

Chapter 19

Novel Developments in Cognitive fMRI

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Introduction: Moving Beyond “Cognitive” Neuroscience

The maturation of functional magnetic resonance imaging (fMRI) as a technology has been paralleled by its application to an increasingly wide range of scientific problems. The lion’s share of fMRI research has come within the domain of “cognitive neuroscience,” which is typically defined by the use of neuroscience data (or brain-based models) to refine our understanding of how people think and behave (Gazzaniga et al. 2008; Purves et al. 2008).

The earliest forays of fMRI into cognitive neuroscience demonstrated that this new technique could map core brain systems for vision (Belliveau et al. 1991), language (Binder et al. 1995), short-term memory (McCarthy et al. 1994), and motor systems (Bandettini et al. 1992). However, these sorts of proof-of-concept experiments largely replicated what had been previously shown using other techniques (e.g., positron emission tomography, PET; lesion studies). Over the ensuing years, fMRI was matched to increasingly complex aspects of cognition, including many novel topics for cognitive neuroscience. By the first years of the twenty-first century, this rapidly growing technique had been used to dissociate control processes within the frontal lobe (Rowe et al. 2000), to distinguish circuits associated with different forms of memory (Cabeza et al. 2002), and to elucidate the mechanisms of attentional control of sensory processing (Hopfinger et al. 2000), among many other topics. In short, fMRI was being applied to nearly all questions of historical interest within the large and vibrant field of *cognitive* psychology.

In recent years, there has been a striking expansion in the breadth of problems to which fMRI is applied. Topics from cognitive psychology are still of primary interest, to be sure, but applications to other areas are becoming increasingly common. Accordingly, researchers no longer affiliate solely with cognitive neuroscience. New interdisciplines have arisen, such as social neuroscience (Lieberman 2007)

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557

and neuroeconomics (Platt and Huettel 2008; Rangel et al. 2008)—with concomitant extensions to real-world problems in education, clinical practice, and business. Broadly considering, fMRI is now applied to questions arising from throughout the experimental social sciences.

This review first considers the factors that have facilitated such remarkable growth in such a short time frame. Of note, technological advances have themselves had minimal influence. As evidence, consider that many, if not most, current studies use pulse sequences (e.g., echo-planar imaging) and scanner hardware (e.g., 1.5 or 3 T field strengths) that would not have been out of place a decade ago. Instead, key advances have come in the areas of experimental design and analysis which together have allowed implementation of much more complex sorts of experiments in the fMRI setting. It then describes new developments in two related domains—decision neuroscience and social neuroscience—each of which illustrates the power of fMRI to identify and describe increasingly complex internal states. It ends with a discussion of some likely directions for future applications of fMRI to new domains of inquiry and new research questions.

Functional MRI as a Tool for the New Social Sciences

Suppose that a researcher from the early days of fMRI was brought, without warning, into the console room of a modern MRI center. Looking through the window into the scanner bay, the researcher would immediately recognize the scanner—even if it seemed rather slick and artificial compared to the workhorse systems from the 1990s. Glancing around the scanner and console rooms would likely reveal some well-known sights: a participant positioned within a head coil, head stabilization systems, response boxes, control computers, and other equipment. Again, each of these devices might appear cleaner, more commercial, or more advanced than before, but their essential purposes would be readily apparent. So, the researcher's initial disorientation would fade away as the surroundings become increasingly familiar. Then, the researcher turns to the experimenter to ask about the current study—which uses pattern classification to identify a visual stimulus based only on brain responses (Kay et al. 2008), involves mapping the brain changes caused by charitable rewards to determine taxation rates (Krajbich et al. 2009), or engages its participants in a complex interactive game with a competitor in another scanner (King-Casas et al. 2005). One can imagine how baffling such an experiment might seem to a researcher striving to see responses in motor cortex to finger tapping! Like in many other fields, what have been most remarkable are not only the advances in the *technology* itself but also its unexpected *applications*.

Three developments have facilitated the extension of fMRI research into new domains, particularly those addressing questions from outside of traditional neuroscience or cognitive psychology: the rise of complex experimental designs and associated methods for their analysis, the emphasis on model-based approaches that

provide insight into underlying mental states, and the increased focus on measures of individual differences.

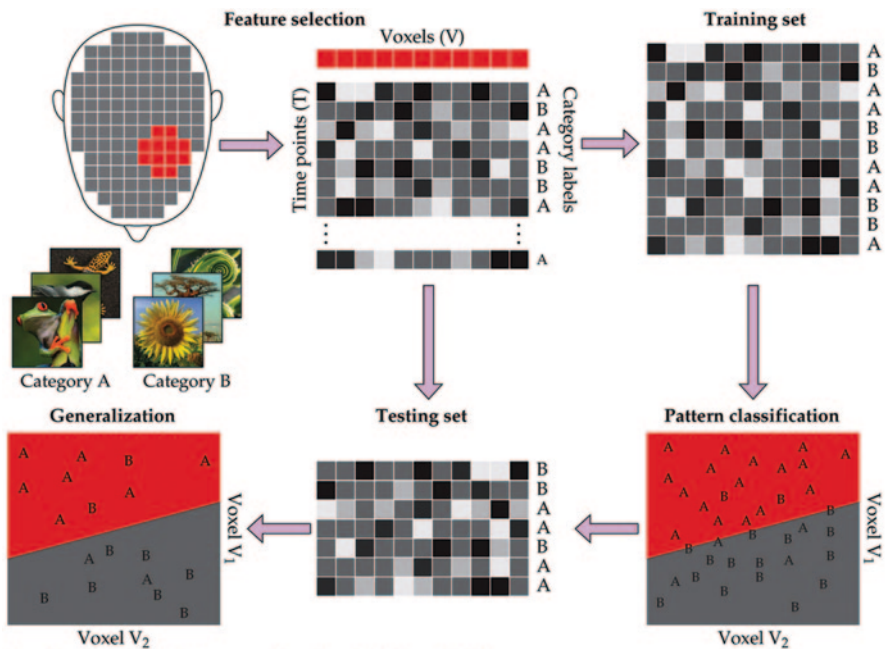
Advances in fMRI Experimental Design and Analysis

The introduction of new topics to fMRI research has progressed hand-in-hand with new approaches to experimental design. The first fMRI studies largely used simple blocked designs adapted from earlier PET research, both because those designs were familiar to many researchers of that time and because the sensitivity of blood oxygenation level-dependent (BOLD) contrast was not yet known (see Huettel et al. 2009) for a more detailed consideration of fMRI experimental design). Blocked designs are heavy but blunt instruments: they have near-optimal power for detecting *that* an experiment evokes a change in the brain, but they provide very little information about *what* aspect of the experiment has any effect. The development of event-related approaches in the late 1990s (Buckner 1998; but see Blamire et al. (1992) for an early example) provided a great deal of flexibility for more complex designs, largely by allowing researchers to separate brain activation associated with different parts of a trial (e.g., distinguishing the act of making a decision from post-decision feedback). Most modern experiments use event-related designs to answer their primary questions of interest, although blocked designs remain common for “functional localizers” that can quickly determine a region of interest for further analyses (Saxe et al. 2006). In practice, the dominant approach to data analysis, multiple regression within the general linear model, effectively models any experimental design as comprising one or more sets of independent events.

An important change has come in the nature of the *events* to be analyzed. Whereas early research used experimenter-defined events (e.g., attending to the left vs. attending to the right), it has become increasingly common for studies to use participant-defined events. Classic examples come from research into mnemonic encoding, as when an individual views a list of words in advance of a memory test. By coding each stimulus according to whether it was later remembered, the researchers can identify brain regions (e.g., the medial temporal lobe) whose activation predicts subsequent memory (Wagner et al. 1998). Analogous approaches are being used in nearly all domains of cognitive neuroscience. Studies of decision-making often label events according to the choice that is made (Paulus et al. 2003), studies of emotional control differentiate events according to whether control was successful (Ochsner and Gross 2005), and studies of drug addiction evaluate cues according to the amount of craving they evoke (McClernon et al. 2005). Importantly, these studies share the common idea that variability in the process of interest is defined by changes in some internal state, not in the external stimuli. This idea will be further developed in the following section on model-based fMRI.

Some analysis approaches dispense with the very idea of matching brain responses to specific events. A striking example (see Fig. 19.1) comes from studies of “free” or “natural” perception (Hasson et al. 2004), as when participants watch an

extended visual stimulus in a normal, unconstrained fashion (e.g., a 10-min movie clip). Any such complex stimulus will evoke activation in a welter of brain regions, from those involved with interpreting visual objects to those that associate current events with past memories. Trying to specify all possible processes—and their timing!—would be an impossible task. Thus, researchers using this technique tend to reverse the direction of typical analyses. First, they identify brain regions that tend to move in the same way across participants, which provides strong evidence that some process is driving different participants’ brains in a similar fashion. Then, they infer the function of those regions by referring back to the original stimulus, for example, if each peak in the common time course is preceded by a clip of someone talking, then that region may be sensitive to images of faces or biological motion. A related approach looks at common patterns of activation in two individuals who are participating in the same task and who are being scanned simultaneously, in different fMRI scanners. Most studies using this “hyperscanning” approach (Montague et al. 2002) have investigated how people play interactive games, as when one indi-



Functional Magnetic Resonance Imaging 2e, Figure 11.17

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Fig. 19.1 In naturalistic “free-viewing” fMRI paradigms, the participants watch a complex visual stimulus like an extended clip from a movie. The participants are not constrained by any particular experimental task or goal; they can freely view and think about the movie in whatever way they choose. Even so, the movie will drive changes in some aspects of brain function in a similar manner across participants. In the region of the posterior fusiform gyrus (pFg) shown here, the relative correlation in activation across participants showed striking peaks (e.g., all participants showed similar increased activation) at particular points in time. When the researchers examined the content of the movie at those time points, they reliably observed that there was a face present in the scene. (From Huettel et al. 2009)

vidual can signal the intention to trust another for mutual benefit (King-Casas et al. 2005). Researchers can use time courses of activation in one participants' brain as a predictor variable for changes in the other participants' brain. The key advantage of this approach, like that of the correlation analysis in natural viewing experiments, is that it provides a data-driven procedure for finding commonalities among participants. Thus, it can help researchers identify unexpected functional changes associated with an experimental task.

Finally, new multivariate analysis methods have greatly increased the complexity of the neural measures that can be related to behavior. (A full consideration of those methods is beyond the scope of this chapter, but see the Chap 23 in this volume for a more extensive introduction.) Two classes of new methods are particularly promising for cognitive neuroscience research: functional connectivity and pattern classification. As typically defined, "functional connectivity" reflects covariance in the fMRI BOLD signals of two regions, presumably based upon some shared aspects of processing. The simplest sort of connectivity analysis examines resting-state fMRI scans (i.e., data collected in the absence of any overt task). Regions whose activation tends to covary over time are often assumed to constitute a functional network (Damoiseaux et al. 2006). Most well-studied is the default-mode network, which consists of regions that exhibit decreased activation during task performance and support internally directed processes like prospective thought, rumination, and reflection (Gusnard and Raichle 2001). Functional connectivity measures can also reveal task-related interactions among sets of regions which, in turn, allows investigation of how different regions combine to support a complex cognitive process (Kouneihier et al. 2009; Venkatraman et al. 2009).

Pattern classification techniques, in contrast, provide more detailed information about a single region. Most current multivoxel pattern analysis (MVPA) techniques (Fig. 19.2) use machine-learning algorithms from computer science (Norman et al. 2006). They first identify a feature space that could include activation from a few tens of voxels to the entire brain. Then, using a portion of the data, they identify a classifier consisting of a combination of features (e.g., voxels and their weights) that maximally differentiates two conditions of interest (e.g., two sorts of visual stimuli). Finally, they test that classifier on new data to evaluate its robustness. While this approach has many strengths, its most critical advantage is increased sensitivity toward the sort of information being represented within a larger region. For example, two classes of visual stimuli (e.g., photographs of equal luminance and complexity, but different content) might evoke fMRI BOLD changes of equal magnitude within ventral visual regions. Using pattern classification, however, may reveal that each evokes a distinct pattern of information and may further provide insight into what features of the stimulus contribute to that pattern. Researchers have applied pattern classification techniques to a remarkably large set of topics, often with great success, including subjective visual experience (Kay et al. 2008), detection of deception (Davatzikos et al. 2005), and economic decision-making (Clithero et al. 2009).



Functional Magnetic Resonance Imaging 2e, Box 11.1, Figure 2

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Fig. 19.2 A conceptual overview of multivoxel pattern classification of fMRI data. In this example, the researchers want to identify voxels whose activation predicts whether the subject is looking at photographs of animals or plants. At the first stage, feature selection, the researchers identify a subset of voxels for subsequent analyses. A typical feature set consists of the activation intensity for each voxel on each trial. The feature set splits into a training set, from which the pattern classifier will be derived, and a testing set that provides a novel test of the generalization of the classifier. Shown here is a simplified example of pattern classification using two features (i.e., two voxels) and two trial categories (A and B). The activation values of those two voxels on each trial are shown as a two-dimensional plot. Note that fMRI pattern classification involves many more dimensions, and thus a much higher dimensional space. In the common technique of support vector machines, the pattern classification algorithm attempts to identify the surface that maximally distinguishes the two categories. Here, a linear classifier optimally separates the two stimulus categories. Once a classifier has been identified, it is tested on the novel training set, to ensure that the classification rule can be generalized to untested data. (Figure and caption from Huettel et al. 2009)

The Growth of Model-Based fMRI

Taken literally, the idea of “model-based fMRI” might seem redundant—after all, do not all fMRI studies employ one model or another for their analyses? Many studies create models based on the experimental stimuli, while others create models based on participants’ behavior. So, to what sorts of models might this refer? Within several domains of cognitive neuroscience, there has been an increased emphasis on deriving models of *internal states*, whose parameters are estimated based on the effects of changing external stimuli on a participant’s behavior (O’Doherty et al. 2007).

To see the value of this approach, imagine that two individuals participate in the same reward-learning experiment. On the 100th trial of each of their sessions, the participants see the same behavioral cue, make the same motor response, and receive the same reward. However, the response in the ventral striatum

(a key reward-related region) is much greater in the first participant than the second. Were this sort of discrepancy just observed on one trial, it could be readily dismissed as some aberration that reflects the limitations of the fMRI setting, not a meaningful effect. But, suppose that we wanted to evaluate the alternative hypothesis that the two participants were approaching the task in systematically different ways. How might this idea be tested? One potential solution comes from the sorts of reinforcement learning approaches that psychologists have used to describe animal behavior (Sutton and Barto 1981). These share the concept that animals form models about how external stimuli and actions combine to predict rewards, such that the parameters of those models can be updated when unexpected events occur (e.g., a reward is predicted but does not occur). The two participants' behavior could be fit to the same reinforcement learning model, and the resulting parameters could be used to estimate the internal state of each participant at each point in time. For example, on that key trial, the first participant might have a weaker association between cues and rewards, leading to a greater ventral striatum response (Glascher et al. 2010).

The core insight of model-based fMRI is that many sorts of interesting internal states cannot be defined based on behavior alone. Instead, those states become evident based on how behavior changes with context. This reflects an important maturation within the field, one in many ways analogous to the developments that led to the rise of cognitive science within psychology. Before the cognitive revolution of the 1960s, the ascendant topics in psychological research focused on rigorously mapping different stimuli to different behaviors (e.g., psychophysics, human factors). Dissatisfaction with the limitations (and sterility) of this approach eventually resulted in its downfall, as researchers began to study internal states through sets of experiments that all converged on a common inference (Garner et al. 1956). Recent examples of model-based approaches can be seen, albeit with a variety of labels, in many areas of recent cognitive neuroscience research: neuroeconomics (Kable and Glimcher 2007), memory retrieval (Han et al. 2010), and even social cognition (Behrens et al. 2009).

New Research on Individual Differences

A core assumption of early fMRI research was that, when faced with an experimental challenge, the brains of all participants in an experiment responded in the same manner. (Note that this assumption was implemented, very literally, in the first, fixed-effects analyses used to determine significance. The move to random-effects analyses meant that the *magnitude* of activation could vary across participants, but the basic assumption still held.) Yet, in many situations, people think and behave in strikingly different ways. As fMRI has matured, researchers have adopted increasingly sophisticated approaches for addressing interindividual variability. Two such approaches will be considered in this section, with further applications provided in the later discussion of decision neuroscience.

The most common approach to individual difference fMRI involves identifying some variable on which participants differ and then including that variable as a

covariate in the across-participants analyses. Major classes of variables include personality traits (e.g., Machiavellianism, Spitzer et al. 2007), cognitive abilities (e.g., intelligence or reasoning scores, Lee et al. 2006), measures of task performance (e.g., attentional conflict, Brown and Braver 2008), and decision preferences (e.g., risk aversion, Huettel et al. 2006). Sometimes, these variables are defined based on some task that is independent of the main fMRI contrasts such as a questionnaire given before the scanning session. Or, behavior in the scanning session can be used to classify people as better or worse performers. The inclusion of any of these variables does not fundamentally alter fMRI analyses; instead of evaluating a potential main effect of some contrast between conditions, researchers evaluate whether the magnitude of that contrast tracks the individual-difference variable. As sample sizes have increased from ten or so participants per study to several times that number, covariate analyses have become an increasingly common approach to fMRI research. Moreover, clinical researchers now use covariate analyses to identify biomarkers (or “endophenotypes”) that may help predict or diagnose disorders (Chiu et al. 2008).

Somewhat less common are studies that investigate individual differences in the pattern of brain response to an experimental task. An early study of variability (Miller et al. 2002) found that the overall pattern of activation in memory retrieval was rather different from participant to participant (e.g., some exhibited substantial activation in lateral prefrontal cortex, others in insular cortex), but those idiosyncratic patterns were consistent within repeated testing of the same participant. This finding—namely, cross-individual variability but within-individual consistency—supports the idea that different individuals perform this complex task using different brain mechanisms. Analogous results have been reported in studies of intergroup differences. For example, older adults who perform well on tests of memory retrieval evoke increased frontal activation compared to their less well-performing peers. This qualitative change in the pattern of activation may indicate functional compensation to improve task performance (Cabeza 2002). Individual differences may also be manifest in patterns of functional connectivity. Recent work has shown that whether someone is adopting a heuristic or analytic approach to decision-making depends not only on the activation of the dorsomedial prefrontal cortex but also on the changes in that region’s connectivity to other, more choice-related regions (Venkatraman et al. 2009). Despite the increased complexity of these analyses compared to simple brain–behavior covariation, the future of individual-difference research will increasingly emphasize interactions among networks of regions that together shape behavior.

Decision Neuroscience/Neuroeconomics

Over the past decade, fMRI has played a central (but not exclusive) role in the growth of “decision neuroscience” or “neuroeconomics.” (The former term will be used hereafter, as a parallel to the “cognitive” and “social” applications of fMRI that

have already been discussed.) For more complete reviews of research in this emerging interdisciplinary, see Platt and Huettel (2008) and Rangel et al. (2008). Instead, this section focuses on some of its major themes and how they have been facilitated by developments in fMRI research.

Identifying and Mapping Decision Variables

Early studies of the brain mechanisms of decision-making and reward primarily used single-unit electrophysiology in nonhuman primates. Consistent with the strengths and limitations of that technique, these studies could detect local processing with exquisite temporal sensitivity, but only within the specific region targeted in each study. Two broad conclusions provided the key foundations for future research: the responses of dopaminergic neurons in the brainstem and their projection targets encoded signals reflecting the value of information and of rewards (Schultz et al. 1997) and that sensory and motor regions encoded information about the probability that actions would lead to those rewards (Newsome et al. 1989). As seen in many other fields, the first related fMRI studies replicated and extended these basic foundations in human subjects. More recently, fMRI has made novel contributions through increasingly complex paradigms that identify neural mechanisms of decision variables well beyond reward and probability (Smith and Huettel 2010; Fig. 19.3).

A major goal for neuroeconomics has been to understand the neural mechanisms underlying choice under uncertainty, considered broadly. The simplest contributor

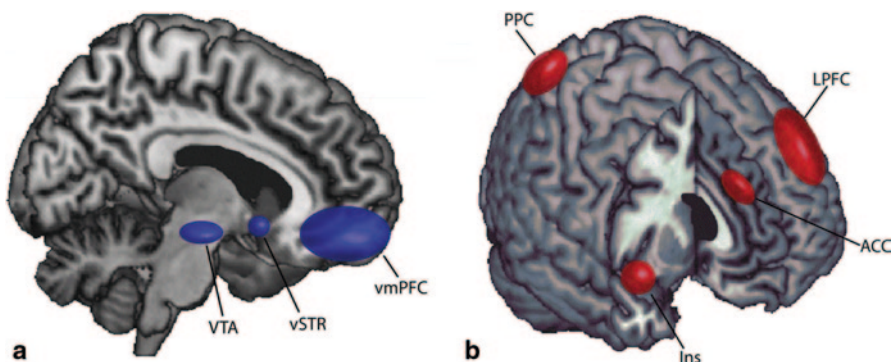


Fig. 19.3 Regions carry information related to variables that shape economic decisions. **a** Processes associated with experiencing and evaluating rewards modulate components of the brain's dopaminergic system including the ventral tegmental area (VTA), the ventral striatum (vSTR), and the ventromedial prefrontal cortex (vmPFC). **b** Processes associated with evaluating and resolving uncertainty (e.g., the absence of information about the timing, content, value, or likelihood of rewards) evoke activation in the insular cortex (Ins), anterior cingulate cortex (ACC), lateral prefrontal cortex (LPFC), and posterior parietal cortex (PPC). (From Smith and Huettel 2010)

to risky choice is the probability with which rewards may occur. Probability has not only effects on low-level sensory judgments, as described above, but also on control systems that contribute to a range of decisions; in particular, regions of dorsolateral prefrontal cortex, posterior parietal cortex, and insular cortex are all modulated by outcome probability (Huettel et al. 2005). Yet, uncertainty also involves other factors, for example, variance in outcome magnitudes, which contributes to “risk” and lack of knowledge about outcomes or their probabilities, which generates “ambiguity.” In these areas, fMRI has made important, novel contributions. Studies of risk, for example, have consistently implicated the anterior insular cortex, a region not considered by previous work using other techniques. Through careful experimental design, researchers have even teased out several distinct risk-related signals within this region (Preuschoff et al. 2008). Research using fMRI has been central to the study of ambiguity, which is central to human decision-making but more difficult to evoke in controlled animal experiments (but see Rosati and Hare 2011). Two early studies implicated lateral prefrontal cortex (Huettel et al. 2006) and orbitofrontal cortex (Hsu et al. 2005), respectively, in the evaluation of economic gambles with ambiguous outcomes. Based on subsequent findings (Bach et al. 2009), it appears that the lateral prefrontal cortex does play a specific role in processing ambiguity (as opposed to risk or complete ignorance about probabilities), whereas the orbitofrontal cortex may have a more general response to decisions with aversive properties.

Another key area of fMRI research has been understanding the neural mechanisms of intertemporal choice (i.e., when outcomes materialize at different points in time). Research from economics and psychology has long shown that humans and other animals exhibit temporal discounting; that is, the value of a reward decreases continuously as it moves farther into the future. One ongoing puzzle from prior literature has been the observation that humans, in particular, discount rewards too quickly (Kirby and Herrnstein 1995). Instead of decreasing with an exponential decay, as would be expected if every unit of time contributed equally, typical discount curves have a rapid immediate decline that more closely resembles a hyperbolic function.

A seminal fMRI study (McClure et al. 2004) postulated that the combination of rapid short-term discounting (i.e., temptation for immediate rewards) and slow long-term discounting (i.e., patience for distant rewards) could reflect the interaction of two brain systems. They found that regions implicated in the processing of rewards—such as the ventral striatum, the ventromedial prefrontal cortex (vmPFC), and the posterior cingulate cortex—were all significantly more active when an immediate reward was present. Conversely, regions including lateral prefrontal cortex and posterior parietal cortex (i.e., those related to executive control) were equally active across all trials, consistent with the postulated role of a patient system. While this set of findings was frequently interpreted to provide strong evidence for a “dual-systems” approach to decision-making, the activation of reward-related regions was insufficient evidence for the existence of a separate, impatient system. In a subsequent study using a similar task (Kable and Glimcher 2007), other researchers analyzed each trial according to its estimated subjective value for each participant. They found that activation in these reward-related regions tracked the value of a

given outcome, regardless of whether it would be delivered immediately or at a delay—which argued strongly against the dual-systems model. Yet, despite their contradictory conclusions, these studies can be reconciled into a common framework (Kable and Glimcher 2009): there is a single, common pathway that calculates value signals for rewards of all sorts, but that pathway can be modulated at different stages by other brain regions. This framework will recur in the following sections.

Integrating Decision Variables

Long before economics considered data from fMRI (or from any other form of neuroscience, for that matter), it was well recognized that decision variables like reward magnitude and probability must be integrated to reach a decision. Some comparison process of integrating and trading-off variables lies at the core of every compensatory model of decision-making (Tversky and Kahneman 1992). Within neuroscience, however, there was the recognition that any such comparison would require value signals that were abstracted from the underlying variables, so that two disparate sorts of rewards (e.g., food and money) could be compared within a “common currency” (Montague and Berns 2002). A primary goal of current fMRI research in decision neuroscience, accordingly, has been to identify potential neural substrates for the comparison process.

A strong candidate for the locus of value integration has been the vmPFC. Studies using primate electrophysiology had shown that activity of vmPFC neurons is proportional to relative value of rewards (Padoa-Schioppa and Assad 2006), lesions to the vmPFC have long been reported to lead to deficits in weighing the cost and benefits of actions (Bechara et al. 2000), and fMRI studies have implicated this region in aspects of valuation, more generally (Paulus and Frank 2003). However, it was not yet clear whether this region processed general subjective value (i.e., how much utility we gain from a reward), decision value (i.e., the value of a reward relative to its cost), or some other property. Because human studies could use a wider range of rewards and more complex paradigms than animal studies, fMRI research was well positioned to help refine our understanding of the specific computations performed by vmPFC. Many fMRI studies of value integration have used paradigms involving simple economic exchanges, as when participants are given a monetary endowment at the outset of the scan and then allowed to purchase real goods from the experimenters. The first studies using this approach showed that activation in vmPFC tracked the prices of simple, desirable consumer goods (Knutson et al. 2007) and the participants’ monetary bids for food to be consumed at the end of the scanner session (Plassmann et al. 2007). These simple initial studies led to an explosion of subsequent research on different contributors to economic transactions. To highlight a few notable examples, all of which implicate vmPFC, fMRI research has investigated how perceived price influences the subjective valuation of wines (Plassmann et al. 2008), whether self-control shapes the relative contributions

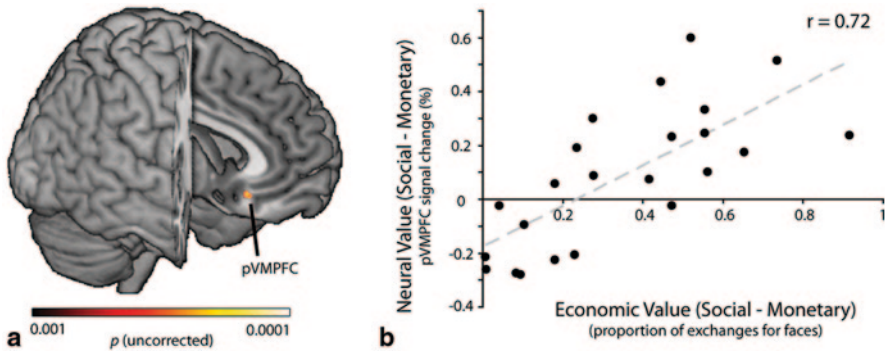


Fig. 19.4 Value integration in ventromedial prefrontal cortex (vmPFC). In recent years, there has been substantial interest in the potential contributions of vmPFC to the computation and integration of value signals in decision-making. Participants viewed a series of images of faces that varied in subjective attractiveness, and then, later made decisions about whether to exchange money to view more attractive faces. **a** Shown are the voxels in posterior vmPFC whose fMRI activation predicted whether a given individual was likely to subsequently trade money to view faces (in the economic exchange task). **b** Within these voxels, increasing activation for social compared to monetary rewards predicted increasing likelihood of economic exchanges. (From Smith et al. 2010)

of healthfulness and taste on the valuation of food (Hare et al. 2009), and how we judge the attractiveness of photographs of other people (Smith et al. 2010).

A particularly important ongoing contribution being made by fMRI research lies in disentangling the mechanisms of different sorts of value signals. Any potential outcome can be evaluated in a host of different ways—is it better than we expected, how much pleasure would we gain, how much does it motivate our action, how much would we give up to obtain it, etc.—and those different evaluations may lead to multiple value signals that are simultaneously computed by the brain. In particular, there is good evidence that the brain separately tracks expectations about the magnitude of current rewards (i.e., reward prediction error) and the value of rewards relative to their potential costs (i.e., decision value), with the former represented in the ventral striatum and the latter in vmPFC (Hare et al. 2008). Recent fMRI work suggests that the brain constructs these value signals in an automatic and obligatory fashion (Fig. 19.4). When young male adults viewed photographs of young female adults of varying attractiveness, two separate value signals were observed in vmPFC: activation in an anterior region increased with attractiveness, whereas activation in a posterior region was proportional to each individual's willingness to pay to view attractive faces (Smith et al. 2010). Of note, these sorts of conclusions would be very difficult to reach with other current techniques in neuroscience, in that they require simultaneous measurement from several brain regions that might be contributing to a complex task in distinct ways.

New Models for Learning

Research using fMRI has also served as an important methodological bridge between decision phenomena (primarily observed in humans) and the basic mechanisms of learning (largely studied in nonhuman animals). It is not the only such bridge, however. Studies of patients with brain lesions have been instrumental in identifying regions that make key contributions to adaptive decision-making, such as the role of the ventral frontal lobe in learning about positive and negative outcomes (Bechara et al. 2000) and in the associated effects of regret on subsequent decisions (Camille et al. 2004). Note that lesion studies can provide more than just examples maladaptive behavior; in some cases, deficits in a particular cognitive function (e.g., regret-based learning) can lead to paradoxical improvements in behavior (e.g., fewer risk-averse mistakes; Shiv et al. 2005). Studies using electrophysiological recordings have provided important insights into error signals that can shape learning. For example, unexpected monetary outcomes evoke a very rapid response in the medial frontal lobe (Gehring and Willoughby 2002) that both depends on magnitude and valence and tracks the prior reward history (Goyer et al. 2008). The temporal precision of event-related potential (ERP) methods, in particular, gives information about the relative timing of events well beyond that provided by fMRI studies. Yet, despite the ongoing importance of these and other methods, fMRI has become the primary tool for understanding how the brain learns information that can guide its decisions.

Two new directions are particularly notable, both because of their topical importance for understanding in uncertain environments and because they illustrate how fMRI research can complement work from other techniques: understanding the effects of *volatility* on learning and characterizing trade-offs between *exploration and exploitation*. Suppose that the world around you were highly stable; that is, the relationships between your actions and their probabilities of rewards changed very slowly over time. Accordingly, your learning rate should be very slow, since short-term fluctuations in rewards would be more likely to be attributable to chance than to a shift in the environment. If the environment were very volatile, however, you should instead learn much more rapidly—so that you can identify when the world shifts under your feet. An elegant series of studies have shown that changes in the volatility of the environment (and the associated changes in learning rate) are associated with changes in the dorsomedial PFC (dmPFC) (Behrens et al. 2007), whose subregions may also signal whether information about volatility comes from a social or nonsocial source (Behrens et al. 2008). The dmPFC has been implicated in a wide range of cognitive functions (Ridderinkhof et al. 2004), but most specifically seems to engage mechanisms for executive control in a context appropriate manner (Kerns et al. 2004). Thus, the volatility signal identified in this region may reflect a special case of a larger contribution to the adaptive control of behavior.

Another evocative recent development comes from research on the trade-off between information and reward which is often characterized as the “explore vs. exploit dilemma.” In a stable environment, an organism’s task is to identify the

behavior that will lead to the greatest reward and then repeatedly engage in that behavior (i.e., exploitation). If the environment might change over time, however, persisting with a single course of action might be suboptimal; there might be other actions that could lead to even larger rewards. Effective decision-making often requires testing out alternative actions (i.e., exploration) that seem suboptimal based on current models of the environment but that will provide new information. (Of note, determining whether any particular choice falls into one category or another requires estimation of the participant's internal state and, in turn, the use of model-based fMRI.) Initial research suggested that exploration behavior evoked activation in frontopolar cortex (Daw et al. 2006), a region now implicated in information integration through a range of cognitive paradigms (Christoff et al. 2009). Note that the understanding of frontopolar cortex itself has been considerably shaped by recent fMRI studies, which have provided new insight compared to other techniques (e.g., frontal lesions often alter a broad range of functions). This result, like those described in the previous paragraph, again provides a link between phenomena studied in decision neuroscience and processes considered by cognitive neuroscience.

Social Neuroscience

Research using fMRI has been instrumental in the development of “social neuroscience,” which broadly considers the neural mechanisms that support our abilities to interact with others, to evaluate others' actions and mental states, and to consider oneself in a social context (Lieberman 2007). Compared with the parent field of cognitive neuroscience and its sibling decision neuroscience, social neuroscience occupies an intermediate place. Its main topics are much narrower than those of cognitive neuroscience, but a bit broader than those of decision neuroscience (e.g., it examines topics ranging from perception to reasoning), and include substantial overlap with each of the others. Considered generally, it has less emphasis on behavioral and computational modeling, substituting instead the experimental diversity and creativity from social psychology. Like for decision neuroscience, any attempt to summarize this growing and diverse field will be incomplete. The following sections, therefore, highlight two areas in which fMRI has made particularly seminal contributions to social neuroscience, along with examples from key studies that illustrate the power of fMRI.

Understanding Others' Minds

How do people infer, interpret, and respond to the thoughts of others? *That* some people (young children, individuals with autism, etc.) have deficits in understanding other people's minds seems readily apparent. The causes and functional implications of those differences, however, are much less intuitive. Studying groups with

such deficits can provide important insight into the specificity of the disorder; for example, individuals with autism have much greater difficulty reasoning about social situations than about nonsocial situations of similar complexity (Baron-Cohen et al. 2005). Group studies can also indicate potential mechanisms for disorders (e.g., individuals with autism make abnormal eye movements when scanning a photograph of a face; Emery 2000), which can in turn indicate potential points of comparison with other seemingly unrelated disorders (e.g., anorexia nervosa). Yet, comparing groups with and without a particular deficit has inherent limitations, especially if the underlying disorder is complex or heterogeneous.

Studies using fMRI have made significant contributions to research on social cognition. An area of ongoing contribution has been in describing the properties of the lateral parietal cortex, specifically a region called the temporal–parietal junction (TPJ; Fig. 19.5). That the lateral parietal cortex contributes to visual attention has been long recognized; lesions to this region can lead to neglect of part of visual space, for example. Yet, how the TPJ supports social cognition has been best illustrated through a now-large literature implicating it in perception of visual and auditory social stimuli, inferring the social context of an event, and in thinking about the thoughts and goals of others (Saxe and Kanwisher 2003). Notably, the fMRI response in this region is so robust that it can be used as a physiological correlate of complex social traits, including interpersonal attitudes like altruism (Tankersley et al. 2007). Recent work has taken advantage of the specificity of this region to study its functional connectivity, both with other regions in a social network, and as input to processing systems elsewhere in the brain (Anticevic et al. 2010). Collectively, these examples demonstrate the flexibility of fMRI: once researchers

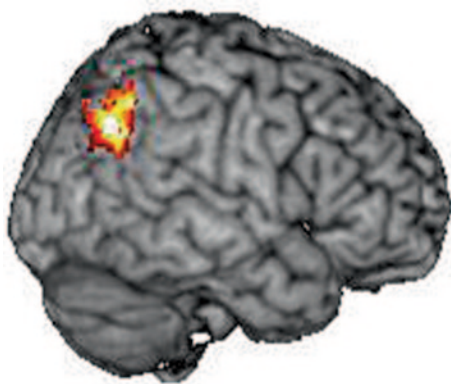


Fig. 19.5 Activation in the temporal–parietal junction (TPJ) associated with social cognition. A region at the intersection of the temporal and parietal lobes, the TPJ, has been frequently linked to processes important for understanding the thoughts and goals of others. Shown here are voxels that were more active when participants were watching another agent plays a simple game than when the participants played the game itself. In turn, the activation difference between those two conditions (i.e., the effect of perceived agency upon TPJ activation) predicted intersubject differences in self-reported altruism. (From Tankersley et al. 2007)

identify a component of a larger network, there are many opportunities for extending that research through related concepts and through links to other parts of the network. That flexibility has allowed fMRI research to explore new domains, like social cognition, at a more rapid pace than research using other techniques.

Interacting with Others in Cooperative Settings

At first consideration, fMRI might seem an inherently solitary technique. Its procedures emphasize separation: the participant is brought into a bland and seemingly sterile environment, is immobilized on a table, is slowly moved into a tunnel, and is cut off from communication with others for most of the duration of the experiment. The MRI environment is, in these and other ways, almost as asocial as possible. Faced with these limitations, trying to study social interactions with fMRI might seem a futile exercise. Yet, as fMRI has matured as a technique, there has been a paradoxical and dramatic increase in research on social interactions—to the point that many researchers now embed manipulations on traditional topics (e.g., memory, executive control) into social settings. How has this growth been possible, given the limitations of fMRI?

Most important to recognize is that the techniques for running fMRI studies are not, in themselves, any more “social” than a decade ago. To a first approximation, researchers use the same sorts of visual displays, position subjects in similarly aseptic scanners, and face the same limitations on communication. Nor has the basic procedure of the fMRI experiment changed to become more like social psychological research. Nearly all studies use within-participant manipulations, scan a single individual at a time, and collect data from a relatively small sample (with some notable exceptions; e.g., the “hyperscanning” approach described previously). Advances have instead come from clever experimental paradigms that abstract the key elements of interpersonal interactions and then instantiate those elements in a reduced-form social setting. This approach has worked in large part because of our brain’s ability to imbue even simple settings with social meaning (see previous section). When participants believe that they are playing a game with another person, as opposed to a computer, there are clear differences in the brain systems engaged—even in the restricted context of the fMRI scanner (Rilling et al. 2002; Sanfey et al. 2003).

An evocative example of a social context within fMRI research comes from research on social exclusion (e.g., ostracism). All of us exist in a web of social relationships; we may be included in some groups, but excluded from others. Given the complexity of our social lives, it might seem impossible to induce social exclusion in a laboratory setting—or, at the least, such trivial sorts of exclusions would lack the emotional impact of real-world interactions. Yet, building on prior social psychology studies (Williams et al. 2000), fMRI researchers created a simple paradigm that could readily introduce feelings of ostracism (and associated mood changes) within the scanner (Eisenberger et al. 2003). Their approach is charming in its simplicity: in a computer game, the participant tosses a virtual ball back and forth with

two other players (i.e., confederates introduced to the participant beforehand). At some point within the game, the other players begin to toss the ball back and forth between themselves, ignoring the participant and excluding her from the game. The magnitude of self-reported distress at this exclusion was related to changes in both cingulate and lateral prefrontal cortices, consistent with these regions role in the evaluation and regulation of painful, unwanted internal states. Subsequent research has extended this paradigm into other areas of importance to social psychologists (e.g., the role of social support in ameliorating negative effects of ostracism; Eisenberger et al. 2007).

Future Applications

This chapter provides only a limited and static snapshot of a rapidly evolving technique. Each of the topics described above has changed dramatically over recent years—and each will undoubtedly take even larger steps forward as new studies build on current findings. Perhaps most striking is the expansion of fMRI into completely new areas of industry and science.

New Disciplines

Concepts from all of neuroscience, not just fMRI, pervade the social sciences. Models in a variety of fields—from traditional cognitive psychology to economics and business—now incorporate neuroscience concepts (if not always neuroscience data). By all accounts, this interdisciplinary academic research will proceed apace in the coming years, as the boundaries between traditional basic science disciplines become increasingly permeable. In parallel, interest in fMRI has grown in *applied* disciplines such as marketing, advertising, and political science. These several new directions—this review will focus on one, as an example—raise important practical and ethical issues that have relevance for all of fMRI research.

The single application of fMRI that has received the most notoriety is its role in “neuromarketing,” which can be roughly defined as the inclusion of biological measurements to supplement traditional measures of consumer preferences (see Ariely and Berns 2010 for a review). (Of note, only a minority of commercial neuromarketing firms uses fMRI; the majority use electroencephalography (EEG)/ERP-based methods. Nevertheless, fMRI has shaped much of the discussions about the possible uses and misuses of neuroscience in marketing research.) In principle, the concept of neuromarketing seems eminently reasonable. By measuring brain responses while representative consumers view commercials (or brand messages, etc.), a neuromarketing company can assess whether a given advertisement evokes a strong emotional response, whether that response is consistent with the desired message, and what parts of the advertisement might be more or less effective. The substantial progress in neuroeconomics has identified potential markers for decision

processes, as well (e.g., nucleus accumbens activation as a measure of changes in perceived value). Neuroscience is especially attractive to industry marketers because its nominally covert measures of *brain* function might be resistant to biases endemic to self-reports about our *mental* states (e.g., misstating one's preferences to please the experimenter or to appear more intelligent). And, fMRI in particular seems to promise a more scientific and cutting-edge approach that could replace simple questionnaires and interviews.

Yet, for all of the promise of neuromarketing, its notoriety is well earned. A quick internet search will reveal several dozen companies, each promising cutting-edge methods for getting into the brain of the consumer. Each of those companies will also emphasize that its own proprietary methods provide superior measures of consumer behavior—without providing more than minimal detail about the procedures for measurement, analysis, and interpretation of the results. In essence, the commercial potential for neuromarketing has effectively cloaked its advances in secrecy. (As a point of comparison, research in basic neuroeconomics is regularly published in top, peer-reviewed, mainstream journals.) It would be difficult for even experts in the field, much less for industry marketers with no neuroscience background, to evaluate the validity of neuromarketing claims.

Some of the ethical issues raised by neuromarketing (or any other commercial application of fMRI) are readily apparent: the use of neuroscience data to make claims seem more real (Racine et al. 2005), the balance between intellectual property and the open peer-review of ideas, and the privatization of research findings that were supported largely by public funding. Still other issues are more subtle. How would the commercial use of fMRI change public attitudes toward its uses in clinical and research settings? Few non-neuroscientists can describe the limitations of fMRI in any detail; in a population already mistrustful of technologies for “mind-reading,” well-publicized commercial applications might lead to overestimation (and fear) of fMRI's capabilities. What role should fMRI researchers play in the oversight of its applications? Scientific fields vary dramatically in the relationship between academic research and commercial practice. In some disciplines, the academic community plays a central role in ensuring standards (e.g., licensing of practitioners in psychology or engineering); for other fields, the connections are much more limited and idiosyncratic (e.g., computer science). And, in those fields where scientific applications carry the greatest potential for profit (e.g., drug discovery), a large fraction of academic research is directed by corporate funding to the questions of greatest commercial interest. Should fMRI become an accepted tool within marketing practice, the fMRI community will need to become more invested in overseeing its ethical and scientific standards.

New Biomarkers

Since the beginning of MRI, researchers have sought to use its measurements as markers for disease or disorders (Damadian 1971). As evidence that this quest continues, consider that fMRI has been applied to essentially every psychiatric disorder,

often the goal of identifying aspects of brain function that differentiate those who have the disorder from those who do not. Yet, against this enormous background of research, there have been few true biomarkers for disorder. That does not mean that this research has been unsuccessful; on the contrary, fMRI research has revealed many functional changes that accompany given disorders (e.g., changes in prefrontal function within schizophrenia; Manoach et al. 2000). But, the vast majority of such results cannot be themselves used to diagnose a disorder, to anticipate the potential development of a disorder, or to predict how a patient might respond to a particular treatment. Considered most generally, the contributions of fMRI to medical practice have been through advances in our understanding of brain function, not through applications to the treatment of individual patients.

Yet, new developments suggest paths by which fMRI could become an important tool for general clinical practice. (Note that fMRI is indeed used to identify functional regions in advance of neurosurgery, although the range of patients and functional regions remains limited.) The integration of fMRI data with genetic markers will be increasingly valuable for understanding much of the heterogeneity among individuals (Hariri and Weinberger 2003). Within just the topics discussed earlier in this chapter, there have already been numerous studies implicating key genes (e.g., those that shape the dopamine system) as modulators of brain function and, in turn, behavior (Krugel et al. 2009). Combined fMRI-genetics studies have also shown that responses to emotional stimuli are influenced by serotonergic genes, as potentially mediated by activity within the amygdala (Hariri et al. 2006). As fMRI develops more complex measures—going from “activation within a region” to “pattern of interaction among a set of regions”—there will be a much larger space of potential biomarkers for clinical testing. This will be particularly important because of the multi-faceted nature of many disorders; as one point of reference, think of the broad array of cognitive deficits evident within schizophrenia. And, fMRI will become increasingly integrated with other techniques that themselves have clinical value. Through fMRI-guided transcranial magnetic stimulation (TMS), researchers can selectively and temporarily deactivate functional regions of the cerebral cortex. Although this approach has important technical limitations (e.g., it can only target superficial regions), it has already shown promise in some clinical settings.

Summary

Over the coming years, fMRI will continue to be the leading neuroscience technique for understanding the neural mechanisms of cognition. Much of its future research will reflect the successes of the past: Using traditional cognitive tasks to map their supporting brain regions. The most striking research will take a very different form, however, through exploration of new topics, new measures of function, and new markers for differences among individuals. In many ways, its applications will expand outward—keeping a core in traditional cognitive neuroscience, but extending tentative forays into a wide variety of new disciplines.

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