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Self-regulation of inter-hemispheric visual cortex balance through real-time fMRI neurofeedback training

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ABSTRACT

Recent advances in neurofeedback based on real-time functional magnetic resonance imaging (fMRI) allow for learning to control spatially localized brain activity in the range of millimeters across the entire brain. Real-time fMRI neurofeedback studies have demonstrated the feasibility of self-regulating activation in specific areas that are involved in a variety of functions, such as perception, motor control, language, and emotional processing. In most of these previous studies, participants trained to control activity within one region of interest (ROI). In the present study, we extended the neurofeedback approach by now training healthy participants to control the interhemispheric balance between their left and right visual cortices. This was accomplished by providing feedback based on the difference in activity between a target visual ROI and the corresponding homologue region in the opposite hemisphere. Eight out of 14 participants learned to control the differential feedback signal over the course of 3 neurofeedback training sessions spread over 3 days, i.e., they produced consistent increases in the visual target ROI relative to the opposite visual cortex. Those who learned to control the differential feedback signal were subsequently also able to exert that control in the absence of neurofeedback. Such learning to voluntarily control the balance between cortical areas of the two hemispheres might offer promising rehabilitation approaches for neurological or psychiatric conditions associated with pathological asymmetries in brain activity patterns, such as hemispatial neglect, dyslexia, or mood disorders.

Introduction

Linking mental functions, such as visual perception, with neural activity in specific brain regions, such as the visual cortex, is a central challenge for contemporary neuroscience. Neuroimaging techniques including functional magnetic resonance imaging (fMRI) have been widely used to study this question (Rees, 2001). These studies have helped to establish a correlation between the recruitment of specialized brain areas, and the processing of features or information that underlie particular cognitions, emotions, and behaviors (Haynes et al., 2004; Rees et al., 2002; Ress and Heeger, 2003; Tong, 2003). For instance, activity in early visual cortex is typically smaller for unseen than for seen visual stimuli, suggesting a direct role of these sensory areas in conscious awareness (Dehaene et al., 2001; Ress et al., 2000; Vuilleumier et al., 2001a).

However, although activity in early visual areas is highly correlated with stimulus perception, it alone is not sufficient to produce a conscious visual experience (Crick and Koch, 1995; Driver and Vuilleumier, 2001). Instead, stimulus perception might require the participation of multiple, interacting visual areas that are interconnected with frontal and parietal areas mediating attentional and executive functions. A good example of this is hemispatial neglect, which results most often from damage to the inferior parietal lobe of the right hemisphere (Driver and Mattingley, 1998; Driver and Vuilleumier, 2001; Halligan et al., 2003; Husain and Rorden, 2003; Milner and McIntosh, 2005). Characteristic neglect symptoms include the lack of awareness for the contralesional side of space, e.g., patients are not aware of visual stimuli on the neglected side even though their visual system is intact (they are not blind). These symptoms are assumed to be due to abnormalities in the asymmetric top-down influence of parietal onto sensory areas after right parietal lesions (Valenza et al., 2004; Vuilleumier et al., 2008), leading to reduced activation of the intact visual cortex of the damaged hemisphere. Indeed, fMRI studies in neglect patients have found that neglected visual stimuli may activate early visual areas of the damaged hemisphere, but that they are consciously perceived only when activation levels are high, and when

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connectivity between visual and fronto-parietal areas of the intact hemisphere is increased (Driver and Vuilleumier, 2001; Vuilleumier et al., 2001a; Vuilleumier et al., 2001b). An imbalance between hemispheric activity has therefore been proposed as a key factor in determining hemispatial neglect and pathological attentional biases after right unilateral lesions (Corbetta et al., 2005; Corbetta and Shulman, 2011; Kinsbourne, 1993). A pathological interhemispheric imbalance in brain networks has also been implicated in several other neuropsychiatric diseases such as dyslexia (Bishop, 2013), schizophrenia (Oertel-Knochel et al., 2012), or mood disorders (Herrington et al., 2010; Sackeim et al., 1982).

However, an important limitation of conventional fMRI studies is that they are purely correlational, and cannot directly confirm the causal role of alternations in interhemispheric asymmetry in disorders such as hemispatial neglect. More direct support has been provided by manipulations that aim at modifying the activation balance between the left and right hemispheres, for example by caloric vestibular stimulation (Bottini et al., 2001; Geminiani and Bottini, 1992), neck vibration (Bottini et al., 2001; Schindler et al., 2002), prism adaptation (Saj et al., 2013), or transcranial magnetic stimulation (TMS) (Kim et al., 2013; Muri et al., 2013). These manipulations alleviate neglect symptoms by partly compensating for altered interhemispheric asymmetries in spatial attention, although their effect on early sensory areas remains unresolved (Saj et al., 2013). However, these treatments are often associated with patient discomfort, and the effects are short lasting.

A complementary approach to manipulating the interhemispheric balance of brain activity is offered by neurofeedback, which allows participants to learn to self-regulate their own brain activity and thus to obtain specific perceptual or behavioral changes. Until recently, neurofeedback was mainly provided using electroencephalography (EEG), but recent advances in neuroimaging methods and computer processing capacity now allow us to deliver neurofeedback with real-time fMRI. Real-time fMRI neurofeedback offers the advantage of learning to control spatially localized brain activity in the range of millimeters across the entire brain (deCharms, 2007; Sulzer et al., 2013a; Weiskopf et al., 2004; Weiskopf et al., 2007). For example, two recent studies used real-time fMRI-based neurofeedback to teach participants to voluntarily increase activity in a circumscribed region of their early visual cortex, which subsequently led to improved visual perception (Scharnowski et al., 2012; Shibata et al., 2011).

Here we extended these previous neurofeedback studies by now training healthy participants to control the interhemispheric balance between their left and right visual cortices, rather than only one specific region of interest (ROI). This was accomplished by providing feedback based on the difference in activity between a target visual ROI (ROI_{target}), and that in the homologous region of the opposite visual cortex ($ROI_{opposite}$). To facilitate neurofeedback learning, participants were encouraged to covertly direct attention to the visual field contralateral to the ROI_{target}, and to engage in visual mental imagery within that side. Visual imagery and shifting visual attention are known to activate the visual cortex in a regionally specific manner (Blankenburg et al., 2010; Bressler et al., 2008; Greenberg et al., 2010; Hopfinger et al., 2000; Kastner et al., 1999; Kosslyn et al., 2001; Lauritzen et al., 2009; Li et al., 2008; Ruff et al., 2006; Silver et al., 2005, 2007; Slotnick et al., 2005; Stokes et al., 2009). We therefore hypothesized that exerting these cognitive strategies in a lateralized manner would recruit visual cortical regions overlapping with the ROI_{target} and thus facilitate control over the differential feedback signal. However, in principle, the differential feedback signal can be controlled by up-regulating the ROI_{target}, by down-regulating the corresponding $ROI_{opposite}$, or both (Chiew et al., 2012; Scharnowski et al., 2004; Weiskopf et al., 2004). Down-regulation of the $ROI_{opposite}$ is not clearly associated with a specific cognitive strategy, but explicit instructions and cognitive strategies are not necessary for neurofeedback learning (Birbaumer et al., 2013; Shibata et al., 2011). More implicit processes based on instrumental operant learning are also known to play an important role (Birbaumer et al., 2013; Fetz, 1969). We therefore hypothesized that down-regulation of the $ROI_{opposite}$ will also contribute to learning control over the differential feedback signal. Our experimental design allowed us to determine whether more efficient learning would be achieved by up-regulation of the target side, down-regulation of the opposite side, or by a combination of both.

Learning to control the interhemispheric balance between left and right cortical regions might be a promising rehabilitation method for diseases associated with interhemispheric imbalance, particularly in the case of attention-dependent asymmetries in left and right visual areas in neglect patients (Vuilleumier et al., 2008). We were therefore particularly interested in the transfer of learned self-regulation to situations where neurofeedback is not available anymore. For that reason, we interleaved the neurofeedback training runs with transfer runs, during which participants performed self-regulation in the absence of neurofeedback. We hypothesized that participants would also be able to perform learned self-regulation without feedback. Finally, we asked whether training to change the interhemispheric balance between the left and the right visual cortex activity might cause changes in visual perception across the two hemifields, perhaps mimicking some of the deficits observed in neglect patients.

Materials and methods

Experimental design overview

We recruited fourteen healthy volunteers, and trained them to control the differential feedback between a target ROI in early visual cortex and its homologue in the opposite hemisphere. The ROIs were delineated in separate functional localizer scans, and represented specific locations in the left and right visual fields (Fig. 1). Training participants to control the differential feedback signal was undertaken in three separate scanning sessions spread over the course of three days. For neurofeedback training, the fMRI Blood Oxygenation Level Dependent (BOLD) signal from the ROIs was processed in near real-time, and the activity difference between the two ROIs was fed back to the participant in the form of a visual thermometer display on a projection screen in the scanner bore. No other visual stimuli were presented. Before every two training runs, and at the end of the session, participants performed a visual detection task and a line bisection task. After every two training runs, participants performed learned self-regulation in the absence of feedback.

MRI data acquisition

All experiments were performed on a 3 T MRI scanner (Trio Tim, Siemens Medical Solutions, Erlangen, Germany) at the Brain and Behavior Laboratory (University of Geneva). Functional images were obtained with a single-shot gradient-echo T2*-weighted EPI sequence (30 slices, matrix size 64×64, voxel size $= 4 \times 4 \times 4\ mm^3$, slice gap $= 0.8$ mm, flip angle $\alpha = 88°$, bandwidth 1.56 kHz/pixel, TR $= 2000$ ms, TE $= 30$ ms), using a 12-channel phased array coil. The first three EPI volumes were automatically discarded to avoid T1 saturation effects. A T1-weighted structural image was acquired at the beginning of each scanning session (3D MPRAGE, $256 \times 246 \times 192$ voxels, voxel size $= 0.9$ mm isotropic, flip angle $\alpha = 9°$, TR $= 1900$ ms, TI $= 900$ ms, TE $= 2.32$ ms).

Visual stimuli and instructions were displayed on a rectangular projection screen at the rear of the scanner bore, viewed through a mirror positioned on top of the head-coil. Stimulus display and response collection were controlled by MATLAB (Mathworks Inc., Natick, MA, USA) using the COGENT toolbox (developed by the Cogent 2000 team at the Wellcome Trust Centre for Neuroimaging and the UCL Institute of Cognitive Neuroscience, and Cogent Graphics developed by John Romaya at the Wellcome Department of Imaging Neuroscience).

The neurofeedback setup used Turbo-BrainVoyager (Brain Innovation, Maastricht, The Netherlands), and custom scripts running on

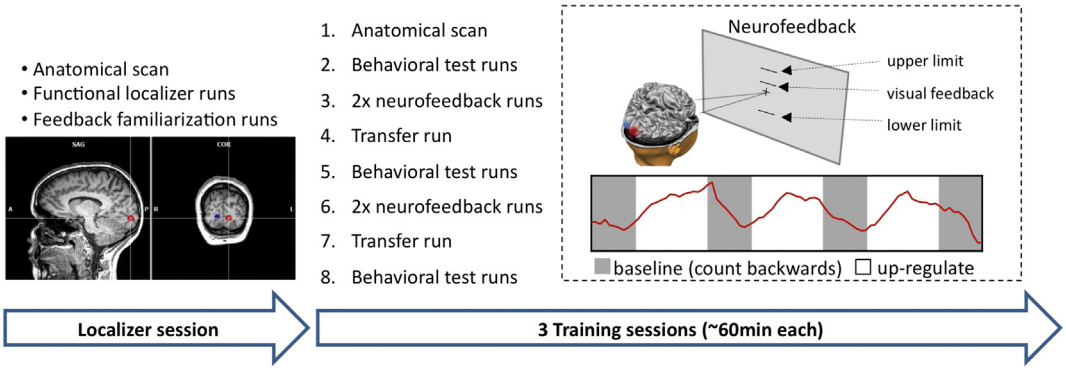

Fig. 1. Overview of the experimental procedure. In the first scanning session, a structural scan was acquired, the visual ROIs in the left and right visual cortex were defined with functional localizer runs, and the participants familiarized themselves with the neurofeedback setup. In 3 subsequent neurofeedback training sessions (on three different days), participants then learned self-regulation of their visual cortex activity. Each training session was composed of a short anatomical scan, two behavioral test runs, two neurofeedback training runs (of 2.8 min each), a transfer run (same as a training run but without feedback), and two behavioral test runs. This sequence was repeated once per session (except for the structural scan). Each training/transfer run was composed of four 20 s resting blocks (in gray) interleaved with three 30 s regulation blocks (in white). The behavioral tests consisted of a line bisection task and a visual extinction task, given at the beginning, in the middle, and at the end of each session.

MATLAB. This allowed participants to be shown visual representations of BOLD signal changes in specific brain regions (in the form of a thermometer display projected into the scanner) with a delay of less than 2 s from the acquisition of the image. Head motion was corrected for in real-time using Turbo-BrainVoyager. Heart rate, respiration, and eye movements were continuously monitored throughout the experiment with a modular data acquisition system (MP150, 1 kHz sampling rate, BIOPAC Systems Inc) and an infrared eye-tracking system (ASL 450, 60 Hz sampling rate, LRO System), respectively. Heart rate was measured using a pulse oximetry sensor, and respiration was measured using an elastic belt around the participant's chest.

Participants

Fourteen volunteers (5 male, ages between 20 and 44 years, 11 right handed) with normal or corrected-to normal vision gave written informed consent to participate in the experiment, which was approved by the ethics committee of the University Hospital Geneva. Participants were naive to neurofeedback. Before the experiment, they received written instructions explaining that they will learn to regulate their visual cortex activity with the help of neurofeedback. The instructions included an explanation of the neurofeedback thermometer display and recommended shifting visual attention covertly to either the left or right visual field as potential regulation strategies (depending on the type of feedback that they received; see below). Importantly, however, it was emphasized that participants should find an individual strategy that worked best for them. Furthermore, they were instructed to fixate on the central fixation point throughout the experiment, to breathe steadily, and to remain as still as possible.

Participants were also told that the feedback signal was delayed by approximately 8 s (the hemodynamic delay plus the real-time analysis processing time). In separate scanning runs before the neurofeedback training, this delay was illustrated to the participants by asking them to move their fingers and to try mental imagery of hand movements while being shown feedback from the motor cortex. By observing the delay of the neurofeedback signal change with respect to the onset and offset of finger movements or imagery, participants gained an intuitive understanding of the delay. All participants reported that they could easily account for the delay during the actual neurofeedback training.

After each scanning session, participants were asked to describe how they tried to manipulate the feedback signal (including any visual imagery), and how effective their strategy was. After the experiment, participants completed the Vividness of Imagery Questionnaire (VVIQ) (Marks, 1973, 1995).

Functional localizer runs

In a separate scanning session before the neurofeedback training, we determined the visual target ROIs from which participants received neurofeedback by acquiring a functional localizer run of 160 volumes. In the localizer run, participants maintained fixation on a central point while a flickering checkerboard wedge (100% contrast, 8 Hz contrast reversal) was presented on a gray background. The checkerboard-filled wedge extended from near the midpoint of the screen to 30° eccentricity along the horizontal meridian at a 45° angle. The checkerboard was presented for 3 blocks of 30 s alternating in the left and in the right visual field, respectively. Visual stimulation blocks were interleaved with baseline blocks during which participants fixated without any visual stimulation.

The left visual ROI used for neurofeedback was restricted to those voxels in the left occipital cortex that exhibited a positive BOLD response to the right checkerboard stimulus ($p < 0.01$, Bonferroni corrected for multiple comparisons using BrainVoyager QX), and vice versa for the right visual ROI (for details about the visual target ROIs, see Table 1). As feedback signal, participants either received the activity difference between the left–right visual ROIs, or the difference between right–left visual ROIs (randomly assigned).

Training protocol

Participants took part in three neurofeedback training sessions spread over the course of three days (one session per week). Each training session started with a 5 minute T1-weighted structural scan of the whole brain. This anatomical image was used for coregistration of the current head position with the T1-weighted structural scan of the functional localizer session using Turbo-BrainVoyager. From the resulting coregistration matrix, the position of the neurofeedback target ROIs in the current head position of the current run was determined. This ensured that the same ROIs were targeted in all training sessions, although they took place on different days.

In each training session, participants performed a bilateral visual detection task (7 min), a perceptual line bisection/landmark task (3 min), two neurofeedback training runs (3 min each), and a transfer run

Table 1
Details about individual participants, the visual ROIs, and neurofeedback learning. For each participant, learning success, age, gender (F: Female; M: Male), handedness, the size of the visual ROI in the target hemisphere and on the opposite side, and the slope of the learning curve are shown. Please note that even though participant S11 improved across sessions (r = 0.47), she was not classified as a learner because she was not able to control the feedback signal, i.e. the beta value in the GLM computed over the differential feedback signal in the last two sessions was negative.

Subjects	Experimental group	Age	Gender	Handedness	Target hemisphere	Size of the ROI_{target} (voxels)	Size of the $ROI_{opposite}$ (voxels)	Linear regression (r)
S01	Learner	27	F	Right	Right	45	32	0.02
S02	Learner	26	M	Right	Left	46	48	0.29
S03	Learner	27	F	Left	Left	37	30	0.44
S04	Learner	40	F	Right	Right	38	24	0.10
S05	Learner	27	F	Right	Right	15	22	0.46
S06	Learner	22	M	Right	Right	32	34	0.39
S07	Learner	34	M	Right	Right	23	28	0.28
S08	Learner	25	F	Right	Right	18	9	0.16
S09	Non-learner	24	F	Right	Left	15	28	−0.01
S10	Non-learner	44	M	Left	Left	43	69	−0.68
S11	Non-learner	36	F	Right	Left	42	74	0.47
S12	Non-learner	24	F	Left	Left	25	35	−0.28
S13	Non-learner	50	M	Right	Left	46	37	−0.44
S14	Non-learner	23	F	Right	Right	32	21	−0.47

without feedback (3 min) (Fig. 1). The visual tasks are described below. Except for the structural scan, all fMRI runs were repeated once in each session.

Neurofeedback procedure

The training runs were composed of four 20 s baseline blocks interleaved with three up-regulation blocks of 30 s each (Fig. 1). During the baseline blocks, the fixation cross at the center of the screen was black, which instructed the participant to mentally count backwards from 100 in steps of −3 in order to maintain a stable baseline activity. During the up-regulation blocks, the fixation cross was white, which instructed the participant to now regulate their brain activity and increase the feedback signal. The background color of the screen was set to gray. Participants were presented feedback about their regulation success via the thermometer display. The thermometer display consisted of a thin horizontal black line that moved up or down depending on the level of the differential feedback signal between the two visual ROIs (Fig. 1). The differential feedback signal was presented throughout the training run (i.e. also during baseline blocks) and was updated every 2 s (i.e. once every TR). It was computed as the difference between the percentages of signal change of the two visual ROIs (Eq. (1)):

$$f = 100 * \frac{\left(ROI_{target}(up) - ROI_{target}(base)\right)}{ROI_{target}(base)} - 100 * \frac{\left(ROI_{opposite}(up) - ROI_{opposite}(base)\right)}{ROI_{opposite}(base)} \quad (1)$$

where f is the current feedback signal, $ROI_{target}(up)$ is the average activity in the first ROI during up-regulation blocks, $ROI_{target}(base)$ is the average activity in the first ROI during baseline-regulation blocks, and $ROI_{contralateral}$ is the same for the second ROI. For some participants, ROI_{target} was the left visual ROI, for others it was the right visual ROI (randomly assigned). We would like to stress that our approach of first calculating signal changes for each ROI separately might be suboptimal in situations where the ROIs are functionally and anatomically very different.

To avoid brisk fluctuations of the thermometer display, we applied temporal filtering by means of a sliding-window average over the previous 3 time points.

To normalize the percentage signal change values to the thermometer scale (which ranged from 25 steps below the fixation point to 25 steps above the fixation point; 5 pixels per step), the differential feedback signal values were scaled according to Eq. (2):

$$t_m = \frac{psc_m - limit_{low}}{limit_{up} - limit_{low}} * (step_{max} - step_{min}) + step_{min} \quad (2)$$

where m is the current time point, t is the temperature reading of the thermometer, psc is the percentage of signal change, $limit_{low}/limit_{up}$ are the mean of the 5 lowest/highest signal change values that have been acquired cumulatively up until the current time point, $step_{max}$ is 25 and $step_{min}$ is −25. The maximum and the minimum level of differential activity were indicated by thin black lines.

After every two neurofeedback training runs, participants performed self-regulation but now in the absence of feedback (transfer run). Transfer runs were identical to the training runs except that the thermometer reading was not visible.

In our subsequent analysis, we distinguished between participants who learned control over the feedback signal (learners) and those who did not learn control (non-learners). To be considered as learners, participants needed to fulfill two criteria: (1) They had to show an improvement of self-regulation over training, i.e. a positive linear regression over the three scanning sessions. (2) They had to show evidence of control over the feedback signal during the last two regulation sessions, i.e., a positive beta value in the GLM computed over the differential feedback signal in these sessions (see Table 1 and section 2.9.2. for further details). Combining these two criteria ensures that we identify as learners those participants who benefit from the neurofeedback training up until a level where they can control the feedback signal.

Behavioral testing: visual detection task

To test for neurofeedback training related effects on visual perception, participants performed two different visual tasks. The first one was a bilateral detection task similar to the one used by Pavlovskaya et al. (2007) to test for visual extinction on simultaneous double-field stimulation. Before running this task for the first time, we determined each participant's contrast detection threshold for a Gabor grating (size = 2°; presentation duration: 120 ms; 1.5 cycles per degree; orientation: 0°; phase = 0.25°; sigma of its Gaussian = 0.65°; trimmed off edges) in the scanner. This individual detection threshold was then used in all subsequent trials of the respective participant. In all cases, Gabor stimuli were presented either at 5° eccentricity to the left of the fixation cross, at 5° eccentricity to the right of the fixation cross, at 5° on both sides, or no stimuli were presented. Thresholds were determined in 40 trials by asking the participant to indicate one of these four possibilities (right, left, both, none) using a keypad, while the

contrast of the Gabor stimuli was adjusted according to the adaptive procedure QUEST (Watson and Pelli, 1983).

After the individual contrast detection threshold was determined, participants performed an additional 60 trials of a Gabor detection task (same parameters as before), but this time the Gabor stimuli were always presented at the participant's individually determined contrast threshold. In 20 of the 60 trials, the Gabor stimuli appeared either on the left, the right, or on both sides of the screen, respectively. The order of trials was randomized. Gabor stimuli were presented at randomly jittered times ranging from 500 ms to 1500 ms from the offset of the previous trial. Auditory cues (duration: 50 ms; frequency: 1000 Hz) were presented simultaneously with the visual stimuli and indicated to the participants that they should respond as accurate and as fast as possible. Except for the individually adjusted contrast of the Gabor stimuli, everything else was identical for all participants. Participants were required to fixate a central fixation cross throughout the run. This behavioral task was performed in the MR scanner.

Behavioral data from the visual detection task were analyzed by calculating a measure for visual extinction, which was defined as the number of stimuli missed on bilateral trials minus unilateral trials, divided by the number of trials per condition. The extinction rate was calculated separately for each visual field. The visual fields contralateral and ipsilateral to the ROI_{target} were labeled target and opposite visual fields, respectively. To assess changes in visual extinction related to neurofeedback training, we performed a repeated-measure analysis of variance (ANOVA) with within-subject factors visual field (target or opposite side), training session (1–3), test run (1–3), and between-subject factor group (learners or non-learners).

Behavioral testing: line bisection task

After the visual detection task, participants performed a computerized version of the perceptual line bisection task (landmark bisection; (Bisiach et al., 1998; Harvey et al., 1995)). Using a keypad, participants were asked to indicate as accurate and as fast as possible whether a marker along a horizontal black line was presented at exactly the center of the line. The line was 20 cm long and the markers were presented either at its center, at 0.2°, at 0.4°, at 0.6°, at 0.8°, or at 1° to the left or to the right from the center. Each of these 11 conditions was presented 5 times in a random order. The line was always presented 500 ms after the previous answer and was displayed for 800 ms. This behavioral task was performed in the MR scanner.

Errors in bisection judgments were calculated for all 11 bisection marker positions, but were predominantly found for the 3 positions around the true midpoint. Our analysis therefore focused on this subset of the data. As for the visual detection task, the visual fields contralateral and ipsilateral to the ROI_{target} were labeled target and opposite visual fields, respectively. To assess changes in line bisection related to neurofeedback training, we performed a repeated-measure ANOVA on the error rates, with factors marker position (deviated to target side, opposite side, or centered), training session (1–3), test run (1–3), and between-subject factor group (learners or non-learners).

Functional MRI analysis

Initial offline preprocessing

Offline data analysis used SPM8 (Wellcome Trust Centre for Neuroimaging, Queen Square, London, UK; http://www.fil.ion.ucl.ac.uk/) and BrainVoyager QX (Brain Innovation). The images were corrected for slice time acquisition differences, realigned to the first scan of each run, normalized to the MNI template, and smoothed with an isotropic Gaussian kernel with 8 mm full-width-at-half-maximum (FWHM).

Offline ROI analysis

The fMRI signal time-courses from the neurofeedback training runs and the transfer runs were extracted from each visual ROI, averaged across voxels, demeaned, and detrended with linear and quadratic terms. Next, we specified GLMs with regressors for the up-regulation and the baseline conditions. The regressors were modeled as boxcar functions convolved with the canonical hemodynamic response function (HRF) in SPM8. The beta values for each regressor were fitted for each run and for each ROI (ROI_{target} and $ROI_{opposite}$), as well as for the differential feedback signal. To assess neurofeedback learning across sessions, we calculated a linear regression of the beta estimates computed for the differential feedback signal over the three scanning sessions. To assess neurofeedback learning within each session, we averaged the beta estimates for all first, all second, all third, and all fourth training runs, and calculated a 2-way repeated-measure ANOVA with factors group (learners and non-learners) and run (1–4). To compare the differential feedback signal between the neurofeedback training and the transfer sessions, we calculated a 3-way repeated measures ANOVA with factors group (learners and non-learners), session (1–3), and feedback type (feedback and transfer run). To assess the contribution of each ROI to variations in the differential feedback signal, we calculated a 3-way repeated measures ANOVA with factors group (learners and non-learners), session (1–3), and ROI (ROI_{target} and $ROI_{opposite}$), as well as a 3-way repeated measures ANOVA with factors feedback type (feedback and transfer run), session (1–3), and ROI (ROI_{target} and $ROI_{opposite}$) independently for the learners and the non-learners.

In addition to the beta estimates, we also investigated the percent signal change time-course during up-regulation blocks. For this, we averaged the percentage of signal change time-courses from the up-regulation blocks separately for the ROI_{target} and the $ROI_{opposite}$, for learners and non-learners, for training and transfer runs, and for each of the three sessions. The time courses were normalized so that the percentage of signal change during baseline activity corresponded to 0%; i.e., the average baseline signal change was subtracted from each time point during the regulation blocks.

Whole-brain analysis

Besides our analyses focusing on the visual ROIs, we also probed for any modulation of activity across the whole brain using a standard block-design analysis in SPM8. In first level analysis, we specified GLMs with regressors for the up-regulation and the baseline conditions, as well as covariates derived from head movement parameters to capture residual motion artifacts. The regressors were modeled as boxcar functions convolved with the canonical hemodynamic response function (HRF) in SPM8. In second level, we calculated fixed-effect group analyses contrasting regulation vs. baseline blocks. This was done separately for the learners and the non-learners, and for the training and transfer runs. Statistical parametric maps were thresholded at $p < 0.01$ corrected for multiple comparisons using FWE. Images of participants whose visual target ROI was located in the left hemisphere were flipped, so that all visual target ROIs were displayed on the right side. Brain regions were labeled using the SPM anatomy toolbox (Eickhoff et al., 2006; Eickhoff et al., 2007; Eickhoff et al., 2005). We also performed random-effects analyses, but these analyses were non-significant apart from changes in the ROI_{target} of the learners that became significant after small volume correction (Worsley et al., 1996). For the small volume corrections, we generated group-average ROI_{target} and $ROI_{opposite}$ by including only those voxels that were part of the individual ROIs in at least half of the learners/non-learners, respectively.

Results

Learning voluntary control of differential visual cortex activity

All participants completed the three neurofeedback training sessions within three weeks. Over the course of this training, eight participants successfully learned to control the differential feedback signal (i.e. increasing the difference in activity between ROI_{target} and $ROI_{opposite}$). These individuals showed a significant increase of the beta estimates

computed for the differential feedback signal across sessions (Fig. 2, learners: solid red line; linear regression: $r^2 = 0.38$, $F(1,10) = 5.68$, $p < 0.05$), and the beta values became significantly positive in the last two training sessions (one sample t-tests; session 1: $t = 0.39$, $df = 7$, $p = 0.72$; session 2: $t = 2.73$, $df = 7$, $p = 0.07$; session 3: $t = 5.52$, $df = 7$, $p = 0.01$). In other words, the size of the interhemispheric difference in activity between ROI_{target} and $ROI_{opposite}$ was systematically larger during feedback periods (relative to baseline) and larger during the last training session (relative to the first).

These voluntary signal changes in visual cortex were not related to cardiorespiratory artifacts or eye movements. Heart rate, respiration, and eye movements showed no difference between baseline and regulation blocks (paired t-tests; heart rate: $t = 0.34$, $df = 7$, $p = 0.74$; respiration: $t = 1.32$, $df = 7$, $p = 0.22$, eye movements x-position: $t = 0.06$, $df = 6$, $p = 0.96$; eye movements y-position: $t = 1.54$, $df = 6$, $p = 0.17$; please note that for technical reasons eye-tracking data from 1 learner was missing).

The learners were also able to exert voluntary control during transfer runs, i.e., in the absence of feedback. This modulation of visual activity during transfer runs also showed a progressive increase across the three training sessions (Fig. 2, learners: dashed red line; linear regression: $r^2 = 0.77$, $F(1,4) = 13.3$, $p = 0.02$).

In contrast, six participants did not learn to control the differential feedback signal (Fig. 2, non-learners: solid blue line; linear regression: $r^2 = -0.27$, $F(1,10) = 3.77$, $p = 0.08$), although they did not differ from the learners with respect to the amount of training (same number of sessions and runs), the size of their visual ROIs (two-samples *t*-test: $t = 0.32$, $df = 12$, $p = 0.75$), or their vividness of visual imagery (two-samples *t*-test: $t = 0.50$, $df = 10$, $p = 0.63$; please note that VVIQ data from 2 learners were not available). Likewise, debriefing after each session indicated that learners and non-learners did not differ in the cognitive strategy used to regulate the neurofeedback signal. As in the learners, the non-learners showed no difference in heart rate, respiration, and eye movements between baseline and regulation blocks (paired t-tests; heart rate: $t = 0.09$, $df = 5$, $p = 0.93$; respiration: $t = 0.28$, $df = 5$, $p = 0.93$, eye movements x-position: $t = 0.84$, $df = 5$, $p = 0.44$; eye movements y-position: $t = 1.10$, $df = 5$, $p = 0.32$). In addition, the non-learners did not achieve control over the feedback signal during transfer runs (Fig. 2, non-learners: dashed blue line; linear regression: $r^2 = 0.40$, $F(1,4) = 2.70$, $p = 0.17$). Noteworthy, the ROI_{target} of the non-learners was predominantly in the left hemisphere (5 out of 6 non-learners), whereas the ROI_{target} of the learners was predominantly in the right hemisphere (6 out of 8 learners) (Fisher's exact test, $p = 0.1$).

Finally, the 3-way repeated-measure ANOVA on beta values with factors group (learners and non-learners), session (1–3), and feedback type (feedback or transfer run) showed a significant interaction between the 3 factors ($F(2,24) = 3.98$, $p = 0.03$). This interaction was produced mainly by a marginally significant difference between feedback and transfer runs in the learner's last session (planned comparisons $F(1,7) = 4.8$, $p = 0.06$). No such difference between the training and the transfer sessions was found for the non-learners (ps > 0.05).

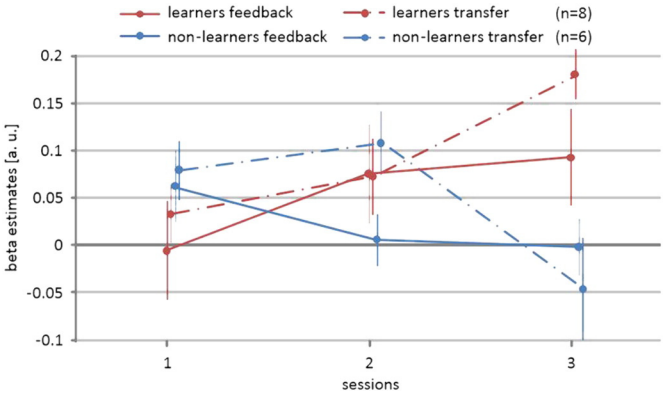

Fig. 2. Neurofeedback learning across sessions. Successful regulation of the differential feedback signal was measured by beta values derived from general linear model statistics, indicating the size of the interhemispheric activity difference during regulation blocks compared to baseline blocks. The eight learners showed an increase in control over the differential feedback signal over the 3 training sessions, both during the feedback runs (solid lines) and during the transfer runs where feedback was not presented (dashed lines). The non-learners did not learn to control the differential feedback signal. Error bars represent one standard error of the mean.

Contributions of ROI_{target} and $ROI_{opposite}$ to controlling the differential feedback signal

To gain further insight into how control over the differential feedback signal was achieved, we investigated the activity in both the ROI_{target} and the $ROI_{opposite}$ separately across the neurofeedback training and transfer sessions. During the neurofeedback training sessions, the learners successfully up-regulated the ROI_{target} in all sessions (Fig. 3A; learners in red, see continuous line). They also co-activated the $ROI_{opposite}$ during the first training session (Fig. 3A, red dotted line), but this co-activation was reduced in subsequent sessions. The ROI_{target} was always more active than the $ROI_{opposite}$, and this difference increased across sessions. In contrast, the non-learners initially activated the $ROI_{opposite}$ more than the ROI_{target} (Fig. 3A, in blue, dotted and continuous lines, respectively), but in subsequent sessions both ROIs showed similar activity levels. Thus, they did not learn to increase the interhemispheric signal difference across sessions. Neither the learners nor the non-learners showed any significant changes in activity for the individual ROIs across the neurofeedback training sessions, suggesting that successful training in the learners did primarily operate on the interhemispheric balance rather than on activity of just one single ROI (linear regression; ROI_{target} learners: $r^2 = 0.42$, $F(1,1) = 0.72$, $p = 0.55$; $ROI_{opposite}$ learners: $r^2 = 0.63$, $F(1,1) = 1.73$, $p = 0.41$; ROI_{target} non-learners: $r^2 = 0.05$, $F(1,1) = 0.05$, $p = 0.86$; $ROI_{opposite}$ non-learners: $r^2 = 0.32$, $F(1,1) = 0.48$, $p = 0.62$). The 3-way repeated measures ANOVA with factors group (learners and non-learners), session (1–3), and ROI (ROI_{target} and $ROI_{opposite}$) did not reveal any significant interaction effects (ps > 0.05).

During the transfer runs (without feedback), the learners achieved a selective up-regulation of their ROI_{target}, whereas activity in their $ROI_{opposite}$ remained at baseline levels (Fig. 3B, learners in red). The ROI_{target} was always more active than the $ROI_{opposite}$, and this difference increased across transfer sessions. Again, the non-learners did not achieve consistent activation of the ROI_{target} which exceeded that of the $ROI_{opposite}$ (Fig. 3B, non-learners in blue). A trend towards significant increases of ROI_{target} activity was seen in the learners, but there were no significant linear changes in individual ROI activity across the transfer sessions (linear regression; ROI_{target} learners: $r^2 = 0.87$, $F(1,1) = 6.69$, $p = 0.24$, $ROI_{opposite}$ learners: $r^2 = 0.72$, $F(1,1) = 2.63$, $p = 0.35$; ROI_{target} non-learners: $r^2 = 0.31$, $F(1,1) = 0.45$, $p = 0.63$; $ROI_{opposite}$ non-learners: $r^2 = 0.40$, $F(1,1) = 0.66$, $p = 0.57$). However, critically, a 3-way repeated-measure ANOVA with factors group and non-learners), session (1–3), and ROI (ROI_{target} and $ROI_{opposite}$) revealed a significant interaction of group × session × ROI ($F(2,14) = 3.41$, $p = 0.01$). This effect was driven by an increasing difference in ROI_{target} activity between session 1 and session 3 for the learners (post hoc planned comparisons; $F(1,12) = 3.54$, $p = 0.08$). No other significant effects were found (ps > 0.5). The 3-way repeated measures ANOVA with factors feedback type (feedback and transfer run), session (1–3), and ROI (ROI_{target} and $ROI_{opposite}$) did not reveal any significant differences between the neurofeedback training and the transfer sessions of the learners and of the non-learners (all ps > 0.05).

In addition to the beta estimates over sessions, we also investigated the percent signal changes in the ROI_{target} and the $ROI_{opposite}$ for the up-regulation blocks relative to the preceding baseline periods. This was

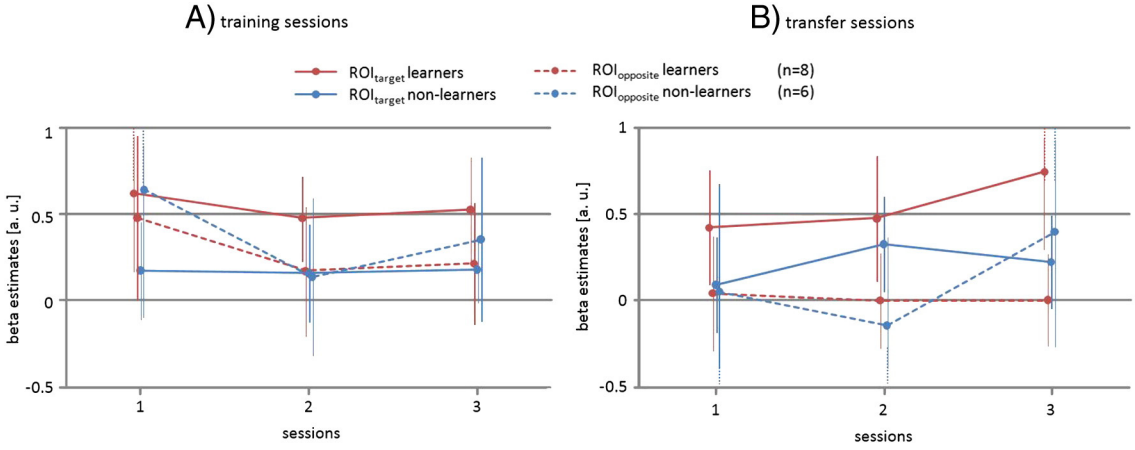

Fig. 3. Contributions of ROI_{target} and $ROI_{opposite}$. Positive beta values for ROI_{target} and negative beta values for $ROI_{opposite}$ indicate that the respective ROIs contributed to successful self-regulation of the differential feedback signal through up-regulation of ROI_{target} and down-regulation of $ROI_{opposite}$, respectively. (A) Across all training sessions (with real-time feedback), the learners achieved a consistent up-regulation of the ROI_{target}. The $ROI_{opposite}$ was co-activated during the first session, but this co-activation was reduced during subsequent sessions. The non-learners activated the $ROI_{opposite}$ more than the ROI_{target} and thus did not learn control over the differential feedback signal. (B) During transfer sessions (without real-time feedback), the learners correctly up-regulated ROI_{target} and showed no changes in the $ROI_{opposite}$. The non-learners did not achieve a consistent activation of the ROI_{target} that exceeded those of the $ROI_{opposite}$. Error bars represent one standard error of the mean.

done separately for the learners and non-learners, for the training and transfer runs, and for the 3 sessions. We found that during training runs, both the learners and the non-learners activated the ROI_{target} and the $ROI_{opposite}$ at the beginning of the regulation blocks (Figs. 4A, B), although in the learners this increase was larger overall. Such activation of the ROI_{target} and the $ROI_{opposite}$ was not maintained throughout the duration of the whole regulation blocks, but after 10–12 s the magnitude of activity in both ROIs returned to near baseline levels and stayed so for the remainder of the regulation blocks. Moreover, over the course of training, activation increased in the ROI_{target} more than in the $ROI_{opposite}$ for the learners, but not for non-learners. The non-learners did not learn to activate the ROI_{target} more than the $ROI_{opposite}$, thus preventing successful regulation of the differential feedback signal.

During transfer runs, the same pattern of results was observed for the learners: initial up-regulation of both ROIs, and return to near baseline activity levels in the second half of the regulation block. The ROI_{target} was consistently more active than the $ROI_{opposite}$, and this activity difference progressively increased across sessions (Fig. 4C). For the non-learners, the initial period of up-regulation was much less pronounced and irregular, and they failed to consistently activate the ROI_{target} more compared to the $ROI_{opposite}$ in the last session (Fig. 4D).

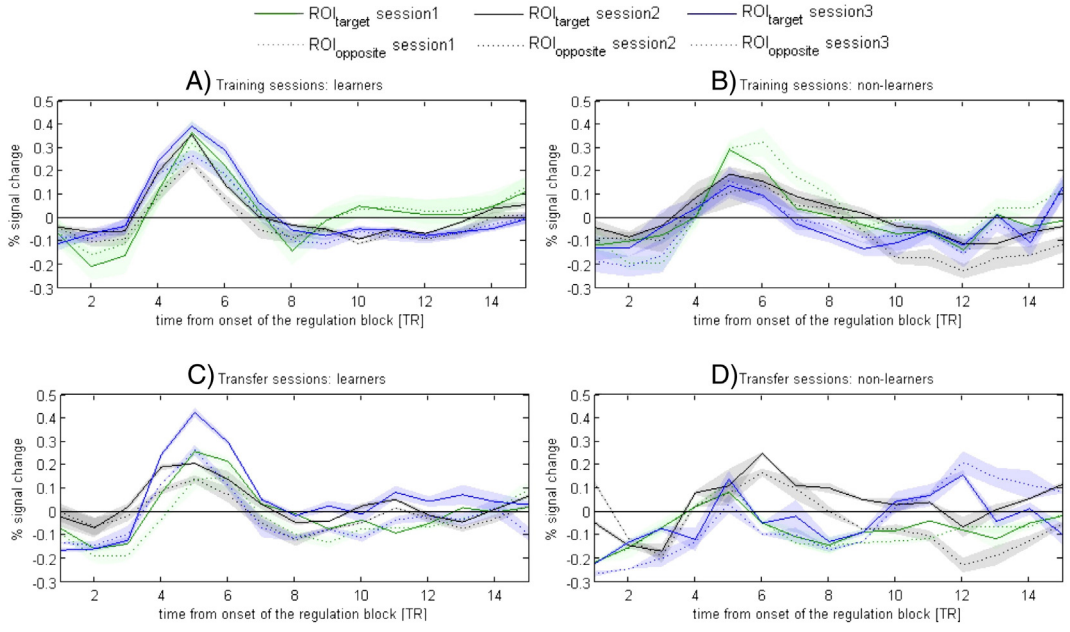

Fig. 4. Time course of percent signal changes in the ROI_{target} and $ROI_{opposite}$ during up-regulation blocks. (A) During neurofeedback runs, the learners activated the ROI_{target} and to a lesser extent co-activated the $ROI_{opposite}$. The difference between the ROI_{target} and the $ROI_{opposite}$ increased across sessions. (B) The non-learners also initially activated the ROI_{target}, but co-activated the $ROI_{opposite}$ to the same level, and thus did not achieve control over the differential feedback signal. (C) During transfer runs, the learners again showed an initial increase in both the ROI_{target} and $ROI_{opposite}$. However the ROI_{target} was more active than the $ROI_{opposite}$ throughout the complete regulation block, and this difference increased across sessions. (D) For the non-learners, up-regulation during transfer runs was much less pronounced, with no consistent difference between ROI_{target} and $ROI_{opposite}$. The time courses were normalized so that the percentage of signal change during baseline activity corresponded to 0%. Shaded areas represent one standard error of the mean.

Whole brain results

Whole-brain group level analyses were performed to determine any concomitant activation in regions outside the trained visual ROIs. Results revealed specific patterns of brain activity for the learners during regulation blocks. In the neurofeedback training runs, learners showed increased activity during regulation in the precentral gyrus ipsilateral to the ROI_{target}, as well as in the contralateral superior frontal gyrus, the superior occipital gyrus bilaterally, plus the intraparietal sulcus and the precuneus bilaterally. In parallel, activity was decreased in the inferior parietal lobe ipsilateral to the ROI_{target} (Fig. 5A, Table 2A). During the transfer runs, the learners showed highly similar increases bilaterally, including in the superior frontal gyrus, the superior occipital gyrus, the superior parietal lobe, the middle temporal gyrus, and in the ipsilateral fusiform gyrus. In parallel, activity was decreased in the contralateral cuneus (Fig. 5B, Table 2B). In addition, we found significant activation in the visual occipital ROI_{target} (random-effects analysis; peak-level $t = 7.21$, $p_{FWE\text{-}corrected} = 0.003$), consistent with successful modulation during neurofeedback.

The non-learners showed only weak effects during the training runs, restricted to increases in the ipsilateral superior frontal gyrus, and decreases in the ipsilateral middle frontal cortex, and the contralateral angular gyrus (Fig. 5C, Table 2C). During the transfer runs, however, they showed more robust and extensive bilateral increases in the superior frontal gyrus, the superior occipital gyrus, the superior parietal lobe, the contralateral orbitofrontal cortex (rectal gyrus), the contralateral inferior frontal gyrus, and the ipsilateral fusiform gyrus. In parallel, activity was also decreased in the contralateral pre-/cuneus, and in the

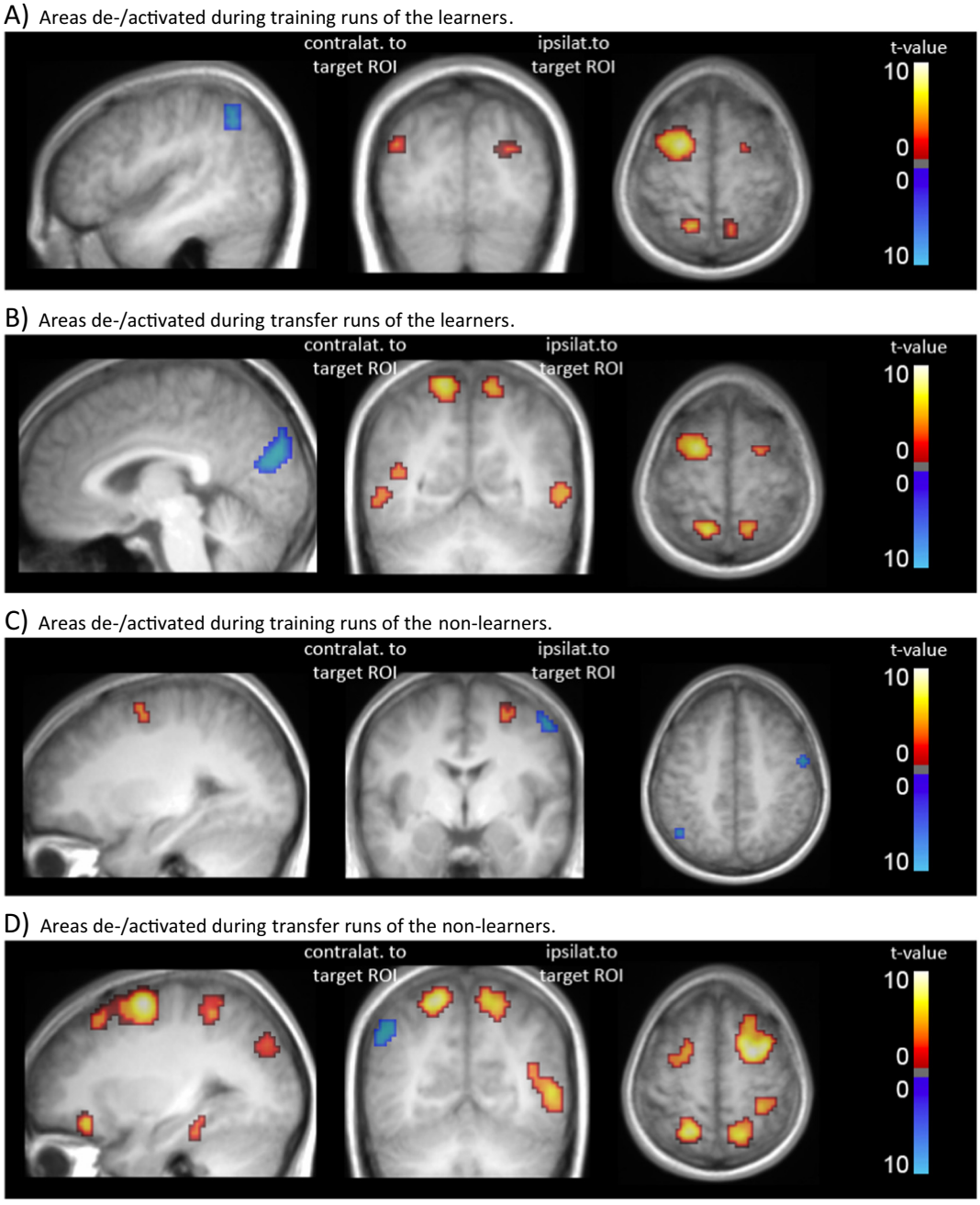

Fig. 5. Whole brain analyses. Shown are brain activation maps during regulation blocks for (A) the training runs in learners, (B) the transfer runs in learners, (C) the training runs in non-learners, and (D) the transfer runs in non-learners. All figures show contrast maps thresholded at $p < 0.05$ (corrected for multiple comparison using FWE) on an MNI template brain. For details of activation peak coordinates, see Table 2.

Table 2
Activation peaks during self-regulation blocks identified by whole-brain analysis.

Anatomical label	t-Value	Cluster size	De-/activation	MNI coordinates x	y	z
A) Areas de-/activated during training runs of the learners.						
Contrala. superior frontal gyrus	9.64	148	+	−21	−4	67
Contrala. superior occipital gyrus	7.26	72	+	−42	−82	25
Ipsilateral superior occipital gyrus	5.85	55	+	24	−94	22
Contrala. precuneus	7.52	44	+	−12	−61	64
Ipsilateral precentral gyrus	6.16	39	+	30	−7	55
Ipsilateral precuneus	5.86	20	+	12	−61	67
Ipsilateral inferior parietal lobe	5.65	37	−	48	−58	52
B) Areas de-/activated during transfer runs of the learners.						
Contrala. superior frontal gyrus	9.09	221	+	−18	−1	70
Contrala. precuneus	8.60	91	+	−12	−61	67
Ipsilateral superior frontal gyrus	6.00	64	+	24	−7	58
Contrala. superior occipital gyrus	7.07	48	+	−39	−79	25
Ipsilateral superior occipital gyrus	5.65	47	+	33	−79	25
Ipsilateral middle temporal gyrus	6.98	42	+	60	−68	6
Ipsilateral superior parietal lobe	6.50	36	+	18	−61	64
Contrala. inferior temporal gyrus	5.60	30	+	−54	−68	0
Contrala. middle temporal gyrus	5.77	22	+	−45	−64	13
Ipsilateral fusiform gyrus	5.37	12	+	33	−38	−21
Contrala. cuneus	6.60	116	−	−9	−94	34
C) Areas de-/activated during training runs of the non-learners.						
Ipsilateral superior frontal gyrus	5.94	23	+	30	−4	58
Ipsilateral middle frontal cortex	6.25	17	−	54	−7	52
Contrala. angular gyrus/IPC	5.33	13	−	−45	−67	43
D) Areas de-/activated during transfer runs of the non-learners.						
Ipsilateral superior frontal gyrus	10.38	1096	+	30	−4	61
Ipsilateral superior occipital gyrus	7.85	379	+	39	−82	28
Ipsilateral superior parietal lobe	7.84	226	+	21	−67	55
Contrala. precentral gyrus	7.40	150	+	−42	2	46
Contrala. superior parietal lobe	9.35	117	+	−18	−64	61
Contrala. rectal gyrus	7.31	78	+	0	47	−17
Contrala. inferior frontal gyrus	6.43	54	+	−39	14	19
Ipsilateral fusiform gyrus	5.29	16	+	33	−38	−18
Contrala. superior occipital gyrus	5.94	11	+	−42	−85	22
Contrala. cuneus	5.63	59	−	0	−79	22
Contrala. angular gyrus/IPC	6.73	45	−	−48	−67	43
Contrala. precuneus	6.38	36	−	−15	−55	34

contralateral angular gyrus (Fig. 5D, Table 2D). No effect was seen in occipital areas.

Behavioral results

Because the interhemispheric visual cortex balance has been linked to attentional and perceptual asymmetries in competitive stimulation conditions, we probed for potential effects of the neurofeedback training on two classic visual-spatial tasks that are typically impaired in neglect patients: bilateral target detection and line bisection (Becker and Karnath, 2007; Bisiach et al., 1998; Deco and Zihl, 2004; Harvey et al., 1995; Pavlovskaya et al., 1997; Pavlovskaya et al., 2007; Posner et al., 1984; Vuilleumier and Rafal, 2000). These two tasks were performed in the scanner at the beginning, in the middle, and at the end of each feedback session (see Fig. 1).

Behavioral data from the visual detection task were analyzed by calculating a measure for visual extinction, which was defined as the number of stimuli missed on bilateral trials minus unilateral trials, divided by the number of trials per condition. As can be expected based on previously reported extinction effects in healthy subjects (Pavlovskaya et al. 2007) and neglect patients (Vuilleumier & Rafal, 2000), the misses tended to be more frequent on bilateral (42%) compared to unilateral (39%) trials (paired *t*-test, $t(13) = 1.58$, $p = 0.07$); however, there was no asymmetry between the two visual hemifields (paired *t*-test, $t(13) = 0.87$, $p = 0.39$). More critically, to determine any modulation of extinction by neurofeedback training, we performed a repeated-measure analysis of variance (ANOVA) with within-subject factors visual field (target or opposite side), training session (1–3), and test run (1–3), and between-subject factor group (learners or non-learners). This test revealed a significant interaction of group × test ($F(2,11) = 4.98$, $p = 0.029$), but no other main effect or interaction (Fig. 6). The interaction was due to decreasing extinction in the target visual hemifield in the third test run in the learners (similarly in each session), whereas extinction tended to increase across successive runs in the non-learners (no interaction with session factor in either group, all $Fs < 1$).

The main effect of factor session ($F(2,11) = 3.32$, $p = 0.072$), and the interaction between session and group ($F(2,11) = 2.99$, $p = 0.091$) were only marginally significant, reflecting an increase of extinction rates across sessions that occurred in the non-learners only. Thus, overall extinction was greater in session 3 than session 1 in the non-learners (mean increase 10.5% vs. mean decrease 0.5% in the learners), but these changes did not reach significance in either group ($p = 0.11$ and $p = 0.88$, respectively). However, neither the reduction of misses within sessions in the learners, nor the increase across sessions in the non-learners, differed between the target and the opposite visual hemifield (no two or three way interaction with side, all $Fs < 2$, all $ps > 0.05$).

For the line bisection task, we computed error rates on trials with markers placed at the true center of the line, as well as those placed to the immediate left and immediate right of the center. Left and right side labels were converted into target and opposite visual fields depending on the side of the trained ROI. Error rates were then submitted to a repeated-measure ANOVA, with factors marker position (deviated to target side, centered, or deviated to opposite side), training session

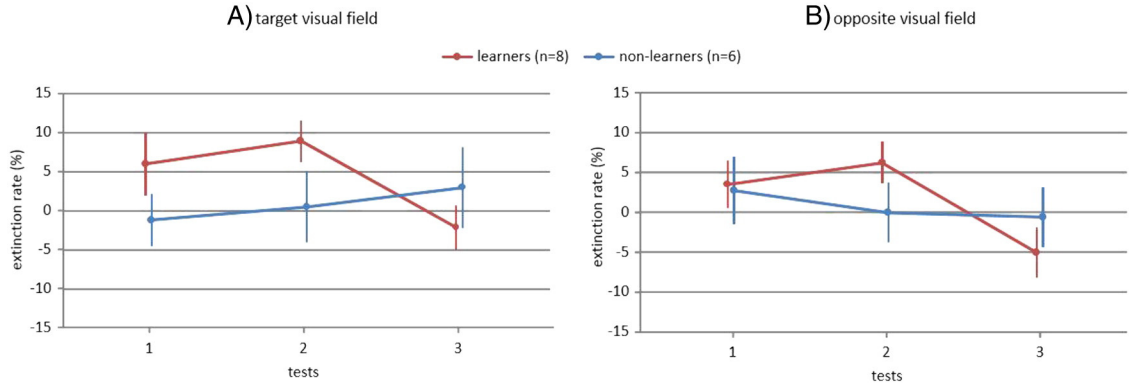

Fig. 6. Extinction rates within sessions. Comparing performance in the visual detection task performed at the beginning, the middle, and the end of each neurofeedback session revealed that the extinction rate of the learners decreased within a session. This improvement was found in the target visual field (A), and in the opposite visual field (B) and was therefore not specific to the side corresponding to the up-regulated occipital ROI (ROI_{target}). No such effects were found for the non-learners. Error bars represent one standard error of the mean.

(1, 2, or 3), test run (1, 2, or 3), and between-subject factor group (learners or non-learners). Results showed a main effect of the marker position ($F(2,11) = 1.54$, $p < 0.0001$), reflecting more frequent errors when judging bisection marks deviated towards the target visual field (79% errors, i.e., most often wrongly perceived as correctly bisected), relative to correct bisection marks at the midpoint (21% errors), or marks deviated towards the opposite visual field (41% errors; see Fig. 7). This pattern of errors was already present in the first test run performed in the first session, prior to neurofeedback training. No other significant main effect or interaction were found.

Discussion

Our study showed that participants were able to use neurofeedback to learn to voluntarily control the interhemispheric balance between their left and right visual cortex activation levels. To accomplish this, participants up-regulated activity in the ROI_{target} more than they down-regulated activity in the $ROI_{opposite}$. Differential control over the left and right visual cortex activity was achieved in the absence of any external visual input overlapping with the ROIs. Furthermore, participants were able to exert voluntary control over the interhemispheric balance even in the absence of neurofeedback, during the transfer runs. Neurofeedback training did not cause lateralized perceptual changes in our detection and line bisection tasks.

Neurofeedback learning

Most existing real-time fMRI neurofeedback studies have trained participants to control activity within one single ROI. This has been accomplished by providing feedback from the ROI alone, or by providing differential feedback between the ROI and a background region (e.g., a large reference slice). Differential feedback has the advantage that global effects such as those related to breathing or movement artifacts are canceled out and thus do not affect the feedback signal. In the present study, we extended the use of differential feedback by using the contralateral homologue of the ROI instead of an unspecific background region, a procedure allowing us to influence the interhemispheric balance of activity between opposite visual cortical areas. So far, only two other studies have used a similar differential feedback approach. In one, a laterality index based on activity in the left and right motor cortex was trained (Chiew et al., 2012); and in another, differential feedback between the parahippocampus and the supplementary motor area was trained (Scharnowski et al., 2004; Weiskopf et al., 2004). A potential disadvantage of using differential feedback is that uncorrelated Gaussian noise of the signals from the two ROIs is additive and may thus reduce the signal-to-noise ratio (SNR). Also, potential signal sensitivity differences, or potential asymmetries in vulnerability to artifacts between the ROIs might negatively affect the differential feedback signal. Despite this potential disadvantage, in our study, 8 out of 14 participants successfully learned to control the interhemispheric

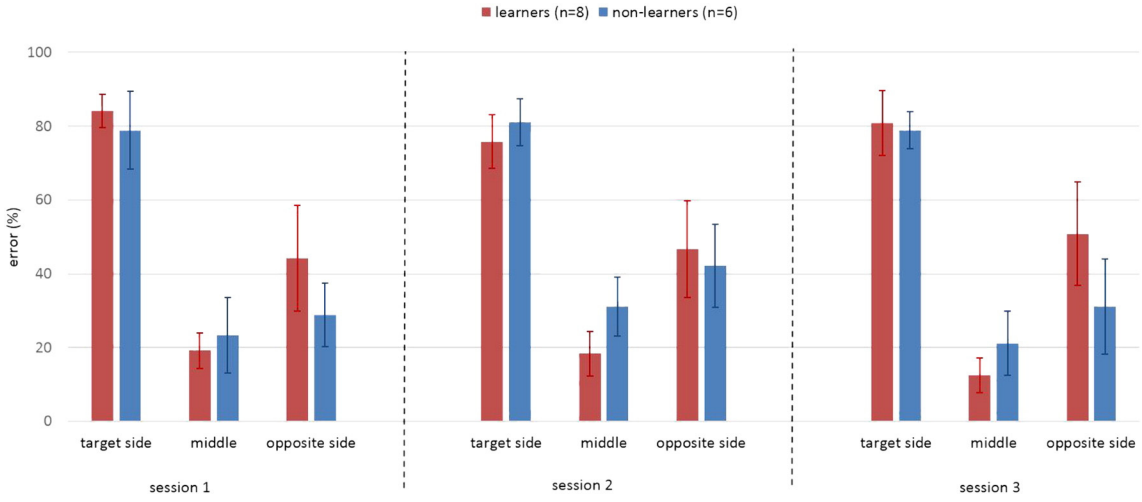

Fig. 7. Line bisection error rate across sessions. Both, the learners and the non-learners made more errors when judging deviations of bisection marks towards the target visual field (corresponding to the up-regulated ROI_{target}). This pattern of errors was already present in the first session, and did not change with neurofeedback training. Error bars represent one standard error of the mean.

balance of activity in their visual cortices (Fig. 2). This success rate is similar to that in a previous neurofeedback study where control over only one single visual ROI was trained (Scharnowski et al., 2012). Likewise, other neurofeedback studies have also reported that subsets of participants failed to learn self-regulation of brain activity (Bray et al., 2007; Chiew et al., 2012; deCharms et al., 2005; Johnson et al., 2012; Yoo et al., 2008). It is still one of the unresolved problems in neurofeedback and in brain–computer-interface (BCI) research, why a non-negligible number of participants (~20%) fail to learn control over the BCI ('BCI-illiteracy'). In the subsequent sections, we will discuss some of the factors that might have contributed to this variability in learning success: (1) potential artifactual self-regulation, (2) cognitive strategies, (3) different contributions of each of the ROIs, (4) experimental design parameters, and (5) concomitant brain activations outside the ROIs.

Excluding effects not related to learned self-regulation

Learning control over the balance between interhemispheric visual cortices cannot be due to visual stimulation related to the visually presented feedback signal: (1) It is unlikely that processing the feedback signal, made of a vertical thermometer, produced any systematic interhemispheric biases, (2) the feedback signal was presented centrally on the screen and did not overlap with the visual field portions activating our occipital ROIs (participants successfully maintained fixation as verified by continuous eye-tracking), and (3) the feedback thermometer was presented during both baseline and up-regulation blocks, and is therefore unlikely to have caused an activity difference between these two conditions.

Cognitive strategies

In order to facilitate neurofeedback learning, we initially suggested the use of mental imagery and of covertly shifting visual-spatial attention to the visual field location overlapping with the ROI_{target} as a possible regulation strategy. According to previous studies, these cognitive strategies should increase activation in the $ROI_{target,}$ thus facilitating control over the feedback signal (Blankenburg et al., 2010; Bressler et al., 2008; Greenberg et al., 2010; Hopfinger et al., 2000; Kastner et al., 1999; Kosslyn et al., 2001; Lauritzen et al., 2009; Li et al., 2008; Ruff et al., 2006; Silver et al., 2005, 2007; Slotnick et al., 2005; Stokes et al., 2009). However, participants were also encouraged to explore any other strategy that they think might be effective. Nevertheless, debriefing after the training sessions confirmed that they predominantly used cognitive strategies related to imagery and attention. They initially attempted to use a variety of strategies such as imagery of positive and negative emotional scenes, passing landscapes as seen from a train, details of colorful objects, or friends and relatives in animated scenes. Over the course of the training, they often converged towards one or two specific strategies that worked best. Covert shifts of attention and imagery of moving stimuli were reported as the most effective regulation strategies.

Contributions of ROI_{target} and $ROI_{opposite}$

Our analysis of patterns of signal change in the visual ROIs indicated that successful control over the differential neurofeedback signal was accomplished by up-regulation of the ROI_{target} (Fig. 3), rather than by down-regulation of the $ROI_{opposite}$. This is consistent with learning that would be expected to arise from the reported cognitive strategies. However, the non-learners used similar cognitive strategies as the learners, demonstrating that the use of these strategies per se does not necessarily lead to successful self-regulation of differential interhemispheric activity. In addition to up-regulation of the ROI_{target}, we had hypothesized that learning to control the differential neurofeedback signal might also partly be accomplished by down-regulating activity in the $ROI_{opposite}$, possibly through implicit learning mechanisms (Chiew et al., 2012; Scharnowski et al., 2004; Shibata et al., 2011; Weiskopf et al., 2004). However, in our study, this was not the case, and activity in the $ROI_{opposite}$ tended to also increase during the regulation blocks (Fig. 3), although to a lesser degree than the ROI_{target}.

Optimization of experimental design

Interestingly, marked increases of BOLD activity in both the ROI_{target} and the $ROI_{opposite}$ were evident only during the first half of the 30s regulation blocks (Fig. 4). Afterwards, activity in the ROIs returned to near baseline levels. It might be that the covert imagery or attentional processes engaged during training produced only weak sustained increases in BOLD signal in the visual ROIs, due to the nature of the task, fatigue, or temporal properties of vascular hemodynamic coupling. Hence, for the present study, regulation blocks of 30s might have been suboptimal given the specific ROIs and the processes underlying control of the feedback signal. Had we used shorter regulation blocks, it is possible that the learners would have shown better control, and more participants might have been able to control the feedback signal. This finding illustrates the need to optimize basic experimental design parameters such as block length, in order to maximize the efficiency of real-time fMRI neurofeedback. Up to now, the basic parameters of training protocols have not been systematically investigated, even though they may well be critical for improving the effectiveness and cost-efficiency of neurofeedback (Sulzer et al., 2013a). It is also worth pointing out that the learning curve did not plateau, which indicates that ceiling performance has not been reached. Hence, additional training sessions would presumably further improve self-regulation competence, and might allow some non-learners to eventually learn control over the differential feedback signal.

Concomitant brain activations

To shed further light on the neural substrates of neurofeedback learning, we applied offline whole-brain analyses aimed at examining brain activations beyond our visual ROIs. Similar to previous neurofeedback studies, we found that self-regulation engaged widespread brain networks (e.g. Chiew et al., 2012; Haller et al., 2013; Rota et al., 2011; Subramanian et al., 2011; Sulzer et al., 2013b; Veit et al., 2012; Zotev et al., 2011). In particular, in the learners, activations concomitant to feedback training arose not only in visual areas, but also in bilateral parietal and frontal areas that are commonly associated with top-down attentional control (Bressler et al., 2008; Greenberg et al., 2010; Hopfinger et al., 2000; Kelley et al., 2008; Lauritzen et al., 2009; Vossel et al., 2012; Yantis et al., 2002) (Figs. 5A,B; Table 2A,B). Such increases might reflect neurofeedback-related attentional and self-reflective introspection processes that contribute to the self-regulation of sensory pathways. Whereas the learners tended to predominantly activate the frontal cortex contralateral to the ROI_{target}, the non-learners showed more bilateral frontal activity (Figs. 5C,D; Table 2C,D). These frontal areas overlap with areas that have been shown to be implicated in top-down control of early visual areas (Moore and Armstrong, 2003; Ruff et al., 2006; Ruff et al., 2009; Schafer and Moore, 2011), suggesting that asymmetric increases in frontal cortex activity may have contributed to more efficient control of the interhemispheric balance between the visual ROIs. Further, in contrast to the learners, the non-learners deactivated the precuneus, a medial parietal region critically involved in visual-spatial imagery and episodic memory retrieval (Hopfinger et al. 2000). On the other hand, activity in superior parietal areas (e.g. posterior intraparietal sulcus) appeared relatively symmetric and identical in learners and non-learners. Taken together, our results suggest top-down influences from regions associated with voluntary control of endogenous attention and imagery, which might be responsible for successful regulation of interhemispheric balance between occipital ROIs.

Self-regulation in the absence of neurofeedback

To test the transfer of learned control over the interhemispheric balance between the left and right visual cortices to situations where neurofeedback is not available, we included transfer runs which were

interspersed with the training runs in our training protocol. Previous real-time fMRI neurofeedback studies either did not include transfer runs, or tested the transfer once the neurofeedback training had been completed (deCharms et al., 2004; deCharms et al., 2005; Hamilton et al., 2011; Lee et al., 2012; Ruiz et al., 2014; Scharnowski et al., 2012; Sitaram et al., 2012). Here we found that participants were able to control the differential visual cortex activity during transfer runs, and that this control increased over sessions (Fig. 2). This is consistent with the results of a few other studies using real-time fMRI, which also reported successful transfer runs (Scharnowski et al., 2012; Sitaram et al., 2012). Several other neurofeedback studies have however failed to show a transfer (Hamilton et al., 2011; Lee et al., 2012; Ruiz et al., 2014; Sulzer et al., 2013b), and none have reported increases in performance during transfer runs across sessions (Sitaram et al., 2012). We therefore speculate that including the multiple transfer runs within the neurofeedback training protocol might be beneficial, a feature especially critical in the context of rehabilitation training.

During transfer runs, the learners showed even better control over the differential feedback signal compared to the neurofeedback training runs (Fig. 2). This may raise the question of whether or not repeated neurofeedback training with real-time fMRI is at all necessary in order to learn to control the interhemispheric balance between the left and right visual cortices. The neurofeedback signal could potentially even interfere with self-regulation because it imposes an additional attention task over and above the self-regulation itself, i.e., evaluating the feedback signal and its modulation by changes in the regulation strategy. Indeed, a recent study reported that for the motor cortex, intermittent feedback was more effective than continuous feedback, which was used in the present study (Johnson et al., 2012). This might be because of increased signal quality due to averaging data over a period of time, and/or because evaluation of the feedback signal no longer interfered with self-regulation. It is likely that such dual task interference is even stronger for visual ROIs when the feedback signal is also presented visually. Nevertheless, despite the potential interference of the continuous visual feedback signal, the majority of our participants (i.e. the learners) successfully learned to use it to improve their self-regulation skills.

When debriefing the participants, they reported the use of the same strategy during training and transfer runs. Accordingly, in the learners, we found quite similar patterns of activity between the training and transfer runs. This indicates that similar regulation processes were likely to underlie both conditions. Indeed, participants reported having explored and evaluated different cognitive strategies during the neurofeedback training runs, and then exerted the strategies that had worked best during the transfer runs. This could explain the improvement across sessions, as well as the improved performance in the transfer compared to the training runs.

Behavioral consequences of neurofeedback training

Given the putative role of the interhemispheric balance between left and right visual cortices in perceptual and attentional asymmetries in healthy controls and brain-damaged patients, we had hypothesized that modulating this balance via neurofeedback might cause changes in visual perception, particularly under conditions with competing stimuli the two visual hemifields. Competitive interactions between visual areas are thought to contribute to attentional deficits observed in hemispatial neglect patients (Corbetta and Shulman, 2011; Driver and Vuilleumier, 2001; Vuilleumier et al., 2008). Moreover, visual deficits associated with neglect have been associated with reduced visual responses in intact right occipital areas (Di Russo et al., 2008; Marzi et al., 2000; Vuilleumier et al. 2001a; Vuilleumier et al. 2008). To test this, we administered a visual detection and a line bisection task after each transfer run.

For the visual detection task, we found that the extinction rate in the learners decreased significantly across successive runs within a neurofeedback training session. Thus, near-threshold visual stimuli presented in both fields simultaneously were more often correctly reported in the third/final test than in the first test run during each training session, but in the learners only. However, at first sight, it seems unlikely that these perceptual effects were related to neurofeedback training because (a) the improvement occurred equally for stimuli in both visual hemifields, without any difference between the side corresponding to the ROI_{target} and the $ROI_{opposite}$, and (b) differential control over the two visual hemispheres in the learners did not increase within sessions ($F(3,36) = 0.18$, $p = 0.91$) in parallel with the perceptual improvement. Furthermore, there was no change in extinction rate across sessions. On the other hand, the fact that such an improvement only occurred in the learners suggests that it may indirectly reflect an ability specific to this group, not shared with the non-learners. One possibility is that the learners might be better able to process visual information in a parallel/independent manner in the two hemispheres, resulting in a progressive decrease of extinction across runs. This might result in reduced competition between the two visual hemifields during bilateral simultaneous stimulation and hence reduced perceptual extinction. However, this speculative interpretation leaves open whether this improvement may result from achieving successful control over the interhemispheric visual cortex balance through neurofeedback, or conversely reflect some individual variability allowing more efficient learning of such interhemispheric control.

For the line bisection task, we found that the learners and the non-learners made more errors when judging deviations of bisection marks towards the target visual field (corresponding to the up-regulated ROI_{target}). However, this effect was clearly not related to neurofeedback training because (a) this pattern of errors was already present in the first session and did not change with neurofeedback training, and (b) the effect was not specific to the learners but was also found in the non-learners.

A possible reason for why we did not find robust behavioral effects related to successful neurofeedback training might have been the limited number of trials for each test (due to time constraints), although previous studies found significant effects of behavioral manipulations using similar numbers of trials (Pavlovskaya et al., 2007; Rueckert et al., 2002). Another reason might have been that participants did not actively self-regulate their visual cortex activity while performing the behavioral task. Most previous fMRI reporting behavioral consequences of neurofeedback training tested for such effects only when active self-regulation was taking place (Bray et al., 2007; Caria et al., 2007; deCharms et al., 2005; Rota et al., 2011; Scharnowski et al., 2012; Shibata et al., 2011; Weiskopf et al., 2003). In the visual system, only Shibata et al. (Shibata et al., 2011) found that neurofeedback training led to enhanced perceptual sensitivity that generalized to situations when participants did not actively self-regulate their visual cortex activity any more (i.e. lasting plastic changes). In contrast, in a previous study where a single visual ROI was trained, we found improved visual sensitivity at the corresponding retinotopic location specifically during visual cortex up-regulation; but these perceptual improvements did not generalize to situations where participants were no longer actively self-regulating (Scharnowski et al., 2012). In the present study, we did not test for behavioral effects during self-regulation because we aimed to identify lasting plastic changes that are independent of active self-regulation, ones which might be more useful for the rehabilitation of neglect patients.

Limitations of the study

The main limitation of this study is the lack of a control group that attempts self-regulation based only on cognitive task instructions but without targeted neurofeedback. Without such a control group, we cannot completely exclude the possibility that mere practice led to the improvement across sessions during training and transfer runs. However, the non-learners also practiced self-regulation for as long as did the learners, but they did not show improvements. Moreover, several

other real-time fMRI neurofeedback studies that included control groups who received either sham feedback or no feedback have firmly established that neurofeedback is necessary for learning to self-regulate brain activity (e.g. for the anterior cingulate cortex (Hamilton et al., 2011), for the inferior frontal gyrus (Rota et al., 2009), and most importantly for the visual cortex (Scharnowski et al., 2012; Shibata et al., 2011)).

Another limitation is the limited amount of training and behavioral testing. Although we trained and tested participants for longer than in most other previous neurofeedback training studies (3 days), the participants were still improving and more participants might have learned control over the feedback signal had we continued to train them.

Conclusions

Learning to control the interhemispheric balance between the left and the right visual cortices is possible using neurofeedback. Such control is also evident during transfer runs, where neurofeedback is not provided. Despite three sessions of training, ceiling performance (i.e. plateauing of the learning curves) has not been reached, which suggests that additional training sessions would further improve self-regulation competence. In this study, neurofeedback training of interhemispheric balance did not cause lateralized perceptual changes that generalize to situations where participants were no longer actively self-regulating visual cortex activity. Visual extinction during bilateral visual stimulation progressively decreased in each session in participants who showed better learning abilities (and not in the non-learners), but equally so for stimuli presented in the target or opposite hemifields, perhaps reflecting greater independence between right and left occipital cortices during bilateral visual processing. However, it is unclear whether such effect may result from or contribute to better learning. Nevertheless, the feasibility of learning control over the interhemispheric balance between homologous brain areas opens new perspectives for potential therapeutic approaches in neuropsychiatric diseases characterized by abnormal asymmetries in hemispheric processing, including but not limited to spatial neglect (Driver and Mattingley, 1998; Driver and Vuilleumier, 2001; Halligan et al., 2003; Husain and Rorden, 2003; Milner and McIntosh, 2005), dyslexia (Bishop, 2013), schizophrenia (Oertel-Knochel et al., 2012), and mood disorders (Herrington et al., 2010; Sackeim et al., 1982).

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