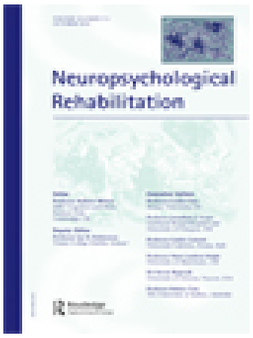

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Using real-time fMRI neurofeedback to restore right occipital cortex activity in patients with left visuo-spatial neglect: proof-of-principle and preliminary results

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ABSTRACT

Hemineglect is common after right parietal stroke, characterised by impaired awareness for stimuli in left visual space, with suppressed neural activity in the right visual cortex due to losses in top-down attention signals. Here we sought to assess whether hemineglect patients are able to up-regulate their right visual cortex activity using auditory real-time functional magnetic resonance imaging (rt-fMRI) neurofeedback. We also examined any effect of this training procedure on neglect severity. Two different neurofeedback methods were used. A first group of six patients was trained to up-regulate their right visual cortex activity and a second group of three patients was trained to control interhemispheric balance between their right and left visual cortices. Over three sessions, we found that the first group successfully learned to control visual cortex activity and showed mild reduction in neglect severity, whereas the second group failed to control the feedback and showed no benefit. Whole brain analysis further indicated that successful up-regulation was associated with a recruitment of bilateral fronto-parietal areas. These findings provide a proof of concept that rt-fMRI neurofeedback may offer a new approach to the rehabilitation of hemineglect symptoms, but further studies are needed to identify effective regulation protocols and determine any reliable impact on clinical symptoms.

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KEYWORDS Spatial neglect; real-time functional magnetic resonance imaging; neurofeedback; self-regulation; visual cortex

Introduction

Hemispatial neglect is among the most common and disabling disorders following focal brain damage, characterised by impaired awareness for the contralesional side of space

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(Driver & Vuilleumier, 2001; Milner and McIntosh, 2005; Vuilleumier and Saj, 2013). This syndrome typically results from lesions in frontal and parietal areas of the right hemisphere (Husain & Kennard, 1997; Mort et al., 2003) or their connections (Bartolomeo, de Schotten, & Doricchi, 2007; Karnath, Rorden, & Ticini, 2009), producing pathological biases in mechanisms of spatial attention controlled by these fronto-parietal networks, while primary sensory (e.g., visual) areas may remain structurally spared (Vuilleumier, 2013). Recent studies using functional brain imaging in patients with stroke and neglect have revealed that losses in awareness may reflect reduced neural responses in intact sensory areas due to a lack of top-down modulation from damaged brain regions and subsequent interhemispheric balance in fronto-parietal attentional networks (Valenza, Seghier, Schwartz, Lazeyras, & Vuilleumier, 2004; Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Vuilleumier et al., 2008).

Here, we investigate the possibility of restoring activity in the right visual cortex of left hemineglect patients by using real-time functional magnetic resonance imaging (rt-fMRI) neurofeedback, thus allowing patients to learn to rebalance top-down attentional modulation in the damaged hemisphere. Neurofeedback is a method where brain activity is recorded, quantified, and then presented back in near real time to the individual by means of some informative signal (e.g., thermometer-like display) representing the ongoing changes in neural activity. Based on this information, the participant can learn to voluntarily control brain activity through appropriate mental strategies. Previous work in healthy volunteers demonstrated the feasibility of self-regulating activation in brain areas involved in visual perception (Robineau et al., 2014; Scharnowski, Hutton, Josephs, Weiskopf, & Rees, 2012), pain (deCharms et al., 2005), motor control (Chiew, LaConte, & Graham, 2012), linguistics (Rota et al., 2009), emotion (Caria et al., 2007), and reward processing (Sulzer et al., 2013). Fewer studies showed successful regulation with clinical improvement in patients with chronic pain (deCharms et al., 2005), tinnitus (Haller, Birbaumer, & Veit, 2010), psychiatric disorders (Linden et al., 2012; Ruiz et al., 2013), and Parkinson's disease (Subramanian et al., 2011); for a review see Ruiz, Buyukturkoglu, Rana, Birbaumer, and Sitaram, 2014. However, except for one study in two hemiparetic patients, who learned to increase ventral premotor cortex activity and improved motor performance (Sitaram et al., 2012), the clinical potential of rt-fMRI neurofeedback in stroke patients has not been explored. Likewise, only rare studies have used electroencephalograph (EEG) neurofeedback for motor training in stroke patients (Young et al., 2014).

Neurofeedback provides an appealing tool to modulate visuo-spatial neglect for two reasons. First, neglect patients exhibit an abnormal functional asymmetry in primary visual cortex (V1) (Vuilleumier et al., 2008) due to impaired top-down attention influences and disrupted interhemispheric balance (Corbetta et al., 2005). Second, recent rt-fMRI studies found that healthy participants can learn to self-regulate V1 activity and exhibit subsequent changes in visual perception (Robineau et al., 2014; Scharnowski et al., 2012; Shibata, Watanabe, Sasaki, & Kawato, 2011). Here we therefore trained patients to increase their right V1 activity during neurofeedback, and tested for any effect on subsequent visual activity without neurofeedback and improvement in neglect tests.

To these aims, we considered that two different neurofeedback methods might be effective: either training patients to up-regulate activity unilaterally within right V1; or training them to control the interhemispheric balance between right and left V1, as previously used for rt-fMRI neurofeedback in healthy volunteers (Robineau et al., 2014).

Because our study was considered as a proof-of-concept to establish the feasibility of rt-fMRI neurofeedback in neglect, we tested a few patients with each of these two methods and then focused on the most effective approach. First, we hypothesised that training neglect patients to recruit early visual areas in their damaged hemisphere, by controlling either the right V1 specifically or the differential activity between the right and left sides, should help reduce functional asymmetries between the two hemispheres. Our main goal was therefore to determine whether patients can learn to up-regulate their visual cortex by using neurofeedback. A subsidiary goal was to test for any impact of neurofeedback on neglect symptoms. We hypothesised that successful increases in right V1 activity might counteract pathological biases in spatial attention and thus reduce neglect severity. However, given the short training procedure and our small patient sample, the current study did not focus on the behavioural correlates of neurofeedback regulation. Finally, a third question was whether the up-regulation of visual areas would recruit the attentional network in intact brain areas not only in the ipsilesional (damaged) but also contralesional (intact) hemisphere, as observed with other neglect rehabilitation methods (such as prism adaptation, see Saj, Cojan, Vocat, Luauté, & Vuilleumier, 2013).

Materials and methods

Participants

Nine patients (three females; six males; mean age: 59 years, range: 46–75) were recruited consecutively among stroke patients in the Neurology Department at the Hopitaux Universitaires de Geneve. We included patients who had a first haemorrhagic or ischaemic right-hemisphere stroke, with a diagnosis of visual spatial neglect (see below), but no visual field loss, and no other major cognitive deficits on clinical neuropsychological examination (Table 1). We excluded patients with bilateral lesions, previous neurological or psychiatric disorders, low visual acuity, and reduced vigilance levels precluding repeated neurofeedback sessions in the MRI scanner. Neglect severity (Table 1) and other neuropsychological deficits were assessed using a standard battery of clinical tests described below (Azouvi et al., 2002). Patients with a clinical score below normative data in at least two out of three tests were classified as having "neglect". Neglect severity was assessed at the time of recruitment in the post-acute phase, as well as before and after the training protocol which took place on average 247 days post-stroke onset (*SD* = 131; range = 68–514). All lesions were confirmed by MRI or CT scan (Figure 1).

Lesion neuroanatomy

For each patient, brain lesions were localised and reconstructed on axial MRI slices using MRIcro (Rorden & Brett, 2000), according to previously described methods (Saj, Verdon, Vocat, & Vuilleumier, 2012; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010). Lesion regions of interest (ROIs) were then overlapped across patients for each neurofeedback subgroup separately (Figure 1).

Experimental design overview

Patients participated in four MRI scanning sessions. In the first session, all participants underwent a functional localiser fMRI scan to delineate the left and the right visual ROIs (Figure 2) and were familiarised with a motor neurofeedback task (see below).

Table 1. Demographic and clinical data of patients.

Subject	Experimental group	Age	Gender	Days since stroke	Aetiology	Visual field lost	Left visual extinction	Bells Cancellation left	Bells Cancellation centre	Bells Cancellation right	Line Bisection (%)	Scene Copy	Representational neglect	Size of the ROI_{target} (voxels)	Size of the ROI_{contra} (voxels)
P1	unilateral	66	F	187	I	No	No	15	5	3	58.23	3	0	8	14
P2	unilateral	48	M	68	H	No	No	13	5	4	74.25	2	1	23	14
P3	unilateral	60	M	335	H	No	No	15	4	9	85.06	3	1	18	23
P4	unilateral	75	M	514	H	No	Yes	15	5	1	81.72	2	0	2	10
P5	unilateral	44	F	235	I	No	No	15	3	2	54.56	1	0	13	9
P6	unilateral	65	M	338	H	No	No	12	1	2	32.45	1	0	9	16
P7	differential	57	M	162	I	No	No	15	5	7	75.12	3	2	14	19
P8	differential	46	F	171	H	No	No	15	4	0	68.84	2	1	25	40
P9	differential	70	M	214	H	No	No	14	2	2	31.82	1	0	31	46

Test results are from the acute phase. ROI size indicates the functionally defined V1 area used for rt-fMRI feedback. Patients underwent either the unilateral feedback (FB_{unilat} group) or the differential feedback (FB_{diff} group) procedure. Days since stroke is the time period between stroke and the first session testing neglect severity prior to the neurofeedback training.

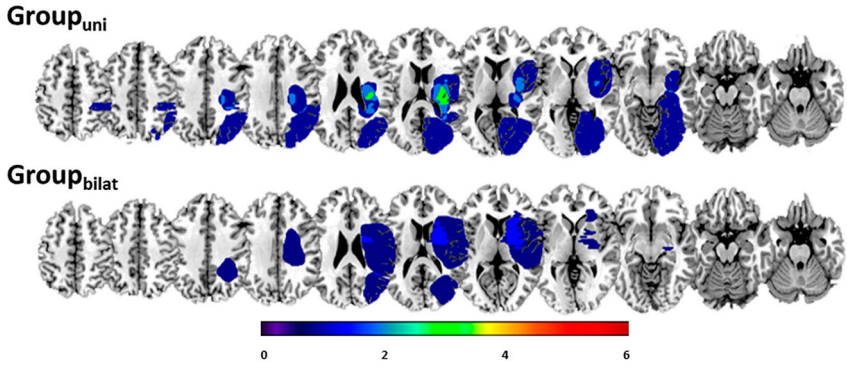

Figure 1. Anatomical reconstruction of brain lesions based on anatomical MRI scans in the two neurofeedback groups, overlaid on axial slices of a normalised brain template. Colours indicate the number of patients with lesions in a given location (from 1 = blue to 6 = red), for each group separately (unilateral: $n = 6$; differential: $n = 3$).

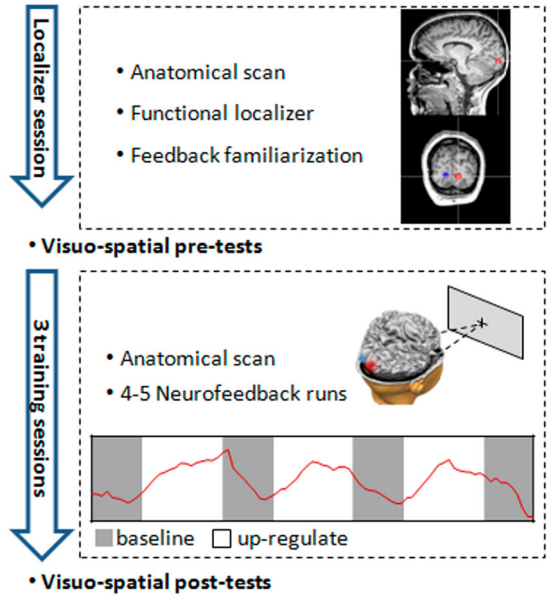

Figure 2. Overview of the experimental procedure. In the first scanning session, a structural scan was acquired, the visual ROIs in the left and right visual cortex were defined with a functional localiser run, and patients were familiarised with the neurofeedback setup by using a short regulation protocol with their motor cortex. The localiser consisted of a unilateral flickering checkerboard wedge (100% contrast, 8 Hz contrast reversal, 30° eccentricity along the horizontal meridian at a 45° angle) presented on a grey background, while the patients focused on a central flashing cross (3 blocks of 30 seconds alternating in the left and in the right visual field, interleaved with baseline blocks). In three other weekly neurofeedback training sessions, participants learned self-regulation of their visual cortex activity. Each training session comprised a short anatomical scan and four to five neurofeedback training runs. A training run was composed of four 20-second baseline blocks (in grey) interleaved with three 30-second regulation blocks (in white). The red curve illustrates visual cortex activity during a neurofeedback run from a representative participant. Standard neglect tests were given after the first (localiser) session and after the last neurofeedback session. In total, each session lasted approximately 60 min.

Baseline neglect severity was assessed during the same session using three paper-and-pencil visuo-spatial tests (see below). Visual attention training itself took place in three additional scanning sessions separated by approximately one week.

Two neurofeedback methods were empirically tested. Patients were randomly assigned to one or the other procedure. A first group of six patients was trained to up-regulate their right visual cortex activity (FB_{unilat} group). A second group of three patients attempted to control the interhemispheric balance between right and left visual cortices (FB_{diff} group); this group was not extended further after it became apparent that regulation was inefficient in these cases (see below). The training procedure and timing was otherwise identical in all respects for both groups (Figure 2).

During training, a measure of the fMRI signal was provided to the patient by intermittent auditory feedback (recorded by a male voice; see details below). Eye movements were continuously monitored in the MR scanner with an infrared eye-tracking system (ASL 450, 60 Hz sampling rate, LRO System), and gaze position (x and y) compared between regulation vs. baseline neurofeedback blocks to ensure that activity changes were not due to eye movements.

Functional localiser runs

To determine visually responsive ROIs in left and right occipital cortex (ROI_{left} and ROI_{right}), for subsequent use as neurofeedback targets, all patients underwent a functional localiser scan, with flickering checkerboard alternately presented in each visual field (Figure 2), as used in a previous study with healthy volunteers (Robineau et al., 2014). To limit eye movements, patients were instructed to count transient colour changes (red) in the central fixation cross (pseudo-random occurrence, approximately once every 25 seconds).

Neurofeedback runs

Three neurofeedback training sessions were distributed over three weeks (one per week). Each training session started with a five minute T1-weighted structural scan of the whole brain. This anatomical image was used for coregistration of the current head position with the T1 image obtained in the initial localiser session using Turbo-BrainVoyager, allowing us to match the position of bilateral visual ROIs across different sessions.

For training proper, patients performed four to five 3-minute neurofeedback runs in each session (Figure 2), depending on their fatigue. Each of these training runs was composed of four 20-second baseline blocks interleaved with three active up-regulation blocks of 30 seconds each. The auditory feedback was a number between 0 and 10, heard through MRI-compatible headphones, with 5 representing the initial baseline activity level (average prior to the regulation block). Regulation blocks were started by a 400 ms high beep (900 Hz), instructing the patients that they should attempt to increase visual cortex activity in order to increase the auditory feedback signal (i.e., numbers > 5) as long as possible. The baseline block started with a 400 ms low beep (300 Hz), indicating to the patients that they had to stop regulation. To obtain stable baseline values, participants were asked to mentally recite the alphabet (from letter A onwards) during the baseline period (until they heard a new high beep). There was no feedback information during baseline periods. Participants had to look at a fixation

cross at the screen centre during the neurofeedback runs (as verified by eye tracking, see above).

Prior to the first visual training sessions, the patients familiarised themselves with the neurofeedback setup using a motor cortex ROI during finger movements (executed and imagined), allowing them to understand the principle and dynamic of the feedback (i.e., approximately 6-second delay given the haemodynamic lag and real-time data analysis time). During subsequent training sessions, patients were encouraged to try different strategies to increase the feedback signal during regulation periods. While they were free to find the most efficient strategy for them, they were told that mental visual imagery and covert attention to their left visual field were often effective. After each run, they were asked to describe their strategies and content of any visual imagery used to manipulate the feedback signal.

Feedback value was computed as the percentage of signal change (psc) of the ROI_{right} compared to the baseline for the FB_{unilat} group, or the difference between the psc of the ROI_{right} minus the ROI_{left} relative to the same difference during baseline for FB_{diff} group (for details of the calculation see Robineau et al., 2014). To maintain smooth feedback values, the signal was averaged over the previous three time points. Then, values were transformed into an auditory numerical scale from 0 (down-regulation) to 10 (great up-regulation) according to Equation (1) below. Five meant no change relative to baseline.

$$\mathrm{num}_t = \frac{\mathrm{psc}_t - \mathrm{limit}_{\mathrm{low}}}{\mathrm{limit}_{\mathrm{up}} - \mathrm{limit}_{\mathrm{low}}} * 10 \quad (1)$$

where t is the current time point, num is the number rounded to nearest integer, psc is the percentage of signal change, $\mathrm{limit}_{\mathrm{low}}$/$\mathrm{limit}_{\mathrm{up}}$ are the mean of the five lowest/highest signal change values that have been acquired cumulatively until the current time point. This calculation allowed us to normalise the feedback value based on the percent of signal change relative to more global fluctuations of MRI blood-oxygen-level dependent values (e.g., spontaneous signal drift over time) and to scale the absolute increase in signal during upregulation ($\mathrm{psc}-\mathrm{limit}_{\mathrm{low}}$) to the range of variations measured during a scanning block ($\mathrm{limit}_{\mathrm{up}}-\mathrm{limit}_{\mathrm{low}}$).

Auditory feedback (400 ms) was presented every 6 seconds (3 TR) to inform participants about brain activity while limiting distraction from the ongoing regulation strategy and visual imagery (Johnson et al., 2012). A standard MRI compatible headphone set and audio system (CONFON HP-SC 01 and CONFON DAP-centre mkII, MR confon GmbH, Germany) was used and controlled by MATLAB (Mathworks Inc., Natick, MA, USA) through the COGENT toolbox (Wellcome Department of Imaging Neuroscience). At the end of each up-regulation block, a 1-second smiley was displayed to motivate patients and inform them about the global success (happy face) or failure (neutral face) of the previous block.

fMRI data acquisition

All experiments were performed on a 3 T MRI scanner (Trio Tim, Siemens Medical Solutions, Erlangen, Germany). Functional images were obtained with a single-shot gradient-echo T2*-weighted echo planar imaging 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 = 2000ms, TE = 30 ms) using a 12-channel phased array coil. The first three

EPI volumes were automatically discarded to avoid T1 saturation effects. At the beginning of each scanning session, a T1-weighted structural image was acquired to optimise co-registration across sessions (3D MPRAGE, 256 × 246 × 192 voxels, voxel size = 0.9 mm isotropic, flip angle $\alpha = 9°$, TR = 1900ms, TI = 900 ms, TE = 2.32 ms).

fMRI data processing

Online neurofeedback was implemented using Turbo-BrainVoyager QX (Brain Innovation, Maastricht) to record brain activity and correct head motion in real time. Offline data analysis used BrainVoyager for ROI definition and SPM8 (Wellcome Trust Centre for Neuroimaging, Queen Square, London) for ROI and whole brain analysis. A standard preprocessing pipeline was employed (see Robineau et al., 2014). Images were corrected for slice time acquisition differences, realigned to the first scan of each run, and smoothed with an isotropic Gaussian kernel with 8 mm full-width-at-half-maximum (FWHM). Functional images were coregistered to the structural image of the patient for ROI analysis and normalised to the Montreal Neurological Institute template for whole brain group analysis.

Offline ROI and feedback analysis

We examined how the feedback signal followed the time-course of regulation blocks as well as concomitant changes in the target ROI activity, using two successive General Linear Models. First, we modelled the time course of the feedback signal by a boxcar over the duration of each regulation block in a run, convolved with the canonical haemodynamic response function (HRF), plus a constant. Based on the analysis of this GLM, we selected for each participant the two training runs in each of the three sessions in which the beta values of the feedback signal were the highest.

A second GLM was then used to model brain activity using BOLD signal in the target ROIs and a similar boxcar function for each regulation period in the six runs, plus a constant for each run. We then extracted beta values for these six runs from the ROI_{right} and ROI_{left}.

Together, these GLMs generated three series (feedback signal, ROI_{right} and ROI_{left}) of six betas for each participant, which were submitted to statistical analyses using general linear mixed models (GLMM) for each group of participants (FB_{unilat} and FB_{diff} groups), with a constant for each session. These analyses were carried out using the lmerTest and GLM2 packages in R software (release 3.1.1).

Whole brain analysis

We performed an additional exploratory whole brain analysis to identify other brain regions modulated during neurofeedback besides the target ROIs. This analysis was conducted on the six best training runs as previously defined. In the first level, for each patient, we specified GLMs with regressors for the up-regulation and baseline conditions, as well as covariates derived from head movement parameters to capture residual motion artifacts. Regulation regressors were modelled as boxcar functions convolved with the canonical HRF in SPM8. Considering the small number of patients, we could not perform a random-effects analysis at the second level. Therefore, we calculated fixed-effect (FFX) group analyses contrasting regulation vs. baseline blocks for each training session, which confine the validity of this exploratory investigation to

the present sample only and cannot be generalised (Friston, Holmes, & Worsley, 1999). Group statistical parametric maps were thresholded at a stringent value of $p < .05$ corrected for multiple comparisons across the whole brain using family-wise error. Brain regions were labelled using the SPM anatomy toolbox (Eickhoff et al., 2005). To assess the overlap of activations in visual cortex at the group level with the individual ROI_{right} and ROI_{left} used for neurofeedback, we computed a ROI conjunction for both sides, including only those voxels that were part of the individual ROIs in at least half of the patient group.

Visual perception assessment: computerised tests

To probe for any short-term effect on visual performance following neurofeedback training, we used two computerised visual tests that were given in the MR scanner: a perceptual line bisection test and a detection task (see details in Robineau et al., 2014). For line bisection (Landmark Test, Bisiach, Ricci, & Modona, 1998), participants used a keypad to indicate whether a marker along a horizontal black line was presented at the exact centre of the line (yes/no). We measured judgement error rates for the midpoint and the two first bisection mark positions on the left and right side around the midpoint, as well as the average response times. For the visual detection task, we calculated the correct detection rate for Gabor patches presented in each visual field (left, right, or both). Visual extinction was quantified separately for each visual field by computing the number of stimuli missed on bilateral trials minus unilateral trials, divided by the number of trials per condition (Pavlovskaya, Soroker, & Bonneh, 2007). Both tests were carried out before neurofeedback and after each training session. No functional BOLD measures were obtained during these tasks since they were too brief to obtain reliable fMRI data.

Visual perception assessment: clinical tests

The severity of unilateral spatial neglect was assessed using a standard paper-and-pencil clinical battery composed of the Bells Cancellation Task (Gauthier, Dehaut, & Joanette, 1989), Scene Copy Task (Ogden, 1985), and Line Bisection Test (Schenkenberg, Bradford, & Ajax, 1980) (see Table 1). These tests were given at the time of recruitment in the post-acute phase, before the first neurofeedback training session (pre-test), and after the last training session (post-test). At recruitment, neglect was considered to be present when the Bells omission score was greater than 20% on the left side, the Bisection line deviation score above 11%, and at least one item missed in the Scene Copy Task (25%). A global neglect severity index was calculated as the average of these three test scores (in percentage).

Behavioural data analysis

We used non-parametric tests in Statistica 12.0 to assess behavioural changes related to neurofeedback training sessions. This analysis was conducted for the two computerised visual tests (landmark line bisection and Gabor detection tasks) and the three clinical tests (Line Bisection, Bells Cancellation, Scene Copy). The Friedman Test was used for within-patient comparisons across the three sessions, while the Wilcoxon signed-ranks test was performed for within-participant comparisons between two sessions.

Results

Neurofeedback control

All patients completed the three neurofeedback training sessions within three weeks. Overall, the patients receiving unilateral feedback (FB_{unilat} group) successfully learned to control the feedback signal during regulation blocks (Figure 3. left). At the group level, beta values representing successful modulation of the feedback were significantly increased for session 2 (0.19) and session 3 (0.16) as compared with session 1 (0.03; GLMM tests: $t = 2.73$, $p = .01$ and $t = 2.25$, $p = .03$, respectively). However, there was no difference between session 2 and session 3 ($p > .05$). Furthermore, the beta values became significantly positive from the last two training sessions (one sample *t*-tests; session 1: $t = 0.84$, $df = 5$, $p = .44$; session 2: $t = 3.19$, $df = 5$, $p = .02$; session 3: $t = 2.21$, $df = 5$, $p = .08$), while they were not different from zero in the first.

Importantly, voluntary control over feedback signal was not related to eye movements, as there was no difference between baseline and regulation blocks (paired *t*-tests, eye mean x-position: $t = 1.88$, $df = 5$, $p = .12$; y-position: $t = 0.71$, $df = 5$, $p = .51$).

Unlike the FB_{unilat} group, patients receiving differential inter-hemispheric feedback (FB_{diff} group) did not learn to control feedback over the successive sessions (Figure 3, right), although they did not differ from FB_{unilat} group with respect to the number of sessions and the cognitive strategy described during debriefing, nor in terms of lesion site and initial neglect severity (see Figure 1 and Table 1). These patients showed significant positive beta values only in the third session (one sample *t*-tests;

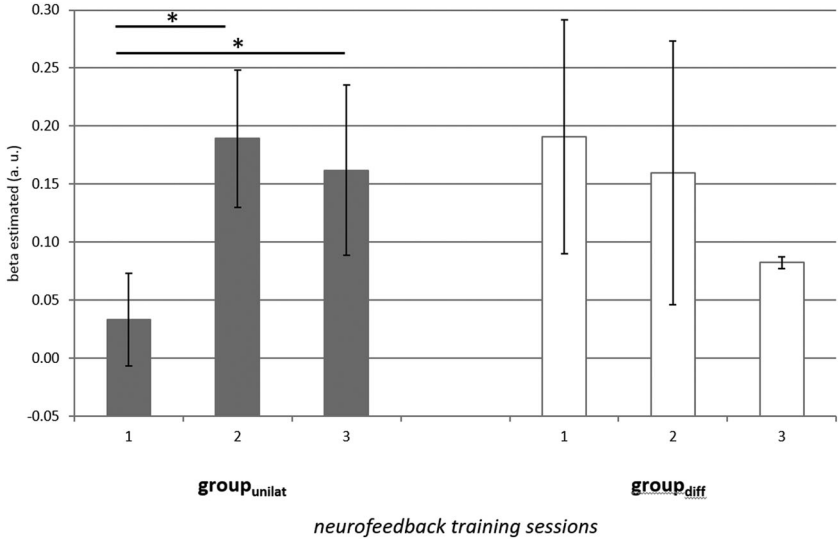

Figure 3. Neurofeedback learning performance. Regulation effects are measured as the beta values from the GLM analysis applied to the feedback signal time course. Higher beta values reflect positive increase of the feedback signal during regulation blocks relative to baseline blocks and therefore successful up-regulation. Patients received either unilateral right feedback (FB_{unilat} group, left grey columns) or differential inter-hemispheric feedback (FB_{diff} group, right white columns). The FB_{unilat} group showed a significant increase of feedback control over sessions. The FB_{diff} group showed no reliable change from session 1 to session 3, with beta values even decreasing over sessions. Vertical lines show the standard error of mean.

session 1: $t = 1.90$, $df = 2$, $p = .20$; session 2: $t = 1.40$, $df = 2$, $p = .30$; session 3: $t = 17.18$, $df = 2$, $p = .003$), but there was no significant difference between sessions (beta values: session 1 = 0.19, session 2 = 0.16, session 3 = 0.08; all $ps > .05$).

Finally, we found no significant correlation even at trend level between regulation effect (difference in mean V1 activity between first and last session) and time since stroke onset (Spearman rho = 0.09, $p = 0.87$ for the FB_{unilat} patients taken alone; Spearman rho = .39, $p = .29$ for entire patient group).

Analysis of visual cortex regions of interest

We then examined neural activity within the target visual ROI in the right hemisphere (ROI_{right}) and the homologue ROI in the left hemisphere (ROI_{left}) for the FB_{unilat} group (Figure 4, A) and the FB_{diff} group (Figure 4, B). For FB_{unilat} patients, we found an overall increase of the ROI_{right} activity over the successive sessions. Average beta values for fMRI signal change in session 1 were significantly lower than in sessions 2 and 3 (respectively, beta = −0.79, 0.17, and 0.92; session 2 > session 1: $t = 1.86$, $p = .07$; session 3 > session 1: $t = 2.51$, $p = .02$). Activity also increased in the ROI_{left} during initial training, although this region was not targeted; but these increases eventually plateaued unlike for the ROI_{right}. Statistical analyses indicated that beta values in ROI_{left} were higher in session 2 (1.55) than session 1 (−0.72, $t = 2.75$, $p = .01$), but there was no difference between the final session 3 (0.24) and session 1 ($t = 1.16$, $p = .26$), or between session 3 and session 2 (all $ps > .05$). In addition, a linear regression analysis performed across all training sessions showed a positive slope for the ROI_{right} but not ROI_{left} (respectively Pearson correlation $r^2 = .96$, $p = .09$, one-tailed; and $r^2 = .18$, n.s.). Figure 5 shows average ROI_{right} beta values over the three sessions for each patient of the FB_{unilat} group.

In contrast, the Linear Mixed Model analyses on the FB_{diff} group data showed no significant difference across sessions, for either the ROI_{right} or the ROI_{left} ($ps > .05$ for all sessions). Moreover, there was no reliable difference between the right and left ROIs for any session ($ps > .05$ for all sessions). In sessions 1 to 3, activity beta values were, respectively, 1.05, −0.03, 0.3 for the ROI_{right}, and −0.1, 0.02 and −1.35 for the ROI_{left}. These

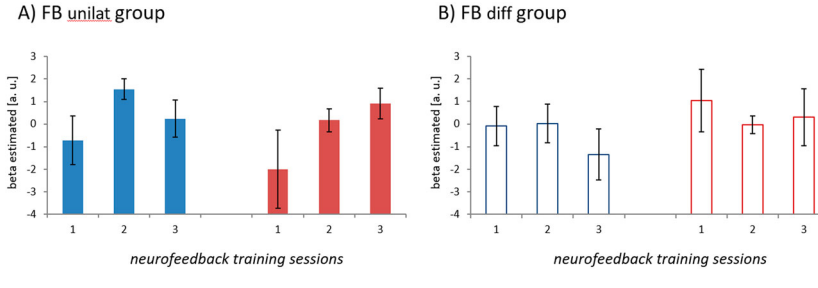

Figure 4. Evolution of neural activity in visual ROI_{right} (in red) and ROI_{left} (in blue) during neurofeedback training sessions. Beta values were obtained from the GLM analysis of BOLD signals measured in the target ROIs in visual cortex across different conditions, as calculated using SPM. Higher beta values indicate successful self-regulation producing increased BOLD signal in the visual cortex during regulation blocks, relative to the baseline blocks. Vertical lines show the standard error of mean. (A) Patients receiving unilateral right feedback (FB_{unilat} group) successfully up-regulated the ROI_{right} in sessions 2 and 3, while activity in the ROI_{left} remained stable between sessions 1 and 3. (B) Patients receiving differential feedback (FB_{diff} group) were not able to control activity in either the ROI_{right} or ROI_{left} through the training sessions.

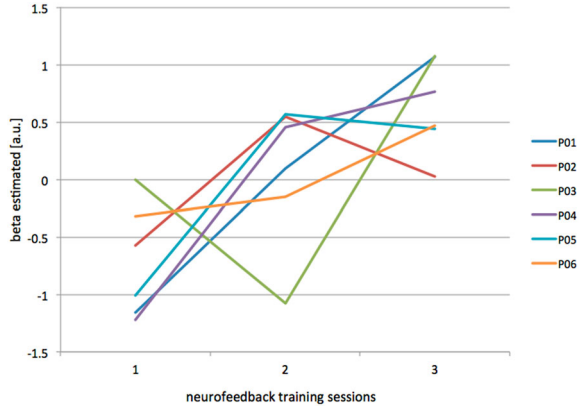

Figure 5. Average beta values from the ROI_{right} over the three neurofeedback training sessions for each patient of the FB_{unilat} group. The plot indicates that all patients were able to increase the right visual cortex activity between the first and the third neurofeedback sessions. To allow comparison between patients, data are mean-centred and normalised to the standard deviation of beta values across all sessions from each individual.

data accord with the feedback signal analysis to indicate that the FB_{diff} group failed to learn how to regulate their visual cortex activity.

Learning success also was evidenced by computing slopes from a linear regression of average beta values of feedback modulation across successive runs in each individual patient. Positive slopes were found in five out of six patients in the FB_{unilat} group. Since the FB_{diff} group did not show any reliable results, all subsequent analyses mainly focused on the FB_{unilat} group data set.

Whole brain results

A whole brain analysis (FFX, FWE corrected) was performed for the FB_{unilat} group in order to determine brain activations outside the visual target ROI during the regulation vs. baseline conditions, reflecting networks engaged by regulation demands and feedback monitoring. This analysis was carried out independently for the three training sessions (Figure 6 and Table 2).

Remarkably, activation maps revealed significant increases in occipital visual cortex (see Figure 6, lower row), with peaks over the calcarine gyrus and middle occipital gyrus, consistent with the required up-regulation. Inspection of these maps suggests that visual activations became more selective and possibly more lateralised to the right hemisphere during sessions 2 and 3. Moreover, small volume corrected (SVC) analyses using the conjunction ROI_{right} in visual cortex (across patients) revealed significant increases for the regulation > baseline contrast in sessions 2 and 3 (respectively peak-level $t = 4.87$, $p_{FWE\text{-}corrected} = .01$; peak-level $t = 4.98$, $p_{FWE\text{-}corrected} < .001$), but not session 1 (no activated voxels), consistent with improved control of visual cortex during neurofeedback in the last two sessions. In contrast, SVC analyses showed no significant activation in the conjunction ROI_{left} for any session. These whole brain data confirm our previous analyses showing selective up-regulation of right occipital cortex across sessions in these patients.

In addition, the up-regulation condition also recruited frontoparietal areas in both hemispheres, overlapping with the attentional network, as predicted (Figure 6 and

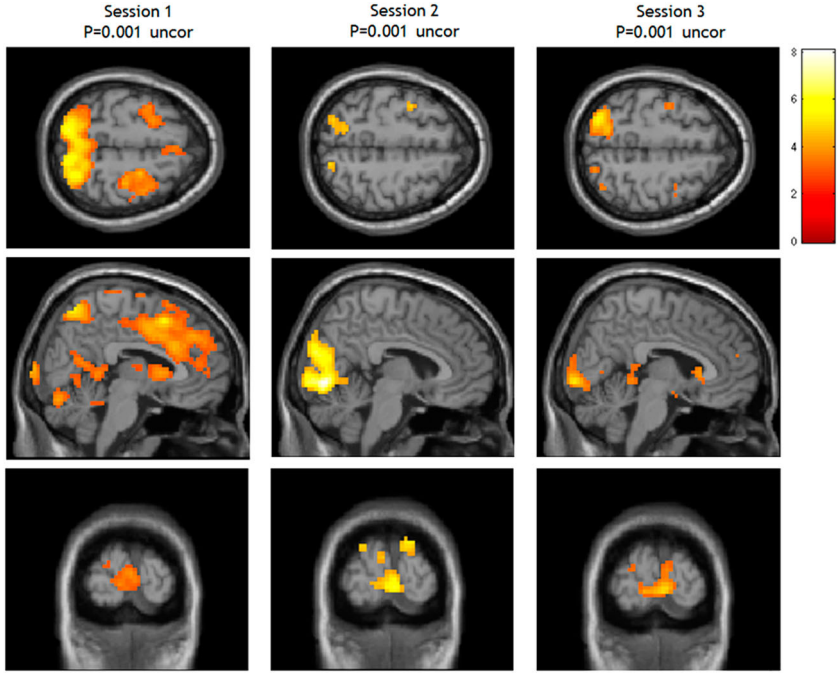

Figure 6. Whole brain analyses. Activation maps are shown for the contrast regulation > baseline blocks for session 1 (left column), session 2 (middle column), and session 3 (right column). Activations are overlaid on a standard MNI template brain. All figures show *t*-test contrasts thresholded at $p = .001$ uncorrected for better illustration of activation patterns. For details of peak coordinates at $p = .05$ FWE corrected, see Table 2.

Table 2. Activation peaks during self-regulation blocks identified by whole brain analysis in the FB_{unilat} group.

Anatomical label	*t*-value	Cluster	MNI coordinates		
			x	y	z
Activated areas during session 1					
Right precentral/mid. frontal gyrus	7.79	3415	42	−1	64
Right superior parietal lobe	7.09		12	−67	64
Left precentral/mid. frontal gyrus	8.05	916	−48	2	46
Left superior frontal gyrus	7.13		−24	−4	46
Left /right SMA	5.95		0	14	49
Right superior frontal gyrus	5.76	52	30	53	28
Right occipital lobe/calcarine	5.67	34	30	−64	7
Left inferior parietal lobe	4.88	11	−51	−49	49
Activated areas during session 2					
Left/right occipital/calcarine/lingual gyrus	6.24	112	3	−79	−5
Right superior occipital lobe/cuneus	5.04	24	3	−82	19
Right superior occipital lobe/cuneus	5.29	15	27	−70	16
Activated areas during session 3					
Left middle occipital gyrus	5.77	24	−27	−88	31
Left inf. frontal/precentral gyrus	5.26	77	−45	2	37
Left superior parietal lobe	5.78	53	−27	−70	55
Left hippocampus	3.33	24	−33	−19	−20
Left/right occipital/calcarine/lingual gyrus	4.98	20	6	−91	−5
Left inf. frontal gyrus/triangularis	5.31	13	−51	41	−2

Note: Results are shown for sessions 1, 2, and 3 independently for the regulation > baseline contrast. SMA, supplementary motor area.

Table 2). Furthermore, from session 1 to session 3, this pattern of activation changed from a bilateral pattern to more asymmetric, left dominant pattern, i.e., mainly contralateral to the lesion. In session 1 (Figure 6, left column), significant activations (FWE corrected) involved widespread regions including the bilateral prefrontal cortex (superior middle frontal gyri, supplementary motor area (SMA), anterior cingulate cortex), the bilateral superior parietal lobe, and the right occipital lobe (calcarine gyrus). In the second session (Figure 6, middle column) significant activations were observed only in the occipital lobe including the calcarine gyrus and the cuneus. Nevertheless, when lowering the threshold ($p = .001$ uncorrected), activation clusters also appeared in the bilateral superior parietal lobes (left > right) and left inferior frontal gyrus (Figure 6). Finally, in session 3 (Figure 6, right), both the frontal and parietal lobes showed significant activations, mainly in the left hemisphere, including the left middle and inferior frontal gyri, and the left superior parietal lobe. Overall, activations appeared less extensive in the final sessions than in the first, possibly reflecting learning and reduced regulation efforts after successful training.

Computerised visual tests

Two visual tasks were given in the scanner (landmark line bisection and visual Gabor detection), before the first training session (pre-test) and then at the end of each neurofeedback session. Because these tests were administered in the subacute/chronic phase (between 2 and 16 months post-stroke, mean = 9.3), when neglect symptoms are generally stable (Kerkhoff & Rossetti, 2006), spontaneous improvement over the three training weeks should be minimal.

For the landmark line test (Figure 7), non-parametric analyses showed that the percentage of bisection judgement errors (averaged for the central midpoint and first two bisection marks around the midpoint) significantly decreased between the pre-training test and session 3, and between session 1 and session 3 (one-tailed Wilcoxon signed-

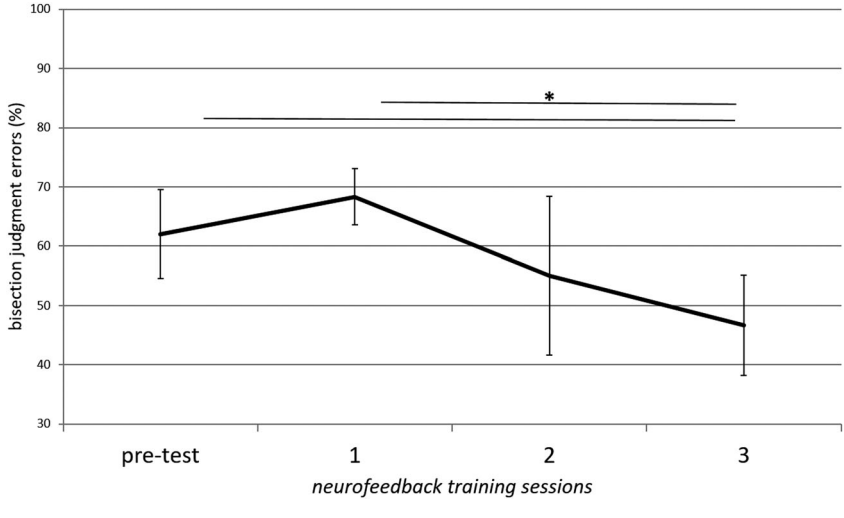

Figure 7. Percentage of deviation errors in the landmark line bisection test for the FB_{unilat} group. Data represent the mean of the two first mark positions toward the left visual field. Vertical lines show standard error of mean.

rank test, respectively, $Z = 1.99$, $p = .05$; $Z = 2.02$, $p = .04$; score for pre-test = 62%, session 1 = 68%, session 2 = 55%, session 3 = 47%). However, pooling all sessions together showed no significant main effect of sessions (Friedman ANOVA, $p > .1$). There were no differences between sessions for the bisection judgement errors for middle point and towards the right side (all $ps > .05$).

In addition, reaction times for bisection judgements showed a trend for speeding over successive sessions (Friedman ANOVA, $\chi^2(3) = 6.76$, $p = 08$), mainly driven by a significant reduction of reaction times between pre-training and session 2 (one-tailed Wilcoxon signed-rank test: $Z = 2.15$, $p = .03$), and marginal reductions between sessions 1 and 2 ($Z = 1.68$, $p = .09$) as well as between sessions 1 and 3 ($Z = 1.81$, $p = .07$). Average reaction times were 2279 ms, 2470 ms, 1680 ms, and 1780 ms from pre-test to session 3, respectively.

For the visual Gabor detection test, no significant change in right or left extinction occurred through the neurofeedback sessions, except for a marginal decrease in left visual extinction during sessions 1 ($Z = 1.82$, $p = .07$) and 2 ($Z = 1.75$, $p = .08$) relative to pre-training. The visual extinction rates were 0.38, 0.18, 0.25, and 0.29 on the left side, and 0.16, 0.16, 0.28, and 0.30 on the right side from the pre-training test to session 3, respectively.

Neuropsychological tests

Clinical neglect tests (Bells Cancellation, Line Bisection, and Scene Copy) were also given in the acute phase, as well as before (pre-test) and after (post-test) the neurofeedback training sessions. A global neglect severity score was calculated by averaging the three neuropsychological tests together.

Overall, there was a significant reduction of global neglect severity across the three timepoints (average error scores: acute phase = 62%, pre-test = 41%, post-test = 18%) in the FB_{unilat} group (Figure 8). This change was confirmed by non-parametric statistical analysis, Friedman ANOVA, $\chi^2(2) = 12$, $N = 6$, $p = .003$, and driven by an improvement

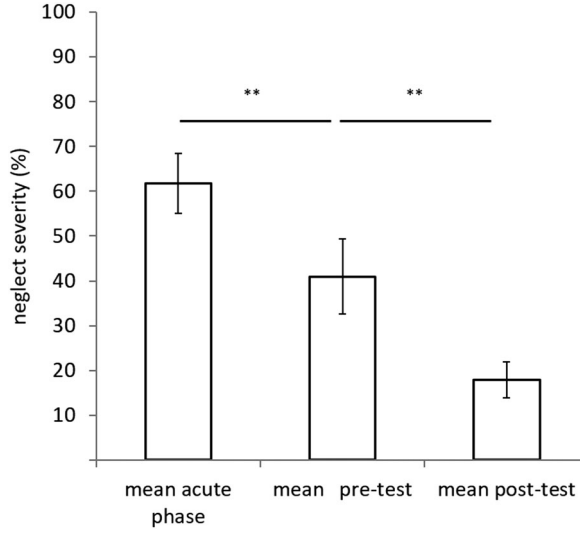

Figure 8. Global neglect severity scores in clinical neuropsychological tasks for each testing phase of the FB_{unilat} group. Error bars represent one standard error of the mean.

not only between the acute phase vs. the pre-test, but also between the pre-test vs. the post-test (Wilcoxon signed-rank test: $Z = 2.20$, $p = .03$ for both). It is important to note that there was an average gap of 9 months between the acute test and the pre-test, but only 3 weeks between the pre- and post-test. Nonetheless, neglect improvement was similar or even larger after the second than the first time interval.

Qualitatively similar results were obtained when considering each neuropsychological test separately. For the Bells Cancellation Test, we observed significant neglect reduction from the acute phase to the pre-training test, but critically also from pre- to post-training (left part: respectively, 94%, 70%, and 36%; Wilcoxon signed-rank test: $ps < .08$; middle part: respectively, 77%, 43%, and 20%; $ps < .1$); and likewise for the Line Bisection Test (respectively, 64%, 38% and 15%; all $ps < .05$). Right omissions in the Bells Cancellation Task showed no significant difference between sessions despite a small numerical improvement (respectively, 23%, 12%, and 7%; all $ps > .05$). Furthermore, the Scene Copy performance improved only between the pre- and post-training (respectively, 50%, 42% and 13%; $p = .04$).

Thus, both computerised visual tasks and clinical neuropsychological tests suggest that some (mild) improvement of left visuo-spatial neglect occurred after the three weeks of neurofeedback training, which appeared to surpass the spontaneous recovery rate expected from evolution over a longer time period since stroke onset (9 months before first training session). However, this improvement is difficult to interpret without a proper control group (e.g., sham neurofeedback). We therefore also tested whether improvement in visual performance was correlated with neurofeedback success across individual patients. Results showed positive correlations between the increased beta values reflecting feedback control and global neglect severity improvement (Pearson $r = .69$), and between increased beta values reflecting activity in the target ROI_{right} and Landmark Bisection score ($r = .37$). However, these positive correlations were only marginally significant for the global neglect score ($p = .06$) and non-significant for the Bisection score ($p = .23$).

For patients in the FB_{diff} group, who showed no successful training and no progressive increase in their visual cortex activity, we found no significant change between the three phases for any of the visual or neuropsychological tests (all $ps > .1$), and no positive correlation slope.

Finally, we obtained systematic verbal reports and drawings from the patients after each training session to document their subjective impression and strategies, but we do not report these data as they are difficult to quantify. Anecdotally, we observed that patients were generally able to recognise which strategy was the most efficient for them to influence the feedback signals and tended to employ variations thereof once they experienced a sense of control over the regulation task. These subjective reports were often corroborated by successful regulation seen during real-time fMRI, but with large variability between sessions and between patients. Interestingly, most of the effective strategies involved lateralised and dynamic mental imagery scenes. For example, among those reported after successful up-regulation, patients reported the following strategies: driving a plane or a car at high speed, imagining loved family members or children on their side, contemplating flowers in their garden, cooking in their kitchen, seeing erotic bodies, playing music in a band, etc. However, even in a given patient, effective strategies could vary from one session to another.

Discussion

Our study shows for the first time the feasibility of modulating visual cortex activity using rt-fMRI neurofeedback in neglect patients. Over successive sessions, the FB_{unilat} group successfully learned to voluntarily up-regulate their right visual cortex, whereas the FB_{diff} group failed to achieve control of interhemispheric feedback. In parallel, visuospatial tests were obtained before and after each neurofeedback training session. Although this was not our main focus, we observed modest but significant changes in visual perception in the FB_{unilat} group, not in the FB_{diff} group. These data thus provide the first proof of principle that rt-fMRI neurofeedback may allow neglect patients to exert top-down modulation on visual cortex activity in the damaged hemisphere, despite pathological attentional biases. It remains to be seen in future studies whether similar or longer training procedures lead to sustained effects in V1 and clinically significant impact on visual performance.

Because our main goal was to demonstrate the feasibility of self-regulation in neglect, we focused on the more effective FB_{unilat} condition without direct comparison between groups. However, given the small sample and exploratory nature of our study, we cannot definitely conclude that a bilateral, differential feedback strategy is ineffective in neglect. Future research should establish whether it is possible to tailor different approaches for different patients or successive training stages.

Successful increase in the target ROI_{right} activity in FB_{unilat} patients was presumably achieved by top-down modulation through internally generated visual representations of the left hemispace. Debriefing after training sessions confirmed that all patients engaged in active mental visual imagery, often involving colourful and dynamic scenes with people and motion, similar to strategies reported by healthy subjects in other visual neurofeedback studies (Robineau et al., 2014; Scharnowski et al., 2012). Since neglect may be associated with deficits in spatial imagery (Bisiach & Luzzatti, 1978), future studies would benefit from including standardised mental imagery tests before neurofeedback training, in order to assess mental representation ability and its link with neurofeedback performance (Bartolomeo, de Schotten, & Chica, 2012; Coslett, 1997; Ortigue et al., 2001). One could argue that because of the absence of a control group (e.g., sham feedback), the increase of ROI_{right} activity in the FB_{unilat} group could be due to the mere practice of mental imagery and not directly related to rt-fMRI feedback. If it were the case, however, the FB_{diff} group would have failed to control the differential feedback but should still have succeeded in increasing visual cortex activity, at least in the ROI_{right}. However, this was not the case and the FB_{diff} group failed to modulate the visual ROIs over the course of training even though they reported similar imagery strategies during debriefing. We can therefore assume that the successful control seen in the FB_{unilat} group is based on the neurofeedback training and cannot simply be attributed to imagery practice.

Moreover, in the absence of a randomised sham feedback control group, we cannot exclude the possibility that our results might at least partly be due to general arousal or motivation-related effects on V1 activity, unrelated to real-time feedback signals. We believe this is unlikely given that patients who trained with differential/feedback signals did not show similar improvements despite the fact that arousal or motivation effects should be similar, but also because modulation of cortical activity was regionally selective (as shown in subsequent whole brain analysis) and progressively improved over sessions when training was successful, which would be unexpected if visual

increase was driven by non-specific arousal only. Nevertheless, future studies with sham feedback will be useful to better disentangle different sources of modulation on V1 activity.

When we explored activation patterns in the entire brain, beyond the target ROIs, we observed that in the first session, when patients were not able to control their visual cortex, these increases were widespread and relatively symmetric. In contrast, in the third session, after successful training, the fronto-parietal activations appeared less extensive and predominated in the left hemisphere. This may seem paradoxical since traditional models of neglect (Corbetta et al., 2005; Kinsbourne, 1970) postulate that neglect is caused by an over-activation of the left parietal lobe, released from inhibition by the damaged right side, while recovery should result from a return to balanced hemispheric activity (e.g., see Corbetta et al., 2005). However, recent fMRI studies in neglect patients reported that improvement in contralesional attention after therapeutic interventions, such as prism adaptation, may actually correlate with improved activation in bilateral, not just right, attentional networks (Thimm, Fink, & Sturm, 2008; Saj et al., 2013). Our neurofeedback results accord with the latter perspective, by suggesting that successful enhancement of right visual activity in the FB_{unilat} group may be achieved by training the preserved left attentional dorsal pathways to modulate the right visual areas, and thus compensate for the damaged right attentional pathways normally responsible for the left side of the visual space.

Our study is also among the first, to our knowledge, to employ auditory feedback during rt-fMRI (see Ramot, Grossman, Friedman, & Malach, 2016, for recent use in healthy volunteers). Most previous studies involving visual regulation used visual feedback (Bray, Shimojo, & O'Doherty, 2007; Robineau et al., 2014; Scharnowski et al., 2012; Shibata et al., 2011). However, to avoid interference with visual imagery strategies, we presented our neglect patients with intermittent auditory cues while they could focus on visuo-spatial imagery in their mental left hemifield. Subsequent debriefing did not reveal any disturbance by this protocol. Using an alternative sensory modality for providing feedback has the advantage of leaving the visual modality free from other unwanted modulations.

The neuropsychological correlates of visual up-regulation were not the main focus of the current study (but see Robineau et al., 2014; Scharnowski et al., 2012). However, our behavioural measures converged with fMRI results, indicating that the FB_{unilat} patients also showed a modest but significant reduction of global neglect severity across time. Neglect was tested on standard tests during the acute phase, as well as before and after the neurofeedback training sessions. The average interval between the acute phase and the pre-test was nine months, whereas the interval between pre-test and post-test was only three weeks. Despite this difference, neglect was globally reduced by approximately 20% from pre- to post-training, which was equal to or even slightly larger than spontaneous recovery during the nine-month interval prior to neurofeedback. These data are corroborated by concomitant improvement in the computerised tests (Landmark Bisection and Gabor detection) given after each session, and by the lack of improvement in the FB_{diff} patients, who failed to control their visual cortex. Although these data are encouraging and provide a first proof of principle, they clearly need to be replicated and extended in a larger cohort. Future investigation of clinical applications should also assess any potential transfer of visual training effects on V1 to daily living activities. It is noteworthy that several studies reported transfer effects from fMRI neurofeedback to subsequent changes in task performance outside the scanner, including

classic work on pain (deCharms et al., 2005) but also more recent work on visual perception (Scharnowski et al., 2012) and emotion perception (Koush et al., 2015; Ruiz et al., 2013).

In summary, our exploratory study reveals that auditory rt-fMRI neurofeedback training may be a promising tool for augmenting rehabilitation therapies in hemispatial neglect, which still remain limited to date. We show for the first time that patients can successfully learn to control their right visual cortex activity. Preliminary results suggest that these visual increases were associated with mildly improved visuo-spatial performance in the contralesional hemifield. However, these findings will need to be confirmed with larger groups and optimised neurofeedback design. While the current study provides novel evidence for the feasibility of self-regulation of visual cortex activity in neglect patients, it has several limitations. First, our small sample size did not allow for systematic comparisons between different strategies. Second, we did not include a sham control group or a more complex cross-over design in this initial study since this might have introduced other unwanted changes or potentially harmful learning effects. Random feedback might not only be frustrating and distressful in patients, with a negative motivational impact on other concurrent therapeutic interventions, but could potentially reinforce counterproductive learning effects that are detrimental to recovery. Third, the small group and short training duration limited our capacity to reliably measure clinical benefits in neglect symptoms.

Given the difficulties of rt-fMRI for stroke patients, from both the technical and clinical points of view, it seems unlikely that such a neurofeedback procedure will become routine in neglect patients. Nevertheless, beyond a proof of principle, this approach may help guide rehabilitation of spatial neglect by defining appropriate training strategies that produce the most effective increases in visual areas and can eventually be transferred outside the scanner. In addition, new paradigms may be developed to test whether feedback based on additional brain regions would be relevant to reduce visuo-spatial neglect, including, for instance, feedback signals based on functional connectivity measures between parietal and visual cortices, rather than a single ROI (see Koush et al., 2013), or using pattern recognition methods to optimise feedback information (see Sato et al., 2013). More generally, we hope our study will help promote novel and promising rehabilitation approaches for stroke patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

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