

Improved modulation of rostralateral prefrontal cortex using real-time fMRI training and meta-cognitive awareness

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ABSTRACT

Recent real-time fMRI (rt-fMRI) training studies have demonstrated that subjects can achieve improved control over localized brain regions by using real-time feedback about the level of fMRI signal in these regions. It has remained unknown, however, whether subjects can gain control over anterior prefrontal cortex (PFC) regions that support some of the most complex forms of human thought. In this study, we used rt-fMRI training to examine whether subjects can learn to regulate the rostralateral prefrontal cortex (RLPFC), or the lateral part of the anterior PFC, by using a meta-cognitive awareness strategy. We show that individuals can achieve improved regulation over the level of fMRI signal in their RLPFC by turning attention towards or away from their own thoughts. The ability to achieve improved modulation was contingent on observing veridical real-time feedback about the level of RLPFC activity during training; a sham-feedback control group demonstrated no improvement in modulation ability and neither did control subjects who received no rt-fMRI feedback but underwent otherwise identical training. Prior to training, meta-cognitive awareness was associated with recruitment of anterior PFC subregions, including both RLPFC and medial PFC, as well as a number of other midline and posterior cortical regions. Following training, however, regulation improvement was specific to RLPFC and was not observed in other frontal, midline, or parietal cortical regions. These results demonstrate the feasibility of acquiring control over high-level prefrontal regions through rt-fMRI training and offer a novel view into the correspondence between observable neuroscientific measures and highly subjective mental states.

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Introduction

In recent years, technological advances in functional magnetic resonance imaging (fMRI) acquisition and processing have opened up the possibility of presenting subjects with near real-time feedback about activation levels in target brain regions (Cohen, 2001; Cox et al., 1995; deCharms et al., 2004; Lee et al., 1998; Posse et al., 2003). Studies employing real-time fMRI (rt-fMRI) training have demonstrated that subjects can learn to enhance their control over cortical and subcortical regions by effectively up- and down-regulating the fMRI signal from these regions (Caria et al., 2007; deCharms et al., 2004, 2005; Posse et al., 2003; Rota et al., 2009). These results are significant because they open the possibility of more directly observing the correspondence between neural activity and subjective mental experience and have promised to inspire new treatment methods in clinical contexts (deCharms, 2007, 2008; deCharms et al., 2005).

A number of brain regions have been examined so far, including unimodal cortical areas such as the primary sensory and motor cortex (deCharms et al., 2004; Weiskopf et al., 2004), multimodal regions such as the inferior prefrontal cortex (Rota et al., 2009), and areas involved in emotional processing such as the insula and the anterior cingulate cortex (Caria et al., 2007; deCharms et al., 2005; Hamilton et al., 2011; Johnston et al., 2010; Posse et al., 2003). However, one large cortical brain area that has remained unexplored so far is the anterior prefrontal cortex (PFC), or Brodmann area (BA) 10, one of the highest-order supramodal cortical association regions (Benson, 1993; Christoff and Gabrieli, 2000; Koechlin et al., 2007; Petrides, 2005; Ramnani and Owen, 2004).

Lesion studies have suggested that a defining function of the anterior prefrontal cortex (PFC) may be meta-cognitive awareness, or the process of reflection upon one's own mental contents (Stuss, 2007; Stuss and Levine, 2002; Wheeler et al., 1997). More recently, neuroimaging studies have focused on possible sub-regional differences in anterior PFC function (Gilbert et al., 2006a,b). The lateral sector, known as the rostralateral prefrontal cortex (RLPFC), has received considerable attention and has been shown to play a critical role in multiple domains including complex reasoning (Bunge et al., 2005; Christoff et al., 2001; Kroger et al., 2002; Monti et al., 2007),

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memory retrieval (Rugg and Wilding, 2000; Velanova et al., 2003), multi-tasking (Braver and Bongiolatti, 2002; Koechlin et al., 1999), moral decision making (Greene et al., 2004), abstract thought (Badre and D'Esposito, 2009; Christoff et al., 2009b), spontaneous thought (Christoff et al., 2009a, 2004), and complex reward processing (Boorman et al., 2009; Huettel, 2006).

Across this diverse set of domains, neuroimaging and single-cell studies have suggested that RLPFC plays a reflective or monitoring function that coordinates, integrates, and evaluates the outputs of prior stages of cognitive processing (Christoff and Gabrieli, 2000; Fletcher and Henson, 2001; Petrides, 2005; Ramnani and Owen, 2004; Tsujimoto et al., 2010). The outputs that RLPFC appears to operate on – a self-generated rule in the context of reasoning, a sub-goal in the context of multitasking, or a memory episode in the context of retrieval – seem more related to conceptual thought than to other possible mental contents such as visceral, emotional, or external body sensations, suggesting that RLPFC may specifically subservise meta-cognitive awareness of one's own thoughts. In contrast, evidence suggests that medial BA10 may be preferentially linked to meta-awareness of one's own emotional states (Lane et al., 1997; Ochsner and Gross, 2005; Ochsner et al., 2004b).

In this study we examined whether individuals can achieve enhanced control over the fMRI signal in their RLPFC, by using rt-fMRI feedback to guide their learning and a meta-cognitive awareness mental strategy. It would be of particular practical and theoretical significance if individuals were able to use rt-fMRI feedback to regulate RLPFC activation given that this area is a large supramodal, association cortical region, subserving some of the most complex cognitive functions including meta-cognitive awareness. Due to the aforementioned theoretical implications and empirical findings, we chose instructions that emphasized meta-awareness of one's own thoughts as most likely to be associated with modulation of RLPFC signal. Specifically, during *up-regulation* blocks, subjects were encouraged to try to increase activation in their RLPFC by turning attention towards their own internal thoughts. During *down-regulation* intervals, they were encouraged to try to decrease activation in their RLPFC by turning their attention away from their own thoughts and directing it toward external perceptions or body sensations (see Appendix 1 for detailed instructions). These instructions were also consistent with prior experimental findings suggesting that RLPFC shows an increase in activation when directing attention to internal thoughts, and a relative decrease in activation when attention is directed externally to incoming sensory information (Burgess et al., 2007; Christoff and Gabrieli, 2000; Christoff et al., 2003; Gilbert et al., 2006a).

Materials and methods

Participants

A total of 30 healthy right-handed subjects took part in this experiment. All subjects provided informed, written consent and received compensation for their participation. Procedures were approved by the UBC Clinical Research Ethics Board. Twelve subjects were assigned to the experimental group ($M_{\text{age}} = 24.3$, $SD = 3.4$) and received real-time feedback throughout training. Another 12 subjects formed the control sham-feedback group ($M_{\text{age}} = 22.8$, $SD = 3.2$); they were given identical instructions to those in the experimental group but, unbeknownst to them, were shown pre-recorded signal from another subject's RLPFC. The sham feedback time-courses were selected from four experimental group subjects who showed median levels of improvement in the course of training, in order to minimize any difference between groups in subjects' perceived training success. After completing all scanning sessions and exiting the scanner, subjects in the sham group were debriefed to find out if they believed the sham feedback was authentic. The remaining six subjects

($M_{\text{age}} = 24.5$, $SD = 5.3$) were used as additional control subjects and were given the same regulation instructions and underwent the same duration of training but did not see any feedback during scanning, allowing us to examine whether improvement in RLPFC regulation would be observed from simply following the regulation instructions in the absence of any feedback.

Task and design

Training consisted of four 6-minute sessions, during which subjects alternated between 30 s blocks of up- and down-regulation, for a total of 24 up-regulation and 24 down-regulation blocks per subject. The first 60 s of each session which included one up-regulation block and one down-regulation block signified by the visually presented arrow cue, did not include real-time feedback. This period was used to calibrate the real-time feedback signal. During the remaining time of each session, real-time feedback about the level of fMRI signal in bilateral RLPFC was provided visually, through a feedback display (Fig. 1) back-projected onto a screen mounted above the subject's head. A fluctuating thermometer bar (Caria et al., 2007) in the upper left panel of the feedback display provided continuously updated information about the current level of RLPFC activation. This thermometer bar was updated once per second, after each volume of data was acquired. A history bar graph showing the average level of fMRI signal in the already completed regulation blocks was shown at the bottom panel of the feedback display. One bar was added to the display at the end of each 30 s block. An arrow cue in the centre of the screen indicated the direction of regulation (up or down) for the current block. In the transition period consisting of the last 3 s of each block, the screen displayed only a gray background with the words "Next Block". At the end of each scanning session, subjects were presented with debriefing questions to survey their subjective experience and specific strategies employed during that session. Questions were displayed on the screen while their verbal responses were recorded.

Prior to training, two pre-training sessions were conducted for all 30 subjects. The first one served to familiarize subjects with the feedback display and the properties of the hemodynamic response and consisted of a 6-minute motor cortex regulation task of alternating 30 s blocks of finger tapping and rest, during which they were presented with feedback from their motor cortex.



Fig. 1. Real-time feedback display viewed by subjects in scanner during real-time feedback training. A fluctuating thermometer bar (Caria et al., 2007) in the upper left panel of the feedback display provided continuously updated (once per second) information about the current level of RLPFC activation. The average level of fMRI signal in the already completed regulation blocks was shown at the bottom panel of the feedback display. An arrow cue in the centre of the screen indicated the direction of regulation (up or down) for the current block.

The second pre-training session (or the “no-feedback session”) consisted of subjects following the same meta-cognitive awareness instructions as those during the subsequent training, however, without observing rt-fMRI feedback. This session was conducted in order to examine the set of activations that are associated with following the meta-cognitive awareness instructions for up- and down-regulation in the absence of feedback and in training-naïve subjects. Similarly to the other training sessions, the no-feedback session lasted 6-minutes and subjects alternated between 30 s blocks of up- and down-regulation.

Data acquisition

Imaging was performed using a 3.0 T Philips Intera MRI scanner (Best, Netherlands). An eight-element, six-channel phased array head coil with parallel imaging capability (SENSE) (Pruessman et al., 1999) was positioned around the subject's head to obtain the MRI signal. Head movement was restricted using foam padding around the head. Functional volumes containing BOLD contrast intensity values were acquired using a T2*-weighted single shot echo-planar imaging (EPI) gradient echo sequence sensitive to BOLD contrast [time of repetition (TR) = 1000 ms; echo time (TE) = 30 ms; flip angle (FA) = 90°; field of view (FOV) = 24 × 24 cm²; matrix size 64 × 64, reconstructed to 64 × 64, SENSE factor = 2.0]. The volumes consisted of 17 slices (each 3 mm thick, separated by a 1 mm inter-slice gap) acquired parallel to the anterior commissure/posterior commissure (AC/PC) line. Prior to the beginning of the RLPFC regulation task, a single functional sample volume was collected to serve as a reference for subsequent motion-correction. For each RLPFC regulation session, 360 functional volumes were acquired. In addition, 4 discarded-acquisition volumes at the start of each session allowed for longitudinal relaxation steady state (T1) and eddy current stabilization.

Prior to functional imaging, a high resolution 3DT1 anatomical volume (TE 3.5 ms; TR 7.7 ms; FOV 256 × 200 × 170 mm³; acquisition matrix 256 × 256; 1 × 1 × 1 mm³ isotropic voxels) was obtained for each subject. An in-plane inversion recovery prepared T1-weighted fast spin-echo anatomic volume was also obtained (TR = 2000 ms; TE = 10 ms; spin echo turbo factor = 5, FA = 90°; FOV = 24 × 24 cm²; acquisition matrix 240 × 235; reconstructed matrix 480 × 480; inversion delay IR = 800 ms). This in-plane scan contained 17 slices (3 mm thick, separated by 1 mm inter-slice gap) acquired in the same slice locations used for functional images.

Anatomical Definition of RLPFC as target ROI

The target ROI was defined as bilateral RLPFC which was identified at the individual level using an anatomical landmark approach. Using an anatomical ROI definition is a common practice for this type of study (Posse et al., 2003; Weiskopf et al., 2003; Yoo and Jolesz, 2002) and is a less biased approach because the defined ROI will not be tied to a specific task, as can happen with functionally defined ROIs.

For each subject, RLPFC was first visually identified on the 3DT1 high-resolution structural scan by locating the intersection of the medial/intermediate frontomarginal sulci in each hemisphere, proceeding vertically up the intermediate frontal sulcus (Petrides and Pandya, 2004). This ROI was then manually drawn onto slices of the in-plane structural scan, and interpolated onto corresponding slices of the subject's sample functional volume. To compensate for signal dropout and geometric distortions, voxels near the edge of the functional ROI were examined and manually removed if they appeared outside the functional volumes. Fig. 2 illustrates the anatomical definition of RLPFC for a representative subject.

Real-time fMRI data processing for feedback visualization

Imaging data was analyzed in real-time using custom software programmed in C++ based on a dynamically linked library (DLL)

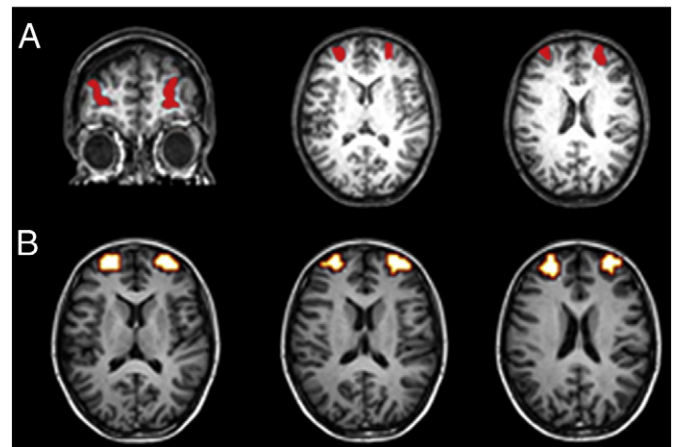


Fig. 2. Anatomical definition of RLPFC for a representative subject. (A) For each subject, RLPFC was first visually identified on the 3DT1 high-resolution structural scan by locating the intersection of the medial/intermediate frontomarginal sulci in each hemisphere, proceeding vertically up the intermediate frontal sulcus (Petrides and Pandya, 2004). This ROI was then manually drawn onto slices of the in-plane structural scan. The ROI was then interpolated onto corresponding slices of the subject's sample functional volume. (B) An example of structurally defined bilateral RLPFC ROI for a representative subject overlaid on the subjects' structural scan.

supplied by Philips for the purpose of real-time data acquisition. Real-time data pre-processing consisted of motion correction, voxel intensity-outlier rejection, ROI signal extraction, temporal spike-rejection and temporal filtering. Real-time motion correction was implemented using code adapted from the FSL motion-correction algorithm, MCFLIRT, employing trilinear interpolation with a 2-stage optimization algorithm (Jenkinson et al., 2002). The sample functional volume acquired for each subject at the beginning of scanning and used for ROI definition was the reference volume to which subsequent functional volumes were aligned. To reduce noise associated with voxels just outside the brain or subject to signal-dropout artifacts, voxel intensity statistics were computed across the training ROI, and voxels with standardized intensity of $z < -2.0$ were excluded. The average intensity was computed across remaining ROI voxels and converted to a percent (%) signal change, using mean ROI intensity recorded from the first 60 s of each session as a baseline. This initial 60 s included one up-regulation block and one down-regulation block as indicated by the visually presented arrow cue, however, no real-time feedback was presented during this period. Next the signal was temporally filtered with a 2nd order Butterworth filter (passband 0.0125 Hz–0.08 Hz). Finally, prior to display, the signal was truncated to fall within the range -1% to $+1\%$ signal change. Real-time data was processed once per incoming volume, generating an average ROI BOLD signal measure updated once per second.

Offline fMRI data analysis to assess modulation improvement

In order to assess modulation improvement, fMRI data were analyzed offline using Statistical Parametric Mapping (SPM5; Wellcome Department of Imaging Neuroscience, London). This off-line processing allowed for rigorous motion correction and the use of standard preprocessing and data analysis routines. The raw data were first subjected to standard pre-processing, including slice-timing correction (voxel time series were interpolated using sinc interpolation and resampled using the middle slice as a reference point), motion correction, and spatial smoothing with an 8 mm Gaussian kernel. The real-time training ROI was used to extract voxel time-courses of BOLD intensity values for each subject and session. These time-courses were then averaged across voxels within the ROI to obtain one time-course per subject per session, and converted to % signal change values. Each timecourse was then bandpass filtered

using a 2nd-order Butterworth filter (passband 0.0156 Hz to 0.15 Hz). In order to account for hemodynamic lag, as well as the cognitive delay involved in switching between attention to thoughts versus attention to sensory/body states, only volumes 12 through 27 from each block were used. Mean ROI size was $M = 154$ voxels ($SD = 108$). Size of ROI was unrelated to level of modulation improvement from session 1 to 4 ($r = -0.089$, $p = 0.64$) and did not differ across groups [$F(2, 27) = 1.462$, $p = 0.249$]. Modulation success was measured in terms of mean % signal change, by subtracting the mean % signal change value within down-regulation blocks from the mean % signal change value within up-regulation blocks. Importantly, we were not concerned with the absolute difference in activation magnitude between up- and down-regulation blocks, rather, our focus was on whether this difference would *increase* across the four training sessions for the real-time feedback group, thus revealing an improvement in the ability to modulate RLPFC activation.

For each subject group, modulation success was calculated across subjects for each of sessions 1–4 and graphed (Figs. 3 and 4), with error bars representing within-subject standard error of the mean (Loftus and Masson, 1994). To compare the Experimental and Sham-Feedback groups, a mixed-model, two-way repeated measures ANOVA was performed on % signal change, with group as a between-subjects factor and session as a within-subjects factor.

We were primarily interested in the ROI analyses which utilized RLPFC time-courses extracted from subject's non-normalized ROIs. However, to examine the spatial specificity of the training effect we also conducted a whole-brain analysis contrasting the experimental to the sham-feedback group, in order to examine if any regions outside of RLPFC also showed enhanced modulation during the course of training. For the whole-brain analysis each subject's brain was normalized to a template; the structural T1-weighted volume was segmented to extract a gray matter image for each subject which was used to spatially normalize each subject's data (Ashburner and Friston, 1999) to a gray matter image of the MNI template. Normalization, however, is known to introduce additional cross-subject variability that may limit statistical power (Brett et al., 2002; Saxe et al., 2006; Smith et al., 2007). To account for the potentially lower power of this whole-brain analysis relative to the non-normalized ROI approach, we chose a relatively lenient threshold ($p < 0.005$ uncorrected), thereby reducing the chance of falsely observing an absence of effects outside RLPFC due to lower detection power of the voxel-based analysis following normalization. Contrasts were overlaid on the canonical MNI normalized anatomical template provided by SPM 5. All coordinates are reported in MNI space.

Brain recruitment associated with meta-cognitive awareness prior to training

To examine the brain regions associated with following meta-cognitive awareness regulation strategy in training-naïve subjects, the

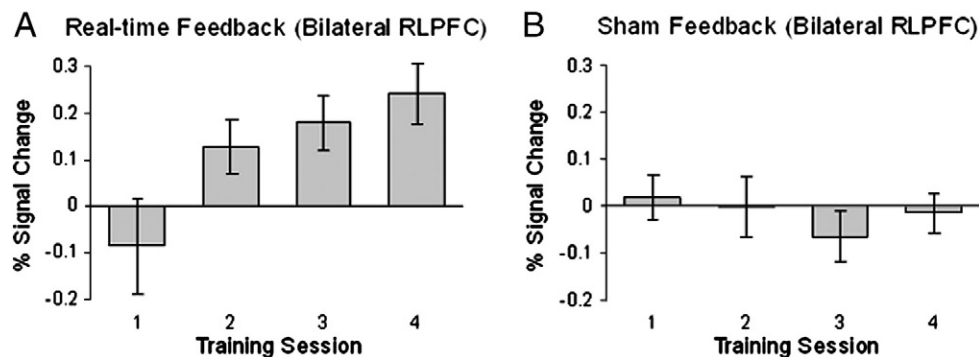


Fig. 3. Mean percent signal change (up- versus down-regulation blocks) for the 4 training sessions in the (A) experimental and (B) sham control group. Error bars indicate standard error of the mean.

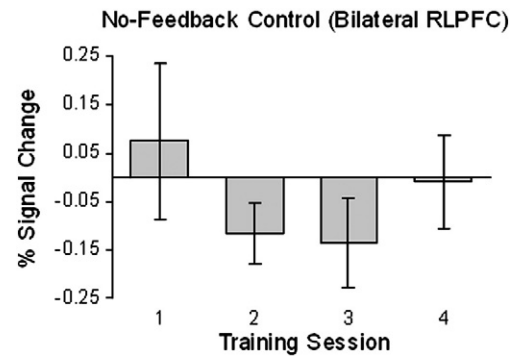


Fig. 4. Mean percent signal change (up- versus down-regulation blocks) for the 4 training sessions in the no-feedback control group. Error bars indicate standard error of the mean.

no-feedback pre-training session during which subjects observed no feedback but followed otherwise identical regulation instructions was examined by performing a voxel-based whole-brain analysis to contrast up-regulation with down-regulation blocks. All 30 subjects were included in this analysis.

Results

ROI-based analysis

The experimental group who saw real-time feedback showed significant improvement in regulating RLPFC activation over the course of training (Fig. 3A), as revealed by a significant main effect of session in a one-way ANOVA ($F_{3,33} = 2.80$, $p < 0.05$) on % signal change values within the bilateral RLPFC ROI. During the first training session, the mean difference between up-regulation and down-regulation blocks across subjects ($M = -0.09\%$ signal change) was not significantly different from zero ($T_{11} = 1.16$, $p = 0.27$). Over the course of training, however, modulation ability increased by a mean of $M = 0.33\%$ signal change improvement from sessions 1 to 4 ($T_{11} = 2.06$, $p < 0.05$). Verbal debriefing after each training session indicated that all subjects relied upon some form of observation of their own thoughts as an up-regulation strategy. Conversely, during down-regulation blocks, most subjects reported that they focused on external sensory information (e.g., the fluctuating thermometer bar on the screen, sounds of the MRI scanner) or noticing bodily sensations as a down-regulation strategy.

In order to ensure that improvement in modulation ability in the experimental group was specifically due to the presence of real-time feedback, we compared learning in this group to a sham-feedback control group (Fig. 3B). The experimental group showed significantly greater improvement in modulation ability compared to the sham-feedback group, as revealed by a significant linear interaction between

session and group ($F_{1,22}=4.37, p<0.05$) in a two-way, mixed-model ANOVA. Furthermore, the sham-feedback control group showed no significant improvement with training ($F_{3,33}=0.33, p=0.80$). On average, sham-feedback subjects showed a non-significant ($T_{11}=0.47, p=0.65$) decrease of modulation ability in the course of training, with an average of 0.034% signal change decline in modulation ability from session 1 to 4 (Fig. 3B). Post-experiment debriefing confirmed that each sham-feedback subject believed they were receiving veridical feedback from their own RLPFC.

Similar to the control sham-feedback group, the additional 6 no-feedback control subjects who underwent otherwise identical training to the experimental group, but without rt-fMRI feedback, showed no improvement with training, as demonstrated by a non-significant ($F_{3,15}=0.73, p=0.55$) decrease in modulation ability ($M=-0.083\%$ signal change) from sessions 1 to 4 (Fig. 4).

Voxel-based analysis comparing modulation improvement in the rt-fMRI versus the sham-feedback group

In order to examine the spatial specificity of modulation improvement, we performed a whole-brain analysis directly contrasting modulation success in the real-time feedback and the sham-feedback groups. This analysis revealed a highly localized pattern of modulation improvement that was greater in the experimental, relative to the control group (see Fig. 5 and Table 1). Consistent with the ROI-based results, modulation improvement was observed in RLPFC (BA10; $x, y, z=44, 52, -4$), indicating significantly greater improvement in the rt-fMRI group than the sham-feedback group in this region. Interestingly, this effect was specifically observed in right RLPFC. Modulation improvement was spatially localized to RLPFC and was not observed in any other frontal lobe regions. The only other regions exhibiting greater improvement in modulation between the two groups were the insula ($x, y, z=40, 12, 0$), putamen ($x, y, z=26, -16, 16$), middle temporal gyrus ($x, y, z=-40, -42, 4$), and thalamus ($x, y, z=20, -30, 4$).

At the same statistical threshold, there were no regions showing a greater decrease across training sessions in the real-time feedback versus the sham-control group.

Brain recruitment associated with meta-cognitive awareness prior to training

Following the meta-cognitive awareness regulation strategy during the no-feedback pre-training session (contrasting up- versus down-regulation blocks) was associated with activation throughout BA10, including both medial BA 10 ($x, y, z=-10, 68, 20$) and RLPFC ($x, y, z=-16, 62, 16$). Additional regions exhibiting activation in this contrast were the left inferior frontal gyrus (BA 45; $x, y, z=-42, 24, -8$) extending into the anterior insula, posterior cingulate cortex (BA 23; $x, y, z=-6, -56, 24$), left temporoparietal junction ($x, y, z=-42, -58, 28$), subgenual anterior cingulate cortex (BA 25; $x, y, z=0$,

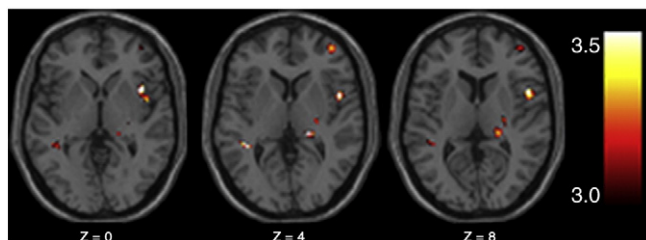


Fig. 5. Two-sample *t*-test contrasting modulation improvement in the real-time feedback group versus the sham-feedback control group. The real-time group displayed greater BOLD response within RLPFC, insula, putamen, and thalamus (pulvinar) based on linear contrast examining areas of increased modulation over the course of four real-time training sessions ($p<0.005, k>20$).

Table 1

Foci of activations from the voxel-based whole-brain analysis identifying regions of significantly greater modulation improvement in the real-time feedback group ($N=12$) compared to the sham-control groups ($N=12$) ($p<0.005, k>20$).

Region	BA	X	Y	Z	N voxels	Z-value
RLPFC	10	42	52	4	32	2.99
Insula	-	40	12	0	84	3.91
Thalamus	-	20	-30	4	26	3.34
Putamen	-	26	-16	16	43	3.08
MTG	21	-40	-42	4	23	3.21

BA = Brodmann area; RLPFC = rostralateral prefrontal cortex; MTG = middle temporal gyrus. All coordinates are reported in MNI space.

14, -16), right parahippocampal cortex ($x, y, z=36, -38, 0$), and right cuneus (BA 17; $x, y, z=22, -76, 12$) (see Fig. 6 and Table 2).

Discussion

The present results show that by using rt-fMRI feedback and a meta-cognitive awareness strategy, subjects were able to achieve enhanced control over the level of activation in their RLPFC. While the experimental group who saw veridical rt-fMRI feedback showed significant improvement in regulating RLPFC activation over the course of training, a sham-feedback control group who saw rt-fMRI feedback from another subject, but believed they were receiving veridical feedback from their own RLPFC, did not show such improvement. This comparison between the experimental and sham-feedback control group indicates that rt-fMRI information played a critical role in the learning process. Prior to training, meta-cognitive awareness was associated with recruitment of anterior PFC subregions, including both RLPFC and medial PFC, as well as a number of other midline and posterior cortical regions. Following rt-fMRI training, however, the regulation effect was specific to RLPFC and was not observed in other frontal, midline, or parietal cortical regions. Thus, while subjects were able to partially regulate RLPFC using meta-cognitive strategy prior to training, this regulation was significantly improved both in magnitude and in spatial specificity following rt-fMRI training. Furthermore, an additional control group of 6 no-feedback subjects who underwent otherwise identical training to the experimental group and followed the same regulation instructions but without observing rt-fMRI feedback, did not show improvement in RLPFC modulation ability, further suggesting that rt-fMRI

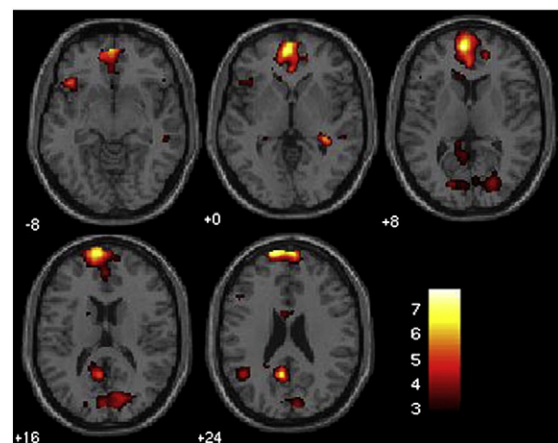


Fig. 6. Brain modulation associated with meta-cognitive awareness in the absence of rt-fMRI feedback. One-sample *t*-test contrasting up-regulation versus down-regulation blocks during a no-feedback session conducted prior to training during which subjects followed the meta-cognitive awareness instructions without observing any real-time feedback (image displayed at a threshold of $p<0.005, k>20$). Activated regions include RLPFC, medial PFC, left temporoparietal junction, left inferior frontal gyrus/anterior insula, posterior cingulate cortex, subgenual anterior cingulate cortex, parahippocampal and cuneus.

Table 2

Foci for activations associated with following meta-cognitive awareness regulation strategy (up- versus down-regulation) in training-naïve subjects. Group results ($N=30$) are from a pre-training session, during which subjects observed no rt-fMRI feedback but otherwise followed identical regulation instructions ($p<0.001$, $k>20$).

Region	BA	X	Y	Z	N voxels	Z-value
MPFC	10	−10	68	20	1009	4.77
MPFC	10	−4	54	0	−	4.74
RLPFC	10	−16	62	16	−	3.87
PCC	23	−6	−56	24	154	4.41
Right PHC	−	36	−38	0	43	4.21
Left TPJ	39	−42	−58	28	48	4.11
Left IFG/Insula	45	−42	24	−8	50	4.02
Subgenual ACC	25	0	14	−16	30	3.94
Right Cuneus	17	22	−76	12	83	3.46

BA = Brodmann area; ACC = anterior cingulate cortex; MPFC = medial prefrontal cortex; RLPFC = rostrolateral prefrontal cortex; IFG = inferior frontal gyrus; PCC = posterior cingulate cortex; TPJ = temporoparietal junction; PHC = parahippocampal cortex. All coordinates are reported in MNI space.

information helped to guide RLPFC regulation above and beyond simply following a cognitive regulation strategy.

This successful improvement in ability to regulate RLPFC demonstrates that subjects are capable of gaining improved control over a brain area associated with some of the most complex, abstract cognitive processes (Badre and D'Esposito, 2009; Boorman et al., 2009; Braver and Bongiolotti, 2002; Bunge et al., 2005; Christoff et al., 2009a,b, 2001, 2004; Greene et al., 2004; Huettel, 2006; Koechlin et al., 1999; Kroger et al., 2002; Monti et al., 2007; Rugg and Wilding, 2000; Velanova et al., 2003). While previous rt-fMRI feedback training studies have shown that subjects could learn to regulate activation within the sensorimotor cortex by imagining hand movements (deCharms et al., 2004), the insula by recalling personal, affectively charged events (Caria et al., 2007), the anterior cingulate by attending to and away from the painful properties of a stimulus (deCharms et al., 2005), and the inferior frontal gyrus through the use of various strategies involving sub-vocal speech (Rota et al., 2009), here we show that subjects can use an abstract mental process such as meta-cognitive awareness of one's own thoughts to regulate activation levels in one of the highest-order cortical association regions.

The finding that subjects learned to regulate RLPFC activation by turning their attention towards and away from the contents of their own thoughts, presents new evidence in support of the previously established connection between anterior PFC and meta-cognitive awareness (Stuss, 2007; Stuss and Levine, 2002; Wheeler et al., 1997) and between RLPFC and meta-awareness of one's own thoughts in particular (Christoff & Gabrieli, 2000). Furthermore, the finding that regulation improvement effects were specific to RLPFC and were not observed in other frontal, midline, or parietal cortical regions, demonstrates that rt-fMRI training can be regionally specific. This finding is consistent with prior work (Caria et al., 2007; deCharms et al., 2004, 2005; Rota et al., 2009) showing that regulation improvement can be spatially localized to a particular and relatively small target ROI. In our dataset, however, training effects that paralleled RLPFC regulation improvement in the course of training were observed in a number of subcortical structures, including the insula, putamen, and thalamus. These regions' modulation improvement in the course of training could reflect an increased recruitment of a larger cortical-subcortical circuit supporting meta-cognitive awareness. The insula in particular seems to play an important role in meta-awareness of interoceptive states and emotions (Craig, 2009; Critchley et al., 2004). Furthermore, Farb et al. (2007) found a significant correlation between activation in the insula and lateral prefrontal cortex, including RLPFC, in mindfulness trained subjects who were asked to become aware of their thoughts, feelings, and body states. Finally, these subcortical regions are known to have direct anatomical connections with the anterior PFC (Petrides and Pandya,

2007). While the present results demonstrate that it is possible to achieve regionally specific training effects confined to a single higher-level prefrontal region, the way in which such regionally specific effects are enabled through cortical-subcortical circuitry remains an important issue for further investigation.

There is now compelling evidence for relative regional specialization within the anterior prefrontal cortex, in particular between medial and lateral sectors (Gilbert et al., 2006a,b). Working memory, episodic retrieval, and abstract thought (Badre et al., 2009; Braver et al., 2002; Christoff et al., 2009b; Rugg et al., 2000; Velanova et al., 2003), especially when they involve meta-cognitive evaluation (Christoff et al., 2000) appear to call upon the lateral, rather than the medial sector. On the other hand, reflecting upon one's own emotions activates primarily the medial, rather than the lateral sector (Lane et al., 1997; Ochsner and Gross, 2005; Ochsner et al., 2004a). The present findings are broadly consistent with this distinction, in that subjects were able to learn to modulate the lateral sector, RLPFC, using meta-awareness of their thoughts as a strategy and with no indication of changes in the medial anterior PFC. It is possible, therefore, that both medial and lateral anterior PFC sectors contribute to meta-cognitive awareness but may be differentially recruited based on whether or not the mental content being reflected upon is affectively charged.

While employing meta-cognitive awareness as a regulation strategy during the no-feedback session prior to rt-fMRI training was associated with partial RLPFC recruitment, the overall pattern of activation extended beyond RLPFC to include robust recruitment of medial BA10, as well as activation of the posterior cingulate cortex (PCC), the temporoparietal junction (TPJ), inferior frontal gyrus and middle temporal gyrus. This pattern of recruitment is remarkably similar to the pattern of activations observed in studies on self-reflective processing (D'Argembeau et al., 2007; Farb et al., 2007; Northoff and Berman, 2004; Ochsner et al., 2005, 2004a; Schmitz et al., 2004), showing that these areas, particularly the medial PFC and PCC, are consistently activated when individuals reflect on self-related traits and feelings. However, these same areas in conjunction with the TPJ, are also recruited when contemplating the thoughts of other people (Amodio and Frith, 2006; Gallagher et al., 2000; Saxe and Kanwisher, 2003), suggesting a broader role in mental reflective processing in general (Buckner and Carroll, 2007; Christoff, Cosmelli, Legrand, & Thompson, 2011). Thus, considering the overall pattern of activation, it is possible that during the initial no-feedback regulation session, subjects engaged not only in meta-awareness of their own thoughts but also in broader mental processes of a general reflective nature. Indeed, such broad reflective processes of relating mental contents to the self appear to be the natural or default tendency in training naïve individuals who are instructed to turn their attention towards internal mental content (Farb et al., 2007).

Given the wide range of cognitive processes that have been linked to RLPFC, it has been difficult to ascribe a core function to this region. Perhaps the most agreed upon idea is that this region monitors and coordinates the outputs of prior stages of high-level cognitive processing (Christoff and Gabrieli, 2000; Fletcher and Henson, 2001; Petrides, 2005; Ramnani et al., 2004; Tsujimoto et al., 2010). The fact that anatomically, the RLPFC is predominantly connected to multimodal association areas in the superior temporal and posterior frontal cortices (Petrides and Pandya, 2007) supports this idea. Moreover, based on evidence that the dorsolateral prefrontal cortex (DLPFC) plays a role in monitoring the contents of working memory and the hierarchical anatomical relationship between the DLPFC and the RLPFC, it has been suggested that RLPFC may monitor the monitoring process in DLPFC (Christoff and Gabrieli, 2000; Fletcher and Henson, 2001; Petrides, 2005). Additional kinds of meta-monitoring have been suggested through interactions between RLPFC and other brain regions such as the inferior frontal, pre-motor, and insular cortices (Sakai and Passingham, 2006; Koechlin et al., 2003; Farb et al., 2007). Thus, the RLPFC

may allow us to become aware that we are aware of something — a self-reflective knowledge of our mental contents. The considerable expansion of this region during the course of primate evolution (Semendeferi et al., 2001) may, therefore, be at least in part linked to the remarkable levels and varieties of self-awareness possessed by humans (Wheeler et al., 1997).

While this study makes a significant step towards exploring the mechanisms of volitional control over higher-order, multimodal brain regions, a number of questions remain to be addressed by future research. One of the important outstanding issues is the precise mechanisms by which modulation improvement occurs. Both explicit (e.g., rule-based) and implicit (e.g., reinforcement-based) learning processes may contribute to improved modulation. However, the extent to which each plays a role is currently unknown. A complicating factor is that subjects have limits on introspective access to higher cognitive processes (Nisbett and Wilson, 1977) and therefore, on accurately reporting the use of a particular cognitive strategy or explicit learning mechanism. One possible venue for future research is to utilize special populations that are trained in introspective access such as expert meditators who may be able to more accurately report on and elucidate the role of explicit mechanisms in the learning process. Additionally, such expert populations may be able to better instantiate distinct cognitive strategies and as a result, may facilitate the testing of hypotheses regarding the functional roles of distinct regions including the lateral, versus the medial, anterior PFC. Another important issue that will need to be addressed by future work is the behavioral significance of modulation improvement. Learning to regulate particular brain regions is only important to the extent that there are corresponding changes in the emotional and cognitive mechanisms supported by those areas and this is especially the case for clinical applications of rt-fMRI training. Studies that specifically aim to examine the behavioral consequence of rt-fMRI training may, through incorporating behavioral tasks into rt-fMRI training protocols, be able to assess potential differences that emerge after real-time training.

In summary, the present demonstration of the feasibility of training high-level prefrontal regions with rt-fMRI supports the notion that this novel methodology represents a valuable new tool for cognitive neuroscience (deCharms, 2007, 2008), able to provide a direct link between highly subjective mental experiences and observable neuroscientific measures. By allowing subjects to see a reflection of their own thought processes in the measured brain activation, rt-fMRI offers a new method for examining the correspondences between highly subjective mental states and neural processes. While a number of questions, including the long-term retention, behavioral significance, and mechanisms for achieving modulation ability, still await further research, this technology already offers new avenues for scientific hypothesis testing and clinical interventions, as well as the promise to enrich our subjective knowledge of the workings of our own minds.

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Appendix 1

General instructions

We are interested in whether people can learn to control the activation in the RLPFC. This region usually becomes activated when people turn their attention internally, towards their own thoughts. Becoming aware of your thoughts would activate this region.

Becoming aware of external sensations (e.g., how your hands feel) would tend to deactivate it. During up-regulation, try to increase activity in your RLPFC by becoming aware of your own internal thoughts and mental processes. During down-regulation, try to decrease activity in your RLPFC by turning your attention away from your own thoughts and directing it towards external perceptions (e.g., touch, vision).

Specific strategies for up- and down-regulation

Up-regulation

In general, try to turn your attention inwards and try to observe your thoughts as they happen. Try letting your thoughts occur by themselves and simply become aware of them, as they arise spontaneously. You could try “labeling” your thoughts as they occur by noticing the nature of any thoughts that appear, e.g. “planning”, “rehearsal”, “worrying”, “judging”. Other kinds of categories are also possible, (e.g., “memory”, “fantasy”). Feel free to come up with your own categories. Try to be accepting towards all thoughts that occur and to use neutral categories (i.e., try to avoid judgments such as “a bad thought” or “a good thought”).

Down-regulation

In general, try to turn your attention away from your thoughts, towards external sensations. For example, try becoming aware of different parts of your body: your hands, your feet, legs, etc. You could also become aware of where your hands are in space, how they feel, etc. Or, you could simply let your attention jump from one part of your body to the next, and label the location (e.g., knee, toes, elbow, etc.). You could also “scan” your entire body for sensations, starting from your head, to your shoulders, and finishing with your feet.

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