Title
Chapter 4 Functional imaging

Author
Kayser, Andrew S

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Abstract

Functional imaging methodology has revolutionized our ability to understand brain – behavior relationships. In contrast with the static images obtained with standard imaging methods, functional images permit us to track brain activity as humans view stimuli, hear sounds, consider choices, and make decisions. The insights now possible because of this technology have not only provided new potential markers for disease, but also permitted questions of neural mechanism to be addressed in living humans. Because of the breadth and depth of research that directly or tangentially touches upon functional imaging, it is impossible to do justice to the various subfields, analysis streams, and methodological complexities in one chapter. Instead, this chapter will provide a brief overview of the underlying conceptual framework, basic analytic techniques, and details of the imaging methodologies available for the acquisition of functional imaging data.

Keywords: functional imaging, cognitive neuroscience, functional specialization, functional integration, MRI, PET, MEG, SPECT

Functional imaging methodology has revolutionized our ability to understand brain – behavior relationships. In contrast with the static images obtained with standard imaging methods, functional images permit us to track brain activity as humans view stimuli, hear sounds, consider choices, and make decisions. The insights now possible because of this technology have not only provided new potential markers for disease, but also permitted questions of neural mechanism to be addressed in living humans. Because of the breadth and depth of research that directly or tangentially touches upon functional imaging, it is impossible to do justice to the various subfields, analysis streams, and methodological complexities in one chapter. Instead, this chapter will provide a brief overview of the underlying conceptual framework, basic analytic techniques, and details of the imaging methodologies available for the acquisition of functional imaging data.

Cognitive Models

The primary focus of this chapter will be on functional imaging as a tool to explicitly evaluate mechanisms of brain function. Studies that capitalize on this approach to functional imaging begin with a model of the cognitive process under study, and use that model to make predictions about function in control or patient groups. For example, models of working memory hypothesize that regions with the dorsolateral prefrontal cortex (dlPFC) are critically involved in the maintenance of memoranda between the time the memoranda are encoded and the time they are retrieved (D'Esposito and Postle, 2015). In patient groups with poorer working memory as measured behaviorally, one model might predict that poorer performance should be correlated with reductions in activity within dlPFC, while another might postulate that weaker working memory maintenance should be reflected by a compensatory, effort-related increase in activity within dlPFC. Neuroimaging can help to distinguish between these possibilities.

This point of view contrasts with the use of functional images solely to define a biomarker – i.e. a factor that distinguishes a given population of subjects from another, agnostic

with respect to mechanism. In a pioneering study of patients with Alzheimer's disease, for example, Greicius and colleagues demonstrated that differences in activity within the default network could distinguish patients with Alzheimer's disease from healthy, age-matched control subjects (Greicius et al., 2004). The default network comprises regions within the medial frontal lobe, posterior cingulate/precuneus, and lateral parietal lobes that tend to be more active when subjects are introspecting or engaged in unconstrained thought, compared to when subjects are explicitly performing a task (Raichle et al., 2001). While it is possible to infer function from this finding, this differential activity can also be used solely as a way to distinguish patient groups, and thereby to potentially inform diagnosis. In this way, it is similar to an anatomical MRI scan, CT scan, or other static imaging modality, though potentially more sensitive to pathology, especially for those cases in which a structural change is not found. Of course, the work done to evaluate cognitive models need not be exclusive of studies to identify biomarkers that distinguish patient groups; once a model-based distinction between subject groups is found, this finding might also serve as a biomarker to differentiate similar groups in the future.

Functional Specialization / Integration

Because of its ability to evaluate and refine such cognitive models, neuroimaging has come to define the discipline of cognitive neuroscience, which seeks to link cognitive processes to their underlying mechanisms (Kosslyn and Shin, 1992). Broadly construed, the models tested by neuroimaging studies, whether clinical or otherwise, address hypotheses about brain-behavior relationships that can be organized along two conceptual domains: *functional specialization,* the idea that areas of the cerebral cortex represent functional modules that are specialized for a specific cognitive process, and *functional integration*, the idea that a cognitive process can be an emergent property of interactions among a network of brain regions, and thus that a brain region can play a different role across many functions. The example in the first paragraph represents an example of functional specialization – i.e. the concept that a specific

area within the dorsolateral prefrontal cortex is somehow important for working memory maintenance – whereas the example in the second paragraph touches upon functional integration – i.e. the concept that large-scale interactions within brain regions collectively known as the default network are somehow relevant to Alzheimer's disease (D'Esposito and Postle, 2015; Greicius et al., 2004; Sreenivasan et al., 2014).

These two notions are as old as the discipline of neurology itself, reflected in discussions as long ago as the debate between Charcot and Brown-Sequard at the Societe de Biologie in 1875 (Goetz, 2000). In this debate, Charcot championed the approach of brain–behavior relationships based on careful observation of individuals with neurological injury resulting in focal brain damage. The idea of functional specialization evolved from hypotheses that damage to a particular brain region was responsible for a given behavioral syndrome, characterized by a precise neurological examination and post-mortem pathological findings. For example, Charcot noted that "destruction of the anterior part of the internal capsule always causes hemiplegia on the opposite side of the body." In contrast, Brown-Sequard, relying on his experimental work in animals, found that similar lesions in his preparations did not reliably produce similar symptoms: "a lesion of the same point may produce a great variety of symptoms, while on the other hand, the same symptoms may be due to the most various of lesions." Approximately a century later, the introduction of structural brain imaging, first with computerized tomography and later with magnetic resonance imaging (MRI), paved the way for more precise anatomical localization in the living patient of the lesions producing cognitive deficits after brain injury. In practice, the superb spatial resolution of structural neuroimaging also reduced the reliance on autopsy for making brain–behavior correlations.

Even more so than structural imaging, however, the introduction of functional neuroimaging methodologies revolutionized our ability to understand the neural mechanisms underlying cognitive processes. Early studies using Positron Emission Tomography (PET), for example, revealed not only that the primary visual cortex could be reliably mapped in retinotopic

fashion (Fox et al., 1986), but also that the default network reliably deactivated during the performance of cognitive tasks (Raichle et al., 2001). As a result, these techniques have contributed much to the above debate. Rather than considering the concepts of functional specialization and functional integration as antagonistic, these technologies have permitted the investigation of more subtle questions in cognitive neuroscience that emphasize the importance of the clinical or scientific question and the nature of the assay. To this end, we will next discuss how functional neuroimaging techniques are used to make inferences about cognitive models – whether they emphasize functional specialization, integration, or both – before moving on to a consideration of the individual technologies themselves.

Correlation versus Causation

A first consideration concerns whether the information that neuroimaging techniques provides should be considered correlated with the behavior of interest, or causal for that behavior. At their foundation, functional imaging techniques interrogate the brain regions whose activities vary with sensation, action, and/or the processes that link them. Demonstrating that activity within a network of motor regions including the supplementary motor area, bilateral premotor cortices, and primary motor cortex, for example, increases during task performance compared to rest is suggestive, but not conclusive, that these regions are necessary for motor actions during task performance. Even in well-designed tasks, the subject may engage other, unwanted cognitive processes that are not directly measured in the experiment, or that are strongly confounded with the process of interest – e.g. increased arousal during motor movements. As a result, neural activity may reflect a confounding computation that is unrelated to the process under study. Thus, neuroimaging methodologies, whether based on MRI, EEG, or otherwise, are correlational in nature.

To make more causal inferences, methods for perturbing activity within a brain region – and model-based predictions about the consequences of those perturbations – must be

available. Such causal inferences were previously possible only when lesions resulted from brain injuries, such as stroke or trauma, and a change in behavior could be readily identified. As Charcot discussed in the case of stroke, for example, damage to the internal capsule, determined by autopsy, could be linked with hemiparesis on the contralateral side as determined by history and examination (Goetz, 2000). Similarly, the famous case of Phineas Gage provided causal evidence that damage to the ventromedial prefrontal cortex affects social function, given the appreciation of his marked personality changes pre- and post-injury together with pathological findings (Damasio et al., 1994). Of course, these "natural" causal tests are not foolproof. Echoing the arguments of Brown-Sequard, such a lesion may exert its effects only because of a resulting change in the function of a connected but physically distant brain region, a phenomenon known as diaschisis (Carrera and Tononi, 2014), or because of injury to critical fibers of passage that traverse the site of the lesion (Van Horn et al., 2012).

Other approaches to causal model testing are now available. When combined with functional imaging techniques, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (TDCS), two techniques for transiently disrupting electrical activity within the brain, can directly perturb brain regions thought to be important for the cognitive process(es) of interest (Parkin et al., 2015). The former method uses magnetic fields to induce an exogenous electrical current inside the brain (Parkin et al., 2015), while the latter uses a cathode and anode to directly apply electrical current (Reinhart et al., 2017). Both methods, when used to alter activity during task performance, can probe models of cognitive processes. Similarly, neuroactive medications can engage specific receptors, neurons, and brain regions in order to influence activity within the brain over a timescale of minutes to hours. Studies of dopaminergic medications, for example, have been used to evaluate neural models of working memory, impulsivity, and other cognitive processes (Cools et al., 2008; Kayser et al., 2012; Saez et al., 2015). Such measures for manipulating brain activity permit the causal evaluation of underlying neural models, but as noted above, these approaches are causal only insofar as they address

specific model predictions. Combining such causal interventions with other approaches that converge upon support for a single model provides greatest inferential power, and such techniques are thus often applied in the context of task and other manipulations within or across studies.

Experimental Design & Analysis

The design of functional imaging experiments to test models of interest depends significantly upon the spatial and temporal resolution possible with the imaging technique(s) employed (see below). However, there are conceptual similarities that underlie most designs. Typically, a comparison is made between a task condition and a control condition that are formulated to differ in only the cognitive process of interest (Courtney, 2012). For example, a condition in which subjects choose between a smaller amount of money available sooner and a larger amount of money available later might be compared to a condition in which subjects view the same amounts and delays but are asked to simply identify the larger financial option (Kayser et al., 2012). Such an approach attempts to match visual stimulation and calculation requirements, while explicitly varying the presence of a motivated decision. Subtracting brain activity across conditions should then produce a more specific picture of what differs between them: in this case, processes related to motivated decision making. This subtraction can be performed independently across all of the channels or spatial subunits acquired by the functional imaging technique – a so-called "univariate" approach – to determine where in the brain neural activity responds differentially to motivated decisions. "Cognitive subtraction", so formulated, accounts for a majority of functional imaging experiments but relies on the assumption of pure insertion – i.e. that adding the cognitive process of interest (assuming it can be added in isolation) is a linear process that does not interact with the other cognitive processes active during the task (Sternberg, 1969). This assumption is almost surely violated to

some extent in many cognitive neuroscience experiments, emphasizing the importance of convergent analyses.

An additional source of flexibility has to do with the sequencing of different task conditions. Initially, because of the temporal constraints of PET imaging, each condition was presented in multi-trial blocks (a “blocked” approach). However, functional imaging techniques with greater temporal resolution permit conditions to be presented as interleaved trials of different kinds (an “event-related” approach) (D'Esposito et al., 1999; Miezin et al., 2000). While the blocked approach can increase the power to detect subtle, sustained cognitive processes, the event-related approach provides much greater flexibility to compare different trial types (even *post hoc*, such as correct versus error trials) or to look at subprocesses within a single trial, as in many working memory studies.

In addition to providing information about the specialization of various brain regions, functional neuroimaging experiments can also be designed to address functional integration by assessing the interactions between brain regions that underlie cognitive processing. Understanding the various techniques that permit these types of analysis has long comprised a very active area of research (Friston, 2011). However, most, if not all, of the techniques used to test for regional interactions are ultimately based on the covariance of activation levels in different brain regions across time: in other words, on the way in which activity levels in different areas of the brain rise or fall in relation to each other. Such statistical techniques are commonly known as “multivariate,” both because they rely on interactions between two or more brain areas, and to distinguish them from the “univariate” methods applied in most tests of functional specialization.

The universe of multivariate techniques is further subdivided into two types, determined by whether the method in question is designed to assess connectivity in a model-free (“functional connectivity”) or model-based (“effective connectivity”) fashion (Friston, 2011). Echoing the distinction between biomarkers and model-based hypotheses, the former refers

simply to methods that measure the temporal covariance in activity between brain areas without *a priori* notions about which brain areas are relevant or how they should interact. Examples of model-free techniques include correlation and its frequency-based analogue, coherence, which can be applied irrespective of hypotheses about the neural events that produced them (Kayser et al., 2009). In addition, mathematical tools based on graph theory have recently emerged as a method to quantify large-scale network properties of the brain (Bullmore and Sporns, 2009; Bullmore and Sporns, 2012), as well as to identify the role of individual brain regions within these large-scale networks (Cohen and D'Esposito, 2016; Gratton et al., 2012). These tools provide a method for understanding how activity within sub-networks, or modules, of the larger brain accounts for the localization of specific cognitive functions, while communication between modules accounts for the distributed nature of most cognitive processing. Moreover, they demonstrate that such modularity is an essential property found in many complex systems that allows the system to easily evolve, develop, and engage in flexible, dynamic behaviors (Gratton et al., 2012).

On the contrary, model-based, or effective connectivity, approaches begin with hypotheses about the interactions between different brain regions, and attempt to support/refute them by evaluating the presence/absence of specific activity covariance patterns. Examples of these techniques include structural equation modeling and dynamic causal modeling, both of which start by postulating the existence of influences (potentially complex, potentially time-varying) between specific brain regions (Penny et al., 2004). Both types of statistical techniques have value, of course; their use is determined by the problem at hand. Model-free approaches are more general, and more easily deployed in exploratory analyses. However, they are not as powerful as model-based methods that address specific hypotheses about how regions interact, but which fail if the model is misspecified. Model-free methods, for example, may be more useful when attempting to explore which networks of brain areas might be involved in a task,

whereas model-based methods may be most appropriate when the nodes of the network are suspected or known, and specific notions about how they interact need to be tested.

Finally, pitfalls in interpretation of the data are present regardless of the type of task design and analysis approach. One of the most common and most misleading has been labeled “reverse inference” (Poldrack, 2006). This erroneous form of inference assumes that if activity is seen in a brain area (or brain network) during some behavior, that activity must reflect a certain cognitive process (Poldrack, 2011). For example, if a group of subjects performs a working memory task and activity is seen in the dorsolateral prefrontal cortex when a probe stimulus is presented after the delay period, a form of reverse inference would be to conclude that lateral frontal activity indicates the retrieval of working memory memoranda. However, a number of other explanations for that activity are possible, including the engagement of attention, the assembly of potential motor plans, and inhibition of competing stimulus-response relationships, among other possibilities (D'Esposito et al., 1998). As this example demonstrates, reverse inference is particularly problematic because a mesoscopic brain area such as the dorsolateral prefrontal cortex is highly likely to support multiple brain functions, and thus its activity cannot be assumed to reflect only one.

Imaging Techniques

Given the existence of a specific clinical or translational research question, a number of techniques permit the acquisition of functional imaging data, including single photon emission computed tomography (SPECT), positron emission tomography (PET), functional MRI (fMRI), and magnetoencephalography (MEG) (Bandettini, 2009; Otte and Halsband, 2006). The principles underlying each of these techniques differ, as do their spatial and temporal resolutions (Figure 1) and, more generally, their relative strengths and weaknesses. Particular attention will be paid to fMRI, as it is perhaps the most widely-employed neuroimaging method. The section concludes with some of the novel ways in which these techniques are being

combined in order to harness their complementary strengths to answer questions in cognitive neuroscience.

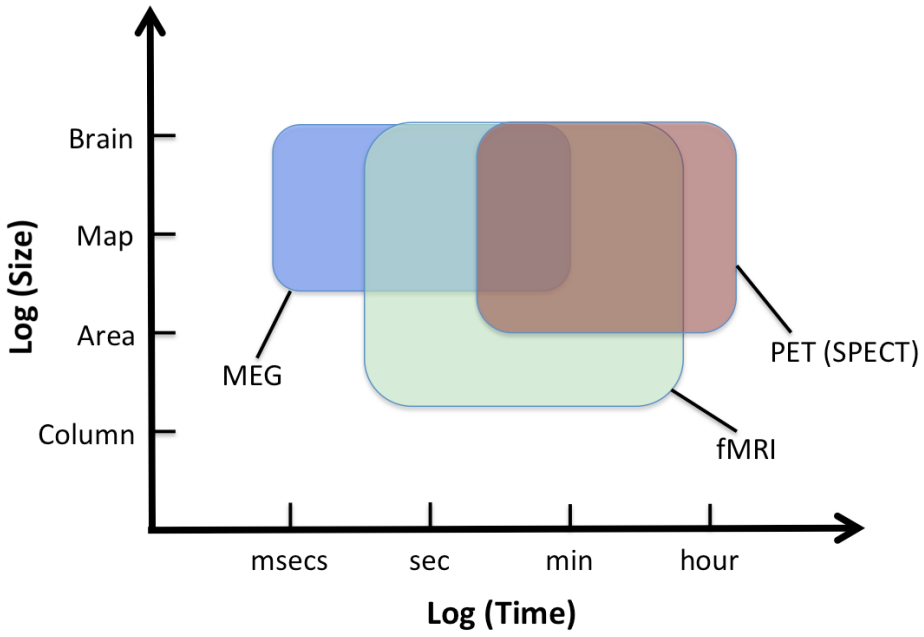

Figure 1. Approximate spatial and temporal resolution of different neuroimaging methods, including SPECT, PET, MRI, and MEG.

Single-Photon Emission Computed Tomography

One of the earliest methods used for functional imaging, SPECT relies on the use of radionuclide-labeled agents (Tsui, 1996). The radionuclide emits photons, primarily in the gamma range, that are detected by a collimator and then used to generate a three-dimensional reconstruction of the distribution of the radionuclide within the brain. In a typical study, a subject receives an intravenous injection of the radiolabeled tracer. Depending on the nature of the tracer, a number of minutes are allowed to pass prior to imaging, in order to allow the agent to distribute throughout the body. Images are then obtained and analyzed.

The first important choice when using SPECT, and one of the primary advantages of this technique, involves the nature of the radioligand. The two commonly used radioisotopes of technetium and iodine, respectively – ^{99m}Tc and ^{123}I – can be incorporated into larger molecules that are relevant to the neuroscientific process of interest (in a fashion similar to PET, and unlike fMRI and MEG) (Saha et al., 1994). Tracers in clinical use, for example, include ^{99m}Tc-hexamethylpropylene amine oxine (HMPAO) and ^{123}I-Ioflupane. The former agent provides a measure of cerebral perfusion. When infused, this lipophilic agent rapidly crosses the blood-brain barrier in proportion to cerebral blood flow. Once inside cells, it undergoes a reaction that renders it hydrophilic, preventing it from leaving the cell and generating a marker for cerebral areas with greater blood flow (Sestini, 2007). In contrast, the latter agent, a cocaine analogue, binds to dopamine reuptake transporters. As such, it provides a marker for the dopamine system, and has been used clinically to investigate, for example, whether subjects with parkinsonism have reduced uptake of the tracer in the basal ganglia. An important note concerns the nature of these markers: they allow the researcher/clinician to obtain a single snapshot of activity, rather than ongoing assessments of activity. At times, this snapshot can be an advantage – clinically, one may be able to capture blood flow during a seizure, then image hours later – or a disadvantage, when a measure of ongoing activity at different points during a process is desired.

Once the radionuclide is absorbed and distributed, the gamma ray signals it generates must be detected. The resolution of the gamma rays is limited by at least two factors: physical factors, such as absorption or scatter of the emitted photons by other structures/tissues within the body; and instrumentation factors, including the detection efficiency and spatial resolution of the collimator (Seo et al., 2008). These factors limit the overall spatial resolution of the sample. In SPECT scanners in everyday use, this limit is on the order of one centimeter, though specialized collimators in use with small animal studies can reduce the spatial resolution to

approximately 5 mm. Because the measure of incident photons is not spatially independent, the SPECT signal cannot be quantified in absolute terms.

In total, SPECT imaging has a number of advantages over PET, with which it is most often compared. The cost of SPECT equipment is considerably cheaper, the radionuclides have longer half-lives and do not require a nearby cyclotron for synthesis, and the radiation levels are lower. Its disadvantages with respect to PET, however, have led SPECT to serve primarily as a clinical imaging technique. These disadvantages are discussed in the next section.

Positron Emission Tomography

Like SPECT, positron emission tomography is a technique that relies upon the detection of signals generated by radionuclides (Placzek et al., 2016). In this case, the radioactive substance emits positrons that collide with, and are annihilated by, nearby electrons. The resulting collision generates two high-energy photons that travel in exactly opposite directions. PET imaging relies on the idea of coincidence detection: i.e. that the coincident identification of two gamma rays traveling in opposite directions permits the localization of the source in space.

Commonly used radionuclides include ^{18}fluoride, ^{15}oxygen, ^{11}carbon, and ^{13}nitrogen (Saha et al., 1994). Due to its longer half-life (approximately 110 minutes), ^{18}F may be most commonly used. As with SPECT, these radionuclides can be incorporated into molecules that are associated with the neuroscientific process of interest – for example, ^{18}F-fluorodeoxyglucose to study energy metabolism, ^{15}O-H_2O to monitor cerebral blood flow, and ^{18}F-DOPA to study dopamine receptor occupancy (Placzek et al., 2016). The tracer of choice is injected into the subject intravenously, and images are obtained, often as subjects perform a task of interest but possibly also as subjects lie quietly in the scanner (depending on the nature of the tracer).

Relative to SPECT, PET has a number of advantages. A primary advantage is the increase in spatial resolution. Unlike SPECT, which relies upon detection of gamma rays,

PET's use of coincidence detection significantly increases the specificity of the signal. Typical spatial resolution is on the order of 5 mm. Moreover, the ubiquity of the radionuclides allows almost any molecule to serve as a tracer, unlike SPECT tracers that are based primarily on the use of ^{99m}Tc, which can be difficult to incorporate into small molecules. Finally, the variety of half-lives allows for studies that provide images at different time points during an experiment. The half-life of ^{15}O, for example, is approximately 2 minutes, permitting frequent imaging (although requiring multiple tracer injections).

An important implication of the ability to image subjects repeatedly has to do with task design. Because multiple images could be acquired, PET permitted the development of the aforementioned block design, in which variations of a task, or contrasting cognitive processes, could be repeated within the same subject in the same session. For example, Roskies and colleagues compared a "synonym" task, in which subjects judged the meaning of two words, with a "rhyming" task, in which subjects implicitly evaluated the sounds of two words, to identify brain regions that were differentially activated by semantic and phonological language tasks (Roskies et al., 2001). This possibility represented a significant advance over SPECT that was subsequently itself trumped by the development of event-related designs in functional MRI (see below). In current usage, PET has now largely been supplanted by functional MRI, for reasons to be discussed in more detail below. However, its capacity to obtain information about specific neurotransmitter systems continues to make it a unique and valuable methodology.

The physiological basis for neuroimaging signals

As has been evident in the discussion of both SPECT and PET (and will become important for fMRI), these methods are based on indirect measurements of neural activity, either hemodynamic or metabolic. (Studies of receptor occupancy can be considered somewhat separately in this case, as they do not purport to measure neural activity. On the other hand, magnetoencephalography, which measures magnetic fields generated by neuronal activity, is in

this sense a more direct measure.) Hemodynamic and metabolic measurements rely on the tight coupling between neural activity and other physiological changes. In the case of metabolic changes – as measured, for example, by the uptake of labeled ^{18}F-deoxyglucose – this coupling is quite direct: as the neural activity in a brain region increases, the metabolic activity in neurons and astrocytes increases, leading to greater glucose demands and greater tracer uptake.

In the case of hemodynamic signals, the local increase in metabolic demands leads to an increase in blood flow and a corresponding rise in the oxygenated:deoxygenated hemoglobin ratio. These increases peak at approximately 6 seconds after onset, then decline to levels that frequently dip below the previous baseline before returning to pre-stimulus levels approximately 10-15 seconds after onset (Aguirre et al., 1998; Bandettini et al., 1992; Boynton et al., 1996). This response is typically described concisely by a hemodynamic response function (HRF), the precise shape of which can vary by brain region (Handwerker et al., 2004). Although neuronal spiking is a prominent feature of neuronal activity, it is thought that the basis for the HRF lies in the post-synaptic activity of large collections of neurons and associated astrocytes. Importantly (as discussed in the relevant sections of this chapter), the nature of the hemodynamic response places constraints on the ultimate spatial and temporal resolution of the detected signal.

Functional Magnetic Resonance Imaging

Functional MRI has now become the predominant functional neuroimaging method for studying the neural basis of cognitive processes in humans. At its foundation, MRI of any kind (functional or structural) relies upon the magnet of the scanner to generate a large magnetic field (commonly 1.5 or 3.0 Tesla) that differentially aligns the spins of hydrogen atoms. When this large magnetic field is briefly perturbed and then returned to baseline, different hydrogen atoms will de-phase and return to alignment with the large magnetic field at different rates, determined by their local chemical environments. For example, a hydrogen atom that is part of a water molecule will “relax” at a different rate than one that is part of a long carbon chain in the

lipid of a fat cell. This differential signal is exploited by structural MRI to distinguish different tissues in the brain.

In most functional MRI, the difference between the local environments of the hydrogen atoms in oxygenated and deoxygenated hemoglobin serves as the basis of the functional signal. Because of the aforementioned tight coupling between neural activity and blood flow, brain regions that show greater activity also show greater blood flow with a larger concentration of oxygenated hemoglobin. This indirect neural signal, the so-called BOLD (blood-oxygen level dependent) signal, can be detected in fMRI and exploited to determine which brain regions are active.

Functional MRI as a cognitive neuroscience tool

Compared to its predecessor, positron emission tomography (PET) scanning, fMRI offers many advantages. For example, MRI scanners are much more widely available, and imaging costs are less expensive since MRI does not require a cyclotron to produce radioisotopes. MRI is also a non-invasive procedure since there is no requirement for injection of a radioisotope into the bloodstream. Moreover, given the half-life of available radioisotopes, PET scanning is unable to provide temporal resolution comparable to that of fMRI, which can provide images of behavioral events occurring on the order of seconds rather than the summation of many behavioral events over tens of seconds. PET scanning is also unacceptable for studies of children, for example, due to the radiation exposure.

Of course, as noted previously, in selected circumstances PET can provide an advantage over fMRI for studying certain questions concerning the neural basis of cognition. PET scanning may remain desirable or necessary when studying certain populations of individuals. For example, patients with amnesia resulting from cerebral anoxia often have implanted cardiac pacemakers that preclude them from having an MRI scans due to the magnetic field. A particular advantage of PET scanning in the study of cognition that can nicely

complement fMRI studies is its ability to assess neurochemical (neurotransmitter and neuromodulator) systems (Poeppel and Krause, 2008). Radioactively-labeled ligands may be used to directly measure density and distribution of particular receptors and even receptor sub-types, as well as the distribution of pre-synaptic terminals or enzymes involved in the production or breakdown of particular neurochemicals .

The MRI scanner, compared to a behavioral testing room, is also less than ideal for performing most cognitive neuroscience experiments. Subjects perform experiments in an acoustically noisy environment in the somewhat awkward supine position, often requiring them to visualize the presentation of stimuli through a mirror. Moreover, individuals can develop some degree of claustrophobia due to the small bore of the MRI scanner and find it difficult to remain completely motionless for the long duration of time that is required for most experiments (typically 60-90 minutes). These constraints of the MRI scanner make it especially difficult to scan children or certain patient populations (e.g., Parkinson's disease patients), resulting in many fewer fMRI studies involving children than adults, and involving neurological patients in general. However, mock scanners with motion devices have been built in many imaging centers to acclimate children (and patients) to the scanner environment before they participate in fMRI studies. This approach has led to an increasing number of fMRI studies of children, which are providing tremendous insight into the mechanisms underlying the developing brain.

All sensory systems have been investigated with fMRI including the visual, auditory, somatosensory, olfactory and gustatory systems. Each system requires different technologies for successful presentation of relevant stimuli within an MRI environment. The most common means of presenting visual stimuli is via a liquid crystal display (LCD) projector system, with the sophistication of the system depending on the quality of image resolution required for the experiment. For auditory stimuli, several options exist, including piezoelectric or electrostatic headphones. However, the biggest challenge remains the acoustic noise produced by the pulsing of the fMRI gradient coils. For example, during echoplanar imaging within a 4 Tesla

magnet using a high performance head gradient set, sound levels have reached 130 dB. As a reference point, Food and Drug Administration (FDA) safety regulations require no greater than an average of 105 dB for one hour.

Acquiring ancillary electrophysiological data such as electromyographic recordings to measure muscle contraction or electrodermal responses to measure autonomic activity enhances many cognitive neuroscience experiments. Devices have been developed that are MR compatible for these types of measurements, as well as for other physiological measures such as heart rate, electrocardiography, oxygen saturation and respiratory rate. The recording of eye movements is commonplace in MRI scanners, predominantly via the use of infrared video camera equipped with long-range optics. Video images of the pupil-corneal reflection can be sampled at 120/240 Hz allowing for the accurate (<1 degree) localization of gaze within 50 horizontal and 40 vertical degrees of visual angle.

EEG recordings have also been successfully performed during MRI scanning (Rosenkranz and Lemieux, 2010). However, the recording of event-related potentials (ERP), a signal that is much smaller in amplitude than the signal in EEG, can be more difficult in a magnetic field due to artifacts induced by gradient pulsing and head movement from cardiac pulsation. New monitoring devices and algorithms to remove artifacts have been developed allowing for reliable measurements of ERPs during MRI scanning. In summary, most initial challenges facing performing cognitive experiments within the MRI environment have been overcome, creating an environment that is comparable to standard psychophysical testing labs outside of a scanner. Although individual laboratories have achieved most of these advancements, MRI scanners originally designed for clinical use by manufacturers are now designed with consideration of many of these research-related issues.

Temporal resolution. Two types of temporal resolution need to be considered for cognitive neuroscience experiments. First, what is the briefest neural event that can be detected as an fMRI signal? Second, how close together can two neural events occur and be resolved as

separable fMRI signals? The time scale on which neural changes occur is quite rapid. For example, neural activity in the lateral intraparietal area of monkeys increases within 100 milliseconds of the visual presentation of a saccade target (Barash et al., 1991). In contrast, as noted above the BOLD signal gradually reaches its peak magnitude within 4 to 6 seconds after an experimentally induced brief (<1 second) change in neural activity, and then decays back to baseline after several more seconds. Thus, neural dynamics and neurally-evoked hemodynamics, as measured with fMRI, are on quite different time scales.

The sluggishness of the hemodynamic response limits the temporal resolution of the BOLD signal to a range between hundreds of milliseconds and seconds, in contrast with the millisecond temporal resolution of EEG or MEG recordings of neural activity. However, it has been clearly demonstrated that brief changes in neural activity can be detected with reasonable statistical power using fMRI. For example, early experiments showed that appreciable BOLD signal can be observed in sensorimotor cortex in association with single finger movements (Kim et al., 1997) and in visual cortex during very briefly presented (34 ms) visual stimuli (Buckner et al., 1996). In contrast, the temporal resolution of fMRI limits the detection of sequential changes in neural activity that occur rapidly with respect to the hemodynamic response – i.e. the ability to resolve the changes in the BOLD signal associated with two neural events often requires the separation of those events by a relatively long period of time compared with the width of the hemodynamic response (Boynton et al., 1996). This limitation results from the fact that two neural events closely spaced in time will produce a hemodynamic response that reflects the summation of activity from both neural events, rendering estimates of the contribution of each individual neural event difficult. In general, evoked BOLD responses to discrete neural events separated by at least 4 seconds appear to be within the range of resolution. However, provided that the stimuli are presented randomly, studies have shown significant differential functional responses between two events (e.g., flashing visual stimuli) spaced as closely as 500 milliseconds apart (Dale and Buckner, 1997). In some tasks, the order of individual trial events

cannot be randomized. For example, in certain types of working memory tasks, the presentation of the information to be remembered during the delay period, and the period when the subject must recall the information, are individual trial events whose order cannot be randomized. In these types of tasks, short time scales (<4 seconds) cannot be temporally resolved. These temporal resolution issues in fMRI have been extensively considered regarding their impact on experimental design.

Spatial resolution. It is yet to be determined how precisely the measured BOLD signal, which arises from the vasculature, reflects adjacent neural activity. Thus, the ultimate spatial resolution of BOLD fMRI is unknown. Functional MRI studies at high field (7.0 Tesla or higher) have begun to validate approaches in which BOLD signal can be reproducibly obtained with high spatial resolution, approximately 0.75 mm^3 (Gorgolewski et al., 2015). In monkeys, with approaches involving a small, tissue-compatible, intraosteally implanted radiofrequency coil, ultra high spatial resolution of 125 x 125 μm^2 has been obtained. Using this method, Logothetis and colleagues demonstrated cortical lamina-specific activation in a task that compared responses to moving stimuli with those elicited by flickering stimuli (Logothetis et al., 2002). This contrast elicited BOLD signal mostly in the granular layers of the striate cortex of the monkey, which are known to have a high concentration of directionally selective cells. Advances in such methods would allow for imaging of hundreds of neurons per voxel as opposed to hundreds of thousands of neurons per voxel, which is more typical for a human cognitive neuroscience fMRI experiment.

Virtually all fMRI studies model the large BOLD signal increase resulting from the local low-deoxyhemoglobin state in order to detect brain changes correlating with a behavioral task. However, studies have demonstrated that preceding this large positive response is an initial negative response reflecting a localized increase in oxygen consumption that causes a high-deoxyhemoglobin state (Kim et al., 2000). This early hemodynamic response is called the “initial

dip" and may be more tightly coupled to the actual site of neural activity evoking the BOLD signal as compared to the later positive portion of the BOLD response. For example, Kim and colleagues, scanning cats in a high field scanner, demonstrated that the early-negative BOLD response (e.g. initial dip) produced activation maps that were consistent with orientation columns within visual cortex (Kim et al., 2000). This finding is quite remarkable given that the average spacing between two adjacent orientation columns in cortex is approximately 1 millimeter. In contrast, the activation maps produced by the delayed positive BOLD response appeared more diffuse and cortical columnar organization could not be identified. Thus, empirical evidence suggests that deriving activation maps by correlating behavioral responses with the initial dip may markedly improved spatial resolution. Several groups have been able to detect columnar architecture (in this case ocular dominance columns) by modeling the positive BOLD response in humans scanning at 4 Tesla (Cheng et al., 2001; Menon et al., 1997).

Recent advances. Ongoing technological advances are further enhancing the ability of MRI to address cognitive neuroscience questions. The advent of simultaneous multi-slice imaging, in which brain images are acquired as volumes rather than single slices, has the potential to greatly increase the rate at which fMRI images are obtained. Using such techniques, typical rates of fMRI whole-brain image acquisition might be reduced from one every 2 seconds to one every 500 milliseconds, thereby increasing the temporal resolution of the BOLD measurements themselves (Chen et al., 2015). In addition, adjunctive measures that constrain and complement fMRI have become more and more commonplace. Diffusion tensor imaging and diffusion spectral imaging provide measures of white matter (anatomical) connectivity by quantifying the asymmetric diffusion of water along, rather than across, white matter tracts (Soares et al., 2013). Such anatomical connectivity can complement and constrain fMRI-derived activity and connectivity maps. Similarly, developments in magnetic resonance spectroscopy permit MRI sequences to assay brain biochemistry within targeted brain regions – e.g. amounts of the inhibitory neurotransmitter gamma amino butyric acid (GABA) within the

primary motor cortex (Rae, 2014). Although many neurotransmitters and neuromodulators of interest cannot currently be defined by such spectra, even the few that are now possible represent an important advance. Thus, considering all the neuroscientific methods available today for studying human brain-behavior relationships, fMRI provides an excellent balance of temporal and spatial resolution. Improvements on both fronts will clearly add to the increasing popularity of this method.

Magnetoencephalography

Unlike the previous three methods, magnetoencephalography (MEG) relies on a much more direct measure of neuronal activity (Schwartz et al., 2010; Wheless et al., 2004). In response to a stimulus, neural activity – specifically, electrical activity – changes within the brain as ion channels open and close. These electrical currents generate an associated magnetic field, oriented according to a right-hand rule in which the magnetic field is perpendicular to the direction of current. In the brain, the source of this magnetic field is thought to be the post-synaptic currents that arise in the dendrites of the neuron and flow to the cell body. Unlike electrical currents, magnetic fields are not distorted by intervening tissues; thus, unlike electroencephalography (EEG), in which the signal recorded by scalp electrodes is compromised by intervening brain, skull, and scalp, magnetic fields arrive outside the brain relatively unaltered.

This lack of distortion is a significant boon to analyses. On the other hand, magnetic fields are compromised by other issues (some technical, some intrinsic) that render them more difficult to record. One factor is their exceedingly small size. Relative to the earth's magnetic field, other magnetic field generators within the body (e.g. the heart), and other magnetic fields produced by ubiquitous electrical currents operating lab equipment, for example, those generated by the brain are many orders of magnitude smaller. Therefore, the MEG recordings must be done in magnetically-shielded rooms. Additionally, they require special sensors for

detection: so-called SQUIDs, or super-conducting quantum interference devices. Current MEG set-ups commonly include SQUIDs numbering well over 100. Because these devices require liquid helium to operate, they are of necessity a distance of 2 cm or more from the scalp, a factor that further decreases signal because these magnetic fields decrease in magnitude with the square of the distance. Despite these hurdles, MEG can obtain very good spatial resolution (on the order of 1 cm or less) and excellent temporal resolution (on the order of 1 millisecond).

To overcome measurement noise, one approach is to repeat tasks studied using MEG numerous times to obtain an event-related magnetic field, or ERF. As with EEG signals, a range of frequencies is obtained, and bands ranging from alpha (~10 Hertz) to gamma (greater than 30 Hz) can be used to search for links to cognitive tasks. These ERFs are then used to estimate the sources of the electrical field (the electrical dipoles) that generated them. Rather than attempting to predict magnetic fields based on the underlying electrical currents (a so-called “forward problem”), the experimenter attempts to reconstruct the underlying currents from their outputs (Hillebrand et al., 2005; Liu et al., 2016). This “inverse problem” has an infinite number of solutions that can be consistent with the observed magnetic field, so the location of the cortical surface, as determined by MRI, and other non-trivial constraints – such as the number of dipoles – are often employed to define a solution. A larger number of dipoles or an incorrectly-estimated number of dipoles can potentially change the solution. The use of the ERF also favors the identification of dipoles that are both time- and phase-locked to the stimulus.

Earlier advances in developing reconstruction techniques included “beamformer” approaches (Hillebrand et al., 2005). In this case, the previously-defined brain space is spatially filtered to reflect the relative contributions of different areas to the signal. Based on the covariance in the data, the relative contribution of each of the SQUID sensors is defined for each subunit in brain space. The activity in different areas in the brain can then be determined by applying the weights to the ongoing MEG signal. In this way, regions that are time-locked, but not necessarily phase-locked, to the stimulus can be identified, and whole-brain maps

produced. These statistical parametric maps can be analyzed in much the same way as previously discussed for fMRI data. Further improving and standardizing these methods remains an active area of research. For example, new research is using Bayesian approaches to incorporate assumptions ("priors") about spatial and temporal smoothness, sparsity, and local homogeneity of signal (Liu et al., 2016) that further constrain the analysis space. In general, these and other techniques take advantage of statistical knowledge about the likely number of magnetic sources and/or temporal relationships to further improve resolution (Baillet, 2017).

Practically, the good spatial and excellent temporal resolution of MEG are also tempered by a factor having to do with the arrangement of cortical neurons and the cortical surface. Signals from structures that consist of parallel current generators – such as pyramidal neurons in layer 5 of the neocortex – are detected with significantly greater fidelity than those generated by other arrangements of neurons, such as those in subcortical structures (in addition to the distance-related reduction in signal strength from these structures) (Baillet, 2017). Even within cortex, because of the right-hand rule, regions that are parallel to the surface of the skull (e.g. cortex that can be found in the walls of sulci) are better detected, because their magnetic fields emerge from the head oriented radially (Baillet, 2017). Improving the detection of magnetic field signals from these other regions remains an ongoing area of research.

With respect to the other neuroimaging methods, MEG has a number of advantages. First and foremost is a temporal resolution on the order of milliseconds, which is at least two orders of magnitude greater than that for fMRI. Its spatial resolution of approximately 1 cm approximates that of PET, approaches that of fMRI, and may continue to improve as MEG analysis techniques are refined. Disadvantages specific to this technique include some difficulty imaging subcortical structures, and limitations in identifying dipoles that are present in the crowns of gyri.

Combination Methods

With the availability of all of these methods, attempts are being made to combine them with other imaging modalities in the same subjects, often simultaneously, to improve spatial resolution, data reconstruction, and other technical factors. Initial work, for example, has combined these functional methods with structural imaging in order to better constrain and localize acquired signals. SPECT-CT and PET-CT took advantage of the anatomical information in the CT scan to co-register functional data across multiple scan sessions. Similarly, as mentioned previously, fMRI analyses rely on anatomical MRI images obtained in the same scanning session to localize fMRI data in the brain; and MEG takes advantage of anatomical MRI images to constrain source localization.

More recently, a particularly exciting area of methods development has focused on the integration of multiple forms of functional neuroimaging. As mentioned, fMRI, for example, has been combined with EEG to obtain timing information at a resolution not possible in whole-brain fMRI images (Rosenkranz and Lemieux, 2010). Additionally, development continues on combined high-field fMRI – PET scanners (Herzog et al., 2010). Because the photomultiplier devices used in PET scanners are very sensitive to magnetic fields, the new systems have either developed optical means for moving the signal outside the magnetic field, or photomultipliers based on MRI-compatible equipment. Such systems open the possibility of visualizing, for example, the location of neurotransmitter systems along with functional activity based on blood flow. Finally, as described above not only structural MRI, but also fMRI, images are being used to constrain MEG sources, in a way that strengthens both localization and timing of functional signals (Hall et al., 2014).

Conclusions

Advances in task design, analysis techniques, and the imaging methodologies themselves have driven a number of discoveries in cognitive neuroscience over the past twenty

to thirty years. As progress in, and synergies between, different methods (e.g. MRI and EEG) and data analysis streams are developed, new approaches to neuroscientific questions continue to arrive, leading to numerous options for testing hypotheses on brain–behavior relationships. Combined with information from other methods (such as studies of patients with focal lesions, healthy individuals undergoing transcranial magnetic stimulation, pharmacological interventions, and event-related potentials), data from studies based on these techniques can provide new insights regarding the organization of the cerebral cortex, as well as the neural mechanisms underlying cognition – many of which are reflected in the other chapters of this handbook. As translational efforts ramp up accordingly, new clinical applications of these techniques will hopefully not be far behind.

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