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Brief History

The development of functional brain imaging has had dramatic effects on modern neuroscience, particularly for research into the neural basis of cognition. To appreciate why imaging techniques have been so influential, one needs to consider the approaches available to the neuroscientist before the advent of functional neuroimaging (e.g., prior to the mid-1980s). Research on in vivo brain function then relied on electrophysiological techniques like single-unit recording and electroencephalography (EEG). Single-unit recording involves implanting electrodes in an animal's brain and recording neuronal activity (generated by action potentials). Despite the many strengths of single-unit recording – which remains central to neuroscience even today – it presented significant limitations: It was time- and labor intensive, it only provided information about a small population of neurons in a single region, and it could not be performed on human participants save for the rare clinical cases. Some of these problems were overcome by the use of scalp electrophysiological recordings, which identifies changes in the overall electrical potential of the brain (generated by dendritic activity). While noninvasive, and thus readily measured in human volunteer participants, historical approaches to scalp electrophysiology provided only very rudimentary spatial information, both because of the limitations of the recording apparatus and because of the inherent electrical conductivity of the brain. Neither these techniques, nor any other at that time, could create a map of how some aspect of cognition was supported throughout the brain. In short, there was no way to create an image of brain function.

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Functional Brain Imaging

What Is a Brain Imaging Technique?

Neuroscientists now have an impressive array of techniques for measuring brain function. Only a few, however, fall within the category of “functional brain imaging” (or “functional neuroimaging”). At a minimum, a brain imaging technique needs to have the following three characteristics:

It should record a *physiological measure* of some aspect of the brain’s information processing. This measure could be direct (e.g., of action potentials themselves) or indirect (e.g., of the metabolic consequences of neuronal activity).

It should collect data associated with performance of a *functional process*; that is, it needs to be feasible to use the technique while the organism’s brain performs the targeted sort of information processing.

It should create a two- or three-dimensional *spatial map* that shows the distribution of that measure across the brain.

Many of the common techniques in neuroscience, while powerful in their own rights, thus cannot be considered functional brain imaging. Some techniques used to understand the properties of individual neurons (e.g., patch-clamp recording) are typically performed in cellular preparations, and thus do not provide information (by themselves) about the functioning of the intact brain. Other approaches like single-unit recording and some forms of optical imaging can provide very detailed information about the function supported by a single brain location (e.g., cells within a particular layer or column of cortex), but do not provide insight into how other regions might contribute to that same function. Techniques that manipulate brain function – whether through stimulation, damage, or drug administration – are critical for understanding causal contributions of particular regions or neurotransmitter systems, but they manipulate the brain rather than measure its activity (Fig. 73.1). And, there are some approaches for imaging brain structure (e.g., structural magnetic resonance imaging, MRI) that can be used to later draw inferences about functional properties of regions; for example, by noting that a lesion in the prefrontal cortex impairs the ability to set long-term goals. However, those techniques do not themselves record neural information processing, directly or indirectly, and so they are still considered structural brain imaging.

In this chapter, the discussion of functional brain imaging will use examples drawn from five techniques that are currently in use: high-density EEG, magnetoencephalography (MEG), whole-brain optical imaging, positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). Each of these techniques is currently used by neuroscientists to understand cognition, although the range of applications they each explore varies according to their strengths and limitations. As a broad overview, the newest of these techniques (fMRI) is now the most common, with several thousand studies published annually, and is applied to questions in all areas of cognition. Other techniques play important roles for specific topics. For example, because PET allows researchers to track radiolabeled metabolites and neurochemicals, it continues to make critical contributions to our

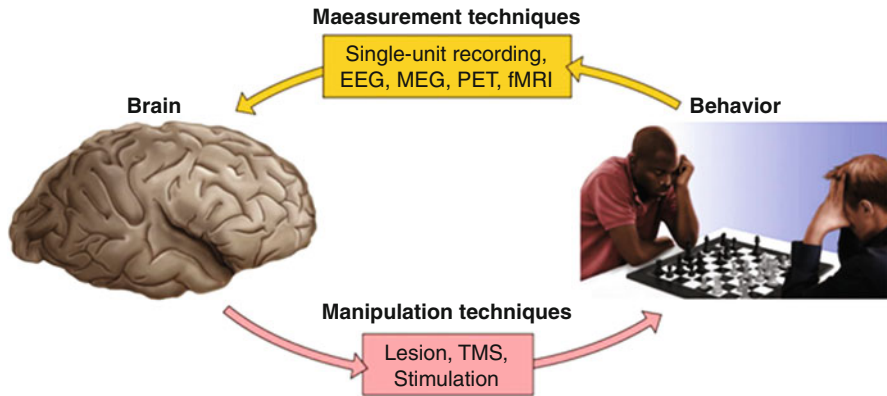


Fig. 73.1 Measurement and manipulation techniques. Researchers using measurement techniques (e.g., fMRI, PET, EEG) ask participants to engage in some behavior and then measure how brain functioning changes while that behavior is executed. Researchers using manipulation techniques examine how changes in brain structure or function – either induced by the experimenter (e.g., transcranial magnetic stimulation) or naturally occurring (e.g., brain lesions) – alter cognition and behavior (Originally published in Huettel et al. 2009)

understanding of neurotransmitter systems. And, EEG and MEG can record changes in brain function with millisecond precision, which can be very important for understanding rapidly changing aspects of cognition (e.g., shifts of attention). Hereafter, this chapter will consider both the value of brain imaging generally and the contributions of these specific techniques to the understanding of cognitive function.

Functional Brain Imaging Plays a Role in Modeling Cognitive Processes

There is a popular misconception that functional brain imaging is necessary for understanding cognition, emotion, and other aspects of our mental lives. At first consideration, this claim seems plausible: Since all of our cognitions (and thoughts, behaviors, etc.) are generated by our brains, then an understanding of those cognitions must require an understanding of the generating brain processes. This viewpoint is inherently reductionist, in that it assumes that low-level biological (i.e., physical) explanations for the mind should supersede high-level psychological (i.e., nonphysical explanations). Many cognitive psychologists, however, view this perspective as simply misguided. Psychological research has long attempted to create models of cognitive phenomena, to partition complex concepts into separate processes, and even to characterize the relative timing and strength of specific aspects of information processing (Fig. 73.2). Studies of learning, memory, and attention, as examples, preceded the advent of functional brain imaging by almost a century. Indeed, some core topics in psychology (e.g., problem solving,

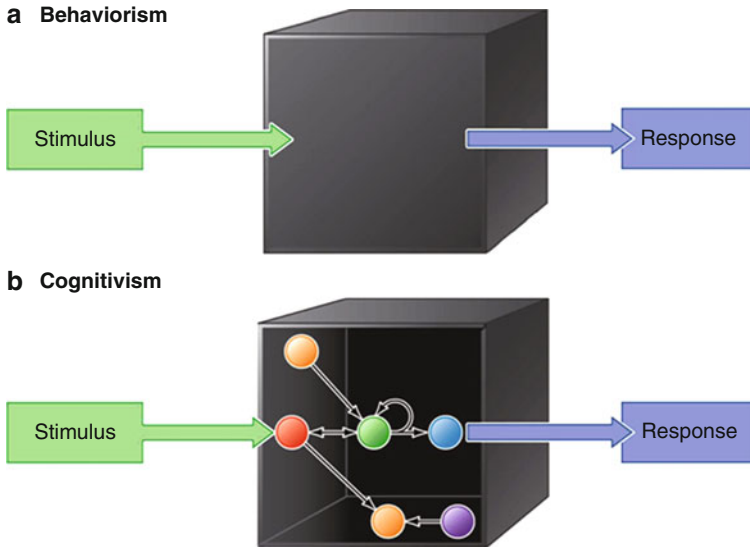


Fig. 73.2 The approaches of cognitive psychology for the study of the human mind. (a) The early twentieth-century approach of behaviorism tried to explain behavior without any reference to underlying mental phenomena (i.e., treating the mind as a “black box”). (b) Cognitive psychology attempts to develop theories that use mental representations (*colored circles*) and mental operations (*black arrows*) to explain the relationships between stimuli and behavior (Originally published in Purves et al. 2008)

self-reflection) remain largely unconsidered by brain imaging research. Many researchers studying cognition – probably even most – will never conduct a functional brain imaging experiment in their career.

Instead, functional brain imaging provides an important tool that can shape the direction of cognitive modeling. One important virtue of brain imaging is that it, like other neuroscience methods, can indicate the biological constraints on a cognitive process. Consider, by analogy, the long history of research on visual perception. Many core perceptual phenomena – from the nature of our color vision to differences in acuity across the visual field – were recognized long before their neural mechanisms had been identified. Even so, as individual properties of the visual system have been identified (e.g., functional specialization of the dorsal and ventral visual streams), those new findings can serve to clarify prior models and constrain new directions of research (e.g., separating spatial localization from object identification). Similarly, models of cognition can benefit from new evidence from brain imaging, as seen in the debates among memory research about one-versus two-process accounts of memory retrieval. Neuroimaging data can also provide new insight about the nature of psychological concepts, especially when different fields of inquiry seem to converge on a common concept. As will be discussed later in this chapter, fMRI studies in a number of cognitive domains (e.g., memory, attention, emotion regulation, decision making) have all implicated specific regions in the lateral prefrontal cortex in the goal-directed regulation of

behavior. These disparate studies have led to the higher-level concept of “cognitive control” processes that span a range of functions and task concepts.

Functional brain imaging methods have also provided critical links between process models – which almost always are built from data collected in normally functioning individuals – and disorders of cognition. In disorders where the locus of damage is known (e.g., lesion cases, degeneration of specific brain systems), understanding the likely functional consequences of those disorders can help interpret the often complex patterns of behavior that arise. Conversely, when the behavioral abnormalities are well understood, but the neural impairments remain unknown, functional brain imaging can guide inferences about what regions are impaired – potentially suggesting new courses of treatment or prevention. There has been an explosion of interest in the use of functional brain imaging for understanding psychiatric disorders, in particular. Schizophrenia and depression, to take just two disorders, have complex etiologies and broad effects on cognition. Using fMRI, researchers have identified a number of potential contributors to these disorders – complementing work in animal models and via analysis of drug effects. Addiction has been extensively studied using both PET and fMRI, with the former providing information about neurotransmitter systems and the latter about impulsivity and self-control.

Functional Brain Imaging Plays a Role in Modeling Neural Organization

Throughout its history, the scope of neuroscience has continually expanded. Early studies tended to focus either on relatively low-level basic science (e.g., the internal structure of neurons, the core methods of signaling) or on very high-level clinical applications (e.g., the effects of lateral prefrontal lesions on speech). Functional brain imaging has filled an important gap between these extremes.

Like the core techniques of the neurobiologist (e.g., single-unit recording), neuroimaging can be used to describe the properties of specific brain regions – typically with spatial resolution of millimeters to centimeters. While having coarser spatial resolution is considered a disadvantage in many domains, it does provide some important benefits for neuroscience. Neuroimaging techniques can record information about the entire brain at once (or within a short temporal window), allowing them to draw inferences about how different regions may work collectively toward a processing goal. One can appreciate why full-brain coverage might be an advantage when examining the enormous recent literature on functional connectivity between brain regions. Connectivity is typically inferred by subjecting fMRI data to statistical techniques that evaluate whether two regions show common patterns of activation over time (e.g., connectivity), whether some psychological variable affects the interaction between two or more brain regions (e.g., psychophysical interaction), or even whether changes in the activation of one region alter the activation of another region (e.g., dynamic causal modeling, Granger causality). Having relative coarse spatial resolution also forces neuroimaging techniques to consider brain function at the level of regions, not smaller

columns, circuits, or neurons. This may not seem like an advantage, since the actual computational units of the brain are not studied, but the relatively coarse scale is well matched to many important questions: Does the medial frontal lobe track response conflict? Do the hippocampus and adjacent rhinal cortex support different aspects of memory? At this time, the functions of large swaths of the cortex – and of many subcortical nuclei – remain incompletely understood, at best. Using functional neuroimaging to understand the properties of the larger regions will be a critical first step in advance of more circumscribed studies using other techniques.

Neuroimaging also provides critical advantages for studying human brain function. All of the techniques mentioned in the previous section can be used with human subjects, just as all can be used with nonhuman animals. Moreover, they each can be used in a largely noninvasive manner that is appropriate for use with healthy volunteers outside of the clinical setting. There are many cases of the same individual doing multiple fMRI or EEG studies over time, both to understand the basic properties of each technique and to understand changes in some cognitive process (e.g., over task learning). Only PET has some constraints on repeated participation, due to the need to inject a radioactive isotope. Having human participants may not seem critical for the progress of science; see, for example, the remarkable advances in the science of vision that were gleaned from recordings in cats and monkeys. But, there are some important neuroscience questions that cannot be answered solely from animal experimentation. Some brain regions' structure and function is less well conserved than others across mammalian species. The human prefrontal cortex, for example, occupies a much larger proportion of our brains than in monkeys, cats, or rats. (Its relative, if not absolute, size is shared with our great ape relatives, who are themselves rarely subjected to invasive neuroscience methods.) Our facility for language, and accompanying brain regions, differs in important ways from the communicative abilities of other species. And, many disorders of cognition (e.g., depression) have only imperfect animal models.

Finally, functional brain imaging has done much to increase the visibility of neuroscience within both the larger scientific community and the public at large. Neuroscience research has become embedded in surprising places. Several decades ago, even the most forward-looking neuroscientist might be dubious about the prospect of neuroscience research being conducted within economics or philosophy departments – yet these fields contribute extensively to studies of economic and moral decision making. Nor would one have expected that political scientists, or linguists, or even legal scholars would now integrate descriptions of brain function into their theories. Just as the interest in neuroscience has expanded, the barriers to conducting research have diminished. In particular, the accessibility of fMRI has increased – advanced dramatically in the past decade. Researchers who wish to use that technique can learn its basics through dedicated textbooks, well-regarded courses, and substantial online material (including sample datasets). The necessary imaging protocols now come standard on modern scanners, facilitating data collection. And, several of the leading analysis packages are provided freely to the scientific community. The sort of study that would have required a large and interdisciplinary team of experts in the

late 1990s can now be conducted by a beginning graduate student, likely with greater success. And, the results of such studies can be easily conveyed to the wider public (for better or worse).

Neuroimaging Techniques Have Distinct Capabilities and Limitations

As reviewed in the last section, neuroimaging techniques provide unique and valuable information regarding the manner in which psychological functions are mapped into brain activity. Neuroimaging techniques have allowed scientists to do something very new within the history of psychology and cognitive science: to peer into the causal chain of processes mediating between the extraction of information from the environment and the execution of behaviors. At some level, neuroimaging observes cognition – or at least its neural substrates.

Given the emphasis on images, as made explicit in the term “neuroimaging,” one might think that creating a global account of the neural substrates of cognition would be simple. Scientists could assemble, like fitting together pieces of a puzzle, a set of images from different neuroimaging methods that each provided information about a particular set of cognitive processes. This approach is not feasible, for two main reasons. First, cognition occurs both in space and time. Neuroimaging techniques are not just concerned with identifying the structures that are involved in particular cognitive processes, but also with identifying the temporal sequence and functional interactions between those regions. Second, neuroimaging refers not to a single method but to a variety of techniques that have strengths and limitations. As reviewed in this section, techniques differ in the type of information they can provide about brain function, such that each measures a single small part of the information processing associated with cognition.

Key Properties: Contrast, Temporal Resolution, and Spatial Resolution

Rather than providing pieces of a puzzle, the contribution of neuroimaging to cognitive neuroscience might be more like the testimony of different witnesses in a trial, each providing a different sort of information with varying certainty. Neuroimaging techniques can be roughly classified according to three factors: what they measure (i.e., contrast), how precisely in space can they measure (spatial resolution), and how often can they take their measurements (temporal resolution) (Fig. 73.3).

Functional MRI and PET base their image contrast (i.e., the factor that distinguishes parts of the image) on aspects of brain metabolism that can be measured in the vascular system. As such, these are sometimes called “hemodynamic” techniques. The most common form of fMRI measures blood-oxygenation-level-dependent (BOLD) contrast, which assesses changes in the amount of

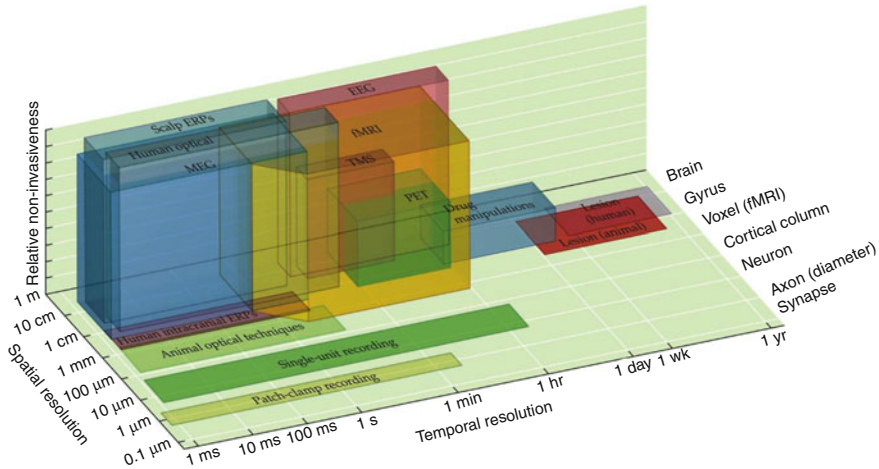


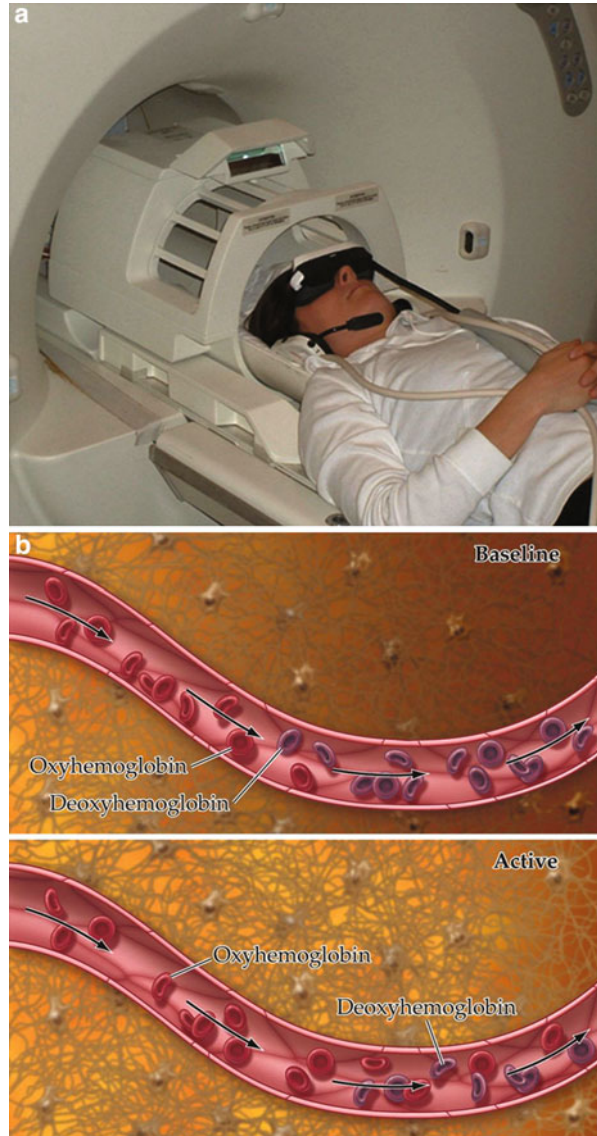
Fig. 73.3 Techniques used in neuroscience differ in their spatial resolution (vertical axes), temporal resolution (horizontal axis), and invasiveness (depth) (Originally published in Huettel et al. 2009)

deoxygenated hemoglobin within the local venous system; this provides a marker of the total metabolic activity of the nearby neurons (Fig. 73.4). PET often takes images sensitive to other markers of neuronal activity, such as oxygen or glucose (Fig. 73.5). (Note that there are many variants of PET imaging; this chapter focuses on those forms of PET most commonly used to study cognition, generally, and not specific receptor systems.)

These hemodynamic techniques are generally considered to have high spatial resolution but poor temporal resolution. Functional MRI can distinguish functional regions separated by millimeters, while PET has somewhat worse spatial resolution but can still provide whole-brain functional maps. These techniques provide a good level of confidence regarding the location of the activation they identify. Yet, their temporal resolution is relatively low; for example, the sampling rate of fMRI is on the order of a few seconds. Note that this pace is less a function of the limitations of scanner hardware than of the biophysics of the BOLD signal, which follows neuronal activity by several seconds and whose amplitude can decrease dramatically when sampled rapidly (i.e., because of MR relaxation effects). Even with those limitations, fMRI still provides much better temporal resolution than PET, which collapses data over a period that can last minutes. Thanks to its good balance between spatial and temporal resolution – along with its noninvasiveness – fMRI has become the dominant technology for imaging brain activity.

Yet, no hemodynamic technique can achieve the level of temporal detail provided by electromagnetic approaches like EEG and MEG. These techniques record signals associated with changes in the electrical potential of neuronal membranes, at extremely high temporal resolution (milliseconds). EEG uses a set of scalp electrodes, ranging in number from only a few to as many as 256, to register

Fig. 73.4 Functional magnetic resonance imaging (fMRI). (a) Participants in fMRI experiments can perform a range of cognitive and motor tasks while in the scanner. (b) The blood-oxygenation-level-dependent (BOLD) signal forms the basis of most current fMRI research. Active regions of the brain receive an oversupply of arterial blood (i.e., containing oxyhemoglobin), which reduces the local concentration of paramagnetic deoxyhemoglobin. Relative changes in the concentration of deoxyhemoglobin can be measured using special types of MR images, providing an indirect measure of local neuronal activity (Originally published in Purves et al. 2008)



small fluctuations of voltage (in microvolt range). Since the ongoing EEG record reflects the summed activity of all ongoing processes in the brain region monitored by each electrode, a further step to relate that activity with specific cognitive functions is to extract event-related potentials (ERPs). ERPs are even smaller fluctuations consistently triggered by cognitive events. To extract those ERPs from the background noise, it is necessary to average multiple EEG epochs that

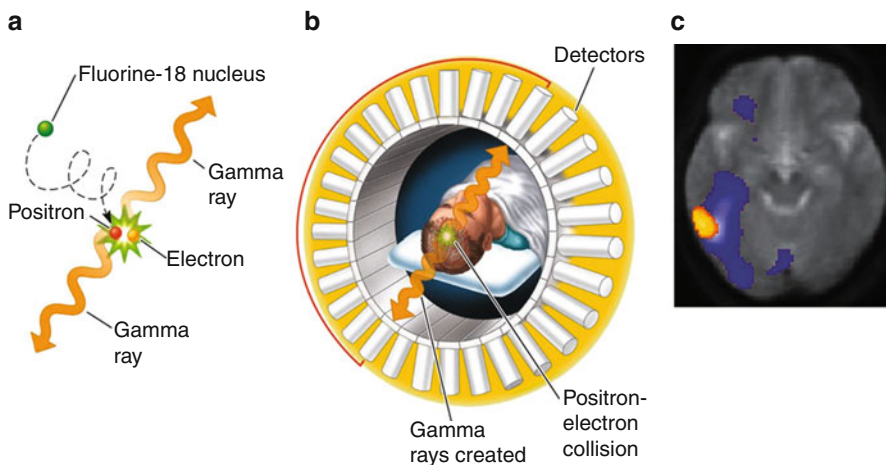


Fig. 73.5 Positron emission tomography (PET). (a) Molecules with radioactively labeled probes are injected into the bloodstream. Blood flows preferentially to areas with increased metabolism, such as active brain areas. When the radioactive compound decays, it emits gamma rays in opposite directions. (b) Those gamma rays are detected by sensors surrounding the head of the subject at the PET scanner, providing (c) an indication of the absolute concentration of that compound in different brain regions (Originally published in Huettel et al. 2009; Courtesy of Dr. David Madden, Duke University)

are time-locked to repeated occurrences of the event of interest. This averaging gradually flattens all the random noise revealing voltage fluctuations that are consistently related with cognitive processing. ERPs can, even if taken from a single electrode, provide important information about the temporal dynamics of neural processing (Fig. 73.6). Nevertheless, they do not represent a form of neuro-imaging until the spatial distribution of these scalp potentials is taken into account. Each electrode measures a different level of voltage depending on its position with respect to the sources of activity in the brain. After interpolating the voltage levels between electrodes, the result is a topographic voltage map that, in conjunction with source analysis algorithms, provides an estimate of the underlying neural activity.

MEG can be considered, with respect to EEG, as the flip side of the same coin. Both techniques measure signals associated with currents within the dendritic trees of cortical neurons. Any time that current flows in a conducting element, like neuronal dendrites, a magnetic field curves around such flow following the “right-hand rule”: If the right hand is made into a fist with the thumb pointing out in the direction of the current flow, then the field curves around that current in the orientation of the other fingers. Modern MEG machines can record these magnetic fields from sites over the entire head, and just as it is possible to extract ERPs from the EEG signal, it is possible to extract event-related magnetic field responses (ERFs) from the MEG signal and map out their topographical distribution to estimate the location of the underlying activity (Fig. 73.7).

The major advantage of electromagnetic brain imaging is its high temporal resolution, which coupled with information regarding the topographical distribution

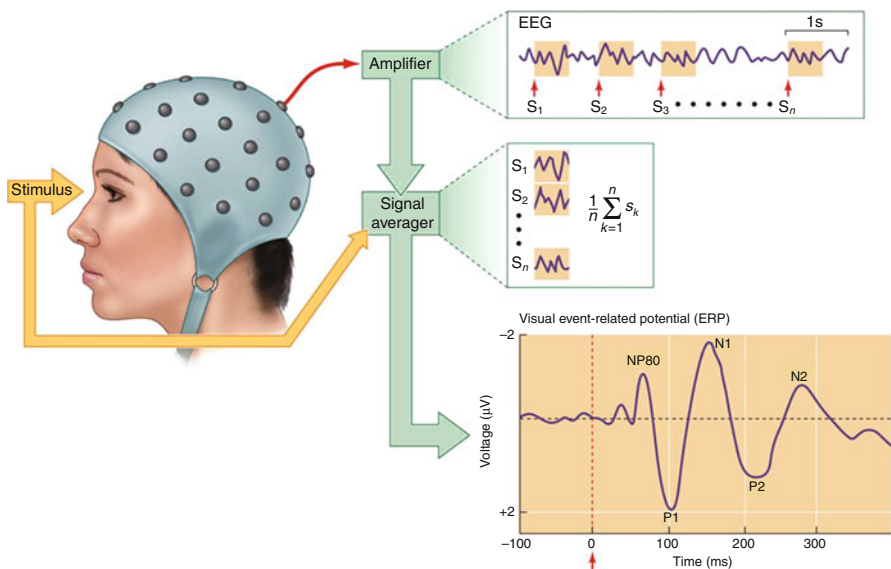


Fig. 73.6 Event-related potentials (ERPs). An ERP can be extracted by averaging portions of the ongoing EEG that are time-locked to repeated occurrences of a sensory, cognitive, or motor event. This procedure allows researchers to average out the EEG signal that is unrelated to the event of interest, revealing the average event-related response to the stimulus. This example shows an ERP that is recorded from the left occipital scalp in response to repeated visual stimulation at the right visual field (Originally published in Purves et al. 2008)

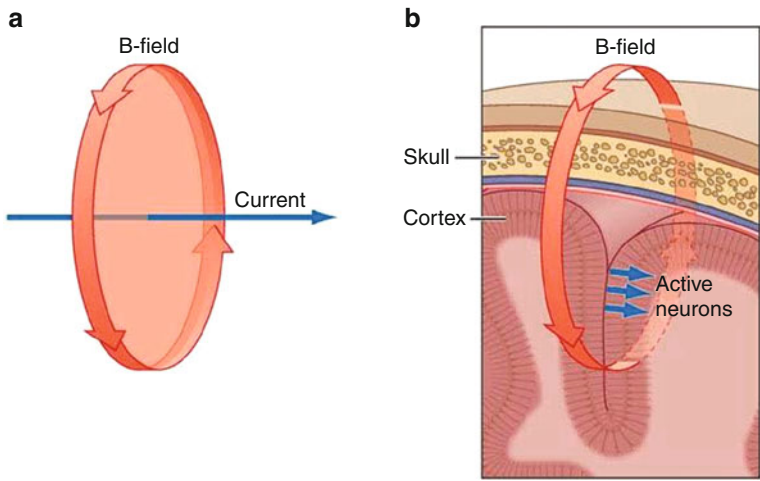


Fig. 73.7 Magnetoencephalographic signals (MEGs). (a) Dendritic currents in cortex produce circular magnetic fields following the “right-hand rule.” The fields that are generated in the sulci are more easily measured because they enter and exit the scalp orthogonally, allowing them to be detected by a magnetometer outside the head (b) (Originally published in Purves et al. 2008)

of ERPs and/or ERFs provides a dynamic picture of brain activity over time. Nevertheless these methods have a relatively low spatial resolution, a limitation even more stark when compared with fMRI. First, both EEG/ERPs and MEG/ERFs are unable to reliably identify activity coming from deep structures, both cortical and subcortical. Some of these structures are particularly relevant for a range of cognitive functions: action selection (basal ganglia), value assessment (ventromedial prefrontal cortex), and emotional arousal (amygdala). Thus, the inability of electromagnetic brain imaging to localize activity to these regions limits the scope of those techniques. Second, EEG and MEG are limited in the populations of neurons they sample. As can be inferred from the right-hand rule, EEG and MEG are selectively sensitive to activity coming, respectively, from the gyri and sulci of the brain cortex. This is because neurons in the gyri tend to be arranged perpendicularly to the skull, and neurons in the sulci tend to be arranged in parallel to it. A third challenge is that a given distribution of electrical or magnetic signals in the scalp could have been generated by any one of several different sets of generators in the brain (i.e., the “inverse problem”).

Optical brain imaging techniques, in their turn, have a different set of strengths and limitations. Diffuse optical imaging (DOI) records how the hemodynamic changes that accompany neural activity alter the scattering of light projected into the brain, which gives it approximately similar temporal resolution to fMRI. While DOI is of low cost when compared with fMRI or PET, it is also an invasive technique: It requires that the skull be opened up to illuminate the cortical surface with near infrared light and to optically record the light reflection. This restricted its application in humans to patients undergoing neurosurgery and to nonhuman animals, limiting its scope for the study of normal or nonpathological human cognition. The more recent technique of event-related optical signal (EROS) overcome this disadvantage by noninvasively transmitting light from sources around the head and then measuring the amount of light that returns to nearby detectors. Its images have contrast based on the proportion of light that is transmitted versus scattered in the underlying brain, which in turn depends on the electrical activity of the neural tissue. EROS has many advantages: It constructs three-dimensional maps of brain activity, it is noninvasive, it has high temporal resolution, it does not suffer from the inverse problem like ERPs/ERFs, and it is a relatively low-cost technique. Yet, it also has a relatively low signal-to-noise ratio, which has restricted its general use. Advances in instrumentation hold promise for improving the signal to noise of this potentially powerful technique.

Integration Across Techniques Carries Complementary Advantages

As described in the previous section, each functional brain imaging method strives for a common goal – linking psychological concepts to the underlying brain processes – and each has relative advantages and disadvantages compared to its peer techniques. Accordingly, growing efforts have been made to use methods in a complementary way. A clear example of this approach comes from the combined

use of EEG and MEG. As already mentioned these methods are, respectively, more sensitive to neural activity in cortical gyri versus sulci. Therefore, using simultaneous EEG-MEG allows a more complete view of how neuronal activity in the folded cortex relates to cognitive processes.

Probably the most active area of work in the context of these cross-methodological efforts refers to the integration of neuroimaging methods having high temporal resolution (i.e., ERPs, ERFs) with methods having a high spatial resolution (i.e., PET fMRI). The goal of this integration is clear; that is, to have at the same time a good spatial and temporal detail of brain activity. This integration can be achieved by using the same experimental paradigms in successive sessions that include one or the other technique, or by simultaneous recording. An increasingly employed approach refers to using data from fMRI or PET to constrain the solution of the algorithms used for source localization analyses for ERPs and ERFs. This approach increases the likelihood of identifying the actual sources of event-related electromagnetic activity, although it does not completely solve the inverse problem. Great efforts are being devoted to the development of simultaneous EEG-fMRI recording, to relate fMRI and ERPs in a more consistent way; for example, allowing to relate cross-trial variations in the BOLD signal with cross-trial variations in ERPs. Despite facing numerous technical difficulties, a good level of success has been achieved, suggesting a route for continuing reducing the trade-off between temporal and spatial resolution.

The Core Goal of Neuroimaging Is Functional Resolution

Resuming the legal analogy introduced previously, in the same way that different witnesses are more reliable regarding different aspects of an event, not all neuroimaging techniques are equally suitable for every question on cognition. The most basic division is between those techniques that better answer questions about the role of brain regions in a particular function (i.e., PET, fMRI), and those that are more suitable for questions about timing (e.g., ERPs, ERFs). Even so, the suitability of a given neuroimaging technique for a given question is not restricted to the notions of spatial and temporal resolution. What is more important is the ability of a given technique to provide new insights into brain function, or its functional resolution.

What makes neuroimaging so unique in the landscape of neuroscience techniques is its ability to provide a broad coverage of the brain in a noninvasive way. Therefore, the relative advantages of different techniques can best be exploited when addressing systems-level questions about brain function. For example, early ERP research was instrumental in identifying top-down modulation of early brain responses to sensory stimuli, a finding that is consistent with attentional bias signals coming from frontoparietal control regions. Rather than just identifying when and where this biasing occurs, more recent neuroimaging studies have asked more complex sorts of questions; for example, how does the interaction between the frontoparietal network and sensory cortex shape subsequent perception and

behavior? Of current techniques, fMRI provides the best combination of spatial and temporal resolution, signal to noise, and experimental flexibility for asking complex questions about brain function. Recent advances in fMRI analysis methods now provide better insight into the interactions among brain regions, without losing track of localized activity that by itself is informative. The next section specifically explores how fMRI have extended the impact of neuroimaging transforming the study and understanding of the brain and the mind.

Examples of Functional Brain Imaging: fMRI Research on Decision Making

The explosion of interest in functional brain imaging –such that there are now several thousand studies published annually – makes a comprehensive survey of the field impossible. Thus, rather than superficially consider the entire field, this section will draw illustrative examples from the use of a specific neuroimaging method to study a particular cognitive domain: fMRI studies of decision making. Of note, decision-making phenomena were studied by neuroscientists and cognitive scientists long before the advent of neuroimaging. Neuroscientists used single-unit electrophysiology to consider topics like information integration in sensory and motor systems, as well as goal-directed behavior in prefrontal cortex. Cognitive scientists – coming from psychology, economics, and other fields – created models that predicted typical decision making and identified biases that often intruded into those decisions. The application of functional brain imaging to problems in decision making served to link these disparate areas of research, leading to a new hybrid discipline often called “decision neuroscience” or “neuroeconomics.” The next section focuses on how neuroimaging has shaped research – and thinking – in this exciting new area of science.

Assessing Variability: State Effects, Context Effects, Group Differences, and Individual Differences

One of the most important contributions of functional neuroimaging is characterizing the dynamic relationship between brain and behavior in neurologically healthy subjects. Traditional accounts based on lesion studies provide important insights into the brain-behavior relationship, but drawing firm conclusions can be challenging, given that individuals with brain lesions differ in many ways from those without such damage. And, some questions about variability across individuals simply cannot be answered in lesion samples. The development of fMRI, in particular, has contributed greatly to the understanding of state effects, contextual effects, group differences, and individual differences in the normal population – with the elucidation of such effects becoming a central topic within decision neuroscience. Selected examples within each of these areas are provided below, making reference to specific recent studies for further exploration by the interested reader.

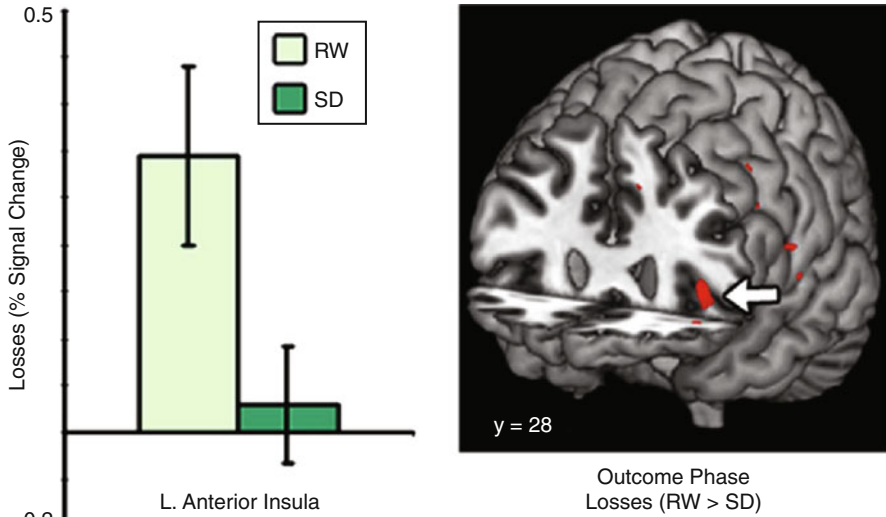


Fig. 73.8 Sleep deprivation diminishes neural sensitivity to losses. There is a reduction of loss-related activation within the left insula after sleep deprivation (SD) compared to rested-wakefulness (RW) state (Originally published in Venkatraman et al. 2011)

One striking example of a state effect can be seen in sleep deprivation (SD), which biases the brain mechanisms underlying risk preferences. Venkatraman and colleagues observed that while non-sleep-deprived individuals are more loss averse than gain seeking, a single night of sleep deprivation reverses that bias. This shift in behavior was correlated with an increase in ventral striatum and ventromedial prefrontal activation (i.e., regions typically involved in value computation) and a decrease in anterior insula activation (i.e., a region typically involved in negative affect) (Fig. 73.8). These changes in valuation were independent of effects on attention and vigilance, both behaviorally and neurally. Evidence for state effects on decision making have important implications for society at large, in the sense that risky behaviors after sleep deprivation do not simply result from a lack of vigilance (i.e., a deficit that could be repaired in part by consuming some stimulant like caffeine), but from more pernicious shifts in the processing of risk and reward outcomes.

Researchers interested in decision-making behavior have long recognized that people are remarkably susceptible to the manner in which options are presented; that is, choices depend on context. In the well-known “framing effect,” presenting a decision scenario as a choice between gains causes participants to become risk averse (gain frame) while presenting that same decision scenario as a choice between losses makes people risk seeking (loss frame). In a seminal study, de Martino and colleagues found that activation in the amygdala and dorsomedial prefrontal cortex was correlated with changes in behavior in the loss and gain frames. This result suggested a causal explanation of the framing effect that was not evident

from behavioral studies, alone: Sensitivity to frame is driven by an affect heuristic (i.e., a simple rule) that alters the emotional response to these decision scenarios.

Psychological studies of decision making have also concentrated on questions of group differences (e.g., Are older adults more risk averse than younger adults?). Functional neuroimaging can extend our understanding of group effects by exploring their biological substrates, which in turn can give clues about how such differences arise from the interplay of brain and environment. The differences between adolescents and adult decision making have been the focus of an important corpus of research during the last years. Traditionally adolescence has been characterized as a developmental period characterized by risky decisions and actions. During the last decade, brain research has shown that part of the explanation of such pattern is that the human adolescent brain exhibits a combination of increased reward sensitivity and decreased control processing, relative to young adults. Even more recently, research groups have been interested in how socioeconomic disadvantage in early development can shape the later functioning of the neural circuitry for decision making. Gianaros and colleagues found that lower parental education, a presumptive indicator of early socioeconomic disadvantage, covaried with anterior cingulate and dorsomedial prefrontal cortex responses to monetary gains. Also, lower parental education was associated with reduced functionality of corticostriatal systems implicated in impulse regulation. This sort of research is notable not just for its implications for brain function, but also because it indicates how functional neuroimaging can contribute to issues in seemingly distant fields.

In recent years, there has been a growing interest in how individual differences – in economic preferences, personality traits, genes, or hormones – modulate the brain mechanisms for decision making. A typical approach seeks correlations among an individual difference variable, choice behavior, and brain activations. For example, Sharot and colleagues studied the neural substrate of optimism bias, or the commonly observed tendency of people to expect positive events in their future (e.g., on average, people expect to live longer than the median life span). They found increased activation in the amygdala and in the rostral anterior cingulate cortex when people imagine positive future events, compared to negative ones. They also found that the increment of activity in the rostral anterior cingulate cortex was correlated with a psychometric measure of trait optimism. This result was consistent with previous evidence showing that depression, which leads to unwarranted negative bias, is associated with abnormal functioning in the rostral anterior cingulate cortex. Another approach to study individual differences in decision neuroscience is using the choice history of each subject to estimate parameters of interest. Such parameters typically correspond to variables studied by behavioral economics, such as risk preference or discounting rate. Using that methodological approach, Huettel and colleagues estimated individuals' preferences for risk (uncertainty with known probabilities) and ambiguity (uncertainty with unknown probabilities) in an economic decision-making task. Their fMRI results showed that lateral prefrontal cortex activation was predicted by subjects' ambiguity preference (the greater the activation, the greater the ambiguity preference) and posterior parietal cortex activation was predicted by risk preference (Fig. 73.9).

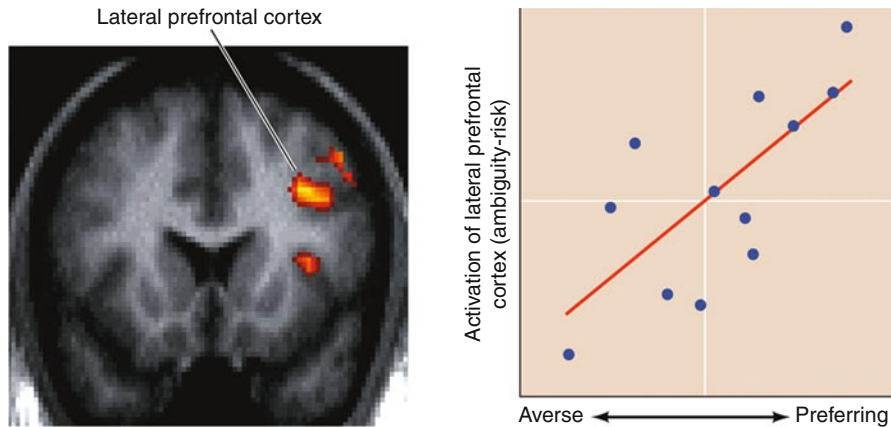


Fig. 73.9 Brain response to economic ambiguity. Ambiguity is defined as a situation in which one must make a decision without knowledge regarding the likelihood of the possible outcomes. Ambiguity evokes increased activation in the lateral prefrontal cortex, and the magnitude of activation depends on whether the subject prefers or is averse to ambiguity (Originally published in Purves et al. 2008)

Along with suggesting that decision making under ambiguity and risky decision making correspond to different processes in the brain, such findings support ongoing work in cognitive neuroscience showing that lateral prefrontal cortex implements contextual analysis and inhibits impulsive responses. This study emphasizes how fMRI studies of decision making can at the same time improve our understanding of individual differences, shed light into conceptual distinctions (e.g., ambiguity vs. risk), and shed light into the functional role of brain regions.

Computational Models: The Case of Reinforcement Learning

Traditionally, experimental paradigms in cognitive neuroscience have been motivated by psychological models. As such, they searched for neural correlates of classical psychological concepts (e.g., episodic memory, attention, language, reasoning, etc.). Although psychological approaches to cognitive neuroscience remain important, an increasing number of studies adopt a complementary computational perspective on research. These model-based studies use paradigms that provide reasonable algorithmic accounts of the operations that the brain may be performing while guiding behavior. Most of these formal models come from computer science, artificial intelligence, and (especially in the case of decision neuroscience) economics. This approach has been inspired by the idea that a full understanding of cognition requires specifying the problem that the brain is trying to solve when producing behavior (i.e., the brain's goal), defining the algorithmic operations through which it achieves that goal, and specifying how such algorithms are implemented in the biological tissue of the brain. The convergence between

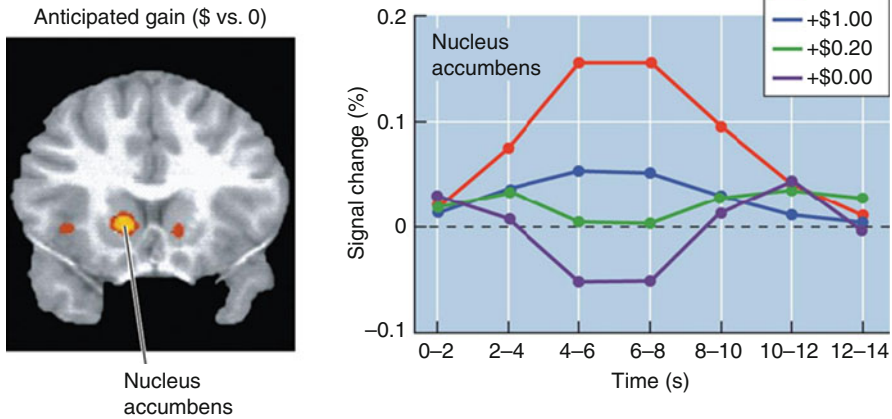


Fig. 73.10 Activation in the nucleus accumbens in response to expected and omitted rewards. Previous single-unit recording studies in monkeys showed that neurons in the brain's dopaminergic system increase their firing in response either to unexpected rewards or to cues predicting rewards. Such neurons also decrease their firing rates when an expected reward is omitted. Shown here are data from a fMRI study by Knutson and colleagues that shows a similar effect in the nucleus accumbens, a region to which dopaminergic midbrain neurons project (Originally published in Purves et al. 2008)

empirical, psychological, and computational approaches predates functional neuroimaging, but functional neuroimaging studies now play a crucial role in extending the computational approach to cognitive neuroscience. Functional neuroimaging have been used to find the neural counterpart of the variables included in such algorithms, extending the range of questions the field can help to solve from “where” to “how” questions.

Model-based approaches are now common within the neuroeconomics literature. The paradigmatic example comes from the study of the neural basis of reward-based and punishment-based learning. Decision making is a learning-guided process, in that the outcomes of decisions are assessed based on the difference with regard to previous expectations (i.e., temporal difference or TD learning) and this difference provides a computationally tractable method for optimizing future decisions. Several fMRI studies show that a TD prediction-error signal is expressed in the human ventral striatum during reward-based and punishment-based learning. Such fMRI findings are in line with single-unit recording studies in monkeys showing TD signals in dopaminergic midbrain neurons projecting to the ventral striatum in the presence of reward consumption and expectation (Fig. 73.10). Thanks to its ability to provide whole-brain coverage, fMRI studies have provided new information about how this value-based learning system interacts with the rest of the brain (e.g., how striatal activity is modulated by prefrontal cortex when people express self-control). These studies are not only a clear demonstration of the role that human functional neuroimaging have played in extending findings from animal models to human cognition, but also of how computationally informed

neuroimaging can connect disparate disciplines (e.g., economics, psychology, neurobiology, computer science). Such convergence is particularly clear in decision neuroscience. On one hand, formal models (e.g., TD learning) are used to advance our understanding of the brain-behavior relationship. On the other, functional neuroimaging studies within neuroeconomics have been used to test or constrain formal accounts of behavior.

Guiding Development of New Models: The Case of Intertemporal Choice

All animals face situations where they have to choose between costs and benefits that are distributed over time. These intertemporal choices are especially relevant for humans who must evaluate even distant future outcomes to guide their current choices. Individuals often sacrifice an often-considerable amount of value to obtain a reward sooner as opposed to later. This phenomenon is highly relevant for economics, since time is involved in many choices with economic consequences (e.g., taking a job now or getting a degree, spending money during youth or saving for retirement). In economics, the rate of delay discounting refers to the degree to which the present value of an outcome is degraded by delay to its receipt. The normative model for such discounting predicts that rational agents will exponentially devalue delayed outcomes at a fixed rate per unit of time (i.e., all intervals of time result in the same proportional discounting). Numerous violations of this model are evident. One of the most important is that of preference reversals where people exhibit much steeper discounting over short time scales; for example, they prefer \$100 now to \$110 in 1 week, but prefer \$110 in 53 weeks to \$100 in 52 weeks.

Descriptive models have been proposed by behavioral economics that better account for human intertemporal choice. Most research has focused on variants of a hyperbolic discounting model in which discount rates are steepest for immediate time intervals and slowest for time intervals in the distant future. An important question, therefore, lies in determining the exact form of such models. Some research is consistent with a single-parameter model according to which discounting is proportional to delay (i.e., leading to a pure hyperbolic function). Other data supports a quasi-hyperbolic model with two discounting parameters: The first (β) defines a rapid devaluation over very short time scales, while the second (δ) defines a constant exponential devaluation over longer time scales.

Several functional neuroimaging studies have tested the biological plausibility of these different sorts of models, leading to an important debate over whether the brain has one or two separate valuation systems. These studies typically have adopted the methods of behavioral economics when exploring time preference, requiring participants to express preference between a narrow set of alternatives, generally two, expressed as a “sooner smaller” versus “later larger” contrast (e.g., \$5 today or \$10 in a month). A highly influential study by McClure and colleagues supported the idea of a dual valuation process like the one suggested by

the quasi-hyperbolic model. Using fMRI, and through a contrast between decisions involving an immediately available reward and those involving only delayed rewards, they found activation specific to the presence of an immediate reward within regions normally associated with value representation, such as the ventral striatum, medial prefrontal cortex, and medial orbitofrontal cortex. On the other hand, a different set of regions had similar activation levels regardless of intertemporal delay: These included the dorsolateral prefrontal cortex, parietal cortex, and lateral orbitofrontal cortex. Thus, the beta and delta systems in the quasi-hyperbolic model could correspond to limbic-paralimbic structures and prefrontal-parietal cortex, respectively. These findings have been interpreted as providing evidence for a dual valuation hypothesis, specifically that choices between immediate and delayed outcomes are determined by the relative activation of two competing valuation systems.

For theorists favoring a single-value system, that some regions show greater activity to choices involving an immediate alternative does not necessarily support the idea that those regions are part of the immediate, beta system. Instead, the reported “beta regions” might actually be computing a common neural currency for valuation, in which the magnitude of activation is proportional to the subjective magnitude of reward. Conversely, involvement of lateral prefrontal activity for delayed rewards would not correspond to a separate valuation process, but to well-studied executive control process which might modulate the value system. In support of this interpretation, Kable and Glimcher demonstrated that the value of a delayed outcome is represented in the activation of canonical reward-related brain regions – and the relationship between activation and subjective value holds regardless of the time until reward delivery (Fig. 73.11). Note that even though most current evidence supports the single-value-system theory, considerable effort remains focused on understanding how control systems feed into that value system to shape choice.

Outlook

Given the remarkable growth in functional brain imaging over the past two decades, that the field will continue to advance over the coming years may seem an obvious prediction. The forms those advances will likely take, however, might be counter-intuitive. For example, even though there will be continual technological improvements in brain imaging hardware, those improvements will be largely irrelevant for further progress in the field. As evidence, consider that many research sites still use MRI scanners with field strength of 1.5T – which was first introduced approximately 30 years ago with the initial “high-field” systems. Similarly, EEG systems of today are clearly superior to those of a decade ago (e.g., more channels, better amplifiers), but that improvement in itself does not fundamentally change the sort of experiment that can be conducted. The techniques of functional brain imaging are well established and mature, but still flexible enough to address the many outstanding questions in cognitive neuroscience.

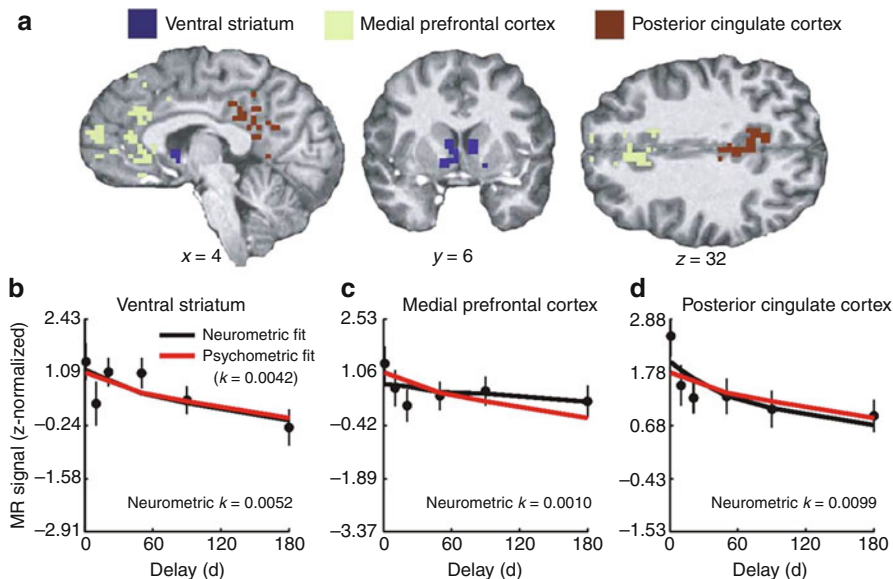


Fig. 73.11 Match between behavior and fMRI data in an intertemporal decision-making task. On each trial, subjects chose between a fixed immediate reward and a larger delayed reward that varied randomly from trial to trial. From each subject's choices, it is possible to infer the rate in which the subjective value of rewards is discounted with delay (K). **(a)** Regions showing greater activity for trials involving the largest objective amount of the delayed reward than for trials involving the smallest amount, or greater activity for trials involving the shortest delay to the delayed reward than for those involving the longest delay. **(b-d)** Neurometric-psychometric comparison. *Red line* represents the predicted brain activity at each delay according to the subject's behavioral discount rate, and *black line* describes brain activity at each delay. There is a relatively close psychometric-neurometric match in each region, such that the same regions appear to represent the subjective value of rewards at all delays (Originally published in Kable and Glimcher 2007)

Nor are new physiological markers likely to push neuroimaging research in new directions. Nearly all current fMRI studies create images sensitive to BOLD contrast, just as they did in the mid-1990s. Electromagnetic techniques, like EEG or MEG, are limited in the sorts of signals they measure by the properties of the brain and skull, and so substantial changes in their basic measures are unlikely. (Note that there is one important exception to this point: Researchers using PET continue to identify new compounds that target distinct brain systems, which in turn leads to fundamentally different sorts of images.) Even the integration of multiple physiological markers – as when researchers simultaneously measure fMRI and EEG signals – will lead to incremental not wholesale changes in research methods.

What will be most critical for progress are new developments in experimental design and analysis. The complexity of experimental designs has been increasing at remarkable pace, such that studies now address much more complex aspects of cognition than would have been considered possible a decade ago. New analysis

approaches extract information from brain imaging techniques that was heretofore ignored by even sophisticated researchers. And, exciting and novel strategies for meta-analysis assess the overall direction of the field – identifying patterns in results that might be missed when looking at single studies. The following sections focus on three aspects: Who will be the new researchers doing functional brain imaging research? What new analysis methods will they use? How will cutting-edge research coalesce into new disciplines?

The Next Generation of Researchers: Who? Where? and, How Many?

One of the most striking aspects of functional brain imaging methods, especially EEG and fMRI, is how accessible they have become. Conducting a study no longer requires rare technical expertise – although having such expertise can, of course, increase one's odds of obtaining a quality result. The novice researcher can often use the hardware at its default settings, create a new paradigm that is modeled on published work, download freely available analysis programs that are supported by a large user community, and publish their work in open-access peer-reviewed journals. The increasing accessibility will lead to two sorts of changes in the composition of the next generation of functional brain imaging researchers. First, researchers will come from a wider range of disciplines (i.e., beyond psychology, neurology/radiology, and neuroscience). There is increasing interest in functional brain imaging within the social sciences and humanities, as researchers address questions in aesthetics, moral philosophy, economics, political science, and many other disciplines. Second, these techniques will become more prevalent within countries that are less well represented within current neuroscience research (e.g., those not within parts of North America, Europe, and the Pacific Rim). The dramatic increase in the availability of high-field MRI scanners, in particular, means that many more researchers have access to fMRI-compatible systems: This will increase the diversity of scientific questions being addressed, while also facilitating important cross-society research (e.g., understanding cultural effects on cognition). Even if the growth of research in the United States and Western Europe slows dramatically, as a result of saturation or funding declines, any slowdown will be more than offset by thousands of new neuroimaging researchers from countries with developing research enterprises – many of whom will be trained in established graduate programs in the coming years, but then will travel back to their home countries to lead burgeoning research programs.

New Analyses and New Research Questions

The most common criticism of functional brain imaging is that it provides nothing more than “colorful pictures of the brain.” Why should we care, its most strident critics argue, whether a cognitive function activates this brain region or that brain region? After all, we already knew that the function was implemented somewhere

in the brain. This criticism is frequently and confidently asserted – yet is ultimately misguided. Localizing a particular function to a particular brain region has been extraordinarily important both for many applications (e.g., understanding neurological disorders) and for building links between diverse areas of basic research (e.g., understanding how processes of attention gate the contents of memory).

In the coming years, however, this criticism will become simply irrelevant. The core goals of functional brain imaging will move well beyond creating lists of activated brain regions to descriptions of the processing connections, both local and global, in the brain. An exciting new approach toward understanding local processing has come from the development of fMRI multi-voxel pattern analysis (MVPA) techniques. Considered in their broadest sense, MVPA extracts information from the relative changes in activation among voxels. To appreciate the potential importance of this technique, imagine a very simple fMRI experiment in which participants view a series of photographs of outdoor scenes. Traditional analysis methods would reveal that there was activation throughout primary visual cortex to the presentation of each photograph. Yet, that would hardly be a compelling result – after all, the participant is looking at a complex visual stimulus. By applying MVPA, information about how each voxel responds to each photograph can provide much more nuanced information about brain function (e.g., how low-level features like orientation and brightness combine to create a complex image). For an example of the power of this approach, researchers using MVPA in combination with computational modeling have been able to take patterns of fMRI activation and then predict the characteristics of an image the person was viewing – in effect, reading out the contents of visual perception (Fig. 73.12). Future research will extend these methods into many new domains, from memory to decision making, which could benefit from a more precise description of local computations.

Conversely, understanding global aspects of brain processing will rely on new methods for mapping functional connectivity across the brain. So far, these techniques are most well developed within fMRI and EEG research. The core idea of functional connectivity is that how regions jointly change over time indicates whether they are part of a common path in information processing, even if our techniques cannot observe the actual flow of information between those regions. Considerable recent work has shown that functional connectivity can change with task context; that is, two regions may be functionally coupled while the participant performs one sort of task, but have no apparent relationship under another task. Many researchers have even been examining connectivity within “resting-state data” collected, while the participant performs no task at all. In the absence of a task, the brain is far from quiescent: Its regions interact in remarkably complex and robust patterns that describe its intrinsic global structure. Connectivity analyses provide a clear counterargument to the idea that neuroimaging only identifies where a given function is manifest in the brain; on the contrary, in many cases neuroimaging shows that a function can be distributed in both time and space. In summary, the goal of functional brain imaging will no longer be the creation of images but of inferences about the computations that underlie cognition.

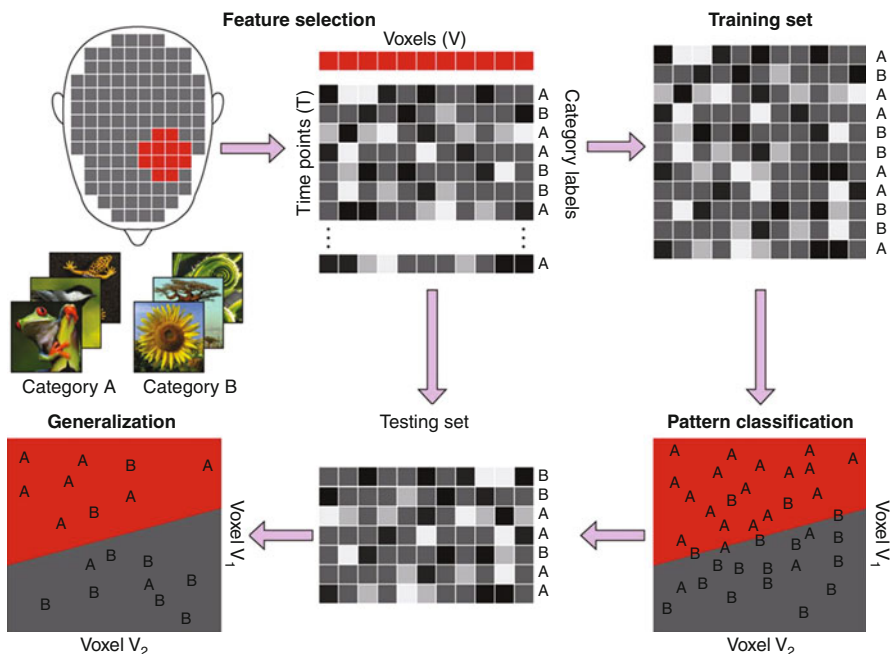


Fig. 73.12 Conceptual overview of multi-voxel pattern classification of fMRI data. In this example, the researchers are interested in identifying voxels whose activation predicts whether the subject is looking photographs of animals (category A) or plants (category B). The first stage of the process is feature selection, consisting in the selection of a subset of voxels for subsequent analyses. The feature set then splits into a training set, from which a pattern classifier will be derived, and a testing set on which the classifier efficacy can be tested. In this example, a linear classifier optimally distinguishes between animals and plants. Note, however, that fMRI pattern classification typically involves many more dimensions (i.e., the surface that distinguishes the categories of interest typically has a much higher dimensional space) (Originally published in Huettel et al. 2009)

New Ways of Synthesizing the Neuroimaging Literature

In many ways, functional brain imaging suffers from its own successes. Each advance attracts new researchers to the field: As these researchers address new sets of questions, they often bring new techniques and new concepts with them. Research becomes increasingly vibrant and diverse – but also more difficult to integrate within a single traditional discipline. In short, the current explosion of interest (and research) in functional brain imaging will lead to even greater need for synthesis.

Rare is the single neuroimaging study that, by itself, conclusively and permanently answers a research question. More frequently, progress in neuroimaging research (like in many other fields) involves the accumulation of information across many studies that together converge on a common conclusion. Such synthesis can

arise in several ways. The most traditional is a literature review, in which one or more experts describe the fundamental insights that can be drawn from current research in a field. For neuroimaging research, the typical literature review can be supplemented by a formal evaluation of activation-function relationships. In what is sometimes called activation likelihood estimation (ALE), researchers combine coordinates of activation across many studies to identify which voxels are regularly associated with a particular function. While ALE and similar approaches have many advantages, they can only provide specific conclusions when combining across studies that use very similar sorts of experiments. To overcome this limitation, researchers have begun to use meta-analytic techniques that break down complex tasks into their constituent processes. So, its data could still be combined across experiments that use rather different sorts of tasks (e.g., memory vs. decision making), as long as those tasks evoked some common process at one point in time (e.g., inhibiting a potent response). This sort of meta-analysis represents, in many ways, the future of neuroimaging research: It goes beyond simple maps of activation, it integrates information across sets of studies, and it allows inferences about not just brain regions but also cognitive processes.

Final Thoughts

Functional brain imaging techniques will remain central to the neurosciences for the foreseeable future. The increasing flexibility and accessibility of these techniques – particularly fMRI and EEG – will make them especially valuable for those new to neuroscience research. They also will remain the most powerful approach for studying the human brain at a systems level, and thus provide highly complementary data to other systems neuroscience techniques (e.g., single-unit recording). Yet, these techniques will surely change, both individually and collectively, as technology advances. Researchers should be prepared to adapt with those changes, so that they can take advantage of the next generation of techniques for creating images of the functioning human brain.

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