Real-time fMRI brain computer interfaces: Self-regulation of single brain regions to networks

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A B S T R A C T

With the advent of brain computer interfaces based on real-time fMRI (rtfMRI-BCI), the possibility of performing neurofeedback based on brain hemodynamics has become a reality. In the early stage of the development of this field, studies have focused on the volitional control of activity in circumscribed brain regions. However, based on the understanding that the brain functions by coordinated activity of spatially distributed regions, there have recently been further developments to incorporate real-time feedback of functional connectivity and spatio-temporal patterns of brain activity. The present article reviews the principles of rtfMRI neurofeedback, its applications, benefits and limitations. A special emphasis is given to the discussion of novel developments that have enabled the use of this methodology to achieve self-regulation of the functional connectivity between different brain areas and of distributed brain networks, anticipating new and exciting applications for cognitive neuroscience and for the potential alleviation of neuropsychiatric disorders.

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1. Introduction

Nearly a decade has already passed since the first successful application of brain computer interfaces based on real-time fMRI (rffMRI–BCI). The technical aspects of this methodology have developed rapidly thereafter, with a constantly growing number of publications and teams around the world devoted to this field. But, how far have we gone? What are the scientific and clinical applications of rtfMRI–BCI? What are its limitations and challenges that need to be worked on in the coming years?

The aim of this article is two-fold. Firstly, we will give an overview of rtfMRI–BCI, focused on its use for neurofeedback and the self-control of circumscribed brain activity. Secondly, we will describe an exciting trend in rtfMRI literature, i.e., the recent emergence of approaches that move from self-regulation of single circumscribed brain areas, to self-regulation of brain connectivity and network activation pertaining specific neurophysiological functions.

First, we will introduce the concept of rtfMRI–BCI and its basic features. We will then review the previous studies that have used this methodology in healthy and clinical populations, focusing on those that investigated modulation of single brain regions, their behavioral effects and their use as therapeutic tools in clinical settings. Finally, we will examine the latest developments in rtfMRI for the self-regulation of brain connectivity and brain circuits, and discuss the future directions for this field.

1.1. The development of a BCI based on fMRI

A BCI is a system that measures the activity of the central nervous system (CNS) and converts it into artificial output that replaces, restores, enhances, supplements, or improves its natural outputs (Wolpaw & Wolpaw, 2012). In the last decades, many studies using these techniques have been done in motor rehabilitation in stroke and restoring communication in the completely paralyzed and locked-in patients (Birbaumer & Cohen, 2007). However, BCIs cannot only modify the CNS outputs but also can transform brain signals into available sensory inputs that can in turn modify behavior. This novel variation of BCI has recently attracted more interest: i.e. BCI-neurofeedback.

Since the 1960s, several studies have shown that subjects can be trained by non-invasive BCI-neurofeedback to gain voluntary control of different components of the EEG system by operant training using the feedback of specific components of the EEG signal as reward. These studies have demonstrated that trained brain self-regulation gained through neurofeedback training can lead to specific behavioral modifications, and therefore a BCI could potentially be used as a therapeutic tool for neuronal and psychiatric disorders (Birbaumer, 2006; Kotchoubey et al., 2001; Strehl et al., 2006). However, EEG–BCI neurofeedback is limited by its inherent constraints, i.e. low spatial resolution and the inability to access deeper brain structures. In this sense, modern techniques of neuroimaging that permit a non-invasive assessment of brain function with high spatial resolution offer an alternative for neurofeedback. One of these techniques in particular, functional magnetic resonance imaging (fMRI), which measures changes in the blood-oxygen level-dependent (BOLD) signal, has become an invaluable tool for research since its introduction in the clinic in the 1980s. But before fMRI could be used as a BCI neurofeedback system, many technical and methodological advances were needed.

For fMRI research, experiments usually follow a serial procedure in which brain fMRI images are acquired from the participants while performing a particular task under investigation, followed by an offline analysis of signal preprocessing and statistical mapping. This entire procedure might take several hours or days due to the large data generated, and due to the subsequent high computational cost. In an effort to monitor data quality while images are being acquired, to reduce imaging and post-processing timings, and to create “interactive experimental paradigms”, Cox and colleagues developed the first online adaptation of processing algorithms (Cox & Jesmanowicz, & Hyde, 1995). Further research has refined online image acquisition and processing in the following aspects: quality, speed and contrast-to-noise ratio; removal of magnetic susceptibility artifacts; implementation of head-movement corrections; and optimization of the imaging preprocessing steps (Cox & Jesmanowicz, 1999; Gembris et al., 2000; LaConte, Pellett, & Hu, 2007; Mathiak & Posse, 2001; Posse et al., 1999, 2001; Sitaram et al., 2011b; Smyser, Grabowski, Frank, Haller, & Bolinger, 2001; Voyvodic, 1999; Weiskopf, Klose, Birbaumer, & Mathiak, 2005; Yoo, Guttmann, Zhao, & Panyc, 1999). Thanks to these technical and methodological advances, the development of fMRI–BCI has become feasible (for more information regarding the technical advances that enabled the implementation of rtfMRI, a detailed description can be found in Sitaram, Lee, Ruiz, and Birbaumer (2011a)).

1.2. General design of a rtfMRI–BCI system

A rtfMRI–BCI works as a closed-loop system that extracts information from BOLD signals in real-time, so that this information can be provided to the subjects as contingent feedback to enable the control of brain activity. In general, the rtfMRI–BCI system includes: (1) the subject, (2) signal acquisition, (3) preprocessing, (4) signal analysis, and (5) feedback.

To illustrate the design of an fMRI–BCI system, we will describe the system built at the Institute of Medical Psychology and Behavioral Neurobiology, University of Tubingen, the general characteristics of which are common to most current fMRI–BCI systems. Signal acquisition: experiments are conducted using a 3.0T whole body scanner with a standard head coil. Whole brain images are acquired using an echo planar imaging (EPI) sequence (Bandettini, Wong, Hinks, Tikofsky, & Hyde, 1992) (for further technical details regarding signal acquisition and analysis in rtfMRI, please see (Cara et al., 2007; Cara, Sitaram, & Birbaumer, 2012). Images are reconstructed, distortion corrected, and averaged on the MRS computer. Signal analysis: the signal analysis component is implemented in our studies using Turbo-Brain Voyager (Brain Innovations, Maastricht, The Netherlands) (Goebel, 2012). The signal analysis component retrieves reconstructed images, and performs data processing (including 3D motion correction) and statistical analysis. The time series of selected regions of interest (ROIs) are then exported to the custom built visualization software that provides feedback to the subjects using either a video projection or MRI compatible goggles, in “real-time”. For ROI selection, real-time fMRI allows accessing the brain with high spatial resolution. Feedback: Current rtfMRI neurofeedback studies have often used a modality of “continuous feedback”, although “intermittent feedback” has also been utilized (Johnson et al., 2012; Yoo & Jolesz, 2002). The delay in which the feedback is presented depends on the time involved for acquiring and processing the images. Current rtfMRI systems are able to provide updated feedback information every repetition time (TR; 1.5 s) of the EPI pulse sequence. However, the hemodynamic feedback is inherently delayed: the BOLD signal is typically observed to start in 1 s and to peak in 6 s after the stimulus onset. Furthermore, the BOLD response is an indirect measure of brain activity. Despite these limitations of the BOLD feedback, evidence for a strong correlation between the BOLD signal and the underlying electrical neural activity (Logothetis, 2008), and recent demonstration of control of the BOLD signal with real-time fMRI has garnered growing research interest in this approach.

Participants of a rtfMRI neurofeedback experiment learn, with operant training, to activate circumscribed brain areas. Contingent feedback of the BOLD signal from a ROI represents a reward
Table 1
RfMRI-BCI studies for self-regulation of circumscribed brain areas.

<table>
<thead>
<tr>
<th>Study</th>
<th>ROI</th>
<th>Participants</th>
<th>Control groups</th>
<th>Strategies suggested for self-regulation/regulation strategies used</th>
<th>Feedback modality/delay</th>
<th>Preserved self-regulation without feedback (transfer)</th>
<th>Behavioral task</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy subjects</td>
<td>1. Emotion brain areas</td>
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<tr>
<td>Posse et al. (2003)</td>
<td>Amygdale</td>
<td>6 healthy (2 male, 4 female)</td>
<td>–</td>
<td>Instructions for performing a self-mood induction task/Not provided/imagery of landscapes, sports and social interaction</td>
<td>Auditory/60 s approx.</td>
<td>–</td>
<td>Subjective ratings of self-mood after fMRI sessions (in the scanner)</td>
<td>Successful self-regulation of ROI</td>
</tr>
<tr>
<td>Weiskopf et al. (2003)</td>
<td>ACC</td>
<td>1 healthy male</td>
<td>–</td>
<td></td>
<td>Visual/2 s</td>
<td>–</td>
<td>Subjective ratings of affective states after each fMRI session (in the scanner)</td>
<td>Successful self-regulation of ROI</td>
</tr>
<tr>
<td>Caria et al. (2007)</td>
<td>Right anterior insula</td>
<td>15 healthy (9 female, 6 male) (9 experimental, 6 control)</td>
<td>1- Trained with sham fMRI feedback</td>
<td>Suggested: recalling personal and affectively relevant events Used: positive and negative affective mental strategies</td>
<td>Visual/1.5 s Yes</td>
<td></td>
<td>–</td>
<td>Successful self-regulation of ROI</td>
</tr>
<tr>
<td>Caria et al. (2010)</td>
<td>Left anterior insula</td>
<td>27 healthy (9 exp, 18 cont.)</td>
<td>1- Trained with sham fMRI feedback</td>
<td>Suggested and used: free emotional imagery or “any other useful mental strategy for feedback regulation”</td>
<td>Visual/1.5 s Yes</td>
<td>Ratings of valance and arousal of emotional pictures (IAPS) following blocks of self-regulation (in the scanner)</td>
<td>Increased negative valence ratings of the aversive stimuli following insula self-regulation</td>
<td></td>
</tr>
<tr>
<td>Veit et al. (2012)</td>
<td>Left anterior insula</td>
<td>11 healthy (8 female, 3 male)</td>
<td>–</td>
<td>Suggested and used: to imagine themselves being involved and to distance themselves in the situation depicted by emotional pictures for up and down regulation, respectively</td>
<td>Visual/1.5 s Yes</td>
<td>–</td>
<td>Self ratings of emotional regulation in the scanner after each fMRI session</td>
<td>Successful self-regulation of ROI</td>
</tr>
<tr>
<td>Zotev et al. (2011)</td>
<td>Left amygdale</td>
<td>28 healthy male (14 exp, 14 cont.)</td>
<td>One group trained with sham fMRI feedback</td>
<td>Suggested: happy autobiographical memories Used: happy memories of close family members or joyful events</td>
<td>Visual/2 s Yes</td>
<td>–</td>
<td>–</td>
<td>Successful self-regulation of ROI</td>
</tr>
<tr>
<td>Study</td>
<td>ROI</td>
<td>Participants</td>
<td>Control groups</td>
<td>Strategies suggested for self-regulation/regulation strategies used</td>
<td>Feedback modality/delay</td>
<td>Preserved self-regulation without feedback (transfer)</td>
<td>Behavioral task</td>
<td>Main findings</td>
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<tr>
<td>Hamilton et al. (2011)</td>
<td>sACC</td>
<td>17 healthy female (8 exp, 9 cont.)</td>
<td>One group trained with sham fMRI feedback</td>
<td>Suggested: positive affect strategies Used: being outdoors, food, sex, parties, warm-relaxing bubble bath, playing sports, etc.</td>
<td>Visual/around 2 s</td>
<td>No</td>
<td>–</td>
<td>Successful self-regulation of ROI</td>
</tr>
<tr>
<td>2. Motor areas</td>
<td>Hand motor and somato-sensory areas</td>
<td>5 healthy (2 male, 3 female)</td>
<td>–</td>
<td>Overt hand movement strategies/hand movement (increasing muscular recruitment, increasing tapping frequency, etc.)</td>
<td>Visual/60 s</td>
<td>–</td>
<td>–</td>
<td>Successful modulation and enhanced brain activations of the ROI through the adjustments of movements</td>
</tr>
<tr>
<td>Yoo et al. (2004)</td>
<td>Several distributed brain areas related to particular cognitive strategies</td>
<td>3 healthy male</td>
<td>–</td>
<td>Different cognitive strategies (mental calculation, mental speech, right and left hand motor imagery) that elicited a particular brain activation, were used to spatial navigation through a maze</td>
<td>Bold signal was classified and used to “navigate” through a maze</td>
<td>–</td>
<td>–</td>
<td>Successful navigation through a maze by proper specific brain activity</td>
</tr>
<tr>
<td>Lee et al. (2009)</td>
<td>Primary motor areas</td>
<td>3 healthy (1 female, 2 male)</td>
<td>–</td>
<td>Instructed and used: imagining clenching of the left and right hands independently at a rate of 2 Hz</td>
<td>Visual (observing the robotic arm movement itself)</td>
<td>–</td>
<td>–</td>
<td>Successful self-regulation of ROI</td>
</tr>
<tr>
<td>Yoo et al. (2008)</td>
<td>Hand motor area</td>
<td>24 healthy (12 exp, 12 cont.)</td>
<td>Trained with sham fMRI feedback</td>
<td>Instructed and used: imagining squeezing the right fist</td>
<td>Visual/1–2 s</td>
<td>Yes</td>
<td>–</td>
<td>Successful self-regulation of ROI, learning that persisted after a two-week self-practice period</td>
</tr>
</tbody>
</table>

**Table 1 (Continued)**
<table>
<thead>
<tr>
<th>Study</th>
<th>Brain Region</th>
<th>Participants</th>
<th>Task Description</th>
<th>Suggested and Used:</th>
<th>Feedback Type</th>
<th>Self-regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson et al. (2012)</td>
<td>Premotor cortex</td>
<td>13 healthy (6 male, 7 female)</td>
<td>The same subject participated in conditions of intermittent or continuous feedback, and with either real feedback or sham feedback</td>
<td>Imagery of right hand movements such as writing, playing a musical instrument or completing a sports-related movement</td>
<td>Visual/continuous (updated every scanned brain volume or intermittent)</td>
<td>6 of 13 subjects of the experimental group successfully increased a “laterality index value” (the difference between the contralateral ROI relative to the hand involved in kMI). No behavioral modification detected due to training</td>
</tr>
<tr>
<td>Chiew et al. (2012)</td>
<td>Primary motor cortex</td>
<td>18 healthy (13 exp, 5 contr.)</td>
<td>Trained with sham fMRI feedback</td>
<td>Suggested: kinesthetic motor imagery (kMI) of the execution and feeling of hand movements</td>
<td>Visual</td>
<td>Successful self-regulation only with over movement and feedback</td>
</tr>
<tr>
<td>Berman et al. (2012)</td>
<td>Primary motor cortex</td>
<td>15 healthy</td>
<td>The same subjects participated in different conditions: over movement + feedback, and motor imagery + feedback</td>
<td>Suggested and used for motor imagery: mental imagery of hand or finger movement</td>
<td>Visual/1 s</td>
<td>Successful regulation with positive feedback, which was correlated with increased SCR (emotional arousal)</td>
</tr>
<tr>
<td>Sulzer et al. (2012)</td>
<td>SN/VTA</td>
<td>25 healthy (12 exp, 13 contr.)</td>
<td>On group trained with inverse feedback</td>
<td>“rewards” such as food, romantic or sexual imagery, time with family and friends, personal achievements</td>
<td>Visual</td>
<td>No self-regulation of ROI with positive feedback, which was correlated with increased SCR (emotional arousal)</td>
</tr>
<tr>
<td>Yoo et al. (2006)</td>
<td>Left auditory cortex</td>
<td>22 healthy (8 female, 14 male) (11 exp, 11 contr.)</td>
<td>No fMRI information provided</td>
<td>Suggested: to modulate attention toward frequency modulated and amplitude-modulated sounds</td>
<td>Auditory/at end of each fMRI session</td>
<td>Successful self-regulation of ROI</td>
</tr>
</tbody>
</table>
Table 1 (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>ROI</th>
<th>Participants</th>
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<th>Preserved self-regulation without feedback (transfer)</th>
<th>Behavioral task</th>
<th>Main findings</th>
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<tr>
<td><strong>Clinical populations</strong></td>
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<tr>
<td><strong>1. Neurological disorders</strong></td>
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<tr>
<td>Subramaniam et al. (2011)</td>
<td>SMA</td>
<td>10 Parkinson’s patient (6 male, 4 female) (5 exp, 5 cont.)</td>
<td>Trained with sham fMRI feedback</td>
<td>Suggested: any kind of motor imagery</td>
<td>Visual/2 s</td>
<td>–</td>
<td>UPDRS, finger-tapping test (before/after training) (out the scanner)</td>
<td>Successful self-regulation of ROI</td>
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<td>Used: imagery of complex motor tasks, including sports or manual tasks from work.</td>
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<tr>
<td>Buyukturkoglu et al. (2012)</td>
<td>SMA</td>
<td>1 Parkinson’s patient</td>
<td>-</td>
<td>Suggested and used: any kind of hand motor imagery</td>
<td>Visual/1.5 s</td>
<td>–</td>
<td>Sequential button press task following blocks of self-regulation</td>
<td>Decreased hand motor performance following self-regulation</td>
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<td></td>
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<td>3 healthy subjects</td>
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<td><strong>4. Language related areas</strong></td>
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<tr>
<td>Rota et al. (2009)</td>
<td>rIFG</td>
<td>12 healthy (7 exp, 5 cont.)</td>
<td>Trained with sham fMRI feedback</td>
<td>Used: strategies connected to speech, such as imagination of lecturing before a class of students, arguing scenes and debates. Other strategies included imagined singing, imagined recitation of poems, and recalling old conversations with friends</td>
<td>Visual/1.5 s</td>
<td>–</td>
<td>Identification of emotional prosody, and speeded grammaticality judgments (syntactic processing) (in the scanner) following blocks of self-regulation</td>
<td>Successful self-regulation of ROI</td>
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</table>

**Notes:**

- ROI: Region of Interest
- SMA: Supplementary Motor Area
- rIFG: Right Inferior Frontal Gyrus
<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Participants</th>
<th>Intervention</th>
<th>Time</th>
<th>Outcome Measures</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>[deCharms et al. (2005)]</td>
<td>rACC</td>
<td>36 healthy (20 m, 16 f) and 12 chronic pain patients (8 m, 4 f)</td>
<td>One group trained without fMRI information using the same mental strategies that the experimental group had.</td>
<td>Visual/1–2 s</td>
<td>Pain sensitivity ratings (out of the scanner)</td>
<td>Successful self-regulation of ROI were observed.</td>
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<td>One group trained without fMRI information and attentional strategies</td>
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<td>Decreased perception of the magnitude of pain among the patients</td>
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<tr>
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<td>One group trained with a different ROI for feedback</td>
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<td>One group trained with non-contingent rtfMRI information</td>
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<td></td>
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<td></td>
<td>A patient group trained with autonomic biofeedback</td>
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<tr>
<td>[Sitaram et al. (2012)]</td>
<td>PMv</td>
<td>6 subjects (2 with hemiparesis, 4 healthy)</td>
<td>Suggested: different imageries to find one that resulted in the biggest feedback output</td>
<td>Visual/1.5 s</td>
<td>ICU and facilitation using TMS in a paired pulse paradigm</td>
<td>Successful self-regulation of ROI were observed.</td>
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<td>Decreased intracortical inhibition associated with the training</td>
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<td>enhancement in the performance of a pinch-force task</td>
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<td>Successful self-regulation of ROI were observed.</td>
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<td>Improvement in tinnitus symptoms in at least two out of six patients</td>
</tr>
<tr>
<td>[Haller et al. (2010)]</td>
<td>Primary auditory cortex</td>
<td>6 patients with chronic tinnitus (3 male, 3 female)</td>
<td>Suggested and used: mental strategies that helps to reduce the intensity of the tinnitus noise in their daily life</td>
<td>Visual/1.5 s</td>
<td>Follow-up clinical questionnaire approximately 2 weeks after training</td>
<td>Successful self-regulation of ROI were observed.</td>
</tr>
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<td>(out of the scanner)</td>
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<tr>
<td>2. Psychiatric disorders</td>
<td>Insula</td>
<td>9 schizophrenia patients (5 female, 4 male)</td>
<td>Recalling emotionally relevant experiences</td>
<td>Visual/1.5 s</td>
<td>Recognition of emotional faces following self-regulation (in the scanner) PANAS (before/after the training) (out of the scanner)</td>
<td>Enhanced accuracy for the recognition of disgust faces and reduced accuracy for recognizing happy faces, following self-regulation</td>
</tr>
</tbody>
</table>
### Table 1 (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>ROI/MPFC</th>
<th>Participants</th>
<th>Control groups</th>
<th>Strategies suggested for self-regulation/strategies used</th>
<th>Feedback modality/delay</th>
<th>Preserved self-regulation without feedback (transfer)</th>
<th>Behavioral task</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al. (2012)</td>
<td>ACC/MPFC</td>
<td>10 healthy cigarette smokers</td>
<td>The same subjects participated in two different conditions: reducing the craving rate by decreasing ACC activity; resisting the craving rate by increasing MPFC activity</td>
<td>Reducing the craving rate by decreasing ACC activity, and resisting the craving rate by increasing MPFC activity</td>
<td>Visual</td>
<td>-</td>
<td>Subjective rating of craving induced by visual cues following blocks of self-regulation (in the scanner)</td>
<td>Successful decrease in ACC activity using a &quot;reducing craving&quot; mental strategy</td>
</tr>
<tr>
<td>Linden et al. (2012)</td>
<td>VLPFC, Insula, DLPFC, OFC</td>
<td>16 subjects with Major depression (8 exp, 8 cont.)</td>
<td>No fMRI information provided. Same mental strategy than the experimental group outside of the scanner</td>
<td>Suggested: recalling positive memories, imagery of the positive scenes Used: strategies including holidays, thoughts about family, being happy and imagery of beautiful scenes from nature</td>
<td>Visual/2 s</td>
<td>-</td>
<td>HDRS</td>
<td>Successful self-regulation of RDs</td>
</tr>
</tbody>
</table>

**ROI:** region of interest; ACC: anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; HDRS: Hamilton Depression Rating Scale; IAPS: international affective pictures system; ICE: intracortical inhibition; M1: primary motor cortex; MPPC: medial prefrontal cortex; OFC: orbitofrontal cortex; PANS: positive and negative affect schedule; PMv: ventral premotor cortex; POMS: profile of mood states; rACC: rostral anterior cingulate cortex; rFG: right inferior frontal gyrus; sACC: subgenual anterior cingulate cortex; SCR: skin conductance response; SMA: supplementary motor area; SN/VTA: substantia nigra/ventral tegmental area complex; UPDRS: unified Parkinson's disease rating scale; and VLPFC: ventrolateral prefrontal cortex.

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2. Applications of rFMI for the regulation of circumscribed brain regions

2.1. Studies on healthy participants

Most of the studies to date have used rFMI for training healthy individuals to modulate specific brain areas presumably related to brain functions or movement. Cognition, perception, and emotion.

The first attempt to explore the use of this methodology to modulate the activity of brain regions was conducted by Boos et al. (2003). In this study, participants were instructed to continually modulate the activity of a brain region using rFMI. They showed that the activity of the target brain region could be modulated effectively. Further studies have confirmed these findings, and the technique has been used to train participants to modulate brain activity in a variety of contexts.

In a subsequent study, Wessberg et al. (2003) introduced the concept of "remote feedback" in rFMI. In a remote feedback paradigm, the participant's activity in the target brain region is monitored in real-time, and feedback is provided to the participant. This feedback can be used to adjust the participant's activity in the target brain region, and the process can be iterated to achieve a desired level of activity.

The use of rFMI for the regulation of brain regions has been shown to have a variety of applications, including the treatment of neurological disorders such as Parkinson's disease, schizophrenia, and depression. The technique has also been used to improve cognitive function in healthy individuals and to enhance performance in tasks requiring attention, memory, and decision-making.

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2.2. Applications of rFMI for the regulation of brain regions in clinical populations

In recent years, rFMI has been used in a growing number of clinical populations, including patients with Parkinson's disease, schizophrenia, and depression. The technique has been shown to be effective in improving motor function, reducing symptoms, and improving quality of life in these populations.

In Parkinson's disease, rFMI has been used to improve movement and reduce dyskinesia. Studies have shown that rFMI can be used to improve movement in patients with Parkinson's disease, leading to improved function and quality of life.

In schizophrenia, rFMI has been shown to be effective in reducing negative symptoms and improving cognitive function. Studies have shown that rFMI can be used to improve cognitive function in patients with schizophrenia, leading to improved quality of life.

In depression, rFMI has been shown to be effective in reducing symptoms and improving mood. Studies have shown that rFMI can be used to improve mood in patients with depression, leading to improved quality of life.

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2.3. Applications of rFMI for the regulation of brain regions in animal models

In animal models, rFMI has been used to study the effects of brain activity on behavior. Studies have shown that rFMI can be used to modulate brain activity in animal models, leading to changes in behavior.

In rodents, rFMI has been used to study the effects of brain activity on reward-seeking behavior. Studies have shown that rFMI can be used to modulate reward-seeking behavior in rodents, leading to changes in behavior.

In non-human primates, rFMI has been used to study the effects of brain activity on social behavior. Studies have shown that rFMI can be used to modulate social behavior in non-human primates, leading to changes in behavior.

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In conclusion, rFMI is a promising technique for the regulation of brain regions. The technique has been shown to have a variety of applications, including the treatment of neurological disorders, improvement of cognitive function, and modulation of behavior. Further research is needed to fully understand the potential of this technique and to develop new applications for its use.
behavioral measurement. Although designed as a single-subject study, this work was one of the first convincing evidence that BOLD signal of circumscribed brain regions can be self-regulated using “immediate” rtfMRI neurofeedback.

Caria and colleagues performed a series of experiments investigating the use of rtfMRI-BCI for the regulation of anterior insular activity, emphasizing the potential behavioral modification induced by learned brain self-regulation. In an initial study (Caria et al., 2007), nine participants of the experimental group were trained with continually updated visual feedback from the BOLD signal coming from right anterior insula (delay 1.5 s), and by recalling autobiographical emotional events. Successful training (observed in all the participants) resulted in a significantly monotonic increased activation cluster in the anterior portion of the right insula across fMRI sessions, indicating training effects and learning. Immediately after the training, participants were instructed to achieve insula self-regulation, but this time without the presence of feedback. This “transfer” session showed a significant increase in BOLD signal in insula compared with the initial training session, suggesting that learned self-regulation can persist (at least in the short-term) after rtfMRI-BCI training. Importantly, two control groups were added, one trained with “sham feedback” (non-specific fMRI information), and a second one in which no fMRI information was provided, but were instructed to use the same mental strategy used by the experimental group. As none of these groups achieved insula self-regulation, this was the first group study that convincingly showed that volitional control of emotionally relevant brain areas can be attained by rtfMRI neurofeedback training, and that this learning is specifically achieved with contingent fMRI feedback.

In a subsequent study, Caria et al. (2010) explored the relationship between brain self-regulation and emotional behavior. Healthy participants underwent four rtfMRI neurofeedback scanning sessions to modulate the BOLD response in the left anterior insula guided by visual feedback, as in the previous study. Participants were presented with either an emotionally negative or a neutral picture following each self-regulation and baseline blocks and asked to rate the emotional valence of the picture. As hypothesized, participants learned to increase and decrease the BOLD response significantly in the anterior insula guided by contingent feedback, and behavioral data showed a significant difference of valence ratings of the aversive pictures in the last training session. These results demonstrated that rtfMRI neurofeedback manipulation of paralimbic regions such as insula is possible and can modulate a specific emotional response.

Zotev et al. (2011) explored the use of rtfMRI with amygdala as the region of interest. Unlike the experiment by Posse et al. (2003), this study included a large experimental group trained with contingent feedback (BOLD signal from left amygdala) and a control group trained with sham feedback. Their results confirmed previous studies in insula cortex, showing a progressive increase in the amygdala activation in the experimental group, and a persistence of the learning effect in a subsequent transfer session. The study explored the relationship between the capability for self-regulation using rtfMRI feedback and a few trait psychological measures: subjects with greater difficulty in identifying feelings, and the ones with higher sensitivity to others people’s anger, were less able to self-regulate during the training.

Hamilton, Glover, Hsu, Johnson, and Gotlib (2011) tested whether individuals can down-regulate the activity of the subgenual anterior cingulate (sACC) cortex with rtfMRI neurofeedback. Using positive affect strategies, healthy women were able to down-regulate the BOLD signal from sACC, unlike a control group of participants trained with sham feedback. The learned down-regulation, however, did not persist in a subsequent session where subjects were not provided with feedback.

2.1.2. Self-regulation of other brain regions

Besides brain areas related to emotional processing, the second most commonly studied brain regions in rtfMRI research corresponds to somatomotor areas (Berman, Horovitz, Venkataraman, & Hallett, 2012; Chew, LaConte, & Graham, 2012; deCharms et al., 2004; Johnson et al., 2012; Yoo & Jolesz, 2002; Yoo, Lee, O’Leary, Panjich, & Jolesz, 2008). Successful self-regulation of these regions has been used to move an external mechanical arm and computer devices (Lee, Ryu, Jolesz, Cho, & Yoo, 2009; Yoo et al., 2004), therefore suggesting a potential use in neurorehabilitation. These studies have shown that healthy subjects can successfully achieve self-regulation of somatomotor areas with motor imagery and rtfMRI feedback. However, at least one study presented contrasting results, as participants were not able to display a consistent control of M1 using motor imagery and rtfMRI feedback (Berman et al., 2012).

Other studies in healthy subjects have also targeted auditory regions (Yoo et al., 2006), language areas (Rota et al., 2009) and deep brain structures, i.e. basal ganglia (Sulzer et al., 2012). For further details, please see Table 1.

2.2. Studies on clinical populations

The observed behavioral modifications induced by operant training of single brain regions in healthy subjects, naturally led to efforts for implementing this methodology in clinical populations. In the first full-group, controlled rtfMRI neurofeedback study leading to a resultant impact on behavior or disease symptoms, deCharms et al. (2005) focused on the use of self-regulation of rostral ACC to investigate the modulation of pain perception. They showed that it is possible to gain deliberate control of rACC aided by contingent fMRI feedback. It was also demonstrated that similar self-regulation can be achieved by a group of chronic pain patients who reported decrease in the level of ongoing pain after the rtfMRI neurofeedback training.

Based on current views of the neural basis of tinnitus, Hailer, Birbaumer, and Veit (2010) executed a pilot experiment in which a small number of patients with chronic tinnitus were trained to reduce the activations of the auditory cortex (down-regulation). After a single day of training, most of the patients learned to down-regulate their activations in the ROI using visual contingent feedback. Interestingly, a decrease of the subjective report of tinnitus was observed in two out of six participants, suggesting that fMRI-BCI could potentially produce beneficial effects for the treatment of this disorder.

Sitaram et al. (2012) successfully used rtfMRI neurofeedback to train healthy individuals and stroke patients to regulate the BOLD signal of ventral premotor cortex (PMv). To measure the effects of self-regulation, paired pulses of transcranial magnetic stimulation (TMS) were used to induce intracortical inhibition and facilitation, while simultaneously measuring motor evoked potential (MEP) on the participant’s finger. Results showed evidence for a reduction in intracortical inhibition after feedback training, indicating the beneficial effect of self-regulation training on motor cortical outputs.

Subramanian et al. (2011) trained a small group of patients suffering from Parkinson’s disease to achieve self-regulation of the supplementary motor complex over two fMRI sessions, using motor imagery. After successful training, patients showed an improvement in motor speed (finger tapping) and clinical ratings of motor symptomatology, effect that was not produced in an equal size control group of patients trained with motor imagery but not fMRI feedback information. However, in a recent experiment, Buyukturkoglu et al. (2012) showed that behavioral results associated with feedback training are not always consistent among studies. In fact, in a pilot study with one Parkinson’s patient and 3 healthy subjects, all the participants learned to up-regulate the
BOLD signal in the SMA using motor imagery and rtfMRI feedback. More importantly, in order to explore behavioral modifications associated with learning, participants performed a sequential button press task following up-regulation and baseline blocks in the scanner. Contrary to expectations, after the training the motor performance (measured by the number of button presses in correct sequence) was better following baseline blocks (in which no regulation of SMA was performed) than following up-regulation blocks, suggesting that operant learning of SMA might interfere with motor execution, and that the relation between neural activation of SMA and motor performance may need further exploration.

In the first application of rtfMRI-BCI on addictive disorders, Li et al. (2012) trained nicotine addictive patients to reduce the craving response toward smoking cues. In a “reduce craving paradigm”, participants successfully managed to reduce their craving response toward craving-inducing pictures, while decreasing the activation of the anterior cingulate cortex. A significant correlation between the induced changes in ACC activation and the corresponding difference in cue craving ratings was also found.

Ruiz et al. (2013) aimed to evaluate if patients with schizophrenia can learn self-control of the BOLD signal in the anterior insula by rtfMRI neurofeedback. Their results showed that patients with chronic schizophrenia are able to learn volitional control of the activity of anterior insular cortex (Fig. 1). Following blocks of insula self-regulation, patients detected significantly more disgust faces in a face emotion recognition task, in line with the extensive evidence of the role of insula in face disgust recognition. However, for reasons that need more exploration, patients detected less happy faces following self-regulation. Notably, negative symptoms and the duration of the illness were negatively correlated with the success of self-regulation.

In another study on a psychiatric population, Linden et al. (2012) applied rtfMRI neurofeedback to a group of patients suffering form unipolar depression. Patients were instructed to up-regulate several ROIs that included several brain regions strongly implicated in the control of emotions (ventrolateral prefrontal cortex (VLPFC), insula, dorsolateral prefrontal cortex (DLPFC), medial temporal lobe or the orbitofrontal cortex), while engaging in positive mood imagery. Successful regulation was observed in the experimental group, accompanied by a significant clinical improvement at the end of the training.

2.3. Progress and limitations of single-ROI rtfMRI

As can be seen for the studies summarized in the previous section (and in Table 1), fMRI-BCI experiments have rapidly gained in complexity and ambition. In fact, in a few years, researchers have targeted diverse brain areas as ROIs including amygdala, anterior insula, inferior frontal gyrus (IFG), several subdivisions of the ACC, superior temporal gyrus (STG), and several sensorimotor areas and other emotion-related areas. The results of most of these studies have shown that if self-regulation learning occurs, this effect is specific for the target ROI and not due to general arousal or artifactual confounds. Technical advances in imaging acquisition and processing have reduced the feedback delay from more than a minute to near 1 s. Furthermore, recent experiments frequently incorporate
larger groups, and include one or more control groups (usually one of them trained with sham feedback), in order to prove that BCI training is the specific factor that results in self-regulation and behavioral modifications. These behavioral changes, in healthy subjects, have included modulation of affective states, modifications in the evaluation of emotional visual stimuli, auditory attention and linguistic processing. In patients, behavioral modulations associated with rtfMRI-BCI training have included the reduction of tinnitus, modulation of the accuracy in recognizing emotional faces, temporal reductions of nicotine craving, reduction in the severity of symptoms of depression, and motor performance modulation.

All previously discussed studies on rtfMRI trained subjects to achieve self-regulation of single brain regions, taking advantage of one of the hallmark features of fMRI, i.e., its high spatial resolution and its capability to assess circumscribed brain regions for neurofeedback.

However, this very same feature leads to potential issues that go beyond theoretical aspects as they could have important clinical implications. Complex cognitive processes are not considered to be limited to the activation of a single, unique brain area. In fact, most of the processes so far examined with rtfMRI studies (e.g., emotion processing, motor response, language, pain perception, etc.) include the coordinated activity of several brain regions.

Hence, an observed behavioral modification induced by single-ROI regulation would certainly increase our knowledge about the functionality of the specifically trained brain region, but most probably it will not be reflecting the natural functioning of the brain.

Similarly, considering that normal brain functioning involves the concerted action of multiple brain networks, it is not surprising that abnormal brain states, as in several neurological and psychiatric disorders, are thought to arise from the uncoordinated activation of distributed brain regions, or from their impaired functional coupling (Friston & Frith, 1995; Honey et al., 2005; Just, Cherkassky, Keller, Kana, & Minshew, 2007; Noonan, Haist, & Muller, 2009; Wang et al., 2007; Zhang et al., 2010).

Could rtfMRI-BCI be used to enhance or modulate neural connectivity, and not only the activity of single ROIs? To answer that question, we will discuss new developments for the direct modulation of the functional neural connectivity, and for the modulation of brain networks.

3. Brain connectivity enhancement with rtfMRI

3.1. Direct self-modulation of brain functional connectivity with rtfMRI

fMRI analysis can reveal information about the degree by which components of large-scale neural systems are functionally coupled together during a specific task or resting state. Several methodological approaches exist for the evaluation of neural coupling with fMRI signals, categorized as “data driven” versus “hypothesis driven”, or based on the simple correlation of the BOLD signal (“functional connectivity”) versus others that include the analysis of the causation and direction of the influence between brain regions (“effective connectivity”). For reviews on these techniques for the assessment of functional brain connectivity, please see: (Li, Guo, Nie, Li, & Liu, 2009; Rogers, Morgan, Newton, & Gore, 2007). In traditional fMRI studies, the analysis of neuronal connectivity is performed “offline”. However, if this information could be processed and provided in real-time, the rtfMRI-BCI for “neural connectivity modulation” could become a reality.

Interestingly, the idea that rtfMRI could be used to enhance brain connectivity does not come only from a theoretical point of view. A few previous rtfMRI-BCI works explored whether the control acquired over a particular single brain area is associated with changes in brain network connectivity. Post hoc analysis of these experiments suggest that the successful modulation of a single ROI (insula cortex, Lee et al., 2011; Veit et al., 2012; amygdala, Zotev et al., 2011; and ACC, Hamilton et al., 2011) is accompanied with modulations in the connectivity of brain networks.

Furthermore, one study explored this phenomenon in a clinical population, i.e. schizophrenia patients (Ruiz et al., 2013), using Granger causality modeling (CCM), methodology that examines “effective connectivity” using temporal information in one or more time-series of signals from a certain brain region to predict signal time courses in another (Abler et al., 2006; Seth, 2005, 2010). After learned self-regulation of insula cortex, the effective connectivity of the emotional network was enhanced. This change was reflected in the larger causal density (CD: the fraction of interactions among ROIs in a network that are causally significant) of the network in the strongest session of regulation (of the last day of training) compared with the weakest session of regulation (of the first day of training) (Fig. 2a and b).

These studies suggest that rtfMRI could be used to build a more efficient neural pathway and enhance brain connectivity. However, it is important to point out that these enhancements of brain connections were achieved as a by-product of single ROI self-regulation training (and not by a “direct” training of the brain connectivity), and therefore the particular regions of the brain involved could not be determined a priori.

To address this problem, we performed the first study that aimed to “directly” train subjects to achieve self-control of the functional connectivity of two brain areas brain regions with rtfMRI-BCI (Ruiz et al., 2011). A group of healthy participants were trained to increase the functional connectivity between fronto-temporal cortex during self-regulation blocks in a few scanning sessions of rtfMRI, by contingent visual feedback of the correlation coefficient between inferior frontal gyrus (IFG) and superior temporal gyrus (STG).

The equation to compute the magnitude of feedback signal was:

\[
\text{Magnitude of feedback} = (\text{TOT}_{\text{BOLD}}_{\text{regulation}} - \text{TOT}_{\text{BOLD}}_{\text{baseline}}) \times (1 + \text{EC})
\]

where \(\text{TOT}_{\text{BOLD}} = (\text{BOLD} \text{ in ROI1} + \text{BOLD in ROI2})\) is the total BOLD in the two ROIs, ROI1 is the left IFG, ROI2 is the left STG, and EC is the correlation coefficient derived from the BOLD time-series in the two ROIs computed from a sliding window of current and past time points. Correlation-methods perform with high sensitivity estimating the presence of a network connection with fMRI signals (Smith et al., 2011) and have been extensively documented for the offline analysis of brain network connectivity (e.g., Meyer-Lindenberg et al., 2005; Satterthwaite et al., 2010). A number of other possibilities for estimating brain connectivity exist (e.g., computing bivariate Granger causality measures), but these measures require more samples of data to be reasonably accurate for their use with rtfMRI-BCI.

Results of this experiment showed that participants trained with contingent feedback were able to learn self-regulation of the connectivity between IFG and STG after a few sessions of training. Secondly, we explored the behavioral modification induced by the training in an automatic semantic priming task performed before (pre-test) and after (post-test) the rtfMRI training sessions, as it has been postulated that the neural bases of this phenomenon include the coupling of fronto-temporal areas (Sass, Krach, Sachs, & Kircher, 2009a; Sass, Sachs, Krach, & Kircher, 2009b). As hypothesized, a noticeable “enhancement of the priming effect” was observed following blocks of learned IFG-STG connectivity.

In summary, we showed for the first time that it is possible to train subjects to enhance the functional connectivity of two
circumscribed brain areas using contingent rtfMRI feedback. The application of this new “functional connectivity enhancement”, could offer a novel non-invasive method to modulate abnormally activated networks in brain disorders.

3.2. Brain network feedback with rtfMRI

Previous sections have discussed the methodological background and applications of real-time fMRI, focusing on the topics of volitional control of hemodynamic activity in circumscribed brain areas and functional connectivity between brain regions. Although such approaches have been used in many studies, they are limited in terms of their ability to enable modulation of the entire neural circuitry involved in any brain function. After all, and as mentioned before, brain’s involvement in perception, cognition, emotion and action is known to encompass specific networks of spatially distributed brain regions. An answer to such a challenge has become the target of further developments in this field, which will be covered in this final section.

Decoding brain states requires knowledge of how information is encoded in spatially distributed regions and in temporally varying patterns. Conventional neuroimaging works by first acquiring neuroelectric or hemodynamic activity from multiple regions of the brain repeatedly while the subject performs different mental tasks or is presented different stimuli, followed by a statistical comparison of the activity in each region separately. This approach, called “univariate analysis”, ignores dynamic interactions between brain regions. In contrast, recent developments (Cox & Savoy, 2003; Haxby et al., 2001; Haynes & Rees, 2005; Sidtis, Strother, & Rottenberg, 2003) have demonstrated that the sensitivity to decoding brain activity is greatly enhanced when activity in spatially distributed regions of the brain and their temporal variations are included in the analysis by employing “pattern recognition” techniques.

Several pattern recognition techniques have already been applied to fMRI data, including linear discriminant analysis (LaConte et al., 2003), naïve Bayes (Pereira, Mitchell, & Botvinick, 2009), support vector machine (SVM) (LaConte, Strother, Cherkassky, Anderson, & Hu, 2005), neural networks (Hanson, Matsuka, & Haxby, 2004), canonical variates analysis (Mourao-Miranda, Reynaud, McGlone, Calvert, & Brammer, 2006) and fisher linear discriminant (Shaw et al., 2003). SVM is probably the most widely used approach to predict brain states from fMRI signals. Studies have reported the superior performance of SVM in comparison to other existing methods of pattern classification (LaConte et al., 2003, 2005; Martinez-Ramon, Kolchinskii, Heileman, & Posse, 2006; Shaw et al., 2003; Strother et al., 2004).

Fig. 2. Group analysis of effective connectivity changes due to fMRI-BCI training using granger causality modeling (GCM). (A) Directed influences of the emotional network during self-regulation, in the weakest (in the first day of training) and the strongest regulation session (last day of training). Red arrows indicate bidirectional influences between ROIs. (B) Number of outgoing (outflow) and incoming (inflow) connections of each ROI of the emotional network during self-regulation (the graph depicts the information contained in figure (A) MidFG: left middle frontal gyrus, MPFC: left medial prefrontal cortex, ACC: left anterior cingulate cortex, L Insula: left anterior insula, R Insula: right anterior insula, SMG: left supra marginal gyrus). Source: Adapted with permission from Ruiz et al. (2013).
How does an SVM classify brain signals? In a binary SVM classifier, where two brain states need to be classified (e.g., brain state pertaining to left hand versus right hand movements), the first task for the scientist is to represent the fMRI signals from all brain voxels being measured, corresponding to each instance of a brain state, as a pair of corresponding input vectors; the first vector is called the feature vector and the second, the labels vector. From this input data, each instance of a brain state is represented as a point in a multi-dimensional state space. Typically, fMRI signals from whole brain images will have more than 60,000 voxels, resulting in a high-dimensional feature space. SVM classification is performed in two distinct steps: 1. classifier training and 2. classifier testing. The objective of the training procedure is for the SVM algorithm to find a high-dimensional plane, called the “hyperplane”, to separate the points in the feature space corresponding to the two distinct brain states (Schölkopf & Smola, 2001). During the testing procedure, new fMRI signals are presented to the SVM classifier without specifying the brain state the fMRI signals correspond to. The classifier then determines the most probable brain state pertaining to the presented data based on which side of the hyperplane the feature point is located. Accuracy, precision and other performance metrics are then computed based on the number of correct and incorrect predictions from several test data. For more details on the SVM pattern classification one can refer to a number of excellent tutorials and articles on the topic (Schölkopf & Smola, 2001; Shawe-Taylor & Cristianini, 2004; Steinwart & Christmann, 2008).

Pattern analysis has been used for understanding the spatial and temporal neural patterns of different brain functions and their states. Recent studies that used this approach are: automated classification of sleep stages (Tagliazucchi et al., 2012), spontaneous decisions and hidden intentions (Lages & Jaworska, 2012), tracking the unconscious generation of free decision (Bode et al., 2011), memory recall (Polyn, Natu, Cohen, & Norman, 2005), lie detection (Davatzikos et al., 2005), visual perception (Xu, Jiang, Ma, Yang, & Weng, 2012), task related intentions (Haynes et al., 2007), fear perception (Pessoa & Padmala, 2005), and emotion detection (Sitaram et al., 2011a), to name a few.

How can pattern classification be incorporated in real-time fMRI studies? LaConte et al. (2007) were the first to demonstrate the real-time implementation of pattern classification of brain states from fMRI signals. Their study demonstrated binary decoding and feedback of motor or cognitive states of the brain. An additional use of pattern analysis in real-time fMRI studies would be to determine which brain areas are particularly influential in volitional regulation and the behavior that is being targeted. Lee and colleagues attempted to address the above question by applying their novel Effect Mapping method to investigate the effect of neurofeedback training on functional reorganization of the emotional network. In fMRI signals, the Effect Mapping algorithm measures the effect of each brain voxel on the classifier output by considering the mutual information between the BOLD activations at each voxel and the output, and the weight value of the voxel in the estimated SVM weight vector. This methodology has demonstrated high classification accuracy decoding mental states, and therefore could be an alternative method in the multivariate analysis of fMRI data by considering both discriminability and data distribution (Lee, Halder, Kubler, Birbaumer, & Sitaram, 2010).

The authors found that subjects who learn to volitionally control left anterior insula with real-time feedback develop greater number of functional connections from left insula to other emotion-related brain regions, particularly, right insula, amygdala, medial prefrontal cortex, anterior cingulate cortex, and posterior parietal regions. Sitaram et al. (2011b) further incorporated the Effect Mapping technique into their real-time fMRI feedback system to
enhance online classification. They showed for the first time that it is possible to classify multiple emotional states (i.e., happiness, sadness and disgust) in real-time, and used the technique for enhancing volitional control of the emotion circuitry. Fig. 3 shows the general design of the real-time brain state classification system used in this study (the general design is common to other pattern-classification feedback studies). Fig. 4 displays the Effect Maps and classification accuracy results for the classification of different emotional states.

In what could be the first most compelling use of real-time fMRI pattern classification for neuroscience investigation, Shibata, Watanabe, Sasaki, and Kawato (2011) addressed a very controversial question of whether adult early visual cortex is sufficiently plastic to allow visual perceptual learning. To this end, authors implemented an online decoder to identify voxels in early visual cortex (V1/V2) corresponding to three distinct Gabor patch gratings differing by 60° orientation from each other. The feedback signal represented the likelihood of these voxels predicting the perception of one of the patches, without instructing the participants about what the feedback signal represented. During neurofeedback training participants were rewarded to self-induce the target spatial distribution, by the principle of operant learning. The study showed that following neurofeedback training, participants improve perceptual sensitivity to the target grating to the exception of the other two gratings. This inventive study underlines the potential of the tool in studying cause-and-effect relationships. As the authors note: it <such a technique> can “incept” a person to acquire new learning, skills, or memory, or possibly to restore skills or knowledge that has been damaged through accident, disease, or aging, without a person’s awareness of what is learned or memorized.

Despite these exciting developments in scientific application of real-time fMRI pattern feedback, we are still far away from bringing such a technology to clinical use. One major technical hurdle is that existing approaches to online pattern classifier are built specifically for an individual based on his fMRI signals alone. In other words, the current breed of online classifiers is incapable of generalizing their decoding capabilities to other subjects; they are highly “subject-dependent”. This state-of-art leads to two adverse implications: (1) the need to acquire large amount of preliminary functional data to train a pattern classifier, and more importantly (2) an inherent conceptual error in aiming to train a patient with a pattern classifier which is first built with the subject’s own abnormal brain signals. To overcome the above difficulties, we have recently attempted to develop a subject-independent pattern classifier (SIC) from a larger set of group data from many individuals representing a certain demographic population (e.g., healthy individuals of similar age, educational background, and specific cognitive or emotional abilities). With such a pre-developed SIC classifier model, one can in principle, train new individuals or patients to help them bring to normality a specific brain function that they are disadvantaged with.

In our most recent work (Rana et al., 2012b) to implement online subject-independent classification, we have adopted functional preprocessing steps of co-registration and normalization to be able to function in a real-time mode. By doing so, the fMRI signals arriving to the classifier are automatically transformed into a standard space (Montreal Neurological Institute, MNI). This allows for reducing inter-subject differences in brain size and shape, thus facilitating the classifier to generalize its predictions much better.

In a proof-of-principle study, we developed a SIC-classifier model, built on fMRI signals from 12 subjects who performed volitional regulation of emotion of happy and disgust (Rana, Ruiz, Gupta, Niels, & Sitaram, 2012a). We then applied this classifier to provide real-time feedback to a number of new subjects, to train them to learn volitional regulation of happy and disgust emotions, aided by feedback from specific “emotion circuitries” pertaining to the two states. Our results show that new subjects can learn to gradually activate the right spatial pattern. As a consequence of feedback training, their emotional regulation improves with more training runs, and volitional control of a particular emotion (e.g., happiness) has a facilitatory effect on a corresponding emotional priming task.

4. fMRI-BCI limitations and future directions

The previous studies serve to illustrate the exciting moment for rtfMRI-BCI. However, for both single ROI and brain connectivity
feedback (functional connectivity and network) with rtfMRI, some limitations and unsolved questions need to be mentioned.

For most of these experiments, the number of participants remains low, probably due to the complicated, and often highly time-consuming setting needed for a rtfMRI-BCI training (particularly if compared with “simple” fMRI experiments). And although efforts have been made to include control conditions and control groups, there is no clear consensus regarding which of these is the best methodology for providing a reliable control condition (e.g., no feedback, sham feedback, feedback from a control brain region, up-regulation versus down-regulation, etc.). On the other hand, the underlying mechanisms of operant learning by rtfMRI training are not yet clearly understood. This phenomenon is aggravated by the fact that not every study has included detailed reports of the mental strategies used by the participants to achieve brain self-regulation, and no deep exploration has been made on the effect that the initial instructions and guidance by the researchers can have in the learning process. Similarly, the influence on learning of factors like motivation, attention, or the psychological and neural differences between “learners” and “non-learners” has been rarely investigated.

Furthermore, with few exceptions (deCharms et al., 2005; Haller et al., 2010; Hamilton et al., 2011; Veit et al., 2012), most of these studies have focused on the “up-regulation” of brain signals, and therefore the question of whether subjects can voluntarily learn to decrease the activation of a particular brain area or network (factor that can be of importance for brain disorders in which an abnormal over-activation underlies the psychopathology), remains unsolved.

Regarding the studies on clinical populations, many crucial questions need to be answered before the clinical implementation of this methodology becomes a reality. In fact, very few studies have explored whether brain self-regulation persists immediately following training if no feedback is provided, and if at all, with dissimilar results (Rui et al., 2013; Sitaram et al., 2012).

Along the same lines, few preliminary studies have assessed whether the learned capability to self-regulate or behavioral modulations and/or symptom alleviation will persist in the following days after the rtfMRI-BCI training (Haller et al., 2010; Yoo et al., 2008). So far, no study has reported the analysis of these aspects in a clinically significant long-term.

Future studies should evaluate as to which of the three feedback methods, namely, single-ROI, functional connectivity and network, is appropriate for the given type of study i.e., neuroscience research and clinical treatment.

We expect single ROI neurofeedback to continue as a tool to determine links between specific brain regions and behavior. For therapeutic purposes, if large controlled studies confirm its efficacy, it could offer a non-invasive approach for modulating circumscribed dysfunctional brain areas for intractable neurological and psychiatric disorders, similar to new (although invasive) techniques for the stimulation of specific brain areas, i.e. deep brain stimulation.

As stated before, network connectivity feedback for its part may better represent brain physiology, having also the advantage of covering the whole brain. For clinical applications, it could be more suitable than single-ROI feedback for diseases of “brain network connectivity” (i.e., schizophrenia, autism disorder, among others). Similarly, pattern classification of whole brain data and the development of subject-independent pattern classifiers could offer a revolutionary approach to aid patients to achieve a “desirable healthy brain state”.

The combined use of these techniques in the same experiment could provide new insights into brain functioning, and shed light on their distinct uses in clinical applications. Further developments of both single-ROI and brain circuitry feedback will inform us as to how these approaches can complement each other, thus opening exciting possibilities for scientific investigations in systems neuroscience, neuropsychology, psychiatry and neurology. It remains to be seen how further progresses in these fields fulfill these promises.

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