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Up-regulation of Supplementary Motor Area activation with fMRI Neurofeedback during Motor Imagery

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Abstract

fMRI Neurofeedback (NF) is a promising tool to study the relationship between behaviour and brain activity. It enables people to self-regulate their brain signal. Here we applied fMRI NF to train healthy participants to increase activity in their supplementary motor area (SMA) during a Motor Imagery (MI) task of complex body movements while they received a continuous visual feedback signal. This signal represented the activity of participants' localized SMA regions in the NF group and a pre-recorded signal in the control group (sham feedback). In the NF group only, results showed a gradual increase in SMA-related activity across runs. This up-regulation was largely restricted to the SMA, whilst other regions of the motor network showed no, or only marginal NF effects. In addition, we found behavioural changes, i.e., shorter reaction times in a go/no-go task after the NF training only. These results suggest that NF can assist participants to develop greater control over a specifically targeted motor region involved in motor skill learning. The results contribute to a better understanding of the underlying mechanisms of SMA NF based on MI with a direct implication for rehabilitation of motor dysfunctions.

Keywords: Neurofeedback, fMRI, Motor Imagery, Supplementary Motor Area.

Significance

- Participants in the NF group specifically learned to up-regulate their SMA fMRI BOLD signal.
- This effect was largely restricted to the BOLD signal of the SMA.
- The neurofeedback was also associated with improvements in motor reaction times.

1 Introduction

We investigate whether healthy participants could increase their Blood Oxygen Level Dependent (BOLD) signal in the Supplementary Motor Area (SMA) with the use of realtime functional Magnetic Resonance Imaging (fMRI) neurofeedback, and whether measures of motor performance would track such changes in brain activity. Previous research addressing this question (Hampson et al., 2011; Scharnowski et al., 2015; Sepulveda et al., 2016) provided mixed results and have not used an experimental design that compares performance of a true neurofeedback group to a sham neurofeedback group. In this experiment, participants were instructed to use motor imagery to increase a "thermometer" representing SMA activity.

Motor Imagery (MI) is a form of motor simulation (Vogt et al., 2013) in the absence of overt movement (Blefari et al., 2015). MI and motor execution (EXE) are thought to share similar neural networks (Jeannerod, 2001), and MI plays an important role in motor learning (e.g., Schuster et al., 2011; Gentili et al., 2010). Further examination using activation likelihood estimation (ALE) analyses highlights that MI activates a large number of primary and secondary motor areas including the premotor area (PMC), primary motor cortex (M1), SMA, inferior frontal gyrus, precentral gyrus, middle frontal gyrus, anterior insula, inferior/superior parietal lobule (IPL/SPL), putamen, thalamus, and cerebellum (Hétu et al., 2013; Hardwick et al., 2018).

Neurofeedback (NF) provides a closed loop system where a participant's brain activity is measured and presented back to them as either a visual or an auditory feedback signal. This signal facilitates a participant's ability to modulate their own brain activity with the aim of improving function. Previous studies using Electroencephalography (EEG) -based NF have shown that healthy participants and patients can be trained to alter their scalp electrical activity in a wide range of applications such as improving cognitive functions using MI (Scherer et al. 2015; for review see: Marzbani et al. 2016). However, limitations of EEG-NF include low spatial resolution and difficulty in providing feedback from subcortical brain areas. An alternative method of NF is provided by

functional Magnetic Resonance Imaging (fMRI), which measures Blood Oxygen Level Dependent (BOLD) levels and enables feedback signals from brain activity of deeper brain structures and with higher spatial resolution, albeit with lower intrinsic temporal resolution.

Several fMRI NF studies have demonstrated that participants can be trained to regulate the fMRI BOLD signal (henceforth referred to as activity) of different brain regions, such as regions responsible for emotions (anterior insula and amygdala, Caria et al. 2010; Zotev et al. 2011; Veit et al. 2012), the auditory cortex (Haller et al., 2010), language areas (Rota et al., 2009a) and the visual cortex (Scharnowski et al., 2012). These studies have reported behavioural changes following NF training. Furthermore, several other NF studies have examined motor and motor-associated cortices, focussing on how NF provided during EXE (Neyedli et al., 2017) or MI (Yoo et al., 2008; Scharnowski et al., 2015; Auer et al. 2015) can enhance motor performance. Clinically, NF from sensorimotor-targeted regions can be used in motor rehabilitation related to stroke and neurological disorders (DeCharms et al., 2005; Subramanian et al., 2011; Sitaram et al., 2012; Linden and Turner, 2016). In addition, real-time fMRI studies have shown that NF-based MI training can alter the functional connectivity between target regions and other brain regions (Marins et al., 2015; Xie et al., 2015), but the related mechanisms and link to improved motor performance is unclear.

For modulating motor cortex activity, fMRI-NF studies have used different motor regions to derive a feedback signal, including the PMC (Sitaram et al., 2012; Zhao et al., 2013; Hui et al., 2014; Marins et al., 2015), M1 (Yoo et al., 2008; Berman et al., 2012; Chiew et al., 2012; Blefari et al., 2015; Neyedli et al., 2017) and the SMA (Hampson et al., 2011; Scharnowski et al., 2015; Sepulveda et al., 2016). Specifically, fMRI-NF studies targeting the SMA have revealed mixed findings: Scharnowski et al (2015) and Sepulveda et al (2016) found that participants were able to increase their SMA activity during the NF training, but the lack of control groups makes these results difficult to interpret. In addition, Hampson et al. (2011) did not find a significant increase in SMA activity, possibly due to the limited number of runs used.

Given these shortcomings in the existing research, in the present study we investigated: 1) Whether healthy participants are able to increase the activation levels in their SMA during MI of complex actions when receiving SMA neurofeedback, and whether brain regions other than the SMA were activated during the neurofeedback; 2) to contrast the brain networks activated during real and sham neurofeedback using whole-brain analyses; and 3) whether successful SMA-NF translates to changes in behavioural measures. In contrast to the fMRI-NF studies reviewed above (Hampson et al. 2011; Scharnowski et al., 2015; Sepulveda et al., 2016), we improved the study design to include both a genuine NF group and a control group that received sham neurofeedback. An assessment of motor function was performed on all participants before and after training. If participants are able to successfully and selectively modulate SMA activity while performing a MI task, we should see improved motor function performance in the NF group only.

2 Methods and materials

2.1 Participants

Twenty healthy participants with normal or corrected-to normal vision were recruited. Seventeen of them were right-handed and one was ambidextrous with a laterality index of 33.3 according to the Edinburgh Inventory (Oldfield, 1971). Participants were randomly assigned to two groups: Ten participants to the NF group (five males, mean age: 26.1±5.1 years) who received true feedback, and ten to the control group (seven males, mean age: 23.2±2.6 years) who received sham feedback. Participants were not informed to which group they were assigned. As apparent from Table 1, there were no systematic group differences regarding age, education, and handedness score. In addition, no systematic differences were found on the Vividness of Movement Imagery Questionnaire-2 (VMIQ-2) (Callow and Roberts, 2010). The ethics committee of College of Science and Engineering approved this study. All participants provided their informed consent for the experiment.

Table 1: Demographic features for participants in the NF and control groups

		NF Group (Mean±SD)	Control Group (Mean±SD)	*p-value* (two tailed *t* test)
Age (years)		26.1±5.1	23.2±2.6	0.175
Education (years)		17.2±2.3	16.6±2	0.621
Handedness		81.4±15.7	74.3±23.7	0.490
MI vividness	**Third person perspective**	21.6±10.1	18.6±4.8	0.462
	First person perspective	18.5±4.2	18.1±4.3	0.839

2.2 Imaging parameters and fMRI neurofeedback platform

The study was performed on a 3T Siemens Tim Trio MRI scanner at the University of Glasgow Centre for Cognitive Neuroimaging (CCNi) with a 32-channel head coil. T1 weighted structural scans were acquired at the beginning of the experiment (TR=2300ms, TE=2.96ms, 192 sagittal slices, 1 mm^3 isotropic voxels and image resolution 256×256). T2*-weighted functional scans were collected with an Echo Planar Imaging (EPI) sequence (TR=2000ms, TE=30ms, whole brain coverage with 32 axial slices, 0.3 mm gap and 3 mm^3 isotropic voxel).

The NF system used Turbo-BrainVoyager version 3.2 (Brain Innovation, Maastricht, The Netherlands) and a custom script running on MATLAB (Mathworks Inc., Natick, MA, USA) to visualize the feedback signal as a thermometer. An LCD projector displayed the thermometer onto a rear projection screen that could be viewed through a mirror mounted on the head coil.

2.3 Experimental procedure

All participants underwent the same procedure, which consisted of: a questionnaire interview outside the scanner, a pre-scan behavioural test, a localizer run, fMRI NF training (true feedback for the NF group and sham feedback for the control group) and a post-scan behavioural test.

2.4 Behavioural test

We used a Go/No-go task to assess motor performance. In this task a response must be given in the “go” trials and inhibited in the “no-go” trials, providing a cognitively engaging scenario. It has been shown that there is activation in the SMA during go trials (Liddle et al., 2001).

Participants completed 250 trials of this task before and after the NF training session, this is task was repeated for each hand separately. They were instructed to press the space bar of a conventional keyboard using their index finger as quickly and accurately as possible when a go-trial was displayed (green target), and to inhibit their response (that is, to keep the index finger positioned above the space bar) when a no-go trial was presented (blue target). The task was run using Inquisit 5 software. Each trial consisted of a fixation point (+) presented for 800ms, followed by a blank white screen for 500ms, followed by a rectangular cue (horizontal 2.5×7.5cm, or vertical 7.5×2.5cm, where stimulus orientation was not informative) that was displayed for one of five intervals (100, 200, 300, 400, 500ms) to reduce the temporal warning effect. Finally, go and no-go targets were coloured green and blue, respectively, and were presented for 1000ms or until a response occurred (Fillmore *et al.*, 2006).

A 3-way mixed effect analysis of variance (ANOVA) (hand×group×pre/post) was performed to analyse between and within group effects. A paired-sample t-test was used as a post-hoc test to compare between the pre-post experiment reaction time of each group and hand separately.

2.5 Functional localizer

The NF training session started with a functional localiser run, to identify the SMA, from which the participant received the feedback signal. The localiser lasted for about 5 minutes and consisted of 7 fixation blocks (16s) interleaved by 6 blocks of bimanual index finger-tapping (30s). Written instructions were given to the participants to either “Rest” or “Tap”. The functional data were pre-processed and analysed online with an accumulative General Linear Model (GLM) embedded in Turbo-BrainVoyager. The SMA-ROI was delineated from the active voxels (threshold of $t > 5.0$) within a rectangle that was positioned anterior to the precentral sulcus and superior to the cingulate sulcus, as shown in Figure 1. The ROIs were defined in each participant’s native space and subsequently used for the NF training runs to derive the NF signal. For further analysis, we

normalized these ROIs into Talairach space, as illustrated in Table 2, and identified them based on the nearest gray matter using the Talairach Daemon (Lancaster *et al.*, 2000).

<Insert Fig.1 here>

Figure 1. Overlap of individual SMA-ROI for the 20 participants of both groups. The subject-specific SMA-ROIs were identified prior to the NF training using a functional localiser run during an index finger tapping task.

Table 2. Subject specific SMA-ROI in Talairach space

	Subject no.	Anatomical area	Talairach coordinates			No. of voxels
			X	y	z	
NF group	1	LH, Medial Frontal Gyrus	-6	-7	52	1163
	2	LH, Medial Frontal Gyrus	-6	-19	58	702
	3	LH, Medial Frontal Gyrus	-3	-10	52	1754
	4	RH, Medial Frontal Gyrus	6	-10	58	1333
	5	LH, Medial Frontal Gyrus	-4	-14	48	1463
	6	LH, Medial Frontal Gyrus	0	-7	49	1520
	7	LH, Paracentral Lobule	-9	-25	52	2984
	8	RH, Medial Frontal Gyrus	9	-10	47	1730
	9	RH, Medial Frontal Gyrus	3	-10	52	2569
	10	RH. Medial Frontal Gyrus	9	-13	52	1186
Control group	11	RH, Medial Frontal Gyrus	2	-11	51	1683
	12	LH, Medial Frontal Gyrus	-10	-8	48	1520
	13	LH, Medial Frontal Gyrus	-7	-17	51	1539
	14	LH, Medial Frontal Gyrus	-4	-5	57	1344
	15	LH, Cingulate Gyrus	-10	-11	45	1408
	16	LH, Medial Frontal Gyrus	-7	-5	57	2086
	17	LH, Medial Frontal Gyrus	-4	-8	57	1792
	18	RH, Cingulate Gyrus	8	-2	48	2072
	19	RH, Medial Frontal Gyrus	8	-8	54	1848
	20	LH, Medial Frontal Gyrus	-4	-10	49	1268

2.6 fMRI neurofeedback

All participants took part in seven 430s long NF training runs, where they were instructed to upregulate their targeted ROI by engaging in a MI task of complex body actions of their choice. Each NF training run consisted of nine 30s long blocks of NF interleaved with ten 16s long fixation blocks, as shown in Figure 2. During the NF blocks, participants saw a thermometer, and were instructed to increase its level by imagining their own execution of complex actions. During the fixation blocks, participants looked at a fixation cross and were instructed to relax and count upwards “1,2,3…” to

keep their baseline signal low. Engaging in more complex mathematical operations has been shown to activate motor related networks (Hanakawa, 2011; Berman *et al.*, 2012).

The control group was presented with sham feedback that was randomly chosen from individual pre-recorded signals across 7 participants in the experimental group (yoked feedback) (Chiew *et al.*, 2012; Hui *et al.*, 2014).

<Insert Fig.2 here>

Figure 2. fMRI NF training paradigm of one run. A run lasted for 430s and consisted of nine 30s long NF blocks alternating with ten 16s long fixation (rest) blocks.

2.7 Online data analysis

Real time fMRI data analysis and NF presentation was performed using Turbo-BrainVoyager software and MATLAB. The scanner transmitted the acquired fMRI data volume by volume to the analysis computer that hosted Turbo-BrainVoyager through a network connection. Functional data were pre-processed in real time, which included linear de-trending, slice timing correction, 3D motion correction and spatial smoothing using a Gaussian kernel with full width at half maximum (FWHM) of 8mm, then added to a cumulative general linear model (GLM).

The feedback signal consisted of a thermometer with a continuously updated red column height at each TR of 2000ms, based on the following equation:

$$Column\ height\ (t) = \left(\frac{ROI_{SMA}(t) - ROI_{SMA\_base}}{ROI_{SMA\_base}}\right) - \left(\frac{ROI_{reference}(t) - ROI_{r\_base}}{ROI_{r\_base}}\right)$$

Where $ROI_{SMA}(t)$ and $ROI_{reference}(t)$ are the average BOLD signals of the SMA-ROI and a reference ROI during the NF block at time *t*. ROI_{SMA_base} and ROI_{r_base} are the average BOLD signals of the last three volumes in the fixation block of SMA-ROI and reference ROI, respectively. The reference ROI, used to correct for global scanning effects, encompassed a rectangular region covering all the voxels within an axial slice (z=10) distant from the motor network, and showed no activation when the localizer run was analysed.

2.8 Offline data analyses

The raw data were pre-processed offline using BrainVoyager QX 2.8.4 (Brain Innovation, Maastricht, The Netherlands). The first two volumes of each run were discarded to allow for T1 equilibration effects. The pre-processing of the remaining functional data involved slice scan-time correction with cubic-spline interpolation, 3D motion correction with Trilinear/Sinc interpolation, linear trend removal, high-pass filtering with a cut-off set to 3 cycles and spatial smoothing with 4mm full-width at half-maximum (FWHM) isotropic Gaussian kernel. All functional images of each subject were aligned to the first functional volume after the anatomical scan and spatially normalized to Talairach space to enable group analysis across participants (Talairach & Tournoux, 1988).

In the first level analysis, all pre-processed functional data of each subject were analysed using a General Linear Model (GLM) with two predictors (tapping and rest for the localiser, feedback and rest for NF), convolved with a hemodynamic response function. Covariates derived from six head motion parameters (Johnston *et al.*, 2010; Dijk *et al.*, 2012), an estimate of the white matter signal (Jo *et al.*, 2010; Zilverstand *et al.*, 2015) and the ventricular signal (Birn *et al.*, 2009; Zilverstand *et al.*, 2015) for modelling physiological artefacts (e.g. respiration and cardiac effects) and scanner instability.

2.8.1 Region of Interest analysis

To examine the NF training success, beta weights were estimated using a ROI-GLM analysis for each NF run of each subject's ROI for the SMA (identified by the functional localiser presented in Table 2) and were used as an indicator for the NF success. This was assessed via a 2-factorial (group×run) repeated-measure ANOVA, as well as via paired t-tests between the first and the last run in each group. Furthermore, a linear regression of the average beta weights over NF runs was used to examine the upregulation over runs as an index of self-learning. In addition, an event-related average time course was computed for the last and first NF runs.

Similarly, the beta weights of six additional regions of the motor network (bilateral M1, PMC, and PPC), that were delineated using RFX-GLM analyses of the NF and localisers runs across the two groups, were estimated to assess the influence of modulating the SMA activity during the NF training on this wider network. Statistically this was tested via 2-factorial (group×run) ANOVAs for each ROI, as well as via linear regressions of the average beta weights of each ROI. In addition, we contrasted the NF effects on the SMA against the effects on the additional regions directly in a 3-factorial contrast analysis (group×ROI×run).

2.8.2 Whole-brain analyses

Group data was evaluated based on a second level random effect analysis general linear model (RFX-GLM). The obtained statistical maps were corrected for multiple comparisons using cluster-level thresholding (Goebel *et al.*, 2006). In this method, the uncorrected voxel-level threshold maps were submitted to a whole-brain correction criterion based on the estimate of the map's spatial smoothness and on an iterative procedure (Monte Carlo simulation) for estimating cluster-level false-positive rates. After 1000 iterations, the minimum cluster-size that produced a cluster-level false positive rate (alpha) of 5% was applied to threshold the statistical maps.

A first whole brain RFX-GLM analysis was performed for the localizer runs. The contrast 'tapping vs. rest' was computed and a threshold was set at $p<0.01$, with a cluster-level thresholding of 899 mm^3. Activations were mostly found in motor-related areas, however the SMA was not included here, most likely because of between-subjects variability .

In addition, a whole brain second level RFX-GLM analysis was conducted for the NF runs for each group separately ($p<0.01$, with cluster-level thresholding of 981 mm^3 for the NF group and 1139 mm^3 for the Control group). A two sample t-test was performed to directly contrast NF and control groups, thresholding at $p<0.01$ with a cluster-level thresholding of 432 mm^3. For examining the interaction between run and group, we also ran a voxel-wise two-way mixed ANOVA with the factors run (7 runs, within subjects) and group (2 groups, between subjects). The interaction effect

of the whole brain ANOVA maps was thresholded at $p<0.01$ uncorrected, with a cluster-level threshold of 1242 mm^3.

3 Results

3.1 Behavioural results

Figure 3 shows the difference in reaction time of the two groups before and after the NF training for both hands. The repeated measures ANOVA of the reaction times showed a significant interaction effect of hand × pre/post-test, F(1,18)=6.1, p=0.02, and a significant hand × group × pre/post-test interaction, F(1,18)=5.2, p=0.03. No significant effects were found for hand (F(1,18)=0.06, p=0.8), group (F(1,18)=0.99, p=0.33), or pre/post-test (F(1,18)=1.02, p=0.326), nor for the hand × group interaction (F(1,18)=2.6, p=0.12), or the group × pre/post-test interaction (F(1,18)=0.1, p=0.74). Paired-sample t-tests between pre/post-test reaction times, run separately for each group and hand, revealed a significant effect of NF training in the right hand of the NF group (t(9)=3.106, p=0.013) but not in the control group (t(9)=0.535, p=0.606). There was no significant effect for the left hand in either group (NF group: t(9)= 0.471, p=0.648; control group: t(9)=0.353, p=0.732).

<Insert Fig.3 here>

Figure 3. Reaction time (ms) differences before and after the self-regulation of both hands for the two groups. Errors bar represent the standard mean error. * p=0.013.

3.2 ROI analyses

Each participant completed 7 NF runs in one session. Participants of the NF group learned to increase the brain activity acquired from their functionally localised SMA regions as shown in Figure 4. Most participants reported that they used motor imagery of bimanual hand punching or boxing. The average beta weights in the SMA estimated off-line during each run of the NF and control group are shown in Figure 5. The 2-way mixed effects ANOVA of the beta weights indicated a significant

main effect of group ($F(1,18)=40.7$, $p<0.0001$), whilst the main effect of run was not significant ($F(1,18)=0.18$, $p=0.98$). More importantly, when testing for a linear trend for run, we found a near-significant effect for the group×run interaction ($F(1,18)=4.2$, $p=0.053$). Subsequent paired t-tests revealed a significant increase in SMA activity from the first to the last run ($t(9)=-1.83$, $p<0.04$) in the NF group, whereas the control group showed no significant change ($t(9)= 0.88$, $p<0.2$).

In addition, a linear regression highlighted a gradual increase in the mean SMA activity across runs in the NF group indicating a learning effect ($y= 0.062x+0.252$, $F(1,5)=15.68$, $r^2=0.75$, $p<0.01$). The control group did not show such learning progress ($y= -0.074x-0.035$, $F(1,5)=2.44$, $r^2=0.32$, $p=0.17$). The difference between slopes was significant, $t(10)=2.73$, $p=0.02$.

<Insert Fig.4 here>

Figure 4. The average PSC of the NF group calculated according to Eq. (1). Error bar indicates standard error of the mean.

<Insert Fig.5 here>

Figure 5. The mean beta weights of NF and control groups across runs. The beta weights were used as an indicator of the success of self-regulation. For statistics see text.

In contrast to the clear trend for a differential effect of the NF training on the SMA, such effects were either less pronounced or absent in the six other regions of the motor network analysed here, namely bilateral M1, PMC, and PPC as shown in Figure 6. That is, in the 2-way ANOVAs for these ROIs, none of the group×run interactions was significant (for bilateral M1: $Fs < 2.4$, $ps > .13$; for bilateral PMC and PPC: $Fs < 0.63$, $ps > .43$). In line with these results, the regression analyses did not show significant increases/decreases in the mean activity across runs of both groups for these ROIs as summarized in Table 3.

Table 3. The linear regression of the six additional frontoparietal regions. It did not show a significant increase/decrease of the estimated beta weights across runs of both groups.

Cortical Area	*x*	*y*	*z*	*Group*	*Regression*	*F(1,5)*	*p*	R^2
LH, M1	-33	-15	47	NF	y= 0.019x+0.229	0.19	0.67	0.03
				Control	y= -0.084x+0.578	5.69	0.06	0.53
RH, M1	25	-25	40	NF	y= -0.03x+0.66	0.49	0.5	0.09
				Control	y= 0.62x-0.11	1.44	0.28	0.22
LH, PMC	-33	-4	46	NF	y= -0.03x+0.66	0.9	0.38	0.15
				Control	y= -0.2x+0.69	0.44	0.53	0.08
RH, PMC	27	-10	46	NF	y= 0.002x+0.34	0.005	0.94	0.001
				Control	y= 0.009x+0.36	0.074	0.79	0.01
LH, PPC	-34	-34	25	NF	y= -0.048x+0.31	0.4	0.55	0.07
				Control	y= 0.21x-0.13	0.13	0.73	0.02
RH, PPC	-46	-46	40	NF	y= -0.02x+0.37	0.19	0.67	0.03
				Control	y= 0.034x+0.1	0.77	0.41	0.13

<Insert Fig.6 here>

Figure 6. The mean beta weights of NF (black line) and control (grey line) groups across NF runs of six frontoparietal motor regions. Primary motor cortex (M1), Premotor cortex (PMC), Posterior Parietal cortex (PPC), Left (L), Right (R), vertical axis: mean beta weights, horizontal axis: run number, the error bars represent the standard error of the mean.

The specificity of the modulatory effects of the NF training for the SMA was examined further in a 3-factorial contrast analysis (group×run×ROI) where each ROI was contrasted against the mean of the remaining ROIs (using the Deviation contrast in SPSS, and linear trends for run). Importantly, this analysis indicated that the group×run effect was significantly more pronounced in the SMA than in the remaining ROIs, F(6,18)=6.1, p=0.024. Note that this contrast analysis also indicated a marginally significant 2nd order interaction for the left M1, F(6,18)=4.5, p=0.046. However, in contrast to the results for the SMA, the 2-factorial ANOVA for the left M1 carried a non-significant group×run interaction, F(6,18)=2.4, p=0.13, as reported above, which compromises the interpretation of the 2nd order interaction for this region. In summary, the effect of the NF training on the BOLD signal was largely restricted to the SMA, whilst amongst 6 other regions of the motor network, only the left M1 showed a similar, but statistically not significant effect.

Additionally, Figure 7 shows the averaged time course of the BOLD signal during the NF blocks of both groups. This figure plots the first and the last runs for both groups and shows an increase in SMA activity for the NF group.

<Insert Fig.7 here>

Figure 7. Average BOLD signal change of target SMA regions of NF and control groups comparing the first and last runs. NF training helped to increase the SMA activity of the NF group (black lines) compared to the control group where it decreased it (gray lines). Error bars are standard error of the mean. Dashed lines represent the task block.

3.3 Whole brain analyses of NF runs

For overview, a whole brain RFX-GLM analysis was performed across runs for both NF and control groups as illustrated in Figure 8 and listed in Table 4. For the NF group, activations were found in the left SMA, IPL, and bilateral precentral gyrus (left PMC and right Broca's area) and in the basal ganglia. For the control group the bilateral basal ganglia, bilateral middle frontal gyrus, left IPL and left middle temporal gyrus were found activated.

<Insert Fig.8 here>

Figure 8. Results of the RFX-GLM analysis of NF runs shown for the (A) NF group and (B) control group. These activations are significant at p<0.01 (cluster size> 981mm3 and >1139 mm3 respectively).

Table 4. Clusters of brain activation for NF and control groups. (Note: x,y,z are given in Talairach coordinates, LH= Left hemisphere. RH= right hemisphere. BA= Brodmann area.)

Group	*Cortical Area*	*x*	*y*	*z*	*t*	*p-value*	*Size*
NF	LH, Lateral Globus Pallidus	-21	-7	4	5.2415	0.00053	1924
	LH, Inferior Parietal Lobule, BA 40	-60	-28	34	7.9406	0.00002	1258
	LH, Supramarginal Gyrus, BA 40	-42	-40	37	7.7510	0.00002	1263
	LH, Precentral Gyrus, BA 6	-30	-13	52	7.2034	0.00005	4863
	RH, Putamen	24	-1	7	5.8323	0.00024	1995
	RH, Precentral Gyrus, BA 44	48	5	10	7.1174	0.00005	1405
Control	LH, Middle Temporal Gyrus, BA 21	-57	-55	4	7.2142	0.00005	1504
	LH, Putamen	-18	-1	13	12.8867	0.00001	24743
	LH, Inferior Parietal Lobule, BA 40	-57	-34	22	7.5089	0.00003	1756
	RH, Caudate Body	21	17	13	11.4746	0.00001	15864
	RH, Middle Frontal Gyrus, BA 6	36	-4	46	6.7628	0.00008	1605

In addition, a two sample t-test was performed to contrast the RFX-GLM maps of both groups directly. The NF group showed higher activations in clusters located in the left sensorimotor cortex (SMA, M1 and Primary sensory cortex) compared to the control group that showed higher activations in the left Claustrum and right middle frontal gyrus, as illustrated in Figure 9 and listed in Table 5.

<Insert Fig.9 here>

Figure 9. A contrast map between the RFX-GLM of NF and control groups. Red/yellow colour represents significant actions in the NF group while the blue/green colour indicates higher activation in the control group. The map was thresholded at P<0.01 (cluster size>432mm3).

Table 5. Comparison of brain activations between NF and control groups. (Note: x,y,z are the Talairach coordinated, LH= Left hemisphere. RH= right hemisphere. BA= Brodmann area.)

	Cortical Area	*x*	*y*	*z*	*t*	*p*-value	*Size*
NF > Control	LH, Medial Frontal Gyrus, BA 6	0	-9	49	4.2104	0.00052	875
	LH, Precentral Gyrus, BA 6	-33	-7	58	5.9098	0.00001	1994
Control > NF	RH, Middle Frontal Gyrus, BA 8	36	26	43	-6.1933	0.00001	2628
	LH, Claustrum	-24	14	13	-4.9600	0.00010	1120

The interaction (groups×runs) of the whole brain 2-factorial ANOVA showed an activation of bilateral middle frontal gyrus, superior temporal gyrus, lingual gyrus, and caudate head as shown in Figure 10 and listed in Table 6. Furthermore, the same figure shows a small cluster of uncorrected activation (p<0.05) in the SMA.

<Insert Fig.10 here>

Figure 10. Two-factorial ANOVA examining the interaction (group×run) effect. The brain slabs (in the white rectangular) show uncorrected activation in the SMA regions. The surface maps were thresholded at p<0.05 (cluster size >1424 mm3).

Table 6. Clusters of brain activation for the ANOVA interactions effect. (Note: x,y,z are the Talairach coordinates, LH= Left hemisphere. RH= right hemisphere. BA= Brodmann area.).

Cortical Area	*x*	*y*	*z*	*t*	*p-value*	*Size*
RH, Superior Temporal Gyrus, BA 42	63	-28	7	3.8164	0.00001	1269
RH, Precentral Gyrus, BA 6	54	-1	13	3.3213	0.00019	2150
RH, Middle Frontal Gyrus	39	22	19	4.8032	0.00001	1871
RH, Caudate Head	12	11	1	3.863	0.00001	3147

LH, Lingual Gyrus, BA 18	-9	-76	-8	4.1983	0.00001	3655
LH, Lentiform Nucleus	-18	2	1	2.9345	0.00053	2115
LH, Precentral Gyrus, BA 44	-51	10	13	3.2926	0.00016	1310
LH, Superior Temporal Gyrus, BA 41	-45	-34	4	3.7605	0.00001	1431

3.4 Correlation between behavioural measures and NF performance

We examined the data for correlations between behavioural measures and NF performance in the NF group. NF performance was measured as the difference in beta weights obtained from the SMA, calculated between the first and last neurofeedback runs. To check for individual differences due to motor imagery capabilities we conducted a linear regression between VMIQ scores and neurofeedback performance. This regression produced a non-significant result (y=1.180-0.034x, $F(1,8)=0.94$, $p=0.36$, $R^2=0.10$), suggesting that our effect was not driven by individual differences. To check for a relationship between reaction time in the behavioural task and neurofeedback performance we calculated a linear regression between the change in reaction time between and neurofeedback performance for the NF group. This produced a non-significant result (y=-17.878+10.021x, $F(1,8)=3.44$, $p=0.10$, $R^2=0.30$) indicating that the change in reaction time was not accounted for by the amount of change in BOLD activation in the SMA.

4 Discussion

In this study we demonstrated that healthy volunteers could learn, in a single session, to increase the activity in their functionally localised SMA region, during a MI task of complex body actions whilst receiving a continuous feedback signal (displayed as a thermometer bar). This feedback signal represented the activity of individually localized SMA regions in the NF group, whereas the control group received a sham feedback signal. In the NF group, the estimated beta weights of the SMA increased with the number of runs, indicating a practice effect in modulating the SMA activation. In addition, the NF group showed faster responses in the reaction time task after the training, whilst no such effect was present in the control group.

403 The first aim of this study was to explore the ability of healthy participants to increase the
404 SMA activity guided by NF in a single training session. Our results showed that participants of the NF
405 group, who engaged in MI and received feedback information from their SMA region, increased their
406 SMA activation. The beta weights of the NF group progressively increased, which would reflect the
407 gradual increase in ability to self-regulate. In contrast to the NF group, participants of the control
408 group, who received a yoked feedback signal, did not increase their SMA activity (or the estimated
409 beta weights). This lack of increase resulted presumably because the provided feedback signal did
410 not correspond to the changes in their targeted brain regions and thus did not reinforce the
411 relationship between brain activity and feedback signal. A complete understanding of the neural
412 mechanisms by which self-regulation is obtained is an unresolved theoretical problem in the field of
413 neurofeedback (Sitaram, et al., 2017). Sitaram and colleagues (2017) proposed the possibility of two
414 distinct neural networks to be involved in neurofeedback, one network involving cognitive factors
415 and explicit processing of reward and another network involving more automatic aspects of reward
416 processing. Such dual-process mechanisms can be related to the current experiment where
417 participants were given the cognitive task of performing MI as a mean to maximize their feedback
418 signal.

419 These findings of increased SMA activity guided by a single NF session confirm those of
420 previous studies (Banca et al. 2015; Scharnowski et al. 2015; Blefari et al. 2015) which indicated that
421 a single session of NF training is sufficient to elicit NF-related practice effects. In contrast, the
422 additional six regions of the motor network did not show significant effects of NF, which
423 demonstrates the specificity of NF training on modulating only the SMA activity. Participants in both
424 groups had a comparable capability to perform MI as measured by the VMIQ-2 questionnaire. The
425 debriefing after the scanning of the participants in NF group revealed that most of them initially
426 struggled to identify the best imagery strategy. A number of different MI strategies during the NF
427 training were reported, including first-person perspective MI of bimanual punching or boxing. In
428 contrast, participants of the control group were frustrated about not being able to control the

429 thermometer level using MI strategies. Common documented strategies in successful modulation
430 include MI of clenching and pitching (Blefari et al. 2015; Chiew et al. 2012; Yoo et al. 2008) and
431 sequential finger movements (Neyedli et al. 2017; Berman et al. 2012). MI and motor execution have
432 been shown to activate common cortical regions including the SMA, bilateral PMC, M1, posterior
433 parietal lobe and the cerebellum (Hanakawa *et al.*, 2008; Hétu *et al.*, 2013; Sharma and Baron,
434 2013). The shared neural substrate between different motor modalities supports the feasibility of NF
435 training using MI to enhance motor performance. Finally, it is worth considering if the increase in
436 SMA beta weights might have been due to the MI instruction per se, rather than a result of the
437 neurofeedback. Typically, neuroimaging studies on practice effects of pure MI tasks, without
438 involving neurofeedback, show neural efficiency effects, that is, activation decreases with practice
439 (e.g., Sakreida et al., 2018). Therefore, we consider it unlikely that the present effect can be
440 attributed to the MI instruction alone.

441 Based on the above, the second aim of this study was to compare between the brain
442 networks involved in NF training during real and sham feedback conditions. The whole-brain RFX-
443 GLM analysis of each group separately revealed widespread brain activation beyond the targeted
444 area (SMA). For the NF group these activations included the left SMA, PMC, IPL, and bilateral basal
445 ganglia, and for the control group the bilateral PMC, basal ganglia, middle frontal gyrus, and right
446 IPL. The SMA is involved in motor planning and control (Grefkes *et al.*, 2008; Nachev *et al.*, 2008).
447 Indeed, the NF group showed an increase in the left SMA activation during the NF training,
448 consistent with previous findings of left hemisphere dominance in practice-related activation
449 increase regardless of the trained hand (Halsband & Lange, 2006). The PMC plays an important role
450 in planning and preparation of movements (Hoshi *et al.*, 2007; Hétu *et al.*, 2013). Our results of
451 activation in the left PMC highlight the dominant role of this area in movement selection (Bestmann
452 *et al.*, 2008) while the right PMC activation are consistent with spatial processing during the early
453 stage of motor learning (Halsband and Lange, 2006). The IPL activation could be related to the
454 integration of visuomotor information (Halsband and Lange, 2006), or the internal recruitment of

455 stored motor representations (Cooke *et al.*, 2003). Particularly, the left IPL is suggested to be
456 involved in the storing/retrieval of motor plans (Van Elk, 2014) and visually guided motor tasks
457 (Torres *et al.*, 2010). Further, the basal ganglia is involved in motor processes and cognitive
458 functions, such as learning based on the assessment of outcomes (Arsalidou *et al.*, 2013).
459 Interestingly, the putamen is thought to be essential in the learning of novel complex motor actions
460 and less important in well trained movements (Ceballos-Baumann, 2003), which is consistent with
461 the pattern of basal ganglia activation observed in the NF group, which suggests that a task can be
462 carried out using fewer neural substrates, as fast learning proceeds (Poldrack, 2000). Importantly, in
463 contrast to the NF group, the control group showed widespread activation in the basal ganglia. This
464 widespread activation is potentially related to processes of executive function when participants in
465 the control group unsuccessfully attempted to adapt their MI to improve the feedback signal. This
466 would have involved trying different MI actions and possibly modulating attention to different
467 aspects of the imagined movement, which would be cognitively demanding. For example, Arsalidou
468 and colleagues (2013) highlight the connection between executive function and different regions of
469 the basal ganglia: planning that activates the head and body of the right caudate, working memory
470 that activates the bilateral putamen, and reward processes that activate anterior parts of bilateral
471 caudate head. Comparison of brain activation between the NF and the control groups revealed
472 significantly higher activations in the left SMA, M1 and PMC of the NF group, further supporting our
473 hypothesis that the NF group was able to increase the activation of SMA during NF training. The
474 interaction (groups×runs) of the whole brain ANOVA showed significant activation in bilateral
475 ventrolateral prefrontal cortex and temporoparietal junction which could be related to the
476 imagination of actions and the integration of imagery and memory by remembering the visual
477 appearance (Zimmer, 2008) respectively. The SMA was not differentially activated in the interaction,
478 but this could be due to the conservative analysis used (no linear trend for the main effect RUN).
479 Given that such an interaction in the SMA would have been congruent with the obtained ROI-GLM
480 results, future research might re-examine this point.

Finally (aim 3), we wished to test the hypothesis that successful self-regulation would be related to changes in measures of motor function. Our results were mixed, with between group differences supporting the hypothesis, while changes in motor performance of individual participants within the NF group failing to support the hypothesis. In the Go/No-go task, participants were instructed to respond as quickly and accurately as possible, and related decreases in reaction time between pre- and post-test were indeed found in both groups for the right hand. Importantly, this decrease was only significant in the NF group. This finding further supports that MI training guided by true NF can be used to bring the brain into a state where movement vigor is enhanced. The Go/No-go task involves planning and initiation of movements during the Go trials, and inhibition of inappropriate actions during the No-go trials. These processes are likely mediated by the SMA (Nachev et al. 2008). The SMA has direct connections to M1, the ventrolateral thalamus, and to the spinal cord via the corticospinal tract (Arai et al. 2012; Nachev et al. 2008; Johansen-Berg et al. 2004) and it has been shown that modulating SMA activity can increase the cortical excitability of M1 (Arai et al. 2012; Shirota et al. 2012). Our finding of faster motor reaction times following SMA-contingent NF training is thus consistent with motor physiology. Despite the positive finding of an overall NF group decrease of reaction times and increase in beta weights our hypothesis was not confirmed at the individual participant level; we did not find a significant correlation between change in reaction times and change in beta weights for individuals in the NF group.

Rounding up, in line with the previous studies of fMRI NF (Bray *et al.*, 2007; Chiew *et al.*, 2012; Sitaram *et al.*, 2012; Zhao *et al.*, 2013; Scharnowski *et al.*, 2015), we demonstrated that the use of a MI task during real-time fMRI NF is effective in up-regulating activity specifically in the targeted motor region (here: SMA), and that it can improve motor performance. Our study presents the first controlled study that highlights the feasibility of increasing SMA activation during a single session. Clinically, learning control over the SMA could be used to treat Tourette's syndrome where SMA activity is linked to motor tics (Hampson *et al*. 2011; Bohlhalter *et al*. 2006) and Parkinson's

Disease where the SMA activity is reported to be underactive (Munzert *et al.*, 2009; Subramanian *et al.*, 2016).

5 Conclusion

Our results demonstrate the feasibility of fMRI neurofeedback to up-regulate SMA activity and illustrate the remarkable plasticity of the brain to adapt its function to novel situations. By learning to influence the height of a visually presented thermometer participants can self-modulate their SMA activity in a single session. Notably, this up-regulation was largely restricted to the SMA, whilst other regions of the motor network did only exhibit marginal effects of the NF training. Furthermore, the sucessful regulation of SMA activity also translated into enhanced motor response times in a visuo-motor task. Although significant theoretical questions remain as to the manner in which learning of self-modulation is achieved (Emmert et al., 2016; Sitaram et al., 2017; Watanabe et al., 2017), how neurofeedback can be developed into therapeutic applications or to answer fundamental questions of brain function is a rapidly expanding area of research (Hampson et al., 2019).

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