Figures and figure supplements

Neural activity related to volitional regulation of cortical excitability

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Figure 1. Outline of experimental setup. Each trial of neurofeedback training commenced with a display of four circles (A) each representing the background EMG in one of the recorded hand muscles (right FDI, ADM and OP, and left FDI). The circles were red if the root mean squared (rms) EMG at rest was greater than seven microvolts. It was essential that all four circles were green for at least 500 ms before the trial could proceed. When this condition was met a fixation cross appeared for a random period (in order to prevent anticipation of the TMS pulse). During the fixation period, it was still essential to keep the background EMG below seven microvolts in order for a TMS pulse to be delivered. (B) The peak-peak amplitude of the motor evoked potential (MEP) evoked by the TMS was calculated in real-time and displayed immediately to the participant on screen in the form of a rectangular bar. (C) Different feedback for UP training and DOWN training. In the UP training if the MEP was greater than the baseline mean, the rectangle was green, with a green tick, a dollar sign to indicate a small financial reward, a display of the current score, and a positive encouraging message. In the DOWN training if the MEP was less than the baseline mean, the rectangle was red, with a red cross, and a message to improve. (D) Transcranial Magnetic Stimulation (TMS) apparatus.
sound bite was heard. If the MEP did not meet the criterion amplitude, the bar was red, there was no dollar sign, and a negative sound bite was heard.

(D) A custom 3D printed ‘coil spacer’ device was used to prevent direct contact of the TMS coil on the EEG electrodes and allow the pre-TMS EEG period to be recorded artefact free.

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Figure 1—figure supplement 1. Power analysis to compute sample size. Conducted using G*Power software version 3.1, based on the inclusion of two groups, an alpha value of 0.05, and an effect size of 0.81 (Cohen’s d reported by Majid et al., 2015) in a study training voluntary modulation of MEP amplitude, for an F-test comparing effect of whether the MEP was cued or uncued. As our core findings are communicated using F-tests following mixed effects models, we selected to perform this power analysis based on the F-tests family.

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Figure 2. MEP amplitudes during neurofeedback. Panel (A) depicts MEP amplitude in millivolts during the two types of MEP neurofeedback. UP training is shown in orange and DOWN training in blue, across all 10 training blocks. Unfilled triangles labelled 'BS' indicate the baseline measurement block that occurred at the beginning of that particular session, prior to any neurofeedback. Dotted vertical lines indicate the separation of the blocks into different ‘sessions’, which occurred on separate days. Panel (B) shows the same data for the control group who received no veridical neurofeedback. Panel (C) shows the UP-DOWN difference (in the normalised % change from baseline data) for each block in the experimental group and the control group. Higher values represent greater deviations between the UP and DOWN data points and therefore more modulation of MEP amplitude. Thus, these values are significantly higher in the experimental group than in the control group. # symbols indicate blocks in which the Cohen’s $d$ effect size for the difference between the experimental and control group was large-very large (> 0.8). All data are shown as mean ± SEM. DOI: https://doi.org/10.7554/eLife.40843.004
Figure 2—figure supplement 1. Percentage change in MEP amplitude. Panel (A) shows the % change from baseline at each block for the experimental group (ie. 0 represents no change in MEP amplitude from baseline). Stars indicate blocks in which the % change deviated significantly from 0 (Wilcoxon signed rank test, all p values FDR corrected for multiple comparisons). Panel (B) shows the same data for the control group. During the UP training sessions, MEP amplitudes were increasingly elevated compared to baseline reaching an increase of 83.8% (±31.1 SEM) during the final block of EEG session (block 10). These elevations in MEP amplitude were significantly different from 0 (indicating no change) by the end of 60 neurofeedback trials (block 2), and remained significantly elevated throughout all the remaining blocks (Wilcoxon Signed Rank test, two tailed, all p < 0.03, p values FDR corrected for multiple comparisons). For the DOWN training MEP amplitudes changed less rapidly than in the UP sessions but were reduced by 30.6% (±8.7 SEM) at the end of the final EEG session (block 10). The decreases in MEP amplitude were significantly different from 0 after 210 neurofeedback trials (block 7, Wilcoxon Signed Rank test, two tailed, p = 0.006) and in the final block (10), after 300 training trials (p = 0.016, all p values FDR corrected for multiple comparisons). For the control group shown in panel (B), there were no significant deviations from 0 (no change) in any of the 10 blocks of UP training or DOWN training (Wilcoxon Signed Rank tests, two tailed, all p > 0.11, p values FDR corrected for multiple comparisons).

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Figure 2—figure supplement 2. MEP amplitudes during neurofeedback for all participants. Panel A and B in this figure are analogous to Figure 2 in the main manuscript, but here all individual participant datapoints are plotted as dots in line with their means (triangles). Panel A shows MEP amplitude data for the experimental group, and Panel B for the control group, across all training blocks. Means are shown ± SEM.

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Figure 2—figure supplement 3. Individual representative subjects’ performance across trials. Change in MEP amplitude from baseline is shown (in mV) for one representative subject from the experimental group (panel A) and control group (panel B) for each neurofeedback training block in each session. Each triangle represents the mean of 30 MEP trials, with the baseline (resting) mean subtracted in order to demonstrate the magnitude of learning related changes across sessions. Orange triangles represent UP blocks and blue represent DOWN blocks.

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Figure 2—figure supplement 4. Scatterplots showing individual MEP data trials across learning. Panels (A) and (B) show MEP amplitudes from individual trials from the UP and DOWN conditions respectively, from a
Figure 2—figure supplement 4 continued

representative subject (same as Figure 2—figure supplement 3) in the experimental group. Separate datapoints are shown for MEPs on all 300 neurofeedback trials (across sessions 1–3). Lines of best fit based on robust regression models are plotted in red, indicating a positive slope for the UP training trials (slope = 0.006, p < 0.0001, Rho = 0.373) and a negative slope for the DOWN training trials (−0.0006, p = 0.008, Rho = −0.20).

Panels (C) and (D) show the same data but only for the first 120 trials of UP and DOWN MEPs (Session 1), from the same subject shown in panels A and B. This is an example of a slow learning subject, who did not exhibit significant trial-related changes in MEP amplitude in the expected direction during the first session of training. Panels (E) and (F) show the same data but from a subject who exhibited faster learning of the task. In this case within the first 120 trials there was a positive slope for UP training (slope = 0.023, p = 0.006, Rho = 0.385) and negative for DOWN training (slope = −0.019, p = 0.021, Rho = −0.399), indicating that their MEP amplitudes were increasing (or decreasing) as trial number incremented. In each the scatterplots shown, all 300 (or 120) MEP amplitudes are plotted as individual dots, with those excluded from analyses due to background EMG indicated as unfilled data points. These are shown in the interests of transparency, but have not been included in any statistical analyses or lines of best fit.

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Figure 3. Retention, aftereffects and feedback-free measurements. Filled bars represent blocks of neurofeedback, and unfilled bars represent MEPs collected at rest. Shown are MEP amplitudes with their preceding resting baseline values subtracted. Values above 0 represent increases relative to baseline, and below 0 represent decreases. State-dependent neurofeedback training feedback effects were still evident in a retention block carried out approximately 6 months following the initial experiment. No aftereffects were observed on resting MEP amplitude 5 and 10 min later. In a separate block participants were capable of upregulating and downregulating MEP amplitudes with feedback removed (FB free). MEPs measured from the opposite hemisphere during neurofeedback exhibited a similar pattern of modulation.

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Figure 4. Investigation into mechanisms of MEP neurofeedback. The data show paired pulse TMS measurements taken during neurofeedback blocks to probe distinct neurophysiological processes. In all subsequent panels, unfilled bars represent baseline MEP amplitudes collected at rest prior to the block. Panel (A) shows that MEP amplitudes from the single pulses (from which neurofeedback was provided) exhibited the same state-dependent modulation as observed previously. In Panel (B) MEP amplitudes are expressed as a percentage of the single pulse (SP) MEPs. While expected levels of inhibition were observed for both SICI and LICI paired pulses, there was no state-dependent modulation. LCD was, however, significantly increased in the UP condition relative to baseline, and relative to the DOWN condition.

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Figure 5. Neural oscillations associated with the trained brain states. Panels (b–f) show topographical representations of the relative power (in % of whole spectrum) in the UP condition minus the DOWN condition, for five distinct frequency bands (averaged group data, n = 14, three other frequency bands shown in Figure 5—figure supplement 2). Red colours indicate regions that demonstrated greater synchronisation in the UP condition. Blue colours indicate greater synchronization in the DOWN condition. The location of the electrode nearest to the TMS hotspot varied between participants but was always within the region indicated in panel (a). Colours are scaled from blue-red by minimum-maximum (range shown to right of each plot). Panel (g) shows the same data (UP-DOWN) extracted for each participant’s hotspot electrode. Values greater than 0 indicate larger amplitude oscillations in the UP condition, and lower than 0 indicate larger oscillations in the DOWN condition. Stars indicate significant deviations from 0 (Wilcoxon Signed Rank tests). Panel (h) shows group level data for regression analyses performed on MEP amplitudes with relative power in each frequency band. This included all 120 trials (60 UP, 60 DOWN) collected during the combined TMS-EEG recording session. The Y axis depicts the slope of the regression model. Stars indicate significant deviations from 0 (0 would indicate no slope, Wilcoxon Signed Rank test). Individual regression plots are shown for one representative participant in Figure 5—figure supplement 3.

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Figure 5—figure supplement 1. Boxplots showing relative power in the Up condition minus the Down condition for the electrode corresponding to the hotspot in the opposite (non-feedback) hemisphere.
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Figure 5—figure supplement 2. Non-significant frequency band topographies. This figure shows the remaining frequency bands not shown in Figure 4. Variations in the power of Delta, Low Beta and High Beta were not significant predictors of MEP amplitude. The blue-red range of the plots is shown to the right of each figure.

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Figure 5—figure supplement 3. Regression plots of MEP amplitude with relative power for one representative subject. Panels (a-d) show scatterplots with lines of best fit for the regression performed on MEP amplitudes with relative power in each frequency band (only those with significant associations are displayed). The data points show all 120 trials (60 UP, 60 DOWN) collected during the combined TMS-EEG recording session, for a single representative participant.

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Figure 5—figure supplement 4. Control group EEG data. Data shown are relative power values in the UP-DOWN states, extracted for each participant’s hotspot electrode. Values greater than 0 indicate larger amplitude oscillations in the UP condition, and lower than 0 indicate larger oscillations in the DOWN condition. EEG recordings were only made in a subset of 5 participants, so individual datapoints are overlaid as red dots. DOI: https://doi.org/10.7554/eLife.40843.015