Real-time Functional Magnetic Resonance Imaging

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Advanced article

Article Contents

Online posting date: 22nd January 2018

Real-time functional magnetic resonance imaging (rt-fMRI) is an increasingly popular noninvasive technique used to study brain function in 'real time'. In contrast to traditional fMRI, rt-fMRI allows researchers to access and manipulate neuroimaging data as they are acquired. This advance allows experimenters to use fMRI data in novel ways, including: quality assessment, biofeedback, dynamically controlled experimental tasks and assistive technologies (e.g. control over prostheses). Cutting-edge research in this field has demonstrated compelling findings in healthy human participants and patient populations alike, including: volitional regulation of multiple brain regions, improved symptoms in several clinical populations and successful nonverbal communication. As rt-fMRI is still in the early phases of development, we anticipate that this technology will continue to be used in novel and exciting ways by current and future generations of scientists.

Introduction

Real-time functional magnetic resonance imaging (rt-fMRI) refers to the technique of accessing and utilising functional MRI brain data as they are being acquired. Unlike standard functional magnetic resonance imaging (fMRI), in which data collected by the scanner are not available to researchers until after a scan has completed, rt-fMRI allows researchers to utilise the data immediately for a host of applications, described in detail below, including neurofeedback training, dynamic task control and use as an assistive technology.

Rt-fMRI first emerged in the late 1990s (Voyvodic, 1999), but in recent years has experienced a surge in interest as computational advances have made running complex analyses more feasible. Between 2013 and 2017, for instance, the number of publications using the term 'real-time fMRI' has increased by over 180% compared with the preceding 5 years. Initially, rt-fMRI was primarily used for online data quality monitoring, correction and basic analysis. By the early 2000s, researchers expanded the use of the technique to explicitly study cognitive and psychological phenomena (deCharms *et al*., 2004; Posse *et al*., 2003). More recently, the use of rt-fMRI methods has increased substantially along with new advances in how this technique is utilised. Examples include volitional activation of key neuromodulatory brain regions (MacInnes *et al*., 2016; Sulzer *et al*., 2013), dynamic task control (whereby the task itself changes based on an individual participant's brain activity, deBettencourt *et al*., 2015; Yoo *et al*., 2012) and brain–computer interfaces (BCIs) designed to augment motor or communication abilities (Sorger *et al*., 2012).

In this article, we aim to give readers an understanding of what rt-fMRI is, how it differs from standard fMRI and how it is being utilised in the field to address cutting-edge basic science and clinical questions. We begin by providing a methodological overview of rt-fMRI, in which we discuss the basic principles of data collection and the technological requirements for conducting rt-fMRI. Historically, the number of research institutions with the resources and technical expertise to conduct rt-fMRI investigations has been low. However, the computational power available on modern MRI scanners has removed many barriers to utilising rt-fMRI, and as a result, has enabled an increasing number of institutions worldwide to adopt these methods. Moreover, many software packages supporting rt-fMRI are now available for free or a fixed cost. After providing an overview of rt-fMRI methods, we will discuss common applications of rt-fMRI. Here, we focus on three primary research areas: neurofeedback training, dynamic task control and assistive technologies. To complement what is discussed in this article, we direct the reader to the following sources for further reading (Caria *et al*., 2012; Weiskopf *et al*., 2007). Lastly, like all techniques, rt-fMRI has limitations, which we will describe before concluding with ideas for areas of future research.

eLS subject area: Neuroscience

How to cite:
MacInnes, Jeff J and Dickerson, Kathryn C (January 2018) Real-time Functional Magnetic Resonance Imaging. In: eLS. John Wiley & Sons, Ltd: Chichester.
DOI: 10.1002/9780470015902.a0027168

Methodological Overview

Rt-fMRI is a variation on standard fMRI methods. To understand the utility and potential of rt-fMRI, it is helpful to begin with a brief discussion of how fMRI works in general and how it can be used to study brain function. With that as a foundation, we next describe the advantages of collecting data in real time and provide a technical overview of how that can be achieved.

fMRI basics

A fundamental aim of cognitive neuroscience is to map brain function to behaviour. This is facilitated by neuroimaging techniques such as fMRI, which safely and noninvasively records brain activation. In an experimental context, fMRI can be used to record brain activation while participants perform various cognitive tasks. By subsequently correlating how brain activations change in response to the task, researchers make inferences about the functional role of specific brain areas. Since it emerged in the mid-1990s, fMRI has matured into a methodology with widespread applications across clinical and experimental domains. Advances in computational power and statistical methods have also enabled increasingly complex information to be decoded from fMRI data, such as reconstructing visual experiences (e.g. movies) by decoding brain activation in the visual cortex (Nishimoto *et al*., 2011).

While novel and more powerful techniques for analysing data continue to develop, the basic principles of how fMRI data are collected remain the same. Understanding these principles is critical to designing experiments, interpreting results and drawing meaningful conclusions. fMRI measures changes in blood oxygenation levels over time. Haemoglobin molecules carrying oxygen have a different magnetic signature than haemoglobin molecules without oxygen. As oxygenated haemoglobin is carried by the blood stream through the body, it causes local disruptions of the magnetic field, which are detectable with MRI. Active neurons require oxygen to keep up with metabolic demands; therefore, blood flow increases to active regions to meet that demand. By repeatedly sampling the magnetic field in the same area over time, fMRI can detect relative changes in the local concentrations of blood oxygenation. As such, the measured response is referred to as the *blood-oxygenation-level dependent*, or BOLD, signal.

Like any brain imaging modality, fMRI offers advantages and disadvantages. One of its chief advantages is the ability to sample BOLD responses throughout the entire brain, more or less simultaneously, permitting hypotheses about functional processing distributed over a disparate network of brain regions. Moreover, fMRI can sample the brain with a spatial resolution of approximately 1–4 mm, permitting inferences about localised subunits of processing at both cortical and subcortical levels. These advantages must be weighed against the limitation that fMRI is not a direct measure of neuronal activity, but rather an inferential measure of brain activation based on which regions receive fresh supplies of oxygenated blood. Physiological limitations on the BOLD response mean that fMRI has a relatively coarse temporal resolution: the BOLD response may take up to 5–7 s to peak, while the underlying neuronal response is on the order of milliseconds. Furthermore, the BOLD response is often weak (a peak signal may be as small as an ∼0.1–1% change from baseline) and susceptible to various endogenous and exogenous sources of noise (e.g. breathing rate). In many cases, these limitations can be mitigated via careful consideration of experimental design features and imaging parameters. Nevertheless, they represent important challenges and the ones that become particularly relevant in the context of rt-fMRI.

Real-time fMRI

Rt-fMRI operates on the same principles as standard fMRI, only in this case, the raw data are accessed and utilised in real time while a scan is occurring. This offers a range of potential benefits to researchers, including: (1) the ability to monitor data quality over the course of an experiment, (2) the ability to show participants their own brain activity – a process referred to as 'neurofeedback' – from areas within their brain and (3) the ability to use brain activation to control various aspects about the experiment including timing and perceptual properties of the experimental task (e.g. control the opacity of a picture based on the individual's brain activity). The last two features in particular present researchers with new opportunities to test hypotheses about brain and behaviour that would otherwise be impractical if not impossible. We describe these approaches in greater detail in later sections. Despite these advantages, there is only a small (but growing) percentage of research institutions equipped to offer rt-fMRI, in part owing to the technical challenges involved.

A typical fMRI experiment may collect data from upwards of 100 000 unique spatial locations throughout the brain. At each of those locations, new data may be sampled every 1–2 s. Dealing with this much information in real time requires fast and efficient data pipelines. These pipelines must have the capacity to simultaneously access the data and apply all denoising, preprocessing and analysis steps at a rate that keeps pace with data acquisition.

While the computational demands of rt-fMRI were a challenge in the past, at present most MRI scanners have multicore processors that are more than adequate to meet this challenge. Increasingly, new software packages are available that offer a variety of options for translating data into meaningful signals for downstream stages of analysis. Commercially available packages such as Turbo Brain Voyager (Brain Innovation, Maastrict, The Netherlands; Weiskopf *et al*., 2003) are joined by open-source options such as FRIEND (Sato *et al*., 2013), OpenNFT (Koush *et al*., 2017) and the 3dsvm plug-in for AFNI (LaConte *et al*., 2005) to offer real-time analysis options to researchers. At the same time, neuroimaging libraries for popular coding languages such as C++, Matlab and Python have enabled many groups to develop in-house analysis tools specifically tailored to their research questions.

Rt-fMRI software forms a bridge between the scanner and experimental control software. Under non-real-time scanning conditions, one computer typically controls the scanner and data acquisition, while a separate computer controls the task and stimuli presentation to the participant (**Figure 1a**). In a rt-fMRI scenario, an additional node (often, but not necessarily, a third computer) is introduced as an intermediary between the scanner and experimental presentation computers (**Figure 1b**). Data

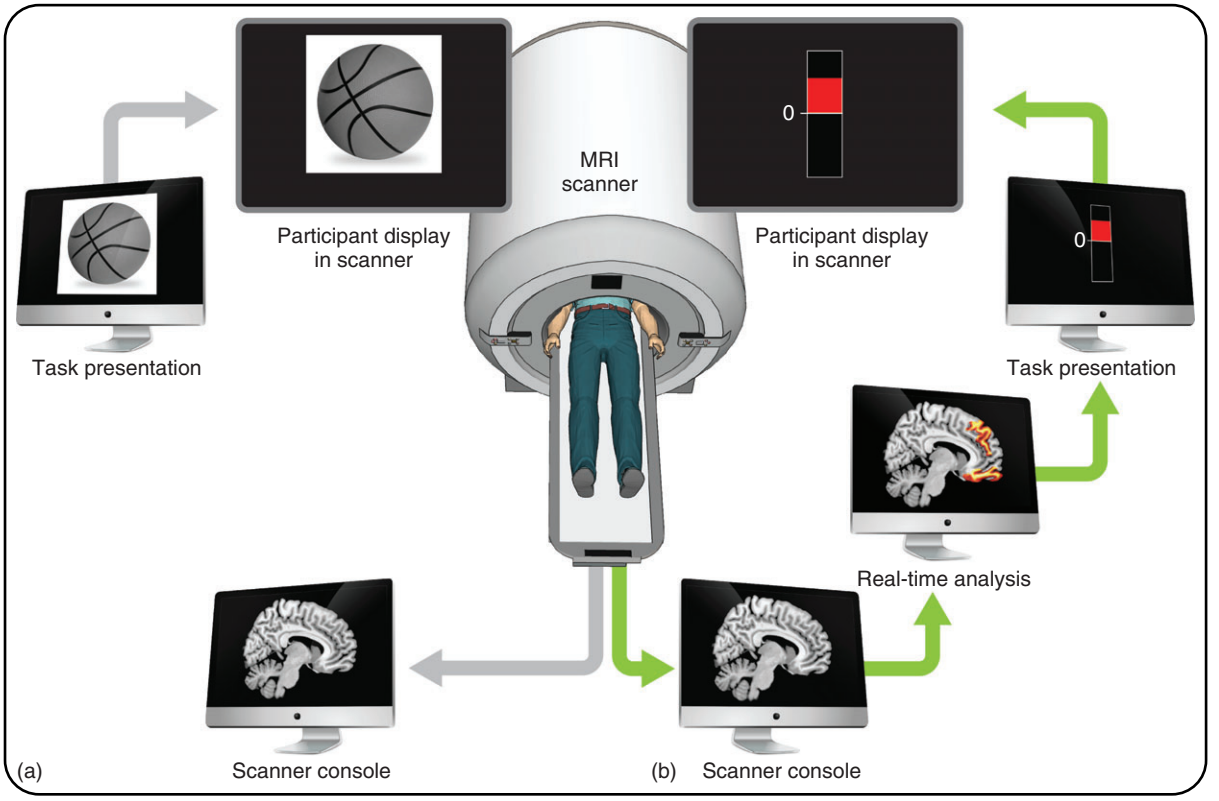

Figure 1 Schematic illustration of (a) standard fMRI (functional magnetic resonance imaging) environment and (b) rt-fMRI (real-time functional magnetic resonance imaging) environment. rt-fMRI involves the addition of another node, often another computer, which allows researchers access to fMRI data as they are acquired. The data are used for a number of functions including providing participants in the MRI machine with 'neurofeedback' – feedback about changes in their brain activation in response to changes in their thoughts (shown here).

from the scanner can be passed through the real-time intermediary node where it is translated into a form appropriate for the experiment, and then made available to the experimental presentation machine. The experimental presentation machine can use the analysed signal for many purposes including controlling the flow of stimuli or presenting neurofeedback to a participant while they perform a task.

Applications

Neurofeedback training

Volitional control

One of the great advantages of rt-fMRI is the ability to analyse BOLD activity immediately and use the signal itself as a form of biofeedback during experiments. This type of biofeedback provides participants with the unique opportunity to observe how changes in thought and cognition can directly influence localised patterns of brain activity. For instance, as a participant attempts to cognitively reframe an emotional image (e.g. reframing an image of a crying individual to imagine the person at a positive event such as a wedding, instead of a funeral), he/she can watch in real time how activation changes in certain emotion-processing regions of the brain. In general terms, neurofeedback training consists of providing participants with interactive feedback during an experimental or clinically based session (**Figure 2**). As such, it has been utilised to study brain function in both healthy volunteers and clinical populations.

An increasingly common use of rt-fMRI is examining participants' ability to volitionally control brain regions (**Table 1**). Indeed, scientists have examined the ability to control many brain areas including motor regions (Berman *et al*., 2012; Chiew *et al*., 2012; deCharms *et al*., 2004; Johnson *et al*., 2012; Lee *et al*., 2009; Sitaram *et al*., 2012; Subramanian *et al*., 2011; Yoo and Jolesz, 2002; Yoo *et al*., 2008), the prefrontal cortex (Linden *et al*., 2012; Li *et al*., 2013), the amygdala (Posse *et al*., 2003; Young *et al*., 2014, 2017a,b; Yuan *et al*., 2014; Zotev *et al*., 2013), insula (Caria *et al*., 2007, 2010; Linden *et al*., 2012; Ruiz *et al*., 2013; Veit *et al*., 2012), cingulate cortex (deCharms *et al*., 2005; Hamilton *et al*., 2011; Li *et al*., 2013; Weiskopf *et al*., 2003), auditory cortex (Haller *et al*., 2010; Yoo *et al*., 2006), nucleus accumbens (Greer *et al*., 2014; MacInnes *et al*., 2016) and midbrain (MacInnes *et al*., 2016; Sulzer *et al*., 2013).

Most experiments have demonstrated successful regulation of brain activation within a given region of interest (ROI) during feedback training. Interpreting such training results can be challenging, however, as it is unclear whether participants are learning to exercise volitional control over brain activation, or

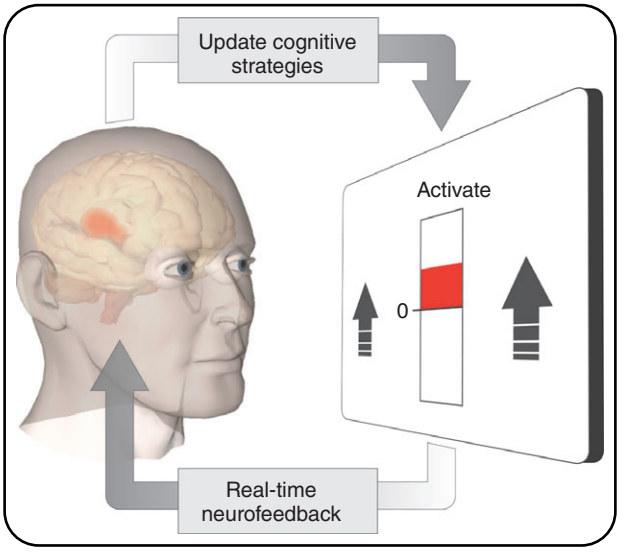

Figure 2 Schematic illustrating a common setup for neurofeedback training. Researchers implement a feedback loop in order for participants to interact with their own brain activation (e.g. thermometer); participants can process this information to update strategies (e.g. thoughts, emotions) with the aim of further modulating their own brain activity.

whether the brain activation is merely caused by the feedback itself. Thus, many experiments test the generalisation of the training effect in a 'transfer' run, in which participants are asked to regulate activation without feedback. Historically, successful activation during transfer runs has been more difficult to achieve. This can be owing to any number of factors, including varying task demands between training and transfer, or simply training phases that are too brief to foster the development of new, generalisable, skills. To date, successful transfer to nonfeedback runs following training has been observed in the insula (Caria *et al*., 2007), amygdala (Young *et al*., 2014, 2017b; Yuan *et al*., 2014; Zotev *et al*., 2011), motor areas (deCharms *et al*., 2004; Sitaram *et al*., 2012; Yoo *et al*., 2008) and midbrain (MacInnes *et al*., 2016). Nevertheless, even without successful transfer to no-feedback conditions, demonstrating activation during training is a critical first step that can reveal the mechanisms involved and suggest ways for optimising the training in the future.

An example of a training-to-transfer neurofeedback study, recently conducted by our group, demonstrated volitional self-activation of the dopaminergic midbrain in healthy adults (MacInnes *et al*., 2016). The study examined whether individuals could learn to volitionally activate the midbrain using internally generated thoughts and imagery. During a training period, participants were presented with neurofeedback (in the form of a continuously updating thermometer) to help develop cognitive strategies that would maximise activation in their midbrain. Whereas before training, participants failed to reliably activate the midbrain, during and after training they were able to significantly increase and sustain activations. Furthermore, following training, there was increased correlated activity among regions known to be important for motivation, learning and memory, including the hippocampus and ventral striatum. This example highlights a few important elements of neurofeedback training paradigms: (1) a pretraining assessment of baseline ability to activate a ROI before neurofeedback training; (2) neurofeedback training with an intuitive display (e.g. thermometer) and (3) a post-training assessment to assess transfer to nontraining runs (e.g. post-test).

Clinical approaches

As a technique for noninvasively measuring brain activity, rt-fMRI lends itself naturally to clinical interventions. To date, rt-fMRI has been applied for the clinical benefit of patients across a variety of disorders. In most studies, patients are asked to up or downregulate an ROI whose activity is disrupted owing to the disorder. In one example by Young *et al*. (2017b), patients with depression were randomly assigned to receive feedback from the amygdala (experimental group) or from the parietal sulcus (control group). Each group attempted to increase the BOLD activity within their target ROI while recalling positive autobiographical memories. Only the experimental group increased amygdala BOLD activation relative to baseline and the control group. Furthermore, participants in the experimental group reported decreased depressive symptoms and fewer met criteria for depression at the end of the study compared to the control group. This study illustrates the power of rt-fMRI to improve clinical symptoms. Importantly, rt-fMRI is safe, noninvasive and carries none of the negative side effects of pharmacological treatments. Other studies have targeted individuals who smoke cigarettes (Li *et al*., 2013), have had a stroke (Sitaram *et al*., 2012), have Parkinson's disease (Subramanian *et al*., 2011), posttraumatic stress disorder (PTSD) (Gerin *et al*., 2016; Nicholson *et al*., 2017), depression (Linden *et al*., 2012; Young *et al*., 2014, 2017a,b; Yuan *et al*., 2014; Zotev *et al*., 2013), schizophrenia (Ruiz *et al*., 2013), attention deficit hyperactivity disorder (ADHD) (Zilverstand *et al*., 2017) and chronic pain (deCharms *et al*., 2005). We anticipate a growing use of rt-fMRI interventions in clinical populations as the technology becomes more widely available.

Dynamic task control

In the earlier cases, the goal has been to deliver neurofeedback that participants can easily interpret as they attempt to modulate their own brain activity. However, monitoring brain activation in real time allows researchers to incorporate the ongoing brain activation directly into an experiment. For example, current brain states can be included as an independent variable to dynamically control aspects of the task presentation, such as stimulus timing or trial order.

Recently, deBettencourt *et al.* (2015) adopted this approach in a study of visual attention. The authors used rt-fMRI in combination with multivoxel pattern analysis (MVPA) to monitor subjects' attentional states in real time. Rather than presenting neural activation as neurofeedback, the authors used the current brain state to control the difficulty of the task. When a participant's attention veered away from the task, the next trial would be set at a higher level of difficulty, thus encouraging a refocus of attention. In contrast to a control group, participants in the rt-fMRI group showed significant improvement when tested after the training

Table 1 Neurofeedback studies examining volitional control of brain regions.

Brain region	Authors	Notes
Amygdala	Posse *et al.* (2003)	Healthy adults increased activation in amygdala for sad > neutral trials during training
	Zotev *et al.* (2011)	Increased activation in amygdala in healthy adults when thinking of positive autobiographical memories; the effect remained in the transfer phase
	Yuan *et al.* (2014)	Hypoconnectivity between the amygdala and several ROIs in individuals with depression is reversed after recalling positive, autobiographical memories. Larger increases in connectivity are associated with larger decreases in depression symptoms
	Young *et al.* (2014)	Increased activation in amygdala when thinking of positive autobiographical memories in individuals with depression; the effect remained in the transfer phase
	Young *et al*. (2017b)	Double-blind, placebo-controlled, randomized clinical trial with individuals with depression. Group that got amygdala neurofeedback learned to regulate it and most showed a decrease in depression symptoms
	Young *et al*. (2017a)	Amygdala neurofeedback training to positive memories improved processing of positive stimuli (e.g. happy face)
Auditory cortex	Yoo *et al.* (2006)	Increased auditory cortex activation during training
	Haller *et al.* (2010)	Individuals with tinnitus learned to decrease activation in ROI; some showed improved symptoms
Cingulate cortex	Weiskopf *et al.* (2003)	A healthy volunteer learned to increase cingulate during the training phase
	deCharms *et al.* (2005)	Healthy adults and those with chronic pain regulated cingulate activation and reported decreased pain symptoms
	Hamilton *et al.* (2011)	Healthy women learned to decrease cingulate activity during training; did not generalize to the transfer phase
	Li *et al.* (2013)	Cigarette smokers decreased cingulate activity during training, which was related to a reduction in craving
Insula	Caria *et al.* (2007)	Healthy adults increased insula activation during training
	Caria *et al.* (2010)	Healthy adults increased insula activation during training; those who increased insula activity more also rated aversive images more negatively
	Linden *et al.* (2012)	Adults with depression increased regions including the insula during training; this correlated with decreased depression symptoms
	Veit *et al.* (2012)	Healthy adults regulated insula activity during training while viewing emotional images
	Ruiz *et al.* (2013)	Adults with schizophrenia regulated insula activity; insula self-activation was correlated with better recognition of disgust faces
Midbrain nuclei	Sulzer *et al.* (2013)	Using romantic imagery, healthy men increased midbrain activation during training phase only
	MacInnes *et al.* (2016)	Using motivational imagery, healthy adults increased midbrain activity during training and transfer

(*continued overleaf*)

Table 1 (*continued*)

Brain region	Authors	Notes
Motor areas	Yoo and Jolesz (2002)	Individuals regulated motor and somatosensory areas
	deCharms *et al.* (2004)	Healthy adults increased activation in somatomotor ROI using imagined actions
	Yoo *et al.* (2008)	Healthy adults learned to increase activation in the hand motor area; the effect remained 2 weeks following training
	Lee *et al.* (2009)	Three adults learned to move a robotic arm by using neurofeedback from hand motor areas
	Subramanian *et al.* (2011)	Individuals with Parkinson's disease upregulated the supplementary motor complex and improved motor speed and motor symptoms
	Johnson *et al.* (2012)	Healthy adults increased activation in the premotor cortex during training; more were successful using intermittent than continuous feedback
	Sitaram *et al.* (2012)	Healthy adults and those with stroke increased activity in the ventral premotor cortex
	Berman *et al.* (2012)	Healthy adults were unsuccessful at increasing primary motor cortex activity using hand motor imagery
	Chiew *et al.* (2012)	Healthy adults had mixed success at increasing primary motor cortex activity (about 50% of participants were unsuccessful)
Nucleus accumbens	Greer *et al.* (2014)	Healthy adults learned to increase (but not decrease) NAcc activity during training, but not the transfer phase
	MacInnes *et al.* (2016)	Healthy adults did not increase NAcc activity during training or the transfer phase
Prefrontal cortex	Linden *et al.* (2012)	Adults with depression increased regions including the PFC (and insula) during training; this correlated with decreased depression symptoms
	Li *et al.* (2013)	Cigarette smokers were unable to learn to increase PFC activation (though they did decrease cingulate activity during training, see above)

period. Each participant performed a task that was dynamically tailored to their own performance, maximising the effectiveness of the training. In this experiment, participants knew that their brain states were being monitored in real time, which is similar to the neurofeedback studies discussed earlier. However, rt-fMRI can also be used independent of feedback, or indeed without participants being aware that their own activation is influencing the task. Both of these task designs – providing neurofeedback with or without participants' explicit awareness – are useful and contribute in different ways to our knowledge of brain function.

A small number of studies have emerged in which rt-fMRI allows ongoing brain activations to control the presentation of stimuli without participants' knowledge. An advantage of this approach is that it uses brain activation as an independent variable, allowing researchers to test stronger hypotheses about causal roles for brain regions in a given behaviour. For example, Yoo *et al.* (2012) used this approach to test the hypothesis that activation in the parahippocampal place area (PPA) is associated with enhanced memory encoding. In previous standard fMRI experiments, researchers have correlated PPA activation during encoding with subsequent memory performance (Brewer *et al.*, 1998). Here, rt-fMRI made it possible to monitor PPA activation and trigger the presentation of images only once activation surpassed a desired threshold. Such an approach represents a powerful new way to test hypotheses about the functional links between brain activation and behaviour.

Rt-fMRI also allows researchers to account for individual differences in selecting task-appropriate stimuli. In emotion research, for instance, it can be a challenge to find a set of stimuli that reliably elicit the desired emotional response in all participants. The traditional approach would ask participants to view and rate a large set of stimuli and then choose a subset of only those stimuli which were rated, *on average,* to represent the desired emotion. Even though the average rating of a given stimulus may place it within a certain emotional category, there can be considerable variability in how an individual participant responds to that stimulus. Thus, this approach can be a source of unwanted noise in the experiment. Rt-fMRI offers a solution by allowing researchers to individually tailor the selection of stimuli to a participant's own brain responses. Instead of showing participants the same stimuli, they can be shown individualised stimuli that elicit the targeted response (Lorenz *et al.*, 2016).

Assistive technologies

Ever since it became possible to record signals from the brain, there has been interest in developing BCIs for the purposes of interacting with external devices. Such technology could form the basis of assistive devices for individuals with compromised motor or communication abilities. A BCI could, for instance, restore a degree of dexterity to a paralyzed individual by decoding signals from the motor cortex and translating them to a robotic prosthetic. Until recently, BCI research has relied almost exclusively

on electroencephalography (EEG) to detect neural signals, which allows for fast sampling rates but with limited and indeterminate spatial localisation. Now, with the advent of rt-fMRI, it is practical and feasible to leverage the advantages of fMRI in building a new generation of powerful BCIs.

Emerging work exploring the use of rt-fMRI for assistive technologies has offered a glimpse of the potential applications. A key area of focus has been on applications to restore or augment motor functions. The aim of these studies has been to demonstrate that rt-fMRI can be used to translate brain signals into commands which control the movement of a virtual or physical device. Examples of this work include teaching subjects to navigate 2D virtual mazes (Yoo *et al*., 2004), control the movement of a cursor across the screen (LaConte *et al*., 2007) or manipulate the movements of a robotic arm in the real world (Lee *et al*., 2009). In a rehabilitative context, this idea can be applied towards training individuals to control the movement of an external prosthetic, which they would then be able to use in everyday life.

The idea of using rt-fMRI for rehabilitation extends to communication contexts as well. Our ability to communicate with others depends critically on the motor system – whether that's speaking, writing, typing, gesturing or making facial expressions. For patients with locked-in syndrome – near-complete paralysis with preserved cognitive capabilities – the ability to communicate may be restricted to eye movements alone. Rt-fMRI presents a potential workaround to this problem by directly connecting brain signals to external speech or language instruments. For example, one proof-of-concept study asked whether healthy adults could spell out answers to questions using their thoughts alone (Sorger *et al*., 2012). By asking participants to choose from 1 of 3 mental imagery tasks, and manipulating the delay and duration of engaging in imagery, researchers could map the participants' brain signals to all 26 letters of the alphabet. Using this approach, the participants attempted to answer a number of free response questions (e.g. 'What is your hobby?'). The computer decoder selected the correct letter at the first attempt in over 80% of cases, and in 100% of cases a human interpreter could correctly infer the answer. Future work should aim to improve algorithms for fast decoding and demonstrate the feasibility of this approach in a patient population. Nevertheless, this work represents an exciting step towards using rt-fMRI in a rehabilitation context.

Limitations and Considerations

While rt-fMRI opens up exciting new experimental possibilities, it is acutely vulnerable to the inherent limitations of fMRI. As described, the BOLD signal is susceptible to numerous sources of thermal and physiological noise (Krüger and Glover, 2001), as well as signal dropout in regions near the sinuses (Glover and Law, 2001). The low signal-to-noise characteristics of BOLD compromise its effectiveness for real-time applications. However, there are a variety of approaches that can be used to counteract this limitation. For example, Hinds *et al.* (2011) have described methods for removing known sources of noise through incremental regression models throughout a scan. Other groups have adapted machine learning algorithms to rt-fMRI contexts, which have been shown to improve the sensitivity in detecting distributed patterns of brain activation.

Another challenge with rt-fMRI studies is compensating for the lag in the BOLD signal. As discussed earlier, relative to actual neural activity (ms), the hemodynamic delay is substantial (~6 s) and is therefore much slower than the interval typically used to provide feedback in rt-fMRI studies (~1–2 s). To compensate for this, experimenters typically instruct participants about the delay, so they are aware of the delay between their cognitive processes and the feedback display. While relatively effective in dealing with this issue, it is a known constraint of rt-fMRI that limits providing immediate feedback to participants.

A main point of discussion in the rt-fMRI community at present is designing effective control conditions. The canonical control condition is sham neurofeedback. This typically involves including an additional group who receives sham feedback, but who believes that the feedback is veridical. Using this approach, experimenters can parse the causal role of real neurofeedback from participant expectations. The disadvantage of sham neurofeedback, however, is that it can be confusing and even frustrating for participants who face the impossible task of trying to regulate a sham signal. Compared to veridical feedback, sham feedback results in widespread recruitment of cognitive control regions (Johnson *et al*., 2012), suggesting that the experience of interacting with sham feedback is more difficult and demanding for participants. One alternative approach is to provide yoked feedback: that is, neurofeedback might be recorded from participant 1, but delivered to participant 2. This way all participants receive a feedback signal from the brain. Another option is to provide veridical neurofeedback from a distinct brain region unrelated to the behaviour of interest (e.g. providing a signal from a brain region not associated with emotion during an emotion neurofeedback task).

Prospective rt-fMRI researchers must carefully consider methodological details such as whether to update the neurofeedback display continuously as new data are acquired or intermittently. One study suggests that updating neurofeedback intermittently may be more effective for participants than continuous updates (Johnson *et al*., 2012). The visual display of the neurofeedback is another important design consideration. Feedback displays have included a thermometer, scrolling line graph, signal bars and even animated fire (LaConte, 2011). The task itself is of course an important factor in determining which feedback display is most effective for participants.

Conclusions and Future Directions

Rt-fMRI represents an exciting new frontier for brain research. Over the past decade, technologies such as fMRI have increased the precision and specificity with which we can decode cognitive processes and link them to distinct brain regions. Rt-fMRI, by offering a means to record data from specific brain regions in real time, has reinvigorated interest in biofeedback and BCI applications. Already, researchers have leveraged the advantages offered by rt-fMRI to develop novel neurofeedback training paradigms and demonstrated that participants can successfully learn to self-regulate a number of distinct brain regions. Learning to volitionally activate brain areas or networks holds significant

promise for both healthy individuals and patient populations with disordered brain function. In addition, rt-fMRI offers a powerful new research tool for cognitive scientists probing the connections between brain and behaviour. Moving beyond the restrictions of preset task parameters, rt-fMRI offers a way to yoke the presentation of task stimuli directly to ongoing brain activations. Researchers can then dynamically control the task to optimise the experiment for each individual participant and better address hypotheses about causal relationships between brain activations and behaviour. Lastly, rt-fMRI offers advantages to the growing field of neural assistive technologies, including the unique potential to decode precise and distributed patterns of brain activation. Decoding complex brain signals in real time is necessary for building successful assistive interfaces for motor and communication rehabilitation.

Rt-fMRI is a relatively new technology, and there are a number of improvements that should be the focus of future development. Despite early successes of neurofeedback studies, there are many open questions about how individuals learn from neurofeedback and how the training procedures could be optimised. Numerous studies have demonstrated increased activation in the target brain regions *during* neurofeedback training, but few have shown that enhanced activation continues once feedback has been removed, and fewer still have demonstrated persistent behavioural changes lasting days or weeks after the training session. These issues should be addressed in order for rt-fMRI to be practical in clinical or behavioural modification contexts.

In addition, advances in computing and brain imaging technology will improve some of the current limitations of rt-fMRI. The ability to collect MRI data faster and with increased spatial resolution will improve the granularity of analyses. As the technological capabilities increase, we anticipate new developments for real-time data preprocessing that will improve signal-to-noise ratios. Similarly, these advances will create a demand for enhanced statistical techniques that are tailored to complex, distributed patterns of activation. As each of these component processes advance, the range of potential research questions and applications will expand dramatically. If the last decade is any indication of how rapidly research technology can evolve, there is an exciting road ahead for rt-fMRI and the future of brain science.

Acknowledgements

This publication was supported by the National Centre for Advancing Translational Sciences of the National Institutes of Health under Award Number 5KL2TR001115. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors would like to thank Dr Kate MacDuffie for her helpful comments and suggestions.

Glossary

Blood level oxygenation dependent (BOLD) signal Measures differences between oxygenated and deoxygenated blood, thereby providing a marker of neural activity; it is the most common technique used to generate images in fMRI studies.

fMRI data preprocessing Important initial step in fMRI data analysis that consists of correcting for head motion, physiological noise (respiration and heart rate) and signal drift that occur over the course of the MRI session.

Neurofeedback A type of biofeedback based on brain activity; it can be fMRI or EEG based.

Real-time functional magnetic resonance imaging (rt-fMRI) A type of fMRI in which the data are analysed and manipulated in 'real-time' during data acquisition.

Sham feedback False feedback (e.g. noise) that is usually described to participants as real; often used as a control condition in rt-fMRI studies.

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