

Training of goal-directed attention regulation enhances control over neural processing for individuals with brain injury

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Deficits in attention and executive control are some of the most common, debilitating and persistent consequences of brain injuries. Understanding neural mechanisms that support clinically significant improvements, when they do occur, may help advance treatment development. Intervening via rehabilitation provides an opportunity to probe such mechanisms. Our objective was to identify neural mechanisms that underlie improvements in attention and executive control with rehabilitation training. We tested the hypothesis that intensive training enhances modulatory control of neural processing of perceptual information in patients with acquired brain injuries. Patients ($n = 12$) participated either in standardized training designed to target goal-directed attention regulation, or a comparison condition (brief education). Training resulted in significant improvements on behavioural measures of attention and executive control. Functional magnetic resonance imaging methods adapted for testing the effects of intervention for patients with varied injury pathology were used to index modulatory control of neural processing. Pattern classification was utilized to decode individual functional magnetic resonance imaging data acquired during a visual selective attention task. Results showed that modulation of neural processing in extrastriate cortex was significantly enhanced by attention regulation training. Neural changes in prefrontal cortex, a candidate mediator for attention regulation, appeared to depend on individual baseline state. These behavioural and neural effects did not occur with the comparison condition. These results suggest that enhanced modulatory control over visual processing and a rebalancing of prefrontal functioning may underlie improvements in attention and executive control.

Keywords: cognitive rehabilitation; neural plasticity; executive control; attention; functional MRI; brain injury

Introduction

Acquired brain injuries have been a leading cause of long-term disability in the USA (Thurman *et al.*, 1999) and have been an increasing concern due to recent military conflicts (Okie, 2005). The most common and persistent deficits tend to be in functions such as paying attention, holding information in mind, organizing and developing efficient strategies for completing activities (Cicerone and Azulay, 2002; Mathias *et al.*, 2004; Fork *et al.*, 2005; Vanderploeg *et al.*, 2005). These 'executive control' functions are important for the regulation of other, more basic processes, and deficits may directly contribute to poor outcomes as well as impede rehabilitation at broader levels (Prigatano and Wong, 1999; Hyndman and Ashburn, 2003; Ownsworth and McKenna, 2004). Effective treatments are needed.

Understanding the neural bases of cognition, including the mechanisms by which improvements occur, may provide guidance for the development of treatments to enhance functioning (Chen *et al.*, 2006; D'Esposito and Chen, 2006; Kennedy *et al.*, 2008; Levine *et al.*, 2008; Whyte, 2006). Functional neuroimaging studies examining the learning-induced plasticity associated with various forms of training in healthy, neurologically intact individuals have shown different patterns of results, primarily in terms of increases or decreases in regional brain activation (reviewed in Kelly and Garavan, 2005; Kelly *et al.*, 2006). The significance of these results remains unclear (e.g. Hillary, 2008). It is also unclear from functional neuroimaging studies of patients with acquired brain injuries as to what neural changes support improved recovery of function (e.g. Rosen *et al.*, 2000; Corbetta *et al.*, 2005; Chen *et al.*, 2008; Sánchez-Carrión *et al.*, 2008). Information regarding neural mechanisms of improvement in executive control functions is particularly sparse. Even the extent to which the neural systems that underlie executive control are plastic, if at all, has remained an open question. The most direct tests of theorized mechanisms would be to intervene and examine the neural changes that occur with treatment response. Only a handful of functional MRI studies to date have examined cognitive rehabilitation following brain injury (Laatsch *et al.*, 2004; Strangman *et al.*, 2008) and even fewer have examined the effects of rehabilitation interventions on executive control functions (Kim *et al.*, 2009). One particularly important but challenging question is to understand the individual variability in mechanisms by which different individuals may achieve improvement in functioning after brain injury.

Selective processing of goal-relevant information, a central component of executive control, is a crucial gateway that filters what information gains access to more in-depth processing (Baddeley, 2001; Cowan *et al.*, 2005; Vogel *et al.*, 2005; Cowan and Morey, 2006; Repovs and Baddeley, 2006; Awh and Vogel, 2008). Information processing from perception to action requires mechanisms of attention for selecting information, as well as maintaining and protecting this information from disruption during working memory, learning, decision-making and/or problem-solving. Deficits in these types of cognitive processes are common with acquired brain injuries, whether lesions are localized to prefrontal cortex, along white matter and interconnecting networks, or

poorly localized, as is often the case with traumatic brain injury (Wolfe *et al.*, 1990; Mesulam, 2000; Fork *et al.*, 2005; Scheid *et al.*, 2006). If one cannot hold key information active in the mind or protect it from distracting information, then subsequent actions are less likely to be guided efficiently or effectively towards goal attainment. Targeting these specific cognitive abilities may therefore lead to improvements in functioning that generalize to broader domains of goal-directed functioning.

The overall objective of this study is to determine the underlying neural mechanisms that support cognitive improvements with rehabilitation training of attention regulation. In a previously reported study of individuals with chronic acquired brain injury (Novakovic-Agopian *et al.*, 2010), we applied a training intervention for improving goal-directed attention regulation that takes into account the links connecting attention, working memory and goal-based direction of behaviour in daily life. In contrast to training via practice on isolated tasks, this training protocol involved application of attention regulation skills and strategies in ecologically valid situations. The experimental training protocol was based on goal-management and problem solving training interventions that have been applied to patients with brain injury as well as other populations (D'Zurilla and Goldfried, 1971; VonCramon *et al.*, 1991; Robertson, 1996; Levine *et al.*, 2000, 2007; Rath *et al.*, 2003; Nezu *et al.*, 2007; Schweizer *et al.*, 2008), with special emphasis on mindfulness-based attention regulation strategies applied to daily life situations and complex, project-based functional tasks. Individuals who completed the training protocol significantly improved on neuropsychological measures of attention and executive control, while participation in a brief educational activity resulted in no such improvements. Furthermore, training generalized to improved functional performance in complex 'real-world' settings.

We hypothesized that training in attention regulation improves cognitive performance by enhancing goal-based modulatory control of neural processing. To test this hypothesis in the current study, we scanned individuals before and after these interventions and examined effects on a functional MRI biomarker designed to index the neural correlates of attentional modulation. Importantly, our functional MRI measurements allowed us to detect neural changes on a within-subjects basis over time and to be robust to interindividual variations in pathological damage. The cognitive task performed during scanning was based on the common situation in everyday life where multiple incoming streams of information compete for attention and processing. For example, although multiple images (such as of faces, scenery and other objects) may be viewed, a person may be interested in learning the faces of individuals in one moment, but identifying scenic views in another. This task requires perception of all images, each resulting in representations within brain networks, but selective processing of some images in preference to others depending on the task goals. Thus, the processing of perceptually derived information would need to be modulated based on goal-relevance to favour clearer representation of some images over others during more in-depth processing. We indexed goal-based modulation of neural processing using a novel functional MRI pattern classifier method to decode the clarity of information representation when stimuli were goal-relevant versus non-relevant. We predicted that

enhanced goal-based modulatory control of neural processing would be evident in changes in neural representations in visual areas involved in stimulus processing as well as in changes in pre-frontal cortex, a likely source of goal-based modulatory control signals.

Materials and methods

Participants

Sixteen patients with chronic acquired brain injury (≥ 6 months) participated in the study after providing informed consent according to procedures approved by the Institutional Review Boards of the California Pacific Medical Centre, University of California, San Francisco and San Francisco VA Medical Centre. Of these, 12 participated in MRI and were eligible for these analyses (four declined due to claustrophobia, concerns regarding discomfort from positioning or fatigue). The mean age of these subjects was 48 (range 24–63) years; seven were female and five were male. All patients had ongoing cognitive dysfunction with corroborated reports of difficulties in personal life functioning consistent with executive control deficits. All were on stable medication regimens and had no active illicit drug use, severe depression, aphasia or other criteria that would impede participation in the intervention or measurements (Table 1). Brain injuries were from trauma, stroke, haemorrhage, tumour resection and chemotherapy. Lesions were visible on fluid attenuated inversion recovery and magnetization-prepared rapid acquisition with gradient echo images for eight participants, with lesion locations predominantly affecting not only the frontal lobes, but also other cortical and white matter regions (Fig. 1).

Interventions

Two intervention conditions were employed: (i) training in goal-oriented attentional self-regulation (*goals training*); and (ii) a comparison educational activity (*education*). The goals training protocol was based on a goal-management training intervention (Robertson, 1996; Levine *et al.*, 2000, 2007), as well as principles highlighted in other attention, mindfulness and problem-solving interventions (D'Zurilla and Goldfried, 1971; Kabat-Zinn, 1990; VonCramon *et al.*, 1991; Rath *et al.*, 2003; Nezu *et al.*, 2007). The *goals training* protocol involved 10 2-h sessions of group-based training, three individual 1-h training sessions and ~ 20 h of home practice over 5 weeks. Training was conducted in a small group format with 2–5 patients and two instructors per group. To ensure consistency of administration, intervention manuals were written for instructors and participants. Clinicians experienced in working with individuals with brain injury (occupational therapists, neuropsychologists) were trained in administering the research intervention and were supervised by one of the authors of the instruction manual.

Mindfulness-based attention regulation training was emphasized in the first half of the *goals training* intervention, and goal management strategies applied to participant defined goals was emphasized in the second half. Thus, initial group sessions focused on incorporating strategies for reducing distractibility, emphasizing principles of applied mindfulness to redirect cognitive processes towards goal-relevant activities even when distracted. This required identifying the primary goal, dividing information into relevant and non-relevant, and working to selectively maintain relevant information while letting go of non-relevant information. Introductory training via in-class exercises began with a brief applied mindfulness exercise as a first step in refocusing on tasks at hand, applied to progressively more challenging situations including maintaining increasing amounts of information in mind, up to maintaining information during distractions. These exercises were

Table 1 Participant characteristics

ID	Age/gender	Brain injury history	Lesion description
4	31M	TBI from fall (1.5 years)	Left frontal haemorrhage and multi-focal white matter T ₂ hyperintensities
5	47F	TBI from fall (1.5 years)	No visible lesions
6	34F	TBI from motor vehicle accident (1.5 years)	Left frontal and inferior parietal white matter T ₂ hyperintensities
7	45M	Leucoencephalopathy from chemotherapy (1 year)	Ventriculomegaly, widened sulci, small foci of sub-frontal white matter T ₂ hyperintensity, right frontal track c/w prior catheter placement
8	62M	TBI from assault, s/p bi-frontal subdural haematoma evacuation (6 months)	Generalized moderately widened sulci, split septum pellucidum
9	60F	TBI from motor vehicle accident (2.5 years)	No visible lesions
10	63F	Right temporal-parietal tumour resection (1.5 years)	Bilateral confluent white matter T ₂ hyperintensities. Left frontal and right temporal-parietal lesions
11	51F	TBI from motor vehicle accident (1.5 years)	Right frontal encephalomalacia, enlarged ventricles and widened sulci.
12	55F	TBI from fall (1 year)	Left orbitofrontal encephalomalacia and T ₂ hyperintensity
13	24M	TBI from fall + multiple blast exposures (4 years)	No visible lesions
14	41M	TBI from fall + multiple blast exposures (6 years)	No visible lesions
15	62F	Left basal ganglia stroke (2 years)	Frontal-subcortical, periventricular occipital white matter T ₂ hyperintensities, widened sulci

Subject numbers are matched to the larger group in Novakovic-Agopian *et al.* (2010), and years since injury are listed in parentheses. Additional information regarding injury history and baseline functioning are presented in Supplementary Table 1.

F = female; M = male; TBI = traumatic brain injury; c/w = consistent with; s/p = status post.

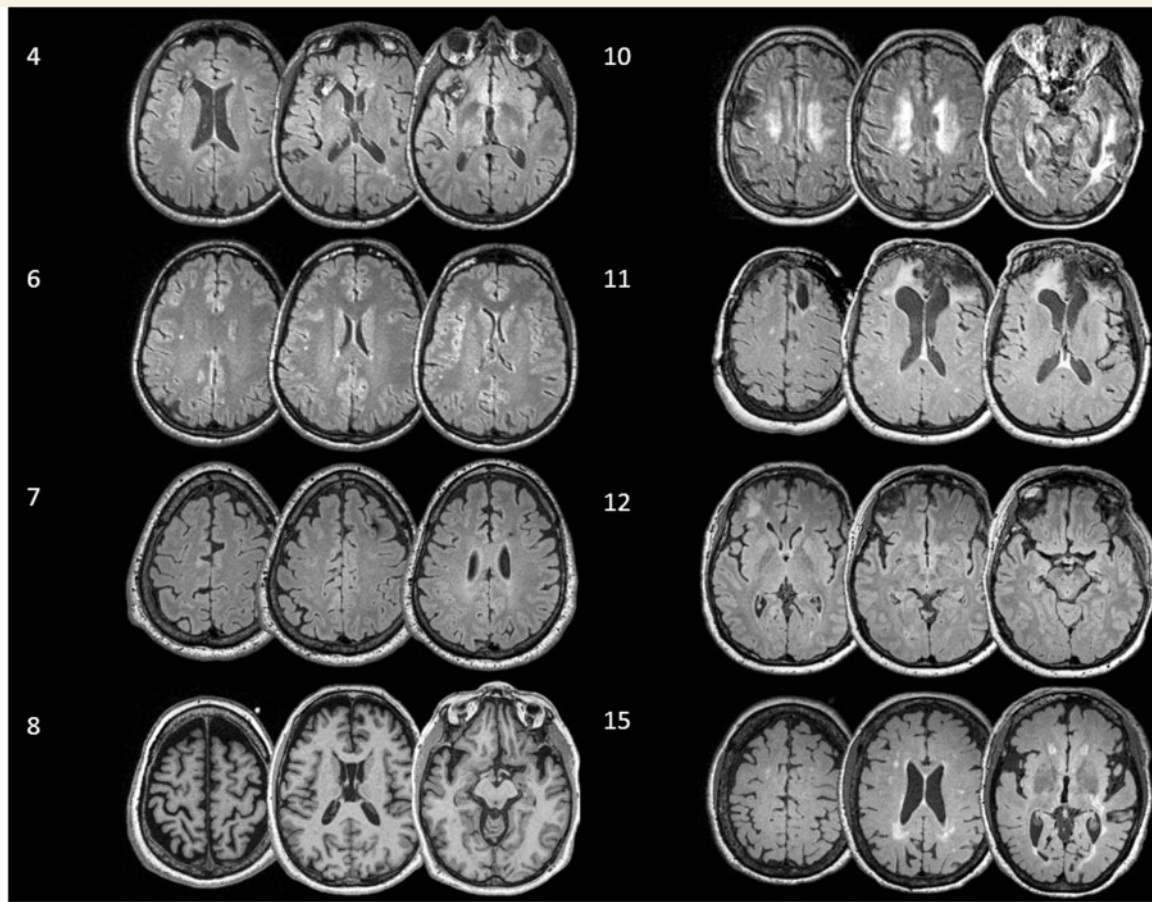


Figure 1 Representative structural MRI images from participants with visible structural brain lesions.

supported by homework including daily practice with mindfulness in a quiet setting, assisted by an audio CD from a traditional mindfulness-based stress reduction course (provided by Kevin Barrows, MD, UCSF). Homework then progressively emphasized application of these skills to challenging situations in each individual's daily life. To assist application in daily life situations, participants were trained in applying a single phrase meta-cognitive strategy ('STOP-RELAX-REFOCUS') to stop activity when distracted and/or overwhelmed, relax and then refocus attention on the current, primary goal.

The second phase of the *goals training* protocol emphasized learning strategies for accomplishing individually-salient, self-generated complex goals. In order to emphasize active application of these strategies, participants were asked to identify feasible and realistic functional goals as individual projects (e.g. planning a meal, learning to use an organizer and follow a schedule) and group projects (e.g. planning a group outing or presentation), and were then trained to apply attention regulation and stepwise goal management strategies on the functional task(s) of their choice. The stepwise goal management and execution strategies we chose to use were modified from Goal Management Training (Robertson, 1996; Levine *et al.*, 2000, 2007) and Problem Solving Therapy protocols (D'Zurilla and Goldfried, 1971). Additional details are provided in the online Supplementary Methods section, with training sessions outlined in Supplementary Table 2.

In the alternate 5-week period, a comparison educational activity was utilized. This involved didactic educational instruction regarding

brain injury (causes, symptoms and effects) and resources for assistance in a 2-h session, and was administered in the same groups by the same trainers. This brief comparison activity was included to allow assessments of the effects of repeated testing in the context of an intervention that was designed without features for training goal-directed control functioning.

Study design and analyses

Study design

Eligible participants were randomized to receive either the *goals training intervention* or *education* during the first 5-week study period. The participants then switched over to the alternative condition for the second 5-week study period. Of the 12 participants, five started with goals training and seven started with education. Behavioural and functional MRI measurements were performed at three time points: (i) Assessment 1 prior to any participation in interventions; (ii) Assessment 2 at the end of the first study period (5 weeks); and (iii) Assessment 3 at the end of the second study period (10 weeks). Some of the 12 participants had fewer than three measurements for some tests and could not be included in all analyses.

Primary study analyses

The primary analysis quantified changes that occurred from pre- to post-*goals training*, testing hypotheses regarding the effects of *goals*

training for each of the measured variables. We tested the hypothesis that training results in behavioural improvements related to attentional self-regulation, evident in improved performance on non-trained neuropsychological tests of attention and executive control, also testing for potential transfer to learning and memory tasks predicted to be influenced by these functions and more general changes such as in motor speed. With functional MRI measurements, we tested the hypotheses that *goals training* would enhance modulation of neural processing in extrastriate cortex and alter processing in prefrontal cortex.

We compared changes that occurred pre- to post-*goals training* with those that occurred pre- to post-*education*. Changes were assessed in a linear mixed model, with the primary factor of interest being intervention condition (*goals training* versus *education*). Some participants received *goals training* first, and some after *education*, so study periods were combined to test the effect of training. We performed this analysis under the assumption that the education intervention would not lead to significant behavioural or neural changes, which we confirmed (refer to Supplementary material). Random effects models accounting for repeated measurements per participant were then used to examine the association of *goals training* (as compared to *education*) on the measured changes.

For each variable, we tested for the possibility that training effects would be modulated by baseline state, given that changes in frontally mediated control functions have been suggested to depend on baseline state in other contexts (Arnsten and Goldman-Rakic, 1998; Kimberg *et al.*, 2001; Cools *et al.*, 2008). Pre-intervention scores were entered as covariates in the mixed models to determine whether changes with intervention participation were related to individual variability in pre-intervention scores.

Secondary study analyses

Secondary analyses were performed in order to corroboratively test the hypotheses. First, a within-subjects assessment of the effects of *goals training* relative to 'multiple baseline' measurements was conducted using paired *t*-tests for the individuals who started with *education*

prior to goals training. This follows a conventional rehabilitation study design for small subject samples, maximizing the power of comparison to a control condition on a within-subjects basis while taking into account possible effects of repeated testing. Second, an across subjects comparison of changes in each variable was performed in the first period only, comparing pre- to post-*education* versus *goals training* as per a traditional randomized design. We utilized this analysis only to corroborate the findings from the primary analyses, as we expected high interindividual variability relative to intergroup variability so that power may not be sufficient to rule out effects even if none were detected.

Baseline characteristics (age, education, attention and executive function test scores) as well as group means and variability in baseline measurements for each of the behavioural and neural variables were assessed. These are provided in the online Supplementary Results section, and only data pertinent to the question of changes with intervention are presented here.

Functional MRI cognitive task design

In all task conditions, participants viewed a series of images composed of two categories (faces and scenes) interleaved in a pseudo-randomized order with jittered timing (3, 5 or 7 s apart) (Fig. 2). Thus, perceptual information was matched, but task demands differed in four attention conditions. In two selective attention conditions (Select Faces, Select Scenes) participants were instructed to selectively attend and hold in mind images from one category. Task performance required recognition of 1-back matches within the relevant category, with button-press responses to every image indicating whether the image was a 'match' or 'non-match' to the preceding image from the relevant category. Therefore, in order to successfully complete the task, participants had to perceive and recognize all images but selectively maintain only relevant images in working memory in the face of potential distraction from non-relevant images. Two non-selective conditions were included in the task but are not reported in the current analyses. These conditions and

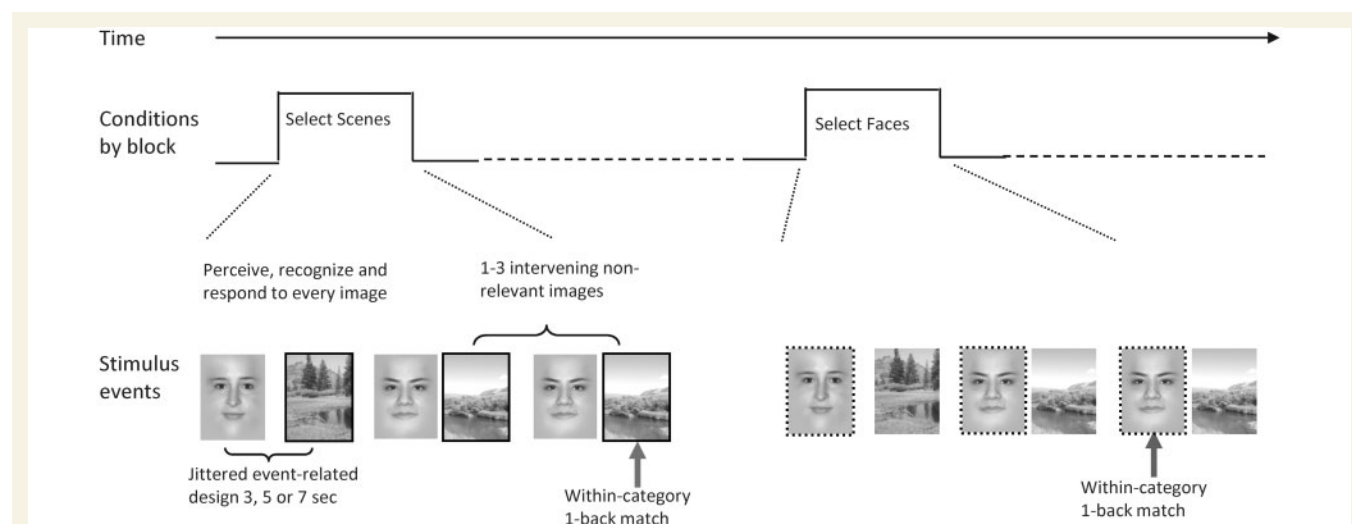


Figure 2 Selection task performed during functional MRI data acquisition. Participants viewed a series of images composed of two categories (faces and scenes). In two selective attention conditions (select faces, select scenes) participants were instructed to selectively attend and hold in mind images from one category. The only difference across conditions was the task instructions, making particular image categories relevant or non-relevant, while the perceptual content did not differ across conditions. Solid and dashed lines are used only for purposes of illustrating task relevance, while only the greyscale images were used in the actual task.

additional details of task design are described in the Supplementary Methods section. Session data were excluded from further analyses if behavioural performance accuracy did not exceed 70%. Data for one session for one subject were excluded on this basis.

In each block, 20 images (10 faces and 10 scenes) were presented sequentially. Jittering and image category orders were balanced across condition blocks and counterbalanced across participants. Five blocks of each experimental condition were presented during the session, resulting in a sample of 100 stimulus events per condition (total sample of 400 stimulus events). Condition orders within runs were balanced over the course of the scanning session. Four alternate sets of stimuli were generated for use in multiple sessions, and set order was permuted across subjects.

Functional MRI data acquisition and preprocessing

Imaging was performed using a 3-T Siemens Magnetom Trio whole-body magnetic resonance scanner with a transmit-receive 12-channel quadrature bird cage head coil at the UCSF Neuroscience Imaging Centre. For each task block, 114 whole-brain T_2^* -weighted echo planar images were acquired (slice thickness, 5 mm; 0.5 mm skip; 18 slices; repetition time = 1000 ms; echo time = 27 ms; flip angle = 62° ; matrix, 64×64 axial field of view). Three volumes were discarded at the beginning of each run to allow for equilibration. A T_1 -weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) and a T_2^* -weighted fluid-attenuated inversion recovery (FLAIR) sequence were acquired for each subject for characterization of structural anatomy.

Image preprocessing was conducted using Analysis of Functional Neuroimaging Software (AFNI: v2008-07-18-1710). Echo planar image data were slice-time corrected and realigned using a nine-parameter affine registration to correct for head motion. No participants exceeded our *a priori* movement limits of 2-mm translation and 2° rotation. Additional details of preprocessing procedures are described in the Supplementary Methods section.

Region of interest definition

Anatomical masks were defined for dorsolateral prefrontal cortex (bilateral middle frontal gyrus) and extrastriate cortex (fusiform, parahippocampal and lingual gyri, bound by the inferior edge of the lateral ventricles superiorly, temporo-occipital fissures anteriorly and intra-occipital sulci posteriorly) (Supplementary Methods section).

Functional MRI data analysis

Analyses of information contained in patterns of brain activity

The cognitive task performed during functional MRI presents multiple stimuli that compete for neural processing, while only goal-relevant stimuli must be selected for further processing. For example, if scenes are relevant, then attention likely sharpens the clarity of neural representations of scenes relative to other perceived stimuli. In contrast, if scenes are not relevant, then scenes may be represented with less clarity. To measure these types of effects with functional MRI, we utilized a multi-layer perceptron pattern classifier (O'Toole *et al.*, 2007 for a general review) as an 'external reader' to determine the clarity of information representation in the neural codes embedded in functional MRI activity patterns. We reasoned that the more clearly stimulus information is represented in these measured neural codes,

the more certain the pattern classifier should be in recognizing that information in each activity pattern.

Multi-voxel signal intensity patterns from task trials were presented to a multi-layer perceptron pattern classifier for classification based on the category of the viewed image (faces or scenes). These analyses were performed using the Multi-Voxel Pattern Analysis toolbox v1.0 with Netlab v3.2 backend, both implemented in MATLAB (The MathWorks, Inc). Procedures were performed for each individual participant, separately for extrastriate and for prefrontal cortex. Training of the classifier was completed on patterns from four of the five condition blocks (20 stimuli for each block) with testing carried out on the fifth block, in a 'leave-one-out' iterative manner (Hanson *et al.*, 2004). One hidden layer of 10 nodes with logistic activation functions was included, and scaled conjugate gradient descent was used in error back-propagation during training of the classifier.

During testing, sample multi-voxel patterns corresponding to the viewing of an image are provided to the pattern classifier (e.g. either scenes or faces; Fig. 3). The output derived from the multi-layer perceptron is a classification assignment based on the output node activations (Fig. 3). The two output nodes correspond to the two category labels (faces and scenes), with their activations reflecting the input pattern's resemblance to the patterns learned during training. The clarity of information representation in brain patterns was indexed by the certainty of the classification decision for each test pattern. This certainty was calculated as the difference between the output node activations. For example, as illustrated in Fig. 3, when the participant is viewing scene images, the certainty score is calculated as 0.90 (scene node output)–0.10 (face node output) = 0.80. This high certainty value (larger difference between values of scene and face output nodes) would be predicted to be found when a participant is instructed to selectively attend to scenes. However, when a participant is instructed to selectively attend to faces while viewing a scene image, the certainty of the classification condition is predicted to be lower (Fig. 3). In this example, the scene output node score is 0.60 and the face output node score is 0.40 resulting in a lower certainty score of 0.20. Thus, the difference in the calculated certainty scores between the opposing attention conditions reflects the difference in the clarity of representation of goal-relevant versus non-relevant information within each brain region. The differential certainty score was obtained at each assessment time point, allowing calculation of changes in modulatory control over neural processing from pre- to post-intervention.

Neuropsychological tasks

An 'Attention and Executive Function Domain' score comprised scores from letter number sequencing, Wechsler Adult Intelligence Scale (third edition) (Wechsler, 1997), auditory consonant trigrams at 9, 18, 36 s (Stuss *et al.*, 1988); Digit Vigilance Test—time and errors (Heaton *et al.*, 2004); Design and Verbal Fluency Switching (Delis *et al.*, 2001); Trails B (Heaton *et al.*, 2004); Stroop Inhibition/Switching—time and errors, and Stroop Inhibition—time and errors (Delis *et al.*, 2001). A 'memory domain' score comprised scores from verbal and visual learning and delayed recall from the Hopkins Verbal Learning Test (Brandt and Benedict, 2001) and the Brief Visual Memory Test Revised (Benedict, 1997). A 'psycho-motor speed domain' score comprised scores from the Trails A test (Heaton *et al.*, 2004) and the Visual Attention Task overall reaction time (Novakovic-Agopian *et al.*, 1999). All neuropsychological test data were scored based on age and, when available, educational and repeated administration norms, and transformed into z-scores for consistency. Additional neuro-behavioural and functional performance

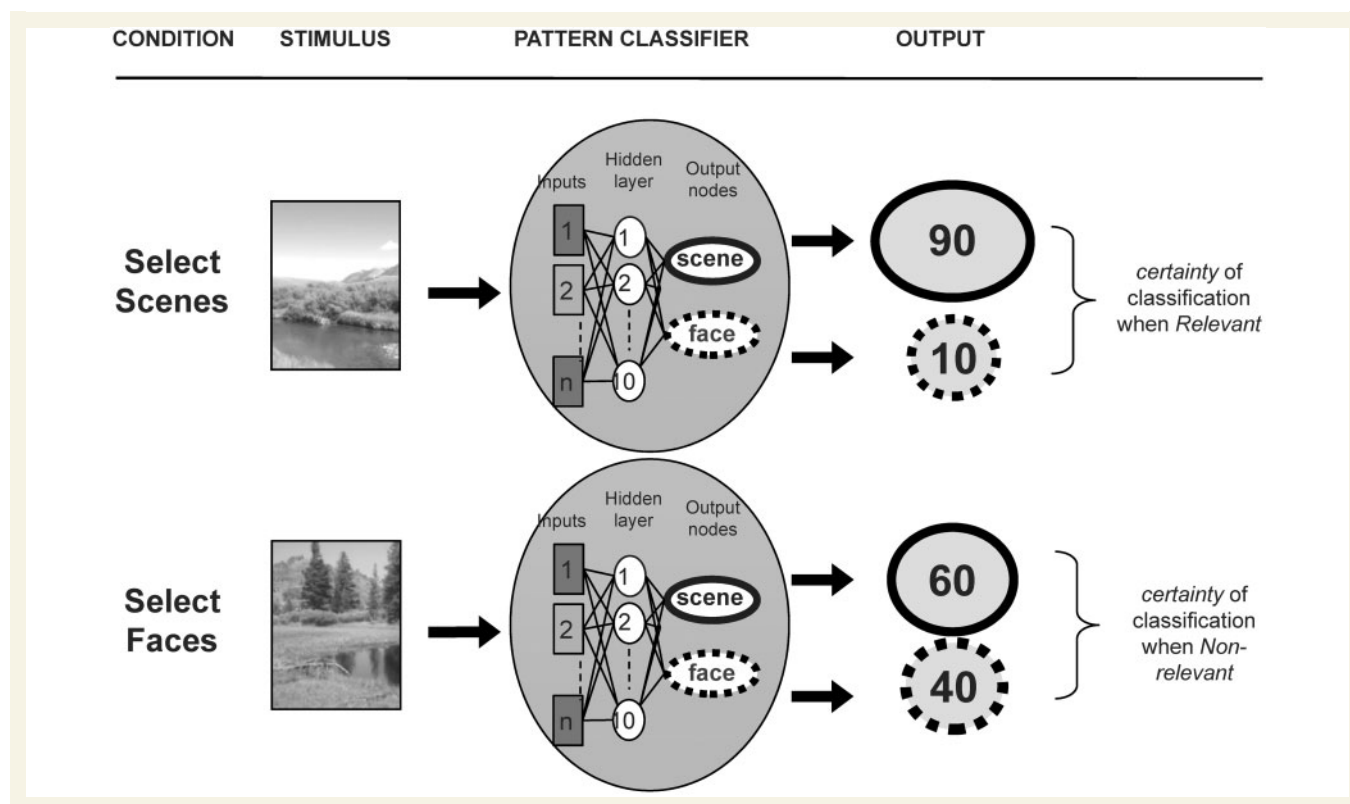


Figure 3 Schematic of the determination of the clarity of information representation in brain activity patterns during the test block. In this example, inputs to the trained multi-layer perceptron are sampled patterns from scene stimulus trials (left) from either the Select Scenes condition (above) or Select Faces condition (below). The output node activations (right) reflect the classifier's recognition of the pattern as representing a face or a scene stimulus. The magnitude of the difference between these output nodes indexes the certainty of classification for samples from a particular task condition. The effect of selective attention is indexed by the difference in certainty when an individual is instructed to select scenes versus select faces (i.e. the differential for when scenes are relevant versus non-relevant). This relevant to non-relevant differential is used as the primary measure for each brain region at each of the assessment time points.

measures are described in detail in a separate report (Novakovic-Agopian *et al.*, 2010), and are not detailed here.

Results

Changes in performance on neuropsychological tests

Attention and executive function domain

We first tested the hypothesis that participation in *goals training* would improve behavioural performance on tests of attention and executive control. All 12 participants showed an increase in performance scores in the domain of Attention and Executive Functions from pre- to post-*goals training*, while 7/12 participants showed an increase from pre- to post-*education* (Fig. 4). To test whether this represented a significant difference, we used mixed-model regression analysis. Performance scores increased an average of 0.78 z-score standard units more after participation in *goals training* than after participation in *education* ($P < 0.0001$). When entered as covariates in the regression analysis, neither the initial performance score nor the order of intervention participation accounted for this difference between intervention conditions.

In order to corroborate the main findings, changes were analysed on a within-subjects basis for participants who started with *education* and crossed over to *goals training* ($n = 7$). In this group, changes from pre- to post-*goals training* were significantly greater than changes pre- to post-*education* ($P < 0.0001$). We performed an additional across-subjects comparison of changes for *goals training* and *education* in the first study period (as in a randomized study), and found that *goals training* also resulted in greater improvements than *education* ($P < 0.0001$) in this analysis.

Learning and memory domain

In order to test for transfer of training effects to functions that are influenced by attention regulation, we measured performance on tests engaging the domain of learning and memory. Eleven out of 12 participants showed an increase in performance scores from pre- to post-*goals training*, while four out of 12 participants showed an increase from pre- to post-*education* (Supplementary Fig. 1). Performance scores increased an average of 0.70 standard units more after participation in *goals training* than after participation in *education* ($P = 0.02$). Neither initial score nor order of intervention participation accounted for these differences between intervention conditions. Corroborative within-subjects analyses of the participants who started with *education* and crossed over to

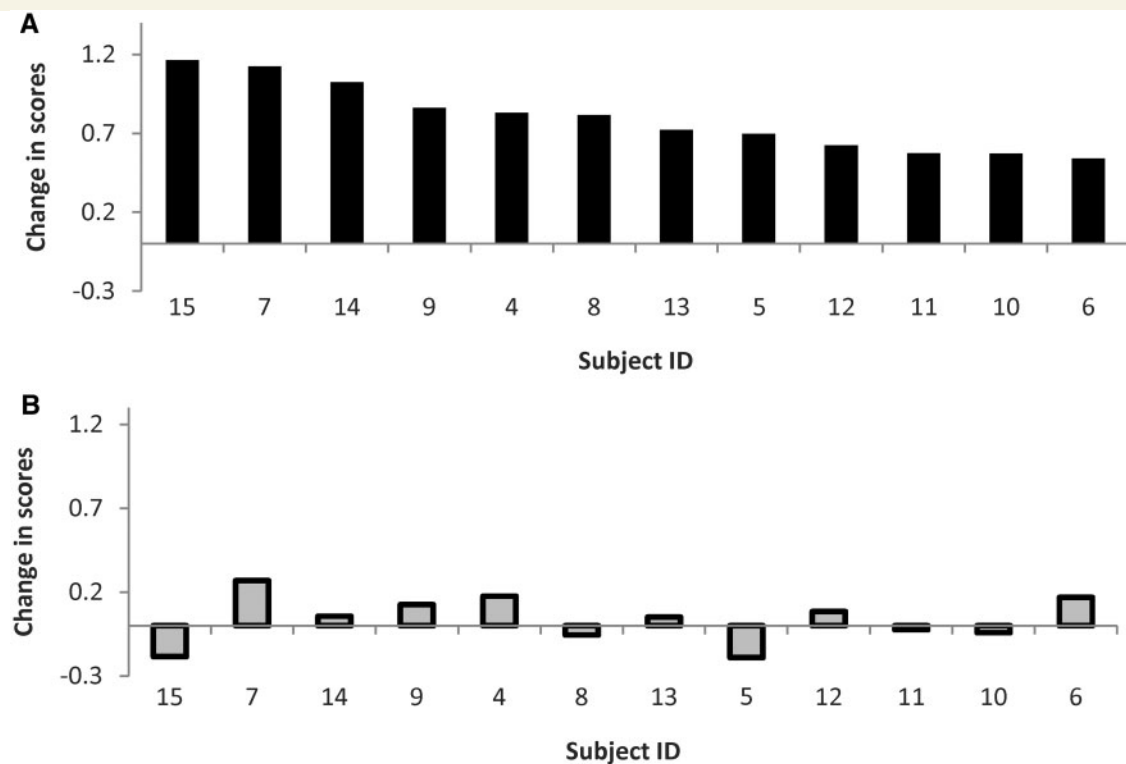


Figure 4 Changes in attention and executive function composite scores for (A) *goals training* and (B) *education*. Bars represent change in z-scores (i.e. post-intervention minus pre-intervention z-score). The individual data are sorted based on magnitude of change, in order to illustrate descriptively the number of individuals with changes in the positive or negative direction with the goals training intervention, and participant identification numbers are matched to each subject's scores pre- and post-education to facilitate direct comparison across intervention conditions.

goals training revealed significantly greater changes from pre- to post-*goals training* than pre- to post-*education* ($P = 0.009$). An additional across-subjects comparison of changes for *goals training* and *education* in the first study period showed that *goals training* resulted in greater improvements than *education* ($P = 0.009$).

Motor speed of processing domain

In order to test for general changes in psychomotor performance, we measured performance on tests of motor speed of processing. Seven out of 12 participants showed an increase in performance scores in the domain of Motor Speed of Processing from pre- to post-*goals training*, while two out of 12 participants showed some increase in performance scores from pre- to post-*education* (Supplementary Fig. 2). There was a non-significant trend where the performance scores for participation in *goals training* increased more than for *education* ($P = 0.07$). Corroborative within-subjects analyses of the participants who started with *education* and crossed over to *goals training* did not show significant effects ($P = 0.28$), and the across-subjects first period analysis comparing *goals training* to *education* also did not show significant effects ($P = 0.09$).

Data for the learning and memory as well as motor speed of processing domains is presented in Supplemental Results. Results for the individual neuropsychological tests that form the composite domain scores are presented in Supplementary Table 3.

Changes in performance on cognitive task during functional MRI scanning

The cognitive task was designed to be easily learned and performed, so that neural changes could be examined without concern for changes in basic task performance. All participants reported being able to learn the basic task rules, and were able to complete the task during functional MRI scanning. Overall, we did not observe any significant changes in task after either intervention. Seven out of 11 participants showed an increase in task accuracy from pre- to post-*goals training*, while four out of five participants showed some increase in performance scores from pre- to post-*education*. We found no difference in task accuracy for participation in *goals training* compared to *education* ($P = 0.65$). Corroborative within-subjects analyses of the participants who started with *education* and crossed over to *goals training* did not show significant effects ($P = 0.41$), nor did the across-subjects first period analysis comparing *goals training* to *education* ($P = 0.40$).

Neural representations in extrastriate cortex

We predicted that *goals training* would enhance top-down modulation of neural processing, measured with functional MRI, which

would manifest as increased clarity of representation of goal-relevant relative to non-relevant information within visual cortex. For each assessment, we calculated a functional MRI index of goal-directed modulatory control in extrastriate cortex by subtracting the recognition certainty scores generated by the pattern classifier when a stimulus category was relevant versus non-relevant (e.g. faces would be relevant in the Select Faces condition, while scenes would be non-relevant, and vice versa in the Select Scenes condition). By definition, a positive differential would indicate relatively greater clarity of representation of goal-relevant information, while a negative differential would indicate relatively greater clarity of representation of non-relevant information. Baseline measurements, prior to any intervention participation, indicated a significant bias towards positive scores, i.e. greater clarity of goal-relevant information (presented in more detail in the online Supplementary Results section). To determine the effects of intervention, change scores were then calculated by subtracting pre-intervention scores from post-intervention scores for *goals training* and for *education*. Thus, by definition, a positive change score would indicate a change in modulation that results in increased clarity of representation of goal-relevant information relative to non-relevant, while a negative change score would indicate a change in modulation that results in an increase in clarity of non-relevant information relative to relevant.

Overall, nine out of 11 participants with pre- to post-*goals training* data showed a positive change in differential certainty

scores, while only one out of five participants with pre- to post-*education* data showed a positive change in this differential (Fig. 5A) Using a mixed-model regression analysis, we found that *goals training* resulted in significantly greater average positive change in the differential scores of 0.11 compared to *education* ($P = 0.04$). When entered as covariates in the regression analysis, neither the initial performance score nor the order of intervention participation accounted for this difference between intervention conditions.

Of the participants who started with *education*, six out of seven participants showed a positive change in differential certainty scores from pre- to post-*goals training* ($P = 0.02$). Comparing across subjects in the first study period, we observed that three out of four participants showed a positive change in score for *goals training*, while zero out of three showed a positive change for *education*. Initial assessment data were not available for some subjects due to scanner technical issues, leaving a sample size too small for across subject's statistical comparison.

Neural representations in dorsolateral prefrontal cortex

As with extrastriate cortex, by definition of the relevant–non-relevant differential index scores, positive values reflect relatively greater clarity of representation for information that is goal relevant and negative values reflect relatively greater clarity

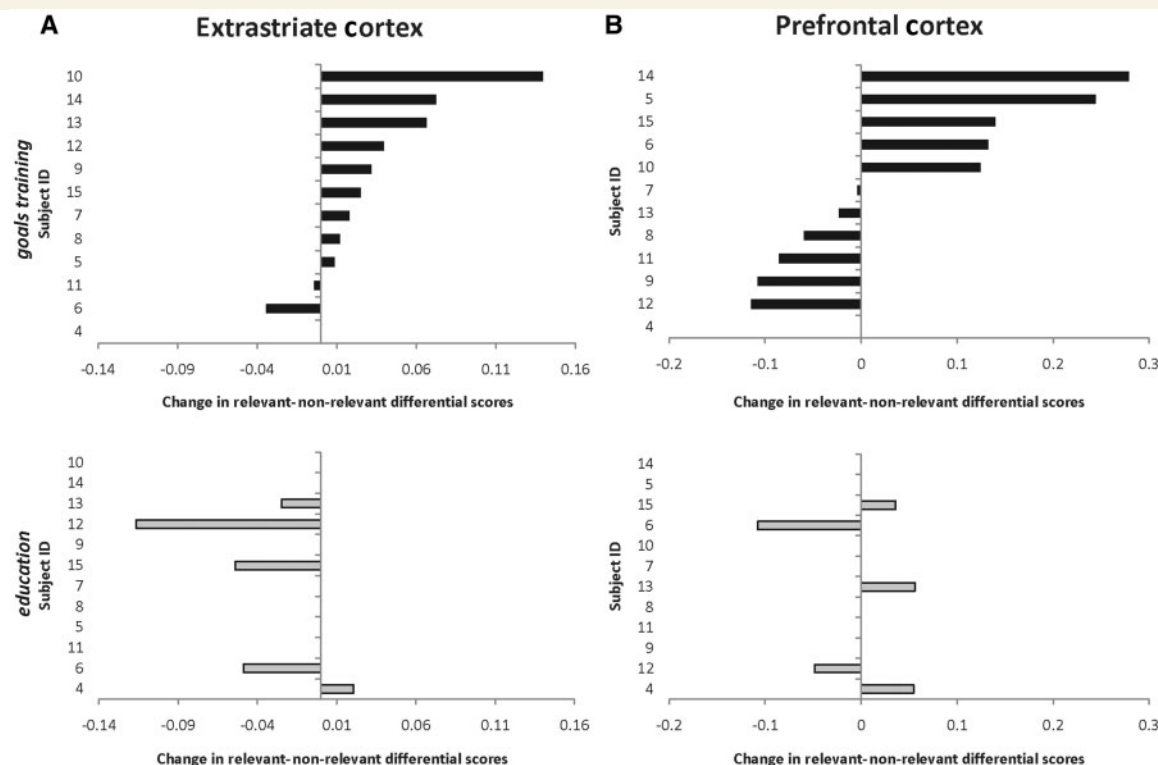


Figure 5 Changes in index scores (relevant–non-relevant differential certainty scores) in (A) extrastriate cortex and (B) prefrontal cortex for *goals training* and *education*. Change scores were calculated by subtracting pre-intervention scores from post-intervention scores for *goals training* and for *education*. Data are presented sorted based on the magnitude of the change and individual subjects are matched across *goals training* and *education*.

of representation for information that is non-relevant. Change scores were calculated to determine the directionality of any changes with intervention participation for *goals training* or *education*.

Changes in the positive direction were observed for five out of 11 participants with *goals training*, reflecting an increase in the representation of goal-relevant relative to non-relevant information, and changes in a negative direction were observed in six participants (Fig. 5B). Changes in a positive direction were observed for three out of five participants with *education*, and changes in a negative direction were observed for two participants. Using a mixed-model regression analysis, we found that *goals training* did not result in an increase in differential scores relative to *education*, consistent with both positive and negative changes being found following *goals training*.

In a mixed-model regression analysis, we found that pre-intervention functional MRI differential score was associated with change scores. A significant interaction between intervention condition and pre-intervention scores indicated that pre-intervention scores had a different effect after *goals training* than *education*. Specifically, there was a significant inverse relationship between the pre-intervention scores and the changes from pre- to post-*goals training* ($P = 0.03$), whereas the relationship between pre-*education* scores and changes from pre- to post-*education* were not inversely related (Fig. 6). We separately tested the correlation of pre-*goals training* scores with changes pre- to post-*goals training* and found a significant inverse correlation ($P < 0.0001$, $r = -0.90$), such that lower pre-intervention scores predicted greater changes in a positive direction and higher pre-intervention scores predicted greater changes in a negative direction (scatter plots for pre-intervention prefrontal cortex scores with changes in prefrontal cortex scores are presented in Supplementary Fig. 3). This correlation was not significant in the *education* group. Based on follow-up analyses, this effect could not be explained solely by regression to the mean (Supplementary Results section, Supplementary Fig. 4).

Discussion

This study investigated the neural mechanisms underlying improvements in cognitive abilities following a training intervention targeted at improving goal-directed attention regulation. Cognitive assessments confirmed improvements in performance on non-trained tasks assaying attention and executive control, with evidence of transfer to learning and memory. Utilizing functional MRI methods for measuring the representations of cognitive task information in neural codes, we found that modulation of neural processing in extrastriate cortex was significantly enhanced by attention regulation training whereas training effects within prefrontal cortex depended on an individual's baseline state.

Modulation of extrastriate cortex with attentional self-regulation training

Our primary functional MRI biomarker indexed goal-directed modulatory control over neural processing. Extrastriate cortex was

investigated because it is involved in the recognition of object categories utilized in our task (e.g. faces versus scenes), and its activity is known to be modulated by attentional demands in healthy individuals (O'Craven *et al.*, 1999; Gazzaley *et al.*, 2005a, b). We specifically measured the tuning of neural codes based on the goal relevance of the visual events, indexed as the relative balance of representation of relevant versus non-relevant information within brain regions. Participants attempted to selectively maintain goal-relevant faces or scenes, while non-relevant, distracting images are perceived. Thus, representations of relevant and non-relevant images competed for processing within extrastriate cortex.

There are a number of ways in which attention could modulate neural processing in extrastriate cortex. For example, during performance of a cognitive task, neural representations of all competing information might be strengthened, or in contrast, only selected representations might be strengthened. We hypothesized that attention training would lead to changes in tuning of neural representations such that the balance of representation would favour goal-relevant information. Our findings with training were consistent with this prediction—neural tuning within extrastriate cortex was shifted to increase the clarity of goal-relevant information relative to non-relevant. We observed these changes in individuals who participated in *goals training*, regardless of whether this training occurred before or after participation in a brief *education* session. Although our sample size was small, these findings were statistically significant and were corroborated by both within-subjects and across-subjects comparisons. Thus, improving the clarity of representations of information in earlier processing areas of the brain when multiple items of information compete for processing could lead to better processing at higher levels, and this may be one neural mechanism underlying the behavioural improvements after attention training. An interesting follow-up question is whether this selective tuning is mediated by up-modulation of neural representations of goal-relevant information, or down-modulation of representations of non-relevant material. For example, a recent neurophysiological study found that attention modulates neuronal firing rates by both increasing firing related to attentional targets and decreasing firing related to distractors (Cerf *et al.*, 2010). Such a mechanism could lead to sharpening of the distributed, overlapping representations of goal-relevant information in the brain.

Modulation of prefrontal cortex with attentional self-regulation training

The lateral prefrontal cortex has been strongly implicated as a source of attentional control signals that could bias neural processing in extrastriate cortex (Desimone, 1998; Miller and Cohen, 2001; Miller and D'Esposito, 2005; Miller *et al.*, 2011). For prefrontal cortex to guide neural processing in extrastriate cortex based on goals, representations of relevant and/or non-relevant information must be coded in prefrontal cortex as well, though the specific nature of these representations should differ from the stimulus-driven representations coded in extrastriate cortex (Fuster *et al.*, 1985; Rees *et al.*, 1997). Overall, the pattern of findings within lateral prefrontal cortex were consistent with the

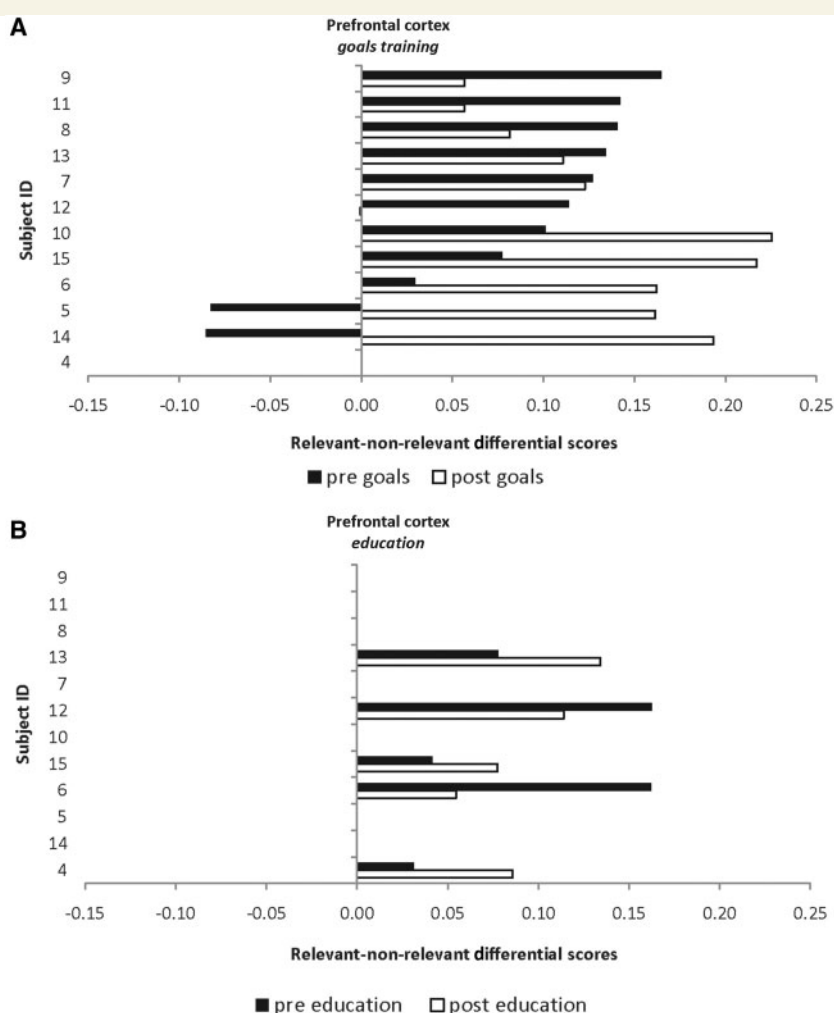


Figure 6 Pre- and post-intervention scores for prefrontal cortex for (A) *goals training* and (B) *education*. Black bars represent pre-intervention scores, and white bars indicate post-intervention scores. Individual data are sorted by pre-intervention baseline score to illustrate the relationship between pre-intervention scores and pre- to post-intervention changes.

general principle that individual improvements in attention regulation are mediated by mechanisms that can vary across individuals, while highlighting that changes in function depend on the baseline state of any given individual. When we examined changes in lateral prefrontal cortex after *goals training*, we found that our functional MRI index of the balance of representation of goal-relevant and non-relevant information shifted for each individual in a direction that depended on that individual's baseline measurement.

Although our findings are consistent with the general concept that changes in prefrontal cortex functioning depend on baseline state (Arnsten and Goldman-Rakic, 1998; Kimberg *et al.*, 2001; Cools *et al.*, 2008), the wide range of individual variability, involving changes in both positive and negative directions, was unexpected and intriguing. For those with baselines tuned to represent non-relevant information more strongly than goal-relevant, the balance shifted towards the goal-relevant after training. For those with baselines more tuned towards goal-relevant information, the balance shifted in the opposite direction. All individuals functioned less well at baseline than post-training, but the findings

suggest the hypothesis that different strategies were utilized by different individuals in order to improve performance. These changes in neural strategies were measurable as changes in prefrontal cortex coding.

This study adds a potential direction for investigating candidate determinants for the significant individual variability observed in response to interventions in clinical practice. In another example, a study using a different functional MRI marker showed a non-linear relationship between baseline prefrontal cortex functioning and memory strategy training effects in patients with brain injury (Strangman *et al.*, 2008). It was found that the strongest and weakest prefrontal cortex activation patterns predicted poor training outcomes whereas intermediate activation predicted the best training outcomes. Beyond the general principle of the baseline dependence of prefrontal cortex functioning, our findings specifically suggest that individual strategies may involve 'tuning' of networks to rely more on the goal-relevance versus non-relevance of a stimulus event to guide behaviour, and that this tuning may shift after effective training. Thus, we suggest that

modulation of the balance of neural processing of information based on goal-relevance underlies improved attentional regulation in each individual. The current findings highlight that mechanisms of improvement in regulatory functioning may be quite different from the more simplistic concept of uni-directionally increasing or decreasing brain activation. Overall, the discovery of these prominent interindividual differences in response to training raises questions to be investigated in future studies. The use of information decoding functional MRI methods may facilitate further hypothesis-driven investigation of mechanisms of improvement in patients with brain injury.

Evaluation of the specificity, transfer and maintenance of intervention effects

Our study was designed with a comparison arm to allow determination of the specificity of effects to participating in cognitive training, as opposed to effects of repeated testing. The comparison *education* instruction did not result in the effects observed with the *goals training* intervention. Comparison conditions are rarely implemented in functional MRI studies of cognitive rehabilitation, yet such comparisons strengthen conclusions regarding the specificity of changes to the training intervention. The current comparison activity was designed, however, only to provide an assessment of test–retest effects and was not matched for time, attention and other factors that may contribute to intervention effects. Another limitation is that although no significant effects of *education* were observed, this does not preclude the possibility that the tests lacked power to detect an effect given the smaller sample of pre- and post-education data. Finally, we were not able to test for maintenance of training effects at 10 weeks in the group that started with *goals training* due to the limited number of data points, although maintenance effects were demonstrated for behavioural outcomes in the behavioural study (Novakovic-Agopian *et al.*, 2010).

Transfer of training effects to non-trained contexts is a major issue in the evaluation of interventions. Such transfer was found in our study in that our intervention led to improvement in cognitive and real-world functional tasks that the patients were not directly trained on (Novakovic-Agopian *et al.*, 2010). Also, during attention training, patients were not exposed to the cognitive task they performed during functional MRI scanning, yet significant neural changes were observed. Thus, the cognitive and neural changes we observed after attention training were not simply due to practice effects, differentiating these results from studies that find changes that are highly specific to the practiced tasks, resulting in more ‘automatic’ performance on the practiced tasks. In such studies of healthy individuals, decreases in brain activation are typically found (Jansma *et al.*, 2001; Kelly *et al.*, 2006). However, decreases, as well as increases in activation have also been demonstrated after injury (McAllister *et al.*, 2006; Turner and Levine, 2008), and after training in healthy (Olesen *et al.*, 2004) and injured individuals (Kim *et al.*, 2009). Thus, the functional significance of changes in the magnitude of brain activation remains an area of active debate (Kelly and Garavan, 2005; Kelly *et al.*, 2006; Hillary, 2008). The functional MRI indices we

adapted to this patient-oriented rehabilitation study provided a specific index of the information represented within brain activity patterns and thus, the neural mechanisms induced by a training intervention.

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Supplementary material

Supplementary material is available at *Brain* online.

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