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Structural and functional connectivity changes in response to short-term neurofeedback training with motor imagery

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ABSTRACT

Recent findings have been challenging current understanding of how fast the human brain change its structural and functional connections in response to training. One powerful way to deepen the inner workings of human brain plasticity is using neurofeedback (NFB) by fMRI, a technique that allows self-induced brain plasticity by means of modulating brain activity in real time. In the present randomized, double-blind and sham-controlled study, we use NFB to train healthy individuals to reinforce brain patterns related to motor execution while performing a motor imagery task, with no overt movement. After 1 h of NFB training, participants displayed increased fractional anisotropy (FA) in the sensorimotor segment of corpus callosum and increased functional connectivity of the sensorimotor resting state network. Increased functional connectivity was also observed in the default mode network. These results were not observed in the control group, which was trained with sham feedback. To our knowledge, this is the first demonstration of white matter FA changes following a very short training schedule (<1 h). Our results suggest that NFB by fMRI can be an interesting tool to explore dynamic aspects of brain plasticity and open new venues for investigating brain plasticity in healthy individuals and in neurological conditions.

1. Introduction

Neural plasticity is critical for brain function and has been extensively explored over the past years using non-invasive imaging, challenging our understanding of the brain's capacity to adapt in response to internal and external stimuli. Using magnetic resonance imaging (MRI) techniques, studies have shown a wide range of brain changes, from subtle gray matter changes after motor learning (Draganski et al., 2004) to formation of aberrant white matter (WM) bundles (Tovar-Moll et al., 2014). At the same time, recent methodological advances in both MRI acquisition sequences and processing power have significantly narrowed the time window of detectable plasticity in the human brain, from weeks to days, hours and even minutes (Draganski et al., 2004; Driemeyer et al., 2008; Maguire et al., 2000; Marins et al., 2015; Sagi et al., 2012; Taubert et al., 2010). Technical and conceptual advances have also paved the way for the development of neurofeedback (NFB), a technique in which brain signal is delivered in real time to a participant, who acquires control over it.

In the functional Magnetic Resonance Imaging (fMRI) domain, NFB can be useful to explore the anatomo-physiological properties of brain plasticity and how this phenomenon translates into behavior. In fact, NFB has successfully been used to induce brain modulation in both healthy volunteers and clinical populations. Previous studies have shown that, with appropriate training, participants can learn to self-regulate circumscribed brain areas (Marins et al., 2015; Ruiz et al., 2013), balance of activity between hemispheres (Chiew et al., 2012; Neyedli et al., 2016) and change functional connectivity among brain regions (Koush et al., 2017, 2013). The accompanied brain changes are seen as fast as 20 min of NFB training as an increased brain activity in trained areas (Marins et al., 2015). Also, the effects of NFB on brain function is shown to last days and even weeks after training (Auer et al., 2015; Yoo et al., 2008) and can lead to behavioral gains (deCharms et al., 2005; Koizumi et al., 2016). Despite this mounting evidence, the impact of short-term NFB on brain structure remains to be shown.

Intriguingly, the effects of NFB training in the brain and behavior are often heterogeneous at both group- and subject-level (Auer et al., 2015; Chiew et al., 2012; Emmert et al., 2016; Sitaram et al., 2017), which may mitigate its benefits and limit its potential application in clinical settings

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as an alternative therapeutic tool. In addition, randomized, double-blind and placebo-controlled studies are scarce and the investigation of the effects of NFB training on brain function, structure and behavior might be hampered by confounding factors such as expectation/frustration, training repetition and biased analysis (Lotte et al., 2017; Thibault et al., 2018).

In the present randomized, double-blind and sham-controlled study, we targeted sensorimotor brain network to explore the impact of short-term NFB by fMRI training on functional and structural connectivity, and behavior in healthy individuals. Less than one hour of NFB training based on motor imagery (MI) led to a strengthening of both functional and structural sensorimotor network connectivity, whereas improvement of motor performance was similar between groups. Thus, the present study broadens our current understanding of NFB-induced brain plasticity and provides the first evidence of WM changes in response to a short training schedule, with potential implications for future clinical applications.

2. Methods

2.1. Participants

Based on sample size calculation for near-optimal statistical power (obtained from a non-published pilot study of our group), forty healthy individuals gave their written informed consent to participate in the present study. Image artifacts due to excessive head movement and to field inhomogeneity led to exclusion of 4 individuals. A total of thirty-six participants were pseudo-randomized to form the NFB (n = 19, 7 males, mean age: 27.7, standard deviation (SD): 4.04) and CTL group (n = 17, 7 males, mean age: 27, SD: 5.76). All participants were right-handed according to the Edinburgh handedness inventory (Oldfield, 1971), had no history of psychiatric or neurologic disease, and were not taking brain active medication. The group randomization was performed via scripting and a file containing the list of participants (anonymized from 1 to 40) in each group was fed to the NFB software. When the experimenter inserted the participant code at the beginning of the NFB training, the software started the procedure according to the predefined, randomized group assignment. The study was approved by the D'Or Institute Ethics and Scientific Committee and conducted in accordance with the ethical standards compliant with the Declaration of Helsinki.

2.2. Experimental design

The study design is represented in Fig. 1 and consisted of the following stages: (i) behavioral and motor performance assessment of each participant immediately before and after image acquisition; (ii) imaging data acquisition when fMRI NFB (or sham) training and additional structural and functional images were acquired.

2.2.1. Behavioral and motor assessments

Before the imaging acquisition, participants sat comfortably in front of a computer screen in a silent room and were briefed about the whole experiment. Kinesthetic and Visual Imagery Questionnaire (KVIQ-10; Malouin et al., 2007) was used to assess their ability to perform MI tasks. Motor performance was assessed as the mean number of correct sequences of a predefined finger tapping task performed with the right hand (4-2-3-1-3-4-2, in which 4 is the little finger, 2 is the middle one, 3 is the ring and 1 is the index). This predefined finger tapping task was used during the whole experiment, either imagined or executed depending on the instruction. Their performance was recorded using a keyboard by pressing the space bar immediately before and after the completion of three sequences. After the brain imaging, participants returned to the room and underwent the very same procedure in order to assess the possible effects of the real or sham NFB intervention on motor performance.

2.2.2. Brain imaging

This stage started with acquisition of resting state fMRI, diffusion-weighted (DW) imaging and kinesthetic MI (named here as 'baseline') of the predefined finger tapping task with their right hand, followed by the NFB (or sham) training: participants were asked to perform an overt motor execution (ME) task of the predefined finger tapping task using their right hand. This task was performed to train the two-class support vector machine (SVM) algorithm to discriminate between ME and rest based on the distributed voxel patterns. Brain areas involved in motor learning (Hardwick et al., 2013) were used as feature selection to restrict SVM classification.

In the three subsequent runs (RUN1, RUN2 and RUN3), participants performed MI of the predefined motor task while watching a dynamic bar graph that varied according to the accuracy in which the SVM algorithm detected ME brain pattern (instead of rest brain pattern). Participants were encouraged to adopt mental strategies to increase the level of the

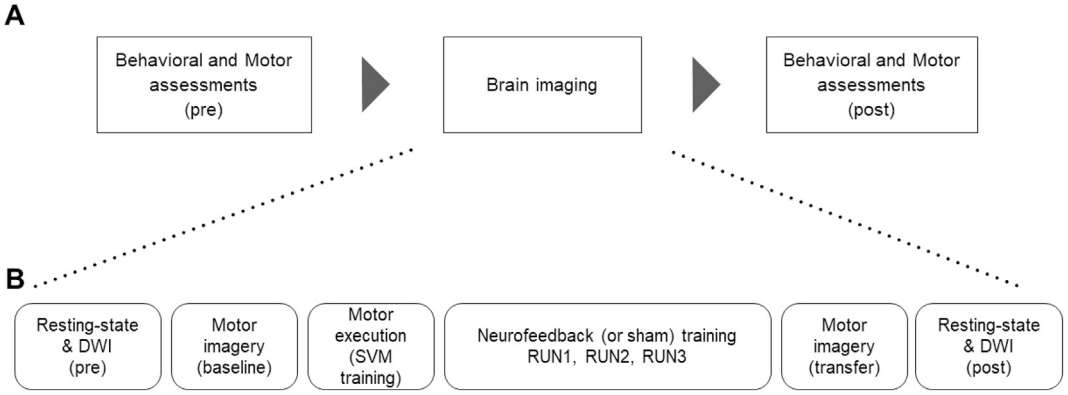

Fig. 1. Experimental design. (A) Participants were submitted to behavioral and motor assessments immediately before and after brain imaging acquisition. (B) Brain imaging consisted of resting state and diffusion-weighted imaging (DWI) followed by a motor imagery task-based without presentation of feedback. Then, motor execution task-based acquisition was performed. The neurofeedback (or sham) training comprised three runs (RUN1, RUN2, RUN3), which were identical: participants performed a motor imagery of the predefined finger tapping sequence task-based while watching a thermometer-like graphic bar which represented the similarity, in real-time, of brain patterns associated with ongoing motor imagery with those patterns associated with motor execution obtained previously. After the neurofeedback (or sham) training, an additional functional run was obtained, which consisted of motor imagery without feedback to evaluate transfer effects, followed by a resting state and a DWI acquisition. Total scan time was approximately 1 h.

graphs, which meant they were reproducing ME brain pattern during a MI task, with no overt movement. Using a random labeled classification model, we observed that the accuracies obtained in our sample were above chance-level (paired *t*-test, $p < 0.001$; mean accuracy obtained: 60.9%, standard deviation: 23.4%; mean random accuracy: 50.6%, standard deviation: 11%). Sham stimuli delivered to the CTL group were based on real NFB presentation of a random participant from the NFB group. All the task-based fMRI procedures consisted of a block design of 'GO' (MI or ME, 20 s long) and 'STOP' (relax, 20 s long), repeated eight times.

After RUN3, we repeated the acquisition of resting state, DW images and MI (without NFB, here referred as the 'transfer' run) in order to investigate the effects of NFB training on brain structure and function.

During the fMRI sequences, right-hand movement was visually inspected and monitored with an acceleration sensor (Brain Products 3D Acceleration Sensor MR; sensitivity: 420 mV/g; Supply voltage: ±5 V DC), which was attached to the distal phalanx of the right middle finger. Root mean square (RMS) values of the x,y,z-acceleration values were calculated for each condition (MI and rest) in each run and used to determine the ratio between 'GO' vs. 'STOP' blocks, which were also compared between NFB and CTL participants.

After each MI task (baseline, RUN1, RUN2, RUN3 and transfer) we obtained self-evaluation of arousal using the Stanford Sleepiness Scale (SSS; Hoddes et al., 1973; 7 point scale; anchor points 1 = feeling active, vital, alert or wide awake, 7 = having dream-like thoughts) and MI vividness using the kinesthetic subscale of the KVIQ-10 (5-point scale, in which anchor points: 5 = as intense as execution, 1 = no sensation). These behavioral measures were collected to ensure that both groups would have similar levels of arousal and vividness of MI, and to allow valid group comparisons.

3. MRI data acquisition

Imaging was acquired with a 3T Achieva scanner (Philips Medical Systems, the Netherlands) using an eight-channel SENSE head coil. DW (2.5mm3 isotropic, no gap, TR/TE (ms) = 5582/65, FOV = 240 × 240, matrix = 96 × 95) with diffusion sensitization gradients applied in 64 noncollinear directions, with a β factor of 1000 s/mm2. Functional images were obtained with a single-shot T2*-weighted echoplanar imaging (EPI) sequence (TR = 2000 ms, TE = 22 ms, matrix 80 × 80, FOV 240 mm × 240 mm × 120 mm, flip angle = 90°, voxel size 3 mm isotropic, no gap, 40 slices) 200 (task-based, either ME or MI) or 240 (resting state) volumes long. Before each functional imaging, five dummy volumes were collected for T1 equilibration purposes. Reference anatomical images were acquired using a T1-weighted three-dimensional magnetization-prepared, rapidly acquired gradient echo (MP-RAGE) sequence (TR/TE = 7.2/3.4 s, matrix/FOV 240/240 mm, flip angle = 8°, 1 mm isotropic voxel size, 170 sagittal slices). Head motion was restricted with foam padding and straps over the forehead and under the chin. The total MRI acquisition lasted about 60 min.

4. Data analysis

Before imaging processing all data were visually inspected for artifacts.

4.1. Resting state

Images were analyzed with Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC, Beckmann et al., 2005), which included motion correction, brain extraction, spatial smoothing using a Gaussian kernel of full-width at half-maximum (FWHM) of 6 mm and high-pass temporal filtering equivalent to 150 s. FMRI volumes were registered to the individual's structural scan using boundary-based registration and then to standard space using non-linear registration. We used multi-session temporal concatenation to create a single 4D dataset containing images (pre and post neurofeedback or sham training) of all participants. Independent component analysis (ICA) was used to find the resting state networks of all participants as a single group. As previously described (Sampaio-Baptista et al., 2015), we conducted a dual-regression approach (Zuo et al., 2010) using FSL to measure the functional connectivity strength of networks of interest. Based on its temporal and spatial aspects, this procedure allowed us to identify specific resting state networks in each participant. Next, the group mean ICA spatial map corresponding to the sensorimotor network (SMN) and default mode network (DMN) were applied as masks in the corresponding maps in each subject. The mean value was calculated yielding to the connectivity strength of the resting state network in each participant (Stagg et al., 2014).

4.2. Task-based data

Pre-processing was performed with Statistical Parametric Mapping (SPM12, Worsley and Friston, 1995) and included realignment of all volumes to the mean image, slice time correction, normalization and spatial smoothing (6 mm FWHM). The first-level analysis was processed using a standard block-design General Linear Model (GLM) with 2 predictors: rest (20 s) and MI (or ME, 20 s). We directly contrasted MI (or ME) vs. rest in the baseline and transfer sessions. The contrast 'transfer vs. baseline' was calculated for each participant and then submitted to a group analysis with searchlight analysis (Kriegeskorte et al., 2006), a multivariate approach using a moving 9 mm-radius sphere across the brain. Statistical significance for this analysis was determined by a cluster-wise $p < 0.05$, FDR corrected.

4.3. Diffusion-weighted (DW) data

Voxel-wise statistical analysis of the FA and MD (mean diffusivity) data were conducted using standard steps of Tract-Based Spatial Statistics (TBSS; Smith et al., 2006). TBSS projected all subjects' FA and MD data onto a mean FA tract skeleton, before applying voxel-wise cross-subject statistics. Between-group comparisons of changes in WM were performed by subtracting post and pre DW data followed by a multivariate two-sample *t*-test. The number of permutations was 5000 using threshold-free cluster enhancement (TFCE).

Besides whole-brain analysis, we performed a statistical analysis focusing on the sensorimotor segment of the corpus callosum. In order to reconstruct WM tracts connecting both sides of the SMN, we conducted a probabilistic tractography analysis using FMRIB's Diffusion Toolbox (FDT; Behrens et al., 2003). Preprocessing steps of DW data included correction of eddy current distortions and modeling of diffusion parameters. Right and left sides of the SMN were used as masks. The resultant connection was overlaid among all participants yielding a single group bundle, which was skeletonized and used for subsequent analysis. We selected the forceps major (splenium of corpus callosum) as a control WM bundle since it connects bilateral occipital areas, brain regions that we believe would not be directly influenced by the NFB training. The forceps major was defined based on JHU White-Matter Tractography atlas (Hua et al., 2008), then skeletonized, and used to investigate the specificity of the NFB training on the sensorimotor network.

4.4. Statistical analysis

Behavioral data collected before, during and after the experiment were analyzed using repeated measures two-way ANOVA (within-subjects factor: 'time'; between-subjects factor: 'group'). Simple-effect analysis with Sidak correction for multiple comparisons was performed when appropriate. Statistical significance was determined as $p < 0.05$. Table 1 shows mean and SD of each analyzed variable.

Table 1
Variable's details. Mean and standard deviation (SD) for each group (a) before and after the NFB (or sham) training, and (b) throughout the training. KVIQ-10 = kinesthetic and visual imagery questionnaire, DMN = default mode network, SMN = sensorimotor network, FA = fractional anisotropy, MD = mean diffusivity, MI = motor imagery, SSS = Stanford Sleepiness Scale.

a)	NFB		CTL	
	Pre	Post	Pre	Post
Accuracy	59.55 (28.73)	60.45 (21.02)	59.5 (24.44)	62.18 (26.83)
KVIQ-10	14.63 (4.54)	15.52 (5.47)	17.58 (4.80)	18.29 (3.70)
DMN	31.06 (5.31)	34.96 (7.51)	34.51 (6.22)	33.75 (6.39)
SMN	26.01 (8.11)	30.63 (11.66)	29.59 (8.80)	29.07 (11.34)
FA	0.59 (0.04)	0.61 (0.02)	0.60 (0.03)	0.58 (0.02)
MD[a]	7.64 (0.53)	7.62 (0.32)	7.82 (0.37)	7.81 (0.37)
Number of correct sequences	7.00 (5.04)	9.73 (5.74)	8.11 (4.93)	12.35 (7.11)
SSS	1.84 (1.06)	1.84 (1.25)	1.82 (0.63)	1.76 (0.9)
MI Vividness[b]	3 (1.49)	3 (1.2)	3.58 (0.79)	3.29 (0.91)

b)	NFB			CTL		
	RUN1	RUN2	RUN3	RUN1	RUN2	RUN3
Accuracy	65.41 (21.35)	62.85 (22.73)	65.86 (23.14)	66.21 (22.81)	53.44 (25.47)	55.46 (21.76)
SSS	1.47 (0.84)	1.68 (1.15)	1.57 (1.16)	1.52 (0.71)	1.42 (0.5)	1.58 (0.87)
MI Vividness[b]	3.21 (1.18)	3.1 (1.28)	3.36 (1.3)	3,7 (0.91)	3.47 (0.87)	3.47 (0.87)

[a] Multiplied by 10^{-4}.
[b] Assessed using kinesthetic subscale of KVIQ-10.

5. Results

Both groups showed similar ability to perform MI tasks before and after ($F(1.34) = 1.45$, $p = 0.24$, $\eta^2 = 0.041$) and throughout the experiment ($F(2.68) = 0.647$, $p = 0.527$, $\eta^2 = 0.019$), as measured using KVIQ-10. On the other hand, an effect of 'time' was observed on arousal in both groups (repeated measures ANOVA $p < 0.05$). However, post-hoc analysis revealed no differences after Sidak correction for multiple comparisons in arousal within groups.

RMS ratio of involuntary hand movement during the experiment revealed no differences between groups for both MI [(effect of 'time': $F(4.132) = 0.286$, $p = 0.887$, $\eta^2 = 0.009$; interaction between 'time' and 'group': $F(4.132) = 0.282$, $p = 0.889$, $\eta^2 = 0.008$)] and ME [(mean = 49.41, SD = 50.74), $t(33) = 0.611$, $p = 0.54$, independent samples *t*-test)] tasks during the experiment.

5.1. Neurofeedback-induced changes in functional connectivity – DMN

As expected, resultant DMN (Fig. 2A) comprised bilateral medial prefrontal cortex, precuneus, posterior cingulate cortex, angular gyrus and left parahippocampal cortex. Between-group comparison of DMN connectivity strength revealed an interaction of 'time' and 'group' ($F(1.34) = 7.352$, $p = 0.01$, $\eta^2 = 0.178$), led by an increase in the NFB group after the experiment ($p = 0.002$, Table 1). DMN connectivity

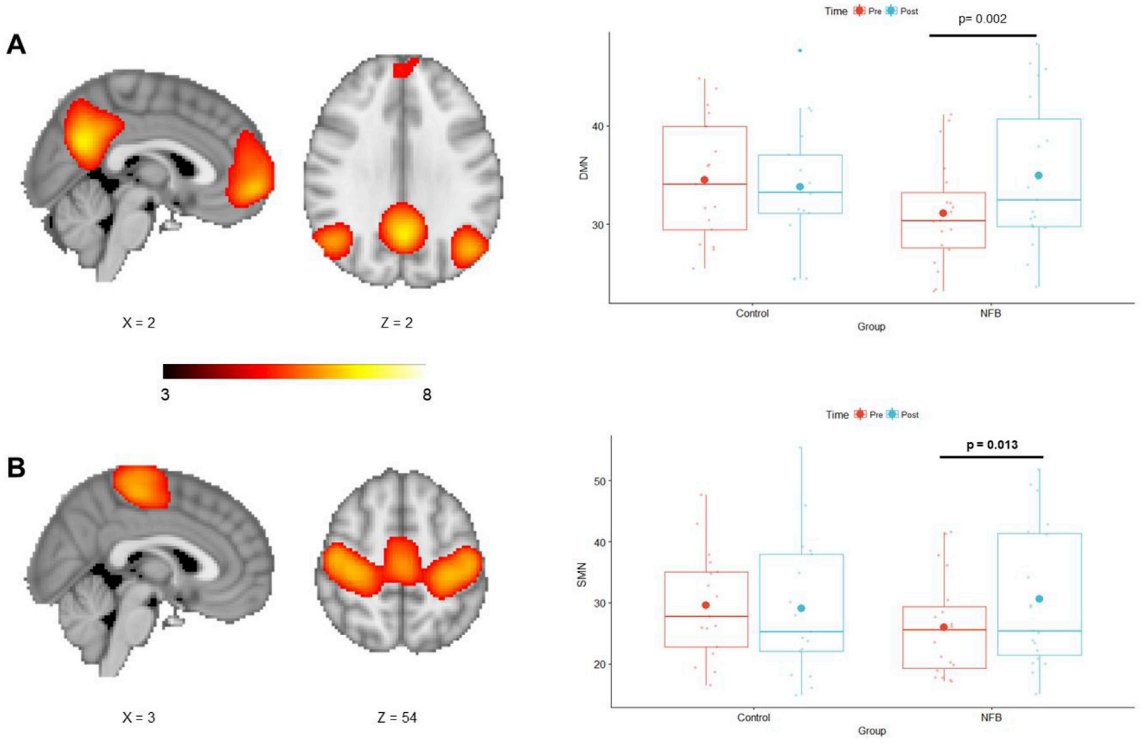

Fig. 2. Functional connectivity of DMN and SMN. (A) Group mean DMN and (B) SMN and the respective boxplots showing mean functional connectivity strength in each group before and after the neurofeedback (or sham) training.

strength remained stable in the CTL group ($p = 0.55$, Table 1).

5.2. Neurofeedback-induced changes in functional connectivity – SMN

The same analysis was conducted for the SMN (Fig. 2B). This network encompassed the bilateral pre- and post-central cortices (including supplementary motor area), and part of the posterior parietal cortex. An interaction between 'time' and 'group' was observed, $F(1.34) = 3.9$, $p = 0.054$, $\eta^2 = 0.105$, with an increase in connectivity strength in the NFB group after the experiment ($p = 0.013$, Table 1). CTL group did not show a significant change of the connectivity strength in the SMN after the experiment ($p = 0.78$, Table 1).

5.3. Neurofeedback-induced white matter changes

In order to investigate the effect of the NFB training on structural connectivity of the SMN, we measured the mean FA and MD of the WM bundle connecting its right and left hemispheres at the level of the corpus callosum (Fig. 3A). For FA, we observed an interaction between 'time' and 'group', $F(1.34) = 10.84$, $p = 0.003$, $\eta^2 = 0.229$. Post hoc analysis revealed that the result was driven by an increase in FA in the NFB group ($p = 0.041$, Table 1), decrease in the CTL group ($p = 0.024$), and significantly FA difference after the experiment ($p = 0.002$).

MD analysis did not show effect of 'time', $F(1.34) = 0.128$, $p = 0.72$, $\eta^2 = 0.004$) nor interaction 'time' and 'group', $F(1.34) = 0$, $p = 1$, $\eta^2 = 0$). Also, whole brain analysis of both FA and MD did not show differences between groups ($p > 0.05$, corrected for multiple comparisons).

To further explore the NFB specificity of these FA changes, we also extracted FA values of an unrelated bundle. Forceps major (splenium of corpus callosum) FA values showed neither effect of 'time', $F(1.34) = 0.000$, $p = 0.991$, $\eta^2 = 0.000$) nor interaction between 'time' and 'group', $F(1.34) = 2.142$, $p = 0.153$, $\eta^2 = 0.059$).

5.4. Reproducing ME-related fMRI patterns during MI

The accuracy in reproducing ME brain patterns during MI was compared between groups in order to evaluate participants' ability to gain control over their own brain function in real time. As a result, we observed the effect of 'time', $F(2.68) = 3.4$, $p = 0.039$, $\eta^2 = 0.09$. Whilst CTL group participants showed a decrease in accuracy over the experiment (RUN1 to RUN2: $p = 0.007$; RUN2 to RUN3: $p = 0.6$ RUN1 to RUN3: $p = 0.027$; Table 1), NFB group participants were able to maintain the initial SVM pattern classification accuracy level, as they did not show significant changes throughout the NFB training ($p > 0.05$; Table 1). We then divided the participants of each group (either from NFB and CTL groups) into responders and non-responders based on individual ability to maintain or increase the accuracy levels from RUN1 to RUN3. Qui-square test of independence was calculated to compare the number of responders to the training between groups. The accuracy of CTL group participants was calculated offline based on their actual brain patterns. We found that there was a positive association between 'responders' and 'group', χ^2 (1, N = 36) = 5.707, $p = 0.023$, Cramer's V = 0.39 led by an increased frequency of responders in the NFB group (adjusted residuals = 2.4).

GLM analysis of the whole brain revealed that areas activated both during the neurofeedback and sham training included bilateral premotor

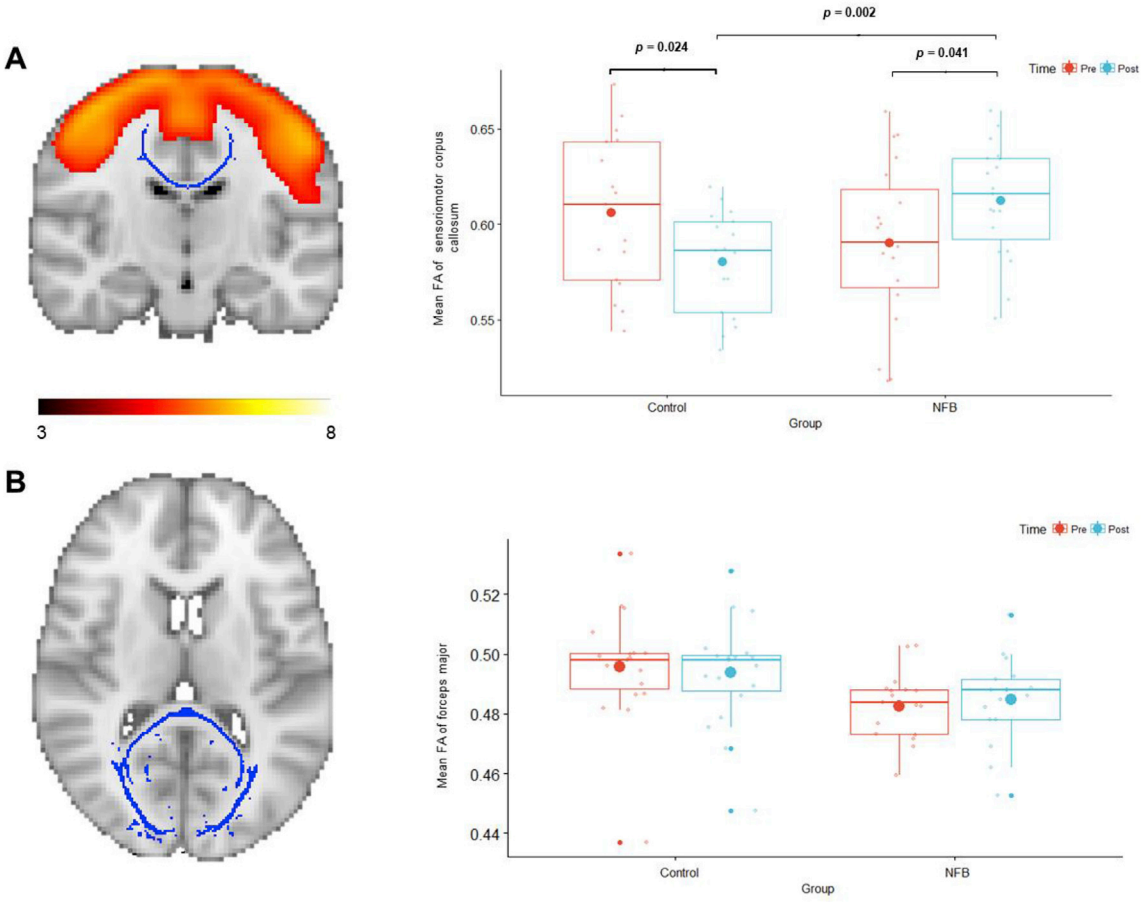

Fig. 3. Structural connectivity. White matter structural connectivity between (A) right and left areas of the SMN in all participants and (B) forceps major (splenium of corpus callosum). In the right side, the boxplots show the mean FA of the sensoriomotor corpus callosum (A) and forceps major (B) in each group before and after neurofeedback (or sham) training.

cortex (PMC), supplementary motor area (SMA), sensorimotor cortex and right cerebellum (lobule VI) (Figure S1). Mean accuracy during each run is shown in Table 1. We mapped the SVM models for each task (baseline, RUN1, RUN2, RUN3 and transfer) as an alternative approach to investigate brain changes throughout the experiment. The images are shown in supplementary figure S2 and S3.

5.5. Impact of NFB on MI

Searchlight analysis of the 'transfer vs. baseline' contrast revealed that the most discriminative areas between groups were left SMA, left anterior cingulate cortex, left superior frontal gyrus, left parahippocampal gyrus and left fusiform gyrus, with mean accuracy of 82.5%. The extracted beta values from the first level analysis revealed that the result was driven by an overall higher activity in the abovementioned brain areas in the NFB group.

GLM analysis of the whole brain during MI performed both before and after the neurofeedback (or sham) training showed that both groups activated sensorimotor brain areas such as left M1, bilateral SMA, left PMC, and left putamen (Fig. S4). The mean accuracies measured offline with the SVM algorithm are shown in Table 1.

5.6. NFB-induced motor improvement

To investigate the effects of the NFB training on motor behavior, we compared the number of correct sequences (7-digits long) performed before and after the experiment. Both groups were able to increase the ability to correctly perform ME of the predefined sequence after the experiment (effect of 'time', $F(1.34) = 35.25$, $p = 0.000$, $\eta^2 = 0.509$). No interaction between 'time' and 'group' was observed, $F(1.34) = 1.63$, $p = 0.211$, $\eta^2 = 0.046$). Details are shown in Table 1.

6. Discussion

In this randomized, double-blind and sham-controlled study we tested the hypothesis that short-term NFB training on brain motor areas can induce functional and structural brain plasticity, which would improve motor behavior. Specifically, we found that less than one hour of NFB training was sufficient for healthy volunteers to acquire control of their own brain signal and reinforce ME-related brain patterns in the absence of overt movement (while performing MI alone), which led to a strengthening of both SMN and DMN functional connectivity and increase of mean FA of sensorimotor segment of corpus callosum. However, improvement of motor performance itself did not seem to depend on NFB training.

MI and ME share similar neural fingerprints by eliciting activation of SMA, PMC, parietal areas, basal ganglia and cerebellum (Gerardin, 2000; Hanakawa et al., 2003; Lotze et al., 1999; Stephan et al., 1995). Several studies have shown that therapeutic interventions based on MI lead to brain reorganization and motor improvement after stroke, especially when associated with conventional strategies (Butler and Page, 2006; Page et al., 2009, 2007; Sharma et al., 2009, 2006; Zimmermann-Schlatter et al., 2008). These studies are in line with previous evidence that brain reorganization leading to recruitment of spared regions is critical for motor recovery after stroke (Calautti and Baron, 2003; Frost et al., 2003; Ward, 2004, 2003), thus suggesting that MI can be a useful, cost-effective strategy to mediate these changes. Here, we tested whether NFB by fMRI training on reinforcing ME-associated brain patterns during MI can boost the effects of MI on sensorimotor areas in healthy volunteers. Despite similar in many aspects, an important distinction between MI and ME is the degree of activation in motor-related areas and the motor response itself, which may explain the lack of high classification accuracies, even though above chance-level. Taken together, our results suggest that when associated with NFB, MI can be used to strengthen brain patterns related with ME, which in turn may provide a promising tool for stroke rehabilitation in future studies.

Evidence suggests that SMN is considered a biomarker of the integrity of the motor system and is altered under different pathological conditions. In healthy volunteers, previous studies have shown that motor training and anodal stimulation using transcranial direct current stimulation (tDCS) strengthens the connectivity of the SMN, which correlates with the decrease in GABA levels on the primary motor cortex (Sampaio-Baptista et al., 2015; Stagg et al., 2014). Impaired sensorimotor connectivity in patients with Parkinson's disease can be partially reestablished by levodopa administration (Esposito et al., 2013; Wu et al., 2009). After stroke, decreased connectivity of the SMN has been linked to motor deficits in both humans (Carter et al., 2010; Golestani et al., 2013; Park et al., 2011) and rats (van Meer et al., 2010), mainly in the acute phase. The close relationship between SMN connectivity and motor impairment/recovery suggests that strategies focusing on modulation of its intrinsic connectivity should improve motor rehabilitation after disease. In the present study, we observed that after being trained with NFB, healthy volunteers displayed increased functional connectivity of the SMN. In addition to the changes in SMN, NFB training also led to a greater connectivity of DMN. Despite not related with the motor system, DMN has been systematically observed as being impaired after stroke (Dacosta-Aguayo et al., 2015; Lassalle-Lagadec et al., 2012; Park et al., 2014; Tuladhar et al., 2013), which might be linked to cognitive aspects of the disease. The present results suggest that the NFB training focusing on the modulation of motor circuits can also impact on different brain networks.

Structural brain plasticity in adults has been assessed by several studies using a wide range of MRI techniques revealing that both GM and WM are susceptible to changes after motor training (Sampaio-Baptista et al., 2018). The recent computational and methodological advances have allowed studies to explore brain plasticity induced by short-term (<1 day) training schedules, revealing so far unknown features of human brain plasticity. However, only a few studies have reported the investigation of WM after a short period of training. Sagi and cols observed that 2 h of training on spatial navigation led to a decrease in MD on hippocampus and parahippocampus of healthy individuals (Sagi et al., 2012). Although controversial, they also reported a decrease in both FA and MD in the fornix in response to the training (Hofstetter et al., 2013). Moreover, eleven hours (over one month) of meditation seem to increase FA in corona radiata (Tang et al., 2010). Extending these observations, the present study brings the first evidence of WM plasticity induced by less than 1 h-long period of training. Here, we observed a selective increase in FA within the sensorimotor segment of corpus callosum induced by NFB. This finding can be explained by a consistent recruitment of the sensorimotor network in response to the training. On the other hand, an explanation of the decreased FA observed in the CTL group is not straightforward. This effect may have been driven by the difficulty in engaging in the task due to the mismatch between the observed feedback (sham) and the cognitive strategies that participants adopted to modulate it.

Cellular mechanisms underlying fast FA changes are still a matter of debate. It is clear however that neuronal activity can alter cellular, molecular and physical proprieties of the microenvironment of axons and myelin in an intra-day time window, which might influence the FA. Studies have shown swelling of axons and modulation of mitochondrial distribution and transport in the axoplasm as being activity-dependent (Iwasa and Tasaki, 1980; Iwasa, Takasi and Gibbons, 1980; Ohno et al., 2011; Itoh et al., 1995). Another explanation may involve myelination or remodeling of existing myelin sheaths (de Faria et al., 2018; Stevens et al., 2002). Despite the formation of myelin can take 2 days to occur in response to neuronal activity, myelination process starts in up to 5 h by initiating the recruitment, proliferation and differentiation of oligodendrocyte precursor cells (Wake, Lee and Fields, 2011; Demerens et al., 1996; Xiao et al., 2016; Gibson et al., 2014; Castro, Bribián and Ortega, 2013). Moreover, the effects of ion channel density and other types of migrating cells should be considered as possible mechanisms underlying FA changes (de Faria et al., 2018; Decker et al., 2000). As previously

shown, the above-mentioned microenvironmental changes can be both up- or down-modulated by axonal activity (de Faria et al., 2018; Decker et al., 2000; Ohno et al., 2011; Stevens et al., 2002, 1998). These phenomena may impact the FA in a bidirectional way by either increasing or decreasing water diffusivity, affecting both NFB and CTL groups. However, future translational studies should further investigate the activity-dependent cellular changes in order to better characterize the underpinnings of FA changes.

The impact of the NFB training on MI brain pattern was subtle and led to increased activity in SMA and anterior cingulum, brain regions previously implicated in motor planning and learning (Hardwick et al., 2013), and neurofeedback-related attentional control and monitoring (Emmert et al., 2016), respectively. In addition, alternative analysis using the SVM model of each task also showed different patterns of brain activity throughout the experiment. We were not able to detect improved motor learning selectively induced by the NFB training, however. We speculate that this was probably due to the gross nature of the motor task here employed for motor assessment. Given the short training schedule, future studies should use more sensitive measurements to investigate gains in finer motor skill.

7. Conclusion

In this randomized, double-blind and sham-controlled study we corroborated the hypothesis that ME-related brain circuitry can be trained and reinforced in the absence of overt movement. Additionally, we brought convergent evidence that very short training schedule with NFB is sufficient to induce changes in both anatomical and functional proprieties sensorimotor system, which has a direct implication on motor rehabilitation after stroke, for example.

Moreover, the present study emphasizes the notion that NFB should be considered a promising tool to investigate subtle physiological and anatomical aspects of brain plasticity. Using multimodal MRI, we were able to assess dynamic proprieties of brain alterations in response to NFB applied to the sensorimotor system. Altogether, the present study can pave the way for the optimization of current strategies to induce brain plasticity in both health and disease. A better use of NFB-related approaches and their application in clinical settings depends on our understanding of the depth of their impact on the normal and diseased brain. The neurofeedback research field would benefit from more widespread use of double-blind, sham-controlled studies in order to be able to establish specific effects of NFB on brain plasticity and behavior.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.03.027.

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