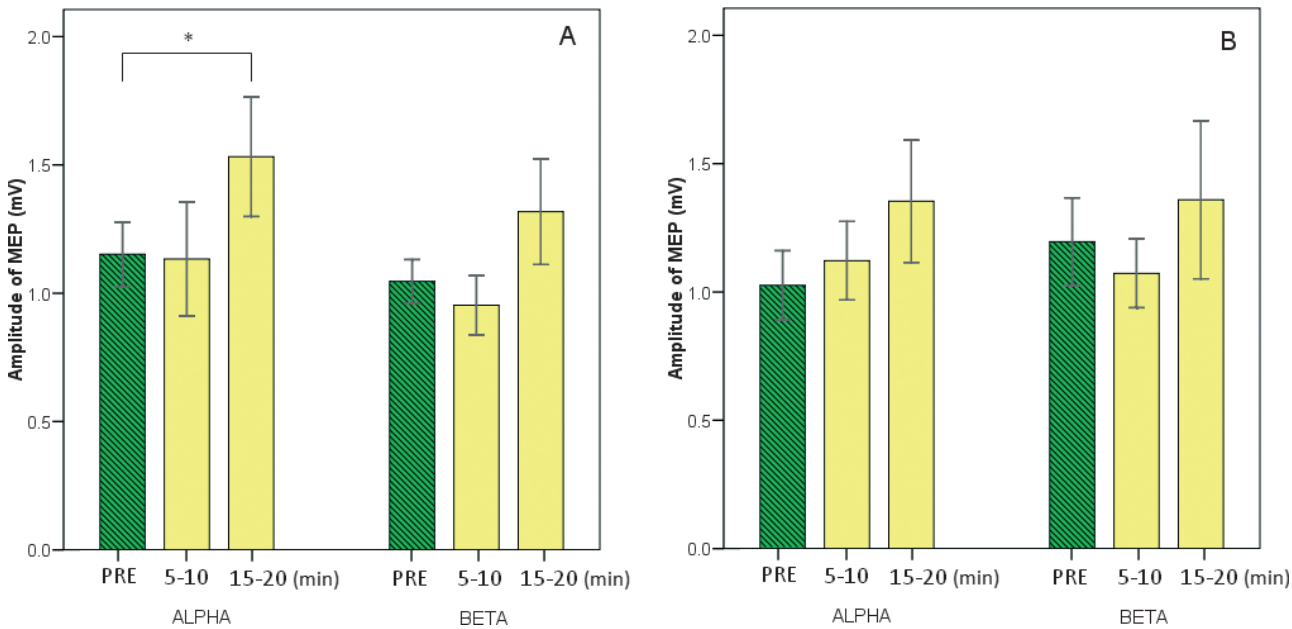


FIG. 3. Mean corticospinal excitability of (A) trained (left) hemisphere, and (B) untrained (right) hemisphere before and after the ALPHA or BETA protocols. Time periods significantly different from PRE are indicated with an asterisk. Error bars represent SEM. MEP, motor-evoked potential.

directly associated with an increase in frequency of high gamma rhythms, and indirectly with a negative drift in DC potentials.

### *Corticospinal and intracortical TMS measures are modified following NFB training*

We measured CSE, SICI and ICF before ($T_0$) and after NFB ($T_1$, ~10 min; $T_2$, ~20 min). A GROUP × TIME (2 × 3) repeated-measures ANOVA for the trained hemisphere CSE revealed a significant main effect of TIME for CSE ($F_{2,44} = 6.8$, $P < 0.01$) and SICI ($F_{2,44} = -4.3$, $P = 0.03$), but not for ICF ($F_{2,44} = 1.6$, $P = 0.2$). Interaction effects were not significant. No significant main effects were detected for the untrained hemisphere. For the ALPHA group Bonferroni corrected *t*-tests on the trained hemisphere (Fig. 3A) showed a significantly enhanced CSE at $T_2$ compared with $T_0$ (130%, $t_{11} = -2.6$, $P = 0.05$), or up to 20 min after termination of NFB training. In the trained hemisphere only, we observed a significant correlation between TIME and MEP amplitude ($r = 0.43$, $P < 0.01$). In addition, as shown in Fig. 4A, there was a significant decrease in SICI in the trained hemisphere at $T_2$ (60%, $t_{11} = -2.6$, $P < 0.05$). Following the BETA protocol, planned *t*-tests in the trained hemisphere revealed no significant long-term (> 20 min) changes in CSE ($t_{11} = -1.4$, $P = 0.36$) or SICI ($t_{11} = -0.6$, $P = 0.9$) at $T_2$. Changes in CSE and SICI in the untrained hemisphere are displayed in Figs 3B and 4B, respectively, revealing no significant changes for both protocols. Lastly, RMT of the trained hemisphere was not significantly altered in the ALPHA ($t_{11} = -0.5$, n.s.) or in the BETA group ($t_{11} = 0.6$, n.s.) after NFB.

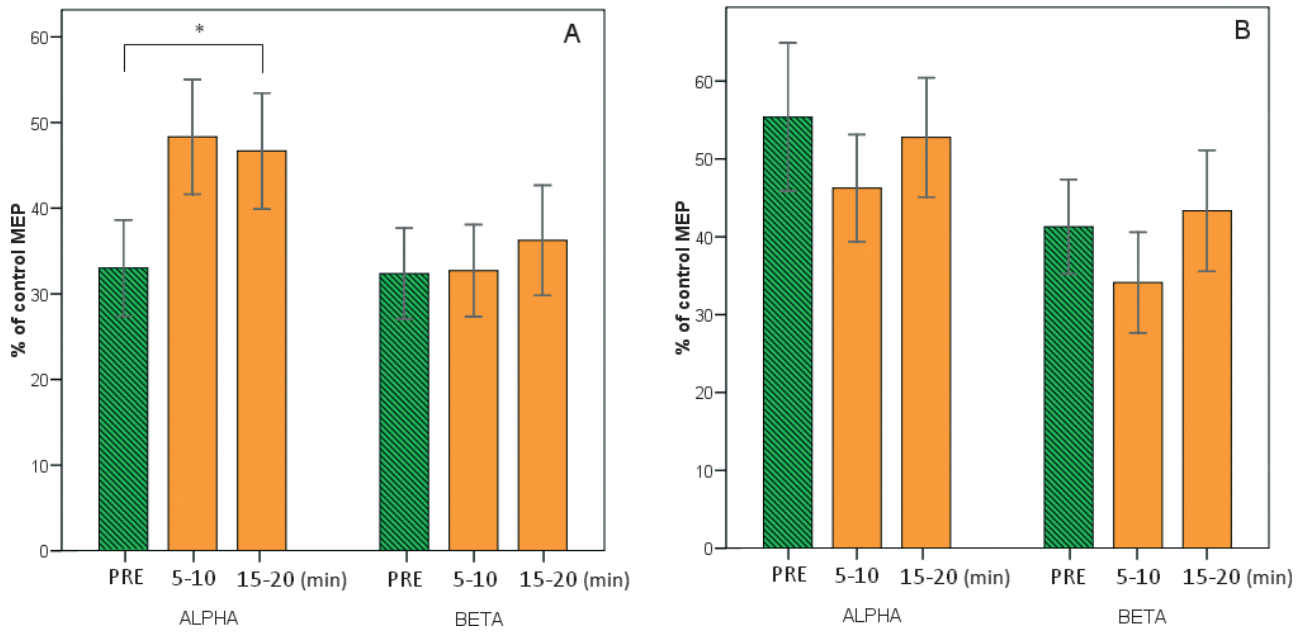


FIG. 4. Mean short interval cortical inhibition (SICI) of (A) trained (left) hemisphere, and (B) untrained (right) hemisphere before and after the ALPHA or BETA protocols. Higher values indicate reduced SICI (disinhibition). Time periods significantly different from PRE are indicated with an asterisk. Error bars represent SEM. MEP, motor-evoked potential.

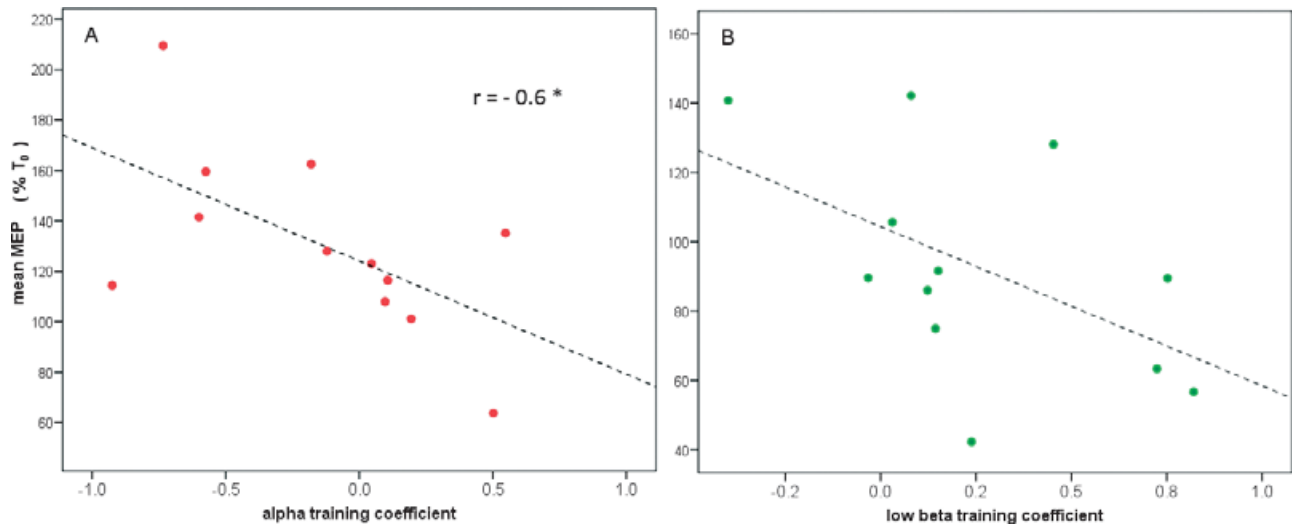


FIG. 5. Scatter plots of each participant's ($n$ = 12) trained hemisphere neurofeedback training coefficient vs. normalized corticospinal excitability for (A) ALPHA group ($r = -0.6$, $P < 0.05$) at $T_2$ and (B) BETA group ($r = -0.5$) at $T_1$. MEP, motor-evoked potential.

Overall, significant changes in TMS measures were present only in the trained hemisphere of the alpha desynchronization group: corticospinal excitability increased whereas intracortical inhibition decreased for at least 20 min after NFB.

### *Neurofeedback and resting EEG changes are linearly proportional to changes in CSE*

As depicted for the trained hemisphere in Fig. 5A, a scatter plot of alpha training coefficient vs. single-pulse MEP amplitude at $T_2$ for the ALPHA group revealed a significant negative correlation ($r = -0.59$, $P = 0.044$), indicating that the larger the relative decrease in alpha from baseline the greater the increase in corticospinal excitability. Moreover, a parallel positive correlation was observed between high gamma mean frequency (60–120 Hz) training coefficient and MEP at $T_2$ ($r = 0.62$, $P = 0.031$). For the BETA protocol (Fig. 5B), the correlation between low beta training coefficient and direction of MEP change was negative at $T_1$, albeit less robust ($r = -0.53$, $P = 0.08$; WLS: $r = -0.62$, $P = 0.03$). This relationship was negligible at $T_2$ ($r = -0.25$, n.s.).

When EEG amplitudes were normalized as a percentage of their 3-min baseline value (% $T_0$), mainly negative correlations occurred between period of alpha amplitude and MEP at $T_2$ (Fig. 6), with a trend for increasing significance from the beginning of the session that reached a maximum around periods 6 and 7 ($r < -0.6$, $P < 0.05$), or during 15–21 min of NFB.

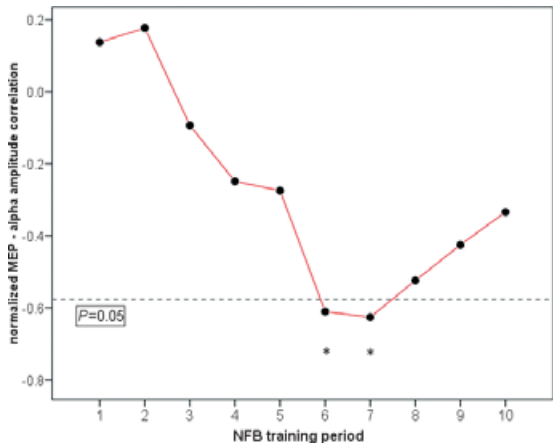


FIG. 6. Corticospinal excitability ($T_2$) vs. alpha amplitude correlation, for all ALPHA group trained hemisphere neurofeedback training (NFB) periods. Period number for which the correlation is statistically significant is indicated with an asterisk. MEP, motor-evoked potential.

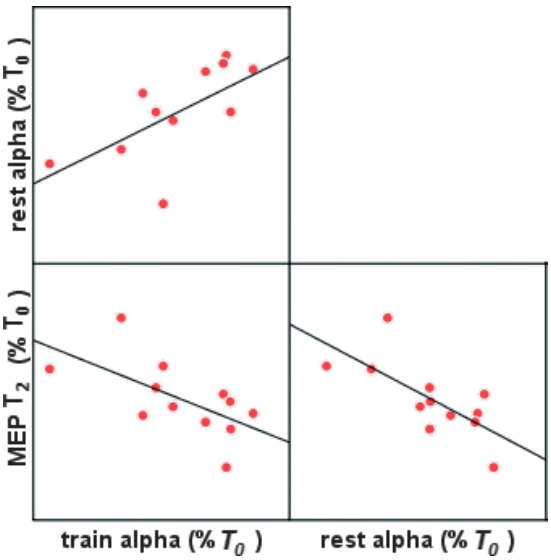


FIG. 7. Matrix plot of normalized training alpha (period 7), resting alpha (second baseline) and corticospinal excitability ($T_2$) amplitudes in the trained hemisphere. All correlations were significant at $|r| > 0.6$, $P < 0.05$.

The resting EEG amplitude change, or ratio of the post-NFB baseline and the pre-NFB baseline power, proved to be another successful predictor of MEP change in all EEG bands below high beta ($r < -0.6$, greatest for alpha: $r = -0.71$, $P = 0.01$), suggesting that the more suppressed the slower EEG amplitudes were after NFB, the greater the enhancement of the MEP ~20 min later. Moreover, alpha during training periods 7, 8 and 9 ($r > 0.6$, $P < 0.05$), but not 10, predicted resting alpha change ($r = 0.65$, $P = 0.02$). As seen in Fig. 7, the overall implication is that a three-way significant association was established between normalized amplitudes of training EEG, resting EEG and CSE.

Analogous analyses were performed on the BETA group for relationships between CSE and normalized low beta amplitudes, indicating a significant association similar to that found with ALPHA between resting low beta and MEP amplitudes at $T_1$ (WLS: $r = -0.58$, $P = 0.050$) as well as a borderline significant correlation between training low beta (period 6) and MEP (WLS: $r = -0.52$, $P = 0.08$). Training low beta amplitude (period 6) was in turn tightly correlated with its subsequent resting amplitude (WLS: $r = 0.67$, $P = 0.02$), mirroring closely but less reliably the three-way relationship reported for the ALPHA group. No significant associations were observed between MEP and the remaining EEG bands in the BETA group (e.g. resting alpha vs. MEP $T_1$: WLS: $r = -0.17$, $P = 0.60$).

In summary, before to after increases in corticospinal excitability were positively (negatively) correlated with both the sustained time-course and relative degree of desynchronization (synchronization) of alpha and low beta rhythms.

### *NFB effects on MEP appear to be indirectly mediated via resting EEG*

To investigate the possible causal relationships between training EEG, resting EEG and MEP amplitudes, we conducted a path analysis of the three-way correlates linking these variables from our experimental data. For ALPHA group training periods 6–9, regression coefficients were consistently higher ($r > 0.5$) for the two indirect pathways of training EEG to resting EEG, and resting EEG to MEP, compared with the direct pathway of training EEG to MEP ($r < 0.5$). Figure 8 shows results for ALPHA training during period 7 and MEP at $T_2$, mirroring Fig. 7. Accordingly, a bootstrap test (see Methods) revealed a statistically significant ($P < 0.05$) indirect effect of training EEG on MEP, mediated via the resting EEG change. Moreover, deletion of the train EEG to MEP direct pathway resulted in a better-fit ($\chi^2 = 1.1$, d.f. = 1, $P = 0.3$) and greater parsimony (change in parsimonious normed fit index = 0.31). We then applied this final model to the BETA group relationships described above (low beta amplitude period 6 vs. MEP $T_1$), which was analogous to the ALPHA group, confirming a good-fit mediation model ($\chi^2 = 0.4$, d.f. = 1, $P = 0.5$), with the indirect effect having a marginal bootstrap significance of $P = 0.08$.

Overall, these modelling results suggest that the general NFB effect may be better explained by its action on the resting/spontaneous EEG, which is in turn a more direct modulator of cortical excitability.

### *Intracortical measures are linearly proportional to shifts in DC potential*

Lastly, we explored the association between EEG and the paired-pulse MEP parameters, namely SICI and ICF, which have been found to be coupled to changes in intracortical neuronal circuitry (Lazzaro *et al.*, 2008). The DC training coefficient was defined as the Pearson correlation between the period number (0–10) and the average DC potential ($\mu$V) of that period. A positive training coefficient therefore reflects a positive drift in DC potential during the NFB session. Bearing in mind that increases in SICI amplitude indicate decreases in intracortical inhibition, the ALPHA group demonstrated a negative correlation between the trained hemisphere DC training coefficient and SICI amplitudes at $T_1$ ($r = -0.6$, $P = 0.04$) and $T_2$ ($r = -0.53$, $P = 0.07$), and ICF amplitudes at $T_2$ ($r = -0.79$, $P < 0.01$). Additionally, ICF amplitude at $T_2$ was positively correlated with SICI amplitude at $T_1$ ($r = -0.63$, $P = 0.03$) and $T_2$ ($r = -0.72$, $P < 0.01$). Weaker links were apparent for the BETA group, where borderline negative associations were observed between ICF at $T_1$ and low beta training coefficient ($r = -0.51$, $P = 0.09$) and resting low beta amplitude change ($r = -0.52$, $P = 0.08$).

ALPHA group decreases in intracortical inhibition were associated with increases in intracortical facilitation. Moreover, subjects in the ALPHA group who had the most consistent negative shifts in DC potentials displayed the greatest decreases and increases in intracortical inhibition and facilitation, respectively.

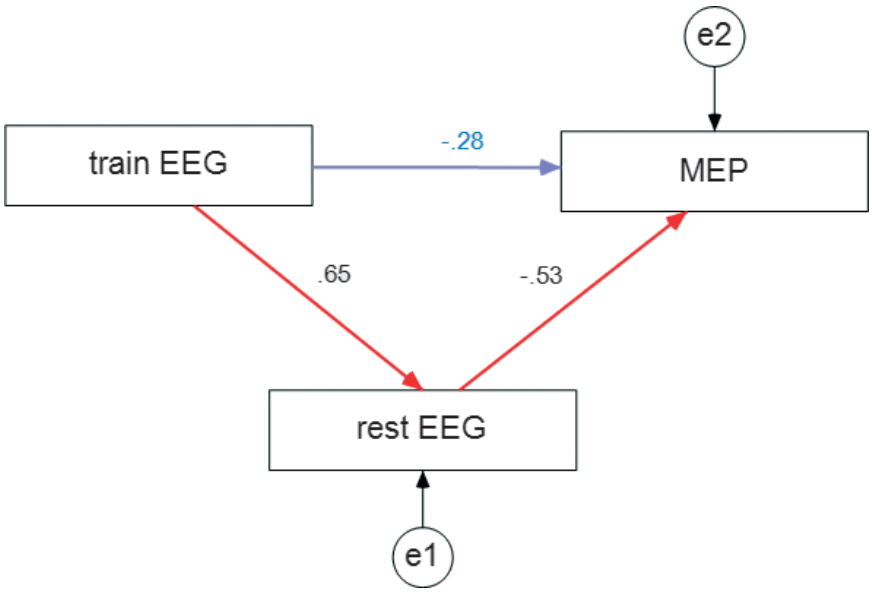


FIG. 8. Path diagram of the hypothesized causal relationship between observed training EEG, resting EEG and corticospinal excitability variables. Here, ALPHA group standardized regression coefficients are illustrated for normalized training alpha (period 7), resting alpha (second baseline) and single-pulse motor-evoked potential (MEP) ($T_2$) amplitudes in the trained hemisphere. Unobserved residual (error) variables are denoted by e1 and e2.

### *Baseline differences*

Independent *t*-tests did not reveal any statistically significant ($P < 0.05$) baseline differences between protocol groups for age, measures of EEG band power (delta to high gamma) or TMS measures (RMT, single-pulse MEP, SICI and ICF) in either the trained (left) or the untrained (right) hemispheres.

## Discussion

Our findings provide evidence that BCI control of natural human brain rhythms leads to sustained (at least 20 min) changes in motor cortex excitability. They provide support for the view that network oscillations are unlikely to be epiphenomenal and that they may lead to changes in cortical function that outlast their phase of entrainment. Thus, brain oscillations could be an additional mechanism harnessed by the brain to mediate plasticity.

The long-term (> 20 min) increase in CSE observed following alpha desynchronization is unlikely to be a consequence of basic changes in psychological arousal after NFB, as there was a significant correlation between increased amplitude and elapsed time following training, while arousal might have been expected to decrease over the same interval. Arousal also seems an unlikely explanation as low beta (12–15 Hz) training failed to change either CSE or SICI. Although we can only speculate as to the mechanisms behind these effects, a slow build up over time is reminiscent of the biochemical cascades known to occur during early long-term potentiation (LTP) (Cooke & Bliss, 2006), as short-term potentiation amplitudes are noticeably extinguished by 15 min (Schulz & Fitzgibbons, 1997). Interestingly, for the ALPHA group, MEP increases were negatively correlated with alpha amplitude and positively correlated with high gamma mean frequency. Alpha amplitude reductions have been locally associated with increased motor cortical excitability (Sauseng *et al.*, 2009), underlying cortical metabolism (Oishi *et al.*, 2007), attention (Thut *et al.*, 2006) and globally with behavioural activation (Rougeul-Buser & Buser, 1997). Conversely, alpha synchronization has been shown to reflect functional inhibition of the motor cortex (Neuper *et al.*, 2006). By contrast, recent findings have linked high-frequency oscillations or high gamma activity with learning (Ponomarenko *et al.*, 2008), attention (Fries *et al.*, 2008), and increased blood oxygen-level-dependent activity, neuronal depolarization and firing rate (Niessing *et al.*, 2005). *In toto*, this could be a candidate mechanism whereby top-down attention or behavioural activation might prioritize and allocate relevant circuits for neuroplastic change. Moreover, the concomitant reduction in intracortical inhibition (SICI), which is likely to be due to a decrease in cortical GABAergic transmission (Ziemann, 2004; Lazzaro *et al.*, 2008) could promote plasticity (Floyer-Lea *et al.*, 2006), as previous reports have found an antagonistic effect of GABAergic transmission on motor learning (Bütefisch *et al.*, 2000) and LTP (Komaki *et al.*, 2007). The novel finding that SICI was correlated positively, and ICF negatively, with slow shifts in DC potential are compatible with evidence that slow cortical negativities are a marker of increased excitability (Niedermayer & Lopes Da Silva, 1999). However, this was significant for the ALPHA group only and because skin short-circuiting was not performed (Vanhatalo *et al.*, 2005), this relationship awaits replication. Moreover, the apparent lack of correlation of DC measures with the oscillatory EEG is noteworthy, as similar independence has previously been documented for slow cortical potentials and may be suggestive of physiologically separate processes (Kotchoubey *et al.*, 1999). It also remains unclear whether the release of neuromodulators is a likely mechanism for the overall alpha desynchronization effects; one attractive candidate may be noradrenalin, which is known to desynchronize alpha rhythms (Rougeul-Buser & Buser, 1997), enhance LTP (Harley, 1987), and concomitantly increase CSE and decrease SICI (Ziemann, 2004).

As low beta entrainment was suboptimal, it is possible that it was associated with an inappropriate training approach in some subjects which was perhaps more desynchronizing than synchronizing, and therefore counterproductive, hence the slightly increased corticospinal excitability observed later. This is supported by the negative correlations between low beta training and MEP, which remain in line with findings that low beta synchronization is associated with motor-cortical deactivation (Oishi *et al.*, 2007) and inhibition (Zhang *et al.*, 2008). The finding that electrical stimulation of sensorimotor

cortex at 10 Hz leads to long-term depression (Werk *et al.*, 2006) may be related to the initial inhibitory-like effect observed in this study at a slightly higher, albeit correlated, frequency of 12–15 Hz. Moreover, it has recently been observed that longer durations of 10-Hz repetitive TMS lead to long-term depression-like effects (Jung *et al.*, 2008).

It is tempting to compare the average effect size(s) in this study with those of existing non-invasive brain stimulation protocols used to induce neuroplasticity. Repetitive magnetic (Ziemann *et al.*, 2008) and DC (Nitsche & Paulus, 2001) stimulation investigations report average corticospinal excitability increases of around 150%, which is comparable with the confidence intervals we observed following alpha desynchronization. Remarkably, this may indicate that regardless of whether endogenous or exogenous techniques are used, they appear to appeal to a common neural substrate, which is intrinsic to the brain. Crucially, however, numerous non-invasive brain stimulation protocols induce after-effects that last for periods of 1 h or more. Therefore, a question of scientific and therapeutic importance is how long can the endogenously driven effects last?

A related issue concerns whether the observed endogenous effects are a direct consequence of longer term changes to the dynamics of 'resting' or spontaneous rhythms (Steriade & Timofeev, 2003; Sauseng *et al.*, 2009; Thut & Miniussi, 2009). This is tempting in view of the structural equation model, which points to an indirect effect of NFB – via the resting EEG – on MEPs. Moreover, this is compatible with online TMS–EEG studies reporting direct modulation of MEPs by cortical oscillations (Romei *et al.*, 2008; Sauseng *et al.*, 2009). Hence, as EEG rhythms are well known to be modulated by top-down mechanisms (Fan *et al.*, 2007; Fries *et al.*, 2008; Schroeder & Lakatos, 2009), our observations suggest that the brain may indeed 'shape itself', whereby past activities (as little as ∼30 min ago) could in turn determine or bias future states of processing (Silvanto *et al.*, 2008). Here, the concept of a 'background' or stable state would cease to be informative, as such a state would be continually in flux and shaped by present activity. As synaptic homeostasis (Abraham, 2008) would need to exert a regulatory role here, a number of studies reporting upregulation of sleep rhythms after plasticity-induction may further implicate EEG rhythms in synaptic scaling (De Gennaro *et al.*, 2008; Huber *et al.*, 2008). The observation that operant entrainment of 12- to 15-Hz rhythms enhances spindle rhythms during sleep (Sterman, 1996) has recently been replicated, with the finding that it boosts memory recall following sleep (Hoedlmoser *et al.*, 2008).

Owing to the non-invasive nature of the experiment, it remains unclear as to exactly where in the brain one could attribute the original cause for the observed effects. One speculation is that thalamocortical circuits (Steriade & Timofeev, 2003) could have played a role, as they are known to orchestrate EEG rhythms (Steriade & Timofeev, 2003) generated by cortical layer pyramidal cells (Silva *et al.*, 1991). Hence, the possibility exists that the motor cortex may have been presynaptically modulated by connections from more distributed cortical or subcortical structures. Direct intracellular recordings of corticospinal tract neurons report increased membrane depolarization during stage shifts towards EEG desynchronization (Ezure & Oshima, 1981). In spite of this we did not observe significant changes in RMT, known to reflect variations in membrane conductance (Ziemann, 2004). In contrast, two recent studies provide cellular evidence of synaptic changes induced by network oscillations (Tsukamoto-Yasui *et al.*, 2007; Tsanov & Manahan-Vaughan, 2009). Conversely, changes in synaptic plasticity have been found to modulate neuronal oscillations themselves (Narayanan & Johnston, 2007; Tsukamoto-Yasui *et al.*, 2007). Our results are also compatible with a framework favouring frequency-dependent forms of synaptic plasticity (Markram *et al.*, 1999).

Finally, in recent years a number of investigations have reported behavioural (Gruzelier *et al.*, 2006) as well as neuronal (Zacksenhouse *et al.*, 2007) changes following long-term repetitive BCI training. Several neurofeedback protocols (Levesque *et al.*, 2006; Fernández *et al.*, 2007; Heinrich *et al.*, 2007; Coben *et al.*, 2009) have been shown to be effective for disorders exhibiting abnormal cortical rhythmicity (Llinás *et al.*, 1999; Uhlhaas & Singer, 2006). A recent study induced long-term reductions in resting theta power that were tightly correlated with improvements in clinical attentional-deficit scores (Gevensleben *et al.*, 2009). In this respect our results provide a first basis for the 'missing link' between the historical long-term training effects of neurofeedback (Sterman, 1973) and direct validation of neuroplastic change after an individual session of training. Accordingly, a repetitive alpha desynchronization protocol could be of therapeutic value in pathophysiologies with poor corticomotor activation or increased inhibition, for example stroke (Daly & Wolpaw, 2008). It has also been observed that neurofeedback may be useful in facilitating the acquisition of complex sensorimotor skills (Ros *et al.*, 2009). Clearly, extensive research of this method is warranted before we can be certain of its neurophysiological mode of action (Sterman, 1996; Lubar, 1997). In light of the extraordinary plasticity displayed by the human brain (Pascual-Leone *et al.*, 2005), EEG-based neurofeedback may be a promising technique to modulate cerebral plasticity in a non-invasive, painless, natural way.

## Acknowledgements

This study was funded by the Medical Research Council (MRC) of the United Kingdom. We thank Robert Sachdev, Michael Cohen and Trevor Thompson for helpful discussions.

## Abbreviations

BCI, brain–computer interface; CSE, corticospinal excitability; DC, direct current; EEG, electroencephalogram; EMG, electromyographic; FDI, first dorsal interosseous; ICF, intracortical facilitation; ISI, interstimulus interval; LTP, long-term potentiation; MEP, motor-evoked potential; NFB, neurofeedback; RMT, resting motor threshold; SICI, short-interval intracortical inhibition; TMS, transcranial magnetic stimulation; WLS, weighted least squares.

## References

Abraham, W.C. (2008) Metaplasticity: tuning synapses and networks for plasticity. *Nat. Rev. Neurosci.*, **9**, 387.

Bütefisch, C.M., Davis, B.C., Wise, S.P., Sawaki, L., Kopylev, L., Classen, J. & Cohen, L.G. (2000) Mechanisms of use-dependent plasticity in the human motor cortex. *Proc. Natl Acad. Sci. USA*, **97**, 3661–3665.

Buzsáki, G. & Draguhn, A. (2004) Neuronal oscillations in cortical networks. *Science*, **304**, 1926–1929.

Coben, R., Linden, M. & Myers, T.E. (2009) Neurofeedback for autistic spectrum disorder: a review of the literature. *Appl. Psychophysiol. Biofeedback*, **35**, 83–105.

Cooke, S.F. & Bliss, T.V. (2006) Plasticity in the human central nervous system. *Brain*, **129**, 1659–1673.

Daly, J. & Wolpaw, J. (2008) Brain–computer interfaces in neurological rehabilitation. *Lancet Neurol.*, **7**, 1032–1043.

De Gennaro, L., Fratello, F., Marzano, C., Moroni, F., Curcio, G., Tempesta, D., Pellicciari, M.C., Pirulli, C., Ferrara, M. & Rossini, P.M. (2008) Cortical plasticity induced by transcranial magnetic stimulation during wakefulness affects electroencephalogram activity during sleep. *PLoS ONE*, **3**, e2483.

Delorme, A. & Makeig, S. (2003) EEG changes accompanying learned regulation of 12-Hz EEG activity. *IEEE Trans. Neural Syst. Rehabil. Eng.*, **11**, 133–137.

Ezure, K. & Oshima, T. (1981) Excitation of slow pyramidal tract cells and their family neurones during phasic and tonic phases of EEG arousal. *Jpn. J. Physiol.*, **31**, 737–748.

Fan, J., Byrne, J., Worden, M.S., Guise, K.G., McCandliss, B.D., Fossella, J. & Posner, M.J. (2007) The relation of brain oscillations to attentional networks. *J. Neurosci.*, **27**, 6197–6206.

Fernández, T., Harmony, T., Fernández-Bouzas, A., Díaz-Comas, L., Prado-Alcalá, R.A., Valdés-Sosa, P. *et al.* (2007) Changes in EEG current sources induced by neurofeedback in learning disabled children. An exploratory study. *Appl. Psychophysiol. Biofeedback*, **32**, 169–183.

Fetz, E.E. (2007) Volitional control of neural activity: implications for brain-computer interfaces. *J. Physiol.*, **579**(Pt 3), 571–579.

Floyer-Lea, A., Wylezinska, M., Kincses, T. & Matthews, P.M. (2006) Rapid modulation of GABA concentration in human sensorimotor cortex during motor learning. *J. Neurophysiol.*, **95**, 1639–1644.

Fries, P., Womelsdorf, T., Oostenveld, R. & Desimone, R. (2008) The effects of visual stimulation and selective visual attention on rhythmic neuronal synchronization in macaque area V4. *J. Neurosci.*, **28**, 4823–4835.

Gevensleben, H., Holl, B., Albrecht, B., Schlamp, D., Kratz, O., Studer, P. Wangler, S. Rothenberger, A. Moll, G.H. & Heinrich, H. (2009) Distinct EEG effects related to neurofeedback training in children with ADHD: a randomized controlled trial. *Int. J. Psychophysiol.*, **74**, 149–157.

Gruzelier, J., Egner, T. & Vernon, D. (2006) Validating the efficacy of neurofeedback for optimising performance. *Prog. Brain Res.*, **159**, 421–431.

Harley, C.W. (1987) A role for norepinephrine in arousal, emotion and learning?: limbic modulation by norepinephrine and the Kety hypothesis. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **11**, 419–458.

Heinrich, H., Gevensleben, H. & Strehl, U. (2007) Annotation: neurofeedback – train your brain to train behaviour. *J. Child Psychol. Psychiatry*, **48**, 3–16.

Hoedlmoser, K., Pecherstorfer, T., Gruber, G., Anderer, P., Doppelmayr, M., Klimesch, W. & Schabus, M. (2008) Instrumental conditioning of human sensorimotor rhythm (12–15 hz) and its impact on sleep as well as declarative learning. *Sleep*, **31**, 1401–1408.

Huber, R., Määttä, S., Esser, S.K., Sarasso, S., Ferrarelli, F., Watson, A. Ferreri, F., Peterson, M.J. & Tononi, G. (2008) Measures of cortical plasticity after transcranial paired associative stimulation predict changes in electroencephalogram slow-wave activity during subsequent sleep. *J. Neurosci.*, **28**, 7911–7918.

Jung, S.H., Shin, J.E., Jeong, Y. & Shin, H. (2008) Changes in motor cortical excitability induced by high-frequency repetitive transcranial magnetic stimulation of different stimulation durations. *Clin. Neurophysiol.*, **119**, 71–79.

Komaki, A., Shahidi, S., Lashgari, R., Haghparast, A., Malakouti, S.M. & Noorbakhsh, S.M. (2007) Effects of GABAergic inhibition on neocortical long-term potentiation in the chronically prepared rat. *Neurosci. Lett.*, **422**, 181–186.

Kotchoubey, B., Busch, S., Strehl, U. & Birbaumer, N. (1999) Changes in EEG power spectra during biofeedback of slow cortical potentials in epilepsy. *Appl. Psychophysiol. Biofeedback*, **24**, 213–233.

Kujirai, T., Caramia, M.D., Rothwell, J.C., Day, B.L., Thompson, P.D., Ferbert, A., Wroe, S., Asselman, P. & Marsden, C.D. (1993) Corticocortical inhibition in human motor cortex. *J. Physiol.*, **471**, 501–519.

Lazzaro, V.D., Ziemann, U. & Lemon, R.N. (2008) State of the art: physiology of transcranial motor cortex stimulation. *Brain Stimulat.*, **1**, 345–362.

Levesque, J., Beauregard, M. & Mensour, B. (2006) Effect of neurofeedback training on the neural substrates of selective attention in children with attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study. *Neurosci. Lett.*, **394**, 216–221.

Llinás, R.R., Ribary, U., Jeanmonod, D., Kronberg, E. & Mitra, P.P. (1999) Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc. Natl Acad. Sci. USA*, **96**, 15222–15227.

Lubar, J.F. (1997) Neocortical dynamics: implications for understanding the role of neurofeedback and related techniques for the enhancement of attention. *Appl. Psychophysiol. Biofeedback*, **22**, 111–126.

Markram, H., Tsodyks, M., Wang, Y. & Uziel, A. (1999) Frequency-dependent synaptic transmission in the neocortex. In Baudry, M., Davis, L. & Thompson, R. (Eds), *Advances in Synaptic Plasticity.* MIT Press, Cambridge, MA, pp. 239–264.

Narayanan, R. & Johnston, D. (2007) Long-term potentiation in rat hippocampal neurons is accompanied by spatially widespread changes in intrinsic oscillatory dynamics and excitability. *Neuron*, **56**, 1061–1075.

Nelson, S.B. & Turrigiano, G.G. (2008) Strength through diversity. *Neuron*, **60**, 477–482.

Neuper, C., Wörtz, M. & Pfurtscheller, G. (2006) ERD/ERS patterns reflecting sensorimotor activation and deactivation. *Prog. Brain Res.*, **159**, 211–222.

Niedermayer, E. & Lopes Da Silva, F. (1999) *Electroencephalography: Basic Principles, Clinical Applications and Related Field*, 4th Edn. Williams & Wilkins, New York.

Niessing, J., Ebisch, B., Schmidt, K.E., Niessing, M., Singer, W. & Galuske, R.A. (2005) Hemodynamic signals correlate tightly with synchronized gamma oscillations. *Science*, **309**, 948–951.

Nitsche, M.A. & Paulus, W. (2001) Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*, **57**, 1899–1901.

Nowlis, D.P. & Kamiya, J. (1970) The control of electroencephalographic alpha rhythms through auditory feedback and the associated mental activity. *Psychophysiology*, **6**, 476–484.

Oishi, N., Mima, T., Ishii, K., Bushara, K.O., Hiraoka, T., Ueki, Y., Fukuyama, H. & Hallett, M. (2007) Neural correlates of regional EEG power change. *Neuroimage*, **36**, 1301–1312.

Pascual-Leone, A., Amedi, A., Fregni, F. & Merabet, L.B. (2005) The plastic human brain cortex. *Annu. Rev. Neurosci.*, **28**, 377–401.

Ponomarenko, A.A., Li, J., Korotkova, T.M., Huston, J.P. & Haas, H.L. (2008) Frequency of network synchronization in the hippocampus marks learning. *Eur. J. Neurosci.*, **27**, 3035–3042.

Romei, V., Brodbeck, V., Michel, C., Amedi, A., Pascual-Leone, A. & Thut, G. (2008) Spontaneous fluctuations in posterior alpha-band EEG activity reflect variability in excitability of human visual areas. *Cereb. Cortex*, **18**, 2010–2018.

Ros, T., Moseley, M.J., Bloom, P.A., Benjamin, L., Parkinson, L.A. & Gruzelier, J.H. (2009) Optimizing microsurgical skills with EEG neurofeedback. *BMC Neurosci.*, **10**, 87.

Rougeul-Buser, A. & Buser, P. (1997) Rhythms in the alpha band in cats and their behavioural correlates. *Int. J. Psychophysiol.*, **26**, 191–203.

Sauseng, P., Klimesch, W., Gerloff, C. & Hummel, F.C. (2009) Spontaneous locally restricted EEG alpha activity determines cortical excitability in the motor cortex. *Neuropsychologia*, **47**, 284–288.

Schroeder, C.E. & Lakatos, P. (2009) Low-frequency neuronal oscillations as instruments of sensory selection. *Trends Neurosci.*, **32**, 9–18.

Schulz, P.E. & Fitzgibbons, J.C. (1997) Differing mechanisms of expression for short- and long-term potentiation. *J. Neurophysiol.*, **78**, 321–334.

Silva, L., Amitai, Y. & Connors, B. (1991) Intrinsic oscillations of neocortex generated by layer 5 pyramidal neurons. *Science*, **251**, 432–435.

Silvanto, J., Muggleton, N. & Walsh, V. (2008) State-dependency in brain stimulation studies of perception and cognition. *Trends Cogn. Sci.*, **12**, 447–454.

Steriade, M. & Timofeev, I. (2003) Neuronal plasticity in thalamocortical networks during sleep and waking oscillations. *Neuron*, **37**, 563–576.

Sterman, M.B. (1973) Neurophysiologic and clinical studies of sensorimotor EEG biofeedback training: some effects on epilepsy. *Semin Pschiatry*, **5**, 507–525.

Sterman, M.B. (1996) Physiological origins and functional correlates of EEG rhythmic activities: implications for self-regulation. *Biofeedback Self Regul.*, **21**, 3–33.

Thut, G. & Miniussi, C. (2009) New insights into rhythmic brain activity from TMS-EEG studies. *Trends Cogn. Sci.*, **13**, 182–189.

Thut, G., Nietzel, A., Brandt, S.A. & Pascual-Leone, A. (2006) Alpha-band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. *J. Neurosci.*, **26**, 9494–9502.

Tsanov, M. & Manahan-Vaughan, D. (2009) Long-term plasticity is proportional to theta-activity. *PLoS ONE*, **4**, e5850.

Tsukamoto-Yasui, M., Sasaki, T., Matsumoto, W., Hasegawa, A., Toyoda, T., Usami, A., Kubota, Y., Ochiai, T., Hori, T., Matsuki, N. & Ikegaya, Y. (2007) Active hippocampal networks undergo spontaneous synaptic modification. *PLoS ONE*, **2**, e1250.

Uhlhaas, P.J. & Singer, W. (2006) Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. *Neuron*, **52**, 155–168.

Vanhatalo, S., Voipio, J. & Kaila, K. (2005) Full-band EEG (FbEEG): an emerging standard in electroencephalography. *Clin. Neurophysiol.*, **116**, 1–8.

Werk, C.M., Klein, H.S., Nesbitt, C.E. & Chapman, C.A. (2006) Long-term depression in the sensorimotor cortex induced by repeated delivery of 10 Hz trains in vivo. *Neuroscience*, **140**, 13–20.

Zacksenhouse, M., Lebedev, M.A., Carmena, J.M., O'Doherty, J.E., Henriquez, C. & Nicolelis, M.A. (2007) Cortical modulations increase in early sessions with brain-machine interface. *PLoS ONE*, **2**, e619.

Zhang, Y., Chen, Y., Bressler, S. & Ding, M. (2008) Response preparation and inhibition: the role of the cortical sensorimotor beta rhythm. *Neuroscience*, **156**, 238–246.

Ziemann, U. (2004) TMS and drugs. *Clin. Neurophysiol.*, **115**, 1717–1729.

Ziemann, U., Paulus, W., Nitsche, M.A., Pascual-Leone, A., Byblow, W.D., Berardelli, A., Siebner, H.R., Classen, J., Cohen, L.G. & Rothwell, J.C. (2008) Consensus: motor cortex plasticity protocols. *Brain Stimulat.*, **1**, 164–182.