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Decoding fMRI brain states in real-time

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ABSTRACT

This article reviews a technological advance that originates from two areas of ongoing neuroimaging innovation—(1) the use of multivariate supervised learning to decode brain states and (2) real-time functional magnetic resonance imaging (rtfMRI). The approach uses multivariate methods to train a model capable of decoding a subject's brain state from fMRI images. The decoded brain states can be used as a control signal for a brain computer interface (BCI) or to provide neurofeedback to the subject. The ability to adapt the stimulus during the fMRI experiment adds a new level of flexibility for task paradigms and has potential applications in a number of areas, including performance enhancement, rehabilitation, and therapy. Multivariate approaches to real-time fMRI are complementary to region-of-interest (ROI)-based methods and provide a principled method for dealing with distributed patterns of brain responses. Specifically, a multivariate approach is advantageous when network activity is expected, when mental strategies could vary from individual to individual, or when one or a few ROIs are not unequivocally the most appropriate for the investigation. Beyond highlighting important developments in rtfMRI and supervised learning, the article discusses important practical issues, including implementation considerations, existing resources, and future challenges and opportunities. Some possible future directions are described, calling for advances arising from increased experimental flexibility, improvements in predictive modeling, better comparisons across rtfMRI and other BCI implementations, and further investigation of the types of feedback and degree to which interface modulation is obtainable for various tasks.

Introduction

Two major advances in functional magnetic resonance imaging (fMRI) have made it possible to perform more flexible experiments and created the potential of using neuroimaging for applications that include rehabilitation and therapy. The first advance is the recognition that multi-voxel patterns of fMRI data can be used to decode brain states (in other words, determine what the volunteer was "doing"—e.g. receiving sensory input, effecting motor output, or otherwise internally focusing on a prescribed task or thought) (Haxby et al., 2001; Haynes and Rees, 2005; LaConte et al., 2003; Mitchell et al., 2004; Strother et al., 2002b). The second are the continued advances in MR imaging systems and experimental sophistication with blood oxygenation level dependent (BOLD) (Ogawa et al., 1990a,b; Turner et al., 1991) imaging that have led to the emergence of real-time fMRI (rtfMRI) as a viable tool for biofeedback (deCharms et al., 2004, 2005; Posse et al., 2003; Weiskopf et al., 2003; Yoo and Jolesz, 2002).

In the fMRI literature, the terms "brain reading" (Cox and Savoy, 2003) and "multi-voxel pattern analysis" (Norman et al., 2006) have been used to refer to supervised learning techniques that were first applied to PET data in the mid 1990s (Hansen, 2007; Lautrup et al., 1994). These include learning algorithms such as neural networks, linear discriminant analysis, and the support vector machine (SVM) applied to fMRI brain volumes. An experiment produces brain measurements comprised of tens-of-thousands of voxels that are sampled at rates around 0.5 to 2 Hz for several minutes to produce image data consisting of a 3D movie of the brain in action. What the brain is doing during the experiment is partially controlled by the fMRI task. In this context, supervised techniques use training data to estimate a relationship between the brain images and the corresponding task conditions that existed during their acquisition. Once a model is trained, it can be used to decode new test images and thus provide estimates of the state of the brain over time. In a real-time fMRI setting, these brain states can be decoded shortly after acquisition and used as a control signal to adapt the stimulus that is presented to the volunteer. We have previously reported such a real-time fMRI implementation (LaConte et al., 2007). Using this system, Papageorgiou et al. (2009) has recently reported the ability to provide feedback based on slow vs. fast inner, automatic speech. Using a similar approach based on neural networks, Eklund et al. (2009) has reported the ability to control the dynamics of a simulated inverted pendulum, using classification of left, right, and resting conditions. Using the relevance vector machine, Hollmann et al. (2009) presented a subject's neuroeconomic decisions to the operator before that subject pressed a button to convey his decision. By explicitly using distributed brain state patterns, the perspective is focused on sensory and behavioral conditions of the fMRI task rather than anatomic

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localization. In (LaConte et al., 2007), it was demonstrated that (i) data collection and machine training can be accomplished in minutes, (ii) near-perfect prediction accuracy is attainable during sustained periods of activation, (iii) stimulus feedback can respond to changes in brain state much earlier than the time-to-peak limitations of the BOLD response, and (iv) this approach is flexible enough to accommodate a broad range of fMRI tasks, while requiring no change in experimental procedures.

As advances continue in rtfMRI, there is a real potential to provide expanded experimental capabilities, and possibly even perform rehabilitation and therapy. If this is possible, the brain would represent a unique target for imaging; going beyond measurement and diagnosis, rtfMRI may be able to use the brain's response to treatment to adaptively guide the rehabilitation process. Changes in the brain that occur from mechanisms such as addiction, emotional disorders, and brain injury can impact our most basic abilities to function in society and can dramatically impact cognitive and emotional well-being; however, there is growing evidence that the human brain is capable of significant functional plasticity after insult, as well as through training. Future work is required to examine the potential for neurorehabilitation using rtfMRI methods, making it possible to provide behavioral treatment while simultaneously imaging the brain's response to that treatment. Moreover, the entire process can potentially happen under adaptive conditions, where the treatment itself can co-evolve with the responding brain. In a manner that has never before been possible, recovery mechanisms such as self-control, learning, and memory functions now have the potential (through real-time fMRI) to actually originate and be reinforced from the feedback that a patient's own brain provides.

Extracting fMRI information during an experiment opens the possibility for changing the stimulus or controlling a brain computer interface (BCI) based on how the brain is responding. The majority of previous rtfMRI work in this area has focused on the use of univariate statistical analysis approaches related to the general linear model (GLM) (Friston et al., 1995b) or to tracking the fMRI signal in one or a few regions of interest (ROIs). In this review, the focus is on rtfMRI that is based on brain state prediction. Often, algorithms in machine learning attempt to estimate a relationship between vector inputs and scalar outputs. In this case, brain volumes are the input to a trained model and the outputs are the predicted brain states. In this review, the desire is to emphasize prediction of brain states from temporally sampled data and the ability to use this as a control signal to adapt the stimulus. Putting all of these considerations together, we refer to this rtfMRI approach as temporally adaptive brain state (TABS) fMRI.

This review discusses the potential that machine learning approaches, coupled with the data acquisition and reconstruction capabilities of modern magnetic resonance systems, can allow for greater flexibility of fMRI experimental designs by enabling adaptive stimuli that are guided by ongoing detection of the sensory and behavioral states encoded in the hemodynamics of a subject's brain. Also discussed are important practical issues related to TABS, including implementation considerations, existing resources and future challenges and opportunities.

Real-time fMRI

The spatio-temporal properties of blood oxygenation level dependent functional magnetic resonance imaging (BOLD fMRI) (Ogawa et al., 1990a) provide feasibility and set the ultimate limitations of real-time approaches that use this imaging technique. BOLD relies on changes in cerebral blood flow, cerebral blood volume, and blood oxygenation to indirectly measure neuronal activity (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1990a,b; Turner et al., 1991). The biophysics relating the BOLD signal to the underlying cellular activity has been avidly studied since the introduction of the method and remains an active area of research (Heeger and Ress, 2002; Logothetis and Wandell, 2004; Sirotin and Das, 2009; Vazquez et al., 2009). Spatial and temporal properties of the BOLD signal are the most crucial factors for useful adaptive feedback of fMRI. During a task, BOLD signal changes take 6–12 s to reach maximum intensity, where it remains relatively constant for sustained long periods of activity, and 8–20 s to return to baseline values after the task is finished (Chen et al., 1998; Kollias et al., 2000). Ultimate limits in timing may be much better than this since early but weak signal changes have been reported to occur roughly 0.5–2 s after the onset of neuronal activity (Kwong et al., 1992; Yacoub and Hu, 1999). Temporal characteristics vary with spatial region (Chen et al., 1998), and it is also important to consider how experimental factors may impact assumptions of linearity of the BOLD response to neural activity (Boynton et al., 1996; Dale and Buckner, 1997; Friston et al., 1998; Glover, 1999; Logothetis et al., 2001; Vazquez and Noll, 1998).

Over the last several years, there has been a growing interest in rtfMRI—see deCharms (2007, 2008) and Weiskopf et al. (2004a,b, 2007) for extensive reviews. It should be noted, though, that enthusiasm for rtfMRI has existed since almost the beginning of this imaging modality. The first published manuscript comes from Cox et al. (1995), which reported the development and use of a recursive partial correlation algorithm for generating fMRI maps in real-time. As stated by the authors, online functional maps enable researchers to (1) monitor data quality, (2) evolve experimental protocols more rapidly, and (3) perform interactive experimental paradigms for neurological investigations. Goddard et al. (1997) described integrating supercomputing with specialized visualization platforms and discussed the advantages of flexible, individual program modules vs. tightly integrated code. They expressed a similar motivation for real-time processing—that a dependence on offline analysis limits fMRI as a technique, precluding the ability to evolve subsequent experiments based on previous ones in the same session. Cohen (2001) provided a comprehensive review of neuroimaging that treated important aspects of sequences, MR systems, and fMRI data processing, and reported a real-time system that could process fMRI data, give feedback to the subject, and detect artifacts. Probably the predominant rationale for early real-time systems was that they could provide a high level of quality control and held great promise for health applications such as surgical planning. From these early examples, though, it is clear that it was also recognized that extracting functional information in a timely manner could fundamentally change the experimental landscape to one in which the experiments and stimuli could adapt based on ongoing real-time results.

Recent rtfMRI studies have demonstrated that subjects are capable of modulating both the strength and spatial extent of local activations when given feedback (deCharms et al., 2004, 2005; Yoo and Jolesz, 2002). At least two rtfMRI reports have discussed the possibility of detecting short-term or transient changes in ongoing experiments in resting state data (Peltier et al., 2004) and using a time-windowed ICA (Esposito et al., 2003). Many rtfMRI studies have focused on this ability and demonstrated the capacity for neurofeedback, brain computer interfaces, and enabling rehabilitation and therapy (Cannon et al., 2007; Caria et al., 2007; deCharms et al., 2004, 2005; Posse et al., 2003; Weiskopf et al., 2003; Yoo and Jolesz, 2002; Yoo et al., 2006). In an early investigation by Yoo and Jolesz (2002), subjects were trained to interpret activation maps for a simple motor task with the goal of increasing activity in a localized brain region. The five subjects examined were successful at manipulating the spatial extent of their blood oxygenation level dependent (BOLD) response in these regions. This result was corroborated and expanded by Weiskopf et al. (2003), who showed significant changes of local BOLD responses in the anterior cingulate cortex in a subject being shown an updated display of the level of activity in this area; Posse et al. (2003) who showed that feedback of amygdala activation in a sad mood task led to increases in both left amygdala activation and self-rated sadness; and deCharms et al. (2004), who directly demonstrated the ability of subjects to exert voluntary control over somatomotor cortex activity using a real-time system.

The work of deCharms et al. (2005) represents a particularly compelling example of the utility of rtfMRI for therapeutic applications. This study examined the impact of providing BOLD signal level changes in the rostral anterior cingulate cortex (rACC) as feedback to affect conscious perception of pain. deCharms showed that when subjects increased (or decreased) activity in this region, there was a corresponding increase (or decrease) in pain perception, for a given pain stimulus. Such training was efficacious, leading chronic pain patients to report decreases in ongoing pain, even after completion of the experiment.

These, and a continually growing number of ROI-based reports, demonstrate great potential for rtfMRI and raise exciting questions about how far these approaches can be extended. How generally can someone learn to control a given volume of their brain? What degree of effort from the volunteer is required? Can practice lead to lasting ability? How does it "feel" to "activate" any given localized area? Can these techniques serve as a complementary or even more sensitive tool to uncover localized areas of brain function? These types of questions reflect the fact that ROI-based rtfMRI approaches present exciting future opportunities.

On the other hand, some existing challenges are well met by TABS approaches. Although tracking ROIs may seem intuitive and straightforward, there are several technical considerations that are not immediately obvious. Some of these issues include the selection of the ROIs (what method is used and how is it standardized across subjects?), robustness in the face of fMRI signal properties (e.g. low SNR, arbitrary and variable raw data values, signal drift), and targeting cognitive strategies that allow individuals to isolate and control the ROI.

Some relevant points about the BOLD signal are that individual intensity values are arbitrary, and these values can vary over time. Because of low-frequency scanner drift, physiological changes, head motion, and changes in the subject' responses, direct comparisons across runs, sessions, and subjects is problematic. If it is desired to give feedback based on an ROI, then it is necessary to know the expected range of numerical values. When presenting data, it is well-known that the scale for a graph can enhance or suppress the significance of signal fluctuations. A display that reflects ROI fluctuations is susceptible to exactly this effect—the goal is to have a slider bar (or any other interface) scale to give feedback that shows major swings in the signal level, but is not overly sensitive to "bouncing" that would arise from smaller signal fluctuations. This is difficult to do, since the difference between inter-task variation and intra-task variation, is, itself, small. Further, the correct mapping onto a computer display can change over time. One way to handle this is to scale the voxel time series into a percent signal change. This, itself, is not a completely standard calculation, but one reasonable approach is to consider the percent change relative to the average of the control conditions. In addition, some of the problems arising from global drift and scaling issues can be mitigated through the use of differential feedback (Weiskopf et al., 2004b), which was demonstrated by subtracting mean ROI values of the parahippocampal place area from the supplemental motor area. This method was suggested for combining multiple ROIs to reduce the BCI signal to a single value. Generalizing this approach to multiple ROIs gives rise to the issue of weighting combinations of multiple ROIs. If a task involves a brain network, do the regions involved contribute equally on a functional level and on a BOLD signal level? The most likely answer is no. The consequence is that the best combination then involves determining the optimal weighting to combine the ROIs. This is a multivariate problem, and one that can be handled directly through brain state prediction methods that use supervised learning. Further, the output of many machine learning techniques are on reliable scales or can be cast as posterior probabilities (Caruana et al., 2008; Platt, 1999), making the feedback data range less problematic.

Beyond the BOLD signal characteristics, the functional organization of the brain is an important consideration. From the functional specialization perspective, there is a large and expanding literature about the function of anatomically specific brain regions—for example, the role of rostral anterior cingulate cortex in pain perception (deCharms et al., 2005; Mackey and Maeda, 2004; Peyron et al., 2000), the role of subgenual cingulate in modulating mood states (Mayberg et al., 1999, 2005; Seminowicz et al., 2004), the role of prefrontal cortex in executive control (Kerns et al., 2004; MacDonald et al., 2000; Miller and Cohen, 2001), the role of insular cortex when substance abusers are exposed to craving cues (Bonson et al., 2002; Brody et al., 2002; Naqvi et al., 2007; Sell et al., 2000; Wang et al., 1999). Beyond these specific roles, however, it is also true that each of these anatomical regions may play vital roles in a number of varied contexts. Further, these regions coordinate activity with a network of other brain regions. Beyond the fact that multivariate strategies avoid ad hoc weightings of multiple ROIs, another consideration is how much is known about the experimental setting and the expected patterns of brain activity. If the problem is well understood and localized anatomically, then tracking ROI fluctuations should provide a sensitive measure in this context. In situations where less a priori knowledge exists or subjects can use different cognitive strategies to perform the same task, supervised learning approaches have the potential to adapt to the individual and the specific experimental context.

Pattern analysis

The focus of this special issue is that of pattern analysis-based decoding of neuroimaging data, which can be interchangeably referred to as supervised machine learning (e.g. classification and regression) and brain state prediction. Readers of this article are encouraged to read its companions in this issue (Haynes, 2010; Kloppel and Ashburner, 2010; Kriegeskorte, 2010; Mitchell, 2010; Muller, 2010) as an invaluable overview on the current state of this topic. We also suggest Kjems et al. (2002)and Strother et al. (2002a) and additional reviews, Hansen (2007), Haynes and Rees (2006) and Norman et al. (2006). To keep the focus relevant to rtfMRI, this section includes a brief treatment of pattern analysis, how it can shape new experimental flexibility, and what aspects make it a natural framework for rtfMRI.

What does it mean to say that TABS relies on predicting brain states? Depending on the context, the use of "brain state" can be used to evoke deeply philosophical debates concerning the connection between mind and brain, or simply to relate a brain measurement to an observable behavioral condition such as EEG-defined frequency bands ranging from delta-wave deep sleep to beta-wave alertness. "Brain state" is often used as a term in the neuroimaging and recording literature, but it is rarely carefully defined. Here we use the term compatibly to its use in (Strother et al., 2002b) – essentially brain states are the sensory/behavioral events or mental processes for which a researcher might hope to find neural correlates through neuroimaging. In a mass univariate context, "brain states" are what could be represented as variates of interest in a design matrix. In a supervised learning context, these regressors serve instead as "labels." When the labels are categorical in nature, we can formulate the modeling problem as a classification problem over a set of experimental categories. When the labels are continuous, the problem can be framed as a regression problem to describe parametrically varying brain states such as task difficulty, behavioral rate, visual angle, etc. It is important to remember that regardless of the analyses performed (supervised, unsupervised, multivariate, mass univariate), the source data are exactly the same and come with the same limitations inherent to fMRI (e.g. voxel size, temporal sampling, and an indirect relationship to cellular brain activity). In many cases, brain states can be empirically observed and brain state predictions can be validated more easily than statistical map predictions, since the experimenter generally has better knowledge of and a greater ability to record and control the temporal aspects of the experiment than the spatial patterns involved. In other words, in an MVPA setting there is usually a training data set (to estimate the parameters for the supervised learning model) and an independent test set (that was never seen by the training step). Since the MVPA predicts brain states (which are often designed or measured) and not brain maps (which are usually not known), the models are easier to validate. In fact, using these concepts it is possible to perform a data driven receiver operating characteristic (ROC) analysis for assessment of fMRI data analysis methodologies (Kjems et al., 2002; LaConte et al., 2003; Shaw et al., 2003; Strother et al., 2002b).

A TABS implementation represents an active system based on these concepts. With it, experiments can be designed and interfaces can be controlled. Importantly, the experiment can fail. If the brain state models do not generalize well, and the human is not able to compensate for deficits in the model, then the human–machine system will not assert meaningful control of the interface. A functioning system implies that it is capturing at least some relevant aspect of the relationship between the brain images and the stimulus or behavioral responses, which can play a vital role in increasing our understanding of brain function.

Decoding brain states is usually done with multivariate, supervised learning approaches. As described by Hansen et al. (1999), supervised and unsupervised learning constitute two important classes of learning problems. Supervised approaches deal with learning from examples, aiming to capture the functional relationships between variables, whereas unsupervised learning captures statistical relationships from the dataset itself. Examples of unsupervised learning applied to fMRI include principal components analysis (Hansen et al., 1999), independent component analysis (Beckmann and Smith, 2004; Calhoun et al., 2001; Himberg et al., 2004; McKeown et al., 1998; Yang et al., 2008), and clustering techniques (Baumgartner et al., 1998; Ngan and Hu, 1999). For brain state analyses, we are interested in the multivariate relationships between fMRI images and the corresponding behavior or sensory parameters, i.e. supervised learning. Emphasizing the multivariate aspect of brain state predictive analyses, several reports refer to this as "multi-voxel pattern analysis (MVPA)" (Norman et al., 2006).

The viewpoint that multivariate approaches can lead to new insights and should be viewed as complementary to univariate analyses has been widely recognized over the years (Friston et al., 1995a; McIntosh et al., 1996; Moeller and Habeck, 2006). Moreover it is known that every method (whether univariate or multivariate) emphasizes particular aspects of the data and cannot be highly sensitive to all possible relationships (Lange et al., 1999; McKeown et al., 1998; Moeller and Habeck, 2006; Strother et al., 2002b). To increase our understanding of brain function with fMRI, we must understand the relationships between highly multivariate brain images and categorical quantities describing discrete stimuli or behavioral responses (Victor, 2005). Comparing both ends of the modeling spectrum, univariate approaches in fMRI have benefited from greater methodological scrutiny, are highly interpretable, and are often more statistically powerful in revealing localized responses. Their primary drawbacks are high vulnerability to detection limitations imposed by multiple comparisons, and validation of the resulting statistical maps is difficult (LaConte et al., 2003; Strother et al., 2002b). Multivariate approaches capture distributed relationships, are more powerful at detecting whether a particular stimulus condition is reflected in the data, and have been reported to reveal more information than univariate analyses (Fletcher et al., 1996; Lin et al., 2003). Some drawbacks are that multivariate models can be more difficult to interpret, especially those that use non-linear kernels. In addition, these techniques are vulnerable to image artifacts such as head motion and eye movement.

Brain state patterns are largely thought to be consistent (across scanning sessions and even across individuals). Cox and Savoy (2003) used classifiers trained for 10 classes of objects and showed that these classifiers were still accurate across sessions separated by more than a week. Fig. 1 shows reproducible prediction accuracies for a single subject using data from scanning sessions separated by 4 days and by 2 years. Brain state can also be predicted across groups for PET, e.g. (Lautrup et al., 1994; Strother et al., 2002b) and fMRI (Mitchell et al., 2004; Strother et al., 2004). This consistency reflects experiments in which human adaptation is not expected. As elaborated upon in the section on future challenges, one exciting challenge for the field is to address the case where these patterns are not consistent. Specifically, in the case of TABS, there is potential to use feedback for performance enhancement, rehabilitation, therapy, etc. This implies changing the "system" (the brain responses) over time. The expectation, then, is that the supervised models will become less relevant over time, and methods of ongoing re-training will need to be explored.

It is very possible that fMRI can help shape future work in machine learning. While not singularly so, fMRI data are rather unique from the point of view of classical statistics, machine learning, and other related fields. Not only are the number of features relatively large (current whole-brain studies can have 10 to 30,000+ voxels), but also the relative ratio of features to observations (ranging roughly from 100 to 1000 time samples) is atypical of many machine learning problems. Because predictive modeling does work, this analysis of fMRI data is unique in another way. Computer vision systems, faced with the problem of trying to achieve recognition capabilities equivalent to the human visual system, generally and predictably fail. No human, though, can learn to sort, image-by-image, fMRI data into two or more categories of sensory and/or behavioral states. In this case, the computer wins, and the deciding factor is the subtle signal structure distributed in the unimaginably huge dimensionality of the data. These considerations strongly suggest that fMRI could be a key to profound progress and deeper insights into modeling special types of very high dimensional data sets. The curse of dimensionality (Bishop, 2006; Cherkassky and Mulier, 2007), which arises when trying to estimate high-dimensional functions with a finite amount of samples, can be helped with improvements in isolating the signal sources present in a given fMRI data set and a focus on understanding voxel interdependencies. There is a great need for ongoing work examining fundamental methodological and statistical issues, such as visualizing and interpreting predictive fMRI models, evaluating preprocessing issues, maximizing information extraction, and characterizing signal-to-noise properties of fMRI data. Further advancement of these technical issues will lead to increased sensitivity to and understanding of fMRI measurements of the brain, and perhaps to entirely new approaches to machine learning and statistical modeling of high dimensional systems.

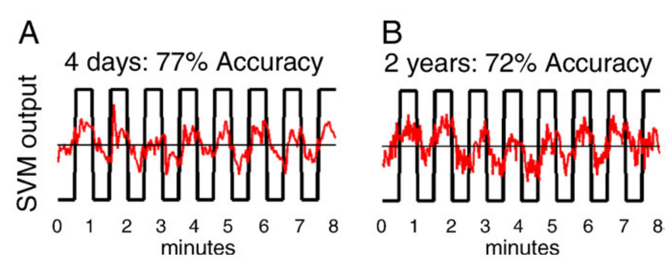

Fig. 1. Brain state classification can be stable over time. Red traces show the raw distance values from a support vector machine classification of each volume in each run. The thin black horizontal line indicates the class decision threshold (red traces below this line are assigned to class 0, while those above are assigned to class 1). The dark black square wave represents the block design timing that alternates between two task conditions. Using the left vs. right. button pressing task in (LaConte et al., 2007), one run was selected as a training run. Using only volume registration to align fMRI volumes across sessions (A) shows the classification results for the same individual four days later, and (B) for 2 years later.

Implementation, resources, and methodology

Implementation

Currently the number of sites actively performing rtfMRI is low, probably because these systems do not exist "out-of-the-box," and they increase experimental complexity. This section discusses aspects of rtfMRI architecture to provide an overview of the trade-offs involved and options that are available to get started. These details should help those who are reading primary reports on this topic as well as those who want to implement their own systems or are interested in currently existing resources. The issue of rtfMRI increasing experimental complexity is not directly discussed, but TABS implementations provide easy flexibility because the same experimental setup can be used for entirely different fMRI tasks (LaConte et al., 2007). Fig. 2 shows an example timeline for a TABS experiment, showing that it is possible to demonstrate a working system in a matter of minutes. Starting up a new experiment should not be much more difficult than preparing the software for a new fMRI stimulus paradigm, which is necessary for any new fMRI study. The only additional aspect to the presentation software is that it must receive and process the real-time feedback signal. For any rtfMRI approach, once a system is physically configured, experimental complexity is largely mitigated by well-designed software.

What is required to build an rtfMRI? Although vendor hardware and software architectures vary greatly, an important subsystem of the scanner is the receiver A/D and image reconstruction hardware. In addition to the vendor-supplied equipment, fMRI usually uses at least one additional computer dedicated to controlling the stimulus delivery and any desired behavioral or physiological recording. To do anything in "real-time" during the fMRI experiment requires at least some access to the reconstruction system, which can range from a shared file system to custom reconstruction code that has direct access to the data. Thus the real-time software could run on a separate computer (with shared file and/or network access) or be integrated with (or even fully replace) the image reconstruction software. In terms of making the actual connections, the physical layout of the machines could favor one solution over another as could the actual hardware on the computers (for example parallel, RS232 serial, and firewire ports are currently rare compared to USB2 availability). Even local computer security policies could impact the design. Ethernet connections through switches support data communication through protocols such as TCP and hard disk file sharing through NFS and SAMBA. Bluetooth and wireless connections are even possible. A detailed comparison of all of these options is beyond the scope of this review (and these details, by their nature, are outdated quickly), but the main concerns are that the processor power and data transmission bandwidth are adequate to perform whatever is needed for the experiment. Again these are similar issues as those recognized early on (Goddard et al., 1997). Image data requires the most RAM and/or disk utilization while BCI control signals from ROIs or classifiers usually require only a few bytes. Further, even "fast" TRs (MR sampling rates) are much slower than existing computer communication protocols, and fMRI signal changes are likely to be the ultimate rate-limiting factor for bandwidth requirements for the foreseeable future.

As stated by Cox et al. (1995), in a real-time application, it is unacceptable to have a calculation that grows as more data are collected. What are some solutions, then? The preferred approach is to develop recursive calculations and/or approximations (Cox et al., 1995). If this is not possible, a compromise might exist that is suitable for performing the experiment at hand, for example, capping the fMRI run to a length that can be safely performed with the given computational limitations. A related method is to use a sliding window that can safely accommodate the calculations and perhaps even help with trade-offs between the amount of data and the sensitivity to changes over time (Gembris et al., 2000). While not intrinsically

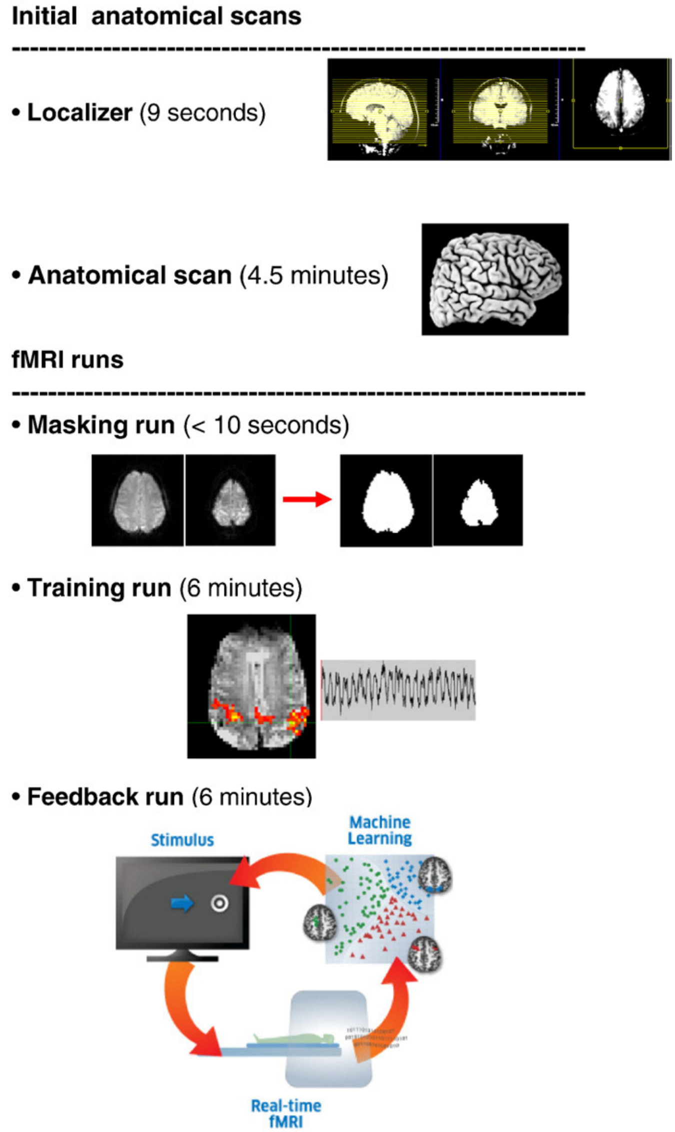

Fig. 2. Progression of a TABS real-time experiment. A basic demonstration of a TABS system can be performed during a session that lasts less than twenty minutes. Initial anatomical scans include a localizer run for prescribing the volume coverage in all subsequent scans as well as a high resolution T1-weighted scan. The high-resolution anatomical scan is not essential, but it provides an anatomical underlay that can be used for the real-time display, and (if desired) for anatomically selecting regions of interest. If anatomically prescribed ROIs are not used, then a brief masking run is performed that consists of a few time-points of a T2*-weighted sequence with parameters matching all subsequent runs. Image processing detects which areas are part of the brain vs. regions outside the brain. Next the scanner is run in training mode; as fMRI brain volumes are being acquired, machine learning algorithms are processing the images and the task condition labels to create a predictive model. Finally, the scanner can be run in feedback mode, using the training run model to decode brain states for each new image and transmitting a control signal to modify the stimulus being presented to the volunteer.

satisfying, as hardware capabilities continue to improve, many "brute force" software implementations are possible. For a TABS system, the situation is fortunate since the prediction of brain states using a trained model is the same for every volume and the computational demand remains fixed for the entire feedback run.

For real-time to be meaningful, at least one of two things also should be available: (1) the capability to display results to the experimenter, and (2) the ability to adapt the stimulus presentation. For a TABS system, training the supervised model requires not only access to the images, but also to the brain state labels. This is also required to generate functional maps with a general linear model. For

ROI-based approaches, a method to define ROIs is required. In theory, everything (stimulus presentation, image reconstruction, and real-time processing) could be completely integrated into one physical "box" and exist as tightly integrated code. This extreme case could be reasonable for MRI vendors in the future, or possibly for some highly demanding experiment in which disk and other I/O communication would be too time consuming. Generally, the greater the integration, the better potential performance, but the more difficult the computer software maintenance and flexibility over time. Also, the implementation has to be more specific to the scanner hardware and is thus difficult to share with research sites having different equipment (but possibly easier among sites that have similar set-ups).

The implementation reported in LaConte et al. (2007) is close to this extreme, but relies on a separate stimulus presentation computer. All of the reconstruction and real-time processing is performed through completely integrated software and executes on the vendor's computer, using port I/O communication (serial or parallel) with the stimulus presentation software. Beyond the fact that this uses an already existing computer, the benefit of this design is that the major data handling of the images are performed with software pointer operations and minimize hard disk and network demands. The I/O transmissions need to only communicate scalar values representing data labels and brain state predictions. Since the stimulus presented to the volunteer gives rise to signal changes in the fMRI data and this can be decoded and used to adapt the stimulus, this configuration constitutes a closed-loop experimental system. In practice, what varies most across experiments is the stimulus presentation. This remains flexible because it is not tightly integrated with the rest of the components, allowing different groups to use their favorite setup for the stimulus. Other than being able to see the feedback signal presented to the volunteer, though, our early system was limited in terms of the display information provided to the experimenters. Our current system is configured as illustrated in Fig. 3. As shown, we have added a new computer for real-time display, using AFNI (Cox, 1996), as described further in the next section. Currently the primary real-time calculations and feedback signal still rely on the image reconstruction computer.

Resources

The major MRI vendors now provide basic capabilities for GLM-based mapping in real-time as well as motion tracking and correction. Beyond this basic support, individual labs have at least three third-party software options. One of these is TurboFire (Gembris et al., 2000). The other two come from major fMRI software packages, namely Turbo-BrainVoyager, a commercial product (Brain Innovation, Maastricht, The Netherlands)(Goebel, 2001), and AFNI (Cox, 1996), which is a free open source package. To use any of these solutions still requires some degree of integration with the scanner, most easily (and commonly) by network file sharing (e.g. via NFS or SAMBA) to access the image data. As discussed previously, whether or not the system is custom-built, it is uncommon to be completely integrated with the scanner. As an improvement over file sharing, the work in Yang et al. (2005) used software that they developed to directly send data from the scanner by TCP/IP. The implementation by LaConte et al. (2007) was almost completely integrated on the vendor-supplied equipment (with only port I/O sending control signals to a separate stimulus presentation computer).

Based on demonstrations and published reports, TurboFire, Turbo-BrainVoyager, and AFNI are fairly similar in their basic functionality. These systems originated with the goal of processing data with a mass univariate approach. BrainVoyager and AFNI both have very good visualization capabilities for browsing through voxel time series and for 3D volume visualization. Currently Turbo-BrainVoyager provides convenient support for GLM contrasts in real-time. Based on published reports (Weiskopf et al., 2004a,b), Turbo-BrainVoyager updates an ROI file that can contain data for multiple ROIs and can be shared (e.g. over SAMBA) and read by presentation software to generate displays,

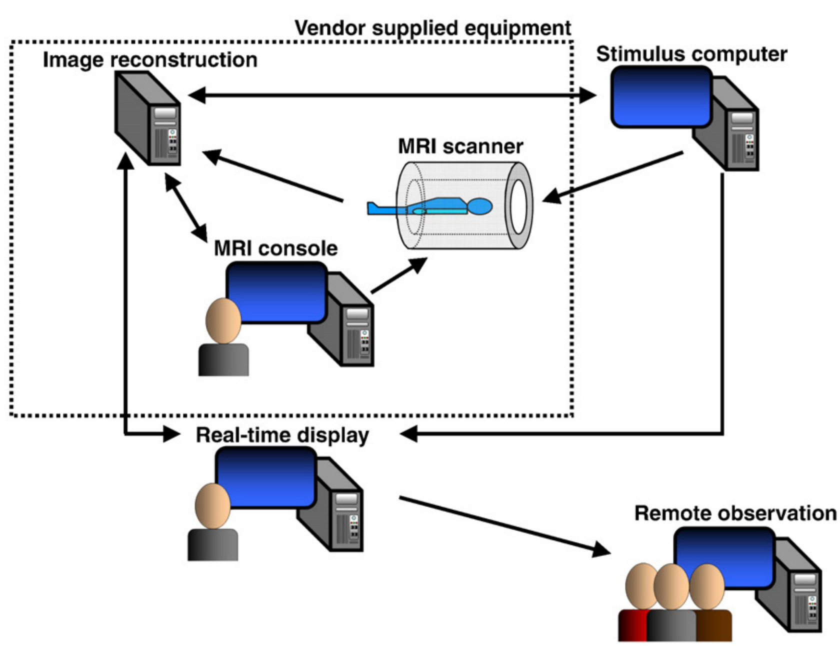

Fig. 3. Schematic of a current TABS hardware setup in which arrows indicate the direction of communication. The dotted box represents the relevant subsystems of a typical MRI system, which include the MRI scanner, console, and image reconstruction. In the implementation reported by LaConte (2007), the image reconstruction system performed all of the real-time calculations (estimating a classification model during training runs and using these models to classify new images during feedback runs) as well as communicating with the stimulus computer. For real-time display, an additional computer running AFNI has since been added. For this to work, additional software was written to run on the image reconstruction computer to send image data to the real-time display computer with TCP/IP, using AFNI's real-time plugin. This machine is currently also used for auxiliary computations, such as generating brain vs. non-brain mask images, tracking motion, and updating brain maps. The real-time display computer can also act as a server for the remote observation computer at a distant site. Future plans include transferring all of the real-time calculations to the real-time display computer to fully utilize AFNI's real-time enhancements and our efforts to build plugins (like 3dsvm—http://lacontelab.org/3dsvm.html) for AFNI.

control BCI devices, etc. AFNI additionally enables TCP and serial transmission of multiple ROIs as well as motion parameters. Fig. 4 shows a screen shot from our display computer in Fig. 3. The layout of maps, time series, and motion plots as well as options like statistical thresholds can be controlled by the user interface, or automatically configured through environment variables, and modified dynamically through plug-out commands that drive AFNI.

None of the available packages currently provide TABS capabilities, but it is very likely that the capability to perform real-time pattern classification will soon be more widely available. Although a good framework for pushing the computational limits of supervised learning-based rtfMRI, one drawback to the system we developed is that it can only be readily shared with sites that are on specific Siemens' software platforms. BrainVoyager QX 2.0 has SVM capabilities, making it possible for this capability to be incorporated into the Turbo-BrainVoyager product. Similarly our group has developed 3dsvm for AFNI. 3dsvm is a command line program and plugin for AFNI, built using SVM-Light (Joachims, 1999) for its core computations. It provides the ability to analyze fMRI data as described in LaConte et al. (2005a). As shown in Fig. 5, 3dsvm enables visualization of SVM maps and model parameters within AFNI's environment. It is distributed with AFNI and reads AFNI-supported formats including NIfTI (http://nifti.nimh.nih.gov/), thus all preprocessing and data manipulation of the major software packages are available. Features that make 3dsvm particularly well suited for fMRI analysis is that it is easy to spatially mask voxels (to include or exclude them in the SVM analysis) as well as censoring training samples. 3dsvm has its own multi-class classification implementation and supports non-linear kernels and regression functionality implemented in SVM-Light (Joachims, 1999). The next step in software development for 3dsvm is for it to be real-time enabled such that its testing mode can utilize AFNIs realtime output capabilities (file, TCP, and serial). Source code and compiled binaries are distributed with AFNI, and descriptions and further information are maintained at http://lacontelab.org/3dsvm.html. Further, since 3dsvm is, itself, open source, this enables other sites to inspect the source code, build custom capabilities for their own experiments, and even contribute to ongoing development efforts.

The core of a TABS implementation is the machine learning approach. Although our reported real-time system used an SVM implementation (Joachims, 1999), this is really a modular part of the system that allows future extensions in which multiple classifiers (either individually or combined) can be used (LaConte et al., 2007). Recently Eklund et al. (2009) have reported a neural network-based system and Hollmann et al. (2009) used the relevance vector machine. For offline analysis, many groups have used their own implementations of machine learning methods or have used general purpose machine learning software. For offline fMRI analysis, BrainVoyager's SVM and 3dsvm in AFNI are convenient to use. Additional recommendations include the Princeton Multi-Voxel Pattern Analysis (MVPA) Toolbox (www.csbmb.princeton.edu/mvpa/), PyMVPA (www.pymvpa.org), PLSNPAIRS (http://code.google.com/p/plsnpairs/), and the Lyngby Toolbox (http://neuro.imm.dtu.dk/software/lyngby/).

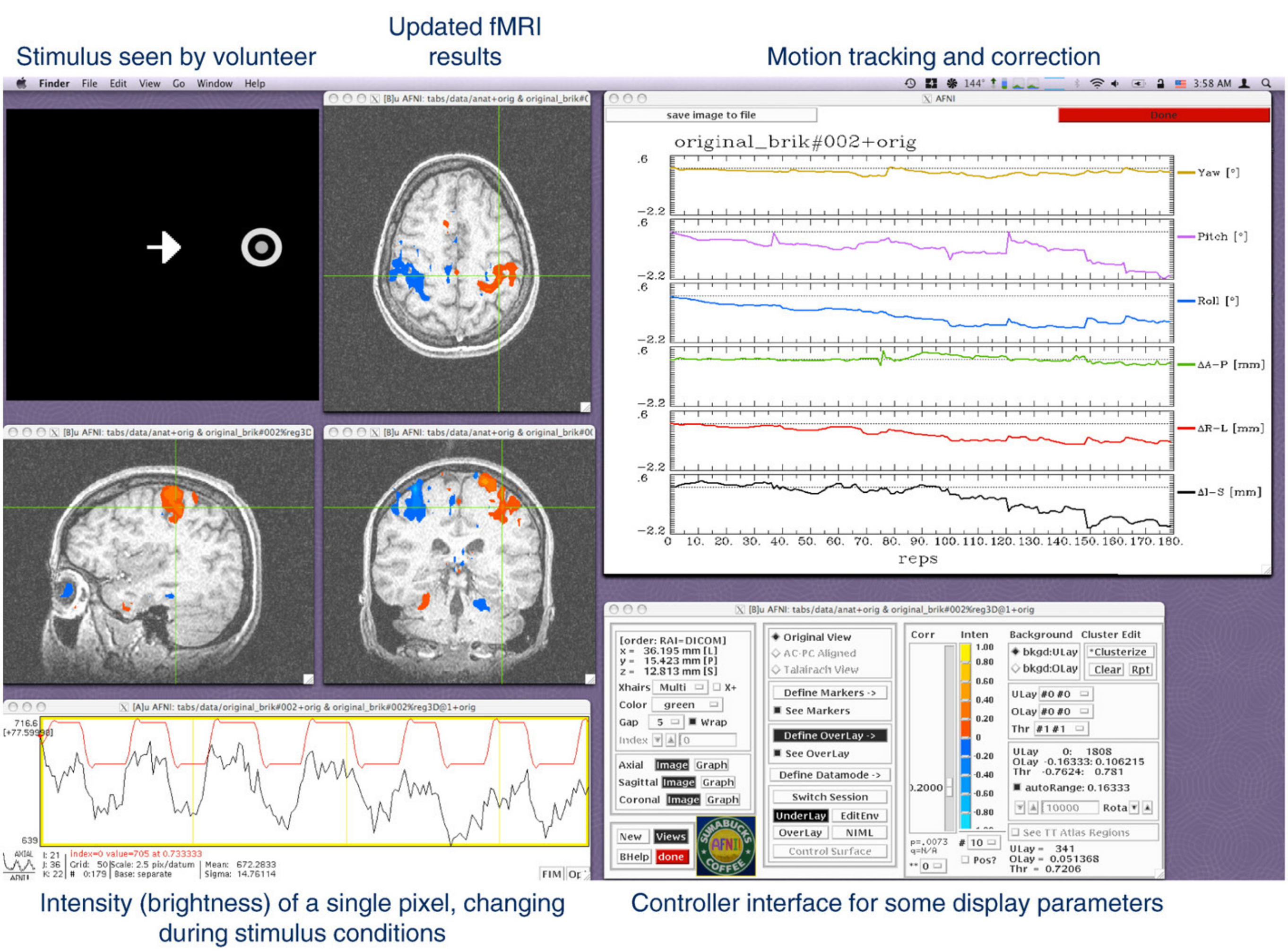

Fig. 4. An example AFNI rtfMRI display with stimulus window. This display allows the experimenter to simultaneously monitor the stimulus seen by the subject, continuously updated fMRI results, real-time motion parameters, intensity of any chosen voxel, and the AFNI interface.

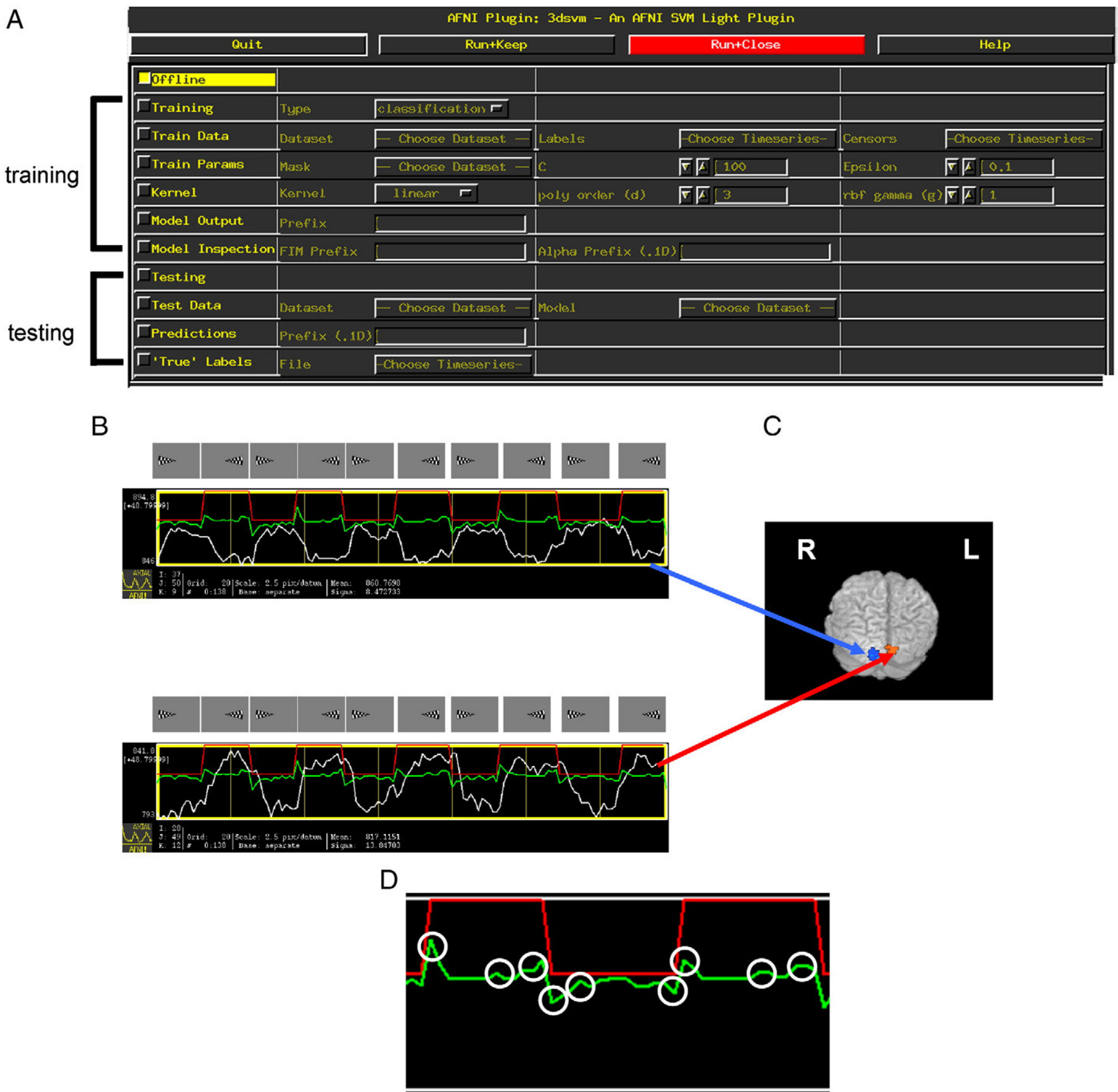

Fig. 5. The 3dsvm plugin. 3dsvm is a command line program and plugin for AFNI, built using SVM-Light (Joachims, 1999) for its core computations. (A) The gui interface allows the user to specify important training and testing parameters. (B) A variable block length task consisting of a left vs. right visual wedge stimulus (screen shots and red time course), support vector machine weightings of each time volume (green), and voxel time series (white). (C) SVM-based map from this paradigm. (D) Closer look at a green trace from B. Circled time points represent support vectors. Source code and compiled binaries are distributed with AFNI, and descriptions and further information are maintained at http://lacontelab.org/3dsvm.html.

Methodology

Supervised learning is one of the last steps in the chain of experimental and data processing for both offline analysis and for TABS. The use of specialized MRI sequences may be beneficial for real-time applications, such as the multi-echo sequences for improving image distortion artifacts (Posse et al., 1999; Weiskopf et al., 2005) and sequences that update to minimize the effects of motion (Thesen et al., 2000) or provide adaptive capabilities during the experiment (Yoo et al., 1999). In addition, parallel MRI acquisition, using multiple coils (Pruessmann et al., 1999; Sodickson and Manning, 1997), is revolutionizing all facets of MRI and will likely be a routine aspect of most future protocols.

Strother (2006) has reviewed the preprocessing steps that occur after data acquisition and before the final statistical test and emphasized their importance to fMRI experiments. Each additional step adds processing time and special considerations (for example, spatial smoothing can be done as soon as an image is reconstructed, but detrending requires multiple time points). At the extreme end of computational execution, Bagarinao et al. (2005) have demonstrated preprocessing and incremental GLM analysis in real-time using computational grid technology done on a network of remote computing resources. Comprehensive real-time analysis that includes behavioral and physiological recordings in the statistical analysis has also been demonstrated (Voyvodic, 1999). Further Bodurka et al. (2009) has recently shown the use of neurofeedback with rtfMRI to suppress physiological noise. For TABS-based systems, feature selection (Craddock et al., 2009; Mitchell et al., 2004), sample selection, and quality of the labels are additional preprocessing steps that could be beneficial (LaConte et al., 2007). Strother et al. (2002a) proposed a framework (called NPAIRS) for evaluating the experimental chain defined by all choices in the acquisition, reconstruction, preprocessing, and data analysis steps that is especially well suited to supervised learning methods (Kjems et al., 2002; LaConte et al., 2003; Shaw et al., 2003; Strother et al., 2002b).

Subject motion may be one of the most critical data quality issues for TABS. In fact head motion is even more problematic in adaptive designs and particularly neurofeedback, since it may be inadvertently "trained" instead of or in addition to the neuronal BOLD response. While intra-image motion is reduced in fast imaging sequences such as single shot echo planar imaging (EPI), inter-image motion remains a problem in routine fMRI data collection and is one of the single largest challenges to data quality for studies involving clinical populations, children, and the elderly. As a source of unwanted variance, motion can reduce sensitivity to true BOLD effects, and, when coupled to the timing of stimulus presentation, even result in erroneous patterns of activity (Hajnal et al., 1994). It has been previously shown that alignment between functional runs and correction for motion within runs can have a major impact on both prediction accuracy of supervised learning models as well as reproducibility of fMRI maps even when motion is small relative to voxel size (LaConte et al., 2003). Rapid retrospective correction of fMRI data is possible (Cox and Jesmanowicz, 1999; Mathiak and Posse, 2001), but these approaches cannot easily correct for large motion, primarily because they are more likely to result in changes in field homogeneity and through-plane spin history effects. Using the implementation of Cox and Jesmanowicz (1999) and Mathiak and Posse (2001), feedback of motion estimates to the volunteer is possible and has been reported to reduce subject motion and (at least for one task) has minimal interference with the fMRI paradigm (Yang et al., 2005).

Given all of the possible processing steps that could be desired, implementing and testing all of them with limited resources and time becomes impractical and represents either a duplication of existing work or raises the question of how to best share any new capabilities. Thus preprocessing demands highlight another advantage to integrating within a major software package, since this gives access to all of the preprocessing and display capabilities that come with it, as well as the ability to readily share any new methods that are developed.

Future challenges

Looking to the future, fMRI will continue to evolve in areas of acquisition, experimental design, and data analysis. As the field furthers its understanding of the BOLD signal, optimal tradeoffs in field strength, voxel size, and stimulus parameters will be refined. MRI is sensitive to a host of physical parameters that can give rise to meaningful contrast in neuroimaging, and work on multimodal imaging is likely to continue. Information rates and data quality will continue to improve, as will statistical approaches. Real-time fMRI could play an important role in the future of fMRI. This section looks ahead to some important challenges, opportunities, and directions for TABS fMRI and rtfMRI in general.

Expanding the experimental capabilities

For a TABS system, the implementation reported in LaConte et al. (2007) primarily served as a proof of principle. As more work emerges in the field, many challenges will be met and new capabilities will be implemented to add experimental flexibility. Two areas that we are exploring include re-using a subject's model across multiple sessions or after head movement and obtaining a brain state model from every run, including feedback runs.

Model-to-scan alignment

The ability to spatially align supervised learning models to new fMRI volumes would add flexibility for a variety of situations, including movement between runs within a session, progressive training and testing across sessions, and the use of group models for neurofeedback applications such as addiction and stroke (where the group could be comprised of recovered individuals and used to guide a new individual's recovery). Alignment across runs in the same session for classification has been previously reported (LaConte et al., 2003), as has the use of group-based models applied to new individuals (Mitchell et al., 2004; Strother et al., 2004), although registering between subjects might benefit from future work using concepts such as similarity of functional organization across the population.

Incorporating this capability into a TABS system would also make it possible to share models across labs. Such an extension would be relatively straightforward, requiring a mechanism to spatially align the supervised model and the test data. One practical way to do this would be to train the supervised learning model prior to the real-time session, find alignment parameters during the session, and apply the transformation only once (to the model). Computationally, this would be preferable to retraining (especially if the models take a long time to converge) or to having to apply a transformation to bring every time-point of the test data to the model space during acquisition.

Model updates during real-time feedback

It could be extremely beneficial to be able to use the images that are being decoded during real-time feedback runs to additionally serve as new training data to update the TABS model. One motivation is that this addresses the requisite start-up cost to brain state feedback–that it is impossible to provide real feedback without an existing model, but during feedback, there might be important differences since the subject is doing the base task and simultaneously monitoring feedback. It is likely that having the capability for ongoing machine learning can significantly decrease training time for therapeutic applications. Given a start-up model, it might be possible to proceed to training and testing with progressively more relevant feedback. Further, the presence of brain state-controlled feedback allows for an adaptive paradigm and for learning and/or change in strategy on the part of the volunteer. Thus using a true brain state feedback experiment allows for human learning and machine re-learning as discussed next.

Detecting and correcting temporal non-stationarity

Like most statistical models, supervised learning methods were developed under the assumption that the measured system (in this case the volunteer's brain response) is constant over time. Indeed, this premise of temporal stationarity underlies the majority of current neuroimaging studies, where the implicit assumption (which is made by repeating stimulus conditions several times throughout a run) is that the measured responses are more or less constant over time. While these assumptions are often reasonably satisfied, in general, a human subject is prone to factors such as varied attention, fatigue, and learning. Moreover, one major goal of rtfMRI can be to stimulate positive change through adaptive feedback experiments. It is currently unknown how a subject's behaviorally demonstrated learning corresponds to detectible changes in the brain and if this is directly observable using pattern-based brain state prediction.

To promote human learning and adaptation while still maintaining the capacity to provide relevant feedback, the feedback system itself must be able to adapt. We have begun to study the issue of the performance of predictive algorithms on a time-varying system using motor learning experiments and support vector machine regression of button press rate as a model system for studying this effect (LaConte et al., 2005b). Our preliminary results support the idea that behaviorally demonstrated learning by a subject (quantified by increases in button press speed, while maintaining a high degree of accuracy) corresponds to changes in the image data and that these changes are directly observable using prediction.

We used a finger sequence task as described in Rao et al. (1993), and adapted the motor learning study of Lafleur et al. (2002), which reported regional activation changes with overt motor learning. Right-handed volunteers were asked to perform a button press sequence (middle, pinkie, ring, index) with their left hand as accurately and rapidly as possible on a four-button, fiber optic button box (Current Designs, www.curdes.com). An experimental run consisted of four, 16 s periods of continued button presses interspersed between five 16-s control periods. Periods were visually guided, with control periods displaying a fixation cross and motor periods displaying text reminding the volunteer of the proper finger sequence. The scanning session consisted of four repeated fMRI runs, each spaced approximately five minutes apart. Volunteers were instructed not to mentally rehearse when not overtly performing the task. Imaging was done on a 3 T Siemens Trio, with 27 axial EPI slices (TR/TE = 2000/31 ms, voxel = $3.4\times3.4\times5$ mm). Scans during motor blocks from run 1 were used to build a support vector regression model relating all brain voxels to the number of button presses at each TR within these blocks. For each subject, models from run 1 were used to estimate the button rate in successive runs.

The degree of increased rate (arising from short-term motor learning) varied greatly across subjects. Nevertheless, data from all subjects demonstrated brain state model errors were highly correlated with their mean performance: (7 subjects: $r = 0.75$, 0.94, 0.94, 0.80, 0.91, 0.99, 0.99). The task's block design convolved with an ideal hemodynamic response function was used to produce t-maps for each run for each subject. These were then thresholded at a FDR-corrected value of 1×10^{-6}. Fig. 6 gives examples of (a) one individual who demonstrated learning, (b) one who did not, and (c) one performing a control task (paced, dominant index finger button press task). Note that the button press behavior, estimation error, and t-maps are all in agreement. Even though this is a uni-manual task bilateral activation is common difficult tasks (Rao et al., 1993). In general for subjects that demonstrate learning, initially have a bimanual BOLD response in primary sensory motor, supplemental motor, and parietal areas with decreasing spatial extent of response in these areas (especially decreased in ipsilateral regions) over time (Fig. 6A). For subjects who do not demonstrate learning and for subjects who perform the control task, the *t*-maps, button press rate and support vector regression accuracy remain relatively constant across runs (Fig. 6B and C, respectively).

These experimental results demonstrate that human learning is observable through increased prediction error in multivariate SVM

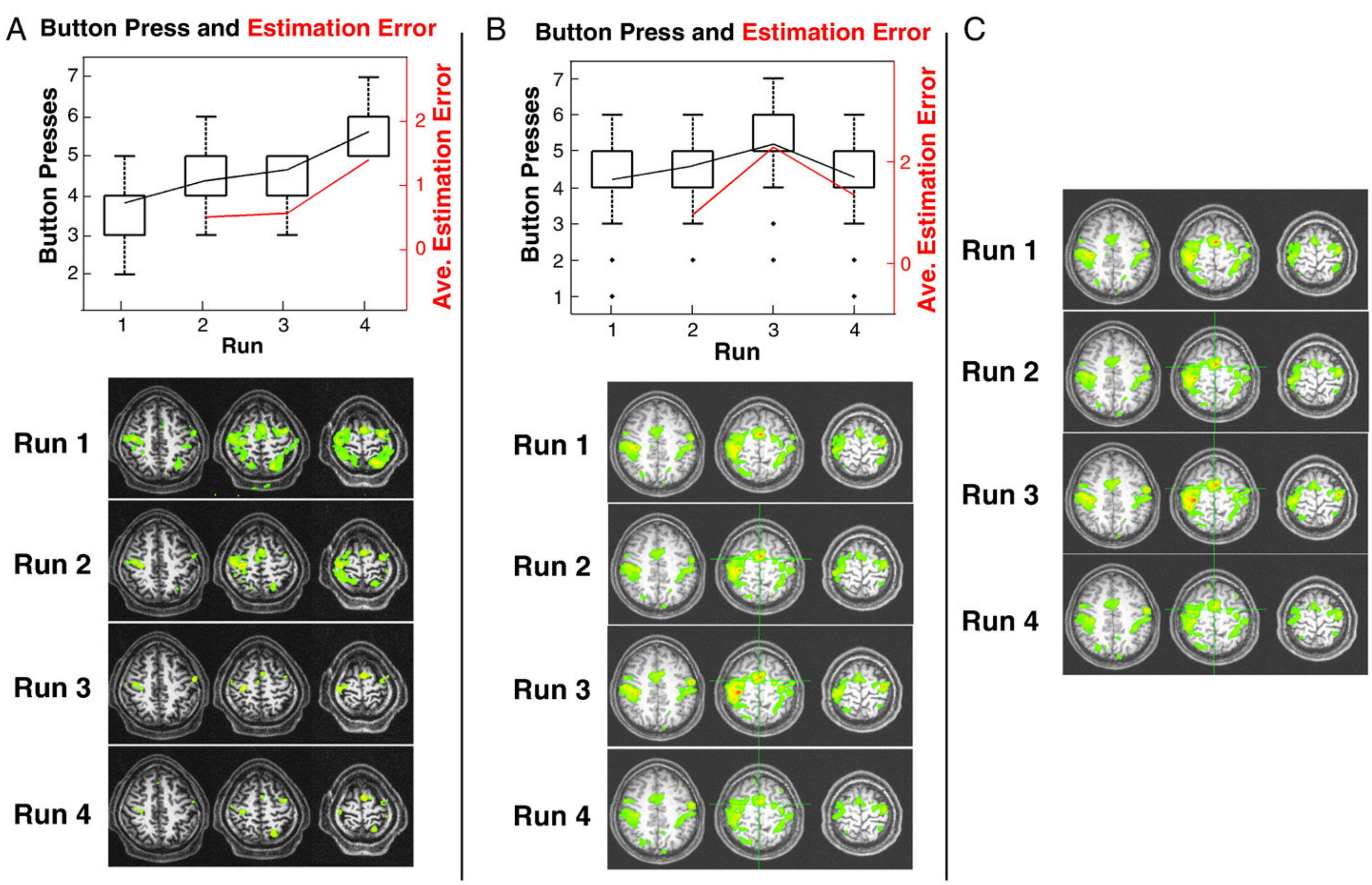

Fig. 6. Motor learning as a model system for studying non-stationarity. (A) Behavior, prediction accuracy and changes in t-maps for a subject who demonstrated learning. (B) A subject with little motor improvement, in agreement with both t-maps and prediction accuracy. (C) Control task. No learning behavior was expected (or observed). *t*-maps were similarly constant, and prediction accuracy was constant as well.

models of fMRI data. As a practical matter, these temporal changes are often a hindrance to the analysis process, but for effects such as learning they represent a fascinating dynamic component to neuroimaging experiments. Motor learning is an ideal experimental model for this phenomenon since it is supported by a vast behavioral and neuroimaging literature and lends itself to behavioral recordings as an external measure of learning.

The future challenge of this line of research is to detect and correct for the time-based changes in volunteers participating in TABS-based rtfMRI studies. Approaches for doing this could be algorithmic or patient initiated. For an algorithmic approach, we note that in the machine learning literature, such changes are often referred to as concept drift. One of the simplest approaches to correct for this effect is to use time windows of data. Intuitively, a window approach tries to balance the quality and quantity of training data. That is, sufficient data is required to obtain reasonable models, but, in the presence of nonstationarity, too much data allows for irrelevant or misleading training examples and poor predictive performance. Klinkenberg and Joachims (2000) note that windowing works well but requires application-specific tuning. For a patient-signaled approach, the idea would be to give the volunteer a way to signal that the interface "is no longer working." For example, rather than having the algorithm detect discrepancies, it might be possible to detect frustration or to have a robust behavior that the volunteer can use to signal the computer to re-train.

Feedback interfaces

Feedback can take on a wide variety of forms. At one extreme task difficulty could be titrated based on brain signals without a subject knowing that feedback was taking place. In this case, the explicit real-time "feedback" might be solely targeted to providing the most information possible to the experimenter. Another goal might be a steadily growing independence from the neurofeedback to promote long-term efficacy or a move from an external to an internal representation of a task. Recently, Bray et al. (2007) proposed monetary rewards, rather than a more direct transduction of BOLD signal in an operant conditioning framework. The appropriate feedback stimulus for the question or task at hand remains an open and intriguing issue. In the rtfMRI literature several variations have arisen in different groups, some of which are demonstrated in Fig. 7. Further work is needed to understand and optimize how controlling an interface ties into reward systems and promotes desired plasticity. This area has great potential as a fascinating new frontier of scientific discovery.

The potential of TABS

This review is intentionally optimistic, but further work is necessary. One outstanding major issue is that current rtfMRI studies fall short of being able to make strong claims that voluntary self-regulation of hemodynamic processes is a main effect of neurofeedback (and not confounded by coaching subjects on potential mental strategies). Another issue is that over the past several decades of EEG-based neurofeedback research, the mechanisms underlying self-regulation are still not well elaborated. A comprehensive treatment of EEG-based neurofeedback is beyond the scope of this review, but many of the same issues that will be important for rtfMRI have been discussed by the EEG neurofeedback and biofeedback community (Hinterberger et al., 2004; Kotchoubey et al., 2002; Fetz, 1969; Lacroix and Roberts, 1978; Elbert et al., 1984; Birbaumer et al., 1999; Kotchoubey et al., 2001).

At the moment we have a wealth of capabilities and the testable hypothesis that TABS and other rtfMRI systems can serve as a valuable tool for measuring brain function and can enable feedback-aided plasticity. This cannot be tested with the next single experiment, but will require a body of converging evidence, hopefully from a broad scientific community. This endeavor is so rich in challenges there can be little doubt that future work will continue to form the foundation for future directions of innovation and discovery.

The best possible trajectory will be fueled by well-designed experiments that include scientific controls. For clinical applications, it is even possible that developing effective protocols will not be enough. Meeting the challenge of efficacy might not remove the specter of cost. Some of the following comments add to and reaffirm similar statements made in deCharms (2008). The issue of cost can be dealt with in a number of ways. One is by making the technology more affordable. Cost can be reduced through MR technology breakthroughs or through economic changes (e.g. increased commercial competition and manufacturing specialized rtfMRI systems). In addition, costs can be better justified for therapies in which rtfMRI provided the best or only solution. It is also quite possible that rtfMRI could serve as an adjuvant to existing therapies and would augment these by improving efficacy or by leading to beneficial results on a faster time scale. Similarly there are several ways in which rtfMRI might complement cheaper and more portable neurofeedback technologies such as electroencephalography or near infrared sensors, and even guide improvements in their use. For now, fMRI is the best imaging tool for providing non-invasive, spatially resolved measurements of brain activity in humans. Thus as a research tool, it remains the method of choice for understanding the neural correlates of BCI-feedback.

In terms of assessing and evaluating TABS fMRI, ROI-based rtfMRI, and other available neurofeedback technologies such as EEG and near infrared spectroscopy (NIRS) (Birbaumer et al., 2009) future work providing direct comparisons are necessary. Within the BCI literature, bit rate is one important characteristic of the system (Wolpaw et al., 2002) that should be considered by the rtfMRI community. This measure captures the capacity with which brain measurements can be translated to useful information to control interfaces such as word processors, slider bars, or even robots. Strategies for increasing bit rate include faster "switching" capability and maximizing prediction accuracy for TABS systems that use classification and regression. For classification, the more categories that the system uses, the higher the number of bits (e.g. classification of two stimulus categories is represented by 1 bit, whereas four classes are represented by 2 bits). For ROI-based methods, bit rate can likely be increased by using multiple locations (Yoo et al., 2004). Sorger et al. (2009) have exploited spatio-temporal properties of the BOLD signal, in order to increase the information transfer rate. In addition, as basic imaging improvements provide greater SNR and more specific image contrast, it may be possible to robustly classify based on the earliest BOLD signal changes (Yacoub and Hu, 1999). Finally, properly designed tasks may ultimately be able to capitalize on the spatiotemporal capabilities of MRI and multivariate techniques to decode complex streams of ongoing sensory and behavioral combinations. With these considerations, the ultimate limit on bandwidth is very much an unexplored matter in rtfMRI.

Of the most exciting possibilities for TABS is that of allowing individuals to gain awareness of brain processes that are not usually consciously accessible or rely on non-reliable self-report. Going beyond what is available from behavioral measures and moving into these realms–like pain, memory encoding and recall, and emotional regulation–makes full use of the technology. At the same time, we cannot hope to build reliable real-time systems and apply them in evidence-based protocols if we are not grounded by behavioral measures when building the system and by experimental controls while developing the protocols. At least three things are desired. First, technology development should use well-parameterized sensory stimuli or measurable behavior. For example, button responses provide a good external measure when building new capabilities into a system. The brain states then correspond to recordings that can be verified in terms of timing and correctness of response. Second,

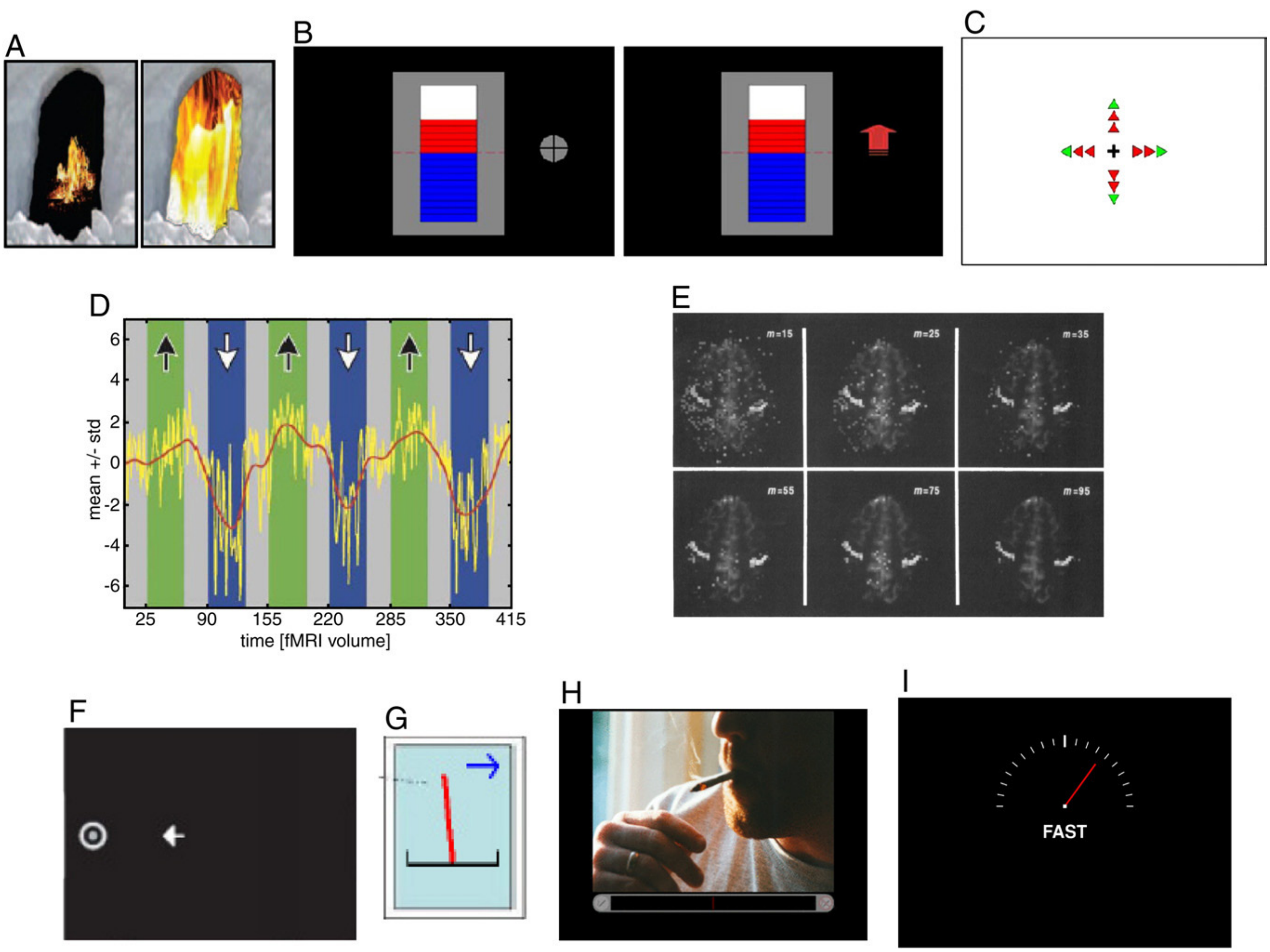

Fig. 7. Real-time interfaces. Currently there are no strong guiding principles to optimize a display's effectiveness of neurofeedback. (A) A continuous display representing percent signal change of rostral anterior cingulate by the size of a virtual fire. Modified from (deCharms et al., 2005). (B) The difference between signal from the right anterior insula and a large reference ROI was used to give feedback with a thermometer display. Task instructions were cued with symbols to the right of the thermometer. Modified from (Caria et al. (2007). (C) A set of inner, middle, and outer four-way arrows, indicating degree of motion (in this case a second level motion threshold has been exceeded). This configuration was found to minimize distractions and be more effective than showing subject their actual direction of motion. Task stimuli are presented in the center of the arrows (the center "+" symbol represents the rest condition in the task). Modified from (Yang et al., 2005). (D) A running plot (yellow trace) of the difference between two brain regions, making the control signal for this interface conceptually similar to the thermometer of B. In the actual experiment, the colored columns indicated the task condition (arrows and red trace were added after the experiment). Modified from Weiskopf et al. (2004a,)b. (E) Images from the first real-time FMRI experiment, showing the evolution of a map using sequential finger tapping task. The display was intended for the experimenter. Modified from Cox et al. (1995). (F) Interface in which the goal is to move the needle cursor to the target. This was demonstrated using classification of whole brain fMRI data in to various task categories for different subjects. Modified from (LaConte et al. (2007). (G) A red inverted pendulum that subjects controlled with a classifier that gave right, left, and rest output signals. Modified from Eklund et al. (2009). (H) A slider bar and smoking cues that show smokers feedback based on "enhanced" or "suppressed" craving states. Modified from LaConte et al. (2009). (I) An unpublished interface used for ongoing rtfMRI development. Subjects fixate on the white base of the feedback needle and task instructions can be displayed below the meter.

experimental controls are necessary. Scientific progress depends on experiments that are backed by positive and negative controls. For example, using technology tested with button presses provides a positive control against a negative result (the experimenter knows the system works for a well-characterized task), and using a model from a completely different task serves as a negative control against a positive result (the experimenter has ruled out the possibility that the feedback results in the test data could be generated from any arbitrary training task). In general, negative controls should be performed for all reasonable alternative explanations for a positive result. For example, deCharms et al. (2005) used four control groups that included extended practice without rtfMRI feedback, doubling the duration of training to focus attention away from pain, training using rtfMRI data from a different ROI, and using sham rtfMRI data taken from a different participant. Third, confirmatory analysis should be performed using brain and behavioral recordings. Just as data-driven results place the burden of interpretation on the experimenter and ROI-based results need to acknowledge other mechanisms for changing localized signal, TABS results need to be scrutinized with an appropriate degree of skepticism. One way to do this is to examine the training model – do the model maps involve areas that are consistent with the task instructions and any related reports in the literature? Thus as non-linear approaches are applied (such as non-linear kernel methods), it will be important to develop interpretation strategies that relate to the brain's anatomy. This scrutiny will be especially important if TABS is to be used for the exciting applications that elude reliable external behavioral measures. Along similar lines, for any feedback system, there can be a real danger that behavioral/imaging artifacts arising from physiology, subject motion, or eye movements get reinforced during the experiment (Zhang et al., 2009). These three concepts are not independent of each other. Further special applications such as rehabilitation will involve several additional considerations, including the demonstration of long-term efficacy, adaptation of training to a clinical setting, and potential side-effects. These are issues that are discussed in the EEG feedback literature (Strehl et al., 2006).

Returning to the issue of controls, negative controls are crucial to the field, and though the proper controls will vary for each study, it is clear that the goal should be to protect against over-stating rtfMRI results. Positive controls, however, should be viewed as important building blocks to move forward. Questions such as "Can this task and real-time system enable a volunteer to control an interface?" are important and non-trivial. In a TABS experiment, if we are trying to control an interface, we do so with supervised models that link task conditions with the degrees of freedom of the interface (e.g. pressing left and right buttons is linked through the training step with the ability to move a cursor to the left or the right). The "treatment" is the task that the subject is asked to perform. As we have stated, simple sensory or motor tasks (e.g. viewing left and right flashing wedges or performing left and right button presses) can generally serve as positive controls. Before being able to embark upon a full-fledged rehabilitation study, it is necessary to investigate an important underpinning—the degree to which interface modulation is obtainable. This is an important step to demonstrate the feasibility for future rehabilitation designs because it disentangles the interface aspect from any feedback-based affects. The feedback interface converts brain patterns into a computer display. It is critical to establish whether variation in a volunteer's fMRI data can be modulated to a great enough extent such that it can be translated into feedback information. Otherwise a null result (no change in the feedback interface) could indicate either that the measure is not appropriate or that the feedback therapy is fundamentally flawed. Thus the first question when studying a new cognitive domain or study population is: Can the subjects learn to control a computer interface based on the task design? For example, can smokers enhance and suppress craving to control an interface (LaConte et al., 2009). Further, the degree of success can be answered quantitatively through measures such a prediction accuracy (or equivalently bit rate (Kjems et al., 2002)).

Conclusion

Feedback-based rtfMRI represents an experimental system that goes beyond observational findings into the domain of falsifiability. This framework can allow investigators to test the neuroscience knowledge base with a system that demonstrably works or fails, based on model generalization as it is used to provide neurofeedback. While predictive models are not guaranteed to capture all relevant fMRI signals, the ability to actively test predictions enables progress toward a more refined understanding of brain function.

The experimental flexibility provided by TABS and other rtfMRI approaches allows the implementation of adaptive paradigms. Conventional fMRI paradigms implicitly rely on a linear systems-based characterization of brain function, because the input stimulus paradigm is not dependent on brain or behavioral respones to previous stimuli. Because rtfMRI enables feedback, it allows for characterization of both the linear and nonlinear properties of brain responses. Breakthroughs will only be possible, though, through a growing research community that is willing to expand current real-time capabilities, share software, and develop experimental frameworks to serve as tangible examples of adaptive paradigms. Going beyond the limitations of conventional stimuli and the harnessing of the utility of feedback and adaptive experiments is an exciting new frontier for scientific discovery.

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References

Bagarinao, E., Matsuo, K., Tanaka, Y., Sarmenta, L.F., Nakai, T., 2005. Enabling on-demand real-time functional MRI analysis using grid technology. Methods Inf. Med. 44, 665–673.
Bandettini, P.A., Wong, E.C., Hinks, R.S., Tikofsky, R.S., Hyde, J.S., 1992. Time course EPI of human brain function during task activation. Magn. Reson. Med. 25, 390–398.
Baumgartner, R., Windischberger, C., Moser, E., 1998. Quantification in functional magnetic resonance imaging: Fuzzy clustering vs. correlation analysis. Magn. Reson. Imaging 16, 115–125.
Beckmann, C.F., Smith, S.M., 2004. Probabilistic independent component analysis for functional magnetic resonance imaging. IEEE Trans. Med. Imaging 23, 137–152.
Birbaumer, N., Ghanayim, N., Hinterberger, T., Iversen, I., Kotchoubey, B., Kubler, A., Perelmouter, J., Taub, E., Flor, H., 1999. A spelling device for the paralysed. Nature 398, 297–298.
Birbaumer, N., Ramos, A., Murguialdav, R.M., Weber, C., Montoya, P., 2009. Chapter 8 Neurofeedback and brain—computer interface: clinical applications. Int. Rev. Neurobiol. 86, 107–117.
Bishop, C.M., 2006. Pattern recognition and machine learning. Springer.
Bodurka, J., Gonzalez-Castillo, J., Bandettini, P., 2009. The use of neurofeedback with real-time functional MRI to suppress physiological noise. Proc Intl Soc Mag Reson Med, Honolulu HI, p. 1592.
Bonson, K.R., Grant, S.J., Contoreggi, C.S., Links, J.M., Metcalfe, J., Weyl, H.L., Kurian, V., Ernst, M., London, E.D., 2002. Neural systems and cue-induced cocaine craving. Neuropsychopharmacology 26, 376–386.
Boynton, G.M., Engel, S.A., Glover, G.H., Heeger, D.J., 1996. Linear systems analysis of functional magnetic resonance imaging in human V1. J. Neurosci. 16, 4207–4221.
Bray, S., Shimojo, S., O'Doherty, J.P., 2007. Direct instrumental conditioning of neural activity using functional magnetic resonance imaging-derived reward feedback. J. Neurosci. 27, 7498–7507.
Brody, A.L., Mandelkern, M.A., London, E.D., Childress, A.R., Lee, G.S., Bota, R.G., Ho, M.L., Saxena, S., Baxter Jr., L.R., Madsen, D., Jarvik, M.E., 2002. Brain metabolic changes during cigarette craving. Arch. Gen. Psychiatry 59, 1162–1172.
Calhoun, V.D., Adali, T., Pearlson, G.D., Pekar, J.J., 2001. Spatial and temporal independent component analysis of functional MRI data containing a pair of task-related waveforms. Hum. Brain Mapp. 13, 43–53.
Cannon, R., Lubar, J., Congedo, M., Thornton, K., Towler, K., Hutchens, T., 2007. The effects of neurofeedback training in the cognitive division of the anterior cingulate gyrus. Int. J. Neurosci. 117, 337–357.
Caria, A., Veit, R., Sitaram, R., Lotze, M., Weiskopf, N., Grodd, W., Birbaumer, N., 2007. Regulation of anterior insular cortex activity using real-time fMRI. NeuroImage 35, 1238–1246.
Caruana, R., Karampatziakis, N., Yessenalina, A., 2008. An empirical evaluation of supervised learning in high dimensions. Proceedings of the 25th international conference on Machine learning. ACM, Helsinki, Finland, pp. 96–103.
Chen, W., Zhu, X.H., Kato, T., Andersen, P., Ugurbil, K., 1998. Spatial and temporal differentiation of fMRI BOLD response in primary visual cortex of human brain during sustained visual simulation. Magn. Reson. Med. 39, 520–527.
Cherkassky, V., Mulier, F., 2007. Learning from data: concepts, theory, and methods, 2nd ed. ed. John Wiley & Sons.
Cohen, M.S., 2001. Real-time functional magnetic resonance imaging. Methods 25, 201–220.
Cox, R.W., 1996. AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. 29, 162–173.
Cox, R.W., Jesmanowicz, A., 1999. Real-time 3D image registration for functional MRI. Magn. Reson. Med. 42, 1014–1018.
Cox, D.D., Savoy, R.L., 2003. Functional magnetic resonance imaging (fMRI) "brain reading": detecting and classifying distributed patterns of fMRI activity in human visual cortex. NeuroImage 19, 261–270.
Cox, R.W., Jesmanowicz, A., Hyde, J.S., 1995. Real-time functional magnetic resonance imaging. Magn. Reson. Med. 33, 230–236.
Craddock, R.C., Holtzheimer III, P.E., Hu, X.P., Mayberg, H.S., 2009. Disease state prediction from resting state functional connectivity. Magn. Reson. Med. 62, 1619–1628.
Dale, A.M., Buckner, R.L., 1997. Selective averaging of rapidly presented individual trials using fMRI. Hum. Brain Mapp. 5, 329–340.
deCharms, R.C., 2007. Reading and controlling human brain activation using real-time functional magnetic resonance imaging. Trends Cogn. Sci. 11, 473–481.
deCharms, R.C., 2008. Applications of real-time fMRI. Nat. Rev. Neurosci. 9, 720–729.
deCharms, R.C., Christoff, K., Glover, G.H., Pauly, J.M., Whitfield, S., Gabrieli, J.D.E., 2004. Learned regulation of spatially localized brain activation using real-time fMRI. NeuroImage 21, 436–443.
deCharms, R.C., Maeda, F., Glover, G.H., Ludlow, D., Pauly, J.M., Soneji, D., Gabrieli, J.D., Mackey, S.C., 2005. Control over brain activation and pain learned by using real-time functional MRI. Proc. Natl. Acad. Sci. U. S. A. 102, 18626–18631.
Eklund, A., Ohlsson, H., Andersson, M., Rydell, J., Ynnerman, A., Knutsson, H., 2009. Using real-time fMRI to control a dynamical system by brain activity classification. Medical Image Computing and Computer-Assisted Intervention – MICCAI 2009. Springer, Berlin / Heidelberg, pp. 1000–1008.
Elbert, et al., 1984. Self-regulation of the brain and behavior. Springer, Heidelberg.

Esposito, F., Seifritz, E., Formisano, E., Morrone, R., Scarabino, T., Tedeschi, G., Cirillo, S., Goebel, R., Di Salle, F., 2003. Real-time independent component analysis of fMRI time-series. Neuroimage 20, 2209–2224.
Fetz, E.E., 1969. Operant conditioning of cortical unit activity. Science 163, 955–958.
Fletcher, P.C., Dolan, R.J., Shallice, T., Frith, C.D., Frackowiak, R.S.J., Friston, K.J., 1996. Is multivariate analysis of PET data more revealing than the univariate approach? Evidence from a study of episodic memory retrieval. NeuroImage 3, 209–215.
Friston, K.J., Frith, C.D., Frackowiak, R.S., Turner, R., 1995a. Characterizing dynamic brain responses with fMRI: a multivariate approach. NeuroImage 2, 166–172.
Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.-B., Firth, C.D., Frackowiak, R.S.J., 1995b. Statistical parametric maps in functional neuroimaging: a general linear approach. Hum. Brain Mapp. 2, 189–210.
Friston, K.J., Josephs, O., Rees, G., Turner, R., 1998. Nonlinear event-related responses in fMRI. Magn. Reson. Med. 39, 41–52.
Gembris, D., Taylor, J.G., Schor, S., Frings, W., Suter, D., Posse, S., 2000. Functional magnetic resonance imaging in real time (FIRE): sliding-window correlation analysis and reference-vector optimization. Magn. Reson. Med. 43, 259–268.
Glover, G.H., 1999. Deconvolution of impulse response in event-related BOLD fMRI. NeuroImage 9, 416–429.
Goddard, N.H., Hood, G., Cohen, J.D., Eddy, W.F., Genovese, C.R., Noll, D.C., Nystrom, L.E., 1997. Online analysis of functional MRI datasets on parallel platforms. J. Supercomput. 11, 295–318.
Goebel, R., 2001. Cortex-based real-time fMRI. NeuroImage 13.
Hajnal, J.V., Myers, R., Oatridge, A., Schwieso, J.E., Young, I.R., Bydder, G.M., 1994. Artifacts due to stimulus correlated motion in functional imaging of the brain. Magn. Reson. Med. 31, 283–291.
Hansen, L.K., 2007. Multivariate strategies in functional magnetic resonance imaging. Brain Lang. 102, 186–191.
Hansen, L.K., Larsen, J., Nielsen, F.A., Strother, S.C., Rostrup, E., Savoy, R., Lange, N., Sidtis, J., Svarer, C., Paulson, O.B., 1999. Generalizable patterns in neuroimaging: how many principal components? NeuroImage 9, 534–544.
Haxby, J.V., Gobbini, M.I., Furey, M.L., Ishai, A., Schouten, J.L., Pietrini, P., 2001. Distributed and overlapping representations of faces and objects in ventral temporal cortex. Science 293, 2425–2430.
Haynes, J.D., 2010. NeuroImage to be determined by publisher.
Haynes, J.D., Rees, G., 2005. Predicting the orientation of invisible stimuli from activity in human primary visual cortex. Nat. Neurosci. 8, 686–691.
Haynes, J.D., Rees, G., 2006. Decoding mental states from brain activity in humans. Nat. Rev. Neurosci. 7, 523–534.
Heeger, D.J., Ress, D., 2002. What does fMRI tell us about neuronal activity? Nat. Rev. Neurosci. 3, 142–151.
Himberg, J., Hyvarinen, A., Esposito, F., 2004. Validating the independent components of neuroimaging time series via clustering and visualization. NeuroImage 22, 1214–1222.
Hinterberger, T., Neumann, N., Pham, M., Kubler, A., Grether, A., Hofmayer, N., Wilhelm, B., Flor, H., Birbaumer, N., 2004. A multimodal brain-based feedback and communication system. Exp. Brain Res. 154, 521–526.
Hollmann, M., Moench, T., Mueller, C., Bernarding, J., 2009. Predicting human decisions in socioeconomic interaction using real-time functional magnetic resonance imaging (rtfMRI), p. 72621K.
Joachims, T., 1999. Making large-scale SVM learning practical. In: Scholkopf, B., Burges, C., Smola, A. (Eds.), Advances in Kernel methods—support vector learning. MIT Press, Cambridge, Mass.
Kerns, J.G., Cohen, J.D., MacDonald III, A.W., Cho, R.Y., Stenger, V.A., Carter, C.S., 2004. Anterior cingulate conflict monitoring and adjustments in control. Science 303, 1023–1026.
Kjems, U., Hansen, L.K., Anderson, J., Frutiger, S., Muley, S., Sidtis, J., Rottenberg, D., Strother, S.C., 2002. The quantitative evaluation of functional neuroimaging experiments: mutual information learning curves. NeuroImage 15, 772–786.
Klinkenberg, R., Joachims, T., 2000. Detecting concept drift with support vector machines. In: Langley, P. (Ed.), Proceedings of the Seventeenth International Conference on Machine Learning (ICML).
Kloppel, Ashburner, 2010. NeuroImage to be determined by publisher.
Kollias, S.S., Golay, X., Boesiger, P., Valavanis, A., 2000. Dynamic characteristics of oxygenation-sensitive MRI signal in different temporal protocols for imaging human brain activity. Neuroradiology 42, 591–601.
Kotchoubey, B., Strehl, U., Uhlmann, C., Holzapfel, S., Konig, M., Froscher, W., Blankenhorn, V., Birbaumer, N., 2001. Modification of slow cortical potentials in patients with refractory epilepsy: a controlled outcome study. Epilepsia 42, 406–416.
Kotchoubey, B., Kubler, A., Strehl, U., Flor, H., Birbaumer, N., 2002. Can humans perceive their brain states? Conscious. Cogn. 11, 98–113.
Kriegeskorte, 2010. NeuroImage to be determined by publisher.
Kwong, K.K., Belliveau, J.W., Chesler, D.A., Goldberg, I.E., Weisskoff, R.M., Poncelet, B.P., Kennedy, D.N., Hoppel, B.E., Cohen, M.S., Turner, R., et al., 1992. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc. Natl. Acad. Sci. U. S. A. 89, 5675–5679.
LaConte, S., Anderson, J., Muley, S., Ashe, J., Frutiger, S., Rehm, K., Hansen, L.K., Yacoub, E., Hu, X.P., Rottenberg, D., Strother, S., 2003. The evaluation of preprocessing choices in single-subject BOLD fMRI using NPAIRS performance metrics. NeuroImage 18, 10–27.
LaConte, S., Strother, S., Cherkassky, V., Anderson, J., Hu, X.P., 2005a. Support vector machines for temporal classification of block design fMRI data. NeuroImage 26, 317–329.
LaConte, S., Chen, J., Peltier, S., Hu, X., 2005b. Humans out-learning the machine: support vector machines applied to fMRI of human motor learning. Proceedings 13th Scientific Meeting. International Society for Magnetic Resonance in Medicine, Miami, p. 568.
LaConte, S.M., Peltier, S.J., Hu, X.P., 2007. Real-time fMRI using brain-state classification. Hum. Brain Mapp. 28, 1033–1044.
LaConte, S.M., King-Casas, B., Cinciripini, P.M., Eagleman, D.M., Versace, F., Chiu, P.H., 2009. Modulating rt-fMRI neurofeedback interfaces via craving and control in chronic smokers. NeuroImage 47, S45.
Lacroix, J.M., Roberts, L.E., 1978. A comparison of the mechanisms and some properties of instructed sudomotor and cardiac control. Biofeedback Self Regul. 3, 132.
Lafleur, M.F., Jackson, P.L., Malouin, F., Richards, C.L., Evans, A.C., Doyon, J., 2002. Motor learning produces parallel dynamic functional changes during the execution and imagination of sequential foot movements. NeuroImage 16, 142–157.
Lange, N., Strother, S.C., Anderson, J.R., Nielsen, F.A., Holmes, A.P., Kolenda, T., Savoy, R., Hansen, L.K., 1999. Plurality and resemblance in fMRI data analysis. Neruoimage 10, 282–303.
Lautrup, B., Hansen, L.K., Law, I., Svarer, C., Strother, C., 1994. Massive weight sharing: a cure for extremely ill-posed problems. Work-shop on Supercomputing in Brain Research: From Tomography to Neural Networks, Juelich, Germany, pp. 137–144.
Lin, F.H., McIntosh, A.R., Agnew, J.A., Eden, G.F., Zeffiro, T.A., Belliveau, J.W., 2003. Multivariate analysis of neuronal interactions in the generalized partial least squares framework: simulations and empirical studies. NeuroImage 20, 625–642.
Logothetis, N.K., Wandell, B.A., 2004. Interpreting the BOLD signal. Annu. Rev. Physiol. 66, 735–769.
Logothetis, N.K., Pauls, J., Augath, M., Trinath, T., Oeltermann, A., 2001. Neurophysiological investigation of the basis of the fMRI signal. Nature 412, 150–157.
MacDonald III, A.W., Cohen, J.D., Stenger, V.A., Carter, C.S., 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science 288, 1835–1838.
Mackey, S.C., Maeda, F., 2004. Functional imaging and the neural systems of chronic pain. Neurosurg. Clin. N. Am. 15, 269–288.
Mathiak, K., Posse, S., 2001. Evaluation of motion and realignment for functional magnetic resonance imaging in real time. Magn. Reson. Med. 45, 167–171.
Mayberg, H.S., Liotti, M., Brannan, S.K., McGinnis, S., Mahurin, R.K., Jerabek, P.A., Silva, J. A., Tekell, J.L., Martin, C.C., Lancaster, J.L., Fox, P.T., 1999. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. Am. J. Psychiatry 156, 675–682.
Mayberg, H.S., Lozano, A.M., Voon, V., McNeely, H.E., Seminowicz, D., Hamani, C., Schwalb, J.M., Kennedy, S.H., 2005. Deep brain stimulation for treatment-resistant depression. Neuron 45, 651–660.
McIntosh, A.R., Bookstein, F.L., Haxby, J.V., Grady, C.L., 1996. Spatial pattern analysis of functional brain images using partial least squares. NeuroImage 3, 143–157.
McKeown, M.J., Makeig, S., Brown, G.G., Jung, T.-P., Kindermann, S.S., Bell, A.J., Sejnowski, T.J., 1998. Analysis of fMRI data by blind separation into independent spatial components. Hum. Brain Mapp. 6, 160–188.
Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. Annu. Rev. Neurosci. 24, 167–202.
Mitchell, T., 2010. NeuroImage to be determined by publisher.
Mitchell, T.M., Hutchinson, R., Niculescu, R.S., Pereira, F., Wang, X.R., Just, M., Newman, S., 2004. Learning to decode cognitive states from brain images. Mach. Learn. 57, 145–175.
Moeller, J.R., Habeck, C.G., 2006. Reciprocal benefits of mass-univariate and multivariate modeling in brain mapping: applications to event-related functional MRI, H215O-, and FDG-PET. Int. J. Biomed. Imaging 1–13.
Muller, 2010. NeuroImage to be determined by publisher.
Naqvi, N.H., Rudrauf, D., Damasio, H., Bechara, A., 2007. Damage to the insula disrupts addiction to cigarette smoking. Science 315, 531–534.
Ngan, S.-C., Hu, X., 1999. Analysis of functional magnetic resonance imaging data using self-organizing mapping with spatial connectivity. Magn. Reson. Med. 41, 939–946.
Norman, K.A., Polyn, S.M., Detre, G.J., Haxby, J.V., 2006. Beyond mind-reading: multi-voxel pattern analysis of fMRI data. Trends Cogn. Sci. 10, 424–430.
Ogawa, S., Lee, T.-M., Kay, A.R., Tank, D.W., 1990a. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc. Natl. Acad. Sci. U. S. A. 87, 9868–9872.
Ogawa, S., Lee, T.-M., Nayak, A.S., Glynn, P., 1990b. Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. Magn. Reson. Med. 14, 68–78.
Papageorgiou, T., Curtis, W.A., McHenry, M., Laconte, S.M., 2009. Neurofeedback of two motor functions using supervised learning-based real-time functional magnetic resonance imaging. Conf. Proc. IEEE Eng. Med. Biol. Soc. 1, 5377–5380.
Peltier, S., LaConte, S., Hu, X., 2004. Online detection of low-frequency functional connectivity. Proc. SPIE Med. Imaging 5369, 683–690.
Peyron, R., Laurent, B., Garcia-Larrea, L., 2000. Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiol. Clin. 30, 263–288.
Platt, J.C., 1999. Probabilistic outputs for support vector machines and comparisons to regularized likelihood methods. In: Smola, A.J., Bartlett, P., Schölkopf, B., Schuurmans, D. (Eds.), Advances in Large Margin Classifiers, pp. 61–74.
Posse, S., Wiese, S., Gembris, D., Mathiak, K., Kessler, C., Grosse-Ruyken, M.L., Elghahwagi, B., Richards, T., Dager, S.R., Kiselev, V.G., 1999. Enhancement of BOLD-contrast sensitivity by single-shot multi-echo functional MR imaging. Magn. Reson. Med. 42, 87–97.
Posse, S., Fitzgerald, D., Gao, K.X., Habel, U., Rosenberg, D., Moore, G.J., Schneider, F., 2003. Real-time fMRI of temporolimbic regions detects amygdala activation during single-trial self-induced sadness. NeuroImage 18, 760–768.
Pruessmann, K.P., Weiger, M., Scheidegger, M.B., Boesiger, P., 1999. SENSE: sensitivity encoding for fast MRI. Magn. Reson. Med. 42, 952–962.

Rao, S.M., Binder, J.R., Bandettini, P.A., Hammeke, T.A., Yetkin, F.Z., Jesmanowicz, A., Lisk, L.M., Morris, G.L., Mueller, W.M., Estkowski, L.D., Wong, E.C., Haughton, V.M., Hyde, J.S., 1993. Functional magnetic-resonance-imaging of complex human movements. Neurology 43, 2311–2318.

Sell, L.A., Morris, J.S., Bearn, J., Frackowiak, R.S., Friston, K.J., Dolan, R.J., 2000. Neural responses associated with cue evoked emotional states and heroin in opiate addicts. Drug Alcohol Depend. 60, 207–216.

Seminowicz, D.A., Mayberg, H.S., McIntosh, A.R., Goldapple, K., Kennedy, S., Segal, Z., Rafi-Tari, S., 2004. Limbic-frontal circuitry in major depression: a path modeling metanalysis. NeuroImage 22, 409–418.

Shaw, M.E., Strother, S.C., Gavrilescu, M., Podzebenko, K., Waites, A., Watson, J., Anderson, J., Jackson, G., Egan, G., 2003. Evaluating subject specific preprocessing choices in multisubject fMRI data sets using data-driven performance metrics. NeuroImage 19, 988–1001.

Sirotin, Y.B., Das, A., 2009. Anticipatory haemodynamic signals in sensory cortex not predicted by local neuronal activity. Nature 457, 475–479.

Sodickson, D.K., Manning, W.J., 1997. Simultaneous acquisition of spatial harmonics (SMASH): fast imaging with radiofrequency coil arrays. Magn. Reson. Med. 38, 591–603.

Sorger, B., Dahmen, B., Reithler, J., Gosseries, O., Maudoux, A., Laureys, S., Goebel, R., 2009. Another kind of 'BOLD Response': answering multiple-choice questions via online decoded single-trial brain signals. Prog. Brain Res. 177, 275–292.

Strehl, U., Leins, U., Goth, G., Klinger, C., Hinterberger, T., Birbaumer, N., 2006. Self-regulation of slow cortical potentials: a new treatment for children with attention-deficit/hyperactivity disorder. Pediatrics 118, e1530–e1540.

Strother, S.C., 2006. Evaluating fMRI preprocessing pipelines. IEEE Eng. Med. Biol. Mag. 25, 27–41.

Strother, S.C., Anderson, J., Hansen, L.K., Kjems, U., Kustra, R., Siditis, J., Frutiger, S., Muley, S., LaConte, S., Rottenberg, D., 2002a. The quantitative evaluation of functional neuroimaging experiments: the NPAIRS data analysis framework. NeuroImage 15, 747–771.

Strother, S.C., Anderson, J., Hansen, L.K., Kjems, U., Kustra, R., Sidtis, J., Frutiger, S., Muley, S., LaConte, S., Rottenberg, D., 2002b. The quantitative evaluation of functional neuroimaging experiments: the NPAIRS data analysis framework. NeuroImage 15, 747–771.

Strother, S., LaConte, S., Hansen, L.K., Anderson, J., Zhang, J., Pulapura, S., Rottenberg, D., 2004. Optimizing the fMRI data-processing pipeline using prediction and reproducibility performance metrics: I. A preliminary group analysis. NeuroImage 23, S196–S207.

Thesen, S., Heid, O., Mueller, E., Schad, L.R., 2000. Prospective acquisition correction for head motion with image-based tracking for real-time fMRI. Magn. Reson. Med. 44, 457–465.

Turner, R., Le Bihan, D., Moonen, C.T., Despres, D., Frank, J., 1991. Echo-planar time course MRI of cat brain oxygenation changes. Magn. Reson. Med. 22, 159–166.

Vazquez, A.L., Noll, D.C., 1998. Nonlinear aspects of the BOLD response in functional MRI. NeuroImage 7, 108–118.

Vazquez, A.L., Fukuda, M., Tasker, M.L., Masamoto, K., Kim, S.G., 2009. Changes in cerebral arterial, tissue and venous oxygenation with evoked neural stimulation: implications for hemoglobin-based functional neuroimaging. J. Cereb. Blood Flow Metab.

Victor, J.D., 2005. Analyzing receptive fields, classification images and functional images: challenges with opportunities for synergy. Nat. Neurosci. 8, 1651–1656.

Voyvodic, J.T., 1999. Real-time fMRI paradigm control, physiology, and behavior combined with near real-time statistical analysis. NeuroImage 10, 91–106.

Wang, G.J., Volkow, N.D., Fowler, J.S., Cervany, P., Hitzemann, R.J., Pappas, N.R., Wong, C.T., Felder, C., 1999. Regional brain metabolic activation during craving elicited by recall of previous drug experiences. Life Sci. 64, 775–784.

Weiskopf, N., Veit, R., Erb, M., Mathiak, K., Grodd, W., Goebel, R., Birbaumer, N., 2003. Physiological self-regulation of regional brain activity using real-time functional magnetic resonance imaging (fMRI): methodology and exemplary data. NeuroImage 19, 577–586.

Weiskopf, N., Mathiak, K., Bock, S.W., Scharnowski, F., Veit, R., Grodd, W., Goebel, R., Birbaumer, N., 2004a. Principles of a brain-computer interface (BCI) based on real-time functional magnetic resonance imaging (fMRI). IEEE Trans. Biomed. Eng. 51, 966–970.

Weiskopf, N., Scharnowski, F., Veit, R., Goebel, R., Birbaumer, N., Mathiak, K., 2004b. Self-regulation of local brain activity using real-time functional magnetic resonance imaging (fMRI). J. Physiol. Paris 98, 357–373.

Weiskopf, N., Klose, U., Birbaumer, N., Mathiak, K., 2005. Single-shot compensation of image distortions and BOLD contrast optimization using multi-echo EPI for real-time fMRI. NeuroImage 24, 1068–1079.

Weiskopf, N., Sitaram, R., Josephs, O., Veit, R., Scharnowski, F., Goebel, R., Birbaumer, N., Deichmann, R., Mathiak, K., 2007. Real-time functional magnetic resonance imaging: methods and applications. Magn. Reson. Imaging 25, 989–1003.

Wolpaw, J.R., Birbaumer, N., McFarland, D.J., Pfurtscheller, G., Vaughan, T.M., 2002. Brain-computer interfaces for communication and control. Clin. Neurophysiol. 113, 767–791.

Yacoub, E., Hu, X., 1999. Detection of the early negative response in fMRI at 1.5 tesla. Magn. Reson. Med. 41, 1088–1092.

Yang, S., Ross, T.J., Zhang, Y., Stein, E.A., Yang, Y., 2005. Head motion suppression using real-time feedback of motion information and its effects on task performance in fMRI. NeuroImage 27, 153–162.

Yang, Z., LaConte, S., Weng, X., Hu, X., 2008. Ranking and averaging independent component analysis by reproducibility (RAICAR). Hum. Brain Mapp. 29, 711–725.

Yoo, S.S., Jolesz, F.A., 2002. Functional MRI for neurofeedback: feasibility study on a hand motor task. Neuroreport 13, 1377–1381.

Yoo, S.S., Guttmann, C.R., Zhao, L., Panych, L.P., 1999. Real-time adaptive functional MRI. NeuroImage 10, 596–606.

Yoo, S.S., Fairneny, T., Chen, N.K., Choo, S.E., Panych, L.P., Park, H., Lee, S.Y., Jolesz, F.A., 2004. Brain-computer interface using fMRI: spatial navigation by thoughts. Neuroreport 15, 1591–1595.

Yoo, S.S., O'Leary, H.M., Fairneny, T., Chen, N.K., Panych, L.P., Park, H., Jolesz, F.A., 2006. Increasing cortical activity in auditory areas through neurofeedback functional magnetic resonance imaging. Neuroreport 17, 1273–1278.

Zhang, X., Ross, T.J., Salmeron, B.J., Yang, S., Yang, Y., Stein, E.A., 2009. Realtime fMRI feedback: single subject task-related artifact. NeuroImage 47, S195.