Published in final edited form as:
Neurosci Lett. 2012 June 29; 520(2): 174–181. doi:10.1016/j.neulet.2012.02.076.

Real-time fMRI applied to pain management

Heather Chapin, Ph.D.[1], **Epifanio Bagarinao, Ph.D.**[1], and **Sean Mackey, M.D., Ph.D.**[1]

Heather Chapin: hchapin@stanford.edu; Epifanio Bagarinao: baggy@stanford.edu; Sean Mackey: smackey@pain.stanford.edu

[1]Department of Anesthesia, Stanford University, Palo Alto, California, United States of America

Introduction

Modern views conceptualize pain as a brain-based phenomenon [74–76]. Advances in neuroscience have allowed us to explore how the varieties of pain experience we observe are mediated by the complex relationships between the mind, brain, and body. We have learned that far from activating a single "pain" center in the brain, pain results in widespread activation of multiple cortical and subcortical regions involved in many functions including primary and secondary somatosensory areas (SI, SII), primary motor (MI) and premotor cortices (PMC), supplementary motor area (SMA), basal ganglia, parietal and insular cortices, periaqueductal gray (PAG), rostral ventromedial medulla, hippocampus, amygdala, parahippocampus, anterior cingulate cortex (ACC), and prefrontal cortex (PFC) [108]. Pain experience can be influenced by many cognitive, emotional, and other factors affecting brain function. Indeed, evidence suggests that many of these areas participate in a pain modulatory pathway and can have a significant effect on pain experience [37, 108]. The brain's central role in pain experience is underscored by the growing appreciation that chronic pain involves dysregulation of central pain modulatory systems [82, 86, 107, 122]. A number of studies have revealed that the brains of patients with chronic pain are functionally and structurally altered compared to healthy controls. Alterations in functional connectivity between brain regions have been found in various chronic pain conditions [6, 7, 19–21, 80]. Some of these connectivity changes involve the "default-mode network" [6, 7, 19, 80], a network of areas correlated at rest and thought to be related to internal self-referential processing [48]. Chronic pain has also been associated with structural changes in the brain, showing *decreases* in gray matter volume in numerous areas including prefrontal cortex [2, 15, 41, 61, 90, 100, 109], insula [41, 61, 90, 109], brainstem [90, 95], thalamus [2, 96, 100], amygdala [15, 90], ACC [15, 90, 109], posterior cingulate cortex (PCC) [109], cingulate [61], SI [95, 122], MI/PMC [61], posterior parietal cortex [61, 100], superior temporal gyrus [96], and ventral striatum [41]. Chronic pain has also been associated with *increases* in gray matter volume in prefrontal cortex [96, 100], pregenual ACC [100], basal ganglia [95, 96, 98, 122], cerebellum [96, 122], thalamus [95, 122], inferior frontal gyrus [122], insula [122], brainstem [122], and parahippocampus/hippocampus [98]. While it is difficult to determine the direction of causality with regard to how these changes relate to chronic pain, several recent studies have shown that structural [49, 83, 90, 101] and functional [101] changes were reversible after chronic pain was resolved through successful treatment (e.g., hip-replacement surgery), suggesting that chronic pain leads to these structural changes rather

Corresponding Author: Sean Mackey, M.D., Ph.D., smackey@pain.stanford.edu, Systems Neuroscience & Pain Lab, Stanford University, 780 Welch Rd #208, Palo Alto, CA 94304, Phone: 650-498-6477, Fax: 650-725-9642.

than the reverse. Importantly, this promising result gives hope that the toll chronic pain has on the brain may be overcome given successful treatment.

Current treatments for chronic pain are varied in both their approach and efficacy. Pharmacologic therapies used in the treatment of chronic pain include opioids, anticonvulsants, and antidepressants [38]. These medications modify brain function, but their lack of specificity can lead to side effects that negatively impact the quality of life for the patient. Psychosocial approaches to pain management include cognitive behavioral therapy (CBT), hypnosis, emotional disclosure, acceptance-based therapies, and partner-based therapies [116]. Among these approaches, CBT is the most widely used and has been shown to be effective in a variety of pain conditions [1, 33, 53, 84], though CBT does not produce significant pain relief in many patients [77]. Hypnosis has been used as an effective treatment for multiple pain conditions and has been shown to alter activation in pain-related areas such as the thalamus [31, 32, 36], ACC [31, 32, 89], S1 [31, 32, 52], insula [31, 32], PFC [31, 32, 36], and parietal cortex [19, 21, 107]. However, hypnosis is most effective for only a subgroup of the population who are highly-hypnotizable. Mindfulness based therapies are another class of psychological interventions that have been used for the modulation of acute [123] and chronic pain [45, 60, 78], though, again, not all respond favorably to mindfulness based treatments [60].

Real-Time Functional MRI

Motivation

Given the essential role of the brain in pain experience and modulation, and evidence suggesting that central modulatory dysfunction may underlie some chronic pain conditions, it is a reasonable hypothesis that directly manipulating brain regions could enhance pain modulatory systems and thereby ultimately reverse the abnormalities underlying chronic pain. A number of methods and therapies have been developed to manipulate brain systems including transcranial magnetic stimulation (TMS), deep brain stimulation (DBS), and electroencephalography (EEG) neurofeedback. Each of these methods has strengths and weaknesses. Some success has been reported with the use of direct stimulation of cortical and subcortical areas using TMS and DBS. DBS of the PAG, internal capsule, and sensory thalamus has been shown to be an effective long-term treatment for chronic pain in selected groups of patients [11]. However, the invasive nature of DBS is an obvious drawback, especially considering it is not effective in all patients [11]. TMS has shown potential as a short-term treatment for the alleviation of chronic neuropathic pain [67, 68], but there is no evidence that there are lasting benefits [66]. EEG neurofeedback has been used as a method of non-invasive central modulatory control for the treatment of pain for a number of years with mixed success [56, 57, 81]. However, the limitations of source localization in EEG [44] pose a challenge to providing accurate feedback of activity in localized brain areas. Also, the EEG signal is biased to more cortical regions [62], limiting control over deeper brain structures that are important in regulatory functions. The need for direct control of cortical and sub-cortical brain systems involved in pain perception and modulation influenced the development of real-time fMRI (rtfMRI).

RtfMRI neurofeedback is a noninvasive technology that allows us to give an individual feedback on activation of single or multiple brain areas shown to be involved in specific functions. An added advantage to using rtfMRI is that we can provide feedback on either activation, connectivity, or both, allowing for a direct yet comprehensive approach to altering brain function. The goal of rtfMRI neurofeedback is to train patients to cognitively manage their own pain, but with the added aid of directly training neural systems underlying their successful modulation. This approach puts the patient in control, promoting a sense of self-efficacy and strengthening the patient’s mind-body relationship, thus giving rtfMRI the

potential for producing long-lasting benefits. Therefore, rtfMRI is perfectly aligned with the recent Institute of Medicine report on pain that emphasizes self-management for the future of chronic pain treatment [55].

Early Technical Development

The first rtfMRI system was reported in 1995 [25]. The system used a Silicon Graphics workstation for real-time reconstruction and analysis of the acquired images. Because of the time constraint in rtfMRI, computationally intensive image preprocessing steps necessary to enhance activation detection were still not possible. To address this computational demand, succeeding rtfMRI systems employed parallel or multi-processor computing systems [3, 5, 40, 43]. These computing systems were linked to the MR control machine to provide the needed power for computationally intensive tasks. As the rtfMRI system further developed, other hardware components and features, such as real-time paradigm control, incorporation of behavioral and physiological data, and global time stamping support, among others [105, 111] were similarly introduced. With the increasing availability of faster personal computers, more MRI vendors are now incorporating real-time capability into their MR systems, making rtfMRI more accessible to researchers.

Aside from technical advances, progress in the development of real-time algorithms also contributed to the growing use of rtfMRI. Important image pre-preprocessing techniques such as real-time motion correction [24, 70], spatial smoothing [88], and physiological noise correction, among others, have significantly minimized image artifacts and improved real-time detection of brain activation. The real-time implementations of existing statistical methods and data analyses have made real-time approaches almost as powerful as their offline counterparts. Incremental implementation of the correlation technique [25], multiple linear regression [105], and general linear model [4] have been reported for real-time applications. Sliding window approaches [35, 42] also make adapting offline methods into real-time settings easier.

Since its introduction, several interesting applications of rtfMRI have emerged. The simplest and most practical are data monitoring and quality control. With the ability to process the data as it is acquired, assessing data quality becomes easier. Subject movement during the scan can be easily monitored and motion parameters computed in real-time can even be used as feedback for voluntary head motion suppression [117]. Real-time fMRI also enables dynamic monitoring [79] of brain activations during the scan, which can be helpful to discover data corruption due to head motion, check the subject's task performance, and detect trouble with the fMRI system while the subject is still inside the scanner. More recently, rtfMRI has been used for neurofeedback studies. In rtfMRI neurofeedback, subjects are trained to regulate the level of activation in identified target brain regions using feedback information extracted by the real-time processing of the ongoing fMRI scan.

Recent Advances/Applications

Investigators have focused on two main goals in using rtfMRI for neurofeedback. The first goal is to characterize the degree to which an individual can learn to have increasing control of localized brain areas underlying specific cognitive and behavioral functions. Evidence has mounted over the last decade that rtfMRI training does allow for the selective alteration of activity in a specific brain region of interest (ROI). Though data processing time in earlier studies posed the challenge of longer delays in feedback presentation (60 seconds or more), near real-time fMRI feedback was shown to alter activation of the trained area in the desired direction [88, 119, 120]. These initial studies, however, did not use control groups and did not show selective enhancement of activity in the targeted brain region. In 2004, deCharms et al. [29] used an imagined motor task to selectively increase and decrease activation in

sensorimotor cortex. This was the first study to introduce a sham feedback control group in which participants received false feedback. A sham feedback group allows greater confidence that the observed effect is due to receiving accurate feedback rather than due to practice effects or trying to control feedback in general. They showed selective control of the targeted area increased over the course of training, and participants were able to maintain enhanced control after training when there was no longer feedback present. Many rtfMRI studies have focused on sensorimotor regions because the fMRI BOLD signal related to real or imagined movement is relatively robust, making it easier to measure signal changes in this region. Recent studies have shown control over regions relevant to more subtle subjective processes, such as emotion, is also possible. Caria et al [18] were the first to show that individuals were able to gain control over the right anterior insula using a strategy involving recall of emotionally salient events. In a more recent study, Hamilton et al. [51] targeted the subgenual ACC (sgACC), an area that has been shown to be more active in those with major depression [71] and to be involved in negative mood in depressed and non-depressed people [69]. Participants viewed negatively valenced pictures while trying to down-regulate activation in sgACC. The real feedback group showed significant reduction in sgACC activation compared to a sham feedback group (though this difference was only seen during training.) This was the first study to show that individuals can learn to down-regulate activity in an emotion related area, indicating a potential clinical application of rtfMRI for emotion regulation. Targeted control of the rostral lateral PFC, an area relevant to higher-level complex meta-cognition, has also been achieved using rtfMRI [72].

The second, and perhaps most relevant, main goal regarding rtfMRI feedback is to characterize the degree to which learned control over specific brain areas modifies cognition, behavior, or disease. Though it is possible to achieve learned control over a specific brain area without a corresponding observed behavioral or cognitive change [59], there is growing evidence that rtfMRI assisted control over specific brain areas can have observable cognitive, behavioral, and even clinical effects. Changes in emotion have been associated with learned control over ACC [114] and insula [17] and enhanced prosodic language processing has been linked to increased control over inferior frontal gyrus (BA 45) [91]. Recent clinical applications of rtfMRI include improving motor function in stroke patients [104], enhancing recognition of emotional expression in schizophrenic patients [92], and reducing tinnitus symptoms [50].

In summary, researchers have used rtfMRI neurofeedback to promote learned control of specific brain regions with corresponding control of the associated functions. These findings have provided the opportunity for rtfMRI neurofeedback to be used in a number of applications including mood regulation, language processing, neurorehabilitation in stroke, enhancement of emotion recognition, and tinnitus. The potential of using rtfMRI as a treatment for pain will be discussed next. The complex experience of pain, which involves widespread neural activation in multiple areas, presents particular challenges in defining the most appropriate target(s) for pain modulation.

rtfMRI and Pain Modulation

Neuroimaging studies reveal multiple areas involved in pain modulation including PFC, ACC, insula, and amygdala, along with the PAG, hypothalamus, nucleus cuneiformis, and rostral ventromedial medulla [37, 97, 108]. The ACC in particular seems to play an important role in pain perception and modulation. The ACC has been generally linked to attention [16, 27, 115], emotion [16, 102], saliency [54, 99], and self-regulation [87], all of which are obviously relevant to pain. In pain studies, regions of the ACC have been linked to pain sensitivity [22], both stimulus intensity [14] and reported pain intensity [23, 26], pain unpleasantness [89], and placebo [9, 85, 112]. The ACC, along with bordering prefrontal regions, has been consistently implicated as a key player in pain modulation in a variety of

modulatory techniques ranging from distraction [8, 110], hypnosis [36, 89], expectancy manipulation [10, 93], and placebo [9, 85, 112]. Moreover, portions of the ACC have been specifically linked to the altered perception of pain when stimulus intensity was kept constant [10, 93]. In a dramatic example of the effect of cognitive influence on pain perception, perigenual ACC (pgACC) activation predicted the effect of expectancy on pain (i.e., the greater the activation in pgACC, the greater the change in pain ratings) [10]. In this study, when participants were told they were no longer receiving a powerful opioid during a painful stimulus, the analgesic effect was completely abolished, despite the fact that the drug was still being administered. These results highlight the malleability of pain perception and point to the possibility of using rtfMRI feedback to enhance the power of the mind over the body.

Given the role anterior cingulate cortex has been shown to play in pain perception, we chose this area as an initial target for the use of rtfMRI feedback to alter pain experience in both healthy controls and patients with chronic pain [30]. We used a heat stimulus to evoke pain in healthy controls who were asked to use cognitive strategies to alternately increase and decrease their pain. Suggested strategies involved shifting attention towards or away from the stimulus, appraising the stimulus as harmful or neutral, perceiving the stimulus as low or high intensity, or trying to control the stimulus or allowing the stimulus to control the percept. Participants were given suggestions for which strategies to use because pilot subjects were more successful at controlling the feedback when they had strategies to choose from. It is noteworthy that it was often difficult for participants to articulate exactly how they were controlling their feedback [30], stressing the importance of allowing participants the freedom to develop customized personal strategies.

Participants underwent a localizer scan in which they were asked to attend toward or away from the stimulus. This was done to identify the specific ACC ROI in each individual subject. Subjects then participated in three rtfMRI training runs which were followed by a final confirmatory test run (without feedback). The feedback was a visual display that showed the BOLD response in the ACC and pictorial representation of ACC activation as either an increasing or diminishing flame. Participants rated both average pain intensity and unpleasantness at the end of each run. Over the course of feedback training, participants were able to increasingly control activation in the ACC and were able maintain this control in the final test run when there was no feedback. The amount of change in pain intensity and unpleasantness ratings also increased over the course of feedback and they were able to maintain this difference in the final test run. Moreover, the change in pain ratings was predicted by the control over activation in the ACC (i.e., the more they were able to modulate activity in the ACC, the more their pain was modulated). One of the biggest strengths of this study was that there were four control groups. Group 1 used cognitive strategies with no feedback over the same number of scans to modulate their pain. Group 2, who did not undergo scanning, received behavioral training to modulate their pain by attention manipulation, which they practiced for twice as long as the experimental group. Group 3 received feedback from another brain area (the PCC) which was thought to not play a significant role in cognitive modulation of pain perception. Group 4 received feedback yoked to another participant's ACC. The experimental group receiving accurate ACC rtfMRI feedback was the only group that showed an increase in ACC activation control and in pain modulation over the course of training. In addition, eight chronic pain patients followed a similar rtfMRI training protocol but modulated their perception of their own endogenous pain rather than an externally applied heat stimulus. They rated their pain on the McGill Pain Questionnaire (MPQ) and gave pain ratings on a 1–10 visual analogue scale (VAS). A group of pain patients that used the cognitive strategies to increase and decrease their pain with autonomic biofeedback served as a control. Similar to the healthy controls, the experimental group exhibited greater changes in pain ratings than the control group and

the percentage change in their reported pain was positively correlated with the change in ACC activation. In fact, patients reported an average 64% decrease in MPQ ratings and 44% decrease in VAS ratings after training. Importantly, all chronic pain patients reported a decrease in their pain following training, and 5 of the 8 reported reductions in pain of 50% or more on the MPQ.

Beyond Single Regions

While rtfMRI feedback of single brain areas shows promise as a useful tool for neurocognitive modulation, this approach does not reflect an accurate picture of brain function. We know a more complete picture of how the brain gives rise to perception involves networks of multiple interacting regions. Fortunately, there are already indications that rtfMRI could also be effective in controlling activation from multiple brain regions. In one rtfMRI study, subjects were able to navigate a two-dimensional maze by using different strategies to control multiple ROIs [119]. Weiskopf et al [113] reported that subjects were able to up-and down-regulate the differential activity between the SMA and the parahippocampal place area (PPA). This implies the feasibility of modulating functional connectivity between two areas by simultaneously controlling activity of the single regions. Controlling functional networks of multiple regions may become possible with independent component analysis, a tool commonly used in functional connectivity studies, used in real-time [35].

Taking a more general network approach, LaConte and others [34, 63, 103] have started to use whole brain pattern classification in conjunction with real-time fMRI. With pattern classification, a computer is taught to be able to differentiate between two (or more) brain states associated with certain tasks. LaConte and colleagues [63] used whole brain activation to classify brain states associated with tapping the right and left finger and gave the participant feedback on the incidence of correct classification. They observed 80% classification accuracy, which improved with feedback training over time. They also showed high real-time classification accuracy with more subtle tasks such as mood induction (happy versus sad), a language task (thinking in Mandarin versus English), and an imagined motor task. In a similar experimental design, Sitaram et al. [103] showed that real-time classification of multiple emotional states (happy, sad, and disgust) is possible and that subjects with multiple training sessions improved classification accuracy. In a recent demonstration of complex rtfMRI feedback control, Eklund [34] used a brain-computer-interface paradigm with pattern classification of real (and imagined) left and right hand movements. Subjects were successfully able to control a dynamical system in the form of an inverted pendulum that they were asked to keep balanced. The advantage with taking a network or whole-brain approach to rtfMRI feedback is that one is not constrained to a specific hypothesis about what brain areas are involved in a task, and individual differences in task strategy that would cause differences in neural activation will not interfere with the quality of the feedback. These advantages are highly relevant to pain modulation where no definitive brain network associated with pain or its modulation has been identified and effective pain modulation strategies vary among individuals [39, 64]. Recent work has shown that it is possible to use pattern classification to determine whether or not someone is experiencing a painful stimulus [13], though future research is needed to determine whether real-time pattern classification could be used for the modulation of pain.

Remaining Questions and Future Directions

There are many unanswered questions that are integral to the progression of rtfMRI feedback research with regard to pain control. For example, we do not know whether the most effective approach would be to target areas involved in pain encoding, in endogenous analgesia, in specific cognitive strategies, or some combination of all of the above. Different

modulation strategies are associated with different neural activation patterns [64, 73]. If specific strategy-related areas are chosen for feedback targets, one issue is that allowing for idiosyncratic variation in strategy implementation [28] could change activation patterns in ways that would interfere with feedback. There are many regions (and numerous combinations of regions) left to be explored with rtfMRI feedback. It is quite possible that there may be regions that are not appropriate for feedback regulation. For example, one can imagine the paradox of asking a participant to down-regulate activation in an area (or network) that happens to be necessary for focused attention or self-regulation. It could also be the case that rtfMRI feedback is not appropriate for specific illnesses or individuals. Certainly, as with any treatment, there are variations in effectiveness for rtfMRI feedback. It remains to be seen what underlies differences in ability to successfully control neurofeedback. Characterizing these differences could lead to improved individualized training methods. The long-term benefits of rtfMRI neurofeedback training are also currently unknown; although there is evidence that activation changes due to training endure at least in the short-term [29, 30, 121] and that functional reorganization takes place over the course of training [65, 92]. Including analysis of structural changes in future research could elucidate the extent to which rtfMRI feedback training results in lasting neural plasticity. Another question that remains concerns whether providing feedback on activation or connectivity between areas is more effective. Perhaps a combination of activation and connectivity would be optimal. Targeting the altered connectivity associated with chronic pain conditions [21, 80, 82, 86] may be beneficial in returning patients to more normal function.

Pattern matching is another approach that takes into account the fact that the activity of multiple brain areas underlies an observed behavior or reported experience. This approach involves having the subject match an ideal (or at least effective) pattern of brain activation that is associated with the desired effect (e.g., pain modulation). The degree of match between the participant's current brain pattern and the target pattern is used as feedback [96]. Though theoretically using a network of areas associated with the desired result could be more effective for feedback, no studies have been published to date testing this hypothesis. One issue with pattern matching is how one determines the appropriate pattern to match. It remains to be seen whether patterns derived from group averages would be effective targets or if individual differences would require personalized patterns tailored to the individual. The disadvantage to the latter approach is that optimal target patterns may not be attainable on an individual basis.

There are also many basic methodological questions that remain unanswered. For example, what feedback modality is most effective? Some options include visual feedback, auditory feedback, a combination of modalities, or completely immersive virtual reality environments. Almost all rtfMRI studies have used visual feedback, which may be most appropriate for the noisy environment of the scanner, but there is no research suggesting this is the most effective feedback delivery for rtfMRI. There is also the possibility of using inherently rewarding and/or aversive feedback (e.g., using consonant and dissonant tones, or pleasant and unpleasant virtual reality environments) in order to increase engagement and motivation and perhaps help condition neural systems to reach the desired result. Along these lines, operant conditioning has been used in conjunction with shaping to reinforce desired signal changes in EEG neurofeedback training (e.g., [47, 106]), but only one rtfMRI study has been conducted using this method [12]. This approach could be useful for rtfMRI because the simplicity and gradual increase in performance criteria may prove to be easier and more effective for a broader range of people.

One of the challenges in controlling rtfMRI feedback is the hemodynamic delay of the BOLD signal response (~6 sec). This delay means that participants do not see any change in

the feedback until about 6 seconds after they adjust their strategies. One way of dealing with this problem is by using intermittent rather than continuous feedback. Johnson et al. [58] tested the effectiveness of intermittent versus continuous feedback on left PMC activation using an imagined movement task. They found that participants performed better overall with intermittent feedback (every 18 seconds) than with continuous feedback. Therefore, having an inter-feedback-interval greater than 6 seconds may mitigate confusion caused by the hemodynamic delay.

A long-term goal of neurofeedback is to identify a cost-effective method of directed brain control. fMRI scans remain highly expensive and primarily relegated to the research realm. Fortunately, there are less expensive methods of imaging the brain, such as EEG and near-infrared spectroscopy (NIRS). Researchers are developing methods of performing simultaneous EEG with rtfMRI so that both the temporal resolution of EEG and the spatial resolution of fMRI can be utilized, which could result in the translation of the knowledge we learn from the fMRI signal to the EEG signal. This would allow a more affordable, mobile form of real-time neurofeedback that could be used in the clinic, but that is more specialized to specific brain areas and functions than what is currently available with EEG neurofeedback. NIRS is another affordable and portable imaging method that measures a signal similar to fMRI (though it is limited to more cortical regions). Information gained from the use of rtfMRI to effectively control pain could also guide the development of real-time NIRS for the treatment of pain and other brain-based disorders.

Conclusion

A central goal of rtfMRI research is to aid in the development of accessible treatment for many conditions involving central nervous system dysregulation including pain, addiction, phobia, anxiety, and depression. On the other end of the spectrum, another possible application for this self-regulatory tool is performance enhancement [46], learning enhancement [118], perceptual enhancement [94] or wellness optimization. RtfMRI also can be used as a novel tool for understanding brain-behavior relationships. Traditional fMRI experiments involve engaging in or changing a specific behavioral or cognitive task in order to measure the effect on neural function. Interpreting the results of such studies sometimes involves building upon a shaky foundation of previous interpretations and assumptions about how the brain works. With rtfMRI, the effect of changing neural function on behavior and cognition is measured, providing an alternate way of testing our hypotheses about how neural processes relate to human experience. Therefore, rtfMRI provides a method of furthering our understanding of how the brain works and pushes the limits of our potential for self-directed change and healing.

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Highlights

- We review neuroimaging literature related to pain and its modulation.
- We review the development of real-time fMRI feedback and potential applications.
- We review work showing control of ACC activation correlates with pain modulation.
- We discuss the future of rtfMRI feedback and its implications for pain research.

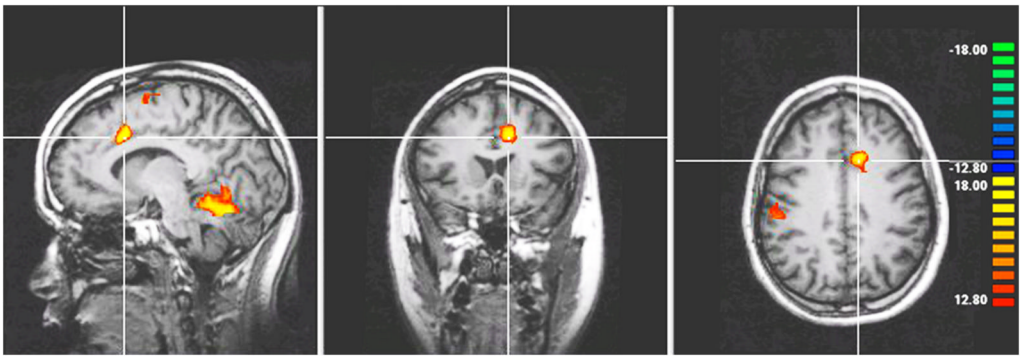

Figure.
rtfMRI assisted control over anterior cingulate cortex (ACC). (A) Change in group mean activation comparing the last training session to the first training session showing activation in the ACC (located at cross hairs), (B) Change in group mean activation comparing the posttest session (after the last rtfMRI training session) to the initial training session, showing similar results. Seven total clusters were observed at this threshold level (t >12.80, top of scale t =18.00). Data are presented as thresholded, Bonferroni-corrected t-maps superimposed on high-resolution T1 data. Color designates the t value, using a general linear model comparing different time periods convolved with a canonical hemodynamic response function. All data are experimental group averages after normalization to Talairach–Tournoux coordinates. Figure used with permission from [31].