

FUNCTIONAL MAGNETIC RESONANCE IMAGING

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Functional magnetic resonance imaging (fMRI) is a powerful technique for measuring the neural activity that underlies cognitive processes. It provides high spatial resolution compared with electroencephalography (EEG) and lesion studies and adequate temporal resolution on the order of seconds, and it accommodates a variety of cognitive tasks. fMRI relies on an indirect measurement of neural activity that is based on the link between local neuronal firing and cerebral blood flow. Because it is a noninvasive technique, it is an ideal tool for repeated measurements, such as longitudinal studies of brain function. These advantages as well as its widespread availability for research have made it a central tool for studies of brain-behavior relations.

MRI scanners create static magnetic fields that are about 30,000 to 80,000 times as strong as the Earth's magnetic field. The most common MRI scanners use field strengths of 1.5 T or 3 T, although the use of 7-T scanners for whole-brain functional studies is becoming possible (Poser, Koopmans, Witzel, Wald, & Barth, 2010). With increasing magnetic field, however, artifacts because of distortion and image loss near the boundary of brain tissue and sinuses become more difficult to control. These artifacts mostly affect the orbitofrontal cortex (OFC) and regions within the anterior and inferior temporal lobe. Improvements can be made using special shimming procedures (Balteau, Hutton, & Weiskopf, 2010), specialized pulse sequences for data acquisition (Weiskopf, Hutton, Josephs, & Deichmann, 2006; Weiskopf, Hutton, Josephs, Turner, & Deichmann, 2007), and distortion correction of functional

images (Hutton et al., 2002; Hutton, Deichmann, Turner, & Andersson, 2004; Yung-Chin, Ching-Han, & Tseng, 2009).

Functional neuroimaging, as well as other functional methods such as EEG (see Chapters 26 and 27 of this volume) and magnetoencephalography (MEG; see Chapter 29 of this volume), relies on correlational analyses whose interpretations are limited and must be made cautiously. Inferences are made about the association between activity in certain brain areas with cognitive processes that are engaged by a pre-defined task. A statistical correlation of this type does not allow researchers to conclude that the observed activity is necessary for the cognitive operation targeted by the task design. It is possible to say, however, that the task manipulation was causal for the observed brain activity (Buchsbaum, 2009; Weber & Thompson-Schill, 2010). This difference is crucial when interpreting fMRI research findings. For example, we can report that stimulus A caused increased activity in a certain brain region compared with stimulus B, but we cannot claim that this increased activity is necessary for processing stimulus A, and we cannot claim that it caused behavioral differences observed between the two stimuli. In addition, the experimenter can often not fully control a participant's cognitive processes during an experiment—for example, a visual memory task or a navigational task may also engage language processes that may not be fully matched in a control condition. Even well-controlled tasks do not provide conclusive evidence that differential brain activity is related to the specific cognitive operation under study.

Another limitation of fMRI studies is that some brain areas may be activated but not necessary for the cognitive process of interest. For example, the hippocampus is activated in many working memory studies, but hippocampal lesions cause impairments only on specific subtypes of working memory tasks (Cashdollar et al., 2009; Nichols, Kao, Verfaellie, & Gabrieli, 2006; Piekema, Kessels, Mars, Petersson, & Fernandez, 2006; Piekema, Kessels, Rijpkema, & Fernandez, 2009). This suggests that some brain areas may be involved in a process and may be part of task-relevant networks but may not perform necessary computations. fMRI can therefore provide information about regional involvement that cannot be easily obtained in lesion studies and provide information about human brain functions that complements the information from animal studies. Its results, however, cannot be taken alone without considering the wider context of the relevant literature from other modalities and populations. In particular, information from lesion studies can be effectively combined with fMRI data (e.g., Badre, Hoffman, Cooney, & D'Esposito, 2009; D'Esposito, Cooney, Gazzaley, Gibbs, & Postle, 2006; Kishiyama, Yonelinas, & Knight, 2009). If a region is activated in healthy subjects during a task and lesions of this region cause impaired performance, then researchers can be more confident that this region supports necessary cognitive processes.

These considerations imply that it is not valid to infer the cognitive operation performed by participants from the activation of brain areas (a practice known as *reverse inference*; D'Esposito, Ballard, Aguirre, & Zarahn, 1998; Poldrack, 2006; Van Horn & Poldrack, 2009). For example, activation of the amygdala in a task cannot be ascribed to negative emotions, such as fear, despite the common activation of the amygdala in aversive conditioning tasks (Sehlmeyer et al., 2009), because amygdalar activations have also been found for other types of tasks (Rademacher et al., 2010; Walter, Abler, Ciaramidaro, & Erk, 2005). This may seem an obvious logical error, but conclusions of this kind are unfortunately not uncommon (Poldrack, 2006).

When the limitations of fMRI are taken into account, it offers a range of excellent methods to help answer questions related to functional

specialization and integration within the brain. For an excellent review on current developments in neuroimaging, see Bandettini (2009); for a summary of the neurophysiological basis of fMRI and the resulting limitations, see Logothetis (2008).

CHARACTERISTICS OF THE SIGNAL: TEMPORAL AND SPATIAL RESOLUTION

To understand the temporal limitations of the fMRI signal, it is necessary to look at its source (for an excellent introduction, see Huettel, Song, & McCarthy, 2008). fMRI measures brain activity indirectly by recording changes in blood flow that are linked to neural activity. The change in blood flow is called the *hemodynamic response*; it is based on increased metabolic demands of active neurons leading to increased blood flow in local capillaries. This leads to a change in blood oxygenation level, which can be detected because oxygenated and deoxygenated hemoglobin have different magnetic properties. The measured signal is called blood-oxygenation-level-dependent (BOLD) response. Cortical neurons can respond to stimuli as early as tens of milliseconds following a sensory stimulus, but the vascular response develops more slowly. It reaches its peak about 5 s to 6 s after a brief neuronal response and goes back to baseline within about 12 s to 16 s (Figure 28.1; Aguirre, Zarahn, & D'Esposito, 1998; Bandettini, Wong, Hinks, Tikofsky, & Hyde, 1992; Boynton, Engel, Glover, & Heeger, 1996). The delay between neural and vascular signals imposes constraints on the study design because events that are presented in close temporal succession cause a summation of the BOLD response, making it more difficult to ascribe activations to single events.

There are two main approaches to account for this hemodynamic delay when analyzing fMRI data (see Figure 28.2). The first solution is to use slow-task paradigms. Researchers use blocked designs with block durations of 20 s to 40 s, during which many stimuli of the same condition are presented in rapid succession. This approach leads to good signal-to-noise ratio, but many cognitive tasks cannot be adapted to long blocks. Researchers may want to examine brain responses to rare events, or they may want to classify trials *a posteriori*. For example, if we

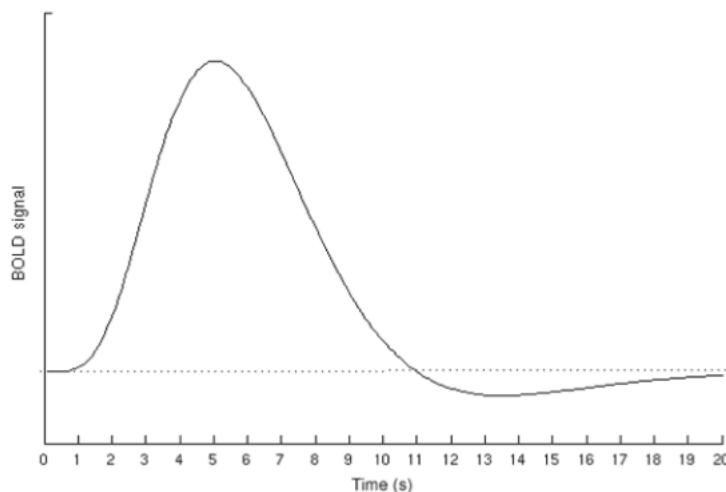


FIGURE 28.1. Schematic representation of the hemodynamic blood-oxygen-level-dependent (BOLD) response. The signal peaks at about 5 s to 6 s after the sensory or behavioral event (at Time 0).

want to dissociate successful memory retrieval from retrieval failure, we need to be able to separate individual trials on the basis of participants' responses (Buckner et al., 1998; Wagner et al., 1998). Often, researchers want to separate short individual phases of a task (Courtney, Ungerleider, Keil, & Haxby, 1997; D'Esposito, Postle, Jonides, & Smith, 1999). Blocked designs do not give satisfactory results in these cases. In addition, estimation of the shape of the hemodynamic response in long blocks is poor. Some of the disadvantages of blocked designs can be avoided by using random stimulus presentation with long intertrial intervals (ITIs); this allows a full sampling of the hemodynamic response. Long ITIs, however, limit the number of stimuli that can be presented in a session of given length, thereby decreasing power (Dale, 1999), and make it more difficult for participants to sustain attention to the task. Researchers cannot exclude the possibility of subjects performing other cognitive operations in the period between stimulus presentations.

The second, currently most common, approach to dealing with the slow hemodynamic response uses random stimulus presentation at variable (*jittered*) ITIs (see Figure 28.2). This solution, called *event-related design*, allows the shape of the hemodynamic response to be estimated despite summation effects (Rosen, Buckner, & Dale, 1998). Its advantages lie in more flexible task presentation that

allows randomizing stimuli and trials, selecting specific time windows during a task (such as delay periods in a working memory task), and classifying trials on the basis of participants' responses. Depending on the experimental hypotheses, a mixed block and event-related design can also be used (Visscher et al., 2003). For a mixed design, trials are jittered and randomly presented within task blocks that alternate with control blocks. This approach can distinguish brain activity that is sustained during an ongoing task from activity elicited by single trials of the task. For example, two types of cognitive processes during memory retrieval are related to an ongoing *retrieval mode* and to successful retrieval of individual items (Donaldson, Petersen, Ollinger, & Buckner, 2001). For a more detailed comparison of available scanning designs, see Amaro and Barker (2006).

The sampling rate of the MRI signal also needs to be considered. The sampling unit for the timing of fMRI data is called *repetition time* (TR). Its duration is defined by the time that is necessary for the acquisition of one functional volume and ranges from a few hundred milliseconds to several seconds. Each functional volume consists of a number of sequentially acquired slices. As a result of sequential acquisition, each slice is measured only once per TR, and the signal has to be interpolated. Depending on the task design, it may be desirable to get an accurate estimate of the shape of the hemodynamic response,

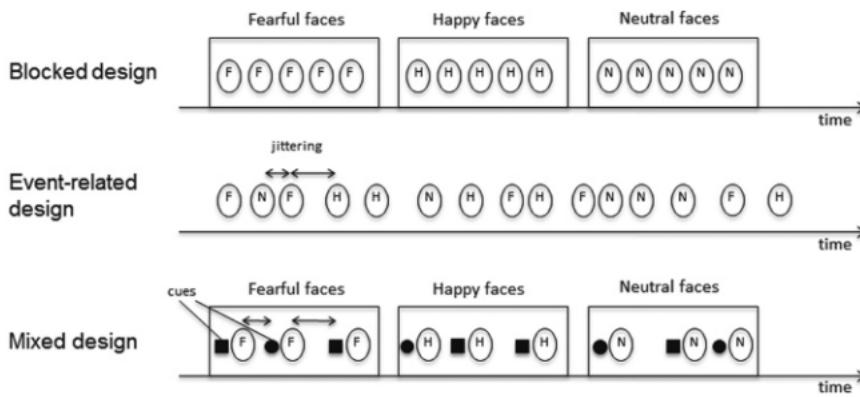


FIGURE 28.2. Schematic representation of blocked, event-related and mixed designs. Top row: In a blocked design, the events of interest (here: presentation of fearful, happy and neutral faces; designated F, H, and N) are separated into blocks of trials. The hemodynamic response is estimated per block. Middle row: In an event-related design, the events of interest are presented in a random sequence. To separate the hemodynamic response between events, individual trials are presented with a temporal jitter. Bottom row: In a mixed design, there are blocks of separated conditions (here: fearful, happy, and neutral faces) within which there are separable, temporally jittered events of interest (here: two types of cues that indicate the task for subjects, e.g., rate faces based on emotion or attractiveness).

and the TR should be kept short to provide more time points for interpolation. This does not increase the temporal resolution of the experiment because the slow hemodynamic response remains unchanged. Short TRs will limit the extent of spatial coverage because the acquisition time for a single slice cannot be decreased beyond a certain limit. With task designs that use longer ITIs or blocks, however, the TR can be extended to several seconds while still providing a sufficient estimate of the hemodynamic response. In practice, most event-related experiments use TRs of 1.5 s to 3 s. If the shape of the hemodynamic response is taken into account in the task design, even brief stimuli of < 50-ms duration can be detected (Savoy et al., 1995).

The spatial resolution of fMRI data is specified as three-dimensional voxel sizes (e.g., $3 \times 3 \times 3 \text{ mm}^3$). The first two values specify the in-plane dimension of a slice, and the third value specifies the slice thickness. Choosing the spatial resolution for a study depends on the research question and on a trade-off between spatial-temporal resolution and coverage that results because slice acquisition times increase with increasing spatial resolution. In other words, if we want to maintain adequate temporal resolution, fewer

slices can be acquired per TR and spatial coverage decreases. This is acceptable if we are interested in a predefined region of cortex, such as the visual occipital cortex (such studies often use voxel sizes of $1.5 \times 1.5 \times 1.5 \text{ mm}^3$). For experiments that require whole-brain coverage, however, voxel sizes increase and a resolution of $3 \times 3 \times 3 \text{ mm}^3$ is widely used. An additional consideration is the change in signal-to-noise ratio with decreasing voxel size (Tabelow, Pięch, Polzehl, & Voss, 2009). The MRI signal depends on the changing amount of deoxygenized hemoglobin per voxel. Smaller voxels yield smaller changes and therefore lower signal-to-noise ratio. Whether this is acceptable may depend on assumptions about the brain region that is being studied. If we assume that a large number of neurons per millimeter will fire in response to our stimulus, the measured brain signal will be larger and a smaller voxel size may be sufficient. On the other hand, if we expect activity of a smaller number of specialized neurons, the measured change will be smaller and larger voxels may be required to dissociate the signal from noise.

Spatial resolution is further decreased during data analysis by common techniques such as smoothing and normalization. *Smoothing* refers

to the use of a three-dimensional Gaussian filter (usually several voxels in width) to average adjacent voxels, resulting in a spread of activity across neighboring voxels. Its main advantage lies in improved signal-to-noise ratio by taking into account correlations in activity between adjacent voxels. Normalization techniques transform individual subjects' data to a common template to facilitate interindividual comparisons and statistical group tests. The difficulty of capturing individual anatomical differences in this step further reduces the final spatial resolution in our statistical tests.

To summarize, fMRI has the potential for both relatively high temporal (hundreds of milliseconds) and spatial (millimeter) resolution. There is a trade-off between high resolution in the spatial and temporal domains and spatial coverage; optimal settings need to be determined for each experiment on the basis of the research question and underlying assumptions about brain activity in the regions of interest.

Statistical Analysis of Regional Specialization

The most common type of fMRI study seeks to determine whether particular parts of the brain are functionally specialized. This is achieved by identifying which regions of the brain become active in response to certain stimuli or tasks. There are many analysis packages designed for MRI data, all of which rely on a statistical comparison of the condition of interest with a control condition. Generally, the raw data from the scanner are processed to some extent before being entered into the statistical analysis (this phase is often called *preprocessing*). These steps deal with common characteristics of data acquisition and analysis goals. Good practice requires that the quality of raw data be assessed before processing. Several automated scripts are available to check and possibly correct for instances of bad data, for example, caused by signal loss on single slices. After data quality has been established, common preprocessing techniques address the following issues: the difference in timing of slice acquisition in areas of the brain that are acquired at different times with respect to the volume acquisition (TR), correction for small head motions (realignment), correction for field inhomogeneities

(unwarp), transformation of each subject's data into a common anatomical space to enable group analysis (normalization), and spatial smoothing.

The statistical analysis of preprocessed data depends on the task design and the research questions. In most experiments, some type of group analysis is performed combining individuals' statistical brain maps, although for some research questions, individual subjects' data are used to obtain better functional localization. For example, research on the visual system often employs retinotopic mapping using functional localizers for each individual because retinotopic maps differ substantially across individuals (McFadzean, Condon, & Barr, 1999; Tootell et al., 1998). Functional localizers are used to identify the voxels that are activated by a pre-defined stimulus or task that is designed to engage the functional system under study. For group analyses, studies suggest that using more than the most commonly reported number of 12 to 16 subjects substantially increases reliability (Bennett & Miller, 2010; Thirion et al., 2007). Most analysis techniques test how well the measured signal fits the expected shape of the hemodynamic signal at a set of specified onsets for each condition, commonly using a general linear model (see Volume 3, Chapter 9, this handbook) and generating a statistical map for each subject. For a group analysis, these individual maps are then tested in a random-effects model for applicability of the findings to the population from which subjects were drawn. An important caveat for all group analyses, independent of the analysis method, is that participants for most studies are young, healthy students, and the results cannot be assumed to reflect other groups in the population. Activation results of group analyses are reported on the basis of normalization to a standard anatomical template. The most reliable way to identify the areas of activation is to compare activation maps to brain atlases, a technique that requires particular care on the part of the researcher (Devlin & Poldrack, 2007). Alternatively, researchers may be interested in predefined functional or anatomical regions. These can be analyzed using region-of-interest (ROI) analyses. The region is defined either anatomically, usually by manually tracing the borders of the region on anatomical images, or functionally by using functional localizers.

The regions that are identified using either of these approaches are then selectively analyzed for activity in the main task of interest.

Advantages of the ROI method are higher signal-to-noise ratio by summing over a number of voxels, and reduction of the problem of multiple comparisons (see the following paragraphs). Its disadvantage lies in the difficulty of ROI definition.

Anatomical definition is labor intensive and may differ among researchers. Additionally, anatomical boundaries may not match the functional system that is being studied. Functional ROIs, on the other hand, increase the likelihood of evaluating the targeted functional system when the functional localizer task is chosen carefully. For example, a study in our laboratory used a functional localizer to define face- and scene-selective regions and then independently investigated reward-related top-down effects on these regions during working memory processing (Krawczyk, Gazzaley, & D'Esposito, 2007).

In addition to analyses based on contrasts of two or more conditions, it is possible to include parametric analyses that examine the effects of a trial-wise covariate on functional activity. The parametric regressor can be based directly on behavior such as reaction times on each trial, or it can test a computational model of functional activity (for an introduction to computational models, see Volume 2, Chapters 20 and 21, this handbook). The combination of computational modeling with fMRI experiments offers exciting possibilities for testing hypotheses about brain function (Deco, Jirsa, Robinson, Breakspear, & Friston, 2008; Horwitz & Smith, 2008). For example, many studies have demonstrated that the human striatum processes rewards in a manner consistent with findings from animal experiments that have identified brain substrates of prediction errors that are described in computational theories of value learning (e.g., O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003; Palminteri, Boraud, Lafargue, Dubois, & Pessiglione, 2009; Valentin & O'Doherty, 2009). Computational models of learning can provide predictions of optimal choice behavior and theories of brain function that can integrate human and animal studies into a common framework and inform research on clinical disorders (Dayan, 2009; Dayan &

Daw, 2008; Gläscher & O'Doherty, 2010; Huys & Dayan, 2009). The computational approach can be further enhanced by combining it with genetic and pharmacological methods (Krugel, Biele, Mohr, Li, & Hecker, 2009; Pessiglione, Seymour, Flannigan, Dolan, & Frith, 2006). Moreover, computational models can also be used to inform studies of the functional integration across brain areas (den Ouden, Daunizeau, Roiser, Friston, & Stephan, 2010; Kahnt et al., 2009).

A fundamental trade-off exists in the analysis of fMRI data between accepting Type I and Type II statistical errors. Type I errors occur when the null hypothesis (that there is no difference in brain activity between two conditions) is falsely rejected, that is, we conclude that there is activity where there is none. Type II errors occur when the null hypothesis is accepted despite a real difference in activation between the conditions. fMRI studies mostly focus on avoiding Type I errors, although some researchers have pointed out the shortcomings of this strategy (Lieberman & Cunningham, 2009). The most common approach to reducing Type I errors is a correction for the multiple statistical comparisons that are performed when analyzing fMRI data. Because a whole-brain scan generates a large number of observations ($>10,000$) that are tested for statistical significance, the alpha values of the statistical test need to be adjusted. If researchers are interested in testing hypotheses using only a limited number of predefined brain regions, then an ROI analysis can be performed. Alpha value correction then only requires correcting for the number of observations within the ROI because a smaller number of independent statistical tests are conducted relative to a map-wise analysis. No inferences about activations in the rest of the brain can therefore be made. ROI analyses can, however, be combined with a stringent whole-brain correction to achieve the sensitivity of smaller volume approaches while permitting inference about brain regions outside the focus of the study.

There are several ways to adjust alpha values, for example, by using a family-wise error rate correction. There is currently no gold standard for error correction in the field. Note that a reduction of Type I errors means an increase of Type II errors. How

stringent a correction is applied will depend on the type of question being addressed. Another approach to reducing Type I errors is cluster-size thresholding, which defines a minimum number of contiguous voxels that have to be activated for the cluster to be considered significant (Forman et al., 1995; Xiong, Gao, Lancaster, & Fox, 1995). Cluster-size thresholding is valid because the probability of activated clusters occurring because of random chance is low, much lower than the probability of a Type I error on single voxels.

Because there is a greater emphasis on avoiding Type I than Type II errors in most fMRI studies, researchers must be careful about overinterpreting negative findings (i.e., “null results”) as evidence of inactivity in a brain region during performance of a task. If a brain region’s inactivity is crucial for the hypothesis being evaluated, a power analysis can be used to estimate the required power to detect activity in that region (Hayasaka, Peiffer, Hugenschmidt, & Laurienti, 2007; Mumford & Nichols, 2008; Van Horn, Ellmore, Esposito, & Berman, 1998; Zarahn & Slifstein, 2001). Power can be increased, for instance, by increasing the number of trials per condition or scanning more subjects (Bennett & Miller, 2010; Desmond & Glover, 2002; Thirion et al., 2007).

Many fMRI studies test hypotheses about the relation between brain activity and behavior or psychological constructs such as personality and mood. A common method involves extracting a measure of average task activity in a region or in a representative voxel from an activation cluster (usually the voxel with the maximum response, *peak voxel*). This value can then be tested to examine correlations with interindividual behavioral measures of interest. For example, researchers have assessed whether amygdala activity in response to emotional faces correlates with an individual measure of anxiety (Stein, Simmons, Feinstein, & Paulus, 2007). Alternatively, the behavioral measure of interest can be included as a covariate in a statistical analysis of whole-brain data, without regional preselection. Both approaches are valid tools for investigating interindividual differences. Recently, however, criticism has arisen concerning invalid double-dipping methods (Baker, Hutchison, & Kanwisher, 2007; Kriegeskorte, Simmons, Bellgowan, & Baker, 2009;

Vul, Harris, Winkielman, & Pashler, 2009): circular analyses that use the same data to identify a set of voxels that show an effect and then to compute the magnitude of the effect on these pre-selected voxels. In statistics, this is known as a nonindependence error. These errors substantially overestimate statistical correlations because a correlation analysis relies on the inclusion of the full data set to produce meaningful values. If one excludes data (voxels) that do not show the correlation, the correlation analysis will be biased toward significance. Care must therefore be taken to avoid this type of error, either by using one of the approaches discussed thus far, in which the voxels of interest are determined from a different task contrast, or by using a cross-validation method. The latter method involves selecting brain regions from a correlation analysis on a subset of the data (e.g., half of the runs) and computing the magnitude and significance of the effect on another subset of the data (e.g., the other half of the runs), or by excluding a number of subjects from the region selection or analysis (Esterman, Tamber-Rosenau, Chiu, & Yantis, 2010). Confounds of this type can also occur in analyses that do not correlate brain activity with behavior or personality. For example, in ROI or pattern classifier analyses (see the section Multivariate Pattern Analysis), researchers also need to be vigilant to avoid these unintentional biases (Kriegeskorte et al., 2009).

Functional Connectivity Analyses

In contrast to univariate approaches toward analyzing fMRI data, which are designed to test functional regional specialization, multivariate approaches are designed to test functional integration in networks of connected brain regions. Unfortunately, the term “network” is often used to describe a group of brain regions that are coactive on a statistical map produced by univariate analysis. Coactivity does not indicate that these regions are connected and form a functional network. For example, two regions can both be activated by stimulation relative to rest, but we cannot conclude that there are direct pathways connecting the regions because both may be influenced by a third region. In addition, coactivation patterns provide no evidence for the direction of the

effects. Region A could affect processing in region B or vice versa, or there may be no asymmetric influence of one region on another.

Researchers can choose from among a variety of techniques for identifying functional networks in fMRI data sets. All such analyses are motivated by the idea that complex cognitive operations do not rely on one brain area alone; rather, they rely on interactions among computations carried out in several areas (Friston, 2002; Mesulam, 1990). These methods are based on the covariance of activation levels in different brain regions, that is, on correlated temporal patterns of activation and deactivation. Two analytic approaches can be distinguished: functional and effective connectivity methods (for an introduction, see Friston, 1994). Effective connectivity analyses such as structural equation modeling, dynamic causal modeling, and Granger causality rely on *a priori* models of expected causal relations among activity in a set of selected regions (Friston, Harrison, & Penny, 2003; Penny, Stephan, Mechelli, & Friston, 2004; Stephan et al., 2010). Functional regions can be selected on the basis of previously published studies or on the results of activation analyses from the same experiment. The models are informed by prior knowledge about anatomical connections between the regions and can be combined with tractography measures such as diffusion tensor imaging (Rykhlevskaia, Gratton, & Fabiani, 2008). In general, the number of existing anatomical connections and possible causal models is very high, and a selection based on the assumed importance of each pathway is needed to simplify the model (Ramsey et al., 2010). These model-based methods are powerful but sensitive to the specifications of the *a priori* model. Functional connectivity analyses, on the other hand, are model-free approaches to identifying brain areas whose activity covaries over time, that is, they do not require *a priori* hypotheses about how brain regions interact. Therefore, they are well suited for exploratory analyses, such as identifying networks that are involved in specific cognitive processes. Analyses can be based on activation patterns (McIntosh, Chau, & Protzner, 2004; Roebroeck, Formisano, & Goebel, 2005) or coherence in periodic temporal fluctuations, that is, in the frequency domain (Havlicek,

Jan, Calhoun, & Brazdil, 2009; Kayser, Sun, & D'Esposito, 2009). Both model-free and model-based connectivity analyses are potentially vulnerable to confounds introduced by the indirectness of the fMRI measurement, such as variability in the shape and delay of the hemodynamic response between regions. Reliable analysis is still possible, however, and phase information (i.e., temporal periodicity) is not affected (David et al., 2008; Deshpande, Sathian, & Hu, in press). The interpretation of connectivity results should always be made cautiously because the method is indirect and, in the case of effective connectivity, because it depends on a correct *a priori* model. In combination with information about the influence of specific brain regions on processing in other areas as gained through lesion and transcranial magnetic stimulation (TMS) studies of human subjects and results from animal models, however, connectivity analyses of fMRI data can provide relevant evidence on the basis of noninvasive studies in healthy participants.

One of the main applications of model-free connectivity analyses is the investigation of the brain's resting state. Interest in intrinsic brain activity while an individual is not performing a task arose because researchers observed task-related activity decreases compared with resting control conditions (Gusnard & Raichle, 2001). This observation gave rise to the hypothesis that there is a baseline state or *default mode* with which all task-related activity can be compared and that this state is relevant to understanding the brain because of the large energy consumption associated with it (Gusnard & Raichle, 2001). Thus, several studies of the resting-state network have used a *reverse cognition subtraction* strategy in which rest is contrasted with cognitive tasks, but most current studies use functional connectivity approaches (Auer, 2008; Damoiseaux & Greicius, 2009; Rogers, Morgan, Newton, & Gore, 2007; Voss & Schiff, 2009). These studies found a consistent network of regions that are active at rest, including posterior cingulate, medial prefrontal, and parietal regions. The idea that the *default mode network* is of special interest in understanding brain function has been questioned (Morcom & Fletcher, 2007), and discussions of its functional significance are ongoing. However, it is of practical use for investigations

of clinical populations (Broyd et al., 2009; Buckner & Vincent, 2007; Greicius, 2008) and can provide additional evidence for interpretation of functional task data (Wang et al., 2010). In addition to providing evidence on the default mode network, resting-state data can reveal other intrinsic networks that can reflect tasks performed before rest, such as working memory (Pyka et al., 2009), long-term memory (Albert, Robertson, Mehta, & Miall, 2009; Tambini, Ketz, & Davachi, 2010; van Kesteren, Fernández, Norris, & Hermans, 2010), and category viewing (Stevens, Buckner, & Schacter, 2010). Analyses of resting-state data can also be based on prior knowledge about task-related connectivity and enable further differentiation of known networks (Dosenbach et al., 2007).

Multivariate Pattern Analysis

Information is not only contained in the regional distribution of activation clusters and in connections among interacting brain regions but also in relatively small-scale patterns of activated and deactivated single voxels. Standard univariate analysis techniques do not reveal this information because each voxel is analyzed independently and because results are displayed as large regional activations; thus, differences between functional representations within a region can remain undetected (Haxby et al., 2001). In contrast, multivariate techniques utilize distributed patterns of small-scale activations to infer the differential representation of the processes being studied, for example, different stimulus categories. Because the brain codes information on many scales down to the level of individual neurons, pattern classification is limited by the spatial resolution of fMRI and benefits from high-resolution scanning techniques (e.g., Diana, Yonelinas, & Ranganath, 2008; Kriegeskorte, Formisano, Sorger, & Goebel, 2007), although the same resolution trade-offs that occur in activation studies need to be considered.

As with other fMRI analyses, there are several approaches to pattern analysis, generally based on training a decoder to classify the conditions on the basis of their (noisy) distributed activation patterns. To assess whether these patterns contain true information about the conditions, the classifier is then

tested on its ability to predict each condition from the brain data. Because of the problem associated with nonindependent analyses, the data need to be split into a training set and a test set, for example, by using alternating runs for training and testing. To reduce the amount of data, it is advantageous to pre-select a set of voxels that are responsive to the conditions of interest before training the classifier. This selection must be made independently of the test set (Kriegeskorte et al., 2009). The results obtained from evaluating the classifier on the test set are usually reported as percent accuracy, and statistical tests are conducted to assess whether the classification results are better than chance. (For an introduction to the most common classification methods, see Mur, Bandettini, & Kriegeskorte, 2009; Norman, Polyn, Detre, & Haxby, 2006; and Pereira, Mitchell, & Botvinick, 2009.)

Pattern recognition is a promising approach that can be used to investigate a large number of scientific questions. Researchers have addressed cognitive operations as diverse as covert intention (Haynes et al., 2007), economic valuation (Clithero, Carter, & Huettel, 2009; Grosenick, Greer, & Knutson, 2008), complex visual categorization (Walther, Caddigan, Fei-Fei, & Beck, 2009), primary and secondary sensory processing (Beauchamp, LaConte, & Yasar, 2009; Okada et al., 2010; Seymour, Clifford, Logothetis, & Bartels, 2010), conscious perception (Haynes & Rees, 2005), cognitive control (Esterman, Chiu, Tamber-Rosenau, & Yantis, 2009), emotional states (Fu et al., 2008), memory retrieval (Polyn, Natu, Cohen, & Norman, 2005), clinical impairments (Yoon et al., 2008), semantic categories (Mitchell et al., 2008), and spatial navigation (Rodriguez, 2010). Multivariate approaches allow the investigation of questions that cannot be answered by univariate analysis, such as detecting reactivation or maintenance of specific patterns over time and detecting the content of novel stimuli on the basis of features extracted from a training set of different stimuli (Kay, Naselaris, Prenger, & Gallant, 2008; Mitchell et al., 2008). The available analytic methods are continually developing (e.g., Jin et al., 2009; Kuncheva & Rodríguez, 2010) and will continue to gain importance in many research areas.

Real-Time fMRI Analysis

Because fMRI studies generate large data sets, standard experiments are analyzed after the scanning is completed (off-line). A particular fascination and challenge lies in recent developments toward enabling real-time (online) analysis of functional data while the participant or patient is being scanned. Real-time monitoring of brain states could be used for (a) subject- and time-specific stimulus presentation (e.g., present certain images only if region A shows high activity), (b) neurofeedback in healthy populations to help elucidate brain function (if participants increase or decrease activity in region A, do they make fewer or more errors on the task?), or (c) neurofeedback in clinical populations (e.g., teach patients to control pain processes; deCharms et al., 2005). In the past decade, there has been growing interest in this methodological approach, and several groups have demonstrated that participants can learn to control the level of activation in a specific region when they receive real-time feedback (for reviews, see deCharms, 2007; Weiskopf et al., 2004; Weiskopf, Sitaram, et al., 2007). Feedback is usually determined by the level of activity in an ROI and provided within seconds after the BOLD change, although more complex patterns can be used (Papageorgiou, Curtis, McHenry, & LaConte, 2009). Clinical interest is mostly focused on two applications: (a) enabling communications with patients unable to communicate in other ways and (b) helping patients to control emotion and attention processes (Birbaumer et al., 2009; Sorger et al., 2009).

Combining fMRI With Genetic and Pharmacological Approaches

fMRI provides measures of brain activity on several levels: small-scale patterns of local activity, large-scale regional specialization, and functional networks. It cannot distinguish neural systems on the basis of molecular properties such as transmitter and receptor expression. Combining fMRI with methods that are designed to investigate these systems holds enormous promise for understanding brain function underlying complex cognition. Two approaches have gained increasing importance in the past decade: imaging genetics and pharmacological imaging. As a

noninvasive approach, imaging genetics relies on correlating interindividual genetic variation with measures of brain activity. Pharmacological imaging investigates the effect of central nervous system-active drugs on brain activity.

The primary interest in imaging genetics studies lies in the investigation of interindividual differences (Hariri, 2009). There is a large degree of variation between individuals on many cognitive and emotional measures, and the contribution of genetic variation to these behaviors and to stable personality traits has long been a matter of speculation and the object of indirect investigations such as twin studies. Developments in the field of molecular biology in the past 15 years have now made it possible to directly assess how participants differ in specified genes and how these differences affect brain functioning. In an imaging genetics study, participants are typically genotyped for one or two common genetic variants (polymorphisms) that are hypothesized to affect behavior or the neural processing that underlies the cognitive process of interest. Individuals can be genotyped beforehand and then be invited to participate in the study on the basis of their genotype, or they can be scanned first and genotyped afterward. The advantages of the first method are that the group size of each genotype can be chosen (results are possible with as few as 12 subjects per group) and that the groups can be matched on age and other variables. Its disadvantages lie in practical matters such as participants having to come to the research site twice, which increases the dropout rate.

The contribution of genetic approaches to the understanding of physiological variation in specific brain systems will increase with better understanding of the functional significance of identified polymorphisms (Green et al., 2008). The physiological changes caused by many known polymorphisms are still unclear. For example, even when there is evidence that a polymorphism causes increased expression of a presynaptic transporter that is involved in reuptake of a transmitter from the synaptic cleft, postsynaptic adaptations to this change in transmission (such as receptor up- or downregulation) can affect the system as a whole and may counteract the primary effect of the

genetic variation. These possibilities have to be considered in the interpretation of any imaging genetics study. In spite of these limitations, however, genetic analysis has already made significant contributions to understanding some brain systems (e.g., prefrontal function; Egan et al., 2001) and will only gain in importance with increased understanding of the effects of individual genetic polymorphisms. It will also become increasingly important to include several polymorphisms that affect the same processes (e.g., Bertolino et al., 2008, 2009; Caldú et al., 2007; Passamonti et al., 2008; Smolka et al., 2007).

Pharmacological imaging directly investigates the contribution of a particular brain system to behavioral and neural processes. Participants either receive placebo or a drug that increases or decreases synaptic transmission in a specified way. They are usually scanned at the expected time of peak drug effect, although it is possible to test the effect of prior drug exposure on brain activity in the drug-free state depending on the experimental hypothesis. For example, researchers can test whether drug exposure during picture viewing affects emotions or memories during reexposure to these pictures. This approach avoids possible confounds arising from drug effects on local vasculature or general cardiovascular effects. Pharmacology can also be combined with genetics, behavioral, and other methods to achieve a more detailed understanding of a cognitive system (Honey & Bullmore, 2004). For example, dopaminergic drugs affect prefrontal function differentially depending on participants' baseline working memory capacity and genotype (Apud et al., 2007; Gibbs & D'Esposito, 2006; Kimberg & D'Esposito, 2003; Mattay et al., 2003).

Data Sharing and Publishing Standards

fMRI is a relatively young and dynamic method that is continually changing, refining the way studies are conducted and published. From the early days, debates on data sharing have been ongoing (Marshall, 2000; Van Horn et al., 2001). To date, it is still the exception, not the norm, although several public databases exist (<https://ida.loni.ucla.edu/login.jsp>; <http://central.xnat.org/app/template/Index.vm>; <http://sumsdb.wustl.edu/sums/index.jsp>; <http://www.rotman-baycrest.on.ca/index.php?section=532#Overview>; and <http://www.fmridc.org/f/fmridc>, which is not accepting any new data but retains a large number of data sets). In addition to databases of raw data, there are also efforts to create databases of functional activation coordinates, for example <http://brainmap.org> (for an overview and comparison, see Derrfuss & Mar, 2009). The applicability and usefulness of data sharing for functional studies of the human brain have been demonstrated (Biswal et al., 2010; Van Horn & Ishai, 2007). The advantages of data sharing lie in the possible combination of data collected at many institutions into large-scale analyses (Kober & Wager, 2010) and in the availability of existing data sets for reanalysis when new techniques become available. Maintaining a large database of raw data, however, requires substantial investments, such as dedicated public funding, and requires researchers' cooperation in uploading data and detailing data-collection procedures. There are also challenges arising from the number of analysis packages and from differences in data structuring and labeling across institutions (Hasson, Skipper, Wilde, Nusbaum, & Small, 2008; Small, Wilde, Kenny, Andric, & Hasson, 2009). The Biomedical Informatics Research Network maintains a database and also offers quality control information and tips on how to conduct multicenter studies (see <http://www.birncommunity.org>).

As in other fields of science, adequate description of the study and analysis protocol is necessary upon publication to ensure transparency of the methods and to enable replication by other researchers. In fMRI, there is special need for detailed methods sections because of the multitude of acquisition and analysis protocols used at different institutions. Some suggestions have been made concerning standards for reporting in the literature, both for methods sections (Poldrack et al., 2008) and for anatomical description of activation results (Devlin & Poldrack, 2007). Researchers should always be aware of these issues when designing, analyzing, and reporting their experiments.

ETHICAL CONSIDERATIONS

With the proliferation of fMRI experiments and the resulting increase in knowledge about the human

brain, fMRI is having an impact on society that raises several ethical questions. The basis of almost all of these issues is the right to what has been called *mental privacy* or *brain privacy* (Alpert, 2007; Farah, Smith, Gawuga, Lindsell, & Foster, 2009). Advances in imaging techniques and analysis methods, such as pattern analysis, are raising the possibility that private thoughts and emotions are becoming accessible to others (Farah et al., 2009; Haynes & Rees, 2006). Even if the current state of the field does not yet support the extraction of reliable information about a single subject's cognitive processes, there is reason to assume that the field will progress to a point at which these issues become problematic. As scientists, we are expected to participate in ethical debates and inform society about developments in our area of specialization (Illes et al., 2010). Several issues are being discussed: privacy issues arising from the use of fMRI for commercial purposes, legal issues relating to lie detection applications, and considerations of the implications of measuring brain activity in patients who are in a locked-in or vegetative state.

Businesses in the field of neuromarketing have become interested in the promise of fMRI for opening a window into the minds of consumers, revealing their hidden preferences and reactions to various forms of product presentation (Ariely & Berns, 2010; Lee, Broderick, & Chamberlain, 2007). Several ethical concerns need to be addressed with respect to these commercial enterprises (Murphy, Illes, & Reiner, 2008). First, participants in these studies are not protected in the same way as participants at research institutions, where experiments are monitored by institutional review boards. A second consideration is damage to the public's understanding of science that can arise from overinterpretation of research findings and overstatement of commercial claims (Murphy et al., 2008). There is considerable potential for influencing public opinion; a notorious example is an experiment on political preferences that was published in the *New York Times*, outside of the peer-review process (Iacoboni et al., 2007), and whose overinterpretation caused an outcry from the imaging community (Aron et al., 2007; "Mind Games," 2007).

There are also ethical and legal issues related to the use of fMRI (and other functional methods such

as event-related potentials) in lie detection. Two main points need to be considered: Are lie detection techniques sufficiently good to tell a lie from what the participant believes to be the truth (with low false positive and false negative rates), and should they be used in criminal trials if they are scientifically reliable? The first point is crucial if our societies want to avoid the consideration of random decisions as legal evidence. The scientific community should take an active part in the decision process on this point, although legal scholars may challenge their participation (Schauer, 2010). The current consensus holds that fMRI-based lie detection is not yet reliable enough (Greely & Illes, 2007; Miller, 2010; Monteleone, Phan, Nusbaum, Fitzgerald, & Irick, 2009; Moriarty, 2008), but the ethical and legal implications of potential future use are being discussed actively (Meegan, 2008, and comments on it; Simpson, 2008, and comments; Tovino, 2007). Scientists are responsible for pointing out the limitations of neuroimaging methods, especially because brain images and neuroscientific statements have been shown to be particularly convincing to laypeople (McCabe & Castel, 2008; Racine, Bar-Ilan, & Illes, 2005; Weisberg, Keil, Goodstein, Rawson, & Gray, 2008), which could have serious consequences in trials involving jury decisions.

A third area for ethical discussion concerns the use of fMRI to detect and decode brain activity in patients who are in a minimally conscious or vegetative state (Monti et al., 2010; Owen & Coleman, 2007, 2008; Sorger et al., 2009; Tshibanda et al., 2010). This application of fMRI holds great promise for improving the lives of these patients by enabling them to communicate. However, we also need to be aware of possible consequences that advancements in the field could have. What kind of treatment decisions will be made on the basis of fMRI results? What paradigms and tasks are suitable as clinical assessment? The relevant techniques will need to be evaluated and confirmed further before they can be used in clinical practice (Bernat, 2009; Farah, 2008; Fins & Shapiro, 2007).

The increase in discriminative power through the combination of neuroimaging and genetics is another area for ethical consideration (Tairyan & Illes, 2009). With the development of technologies

and the advancement of understanding in brain research, researchers need to be aware of the implications for society and should take an active part in discussing these matters. On the most fundamental level, this can be done by carefully communicating one's own research to the public (Illes et al., 2010).

CONCLUSION

fMRI is a flexible tool for studying the human brain, allowing adjustment of the acquisition and analysis parameters to suit the experimental question and allowing investigations both of whole-brain networks and of strongly localized functions. New approaches in experimental design and analysis are constantly being developed and add to this flexibility. The integration of information gained from these different approaches with results from EEG, MEG, TMS, intracranial recordings, and lesion studies in humans will advance our understanding of functional processes in the brain. fMRI has opened a window onto cognitive functions in healthy humans that offers an exciting glimpse of future insights.

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