CHAPTER 14

The Immediate Effects of EEG Neurofeedback on Cortical Excitability and Synchronization

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INTRODUCTION

In comparison with the much larger number of studies demonstrating long-lasting clinical and behavioral effects of neurofeedback (NFB), very few investigations have been carried out to date on the mechanisms and neurophysiological substrates of EEG-based NFB other than EEG measures. Most NFB involves multiple sessions repeated on at least a weekly basis, whose effects generally accumulate over time, reputedly as a result of neuroplastic changes in the brain (for peak performance at least eight sessions, for clinical application >20) (Doehnert, Brandeis, Straub, Steinhausen, & Drechsler, 2008; Hanslmayr, Sauseng, Doppelmayr, Schabus, & Klimesch, 2005; Lévesque, Beauregard, & Mensour, 2006). Over the years numerous studies have demonstrated behavioral as well as

Neurofeedback and Neuromodulation Techniques and Applications
DOI: 10.1016/B978-0-12-382235-2.00014-7

neurophysiological alterations after *long-term* NFB training, such as improvement in attention and cognitive performance and their accompanying EEG/ERP changes (Egner & Gruzelier, 2004; Gruzelier, Egner, & Vernon, 2006). However, to date and to the best of the authors' knowledge, no work exists or provides evidence for a causal and more direct temporal relationship between self-regulation of brain activity and concomitant short-term change in brain plasticity, or its mechanisms. This may possibly be due to a belief that the putative modulatory effect(s) that follow a discrete session of neurofeedback are too fine to be detected immediately thereafter, or alternatively, occur at some later stage, for example during sleep. However, as is common for all learning paradigms, NFB training occurs within a temporally distinct period or "session", and if it is ever to claim the grail of inducing lasting neuroplastic changes (and thus be taken seriously as a non-invasive tool for neuromodulation, such as rTMS and tDCS) (Wagner, Valero-Cabre, & Pascual-Leone, 2007), a stronger association is clearly warranted between a single training session and the reputed plasticity, if any, it engenders. Accordingly, there has been no demonstration to date of a chronologically direct neuroplastic effect following NFB. That is, of a robust and durable change in neurophysiological function immediately after discrete exposure to NFB. On the other hand, a substantial corpus of transcranial magnetic stimulation (TMS) literature purports significant and durable changes in brain plasticity following brain stimulation techniques such as rTMS and tDCS (Wagner, Valero-Cabre, & Pascual-Leone, 2007), hence similar investigations with NFB may ultimately enable more direct comparisons of effect size with other stimulation techniques.

Nowadays, the study of neuroplasticity in the intact human brain has been made possible with the advent of TMS. Here, evidence of neuroplastic change may be demonstrated non-invasively by an altered neurotransmission of the corticomotor projection to the hand, a method that has been physiologically validated by invasive recordings of human and animal corticospinal nerve impulses (Lazzaro, Ziemann, & Lemon, 2008). Although neuroplasticity appears to involve diverse cellular processes in the central nervous system (Nelson & Turrigiano, 2008), in TMS methodology it is operationally defined as a significant and lasting change in the motor evoked potential (MEP), evoked by a magnetic pulse, whose amplitude is representative of the strength of neurotransmission from motor cortex to muscle. A growing body of evidence (Lazzaro, Ziemann, & Lemon, 2008) indicates that MEPs from a single TMS pulse best reflect the overall responsiveness of the

corticospinal pathway, or corticospinal excitability (CSE), whereas those originating from paired pulses (with interstimulus intervals of milliseconds) enable the discrimination of intracortical mechanisms, such as short intracortical inhibition (SICI) and facilitation (ICF), which are modulated by transynaptic neurotransmission (Ziemann, 2004).

Our initial hypothesis was that NFB-induced alpha (8−12 Hz) rhythm desynchronization, generally considered a marker of cortical activation (Neuper, Wörtz, & Pfurtscheller, 2006), would enhance both corticospinal excitability and intracortical facilitation, while effecting a reduction in intracortical inhibition. Conversely, low beta ("SMR", 12−15 Hz) synchronization, which has been associated with cortical deactivation (Oishi et al., 2007), sleep spindles (Sterman, 1996), and GABAergic function (Jensen et al., 2005), was expected to induce an opposite corticospinal and intracortical pattern. Although endogenous oscillations have thus far been implicated in many "on-going" functions such as binding and attention (Schroeder & Lakatos, 2009), explicit evidence is still scarce on their role, if any, in neuroplasticity (Axmacher, Mormann, Fernández, Elger, & Fell, 2006). We therefore postulated that, in line with previous stimulation research, the more pronounced as well as persistent the oscillatory patterns would prove to be during NFB, the more substantial and long-lasting (plastic) would turn out to be their after effects.

METHODS

Participants

Twenty-four healthy participants (12 women, age 31 ± 5 years), all with normal or corrected-to-normal visual acuity, participated in the experiment. All were recruited via the participants' database of the Department of Psychology, University College London, and were *naive* to the neurofeedback protocols used in this study. Experimental procedures were approved by the local ethics committee and in accordance with the Declaration of Helsinki.

Study Design

Subjects were randomly allocated to two protocol groups for a single 30 minute NFB session: alpha suppression (N = 12) or low beta enhancement (N = 12). For the purpose of testing hypotheses concerning protocol-specific effects on target EEG frequency components, subjects underwent resting EEG recordings for 3 minutes immediately before and after their

NFB training session. In order to test the hypotheses concerning the protocol-specific effects on corticospinal excitability (CSE), TMS motor evoked potential (MEP) responses were collected before (*pre*) and twice after (*post 1*, *post 2*) each NFB session, consecutively at right and left hand muscles.

Neurofeedback (NFB)

Apparatus and EEG Analysis

EEG signals were recorded using a NeXus-10 DC-coupled EEG amplifier using a 24-bit A−D converter (MindMedia, The Netherlands), and visual NFB training was carried out with the accompanying Biotrace + software interface on an Intel DualCore computer with a 15-inch screen. The EEG used for feedback was sampled at 256 Hz with Ag/Cl electrodes at the right first dorsal interosseous muscle (FDI) cortical representation/"hot spot" (approx. C3) 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. The signal was IIR bandpass filtered to extract alpha (8−12 Hz) and low beta (12−15) amplitudes (μV peak-peak) respectively with an epoch size of 0.5 seconds. In the same way EEG was co-registered at the left FDI representation (approx. C4) referenced to its contralateral mastoid. IIR digital filtered (Butterworth 3rd order) EEG amplitude data of each band (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/second and voltage-threshold artifacted for ocular, head movement, and EMG contamination. Outlying data points were rejected at >3 standard deviations using histogram analysis. Moreover, the Fast Fourier Transform (FFT) of raw (256 samples/sec) data was used in the calculation of *mean frequency* for each band. Averages of all measures were computed offline for 3 minute epochs, each defined as a training "period". Periods 1 and 12 consisted of feedback-free pre- and post-resting EEG measurements in the eyes-open condition. Periods 2−11 consisted of feedback training.

Neurofeedback Training Procedures

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). Accordingly, reward thresholds were set to be either 30% of the time above or below the initial alpha or low beta mean

amplitude (baseline) respectively. The first baseline was recorded during a 3 minute eyes-open EEG recording at rest immediately before the start of feedback, and the second 3 minute recording was made immediately after the end of training. Subjects were given no explicit verbal instructions and were told to be guided by the feedback process instead. This was achieved via a collection of different visual displays/games whose control reflected the modulation of the trained EEG amplitude. Both protocols employed the same series of five Biotrace + software games, which were played in a random order for approximately 6 minutes each (Mandala, Space Invaders, Mazeman, Bugz, puzzles). In the case of the low beta down protocol a supplementary inhibit was coupled to excess mastoid and EMG activity to ensure low beta reward was not artifact-driven.

Neurofeedback Data Analyses

The degree of NFB-mediated EEG change for each subject was estimated by the *ratio* of EEG amplitudes between the neurofeedback EEG and the initial baseline EEG. This was calculated for each of the 10 training periods, and designated as change in the *training EEG*. Additionally, any pre-to-post change in the resting EEG following training was expressed by the ratio of the second divided by the first mean baseline amplitude, and designated as change in the *resting EEG*.

Transcranial Magnetic Stimulation (TMS): Apparatus and Procedure

The course of the experiment that was used to test the impact of NFB training on corticomotor measures of corticospinal excitability (CSE), short intracortical inhibition (SICI), and intracortical facilitation (ICF) is shown in Figure 14.1. TMS parameters (CSE, SICI, and ICF) were measured before (pre) and twice after NFB (post 1 and post 2). In random order, 78 TMS responses were measured, which required approximately 6 minutes per hemisphere. We evaluated the TMS parameters of both

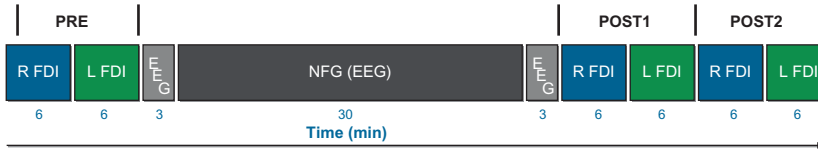

Figure 14.1 Scheme of the study. R FDI = trained left hemisphere, L FDI = untrained right hemisphere.

hemispheres, first left (trained) and then right (untrained) hemisphere, to investigate hemispheric effects of NFB. The post 1 measurement was performed circa 3−15 minutes after NFB training, and post 2 after 15−27 minutes. Well-established standard TMS paradigms were used to measure the corticospinal and intracortical parameters (Lazzaro, Ziemann, & Lemon, 2008). All measurements were carried out with two monophasic Magstim 200 magnetic stimulators (Magstim, Whitland, UK), which were connected with a "Y-cable" to a 70 mm figure-of-eight coil. We determined the cortical representation of the first dorsal interosseous muscles (FDI) 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 motor evoked potentials (MEPs) of at least 50 μV peak-to-peak amplitude in the FDI muscle in at least half of 10 trials. Active motor threshold (AMT) was defined as the intensity needed to evoke an MEP of about 200 mV during a 5−10% maximum voluntary contraction. Corticospinal excitability (CSE) was quantified by the amplitude of the motor evoked potential (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 (pre), and was kept constant throughout the experiment. Short latency intracortical inhibition and intracortical facilitation (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% AMT) with an interstimulus interval (ISI) of 2, 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, where 48 paired-pulse (12 for each ISI) and 30 single-pulse MEPs were recorded. Single-pulse MEP amplitudes were normalized respectively as post 1 divided by pre, and post 2 divided by pre. For SICI and ICF the amplitude of the conditioned response was expressed as a percent of the amplitude of the test response alone. Ratios <1 indicate inhibition, whereas ratios >1 indicate facilitation.

Electromyographic Measures and Analysis

Surface electromyographic (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 $\times$ PERIODS (2×11) repeated measures ANOVA, from period 1 (baseline) to period 11. 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 $\times$ TIME (2×3) repeated measures ANOVA; Greenhouse–Geisser correction was used where necessary. Subsequent to reliable main effects, planned comparisons were conducted by Bonferroni corrected *t*-tests for long-term (>20 min) changes after NFB (post 2 − pre). A regression analysis was performed between normalized EEG (% baseline) vs. normalized TMS parameters (% baseline), as well as between training vs. resting EEG (% baseline). With regards to the weighted least squares (WLS) regression analysis, the reciprocal variance of the relevant training period amplitude (32 samples/sec) was used as each subject's weighting factor. Statistical analyses and structural equation modelling (SEM) were respectively carried out with SPSS 15.0 and Amos v7.0 (SPSS Inc., Chicago, IL, USA). For SEM 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 (CMIN) and baseline fit measures (e.g. NFI) were used to estimate relative goodness-of-fit, along with parsimony measures (e.g. PNFI).

RESULTS

One-Way ANOVAs did not disclose any statistically significant differences ($p < 0.05$) between protocol groups neither for age nor baseline measures of EEG band power (delta to high gamma), or TMS measures (RMT, single-pulse MEP, 3 ms SICI, and ICF) in either the trained or untrained hemispheres.

NFB Training Dynamic

Mean alpha and low beta amplitude during each 3 minute period of the neurofeedback training session is depicted in Figure 14.2, for the ALPHA and BETA groups respectively for each hemisphere. Period 1 denotes the eyes-open, feedback-free, baseline at rest. Mean ALPHA-group amplitude for the trained hemisphere exhibited a general decrease from baseline (9.08) to period 11 (8.50), with a minimum at 15−18 minutes, or period 7 (7.93, $t_{11} = 4.0$, $p = 0.002$), in line with training direction, and largely paralleled by the contralateral hemisphere. Paired t-test comparisons of baseline with period means revealed a significant reduction ($p < 0.05$) for all periods except periods 3, 9, and 11. For the BETA-group, whose aim on the other hand was to increase low beta, mean amplitude became statistically higher than baseline (5.95), uniquely between 24 and 27 minutes, or period 10 (6.62, $t_{11} = -2.4$, $p = 0.034$). No significant increases were observed in the contralateral hemisphere.

Across periods, within-subject EEG amplitude correlations between theta, alpha, low beta, and high beta EEG band pairs during training were consistently positive at the $p < 0.01$ level, within a range of $0.5 < r < 0.9$. In other words, amplitude increases/decreases in all EEG bands <25 Hz covaried in parallel with each other. Furthermore, for the ALPHA group, high gamma mean frequency (60−120 Hz) was *inversely* correlated with alpha amplitude during training ($r = -0.25$, $p < 0.01$). No significant online associations were detected between EEG bands and direct current

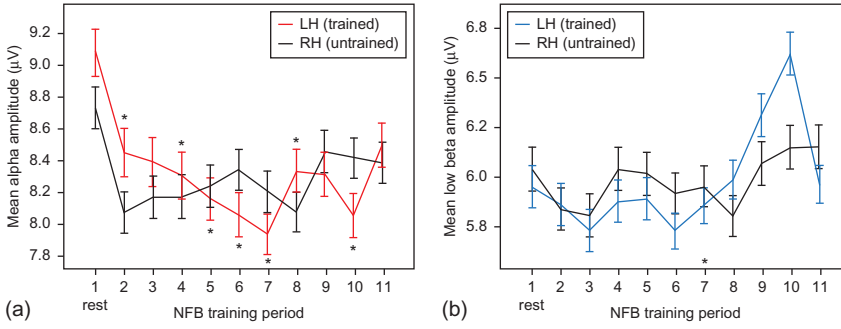

Figure 14.2 Time-course of the mean training EEG amplitudes for (a) ALPHA and (b) BETA groups, during a session of neurofeedback. Each session began with a 3-min baseline at rest (period 1), followed by 30 min of EEG feedback training (periods 2−11) on the left hemisphere (LH). * denote periods significantly different from baseline. Error bars represent SEM.

(DC) shifts, although the latter exhibited a negative correlation with period number ($r = -0.31$, $p < 0.01$) in the ALPHA group.

TMS Main Effects

A GROUP × TIME (2 × 3) repeated measures ANOVA for the trained hemisphere CSE revealed a main TIME effect of significance for CSE ($F(2,44) = 6.8$, $p < 0.01$) and SICI ($F(2,44) = -4.3$, $p = 0.03$), while insignificant 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. Figure 14.3(a) depicts the mean effect of alpha suppression NFB training on corticospinal excitability (CSE) in the trained hemisphere. Single-pulse MEP amplitudes were significantly increased at post 2 compared to pre (130%, $t_{11} = -2.6$, $p = 0.025$), or circa 20 minutes after termination of NFB training. For the untrained hemisphere a similar albeit non-significant increase in MEP amplitudes was found post 2 (135%, $t_{11} = -1.691$, $p = 0.12$). Interestingly, no facilitatory effects were found just after (<10 min) NFB in the trained hemisphere (post 1), while an intermediate enhancement of 115% became manifest at around 10 minutes in the untrained hemisphere (Figure 14.3b, post 1, n.s.). A reliable trained hemisphere within-subject correlation between testing order (pre, post 1, post 2) and MEP amplitude was also detected ($r = 0.43$, $p < 0.01$). As detailed in Figure 14.4(a), we observed a significant and sustained decrease of intracortical inhibition (SICI 3 ms) at post

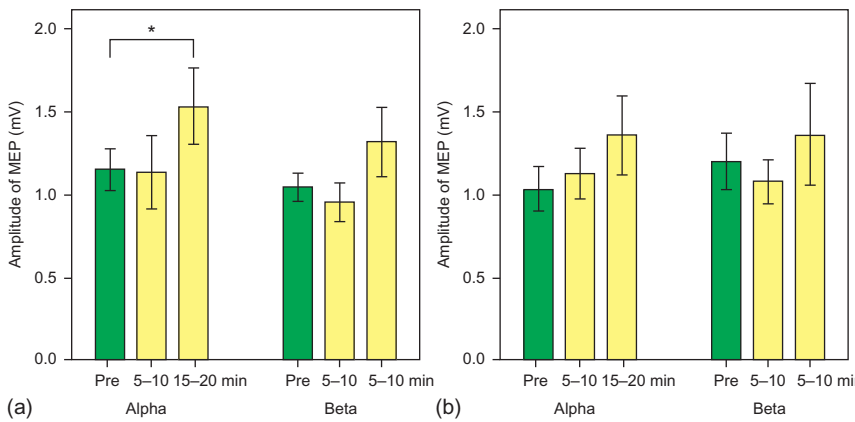

Figure 14.3 Mean corticospinal excitability (CSE) of (a) trained (left) hemisphere, and (b) untrained (right) hemisphere following the ALPHA and BETA protocols at times post 1 and 2. Error bars represent SEM.

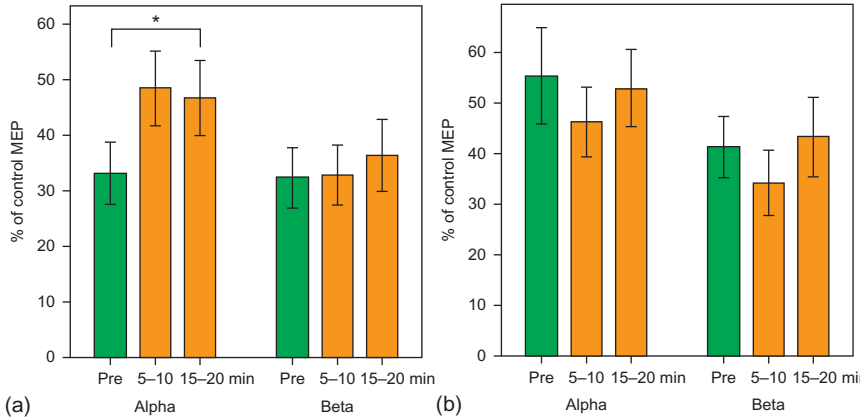

Figure 14.4 Mean short intracortical inhibition (SICI) of (a) trained (left) hemisphere, and (b) untrained (right) hemisphere following the ALPHA and BETA protocols at times post 1 and 2. Higher values signify lower SICI (disinhibition). Error bars represent SEM.

1 and post 2 uniquely in the trained hemisphere (post 1: 174%, $t_{11} = -3.5$, $p < 0.01$; post 2: 165%, $t_{11} = -2.6$, $p = 0.023$). No other intracortical parameters were significantly altered following ALPHA protocol training.

As can be seen in Figure 14.3 depicting corticospinal excitability, no significant differences in CSE were found following low beta enhancement, although an initial decrease followed by increase was seen in both hemispheres at post 1 and post 2, respectively. No significant changes in SICI were observed in the trained (Figure 14.4a) or untrained hemisphere (Figure 14.4b).

TMS–EEG Relationships

Corticospinal Excitability (CSE)

Effective NFB training for each subject was defined by a training coefficient, or the Pearson correlation between the period number (1 to 11) and its corresponding mean EEG amplitude (alpha and low beta amplitude, for ALPHA and BETA groups respectively). This has previously (Gruzelier & Egner, 2005) proven to be a good estimator of the temporal consistency of either an increase or a decrease in the training EEG amplitude from baseline, which can be expressed in the range of −1 (steady decrease) and +1 (steady increase).

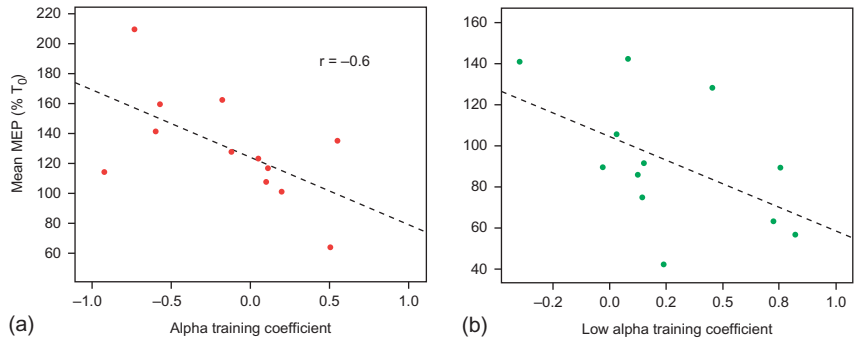

Figure 14.5 Scatter plots of each subject's (N = 12) training coefficient vs. mean single-pulse MEP change for (a) ALPHA group at post 2 and (b) BETA group at post 1.

As depicted in Figure 14.5a, a scatter plot of alpha training coefficient vs. post 2 MEP amplitude for the ALPHA group revealed a significant negative correlation ($r = -0.59$, $p = 0.044$), meaning that in general greater temporal consistency of alpha decrease from baseline is associated with greater increase in corticospinal excitability. Moreover, a parallel *positive* correlation was observed between high gamma mean frequency (60–120 Hz) training coefficient and MEP post 2 ($r = 0.62$, $p = 0.031$). No significant correlations were evident at post 1 ($r = -0.32$, n.s.). For the BETA protocol (Figure 14.5b), the correlation between reliable low beta synchronization and direction of MEP change was similarly negative at post 1, albeit less robust ($r = -0.53$, $p = 0.08$; weighted least-squares (WLS) regression $r = -0.62$, $p = 0.03$). This relationship was absent at post 2 ($r = -0.25$, n.s.).

Regarding the relation between TMS changes and absolute EEG parameters, first, no reliable relationships were evident between MEP change and absolute EEG amplitudes in any band, during any period of the neurofeedback session. However, when the EEG amplitudes were normalized as a percentage of their 3-min baseline value at rest (period 1), strong associations appeared, signalling that a change in the EEG was closely coupled to a change in MEP. Figure 14.6 illustrates the Pearson cross-correlation value between the post 2 MEP amplitude (outcome variable) and normalized alpha amplitude of each period (predictor variable) during neurofeedback in the ALPHA group. As anticipated, we observed mainly negative correlations between alpha power and MEP increase, with a gradual trend of increasing significance from the beginning of the session that reached a maximum at around the middle of the session,

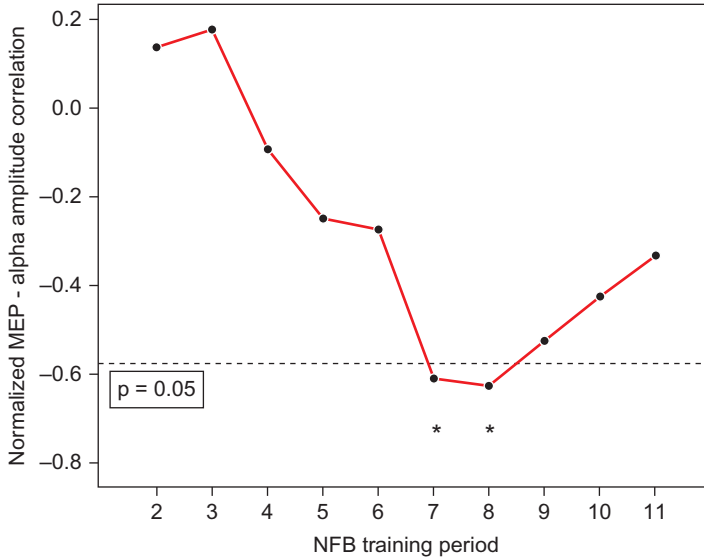

Figure 14.6 Post 2 MEP (%pre) vs. alpha amplitude (%pre) correlations, for all ALPHA periods.

during periods 7 ($r = -0.61$, $p = 0.35$) and 8 ($r = -0.63$, $p = 0.30$), or between 15 and 21 minutes of neurofeedback. Interestingly, period 7 also coincided with the minimum alpha amplitude during training (see Figure 14.2a).

The EEG amplitude ratio of the post-neurofeedback resting baseline and the pre-baseline (period 12/period 1) proved to be another successful predictor of post 2 MEP change in all bands investigated below *high* beta (delta: $r = -0.64$, $p = 0.03$; theta: $r = -0.7$, $p = 0.012$; alpha: $r = -0.71$, $p = 0.01$; low beta: $r = -0.62$, $p = 0.03$), suggesting that the more suppressed the slower EEG amplitudes were after NFB training the greater the enhancement of the MEP 20 minutes later. This also appeared to be positively the case for resting change in the high gamma mean frequency ($r = 0.53$, $p = 0.07$). Lastly, during periods 8, 9, and 10 correlations remained significantly positive ($r > 0.6$, $p < 0.05$) and predicted resting alpha amplitude change from *training* alpha amplitudes.

As seen in Figure 14.7, the overall implication is that a three-way significant association was thus established between core changes in the training EEG, the subsequent resting EEG, and corticospinal excitability.

Analogous analyses were performed on the BETA group for relationships between single-pulse MEP and low beta amplitudes, disclosing a

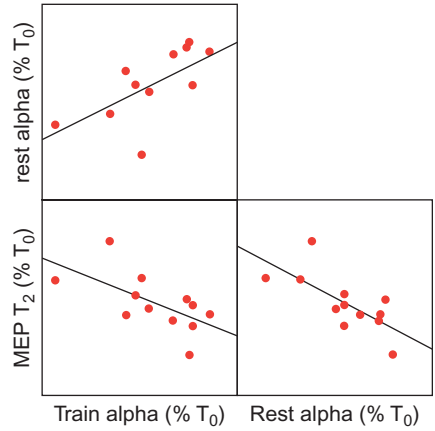

Figure 14.7 Matrix plot of training alpha (period 8 %pre), resting alpha (period 12 %pre), MEP (post 2 %pre) amplitudes. All correlations were significant at $r > |0.6|$, $p < 0.05$.

significant association similar to that found with ALPHA between resting low beta change and post 1 MEP (WLS $r = -0.58$, $p = 0.050$) as well as a borderline correlation between training period 7 and post 1 MEP (WLS $r = -0.52$, $p = 0.08$). Low beta amplitude during period 7 was in turn also tightly correlated with its subsequent change at rest (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 post 1: WLS $r = -0.17$, $p = 0.60$).

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

SICI/ICF

For the ALPHA group, there was significant positive correlation ($r = 0.58$, $p = 0.050$) between alpha training coefficient and 3 ms SICI (% pre) change at post 1, suggesting that it was the weakest performers that had the greatest reductions in SICI. However, relatively robust correlations were discovered for the DC training coefficient and SICI post 1 ($r = -0.6$, $p = 0.04$), SICI post 2 ($r = -0.53$, $p = 0.07$), and ICF post 2 ($r = 0.79$, $p < 0.01$). Moreover ICF post 2 (but not post 1) change was

inversely proportional with SICI at post 1 ($r = 0.63$, $p = 0.03$) and post 2 ($r = 0.72$, $p < 0.01$), suggesting that SICI decreases may have preceded ICF increases. No significant links were apparent for the BETA group; however, negative associations of marginal statistical significance were observed between ICF at post 1 and the low beta training coefficient ($r = -0.51$, $p = 0.09$) and resting (period 12) low beta amplitude ($r = -0.52$, $p = 0.08$). Resting alpha amplitude (in the BETA group) was uncorrelated ($r = 0.14$, $p = 0.67$).

Path Analysis

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. Figure 14.8 shows the Path Analysis results for ALPHA training during period 7 and MEP at post 2, mirroring Figure 14.7. For ALPHA group training periods 6, 7, 8, and 9, regression coefficients were consistently higher ($r > 0.5$) in the Path Analysis for the two indirect pathways (dark gray) of training EEG to resting EEG, and resting EEG to MEP, compared to the direct pathway (light gray) of training EEG to MEP ($r < 0.5$) as shown in Figure 14.8. Accordingly, a bootstrap test (see Methods for

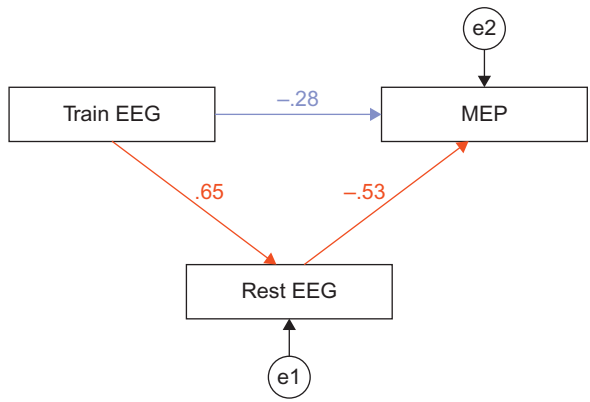

Figure 14.8 Path Analysis of the hypothesized causal relationship between observed training EEG, subsequent resting EEG and corticospinal excitability (MEP) measures. Here, the indirect pathway (dark gray arrows) emerges as a better predictor of the training EEG effect on MEP than the direct pathway (light gray arrow). ALPHA group standardized regression coefficients are illustrated for normalized training alpha (period 7), resting alpha (second baseline), and single-pulse MEP amplitudes at post 2 in the trained hemisphere. Unobserved residual (error) variables are denoted by e1 and e2.

details) revealed a statistically significant ($p < 0.05$) *indirect* effect of training EEG on MEP, *mediated* via the resting EEG change. Moreover, deletion of the training EEG to MEP direct pathway resulted in a better-fit (chi-square = 1.1, df = 1, p = 0.3) and greater parsimony (change in PNFI = 0.31). We then applied this final model to the BETA group relationships described above (low beta amplitude period 6 vs. MEP post 1), which turned out analogous to the ALPHA group, confirming a good-fit mediation model (chi square = 0.4, df = 1, p = 0.5), with the indirect effect having a marginal bootstrap significance of p = 0.08.

Overall, these modeling 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 reflection of cortical excitability.

DISCUSSION

In summary, sustained neurofeedback-mediated EEG changes in the ALPHA group (Figure 14.2a) resulted in a statistically reliable (>20 min) overall increase in corticospinal excitability (130%) (Figure 14.3a) and decrease in short intracortical inhibition (174%) (Figure 14.4a), when compared to the negligible longer-lasting changes in the BETA group which showed less evidence of learning. Most importantly, correlation analyses revealed robust relationships between the historical activity of certain brain rhythms during neurofeedback and the resultant change in corticospinal excitability. Specifically during neurofeedback, alpha (8−12 Hz) desynchronization (Figure 14.5a) coupled with increased mean frequencies of high gamma rhythms (60−120 Hz), was tightly correlated with long-term potentiation-like (>20 min) enhancement of single-pulse motor evoked potentials. In contrast, neurofeedback involving low beta (12−15 Hz) synchronization was inversely correlated with short-term depression-like (>5 min) reductions of corticospinal excitability (Figure 14.5b). Thirdly, in both groups, changes in resting EEG amplitudes were *predicted by* the neurofeedback training EEG, and were also a *predictor of* the later motor evoked potential amplitudes (Figure 14.7).

In this experiment, the longer-term neuroplastic effects following alpha desynchronization are highly unlikely to be consequences of basic changes in psychological arousal after neurofeedback, as the within-subject motor evoked potential data denotes a significant positive correlation between amplitude and elapsed time following training, while the

reverse would be otherwise expected (moreover, the BETA group did not demonstrate equivalent changes, discounting the likelihood of a placebo effect). Bearing in mind that neuroplastic induction may have already begun mid-session (see Figure 14.6, where correlations are highest around 20 min), such a progressive dynamic could also be suggestive of a time course involving cellular cascades known to occur during early long-term potentiation (Cooke & Bliss, 2006). In contrast, short-term potentiation amplitudes are markedly extinguished by 15–20 min (Schulz & Fitzgibbons, 1997). A reduction in alpha band power has commonly been found to be associated with increased cortical excitability (Sauseng, Klimesch, Gerloff, & Hummel, 2009), cortical metabolism (Oishi et al., 2007), attention (Fries, Womelsdorf, Oostenveld, & Desimone, 2008), and behavioral activation (Rougeul-Buser & Buser, 1997). Critically, in the current study a negative correlation between low-end frequencies (especially alpha) and high gamma mean frequencies during neurofeedback was also detected, as well as a positive correlation between the latter and single-pulse MEP increase. This is supported by recent reports linking high-frequency oscillations (HFO) or higher gamma activity with learning (Ponomarenko, Li, Korotkova, Huston, & Haas, 2008) and attention (Fries, Womelsdorf, Oostenveld, & Desimone, 2008), as well as with increased BOLD activity (Niessing et al., 2005), neuronal depolarization and firing rate (Grenier, Timofeev, & Steriade, 2001; Niessing et al., 2005). Interestingly, the ALPHA group reduction in short intracortical inhibition at post 1 and 2 may be attributed to a decrease in cortical GABAergic transmission (Hallett, 2007). This could possibly be the system's intrinsic reaction in order to further facilitate plasticity, as previous reports have found an antagonistic relationship between inhibitory and excitatory transmission on motor plasticity and long-term potentiation (Bütefisch et al., 2000; Komaki et al., 2007). At present, however, we can neither confirm nor rule out the release of endogenous neuromodulators as an interacting mechanism for the observed effects. One potential candidate may be noradrenaline, which is released during attentive behavior (Berridge & Waterhouse, 2003; Rougeul-Buser & Buser, 1997) and has previously been reported to enhance long-term potentiation (Harley, 1987), desynchronize alpha rhythms (Rougeul-Buser & Buser, 1997), and increase corticospinal excitability and decrease short intracortical inhibition concomitantly (Ziemann, 2004).

As low beta learning was less effective it is possible that it was associated with an inappropriate training approach in some subjects which was

perhaps more desynchronizing than synchronizing, and therefore confounded the group result; hence the slightly increased corticospinal excitability observed later on. This is supported by the negative correlations found 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, Chen, Bressler, & Ding, 2008). The finding that electrical stimulation of sensorimotor cortex at 10 Hz leads to long-term depression (Werk, Klein, Nesbitt, & Chapman, 2006) may be related to the short-term depression-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, Shin, Jeong, & Shin, 2008).

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

Another intriguing question is whether the observed plasticity effects are a direct consequence of longer-term changes to the dynamics of "resting" or spontaneous rhythms (Sauseng et al., 2009), and associated thalamocortical networks (Steriade & Timofeev, 2003; Thut & Miniussi, 2009). This seems a tempting account in light of the significant three-way correlations between amplitude changes in training EEG, subsequent resting EEG, and the motor evoked potential (Figure 14.7). Moreover, path analysis and structural equation model results (Figure 14.8) point to an indirect effect of neurofeedback (via the resting EEG) on the single-pulse motor evoked potential. If ultimately confirmed, this would suggest that the brain indeed "shapes itself" (Rudrauf, Lutz, Cosmelli, Lachaux, & Le Van Quyen, 2003), whereby past activities perpetually influence or bias future (baseline) states of processing (Silvanto, Muggleton, & Walsh, 2008). In this case, the notion of a "background" or baseline brain state

would cease to be informative, as it would be continually in flux and shaped by past/present activity. We hope that future studies will elucidate these complex activity-dependent relationships further.

The novel finding that short intracortical inhibition was positively correlated with slow shifts in DC potential are compatible with the established view that slow cortical negativities are a marker of increased excitability and/or cortical disinhibition (Niedermayer & Lopes Da Silva, 1999). As this was for the ALPHA group only, this relationship awaits replication, and supports the online/offline use of TMS full-band EEG co-registration. The lack of relation of paired-pulse or DC measures with oscillatory EEG in this study is especially noteworthy. The latter effect has been documented previously and may suggest physiologically separate mechanisms of action (Kotchoubey, Busch, Strehl, & Birbaumer, 1999). We have to acknowledge that our recording conditions were suboptimal, as we did not additionally short-circuit the skin (Vanhatalo, Voipio, & Kaila, 2005); although random fluctuations of skin/sweat voltages would be unlikely to account for this phenomenon. Overall our results remain consistent with traditional evidence from both cellular and non-invasive studies reporting that very high frequency stimulation usually induces synaptic potentiation whereas lower frequencies may engender synaptic depression (Cooke & Bliss, 2006). It is well-established that EEG activity is generated by the summed electrical fluctuations of postsynaptic potentials (Niedermayer & Lopes Da Silva, 1999), and so may potentially be a close correlate of changes in synaptic transmission frequency or dendritic activity (Williams, Wozny, & Mitchell, 2007). Higher frequencies could reflect denser temporal incidence of EPSPs and hence greater influx of calcium (a trigger of long-term potentiation) through voltage-gated ion channels (Na^{+}, Ca^{2+}). Intracellularly, second messengers such as Cam Kinase II have also been found to be sensitive to the frequency of calcium oscillations (De Koninck, 1998). On the other hand, a recent study observed that zero net-current extracellular high-frequency stimulation in cultured neurons gave rise to an overall depolarization of the cell membrane (Schoen & Fromherz, 2008), which could hypothetically lower activation thresholds for voltage-gated ion channels. However, our data did not reveal significant changes in the resting motor threshold (considered to reflect changes in membrane excitability), making a case for a transynaptic effect more likely. On the whole, the activity-dependent relationships observed in this study, together with the cited works above, vouch for the possible involvement of endogenous oscillations in the

mediation of synaptic plasticity (Steriade & Timofeev, 2003). Latest findings that appear to support this role report neuroplasticity induction based on slow-wave sleep, sleep spindle (Rosanova & Ulrich, 2005), and theta (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005) endogenous rhythms.

In light of the initial neurophysiological evidence presented in this study, a repetitive alpha suppression protocol could theoretically be of significant therapeutic value in clinical cases where the pathophysiology consists of poor corticospinal activation and/or increased inhibition; in a motor disorder such as stroke, for example. Moreover, as other methods of neuromodulation are reported to facilitate motor learning by inducing increases in cortical excitability (Ziemann et al., 2008), this particular protocol may be potentially useful in enhancing practice-dependent motor performance in healthy subjects (Ros et al., 2009). Lastly, whilst additionally supporting previous clinical applications of neurofeedback (Heinrich, Gevensleben, & Strehl, 2007), a similar NFB approach aimed at cortical activation may eventually prove to be appropriate for brain disorders exhibiting low cortical excitability or elevated slow-wave EEG power, such as attention-deficit hyperactivity disorder (ADHD) (Lubar, 1991), traumatic brain injury (Thatcher, 2000), and depression (Korb, Cook, Hunter, & Leuchter, 2008).

In conclusion, our results provide a first basis for the "missing link" between the historical long-term training effects of neurofeedback and direct validation of neuroplastic change after an individual session of training.

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