REGULATING THE ANTERIOR MEDIAL PREFRONTAL CORTEX: EXPLORATORY INVESTIGATION OF REAL-TIME fMRI TRAINING

by

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Abstract

The feasibility of using real-time functional magnetic resonance imaging (fMRI) feedback regarding the level of activation in rostromedial prefrontal cortex (rMPFC) to learn improved regulation of this brain area was examined in a group of 5 young adults. Subjects received real-time feedback from the target brain region while engaging in a blocked-design task involving alternating blocks of attempted up-regulation and down-regulation of the target brain region. A transient negative emotional state was induced prior to each scanning session. Subjects completed 6 scanning sessions (a pre-training session, 4 feedback sessions and a post-training session - no feedback was provided for pre and post-training sessions). The guideline strategy provided to subjects of engaging in emotional awareness during up-regulation and bodily awareness during down-regulation was found to consistently regulate the region in the pre-training session prior to the fMRI feedback sessions. This finding is in line with the previously proposed role of the rMPFC in emotional awareness. In contrast to previous real-time fMRI findings, greater recruitment of the region was observed in the pre-training session compared to the post-training session, with a non-significant negative trend observed across feedback sessions. These results suggest that there may be limitations to which the feedback techniques successfully employed for other brain regions extend to yet unexplored brain regions.

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1. Introduction

It is a common human tendency to think about the emotional states and moods we experience. Whether reflecting on our emotions in response to the present situation or reminiscing on our feelings about a past event, emotional awareness takes up a substantial portion of our daily personal introspection. Emotional awareness (also referred to as reflective awareness) can be defined as attending to and reflecting on one's own emotional experience (Lane & McRae, 2004). Functional neuroimaging research has demonstrated the involvement of the rostromedial prefrontal cortex (rMPFC –medial aspect of Brodmann areas (BA) 10 and 9) in this process (Bechara, Damasio, Damasio, & Lee, 1999; Lane, Fink, Chau, & Dolan, 1997; Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner, Knierim et al., 2004; Ochsner, Ray et al., 2004). While emotional awareness can be useful in helping us to identify and learn from our emotional experiences, it can become maladaptive when one begins to focus excessively on negative thoughts and emotions as occurs with rumination.

While rumination has been generally defined as a passive, repetitive focus on one's symptoms of distress and on the meanings of those symptoms (Nolen-Hoeksema, 1998) and the tendency to focus on negative aspects of self and negative interpretations of events (Ray et al., 2005), two forms of ruminative self-focus have been identified: experiential (concrete, process-focused) and conceptual-evaluative (abstract, analytic) self-focus (Moberly & Watkins, 2006; Watkins, 2004). Experiential self-focus is characterized by a non-evaluative, intuitive, direct experiential awareness of moment-by-moment experience while conceptual-evaluative self-focus is characterized by analytic,

meta-cognitive thinking about the self with a focus on the causes, meaning, consequences and implications of self-experience (Moberly & Watkins, 2006; Watkins, 2004) .

Experiential self-focus has been associated with more positive outcomes, while conceptual-evaluative self-focus has been associated with a greater number of negative intrusions (following negative mood induction) and more over general memory and increased global negative self-judgements (in depressed individuals) (Watkins, 2004); (Rimes & Watkins, 2005; Watkins & Teasdale, 2004). A number of studies have explored the links between rumination and depression. These studies have provided evidence that a ruminative response style (referring here to the conceptual-evaluative form) contributes to the development of depression and that rumination can lead to increased negative mood in depressed individuals, an increase in negative thoughts and emotions regarding past events and an increased focus on negative future events (Kuehner & Weber, 1999; Lavender & Watkins, 2004; Nolen-Hoeksema, 1998; Nolen-Hoeksema & Morrow, 1991). These findings suggest that individuals with depression have a deficit in their ability to properly regulate their emotions with an increased awareness of their negative emotions. Traditionally, cognitive behavioural therapy (CBT) and/or pharmacological interventions have been used to address the mood disturbance associated with this emotion dysregulation (Gross & Munoz, 1995). A relatively novel methodology known as real-time functional magnetic resonance imaging (real-time fMRI) has recently emerged, which presents a potential alternative method to bring about a beneficial change in the cognitive processes involved in emotion regulation by first helping the individual to learn to modulate the neural processes proposed to underlie these emotion regulatory processes.

1.1 Real-time functional Magnetic Resonance Imaging

Real-time fMRI presents the unique opportunity to present subjects with feedback regarding the level of activity in a given brain region(s) while they are being scanned. Unlike traditional fMRI where data is first acquired then activation results are computed at a later time, real-time fMRI allows for the activation results to be computed simultaneously with data acquisition, with a delay of 1-3 seconds (deCharms, 2007; Posse et al., 2001). As such, participants can directly monitor the effect of particular mental processes on activation in selected brain region(s). Early investigations utilizing this technique illustrated the feasibility of using feedback presented with a delay of approximately 60 seconds to influence the resulting brain activation (Posse et al., 2003; Yoo & Jolesz, 2002). These early studies focused on regions with well-defined functions, such as the somatosensory cortex and amygdala. Yoo and Jolesz displayed functional maps to their subjects following a 60 second period during which subjects engaged in alternating blocks of rest and finger movements. The authors reported an increase in the extent of activation of the somatosensory cortex following feedback training. In a study focusing on sadness induction, Posse et al. (2003) provided subjects with a rating of amygdala activation and found an increase in amygdala activation correlated with self-rated sadness (although the effects of training were not examined).

The first study to illustrate the ability of subjects to learn from a continuously updating feedback display with a minimal delay from the time of image acquisition (<2 seconds) was a single subject investigation focusing on the anterior cingulate (Weiskopf et al., 2003). Weiskopf and colleagues reported a trend of increasing activation in the rostral-ventral subdivision of the anterior cingulate cortex (ACC) across training sessions.

A similar effect was reported by deCharms et al. (2004) who observed an increase in percent signal change across sessions in a group of subjects engaging in imagined hand movements while viewing continuously updated real-time feedback from the somatomotor cortex. Weiskopf and colleagues (2004) demonstrated a similar effect of training on the ability of subjects to manipulate the difference in activation between the supplementary motor area and parahippocampal place area. As well, Phan and colleagues (2004) demonstrated that activation can be detected in real-time from cortico-limbic regions, namely the insula, and medial frontal cortex, while subjects view external emotional stimuli.

More recently, Caria and colleagues (2007) demonstrated that regulation of the anterior insula can be trained using real-time fMRI feedback. The potential for clinical application of real-time fMRI was explored by deCharms et al (2005) in a study of the rostral ACC in pain perception. deCharms and colleagues demonstrated that subjects could learn to control activation in the rACC and that this learned regulation was associated with changes in pain perception of both chronic pain and pain in response to a painful thermal stimulus.

While real-time fMRI overcomes a number of the limitations posed by alternate neurofeedback methods, such as electroencephalography (EEG) feedback, which is limited by poor spatial localization and single neuron recordings and local field potentials, which require invasive procedures, some limitations remain (deCharms, 2007). These include the limited temporal resolution due to the nature of the blood-oxygen-level dependent (BOLD) response, which takes approximately 2 seconds to develop and 6 seconds to reach its peak, limited spatial resolution (as compared to that of

neurons) and noise in the data arising from signal drop out/distortion, motion artifacts and global fluctuations in signal intensity (due to changes in respiration) (deCharms, 2007). Given the potential advances this technology may bring about both in basic science and in clinical settings, it is a worthwhile endeavour to work towards overcoming these limitations. Furthermore, despite the limitations inherent in real-time fMRI, the promising results outlined above coming from various investigative groups, focusing on different brain regions and employing varying task instructions, highlight the potential importance of this method for understanding and shaping both normal and pathological cognitive and neural processes.

1.2 The Anterior Medial Prefrontal Cortex as a Target for Regulation

The anterior MPFC represents an intriguing regulation target for real-time fMRI training for multiple reasons. First, the theoretical question of how far the positive findings from previous real-time fMRI studies extend in terms of which brain areas individuals are able to learn to regulate using this method remains to be addressed. There is additional motivation beyond this theoretical interest, however, which comes from findings in both healthy and depressed individuals suggesting that alterations in activity of this region may be of clinical significance. The limbic-cortical dysregulation model of depression proposes that the rMPFC is one of many brain regions with abnormal functioning in depression (Mayberg, 2003). In support of the involvement of the rMPFC in depression, deactivations have been observed in this region during transient sadness in both remitted and acutely depressed individuals, which are not observed in healthy individuals (Liotti, Mayberg, McGinnis, Brannan, & Jerabek, 2002). In addition,

abnormal activation of the rMPFC not specific to transient sadness in individuals suffering from depression has been reported (Drevets, 2001). The remediation of this abnormal activation as evidenced by reduced activity in the MPFC following cognitive therapy, suggests a link between alterations in cognition and changes in brain activation (Goldapple et al., 2004). Furthermore, changes in fronto-frontal pathways distinguish between patients who responded to CBT versus those who responded to anti-depressant (paroxetine) treatment (Seminowicz et al., 2004).

Two recent studies in healthy individuals provide additional evidence in support of altered activation in rMPFC following changes in cognitive style (Davis IV et al., 2008; Farb et al., 2007). Davis and colleagues examined the effects of a short cognitive intervention (CI) on the neural correlates of negative self-reference in a group of elite athletes. Prior to and after participating in a short CI, athletes viewed videos of their failed performances while re-experiencing the way they felt during and after the performance. Greater activation was reported in both ventral and dorsal MPFC during the first failure viewing prior to the CI as compared to the viewing following the CI. A similar decrease in activation of the rMPFC was reported by Farb and colleagues who found a greater decrease in activation in the rMPFC in a group of individuals who had undergone a course in mindfulness training as compared to a novice group who did not undergo such training. The mindfulness course involved exercises concerned with focusing on present moment experience. While viewing trait words, subjects engaged in narrative self-focus (focusing on personal relevance) and experiential self-focus (focusing on present moment experience – noticing rather than judging). Consistent with findings from previous studies examining self-referential processing (e.g. Fossati et al., 2003;

Johnson et al., 2002; Northoff et al., 2006; Schmitz, Kawahara-Baccus, & Johnson, 2004), the MPFC was found to be activated for narrative versus experiential self-focus for both groups. In addition, the mindfulness group exhibited greater decreases in rMPFC when they engaged in experiential self-focus compared to narrative self-focus than the novice control group, thus, providing evidence for changes in the functioning of this brain region as a result of mindfulness training.

In sum, given the findings of altered activation in the rMPFC following changes in cognitive style in both healthy and depressed individuals, this region appears to represent a prime target for real-time fMRI training. While the ultimate aim would be to develop a real-time fMRI training protocol which could be used in combination with CBT to help correct the emotion dysregulation associated with depression and thereby, potentially help decrease depression relapse, it is necessary to first explore the ability of healthy, motivated individuals to learn to modulate activation in this brain region using real-time feedback of the level of activation in this region as they engage in emotion reflective processing.

1.3 Dorsal versus Ventral Anterior Medial Prefrontal Cortex

There has been much debate over potential functional dissociations between dorsal and ventral MPFC. Phan and colleagues (2002) reported that the MPFC is consistently activated across multiple emotions (e.g. happiness, sadness, anger) and emotion induction tasks and suggested that this may be due to the involvement of processes such as emotional evaluation and regulation across emotion tasks. Their meta-analysis failed to find support for an affective-cognitive division along the dorsal-ventral axis of the MPFC as has been reported for the ACC (Bush, Luu, & Posner, 2000). In contrast, Steele and

Lawrie (2004) in their meta-analysis of fMRI and PET studies of cognitive and emotional tasks involving the lateral and medial prefrontal cortices found support for the assertion that this distinction extends beyond the ACC. They reported a tendency for emotion induction activation loci (mean MNI coordinates: 5, 46, 18) to fall inferior to cognitive task activation loci (mean MNI coordinates: 5, 28, 31) although there was substantial overlap in activation areas. Gilbert and colleagues' (2006) meta-analysis of BA10 activation loci reported a significant difference between lateral and medial BA10 in terms of emotional processing with medial BA10 more consistently activated for studies of emotion, thus, providing further support for a role of this region in emotional awareness. Moreover, medial BA10 was found to be most consistently activated for tasks involving both emotional materials and mentalizing (reflecting on one's own or on another's emotional and mental state). The authors also tested for a dorsal-ventral distinction within medial BA10, but failed to find a significant distinction.

1.4 Research Approach and Objectives

The present study aimed to explore the ability of healthy individuals to learn to modulate activity in their rostromedial prefrontal cortex based on feedback presented to them in real-time regarding the level of activity in this region. An additional aim was to further explore the role of the rMPFC in emotion reflective processes. A transient negative emotional state was induced prior to each scanning session. Subjects were provided with initial task instructions for regulation of the target region. The up-regulation strategy (referring to up-regulation of the target brain region – the rMPFC) involved engaging in emotional awareness. Bodily awareness of the sensations arising in association with the emotions was selected as the down-regulation strategy (referring to

down-regulation of the target brain region) with the purpose of both down-regulating the activity in the rMPFC and providing an alternative perspective from which to experience the negative emotions which may result in a decreased level of experienced negative affect.

Given the unresolved debate over functional specialization within rMPFC along the dorsal-ventral axis, to avoid potential difficulties which may arise due to differences in activation and deactivation between dorsal and ventral rMPFC we chose to provide real-time feedback regarding the level of activity in the more dorsal aspect of rMPFC (dorsal BA10 extending into BA9) rather than from the rMPFC as a whole. We chose to focus on the more dorsal aspect of this region due to the consistently reported finding of its recruitment during emotional awareness (e.g. Lane, Fink, Chau, & Dolan, 1997; Ochsner, Ray et al., 2004; Gusnard, Akbudak, Shulman, & Raichle, 2001). However, data was collected from the entire expanse of the anterior MPFC allowing for later exploration of the extent of activation in the MPFC.

1.5 Hypotheses

It was predicted that the rMPFC would be selectively recruited when subjects focused their attention and reflected on the emotions experienced in association with an emotionally significant sad personal memory. More specifically, it was predicted that activity in this region would increase when subjects engaged in emotional awareness and decrease when they engaged in awareness of the sensations that arose associated with the emotions (bodily awareness). Moreover, it was hypothesized that subjects could learn improved regulation of the level of activity in the rMPFC using real-time fMRI feedback provided to them while they engaged in the above processes. This learning was predicted

to be evident in improved modulation in a post-training session in the absence of real-time feedback compared to a pre-training session also without real-time feedback.

2 Methods

2.1 Subjects

Ten subjects (21-31 years of age, M=25.7; 7 female) from the Vancouver community gave their written consent to participate and received $20/hour as compensation. Subject numbers have been randomly assigned and do not reflect the order in which the data was collected. One subject was excluded due to excess motion (range of motion >3mm, subject six). Three subjects were excluded due to excess motion combined with high task-correlated motion in the same sessions (range of motion >2mm within session, $r > 0.3$, subjects seven, eight and nine – See Appendix A for motion parameters). One subject was excluded due to signal dropout along the anterior expanse of the frontal cortex (subject nine). Included subjects ranged from 22-28 years of age (M=25); 4 female, 1 male. All subjects had normal or corrected vision, had no history of psychiatric illness and were screened for MRI compatibility. Procedures were approved by the UBC Clinical Research Ethics Board and by the UBC High Field Magnetic Imaging Centre.

2.2 Clinical and Personality Measures

Prior to the scanning session, subjects completed a series of questionnaires, including the Rumination-Reflection Questionnaire (RRQ), the Kentucky Inventory of Mindfulness Skills (KIMS), the Big Five Inventory-44 (BFI-44) and the Beck Depression Inventory (BDI). The first 4 questionnaires were administered to assess the tendency to ruminate versus reflect, mindfulness factors and the big five personality traits of

neuroticism, extraversion, openness, agreeableness and conscientiousness, respectively. The BDI was administered to screen for depression.

2.3 fMRI Data Acquisition

Data acquisition was performed using a 3.0 Tesla 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 participant's head to obtain the MRI signal. Head movement was restricted using a memory foam pillow around the head. The functional volumes contained BOLD contrast intensity values and 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) = 224 x 244 x 67 mm; matrix size 64 x 64, SENSE factor = 2.0]. The volumes consisted of 17 slices (each 3 mm thick, separated by a 1 mm inter-slice gap) excluding the most inferior part of the brain for the motor task and the most superior part for the MPFC regulation task acquired parallel to the anterior commissure/posterior commissure (AC/PC) line. 365 functional volumes were acquired in this orientation for each participant per each 6 minute session. Subjects completed 6 sessions. Prior to functional imaging, an inversion recovery prepared T1-weighted fast spin-echo anatomic volume was obtained for each participant (TR = 2000 ms; TE = 10 ms; spin echo turbo factor = 5, FA = 90°; FOV = 224 x 224 mm; acquisition matrix 240x235; reconstructed matrix 480x470, inversion delay IR = 800 ms), containing 17 slices (3 mm thick, separated by 1 mm skip) acquired in the same slice locations used for functional images and was used for region of interest (ROI – referring to the region from which real-time feedback was provided to the subject) specification. Following

completion of the functional imaging runs, a high resolution 3DT1 anatomical volume (TE = 3.5 ms; TR = 7.7 ms; FOV = 256 x 200 x170; acquisition matrix 256 x 200; 1x 1x1 isotropic voxels) was acquired for normalization and spatial localization of activations.

2.4 Pilot Study

Real-time studies of higher order regions which are involved in a number of cognitive processes such as the rostral ACC and the insula, have generally reported that subjects require initial task instructions in order to learn from the feedback display (e.g., Caria et al, 2007; DeCharms et al, 2005). In light of this, one subject underwent pilot testing to determine the best strategy to provide subjects which would involve a process relevant to emotional reflection and regulation and would reliably recruit the rMPFC. Four combinations of strategies involving engaging in different reflective processes while re-experiencing a negative emotional event were piloted. The two up-regulation strategies which were tested were emotional self-awareness and self-relevant reflection. Emotional self-awareness involved focusing on the emotional aspects of the experience and labelling the experienced emotions while self-relevant reflection involved focusing on the personal significance of the event. The two down-regulation strategies were re-experiencing the event as a distant observer and focusing attention on bodily sensations associated with the experienced emotions. The pilot subject tested all combinations of these strategies in separate block design scanning sessions and tried each combination of strategies with two different emotional memories (real-time feedback was not provided during piloting). Based on this pilot testing the following strategies were selected: emotional awareness for up-regulation and bodily awareness for down-regulation.

2.5 Experimental Protocol

2.5.1 Region of interest definition

2.5.1.1 Motor task

Five dynamics consisting of the most superior 17 slices of the brain were collected to specify the ROI for the motor task. A bi-lateral rectangular area was outlined on the motor cortex on at least two upper slices.

2.5.1.2 rMPFC regulation task

Five dynamics consisting of 17 slices excluding the most superior part of the brain and the IR T1 image collected in the same alignment were used to specify the ROI for the rMPFC regulation task. The ROI was outlined on the superior frontal and medial frontal gyri of five slices (corresponding approximately to Z = +10 to +30). The uppermost extent of the lateral ventricles was used as a landmark to identify the top slice with the remaining slices consisting of the four slices falling below this slice. The ROI was initially specified manually on the IR T1 image (allowing for more precise localization as a result of its higher resolution) then mapped onto the corresponding slices of the functional volume. Voxels were then added or removed based on visual inspection to accommodate for dropout and distortion of the functional volume. The number of voxels in the ROI were subject dependent: 140 (subject one), 73 (subject two), 308 (subject three), 207 (subject four) and 200 (subject five) voxels.

2.5.2 Real-time feedback display

While being scanned, subjects were presented with a visual display containing two feedback panels and a central arrow (Fig. 2.1). The upper left panel (Fig. 2.1a) was modeled after the feedback display employed by Caria et al (2007). As such, it consisted of a fluctuating thermometer which displayed the current level of activation: rising and becoming red as the activation went above and becoming blue as it fell below the average (as indicated by the central line). The average was calculated from the first 60 second calibration period during which the subject performed the regulation task in the absence of feedback. The boundaries of the thermometer represented +/- 1% signal change. The bottom panel consisted of a history bar graph with each black bar representing the average activation during the corresponding block (Fig. 2.1b). A new black bar appeared at the end of each block. The first 2 and last 3 TRs from each block were excluded from the calculation for each bar. The white bar outline indicated the desired pattern of regulation. The central arrow acted as a cue to indicate the current regulation task (Fig. 2.1c). An upwards red arrow indicated up-regulation while a downwards blue arrow indicated down-regulation.

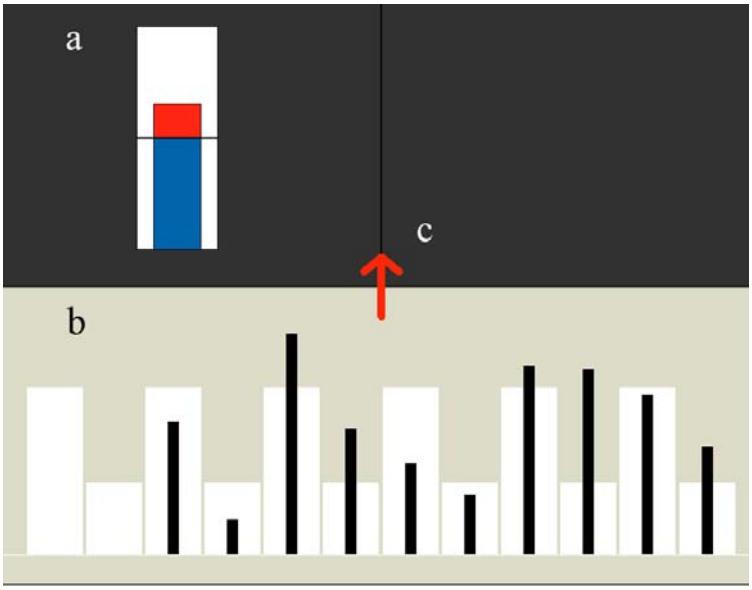


Figure 2.1: Real-time feedback display
Feedback display viewed by subjects during real-time training sessions. a) Continuously updating thermometer showing current level of activation b) History bar graph, black bars represent average activation for each session c) Arrow cue indicating type of regulation block (up-regulation shown here).

2.5.3 Task instructions

2.5.3.1 Motor task

Prior to commencing the rMPFC regulation task, subjects were familiarized with the feedback display and the delay in the activation signal due to data reconstruction and the inherent delay of the hemodynamic response, by completing a finger tapping task. This task consisted of alternating blocks of rest and finger tapping with real-time feedback provided from the motor cortex.

2.5.3.2 rMPFC regulation task

Prior to the day of scanning, subjects were instructed to come up with 3 sad personal memories of similar emotional intensity as well as a cue word to identify each of

these memories. Before the commencement of each scanning session, subjects were given one of these words as a cue to begin recollecting the memory and re-experiencing the emotions associated with that memory. Scanning began when subjects reported that they had begun to experience some level of negative affect. The instructions for increasing the activation signal (up-regulation/emotional awareness) were to focus on the emotions associated with the memory and to label these emotions. While the instructions for decreasing the activation signal (down-regulation/bodily awareness) were to focus on the bodily sensations associated with the emotions, noticing such characteristics as their quality, location and intensity, trying to stay focused on the physical qualities rather than their implications for the emotions experienced. Subjects were instructed that this task was to be used as a guideline to help them control the activation signal, but that they should attempt to use the feedback display to help them gain further control over the activation signal.

Each scanning session consisted of alternating 30 second blocks of up-regulation and down-regulation for a total of 12 regulation blocks (6 up-regulation and 6 down-regulation). The first (pre-training) and last (post-training) sessions were completed using the same memory in the absence of feedback – only the central arrow cue was provided to indicate the direction of regulation for the current block. During the middle four (or five for subject one) sessions (session 1 - 4), visual feedback regarding the level of activation in the rMPFC was provided while subjects performed the task Subjects were allowed to switch memories between the middle sessions if they felt a memory was no longer producing sufficient emotion.

2.6 Subject Debriefing

Participants verbally answered visually displayed questions following each training session (see Appendix B for list of questions). The questions consisted of rating scales to measure the strength of negative affect on a scale of 1-7 with 1 being no negative affect and 7 being strongest negative affect and a similar scale to measure the level of arousal experienced during the up/down-regulation blocks, the level of difficulty, and open-ended questions regarding the specific emotions/bodily sensations experienced. In regards to the feedback display, subjects were asked to rate how much they made use of the visual feedback display and whether they noticed a link between their attempts to modulate and the activation signal and finally, whether the feedback display was helpful.

2.7 Data Analysis

2.7.1 Real-time analysis

Data was processed in real-time using custom software programmed in C++ based on a DLL (dynamically linked library) created by Philips for the purpose of real-time data scanner acquisition. Analysis consisted of motion correction, continuous measurement of ROI activation as indexed by percent signal change from the average (based on the first 60 second calibration period). Data was temporally filtered using a second-order butterworth bandpass filter (0.0125 - 0.08Hz). In addition, the average activation level for each block was computed. Motion estimates and subsequent correction was performed on each incoming volume for subjects one and two. However, this version of the software was found to cause variability in the motion estimates that lead to an undesirable fluctuation of the signal. For subjects three, four and five motion estimates

were computed based on the first volume only and was subsequently applied to all volumes, thereby, correcting for between session motion only.

2.7.2 Off-line data analysis

Data were preprocessed and analyzed using SPM5 statistical parametric mapping (Wellcome Department of Imaging Neuroscience, London). Data underwent slice timing correction to correct for the different sampling times of the slices and was performed by interpolating the voxel time series using sinc interpolation and resampling with the middle (eighth) slice as a reference point. All functional volumes were realigned to the first volume of the 5 dynamic functional scan to correct for between-scan motion. Data was then spatially smoothed using a Gaussian kernel with 8 mm full-width at half-maximum (FWHM). To ensure that statistical analysis was confined to the brain and included brain regions where signal may have been low as a result of susceptibility artifacts, an anatomically defined gray and white matter mask was created and explicitly specified during analysis. ROI analysis was conducted on non-normalized data to minimize the impact of additional preprocessing steps, helping to ensure that the time courses obtained off-line were comparable to those observed online by the individual subjects. For group fixed effects analysis of the pre-training session and functional ROI analysis, the structural T1-weighted volume was co-registered to the mean functional image. The co-registered structural T1-weighted volume was then segmented to extract a gray matter image for each subject, which was spatially normalized (Ashburner & Friston, 1999) to a gray matter image of the MNI template and resliced to a voxel size of 2x2x4 mm. The derived spatial transformations for each subject were applied to the realigned functional volumes, in order to bring them into standardized MNI space. For

all analyses, the first three functional images from each session were excluded to account for the reconstruction delay during scanning (i.e. the lag before subjects were able to observe changes in the feedback display not attributable to the delay of the hemodynamic response function - HRF) as well as the last two images which were collected in case there was additional delay during the scan.

2.7.3 Region of interest analysis

2.7.3.1 Training ROI from scanning session

Signal time courses were extracted from the non-normalized images from every session for each individual subject using the SPM5 volumes toolbox. The extraction volume was specified using the ROI image file from the scanning session. The time course data were high and low-pass filtered to remove low frequency signal drift (0.0078 and 0.15, respectively) and linear detrended. The correlation between the mean intensity value for each time point and an HRF-convolved boxcar task function was then computed. Higher positive r-values indicated better performance (i.e. improved regulation of the target region).

2.7.3.2 Functionally defined ROI from pre-training session

Signal time courses were extracted from the normalized images from every session for each individual subject using the SPM5 volumes toolbox. The extraction volume was specified as a sphere with a 4 mm radius centred at the most significant local maxima falling within the hypothesized dorsal region of the rMPFC. The time course data were high and low pass filtered to remove low frequency signal drift (0.0078 and 0.15, respectively) and linear detrended. The correlation between the mean intensity

value for each time point and an HRF-convolved boxcar task function was then computed.

2.7.4 Pre-training session analysis

A group fixed effects analysis was conducted on the pre-training session from all 5 subjects to examine whether the given strategy consistently activated the rMPFC across subjects. Condition effects at each voxel were estimated according to the general linear model, using two regressors of interest (boxcar convolved with the canonical HRF), modeling the up-regulation and down-regulation tasks, respectively. Regionally specific effects for up-regulation were estimated by positively weighting the parameter estimate for the up-regulation regressor and negatively weighting the parameter estimate for the down-regulation regressor in a linear contrast.

2.7.5 Individual subject activation maps

To examine the pattern of activation for each session separately for each subject as well as the overlap between the ROI specified on the day of scanning and the activated area, individual sessions were specified within separate models using the non-normalized data. The contrast vector was specified in the same manner as for the pre-training session analysis.

2.7.6 Training effects

Training effects were assessed by conducting a repeated measures ANOVA on the correlations (converted to Fisher's z scores) between the signal time course and task function. Pre and post-training sessions were directly compared using a paired t-test of the contrast images from the up versus down-regulation contrast.

3 Results

3.1 Pre-training Results: Validation of Paradigm

The group fixed effects analysis of the pre-training session revealed a large cluster of activation in MPFC consisting of 1989 voxels spanning BA 9/10/11/32/24 for the up-regulation versus down-regulation contrast, $p < 0.05$ corrected (Fig. 3.1). The cluster extended from Z = -12 to +28 with the most significant local maxima located at MNI coordinates: 2, 60, -8.

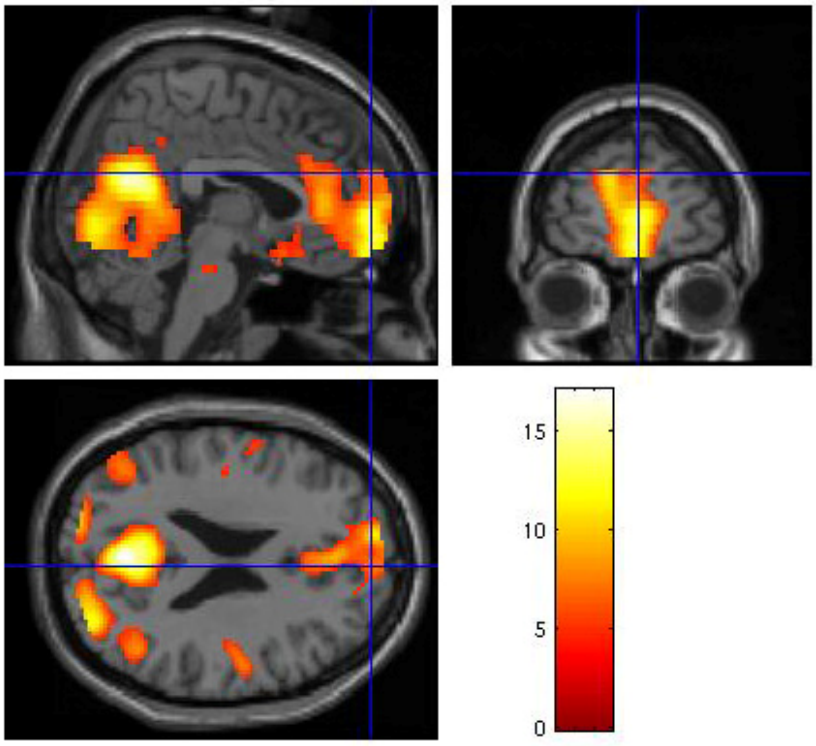


Figure 3.1: Pre-training session group analysis: up-regulation versus down-regulation contrast. Crosshairs centred at MNI coordinates: 4, 58, 24, (t = 7.20, $p < 0.05$ corrected). MNI coordinates of most significant voxel within this medial prefrontal cluster: 2, 60, -8 (t = 13.69, $p < 0.05$ corrected). Activation map is overlaid on single subject T1 template.

3.2 Clinical and Personality Measures

See Appendix C for subject scores on the RRQ, KIMS, BFI-44 and BDI.

3.3 Individual Subject Results

3.3.1 Subject One

Subject one attempted to engage in the provided strategy across sessions. The activation maps illustrate that the activated region of the ROI increased in extent and intensity at post-training compared to pre-training (Fig. 3.2). Significant positive correlations between the ROI time course and task function were observed for pre-training, session 2, 3 and post-training, $p < 0.05$ (Fig. 3.3a). A similar pattern was observed for the correlation between the functionally defined ROI time course and the task function, with positive correlations observed for all sessions with the exception of session 5 which had a negative correlation (Fig. 3.3b). The global signal was positively correlated with the task function during session 2 and negatively correlated for sessions 1 and 4 (Fig. 3.3a).

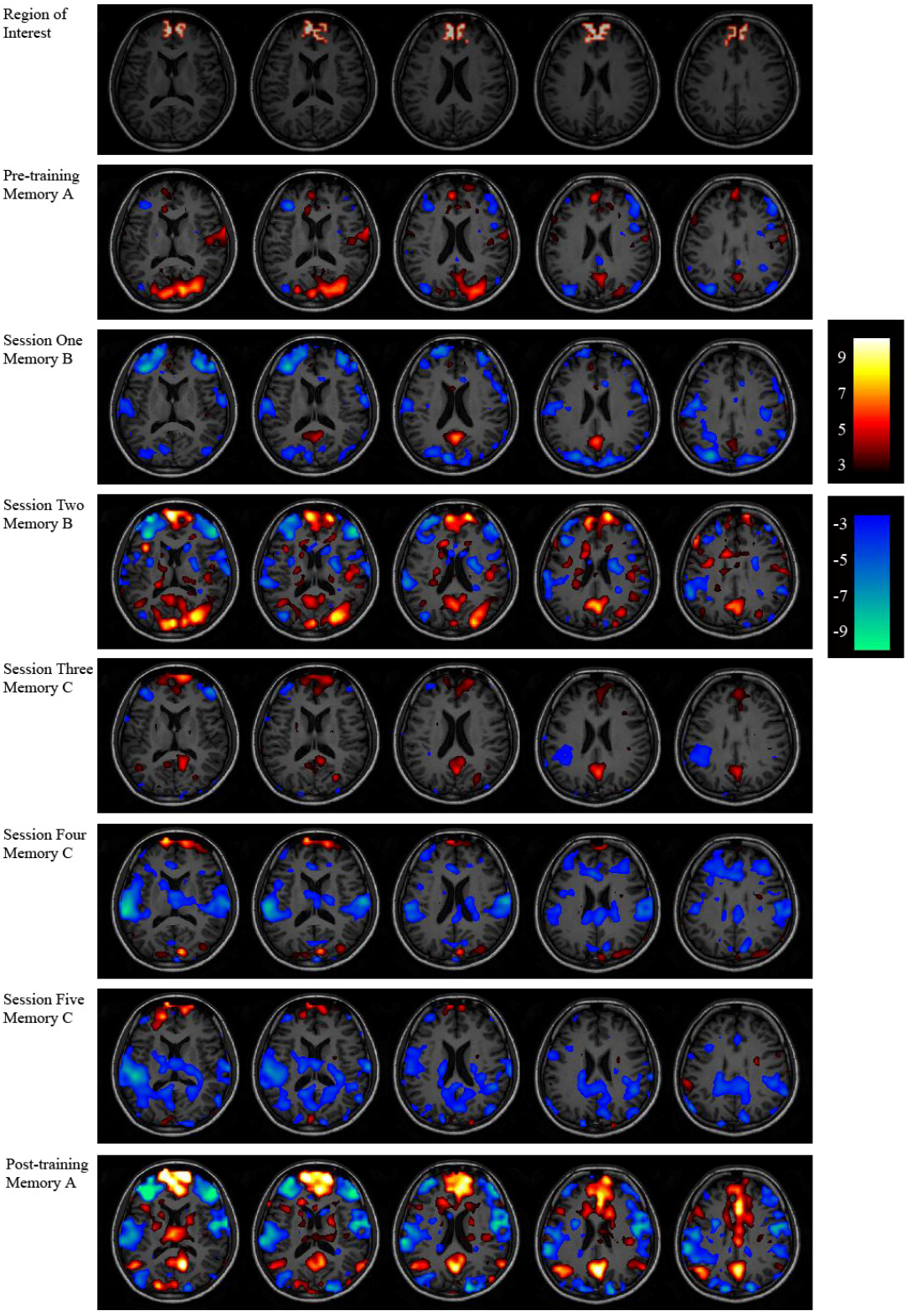
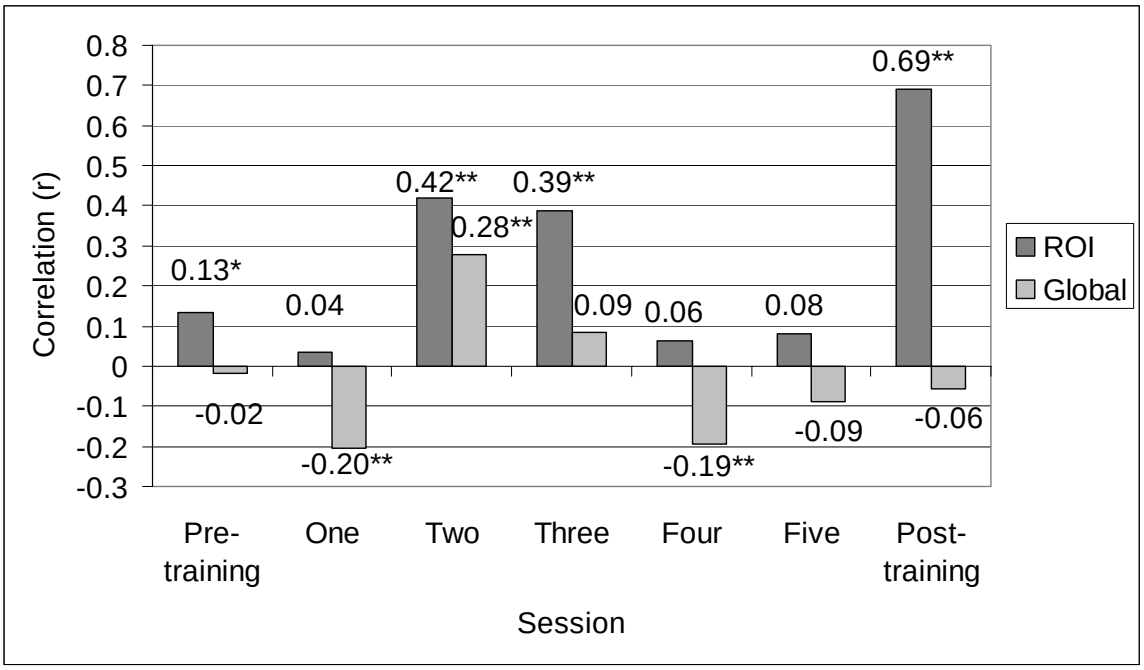


Figure 3.2: Subject one activation maps.
Activation maps overlaid on subject's non-normalized IR T1anatomical image. Voxels more active during up-regulation blocks displayed as hot activations (red-yellow); voxels more active during down-regulation blocks displayed as cold activations (blue-green) ($p < 0.005$, uncorrected).

a)



b)

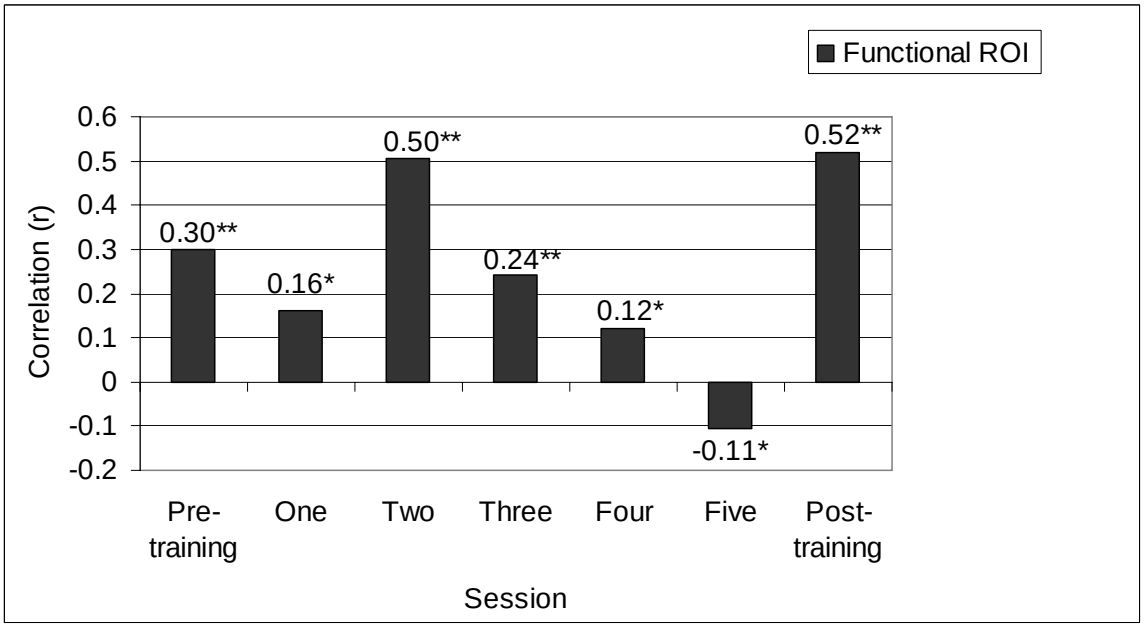


Figure 3.3: Subject one - correlations between task function & activation signal.
a) Correlations between the task function convolved with the HRF and the time courses extracted from the ROI as defined from the scanning session and the global signal. b) Correlation between the time course extracted from the functional ROI as defined from the pre-training session (MNI coordinates: -8, 64, 20) and the task function convolved with the HRF for each session.
High positive correlations between the task function and ROI time course represent good performance. *p<0.05, **p<0.001

3.3.2 Subject Two

Subject two attempted to engage in the provided strategy across sessions. The activation maps illustrate that the activated region of the ROI did not increase in extent or intensity of activation from pre- to post-training (Fig. 3.4). Significant positive correlations between the ROI time course and task function were observed for pre-training, session 1 and post-training (Fig 3.5a). Significant positive correlations for the functionally defined ROI were observed for pre-training, session 1 and 3 (Fig 3.5b). Significant negative global correlations were observed for session 3 and 4 (Fig 3.5a).

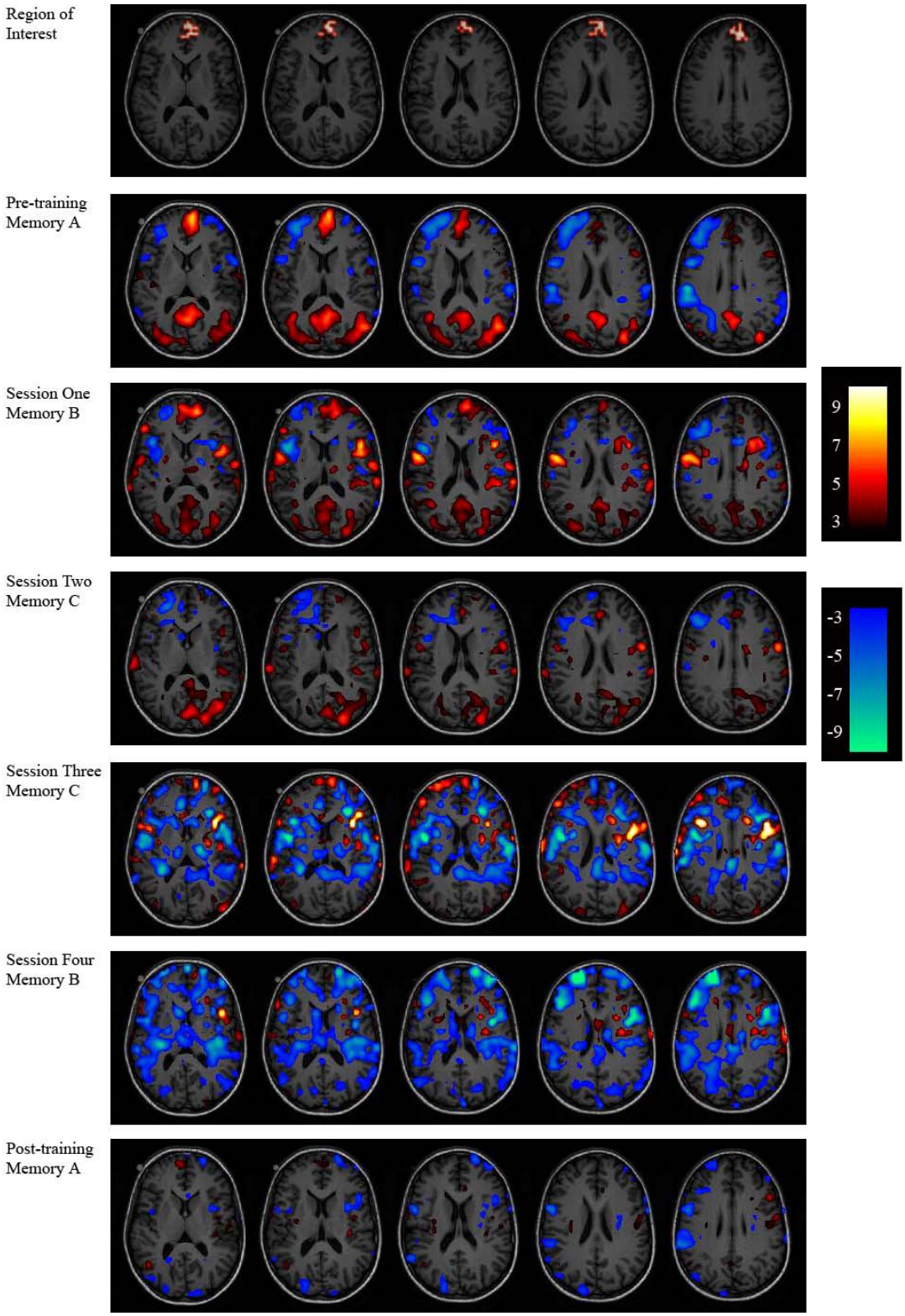
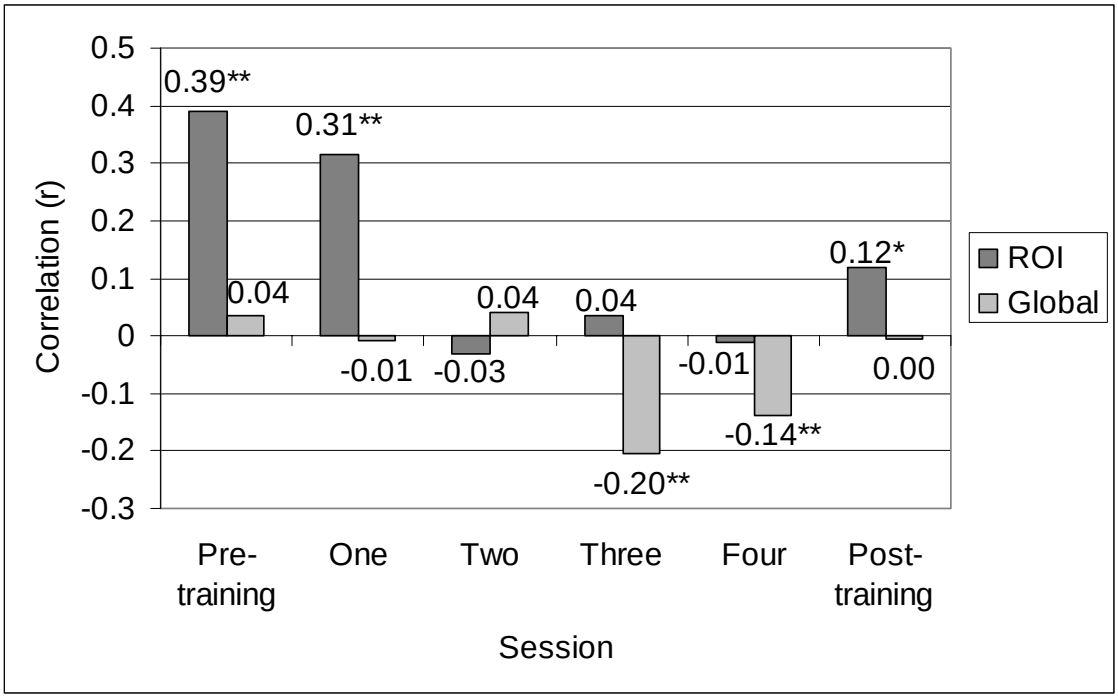


Figure 3.4: Subject two activation maps.
Activation maps overlaid on subject's non-normalized IR T1anatomical image. Voxels more active during up-regulation blocks displayed as hot activations (red-yellow); voxels more active during down-regulation blocks displayed as cold activations (blue-green) ($p < 0.005$, uncorrected).

a)



b)

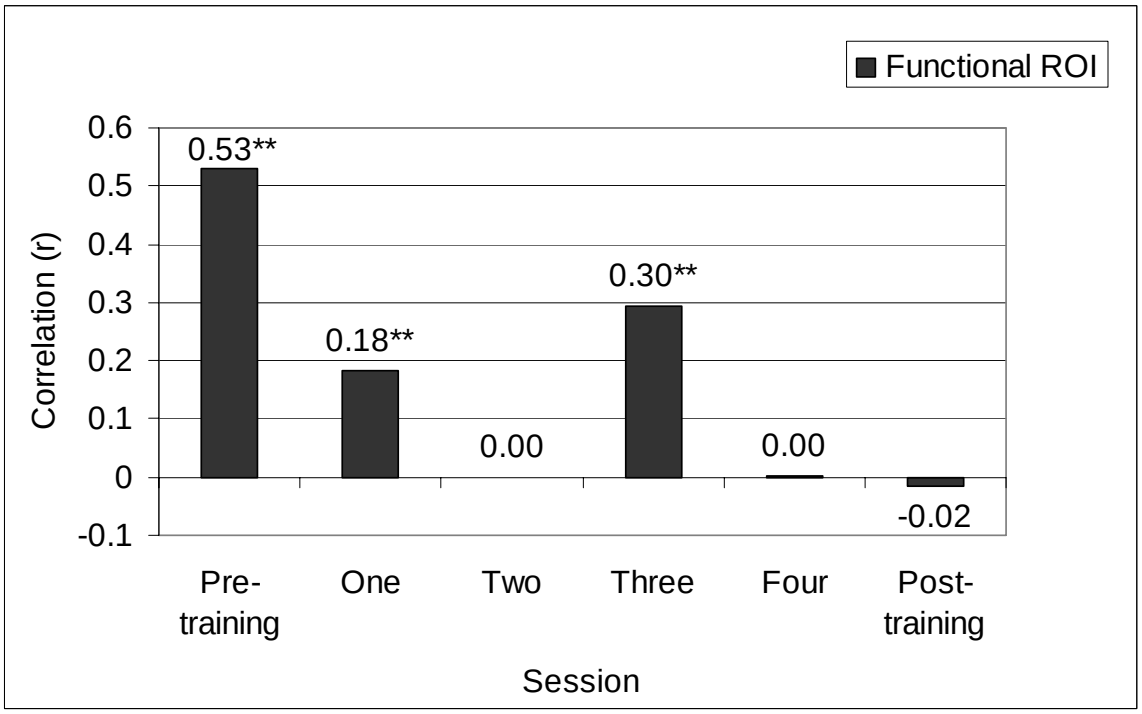


Figure 3.5: Subject two - correlations between task function & activation signal.
a) Correlations between the task function convolved with the HRF and the time courses extracted from the ROI as defined from the scanning session and the global signal. b) Correlation between the time course extracted from the functional ROI as defined from the pre-training session (MNI coordinates: -14, 66, 20) and the task function convolved with the HRF for each session. *p<0.05, **p<0.001

3.3.3 Subject Three

Subject three attempted to engage in the provided strategy across sessions. The activation maps illustrate that the activated region of the ROI did not increase in extent or intensity of activation from pre- to post-training although there was less extensive global activation (Figure 3.6). Significant positive correlations between the ROI time course and task function were observed for pre-training, session 1, 2, 3 and post-training (Fig. 3.7a). Significant positive correlations for the functionally defined ROI were observed for all sessions with the exception of session 4 for which there was no correlation (Fig. 3.7b). Significant positive global correlations were observed for pre-training, session 2 and post-training while session 4 was significantly negatively correlated (Fig. 3.7a).

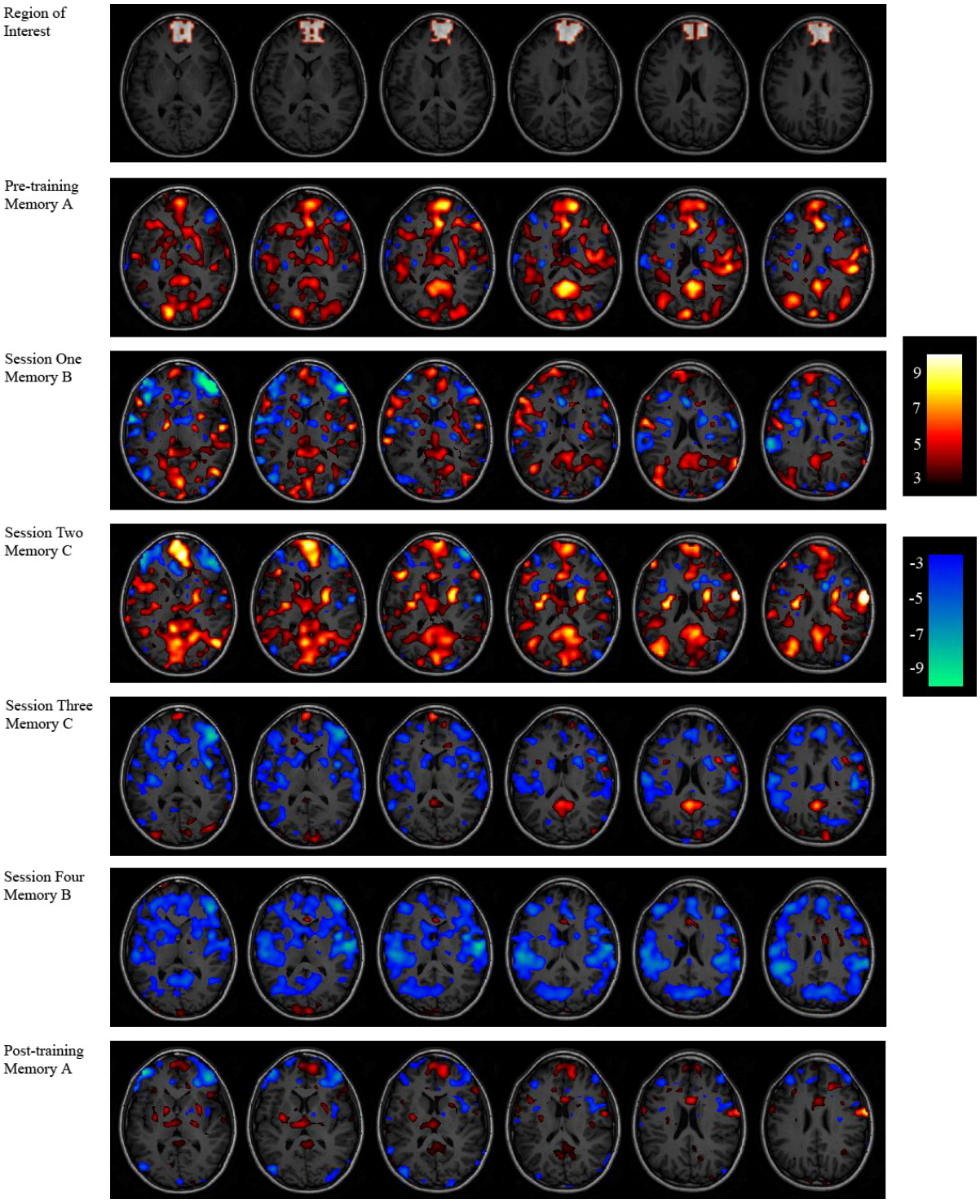
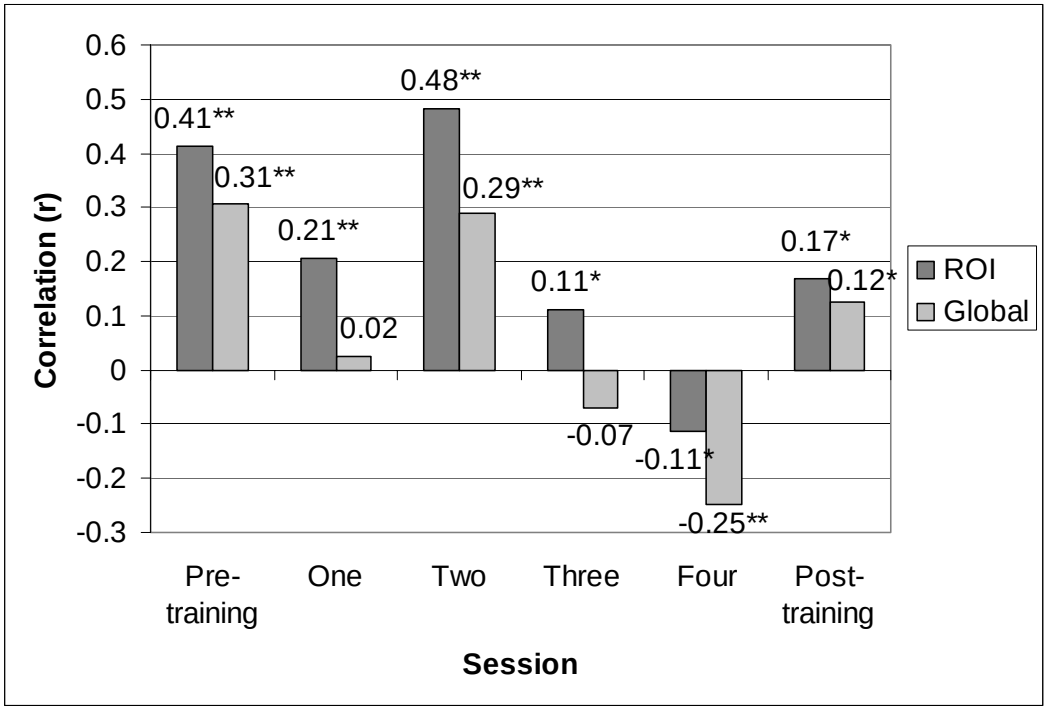


Figure 3.6: Subject three activation maps.
Activation maps overlaid on subject's non-normalized IR T1anatomical image. Voxels more active during up-regulation blocks displayed as hot activations (red-yellow); voxels more active during down-regulation blocks displayed as cold activations (blue-green) ($p < 0.005$, uncorrected).

a)



b)

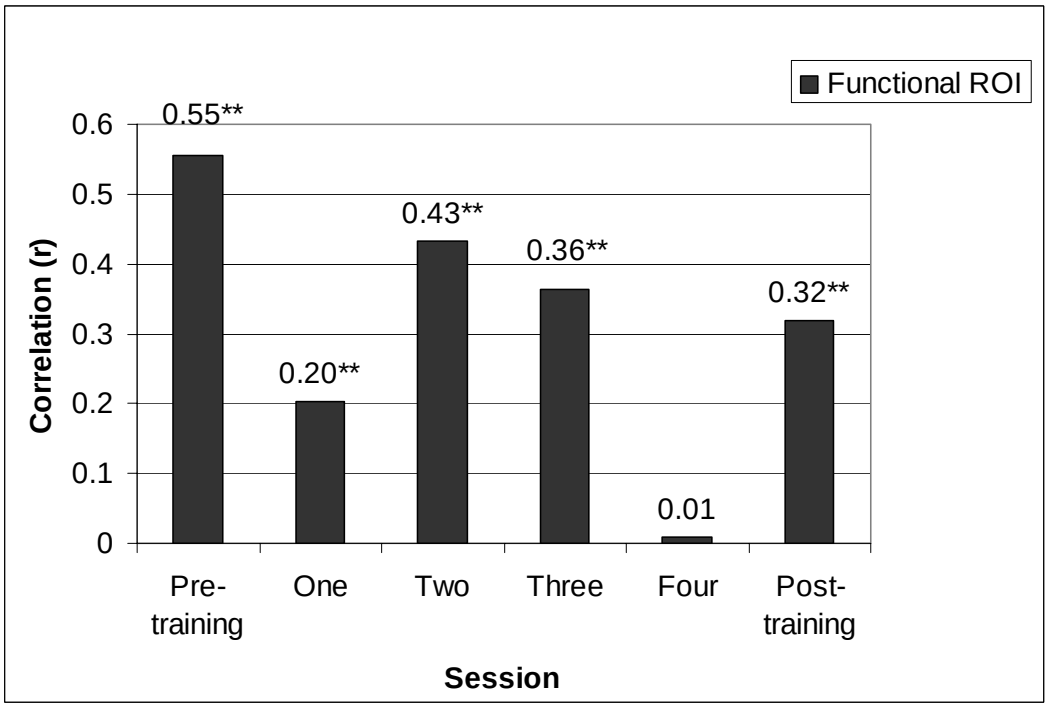


Figure 3.7. Subject three - correlations between task function & activation signal.
a) Correlations between the task function convolved with the HRF and the time courses extracted from the ROI as defined from the scanning session and the global signal. b) Correlation between the time course extracted from the functional ROI as defined from the pre-training session (MNI coordinates: 12, 58, 8) and the task function convolved with the HRF for each session. *p<0.05, **p<0.001

3.3.4 Subject Four

Subject four attempted to engage in the provided strategy for up-regulation, but engaged in a strategy involving relaxation during down-regulation. They reported fatigue and difficulty focusing during the post-training session. The activation maps illustrate that the activated region of the ROI did not increase in extent or intensity of activation from pre- to post-training (Fig. 3.8). Significant positive correlations between the ROI time course and task function were observed for pre-training, session 1 and 2 (Fig. 3.9a). Significant positive correlations for the functionally defined ROI were observed for all sessions with the exception of session 3 for which no significant correlation was observed (Fig 3.9b). Significant positive global correlations were observed for all feedback sessions (sessions 1, 2, 3 and 4) (Fig. 3.9a).

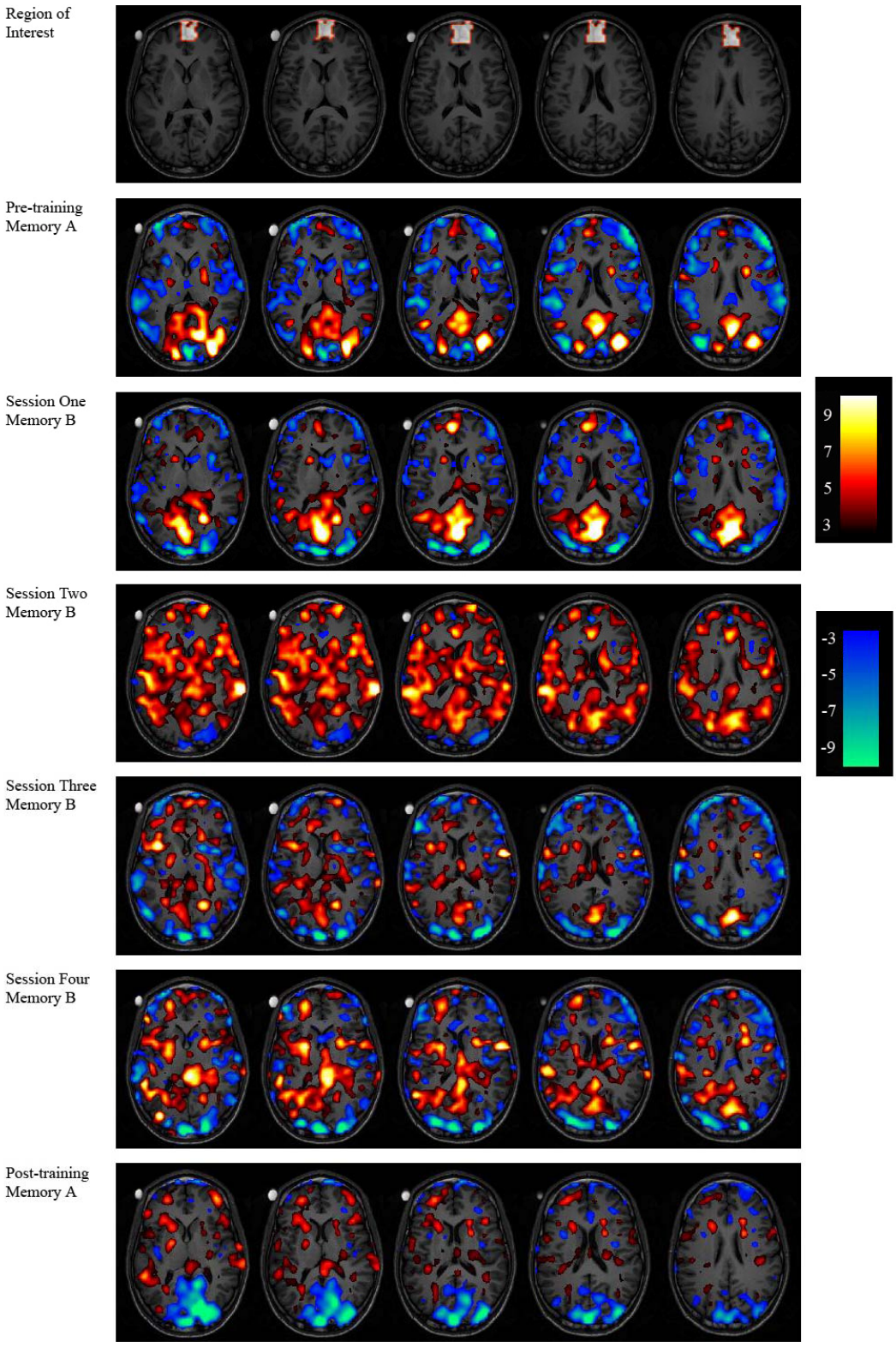
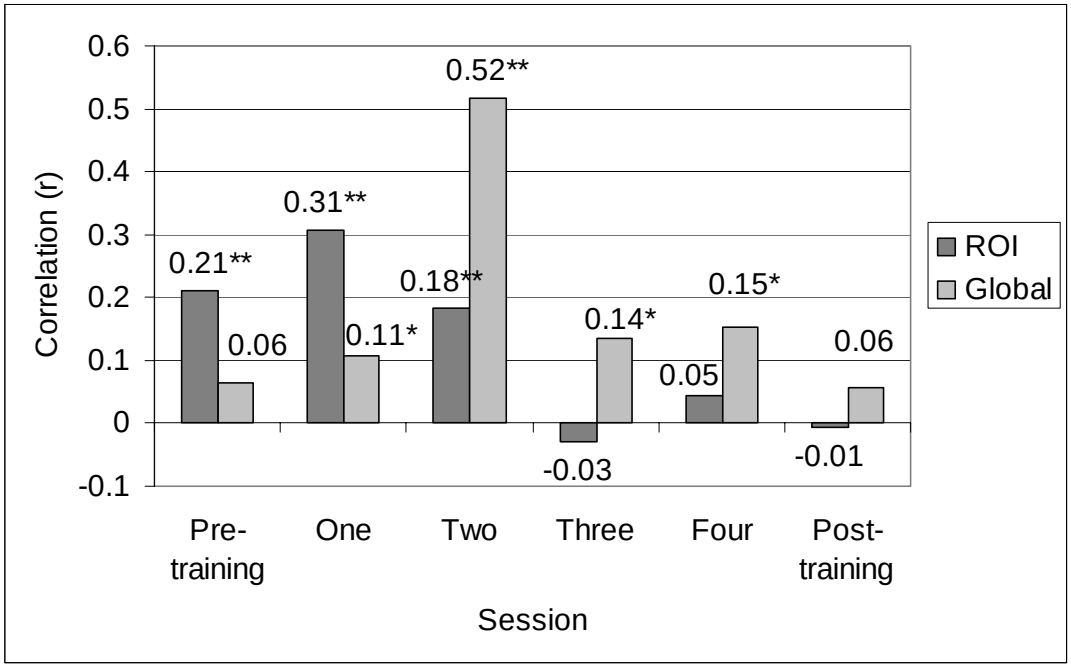


Figure 3.8: Subject four activation maps
Activation maps overlaid on subject's non-normalized IR T1anatomical image. Voxels more active during up-regulation blocks displayed as hot activations (red-yellow); voxels more active during down-regulation blocks displayed as cold activations (blue-green) ($p < 0.005$, uncorrected).

a)



b)

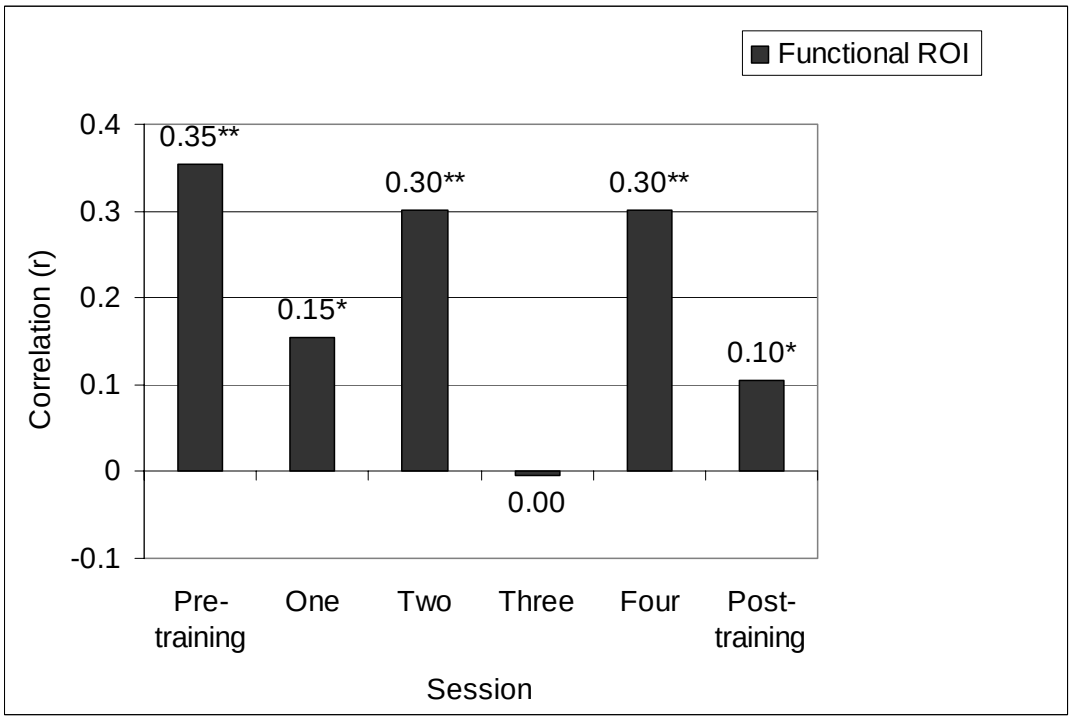


Figure 3.9: Subject four - correlations between task function & activation signal.
a) Correlations between the task function convolved with the HRF and the time courses extracted from the ROI as defined from the scanning session and the global signal. b) Correlation between the time course extracted from the functional ROI as defined from the pre-training session (MNI coordinates: -12, 56, 28) and the task function convolved with the HRF for each session. *p<0.05, **p<0.001

3.3.5 Subject Five

Subject five generally stayed with the provided strategy during up-regulation, but tried variations of the provided strategy for down-regulation – trying to recall the sensations experienced at the time of the event or focusing on unrelated bodily sensations. In session 2 and 4, they reported experiencing performance anxiety and trying to compete with the bar during up-regulation. In session 2, they reported being distracted by meta-cognitive thinking about their body during down-regulation. In session 4, they reported that they were focusing on their failure to feel their body during down-regulation. The activation maps illustrate that the ROI did not increase in extent or intensity of activation from pre- to post-training (Figure 3.10). Significant positive correlations between the ROI time course and task function were observed for pre-training, session 1, 3, 4 and post-training (Fig. 3.11a). Significant positive correlations for the functionally defined ROI were observed for pre-training, sessions 2 and 4 and post-training (Fig 3.11b). Significant positive global correlations were observed for pre-training, session 1, 3, 4 and post-training while a negative correlation was found for session 2 (Fig 3.11a).

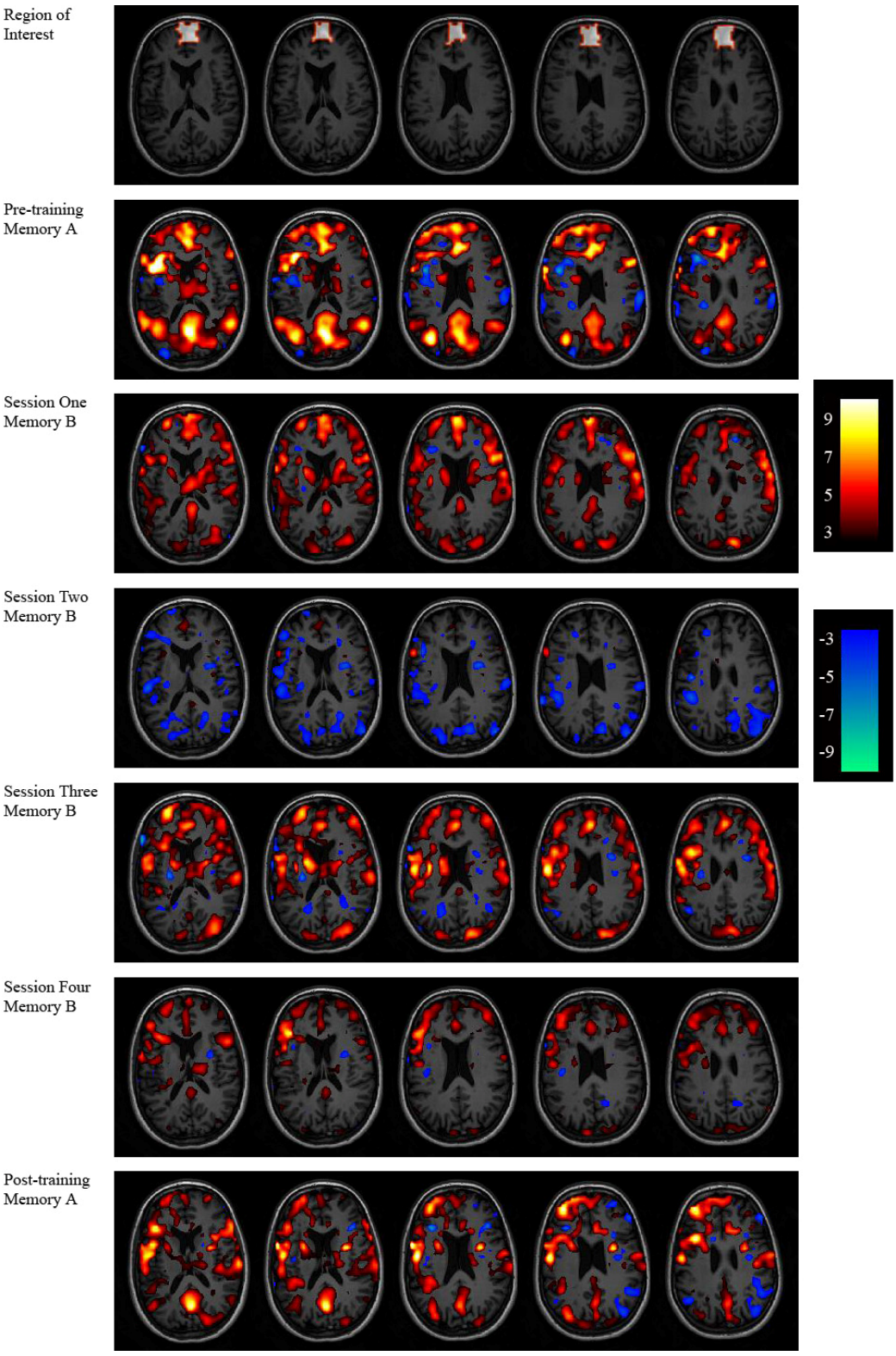
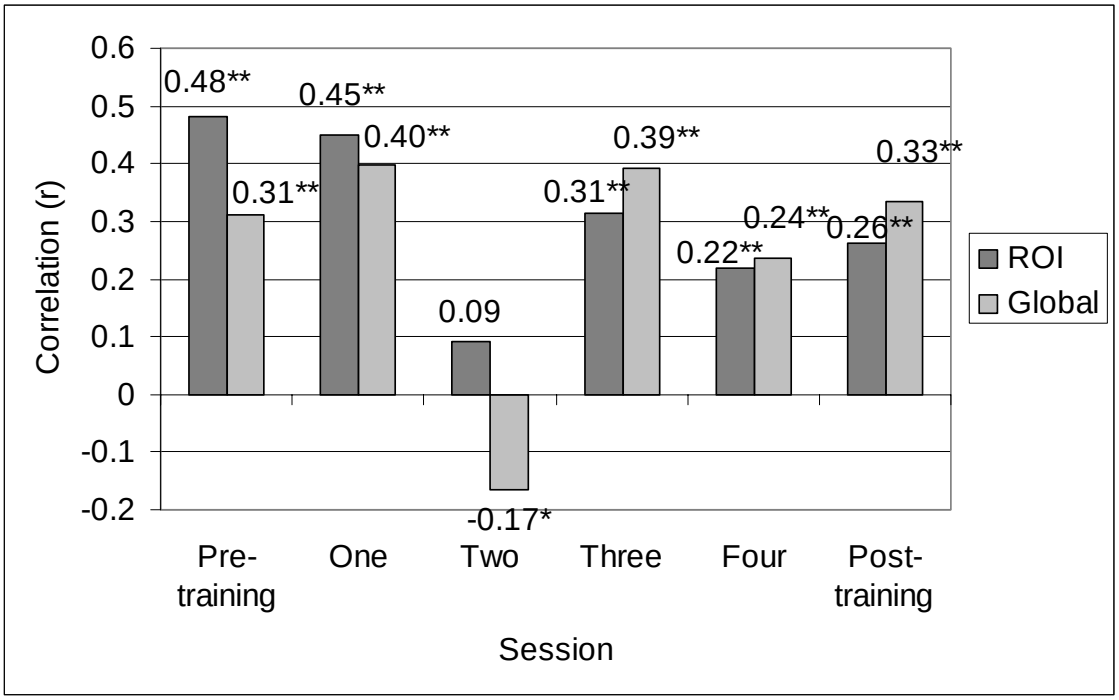


Figure 3.10: Subject five activation maps.
Activation maps overlaid on subject's non-normalized IR T1anatomical image. Voxels more active during up-regulation blocks displayed as hot activations (red-yellow); voxels more active during down-regulation blocks displayed as cold activations (blue-green) ($p < 0.005$, uncorrected).

a)



b)

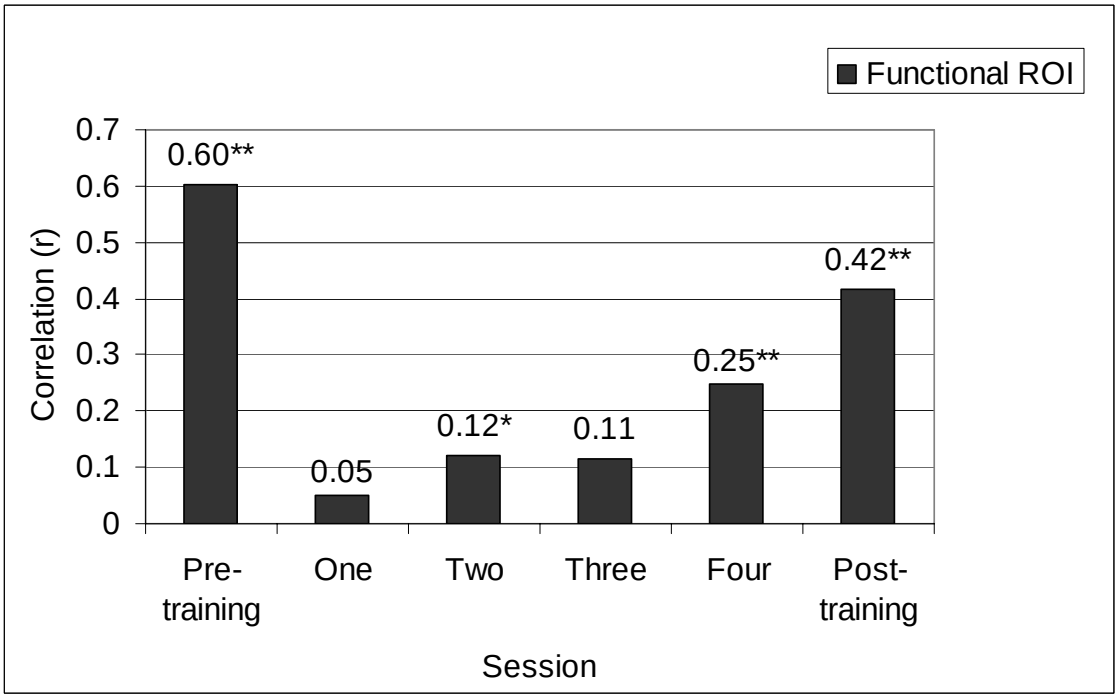


Figure 3.11: Subject five - correlations between task function & activation signal.
a) Correlations between the task function convolved with the HRF and the time courses extracted from the ROI as defined from the scanning session and the global signal. b) Correlation between the time course extracted from the functional ROI as defined from the pre-training session (MNI coordinates: -12, 64, 20) and the task function convolved with the HRF for each session. *p<0.05, **p<0.001

3.4 Subject Debriefing

3.4.1 Subjective ratings

To examine potential individual differences in the debriefing scale measures, ANOVAs with subject and regulation condition as fixed factors and level of negative affect, level of arousal, level of difficulty and use of feedback as dependent factors were conducted and revealed a significant subject by regulation condition interaction for negative affect, $F(4, 50) = 4.34$, $p < 0.05$ and level of arousal, $F(4, 50) = 6.81$, $p < 0.001$. No significant interaction was found for level of difficulty, $F(4, 50) = 1.81$, *ns*, or use of feedback, $F(4, 30) = 0.41$, *ns*. Paired t-tests on the individual subject data were conducted for level of negative affect and level of arousal to follow up on the significant interactions. For subject one, ratings of negative affect were greater during up-regulation than down-regulation, $t(6) = 2.75$, $p < 0.05$, while ratings of arousal did not differ between conditions, $t(6) = 2.27$, *ns*. For subject two, neither ratings of affect, $t(5) = 0$, *ns*, nor ratings of arousal, $t(5) = 0$, *ns*, differed between up and down-regulation. For subject three, ratings of negative affect were greater during up-regulation than down-regulation, $t(5) = 2.71$, $p < 0.05$, while ratings of arousal did not differ between conditions, $t(5) = 1.46$, *ns*. For subject four, both ratings of negative affect, $t(5) = 4.66$, $p < 0.05$, and ratings of arousal, $t(5) = 10.00$, $p < 0.05$, were greater during up-regulation than down-regulation. For subject five, neither ratings of affect, $t(5) = 2.00$, *ns*, nor ratings of arousal, $t(5) = 0.89$, *ns*, differed between up and down-regulation.

Table 3.1 Mean subjective rating scores from debriefing sessions

	Negative Affect		Arousal		Difficulty		Feedback	
Subject	UR	DR	UR	DR	UR	DR	UR	DR
One*	6.2	4.5	5.8	4.3	3.5	2.5	3.8	3.2
Two	4.2	4.2	4.5	4.5	4.0	5.0	5.8	5.8
Three	3.8	3.0	3.2	2.7	3.7	3.3	4.3	4.8
Four	5.3	2.0	5.3	2.0	5.8	4.8	5.0	3.8
Five	4.0	3.3	5.7	5.2	5.7	4.0	4.5	4.8
Group	4.7	3.4	4.9	3.7	4.5	3.9	4.7	4.4

Note. Rating scales ranged from 1 – 7 with larger values indicating higher levels. *Session 5 ratings not included in calculation of means for Subject one UR = up-regulation condition; DR = down-regulation condition; Feedback = amount the subject used the feedback.

3.4.2 Subjective experience

See Appendix D for detailed summary of subject responses to the open-ended debriefing questions. All subjects reported feelings of sadness. Other emotions reported include feelings of depression, worry, disappointment, fear, confusion, regret, anger, loss, humiliation, nervousness, anxiousness, betrayal, tension, loss of control, upset, frustration, surprise, annoyance and generally feeling emotional. Two subjects reported tearing up. Bodily sensations reported include breathing (general sensation of, shortness of, intense, heavy), general tenseness, chest tension, sensations related to the eyes (tiredness, squinting), warmth, heart beat, salivation and knots in the back and neck

Sensations unrelated to the emotions were also reported by some subjects these included sensations related to the discomfort of lying in the same position in the scanner, hunger and related stomach rumbling. One subject reported attempting to relax during down-regulation and thinking about the arrow (subject four). Another subject reported

trying to recreate the sensations felt during the initial emotional event as well as meta-cognitive thinking about bodily sensations (subject five).

3.4.3 Use of feedback display

Subjects generally reported that the feedback was helpful only when it was positive. All subjects reported that the feedback display was distracting, particularly when the thermometer went in the opposite direction of what they anticipated or when the bottom display exhibited a seemingly opposite pattern. Four out of five subjects reported looking at the central arrow. One subject reported that they occasionally closed their eyes (subject three). Two subjects reported looking at the feedback from the periphery (not focusing on it directly) (subjects four and five). One subject reported competing with the feedback and trying to mentally force it to go up (subject five). Two subjects (subject two and three) reported looking at the bottom feedback display as well as the central arrow with subject three also reporting that they looked at the thermometer. Subject one reported only that they looked at the central arrow, but their other responses suggest that they also observed the two feedback panels.

3.5 Training Effects

A repeated measures ANOVA of the correlation coefficients (converted to Fisher's z scores) between the task function and signal time course extracted from the ROI defined on the day of scanning with session as the factor of interest indicated that the regulation of the target region did not significantly differ across sessions, $F(5,20) = 1.30$, *ns*. A non-significant negative trend across sessions was observed (Fig. 3.12).

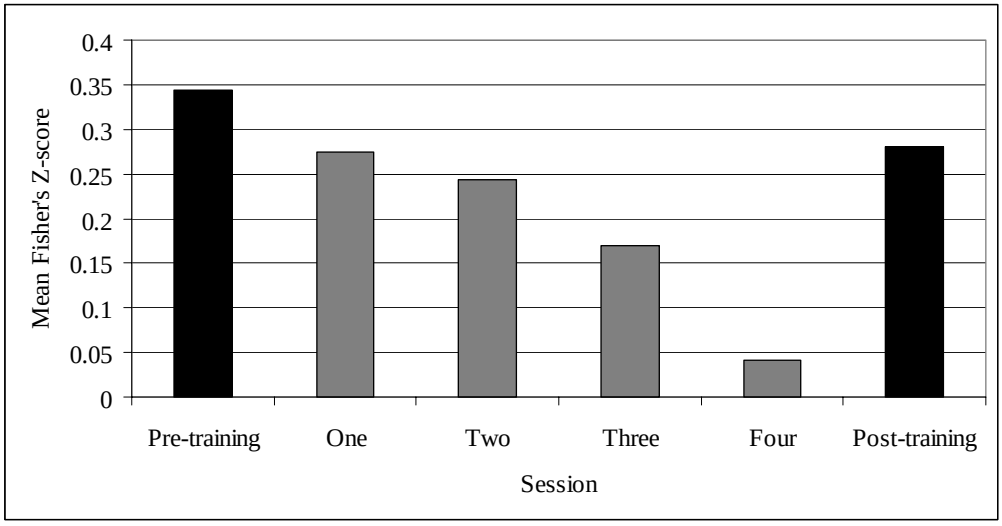


Figure 3.12: Effects of training
Mean Fisher's Z-scores calculated from the correlation between the task-function and the signal time course from the ROI. A higher value represents better performance. Black bars indicate sessions for which no feedback was provided. A non-significant negative trend across sessions was observed.

A paired t-test of the up-regulation versus down-regulation contrast images from pre and post-training resulted in significant clusters of activation in rMPFC in the pre versus post-training contrast (Fig. 3.13) while the post versus pre-training contrast resulted in no significantly activated voxels in the region of interest.

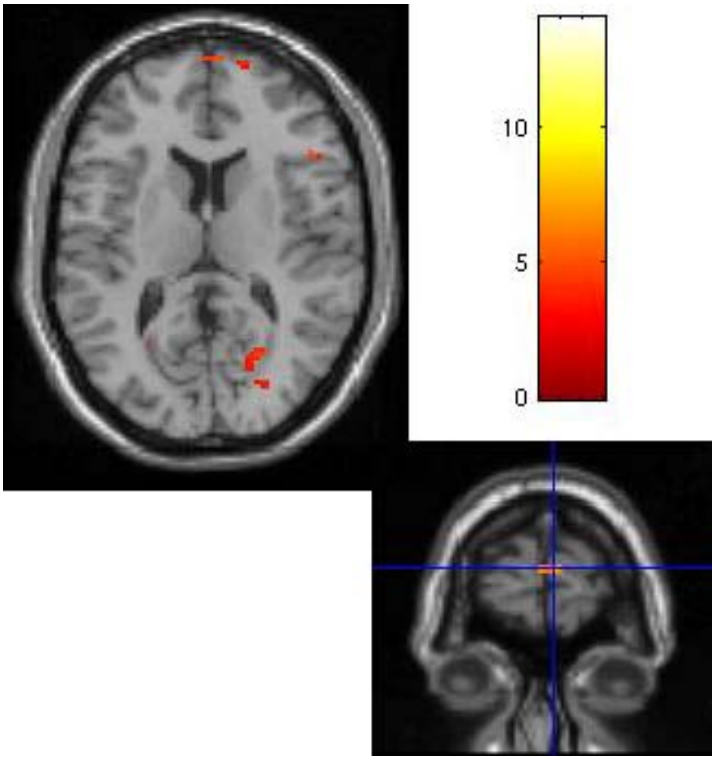


Figure 3.13: Pre-training versus post-training contrast.
Paired t-test of up-regulation vs. down-regulation contrast showing areas more active during the pre-training session than the post-training session. Crosshairs centred on 5 voxel cluster at MNI coordinates: 6, 68, 12 (t = 7.20, p < 0.005 uncorrected). MNI coordinates of 18 voxel prefrontal cluster: 16, 64, 16 (t = 13.92, p < 0.005 uncorrected). Activation map is overlaid on single-subject T1 template.

4 Discussion

The results provide evidence in support of the first hypothesis that the strategy of engaging in emotional awareness to up-regulate activity and bodily awareness to down-regulate activity in the rMPFC is effective in modulating activity in this brain region. This is evident in the positive correlations found for all subjects between the task function and signal time course from the pre-training session as well as from the large rMPFC activation cluster observed for the group analysis of the pre-training session. These findings are in line with the previously proposed role of the rMPFC in emotional awareness (Gusnard, Akbudak, Shulman, & Raichle, 2001; Lane, Fink, Chau, & Dolan, 1997; Ochsner, Knierim et al., 2004; Ochsner, Ray et al., 2004) and with the previously observed decreases in this region reported with experiential awareness (Farb et al., 2007). However, the up-regulation condition was not always associated with a greater level of experienced negative affect. This is not an entirely unexpected finding as subjects were not instructed to suppress their emotions during down-regulation, but rather to turn their attention to a different aspect of the emotional experience i.e. the associated bodily sensations. Three out of five subjects reported significantly greater affect during emotional awareness (up-regulation) while for the remaining two subjects, negative affect did not differ between regulation conditions. Regulation of the target region does not appear to be due to differences in emotional arousal. The subject (L.F) whose arousal ratings differed significantly between the regulation conditions employed a slightly different strategy involving relaxation during down-regulation. The positive global signal correlations observed for this subject in the 4 feedback training sessions suggest

that this difference in arousal may have resulted in global signal modulation rather than selective regulation of the target region.

The second hypothesis that subjects would learn improved regulation of the target region by making use of the feedback display showing the level of activation in that region was not supported. Rather, both subject reports and the activation data suggest that the feedback was detrimental to task performance. Subjects generally performed better during the pre-training session as compared to the post-training session and a general decline in performance across sessions was observed. Fatigue was likely also a contributing factor to this decline in task performance with one subject explicitly identifying this as affecting their performance in the post-training session. In order to assess whether the decline in performance was simply due to fatigue rather than frustration with and interference from the feedback display, control subjects could undergo the same procedure in the absence of the feedback display. In order to minimize the influence of fatigue, the real-time training could be broken into a series of shorter sessions spread across a number of days. Scanning was done only on one day in the present study due to scheduling issues and the finding that head position could not be adequately reproduced to ensure that the same ROI was specified on the separate days.

While an effect of training was not found in the present study, if a training effect had been observed it would have been important to run appropriate control subjects to verify that the effect was specific to the real-time feedback. Such controls should include a sham feedback group with feedback provided from an unrelated brain region as well as a no feedback group who would perform the same experimental task while viewing only the central arrow. It should be noted that the present investigation may have been

somewhat limited in its ability to detect a significant effect of training (whether positive or negative) due to its relatively low power as a result of the small sample size remaining after subject exclusion. A random effects analysis is necessary to examine for the effects of learning and this type of analysis typically requires at least 8 subjects to have sufficient power to detect an effect (Friston, Holmes & Worsley, 1999).

These results suggest that feedback methods which have previously been shown to be useful for helping subjects to learn to self-regulate brain activation may be limited in the extent to which they apply to other brain regions. As such, it may be necessary to explore and develop unique forms of feedback for select regions. Since real-time fMRI is a relatively novel methodology, such information is only beginning to emerge. As the methodology is studied more extensively, certain techniques may be found to be more appropriate for a region or group of regions depending on both the function of the region and its location (as this may influence such aspects as the region's susceptibility to the effects of motion, distortion and signal attenuation).

4.1 Feedback Method

The method of feedback for the present study was designed based on principles outlined in reviews of the real-time fMRI method. As such, the display provided information regarding the level of activation with as minimal a lag possible given the inherent delay of the HRF combined with the additional data processing delay. Previous reviews of the method have suggested that minimal lag between the activation (or task performance) and the feedback enables optimal learning of self-regulation (Weiskopf, Scharnowski et al., 2004). Both the fMRI results as well as the subject debriefings from the present study suggest, however, that this may not be the optimal strategy when the

rMPFC is the target region of interest. Rather, the subjects' comments generally indicated that the continuously updating feedback display was distracting and detrimental to task performance, particularly when it differed from their expectations. It may be the case that for this brain region (and other regions involved in evaluative processes) more discrete feedback as well as more positive, encouraging feedback could be more beneficial.

Similar to Posse et al. (2003), feedback could be provided at the end of a short block or at more intermittent intervals, thereby, allowing subjects to focus on performing the regulation task without the necessity of concurrently evaluating their task performance. This would allow for the evaluation of task performance to occur during discrete periods of each regulation block or even outside of the regulation blocks. This could be of particular importance for strategies requiring subjects to focus on emotional experiences since continuous feedback could act to produce emotional responses resulting in fluctuations in the signal which may be misinterpreted by the subject to suggest that their strategy is incorrect. Discrete feedback would also help to decrease the tendency for subjects to continuously engage in a process of self-monitoring during both regulation conditions, which may have the undesired effect of producing activation of the target region across both regulation conditions. This is of particular concern given the finding that multi-tasking – performing more than one task per block – consistently recruits medial BA10 (Gilbert et al., 2006).

In terms of more positive feedback, as suggested by Weiskopf et al. (2004), small improvements could be rewarded at the outset of the experiment with larger improvements required as the experiment progresses. A practice session prior to the

scanning sessions may be useful in determining a subject's natural ability to perform the regulation tasks (i.e. the ease with which they are able to switch from focusing on higher level emotions to focusing on bodily sensations). An additional measure which could be taken to help minimize the anxiety subjects may experience as a result of negative feedback would be to familiarize them with the variability commonly observed in the feedback display. This could be accomplished by having them view a video of sample feedback prior to their scanning session. Such a measure may help reduce the negative self-evaluations which may otherwise occur. It may be of particular importance to minimize the occurrence of negative feedback particularly at the outset of training given previous findings on the relationship between anxiety and negative feedback. For example, lower ratings of self-efficacy (Waldersee, 1994) and poor performance have been associated with negative feedback in individuals high in trait anxiety (Thompson, Webber, & Montgomery, 2002). As well, an increase in state anxiety and heart rate has been associated with negative feedback (Kieffer & Tennyson, 1973) while performance detriments have been associated with negative feedback in individuals with low self-esteem (Shrauger & Rosenberg, 1970). In terms of findings specific to depression, it has been found that while misleading negative feedback disrupts performance in depression, accurate feedback does not (Murphy, Michael, Robbins, & Sahakian, 2003).

The one subject (subject one) who did show an improvement in regulation of the target region from pre to post-training had the lowest rumination score among the subjects. It is possible that this subject was able to use the feedback display more effectively, being less concerned when it fluctuated in the opposite direction from that desired. In contrast, the subject with the highest rumination score (subject five) focused

so intently on their performance that they reported for one of the sessions that they were unable to perform the task as they found themselves willing the activation signal to increase and this was reflected clearly in their resulting activation pattern (see Fig 3.10, session 2). As one of the goals of developing a real-time protocol is to develop it in such a way that it could be effectively implemented in a clinical setting, this further underscores the necessity of exploring alternate options regarding the type of feedback provided. While other variables may account for or contribute to the differences observed between subject one and five, the possibility that at least part of the difference may lie in their ruminative tendencies is important to consider. Given the association between rumination and depression, it is important to ensure that individuals high in rumination are able to effectively use the provided feedback.

4.2 Motion Effects

Task-correlated motion is an issue which may result in the exclusion of a large portion of collected data (Friston, Williams, Howard, Frackowiak, & Turner, 1996). This is partly due to the fact that correction measures intended to remove the effects of motion will also inadvertently remove signal changes attributable to task performance (Friston, Williams, Howard, Frackowiak, & Turner, 1996) or result in the appearance of false activations if the motion is not corrected (Bullmore et al., 1999). As well, it has been demonstrated that for highly correlated task movements ($r > 0.67$) even small movements of less than 1mm can result in false activations that remain after image realignment (Field, Yen, Burdette, & Elster, 2000). This is a particularly relevant issue when investigating the anterior prefrontal cortex as in the present study as it has been shown that motion can result in the appearance of false activations in areas next to air/tissue or

bone/tissue interfaces such as the anterior frontal cortex due to its close proximity to the ethmoidal and frontal sinuses (Wu, Lewin, & Duerk, 1997). This occurs as result of the reorientation of areas with differing susceptibility within the main magnetic field, leading to changes in the spatial variation of signal loss (Wu, Lewin, & Duerk, 1997).

Indeed motion was an issue in the present study with three subjects excluded due to large task-correlated motion and one subject excluded due to excessive motion. Given the substantial subject dropout attributable to this phenomenon, future studies employing this or a similar paradigm should attempt to address this issue by taking further steps to minimize such motion. Subject debriefing reports suggest that the visual display may have acted to induce task correlated motion. Subjects tended to follow the direction of the arrow: looking up during up-regulation when the arrow pointed upwards and looking down during down-regulation when the arrow pointed downwards. To eliminate or reduce movement associated with the alternation between the regulation tasks, the use of other cues to signal the current regulation task should be explored. Some potential cues include an auditory cue or a cue that changes in size, brightness or colour. Subject head motion was minimized using a memory foam pillow around the head to maximize subject comfort due to the long duration of the present investigation. However, the use of other more restrictive measures such as a restricting band across the subject's forehead, a bite bar or a vacuum pack could be explored. An additional precaution that could be taken would be to train subjects to minimize motion in a mock scanner environment prior to the actual scanning session. As well, efforts should be made to ensure that the motion correction procedures performed in real-time are optimal in order to minimize the

occurrence of fluctuations in the signal due to motion which could be misinterpreted by the subject as meaningful.

4.3 Signal Dropout and Distortion

One issue which arises in studies of the anterior prefrontal cortex is the commonly observed blood oxygenation level-dependent (BOLD) signal attenuations and distortions due to susceptibility artifacts in this region (Ojemann et al., 1997). Such artifacts arise due to susceptibility differences between ethmoidal air cells and brain tissue, which result in signal attenuation in regions adjacent to bone and air sinuses (Ojemann et al., 1997). These artifacts may result in partial or complete signal loss from the ventromedial and frontopolar regions. Whereas distortions can be corrected (Jezzard & Balaban, 1995), signal loss cannot be compensated for. The quality of signal in susceptibility regions can be enhanced through region-specific shimming (Guo & Song, 2003) or by optimizing the amplitude of the slice-select refocus gradient for each individual slice (Wild, Martin, & Allen, 2002), however, these techniques may reduce the sensitivity and decrease signal quality in other brain regions. A whole brain shim was applied to the present data set as it was intended that connectivity analysis would be conducted had a positive effect of real-time fMRI training been observed.

Another method to potentially increase image resolution and decrease signal dropout would be to increase the time of repetition (TR), thereby, allowing for the collection of a greater number of slices in each volume. In the present study, a TR of 1 second was selected to minimize the delay between data collection and presentation of the updated activation signal. The use of discrete feedback presents with the advantage of increasing the signal to noise ratio due to signal averaging as well as allowing for the

TR to be increased beyond 1 second. An additional step that could be taken to increase the quality of the signal and decrease distortion would be to collect field maps prior to the experimental scanning session (Jezzard & Clare, 1999). Field maps help to correct for geometric distortion which arises due to inhomogeneity of the magnetic field (Jezzard & Clare, 1999). Decreasing the effect of distortion may allow for a more reliable and precise definition of the feedback region than was possible in the present investigation.

4.4 Region of Interest Definition

The ROI for the present study aimed to consist of the dorsal aspect of BA10 extending into BA9. The definition given by D'Argembeau et al. (2007) of ~Z = +10 to +30 was applied. While the correlations between the task function and the signal time course derived from the ROI from the scanning session and the ROI defined functionally from the normalized pre-training session data generally followed a similar pattern, some differences were observed. These differences highlight the influence that ROI definition could have on the outcome of real-time fMRI studies. In addition, the results indicate that the activated area consistently extended ventrally beyond the defined region. This finding is in line with the lack of a functional distinction along the dorsal-ventral axis as previously reported in a meta-analysis of BA10 function (Gilbert et al., 2006).

While the present study attempted to define the feedback region anatomically, another approach would be to use either a functional localizer or anatomic criteria in combination with a functional localizer to identify the feedback region. One method for functional localization would be to use the first session with no feedback to functionally define the ROI, selecting the most significantly activated voxel (and the surrounding voxels) falling within the anatomically defined ROI. This is the method that was

employed by deCharms et al. (2005) in their study of the rACC in pain perception. Alternatively, a separate task could be used to functionally define the ROI. This method was employed by Weiskopf et al (2004) in their study of learned regulation of differential activation of the supplementary motor area (SMA) and the parahippocampal place area (PPA). For the SMA, the functional localizer consisted of a finger tapping task while for the PPA, a task involving viewing outdoor scenes with houses alternating with blocks of faces was employed. There are at least two short tasks either of which could potentially serve as appropriate functional localizers for the rMPFC. One is the task previously employed by Lane et al. (1997), involving emotional and perceptual judgements of emotional pictures. The second task is that employed by Cato et al. (2004) involving the generation of emotional words.

4.5 Global Signal Modulation

Global modulation of the activation signal was apparent in some of the sessions. Reviews of the real-time fMRI method have previously identified changes in respiration as a potential confound due to its influence on global signal intensity (Weiskopf et al, 2004). In a study of voluntary breath holding it has been shown that focal increases in activation of the ACC, PCC, insula and caudate may arise as a result of even short durations (6 seconds) of breath holding (Abbott, Opdam, Briellmann, & Jackson, 2005). While more widespread, global activation is observed for longer durations (18-30 seconds) of breath holding (Abbott, Opdam, Briellmann, & Jackson, 2005; Li, Kastrup, Takahashi, & Moseley, 1999). Respiration effects may arise due to increased cerebral blood flow as a result of reduced oxygen and increased levels of CO_2 associated with breath holding (Abbott et al., 2005) as well as fluctuations in the magnetic field strength

due to changes in the thoracic cavity (Glover, Li, & Ress, 2000; Raj, Anderson, & Gore, 2001). As such, subjects may have with or without their awareness adopted a strategy involving regulating their pattern of respiration with the observed global signal modulation arising due to differences in respiration patterns between conditions. Subject four's session 2 presents with an example where the global modulation may have been due in part to respiration differences between the conditions (see Fig. 3.8). One potential method to address this issue would be to monitor respiration over the course of the scanning session and to continually remind subjects to try to breathe normally throughout the course of the experiment. As a further precaution, information regarding global signal change could also be provided to subjects to help them identify whether they are learning to selectively regulate the region or alternatively, global signal modulation could be cancelled out by providing feedback regarding the difference between two regions (Weiskopf, Scharnowski et al., 2004).

4.6 Regulation Strategies

The down-regulation strategy employed in this study was one of a number of different emotion regulation strategies that could have been tested which may also have been associated with a decrease in activation of the rMPFC. The particular strategy of bodily awareness was selected due to the promising findings from the pilot testing and its similarity to the experiential focus which was previously shown to down-regulate MPFC by Farb et al. (2007). In addition to the detached observer strategy which was piloted and has been previously employed in fMRI studies of emotion regulation (e.g. Ochsner, Ray et al., 2004), a strategy aimed at changing the focus of attention could be tested (Gross,

1998). This strategy would involve the shifting of attentional focus to the cognitive non-emotional aspects of an emotional experience during down-regulation.

If learned regulation of the rMPFC is to be explored further it would be important to investigate different approaches to down-regulation of activity in rMPFC particularly if the experimental paradigm was to be applied to clinical populations. An approach involving focusing attention on the body may not be beneficial to some individuals with depression presenting with an excess negative focus on physical symptoms (Wise & Mann, 1995). Some models of depression such as the Interacting Cognitive Subsystems model (Teasdale & Barnard, 1993) purport that sensory feedback plays a role in depression; consistent with this model somatic symptoms are commonly found in depression (Tylee & Gandhi, 2005). As well, recent evidence of impaired heartbeat perception in moderately depressed individuals suggests that the subjective experience of bodily sensations may be altered in depression (Dunn, Dalgleish, Ogilvie, & Lawrence, 2007). In support of the use of bodily awareness as an emotion regulatory strategy, there is evidence that the ability to describe and be aware of sensations in the absence of judging the cause and implications of these sensations is associated with lower negative affectivity (McKee, Zvolensky, Solomon, Bernstein, & Leen-Feldner, 2007). In light of this finding, training individuals to focus on the physical qualities of their bodily sensations as they arise, rather than on their cause and implications, may be of some benefit in reducing negative affect.

4.7 Future Work

Future research should work towards addressing the methodological issues which arose in the present study, such as the motion, distortion and respiration effects described

above. As well, different feedback methods, such as more discrete feedback, should be investigated as they may prove more beneficial for learned modulation of the rMPFC. Methods for minimizing the potentially detrimental effects of negative feedback on subject experience and performance should also be explored. The possibility of improving regulation of other brain regions involved in autobiographical memory such as the posterior cingulate (Svoboda, MCKinnon, & Levine, 2006) or other regions implicated in depression such as the subgenual cingulate (Drevets et al., 1997; Mayberg et al., 1999) should also be investigated as these areas may prove more amenable to real-time fMRI training.

4.8 Conclusions

The results presented in this thesis are promising in that they show that a meaningful emotion reflective paradigm can result in reliable regulation of the rMPFC at the single session level. It would be premature to conclude from the present results that it is not possible to use real-time fMRI feedback to learn improved regulation of the rMPFC. Rather, the results highlight the methodological issues which are of particular relevance in exploring regulation of this region and suggest that further investigation is needed to address the form of feedback which may prove beneficial.

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6 Appendices

6.1 Appendix A: Motion Parameters

Table 6.1A: Range of motion (in mm) for included subjects.
Translation equals mean of x, y, z and rotation equals mean of pitch, roll and yaw.

Subject	Session	x_mm	y_mm	z_mm	pitch	roll	yaw	translation	rotation
One	Pre-train	0.06	0.41	0.24	0.01	0.00	0.00	0.47	0.01
	1	0.13	0.66	0.74	0.02	0.00	0.01	0.92	0.02
	2	0.14	0.60	0.85	0.01	0.00	0.01	1.17	0.01
	3	0.11	1.13	2.25	0.07	0.01	0.01	2.53	0.07
	4	0.34	1.50	1.03	0.08	0.01	0.01	1.72	0.08
	5	0.20	1.07	1.82	0.09	0.00	0.01	2.00	0.09
	Posttrain	0.12	0.55	0.44	0.03	0.01	0.01	0.57	0.03
Two	Pre-train	0.23	0.42	0.43	0.01	0.01	0.00	0.45	0.01
	1	0.13	0.36	0.63	0.01	0.01	0.01	0.78	0.01
	2	0.21	0.40	0.39	0.01	0.01	0.01	0.64	0.01
	3	0.33	0.40	0.74	0.01	0.00	0.01	0.77	0.01
	4	0.25	0.45	0.43	0.01	0.01	0.01	0.61	0.02
	Posttrain	0.47	0.34	0.45	0.01	0.01	0.01	0.82	0.02
Three	Pre-train	0.07	0.51	0.60	0.03	0.01	0.00	0.92	0.03
	1	0.15	0.58	0.87	0.02	0.01	0.00	0.87	0.03
	2	0.30	0.53	0.89	0.03	0.01	0.00	0.89	0.03
	3	0.20	0.63	0.95	0.03	0.02	0.01	1.10	0.05
	4	0.27	0.73	1.13	0.03	0.01	0.01	1.28	0.03
	Posttrain	0.23	0.46	1.19	0.03	0.01	0.00	1.23	0.03
Four	Pre-train	0.17	0.41	0.56	0.01	0.01	0.01	0.70	0.02
	1	0.12	0.35	0.52	0.01	0.02	0.00	0.59	0.03
	2	0.11	0.43	0.68	0.01	0.02	0.01	0.82	0.03
	3	0.14	0.40	0.97	0.01	0.02	0.00	1.25	0.03
	4	0.13	0.37	0.50	0.01	0.01	0.00	0.53	0.02
	Posttrain	0.13	0.28	0.55	0.01	0.01	0.00	0.61	0.01
Five	Pre-train	0.24	0.87	0.48	0.00	0.00	0.00	0.99	0.00
	1	0.26	1.04	1.71	0.01	0.01	2.46	0.01	2.46
	2	0.21	1.15	1.13	0.00	0.00	0.00	1.89	0.01
	3	0.34	0.83	1.16	0.02	0.00	0.00	1.84	0.02
	4	0.17	0.68	0.96	0.01	0.00	0.01	1.50	0.01
	Posttrain	0.14	0.71	0.35	0.01	0.00	0.00	0.71	0.01

Table 6.2A: Range of motion (in mm) for excluded subjects.
Translation equals mean of x, y, z and rotation equals mean of pitch, roll and yaw.

Subject	Session	x_mm	y_mm	z_mm	pitch	roll	yaw	translation	rotation
Six	Pre-train	0.32	1.03	2.67	0.03	0.01	0.00	3.32	0.03
	1	0.27	0.80	0.57	0.02	0.01	0.01	0.84	0.02
	2	0.24	0.56	0.88	0.02	0.01	0.01	1.20	0.02
	3	0.30	2.37	1.35	0.03	0.01	0.01	2.37	0.03
	4	0.40	0.67	1.38	0.01	0.01	0.01	1.70	0.02
	Posttrain	0.24	2.10	1.50	0.03	0.01	0.00	2.17	0.03
Seven	Pre-train	0.22	0.60	0.42	0.01	0.01	0.00	0.70	0.01
	1	0.30	0.80	0.61	0.01	0.01	0.00	0.82	0.02
	2	0.27	1.19	1.00	0.02	0.01	0.01	1.19	0.02
	3	0.39	1.28	1.35	0.04	0.01	0.00	1.93	0.04
	4	0.41	2.73	1.38	0.04	0.01	0.00	2.76	0.04
	Posttrain	0.26	0.82	0.76	0.04	0.01	0.01	1.01	0.06
Eight	Pre-train	0.62	0.58	2.50	0.01	0.01	0.01	2.85	2.85
	1	0.68	0.53	2.15	0.01	0.01	0.01	2.71	0.03
	2	0.55	0.73	1.17	0.02	0.01	0.01	1.48	0.03
	3	1.17	0.93	2.36	0.02	0.01	0.01	2.36	0.03
	4	0.55	0.55	2.59	0.02	0.01	0.01	3.04	0.03
	Posttrain	0.55	0.56	1.14	0.01	0.01	0.01	1.19	0.01
Nine	Pre-train	0.21	0.40	0.86	0.03	0.00	0.01	0.86	0.03
	1	0.34	0.85	1.10	0.03	0.01	0.01	1.17	0.03
	2	0.22	0.81	1.05	0.03	0.01	0.01	1.10	0.03
	3	0.17	0.58	0.76	0.02	0.01	0.00	0.76	0.02
	4	0.06	0.55	0.30	0.01	0.00	0.00	0.55	0.01
	Posttrain	0.12	0.38	0.35	0.01	0.01	0.00	0.43	0.01
Ten	Pre-train	0.45	0.64	0.93	0.03	0.01	0.01	1.08	0.03
	1	0.31	1.08	1.81	0.05	0.01	0.01	2.61	0.06
	2	0.39	0.87	1.24	0.03	0.01	0.00	2.02	0.03
	3	0.44	1.07	2.11	0.06	0.01	0.01	2.89	0.06
	4	0.50	1.14	2.05	0.07	0.02	0.01	2.78	0.08
	Posttrain	0.35	0.79	0.79	0.04	0.01	0.00	1.42	0.04

6.2 Appendix B: Debriefing Questions

The following questions were presented visually to subjects at the end of each scanning session. Only one question was displayed at a time. When subjects indicated that they had finished answering a question, the next question was displayed. Subjects' verbal responses were recorded and later transcribed. Questions marked with an asterisk were displayed for sessions with feedback only.

Questions pertaining to up-regulation

Where were you looking during up-regulation?*

Please describe your experience during up-regulation. What emotions did you notice?

During up-regulation, were you able to keep your attention on the emotional aspects of the experience? (If your answer is no, please tell us what you thought about instead.)

Rate on a scale of 1-7 the strength of negative affect you experienced during up-regulation.

Rate on a scale of 1-7 the level of emotional arousal you experienced during up-regulation.

Rate on scale of 1-7 how much you used the feedback in order to assist you in completing the up-regulation task.*

Rate on a scale of 1-7 the level of difficulty of up-regulation. Please tell us why it was easy or difficult.

Did you notice any link between what you were doing and the activation signal? If yes, was it helpful for regulating the activation?*

Questions pertaining to down-regulation

Where were you looking during down-regulation?*

Please describe your experience during down-regulation. What bodily sensations did you notice?

During down-regulation, were you able to keep your attention on the bodily sensations associated with the emotions? (If your answer is no, please tell us what you thought about instead.)

Rate on a scale of 1-7 the strength of negative affect you experienced during down-regulation.

Rate on a scale of 1-7 the level of emotional arousal you experienced during down-regulation.

Rate on scale of 1-7 how much you used the feedback in order to assist you in completing the down-regulation task.*

Rate on a scale of 1-7 the level of difficulty of down-regulation. Please tell us why it was easy or difficult.

6.3 Appendix C: Clinical and Personality Measures

Table 6.3B: Mean scores for Rumination-Reflection Questionnaire and Beck Depression Inventory

	Rumination-Reflection Questionnaire		Beck Depression Inventory
Subject	Rumination	Reflection	
One	2.50	4.50	1.00
Two	3.92	4.33	0.00
Three	2.83	3.08	0.00
Four	4.00	3.33	4.00
Five	4.75	4.25	3.00
Group	3.60	3.90	1.60

Table 6.4B: Mean scores for Big Five Inventory-44

	Traits				
Subject	Extraversion	Agreeableness	Conscientiousness	Neuroticism	Openness
One	4.38	4.56	3.56	2.38	4.60
Two	3.13	4.11	4.00	3.25	3.90
Three	2.88	4.22	3.56	1.88	2.70
Four	3.38	3.22	3.22	2.88	3.60
Five	4.25	3.89	4.44	2.75	4.4
Group	3.60	4.00	3.76	2.63	3.84

Table 6.5B: Mean scores for Kentucky Inventory of Mindfulness Skills questionnaire

	Mindfulness Factors			
Subject	Observe	Describe	Act with Awareness	Accept without Judgment
One	2.50	5.00	3.80	2.00
Two	3.50	3.50	2.90	3.33
Three	3.58	3.63	3.40	3.67
Four	2.42	3.00	3.50	4.00
Five	4.25	4.00	3.50	3.44
Group	3.25	3.83	3.42	3.29

6.4 Appendix D: Debriefing Summary Tables

Abbreviation legend for debriefing summary tables:

Sess: session
Pre: pre-training session
Post: post-training session
↑ : up-regulation blocks
↓ : down-regulation blocks

Table 6.6C: Subject One Debriefing Summary

Sess		Question	Answer Summary	Ability to focus
Pre	↑	Emotions	Scared, worried, confused	Yes
	↓	Sensation	Tense, fast breath. Tired eyes	Yes
1	↑	Area of focus		
		Emotions	Suddenly sad, emotional, tearful	Yes
		Difficulty	Seeing bar fluctuate & unsure what level to maintain; trying to focus on emotions & maintain pattern	
		Link & helpfulness	Yes, was helpful	
	↓	Focus	Down arrow	
		Sensations	Faster breath, tired eyes, focused on body	Yes
		Difficulty	Easy to just focus on breath	
2	↑	Focus	Arrow	
		Emotions	Sad, disappointed, scared	Yes
		Difficulty	Mind wandered to bodily sensations sometimes	
		Link & helpfulness	Yes, was helpful	
	↓	Focus	Arrow	
		Sensations	Shortness of breath, tired eyes and back	Yes
		Difficulty	Easy to focus on body	
3	↑	Focus	Red arrow	
		Emotions	Depressed, sad, fearful, and disappointed	Yes
		Difficulty	Easier from practice and increased focus	
		Link & helpfulness	Yes, was helpful	
	↓	Focus	Down arrow	
		Sensations	Breath shortness, relaxed body	Yes
		Difficulty	Was easier	

Subject One Debriefing Summary Continued

Sess		Question	Answer Summary	Ability to Focus
4	↑	Focus	Red arrow	
		Emotions	Scared, frustrated, disappointed	Yes
		Difficulty		
		Link & helpfulness	Yes, was helpful	
	↓	Focus	Down arrow	
		Sensations	Tenseness, breath shortness	Yes
		Difficulty		
5	↑	Focus	Up arrow	
		Emotions	Nervous, hard to focus, tense	Yes
		Difficulty		
		Link & helpfulness	Yes, was helpful	
	↓	Focus	Down arrow	
		Sensations	Tense body, heartbeat, breath shortness	Yes
		Difficulty		
Post	↑	Focus	Up arrow	
		Emotions	Nervous, trying to understand what happened, scared	Yes
		Difficulty		
	↓	Focus	Down arrow	
		Sensations	Body relaxed, slight breath shortness	
		Difficulty		

Table 6.7C: Subject Two Debriefing Summary

Sess		Question	Answer Summary	Ability to focus
Pre	↑	Emotions	Intense sadness	Yes
		Difficulty	Easy to recall memory and be affected	
	↓	Sensations	Tense and contracting throat	Yes, but harder
		Difficulty	Difficult to focus on physical aspects	
1	↑	Area of focus	Regulation bars and arrows	
		Emotions	Sad and tense	Yes
		Difficulty	Harder to bring the emotion to memory	
		Link & helpfulness	Sometimes, and was helpful when in the right direction	
	↓	Focus	Arrows and fluctuating bars	
		Sensations	Tense	Mostly yes
		Difficulty	Difficult to focus on physical aspects	
2	↑	Focus	Arrows and regulation bars	
		Emotions	Sadness, surprise, frustration	Yes
		Difficulty	Hard to remain focused on emotion	
		Link & helpfulness	Sometimes, and was helpful when in the right direction	
	↓	Focus	Arrow and Activation	
		Sensations	Warm temperature and tenseness	Sometimes
		Difficulty	Hard to not ignore emotion	
3	↑	Focus	Arrows and bars	
		Emotions	Sadness	Yes
		Difficulty	Difficult to keep memory in mind and focus on emotion	
		Link & helpfulness	Did not notice link	
	↓	Focus	Arrow and bar	
		Sensations	Heartbeat increased, tenser	Yes, but harder
		Difficulty	Hard to focus on physical aspects	
4	↑	Focus	Arrow and upward bars	
		Emotions	Sadness and regret	Yes
		Difficulty	Easier to focus on emotion aspects	
		Link & helpfulness	Yes, was more helpful	
	↓	Focus	Arrows and occasionally at bars	
		Sensations	Warm and tense	Mostly yes
		Difficulty	Harder to keep physical aspects in mind	
Post	↑	Emotions	Sadness and disappointment	Yes
		Difficulty	Easy to bring memory and emotion to mind	
	↓	Sensations	Tense	Sometimes
		Difficulty	Hard to quantify the physical aspects and focus on them.	

Table 6.8C: Subject Three Debriefing Summary

Sess		Question	Answer Summary	Ability to focus
Pre	↑	Emotions	Sadness	Yes
		Difficulty	Easy to recall and think of memory and emotions	
	↓	Sensations	Pounding heart, tingly sensation	Yes
		Difficulty	Easy to focus on bodily sensations	
1	↑	Area of focus	Arrow, sometimes look up	
		Emotions	Upset	Yes
		Difficulty	Hard to deal with feedback, tried to focus on emotions	
		Link & helpfulness	Believe there is a link, but sometimes saw the opposite	
	↓	Focus	Arrow	
		Sensations	Watery eyes, pounding heart, intense breathing	Yes
		Difficulty	Hard to focus on bodily sensations	
2	↑	Focus	Arrows, feedback, sometimes closed eyes	
		Emotions	Sad, upset	Yes
		Difficulty	Easy due to recent detailed memory	
		Link & helpfulness	Yes, was helpful	
	↓	Focus	Arrow, feedback, and bars	
		Sensations	Eyes tearing & squinting, salivation, heart pumping,	Yes
		Difficulty	Easy due to feeling more emotional & aroused	
3	↑	Focus	Arrow, feedback, bar, sometimes closed eyes	
		Emotions	Sadness, but less intense than at first	Yes - harder
		Difficulty	Hard to focus on emotion & see feedback drop	
		Link & helpfulness	No	
	↓	Focus	Arrow, feedback, closed eyes	
		Sensations	Calmer, less bodily sensations, heavier breathing	Yes - harder
		Difficulty	Less intense bodily sensations, unexpected feedback directions	
4	↑	Focus	Feedback, bar, closed eyes	
		Emotions	Sad, anxious	Yes
		Difficulty	Hard due to distracting feedback	
		Link & helpfulness	No	
	↓	Focus	Feedback, closed eyes	
		Sensations	Breathing	Yes
		Difficulty	Getting opposite feedback was almost distracting	
Post	↑	Emotions	Anxiousness, sadness	Yes
		Difficulty	Easier to focus without feedback	
	↓	Sensations	Heavier breathing, salivation, eyes squinting	Yes
		Difficulty	Easier to focus without feedback	

Table 6.9C: Subject Four Debriefing Summary

Sess		Question	Answer Summary	Ability to focus
Pre	↑	Emotions	Sadness, loss	Yes
		Difficulty	Difficult to think of the context and the details.	
	↓	Sensations	Tension in arm and chest, relaxed eyes – tried to relax	No
		Difficulty	Difficult while wanting to just relax	
1	↑	Area of focus	Centre arrow, bar in periphery	
		Emotions	Sadness, loss, disappointment	Yes
		Difficulty	Reasonably easier, difficult when bar wasn't moving	
		Link & helpfulness	No	
	↓	Focus	Central arrow, bar in the peripheral vision	
		Sensations	Chest tension, body strain from lying still	In the middle, yes
		Difficulty	Attention on bodily sensation, less on feedback. Relaxing too much	
2	↑	Focus	Bar, arrow	
		Emotions	Sadness, slight anger and annoyance	Yes
		Difficulty	Lots of things to focus on	
		Link & helpfulness	Yes, was helpful	
	↓	Focus	Mostly arrow, bar	
		Sensations	Chest pain, breathing, discomfort from scanner position	Partially
		Difficulty	Hard to focus and notice bodily sensations.	
3	↑	Focus	Arrow and bar	
		Emotions	Anger and sadness	Yes - harder
		Difficulty	Certain memories details work and some don't. It's hard to see what works with the bar	
		Link & helpfulness	Yes, but difficult to link together	
	↓	Focus	Down arrow, sometimes bar	
		Sensations	Chest tension, heavier breathing – was relaxing	No
		Difficulty	Hard to explain feedback and to relax	

Subject Four Debriefing Summary Continued

Sess		Question	Answer Summary	Ability to focus
4	↑	Focus	Bar, sometimes arrow	
		Emotions	Sadness, annoyance, anger	Yes
		Difficulty	Hard to focus on emotion and bar, emotion distracting	
		Link & helpfulness	Yes, was helpful but not always clear	
	↓	Focus	Arrow and bar	
		Sensations	Arms and legs tense - hard to focus, trying to relax arms, scanner discomfort	No
		Difficulty	Easier, more relaxing, replace body focus with thinking about the word, “down”	
Post	↑	Emotions	Tired, loss, sadness	Yes - harder
		Difficulty	Hard from feeling tired and uncomfortable.	
		Sensations	Arms stress, breathing, scanner discomfort – was relaxing	No
		Difficulty	Hard to focus from tiredness	

Table 6.10C: Subject Five Debriefing Summary

Sess		Question	Answer Summary	Ability to focus
Pre	↑	Emotions	overwhelming sadness, hurt, loss, not being in control	No, trying to ignore down regulation, body, and environment
	↓	Sensations	body, blanket, elbows, knees, hunger	Easier than Up regulation
1	↑	Area of focus	Peripheral feedback	
		Emotions	Betrayal, humiliation, sad, anxiety, tension, loss, regret	Yes
		Difficulty	Hard to switch thinking fast	
		Link & helpfulness	Yes, but did not pay attention to it	
	↓	Sensations	limbs, knots in back, neck, head tension/ache	
		Difficulty	Recalled emotion in memory	
2	↑	Emotions	Recreated experience – sad, hurt, anger	
		Difficulty	Hard to focus, bar distracts, performance anxiety	
		Link & helpfulness	Yes, but focused on bar instead of memory, mind wandering	
	↓	Sensations	Trying to hard to feel same sense (distracting)	No
3	↑	Focus	Tried not to look at bar	
		Emotions	Sadness, humiliation, loss, regret, humiliated	Yes
		Link & helpfulness	Tried to avoid paying attention to feedback	
	↓	Focus	Feedback, but did not pay attention to it	
		Sensations	Back, neck tension, limbs	recalled sensations, tiredness, crying during memories
4	↑	Emotions	Sadness, hurt, anger, loneliness	No, focused away from screen, tired
		Link & helpfulness	Yes, but not helpful- tried to compete with it	
	↓	Sensations	Really tense, discomfort	No, focused on failure to feel body and emotions
Post	↑	Emotions	Sadness, loss, regret, anxiety	Focused on labels instead
		Difficulty	Trying to focus on emotion and bring up memory	
	↓	Sensation	Limbs, clip on finger	No, focused on current sensations
		Difficulty	Easy to focus on present sensations	

6.5 Appendix E: Ethics Approval Certificate

The University of British Columbia
Office of Research Services
Clinical Research Ethics Board – Room 210, 828 West 10th Avenue, Vancouver, BC V5Z 1L8

ETHICS CERTIFICATE OF EXPEDITED APPROVAL: RENEWAL WITH AMENDMENTS TO THE STUDY

PRINCIPAL INVESTIGATOR:	DEPARTMENT:	UBC CREB NUMBER:
Kalina Christoff	UBC/Arts/Psychology, Department of	H06-03324

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
UBC	Vancouver (excludes UBC Hospital)

Other locations where the research will be conducted:
N/A

CO-INVESTIGATOR(S):

Ivan Kouznetsov
Rachelle Smith
Irene Liu
Ronald Graeme McCaig
Kamyar Keramatian

SPONSORING AGENCIES:

Canadian Institutes of Health Research (CIHR) - "Investigating prefrontal cortex functions using real-time fMRI"

PROJECT TITLE:
Investigating prefrontal cortex functions using real-time fMRI

The current UBC CREB approval for this study expires: February 1, 2009

AMENDMENT(S):

AMENDMENT APPROVAL DATE:
February 1, 2008

Document Name	Version	Date
Protocol:		
Investigating prefrontal cortex functions using real-time fMRI: Protocol	N/A	November 20, 2007
Consent Forms:		
Consent form Investigating Prefrontal Cortex Functions using Real-time fMRI	N/A	January 9, 2008
Questionnaire, Questionnaire Cover Letter, Tests:		
Need for Cognition Scale	N/A	November 20, 2007
Rumination-Reflection Questionnaire	N/A	November 20, 2007
Big Five Inventory	N/A	November 20, 2007
Other Documents:		
Study Requirements Checklist	N/A	November 20, 2007

CERTIFICATION:

In respect of clinical trials:

1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.

2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.

3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

The Chair of the UBC Clinical Research Ethics Board has reviewed the documentation for the above named project. The research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved for renewal by the UBC Clinical Research Ethics Board.

Approval of the Clinical Research Ethics Board by:

[redacted]

Dr. James McCormack,
Associate Chair