

CHAPTER 4

The imaged brain

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If George Orwell had written *Nineteen Eighty-Four* during our times, would he have put an MRI scanner in the Ministry of Truth? Could we ever really know the content of someone else's thoughts using functional imaging technology? Already, there have been attempts to introduce fMRI-based lie detection into US courts (Farah *et al.*, 2014). This chapter will consider how functional imaging methods work, focusing in particular on fMRI (functional magnetic resonance imaging). This chapter is broadly divided into three parts. The first part considers how structural and functional brain imaging works, with particular reference to underlying neurophysiology. The second part considers methodological factors that are important in ensuring that the results obtained can indeed be meaningfully linked to cognitive theory. The third part covers how functional imaging data are analyzed to find regions of activation and considers some of the pitfalls in their interpretation. Finally, the chapter returns to the question of whether functional imaging could be used as an Orwellian-like mind reader.

KEY TERMS**Structural imaging**

Measures the spatial configuration of different types of tissue in the brain (principally CT and MRI).

Functional imaging

Measures temporary changes in brain physiology associated with cognitive processing; the most common method is fMRI and is based on a hemodynamic measure.

STRUCTURAL IMAGING

One key distinction is the difference between **structural imaging** methods and **functional imaging** methods. Structural imaging is based on the fact that different types of tissue (e.g., skull, gray matter, white matter, cerebrospinal fluid) have different physical properties. These different properties can be used to construct detailed *static* maps of the physical structure of the brain. The most common structural imaging methods are computerized tomography (CT) and magnetic resonance imaging (MRI). Functional imaging is based on the assumption that neural activity produces local physiological changes in that region of the brain. This can be used to produce *dynamic* maps of the moment-to-moment activity of the brain when engaged in cognitive tasks.

Computerized tomography

Computerized tomography (CT) scans are constructed according to the amount of X-ray absorption in different types of tissue. The amount of absorption is related to tissue density: bone absorbs the most (and so the skull appears white), cerebrospinal fluid absorbs the least (so the ventricles appear black) and the brain matter is intermediate (and appears gray). Given that CT uses X-rays, the person being scanned is exposed to a small amount of radiation.

CT scans are typically used only in clinical settings, for example to diagnose tumors or to identify hemorrhaging or other gross brain anomalies. CT cannot distinguish between gray matter and white matter in the same way as MRI, and it cannot be adapted for functional imaging purposes.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) was one of the most important advances in medicine made during the twentieth century. Its importance was recognized by the awarding of the 2003 Nobel Prize to its inventors—Sir Peter Mansfield and Paul Lauterbur. There are a number of advantages of this method over CT scanning, as summarized below:

- It does not use ionizing radiation and so is completely safe (people can be scanned many times).
- It provides a much better spatial resolution, which allows the folds of individual gyri to be discerned.
- It provides better discrimination between white matter and gray matter; this may enable early diagnosis of some pathologies, and can be used to explore how normal variation brain structure is linked to differences in cognitive ability.
- It can be adapted for use in detecting the changes in blood oxygenation associated with neural activity, and in this context is called functional MRI (fMRI) (Figure 4.1).



FIGURE 4.1: An example of CT (left), T1-weighted MRI (center) and T2-weighted MRI (right) scans of the brain. Note how the MRI scans are able to distinguish between gray matter and white matter. On the T1-weighted scan (normally used for structural images), gray matter appears gray and white matter appears lighter.

MRI physics for non-physicists

MRI is used to create images of soft tissue of the body, which X-rays pass through largely undistorted. Most human tissue is water-based and the amount of water in each type of tissue varies. Different types of tissue will thus behave in slightly different ways when stimulated, and this can be used to construct a three-dimensional image of the layout of these tissues (for an accessible but more detailed description, see Savoy, 2002).

The sequence of events for acquiring an MRI scan is illustrated in Figure 4.2. First, a strong magnetic field is applied across the part of the body being scanned (e.g., the brain). The single protons that are found in water molecules in the body (the hydrogen nuclei in H_2O) have weak magnetic fields. (Other atoms and nuclei also have magnetic properties, but in MRI it is the hydrogen nuclei in water that form the source of the signal.) Initially, these fields will be oriented randomly, but when the strong external field is applied a small fraction of them will align themselves with this. The external field is applied constantly during the scanning process. The strength of the magnetic field is measured in units called tesla (T). Typical scanners have field strengths between 1.5 and 3 T, although 7 T is becoming more common; the Earth's magnetic field is of the order of 0.0001 T.

When the protons are in the aligned state a brief radio frequency pulse is applied that knocks the orientation of the aligned protons by 90 degrees to their original orientation. As the protons spin (or precess) in this new state, they produce a detectable change in the magnetic field and this is what forms the basis of the MR signal. The protons will

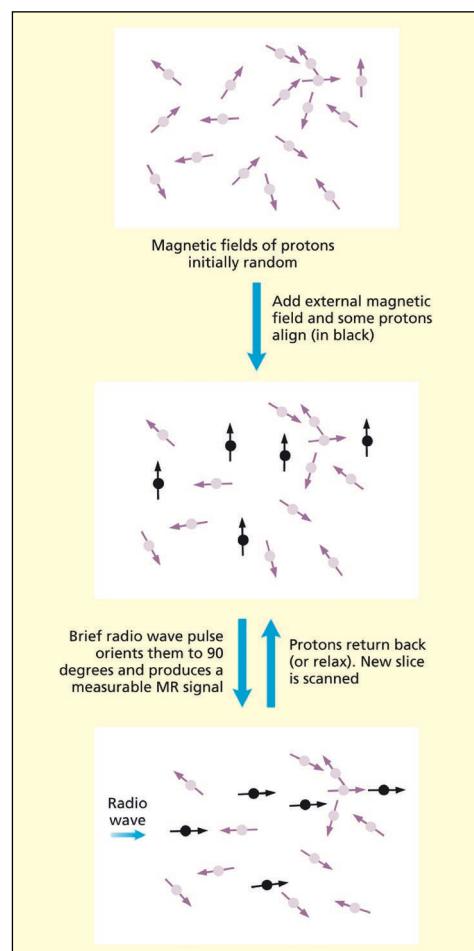


FIGURE 4.2: The sequence of events in the acquisition of an MRI scan.

eventually be pulled back into their original alignment with the magnetic field (they “relax”). The scanner repeats this process serially by sending the radio wave to excite different slices of the brain in turn. With the advent of acquisition methods such as echo planar imaging, a whole brain can typically be scanned in about 2 s with slices of around 3 mm.

Different types of image can be created from different components of the MR signal. Variations in the rate at which the protons return back to the aligned state following the radio frequency pulse (called the T1 relaxation time) can be used to distinguish between different types of tissue. These T1-weighted images are typically used for structural images of the brain. In a T1-weighted image, gray matter looks gray and white matter looks white. When in the misaligned state, at 90 degrees to the magnetic field, the MR signal also decays because of local interactions with nearby molecules. This is termed the T2 component. Deoxyhemoglobin produces distortions in this component and this forms the basis of the image created in functional MRI experiments (called a T2* image, “tee-two-star”) (Figure 4.2).

WHY ARE MR SCANNERS SO NOISY?

Very strong magnetic fields are created by passing electric currents through coils and switching them on and off rapidly. When the current is switched on it causes the coil to expand very slightly, but suddenly, and this generates a loud banging noise. Most MR scanners generate noise in excess of 100 dB.

FUNCTIONAL IMAGING

Whereas structural imaging measures the permanent characteristics of the brain, functional imaging is designed to measure the moment-to-moment variable characteristics of the brain that may be associated with changes in cognitive processing.

Basic physiology underpinning functional imaging

The brain consumes 20 percent of the body’s oxygen uptake; it does not store oxygen and it stores little glucose. Most of the brain’s oxygen and energy needs are supplied from the local blood supply. When the metabolic activity of neurons increases, the blood supply to that region increases to meet the demand (for a review, see Raichle, 1987; but see Attwell & Iadecola, 2002). Techniques such as PET (positron emission tomography) measure the change in blood flow to a region directly, whereas fMRI and the emerging method of fNIRS (functional near-infrared spectroscopy) are sensitive to the concentration of oxygen in the blood. All of these techniques are referred to as hemodynamic methods. PET requires administration of a radioactive tracer whereas fMRI uses a naturally occurring signal in the bloodstream. The use of PET in cognitive neuroscience has effectively been replaced by fMRI, although it can still be useful for selectively targeting certain neurotransmitter pathways (through specialist tracers).

LINKING STRUCTURE TO FUNCTION BY IMAGING WHITE MATTER AND GRAY MATTER

Small-scale differences (at the millimeter level) in the organization and concentration of white matter and gray matter can now be analyzed noninvasively using MRI. This is providing important clues about how individual differences in brain structure are linked to individual differences in cognition. Two important methods are **voxel-based morphometry**, or VBM, and **diffusion tensor imaging**, or DTI (Figure 4.3).

Voxel-based morphometry (VBM) capitalizes on the ability of structural MRI to detect differences between gray matter and white matter (Ashburner & Friston, 2000). VBM divides the brain into tens of thousands of small regions, several cubic millimeters in size (called **voxels**), and the concentration of white/gray matter in each voxel is estimated. It is then possible to use this measure to compare across individuals by asking questions such as these: If a new skill is learned, such as a second language, will gray matter density increase in some brain regions? Will it decrease in other regions? How does a particular genetic variant affect brain development? Which brain regions are larger, or smaller, in people with good social skills versus those who are less socially competent? Kanai and Rees (2011) provide a review of this method in relation to cognitive differences.

Diffusion tensor imaging (DTI) is different from VBM in that it measures the white matter connectivity (Le Bihan et al., 2001). (Note: VBM

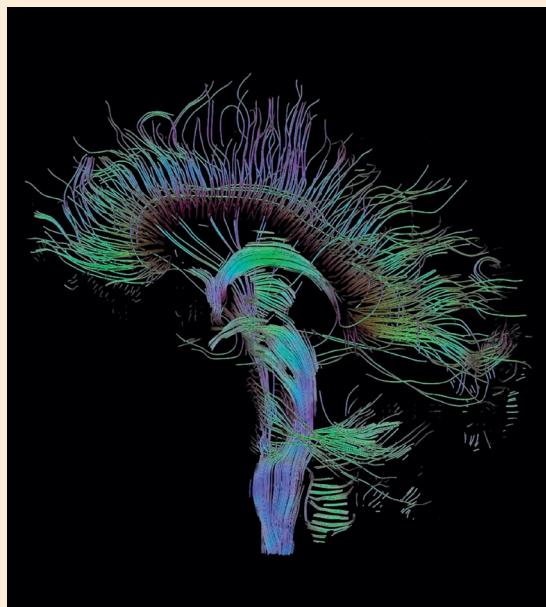


FIGURE 4.3: Visualization of a DTI measurement of a human brain. Depicted are reconstructed fiber tracts that run through the midsagittal plane.

Image by Thomas Schultz from <http://upload.wikimedia.org/wikipedia/commons/8/82/DTI-sagittal-fibers.jpg>.

KEY TERMS

Voxel-based morphometry (VBM)

A technique for segregating and measuring differences in white matter and gray matter concentration.

Diffusion tensor imaging (DTI)

Uses MRI to measure white matter connectivity between brain regions.

Voxel

A volume-based unit (cf. pixels, which are 2D); in imaging research the brain is divided into many thousands of these.

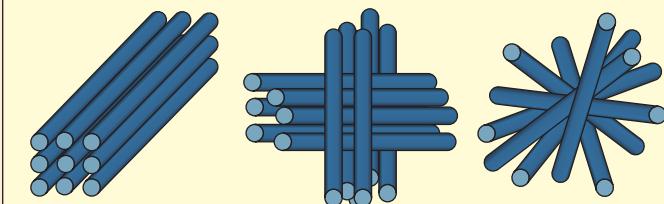


FIGURE 4.4: Diffusion tensor imaging (DTI) measures the degree of organization of white matter tracts using a measure called fractional anisotropy (FA). The image on the left has an FA close to 1, the image on the right has an FA close to 0 and the image in the middle is intermediate in FA.

measures the *amount* of white matter without any consideration of how it is connected.) It is able to do this because water molecules trapped in axons tend to diffuse in some directions but not others. Specifically, a water molecule is free to travel down the length of the axon but is prevented from traveling out of the axon by the fatty membrane. When many such axons are arranged together it is possible to quantify this effect with MRI (using a measure called **fractional anisotropy**). This is illustrated in Figure 4.4. As an example of a cognitive study using DTI, Bengtsson et al. (2005) found that learning to play the piano affects the development of certain white matter fibers. However, different fibers were implicated depending on whether the piano was learned during childhood, adolescence or adulthood.

KEY TERM

Fractional anisotropy (FA)

A measure of the extent to which diffusion takes place in some directions more than others.

The brain is always physiologically active. Neurons would die if they were starved of oxygen for more than a few minutes. This has important consequences for using physiological markers as the basis of neural “activity” in functional imaging experiments. It would be meaningless to place someone in a scanner, with a view to understanding cognition, and simply observe which regions were receiving blood and using oxygen because this is a basic requirement of all neurons, all of the time. As such, when functional imaging researchers refer to a region being “active,” what they mean is that the physiological response in one task is greater *relative* to some other condition. There is a basic requirement in all functional imaging studies involving cognitive tasks that the physiological response must be compared with one or more baseline responses. Good experimental practice is needed to ensure that the baseline task is appropriately matched to the experimental task, otherwise the results will be very hard to interpret.

It is also worth pointing out that hemodynamic methods are not measuring the activity of neurons directly but, rather, are measuring a downstream consequence of neural activity (i.e., changes in blood flow/oxygen to meet metabolic needs). This is to be contrasted with methods

such as EEG (electroencephalography) and MEG (magnetoencephalography) that measure the electrical/magnetic fields generated by the activity of neurons themselves (Figure 4.5).

Functional magnetic resonance imaging

The component of the MR signal that is used in fMRI is sensitive to the amount of deoxyhemoglobin in the blood. When neurons consume oxygen they convert oxyhemoglobin to deoxyhemoglobin. Deoxyhemoglobin has strong paramagnetic properties and this introduces distortions in the local magnetic field. (Note: a paramagnetic material isn't magnetic in its own right but acts like a magnet when put in a magnetic field, e.g., a paper clip becomes magnetic when next to a magnet.) This distortion can itself be measured to give an indication of the concentration of deoxyhemoglobin present in the blood. This technique has therefore been termed **BOLD** (for blood oxygen-level-dependent contrast; Ogawa *et al.*, 1990). The way that the BOLD signal evolves over time in response to an increase in neural activity is called the **hemodynamic response function (HRF)**. The hemodynamic response function has three phases, as shown in Figure 4.6 (see also Hoge & Pike, 2001):

1. *Initial dip*. As neurons consume oxygen there is a small rise in the amount of deoxyhemoglobin, which results in a reduction of the BOLD signal (this is not always observed in 1.5 T magnets).
2. *Overcompensation*. In response to the increased consumption of oxygen, the blood flow to the region increases. The increase in blood flow is greater than the increased consumption, which means that the BOLD signal increases significantly. This is the component that is normally measured in fMRI, and the size of this peak is taken as indicative of the extent to which this region is active in the task.
3. *Undershoot*. Finally, the blood flow and oxygen consumption dip before returning to their original levels. This may reflect a relaxation of the venous system, causing a temporary increase in deoxyhemoglobin again.

The hemodynamic signal changes are small—approximately 1–3 percent with moderately sized magnets (1.5 T). The hemodynamic response function is relatively stable across sessions with the same participant in the same region, but is more variable across different regions within the same individual and more variable between individuals (Aguirre *et al.*, 1998).

The spatial resolution of fMRI is up to around 1 mm depending on the size of the voxel. The temporal resolution of fMRI is several seconds and related to the rather sluggish hemodynamic response. This is very slow compared with the speed at which cognitive processes take place. The sluggishness of the hemodynamic response to peak and then return to baseline does place some constraints on the way that stimuli are presented in the scanning environment that differ from equivalent tasks done outside the scanner. However, it is not the case that one has to wait for the BOLD response to return to baseline



FIGURE 4.5: A typical MRI scanner used in functional imaging research. Testing of a single participant can normally be completed in under an hour, allowing 30–40 min to complete the experiment and 10 min for a high-resolution structural MRI scan to be obtained.

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KEY TERMS

BOLD

Blood oxygen-level-dependent contrast; the signal measured in fMRI that relates to the concentration of deoxyhemoglobin in the blood.

Hemodynamic response function (HRF)

Changes in the BOLD signal over time.



ONLINE RESOURCES

For videos of lectures given by Professor Geoffrey Aguirre on the physics and biology of fMRI, as well as various other issues such as study design and analysis, visit the companion website (www.routledge.com/cw/ward).

FIGURE 4.6: The hemodynamic response function (HRF) has a number of distinct phases.

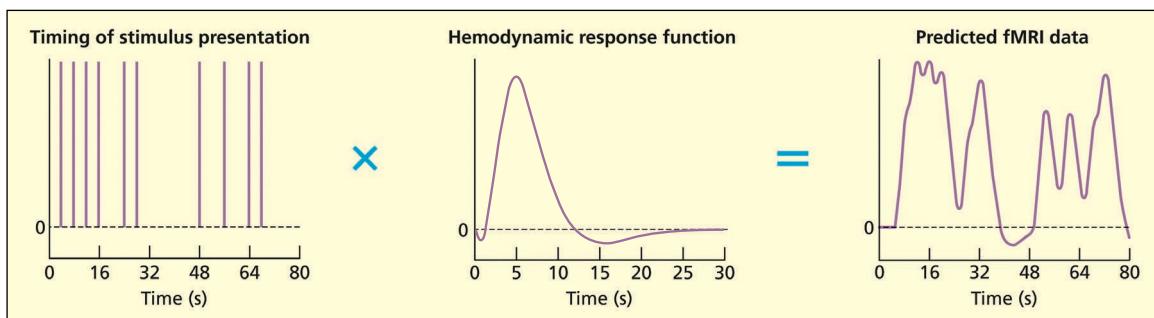
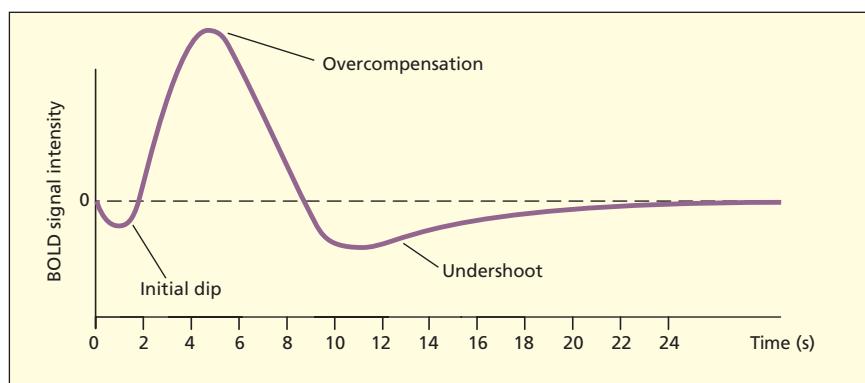


FIGURE 4.7: Unless the stimuli are presented far apart in time (e.g., every 16 sec), the predicted change in BOLD response will not resemble a single HRF but will resemble many superimposed HRFs. Statistically, the analysis is trying to find out which voxels in the brain show the predicted changes in the BOLD response over time, given the known design of the experiment and the estimated shape of the HRF. To achieve this there has to be sufficient variability in the predicted BOLD response (big peaks and troughs).

before presenting another trial, as different hemodynamic response functions can be superimposed on each other (Dale & Buckner, 1997), as illustrated in Figure 4.7. In general, during fMRI, there may be fewer trials that are more spaced out in time than standard cognitive testing, and it is common to have “null events” (e.g., a blank screen). These null events allow the BOLD signal to dip toward baseline, essentially providing the necessary variability in the signal needed for the analysis. In standard cognitive psychology experiments (e.g., using response time measures) the amount of data is effectively the same as the number of *trials and responses*. In the equivalent fMRI experiment, the amount of data is related to the number of *brain volumes* acquired rather than the number of trials or responses.

Functional near infrared spectroscopy

The newer method of fNIRS measures the same BOLD signal as fMRI although it does so in a completely different way (Ferrari & Quaresima, 2012). It does not require the use of magnetic fields but, instead, it sends “light” of a particular wavelength to the brain; specifically, in the near infrared range, about 800 nanometers (i.e., not visible light). This signal passes relatively freely through bone and skin but is more strongly scattered by oxy- and

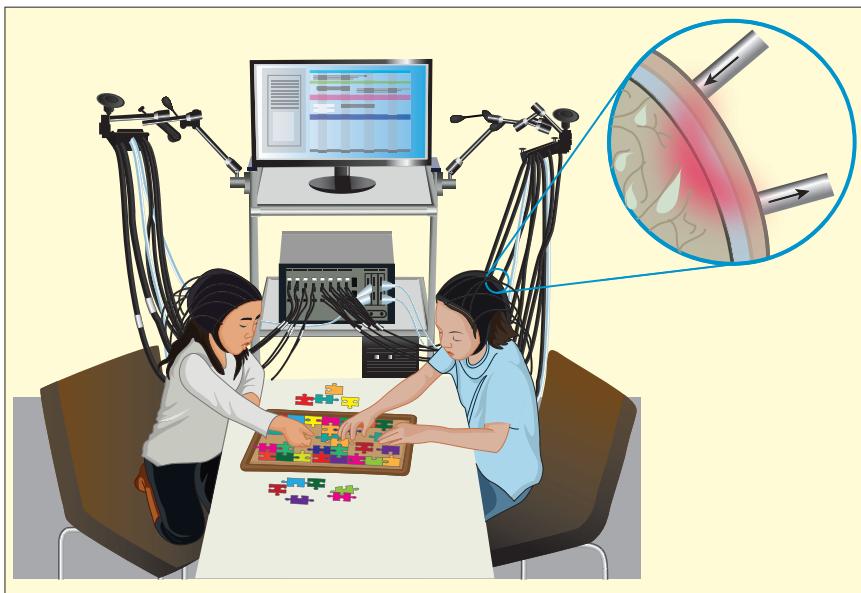


FIGURE 4.8: fNIRS involves an optical signal that is absorbed differently by oxy- and deoxyhemoglobin. The equipment can be fixed on a cap, allowing more naturalistic behavior during scanning.

deoxyhemoglobin, each of which is sensitive to slightly different wavelengths in the near infrared range. The extent to which the signal is scattered by these different wavelengths is then used to compute the BOLD response. As with fMRI, a larger BOLD response is interpreted as reflecting more cognitive and neural activity.

fNIRS is more portable and more tolerant of movement than fMRI and, for these reasons, it has become popular in developmental research (Lloyd-Fox *et al.*, 2010). It is also far cheaper. However, it can only be used to image shallow neural activity that is close to the scalp (Figure 4.8).

FROM IMAGE TO COGNITIVE THEORY: EXPERIMENTAL DESIGN

An example of cognitive subtraction methodology

One of the groundbreaking studies for establishing the use of functional imaging of cognition was that by Petersen *et al.* (1988), which was designed to look for brain regions specialized for the processing of written and spoken words. A consideration of this study provides a good introduction to the principle of **cognitive subtraction**. The idea behind cognitive subtraction is that, by comparing the activity of the brain in a task that utilizes a particular cognitive component (e.g., the visual lexicon) to the activity of the brain in a baseline task that does not, it is possible to infer which regions are specialized for this particular cognitive component. As has been noted, the brain is always active in the physiological sense and so it is not possible to infer from a single task which regions are dedicated to specific aspects of the task; a comparison between two or more tasks or conditions is always needed.

Let's consider the different processes involved with reading and understanding isolated written words. A simple model of written word

KEY TERM

Cognitive subtraction

A type of experimental design in functional imaging in which activity in a control task is subtracted from activity in an experimental task.

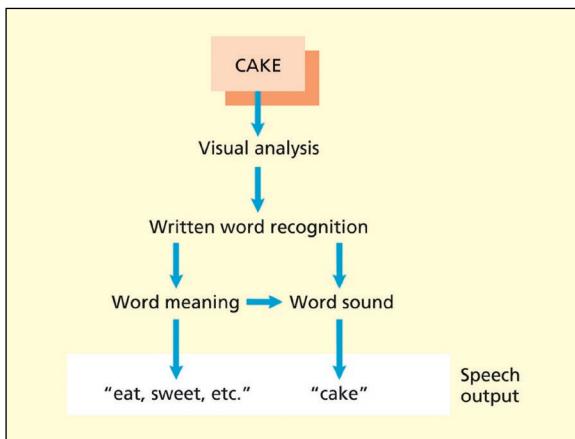


FIGURE 4.9: Basic cognitive stages involved in reading written words aloud and producing spoken semantic associates to written words.

recognition is given in Figure 4.9, which forms the motivation for the imaging study to be described. The study by Petersen *et al.* (1988) was concerned with identifying brain regions involved with: (1) recognizing written words; (2) saying the words; and (3) retrieving the meaning of the words. To do this, the researchers performed a number of cognitive subtractions.

To work out which regions are involved with recognizing written words, Petersen *et al.* compared brain activity when passively viewing words (e.g., CAKE) with passively viewing a cross (+) (see Figure 4.10). The logic is that both experimental and baseline tasks involve visual processing (and so a subtraction should cancel this out), but only the experimental task involves visual word recognition (so this should remain after subtraction).

What regions of brain used for recognizing words?

EXPERIMENTAL <ul style="list-style-type: none"> • passive viewing of written words <i>Cognitive components</i> visual-processing word recognition	BASELINE <ul style="list-style-type: none"> • passive viewing of fixation cross (+) <i>Cognitive components</i> visual-processing
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What regions of brain used for saying words?

EXPERIMENTAL <ul style="list-style-type: none"> • read aloud a written word <i>Cognitive components</i> visual-processing word recognition phonology/articulation	BASELINE <ul style="list-style-type: none"> • passive viewing of a written word <i>Cognitive components</i> visual-processing word recognition
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What regions of brain used for retrieving meaning?

EXPERIMENTAL <ul style="list-style-type: none"> • generate an action e.g. see CAKE say "eat" <i>Cognitive components</i> visual-processing word recognition phonology/articulation retrieve meaning	BASELINE <ul style="list-style-type: none"> • read aloud a written word <i>Cognitive components</i> visual-processing word recognition phonology/articulation
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The diagram shows the left lateral surface of a brain with several colored regions highlighted to indicate areas of activity. An orange oval is located in the left inferior frontal gyrus, labeled "(verb generation – reading)". A green circle is located in the occipital-temporal junction, labeled "(word – cross)". A purple oval is located in the motor areas, labeled "(reading aloud – passive)".

FIGURE 4.10: Cognitive subtraction is founded on the assumption that it is possible to find two tasks (an experimental and baseline task) that differ in terms of a small number of cognitive components. The results show several regions of activity, but only the main results on the left lateral surface are depicted here.

To work out which regions are involved with producing spoken words they compared reading aloud the word (see CAKE, say “cake”) with passive viewing of written words (see CAKE). In this instance, both experimental and baseline tasks involve visual processing of the word and word recognition (so subtracting should cancel these out), but only the experimental task involves spoken output (so activity associated with this should remain after subtraction).

To work out which regions are involved with retrieving the meaning of written words, they compared a verb-generation task (e.g., see CAKE, say “eat”) with reading aloud (e.g., see CAKE, say “cake”). In this instance, both experimental and baseline tasks involve visual processing, word recognition and spoken output (so subtracting should cancel out the activity associated with these processes), but only the experimental task involves generating a semantic associate (so activity associated with this should remain after subtraction).

The results of these subtractions show activity in a number of different sites. Only the principal sites on the left lateral hemisphere are depicted in the diagram. Recognizing written words activates bilateral sites in the visual (striate) cortex as well as a site on the left occipitotemporal junction. Producing speech output in the reading aloud condition activates the sensorimotor cortex bilaterally, whereas verb generation activates the left inferior frontal gyrus. This last result has provoked some controversy because of an apparent discrepancy from lesion data; this is discussed later.

Problems with cognitive subtraction

With the benefit of hindsight, there are a number of difficulties with this study, some of which are related to the particular choice of baseline tasks that were employed. However, there are also more general problems with the method of cognitive subtraction itself (Friston *et al.*, 1996). Consider the subtraction aimed at identifying brain regions associated with written word recognition. The assumption here was that both tasks involve visual processing but that one has the added component of word recognition. That is, one assumes that adding an extra component does not affect the operation of earlier ones in the sequence. This is referred to as the assumption of **pure insertion** (or pure deletion). This idea was already encountered in Chapter 3 in the context of the additive factors method. However, it could be that the type or amount of visual processing that deals with written words is not the same as for non-linguistic vision. The fact that the visual information presented in the baseline task (viewing a cross, +) was simpler than in the experimental task makes this a real possibility. However, a more basic problem is common to all functional imaging experiments that employ this methodology. The addition of an extra component in the task has the potential to change the operation of other components in the task. That is, **interactions** are possible that make the imaging data, at best, ambiguous. The next sections consider other types of design that allow one to eliminate or even directly study these interactions.

The choice of baseline is crucial in imaging experiments and can have substantial impacts on the data obtained. Ideally, the baseline should be as similar to the experimental task as possible. For example, to find brain regions involved with producing spoken words, Petersen *et al.* (1988)

KEY TERMS

Pure insertion (also pure deletion)

The assumption that adding a different component to a task does not change the operation of other components.

Interactions

The effect of one variable upon another.

compared reading aloud with viewing of written words. This is likely to involve several stages of processing. It will involve retrieving the word from the brain's store of vocabulary (the mental lexicon), preparing and executing a motor command (to speak) and also listening to what was said. The pattern of activity observed is therefore ambiguous with regards to linking a precise cognitive function with brain structure. Another baseline that could be used is to get the participant to articulate generic verbal responses, such as saying the word "yes" whenever a word comes up (Price *et al.*, 1996a). This would enable one to study the lexical retrieval component while factoring out the articulation and auditory feedback components.

In summary, functional imaging requires comparisons to be made between different conditions because the brain is always physiologically active. Regions of "activity" can only be meaningfully interpreted relative to a baseline, and the selection of an appropriate baseline requires a good cognitive theory of the elements that comprise the task. The simplest way of achieving this is the method of cognitive subtraction that compares activity in an experimental task with activity in a closely matched baseline task. However, the main problem with cognitive subtraction is that it assumes that a cognitive component can be added on to a task without changing the other components in the task (the problem of pure insertion). Adding a new component to a task may interact with existing components and this interaction may show up as a region of activity. Other types of experimental design that reduce this particular problem have been developed and are discussed in the next section.

Cognitive conjunctions and factorial designs

The method of cognitive conjunction requires that one is able to identify a set of tasks that have a particular component in common. One can then look for regions of activation that are shared across several different subtractions rather than relying on a single subtraction. A baseline task (or tasks) is still required, but the problem of interactions can be reduced. This is because the interaction terms will be different for each pair of subtractions.

Let's consider one concrete example from the literature: why can't we tickle ourselves? Tactile sensations applied to the skin are rated as less ticklish if produced by oneself relative to if they are elicited by another person. The key to explaining this lies in the fact that it is possible to predict the sensory consequences of our own actions. The motor commands that we generate specify where and when the touch will occur and the manner of the touch (e.g., a rough or gentle tickle). This information can then be used to predict what the action will feel like. Thus a representation of the motor command (a so-called **efference copy**) is sent to the relevant sensory area, touch in this example, so that the perceptual system knows what to expect. This may help the brain to prioritize incoming sensory information toward the most relevant stimuli in the environment. Being touched by someone or something else is arguably more important to the organism in terms of detecting potential threats than being touched by oneself.

To investigate this, Blakemore *et al.* (1998) set up a factorial design with two factors. The first factor was whether a tactile stimulus was felt; the

KEY TERM

Efference copy

A motor signal used to predict sensory consequences of an action.

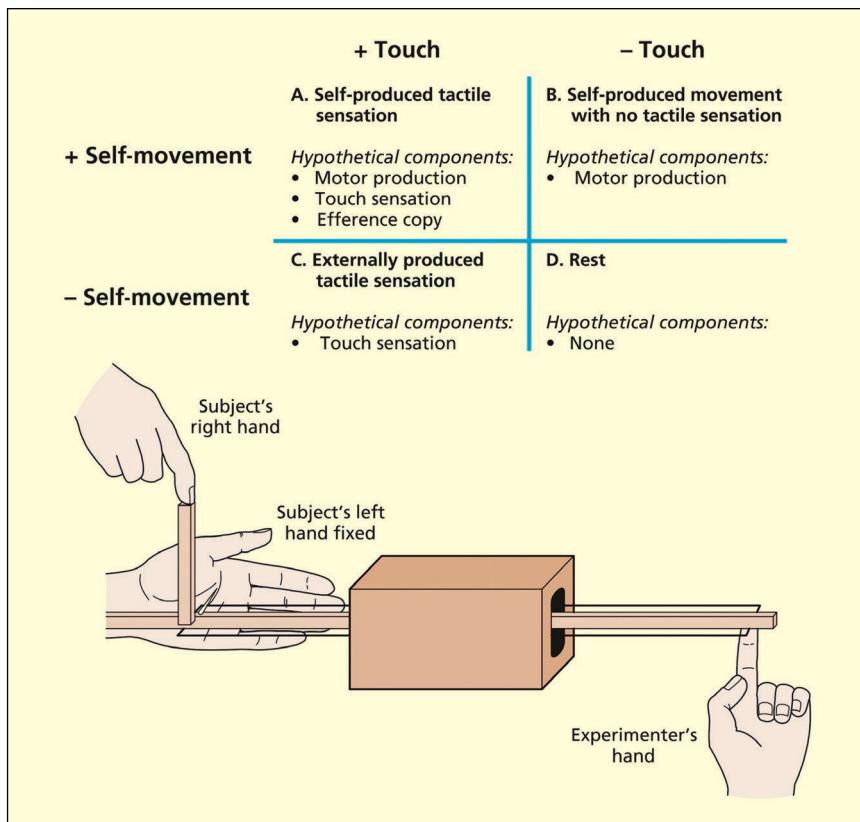


FIGURE 4.11: Why can't we tickle ourselves? Self-produced touches (condition A) are less tickly because we can predict their sensory consequences using an "efference copy" of the motor command.

Bottom diagram adapted from Blakemore et al., 1998. © 1998 Elsevier. Reproduced with permission.

second factor was whether the participants moved their arm. The experiment involved moving a felt rod that tickled the palm. The rod could be moved either by the experimenter or the participant. It could either make contact with the palm or miss it altogether. In total, this produced four experimental conditions, which have been labeled A to D in Figure 4.11.

Before going on to consider the neural basis of the less tickly sensation associated with condition A (hypothetically due to an efference copy), one can perform two cognitive conjunctions to identify regions involved in motor production and the tactile sensation per se. Consider the two pairs of subtractions, A – B and C – D. If one asks the question, “What regions do these subtractions have in common [i.e., (A – B) and (C – D)]?”, then this can isolate regions involved in tactile sensation. The experiment found activity in the primary and secondary somatosensory cortex in the hemisphere opposite the hand that was stimulated. Consider the two pairs of subtractions, A – C and B – D. If one asks the question, “What regions do these subtractions have in common [i.e., (A – C) and (B – D)]?”, then this can isolate regions involved in motor production. In this analysis, the experiment found several active regions, including primary motor, premotor and prefrontal regions. In terms of methodology, the key point to note is that both of these results are based on conjunctions between two different tasks and baselines and this is sufficient to minimize the problem of pure insertion faced by using a single subtraction alone.

However, these conjunction analyses do not enable one to analyze the neural basis of the efference copy or the reduced ticklishness when self-produced. To find this out, one can examine the interaction directly by performing the following analysis: $(A - B) - (C - D)$. This effectively asks the question: is the difference between A and B more (or less) than the difference between C and D (an interaction is simply a difference of differences)? In the present example, it would ask whether the effect of touch is greater in the presence of self-movement than in the presence of other-movement. Blakemore *et al.* (1998) report that there was decreased activity in the somatosensory cortex. This is likely to be the neural correlate of reduced ticklishness. There were also changes in cerebellum activity that were not found in any other condition and were interpreted as the neural correlate of the efference copy that links self-movement with touch.

Parametric designs

The main difference between a parametric design and a categorical design is that, in a parametric design, the variable of interest is treated as a continuous dimension rather than a categorical distinction (Friston, 1997). In intuitive terms, one is measuring *associations* between brain activity and changes in the variable of interest, rather than measuring *differences* in brain activity between two or more conditions. Thus, one is ultimately likely to use correlations (or similar) to analyze data collected using a parametric design.

Price *et al.* (1992) conducted an imaging study in which participants listened passively to lists of spoken words spoken at six different rates between 0 words per minute (i.e., silence, or rest) and 90 words per minute. The change in activity in various regions could then be correlated with the rate of speech. Note that in a parametric design such as this, a separate baseline condition is not necessary (the effects are evaluated globally across all levels of the factor). In terms of the results, a number of interesting findings were observed. In areas involved in auditory *perception* (e.g., the primary auditory cortex), the faster the speech rate, the greater the activity. However, in regions involved in non-acoustic processing of *language* (e.g., Wernicke's area), the activity was related to the presence of words irrespective of speech rate. In a region often associated with verbal *working memory* (the left dorsolateral prefrontal cortex), a more complex picture was found (Friston, 1997). Activity increased with speech rate but then decreased as the speech rate got faster (an inverted-U function). It suggests that the region has an optimal level at which it functions, beyond which it fails to keep up. This is consistent with the notion of working memory having a limited capacity. One interesting point to note is that, if the experimenters had compared 20 words per minute with 50 words per minute in a cognitive subtraction or a factorial design, this region would not have appeared to be implicated in the task (Figure 4.12).

Functional integration: measuring networks in the brain

Most of the functional imaging studies described in this book could be labeled as studies of *functional specialization*. Functional specialization implies that a region responds to a limited range of stimuli/conditions and that this

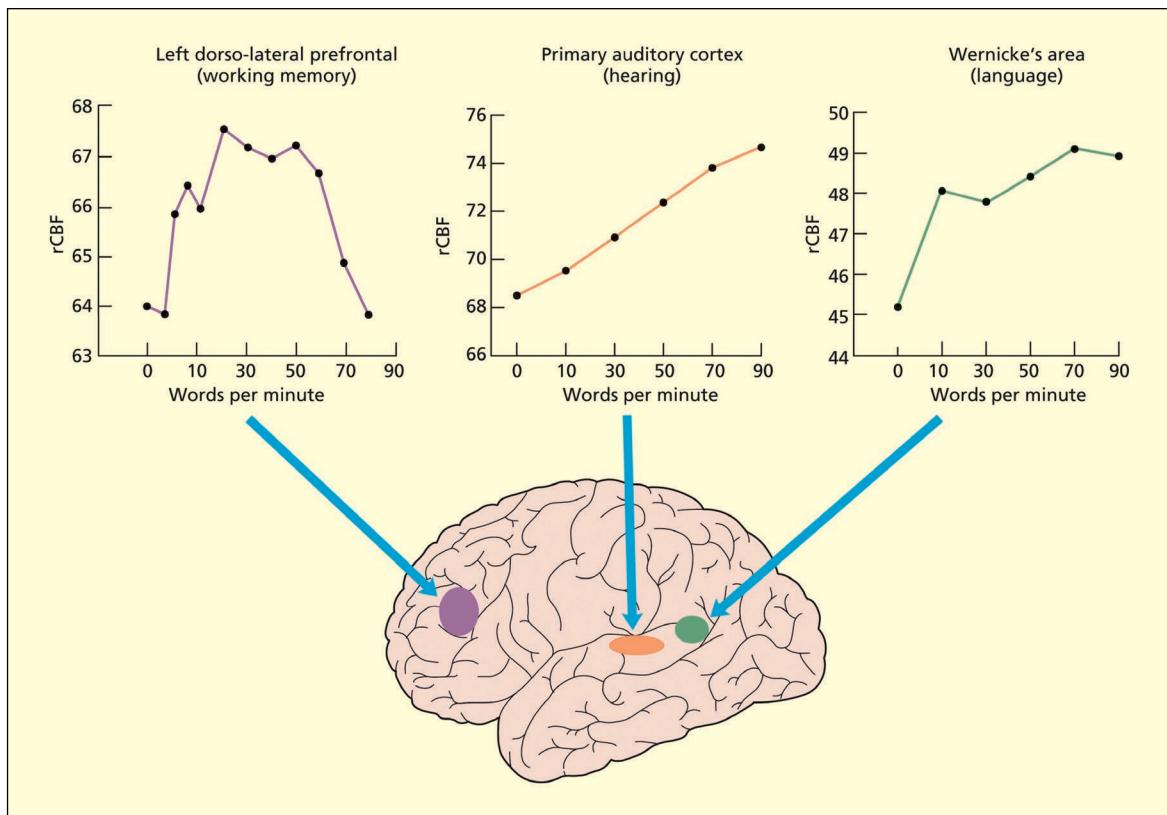


FIGURE 4.12: Different regions of the brain respond to changes in speech rate (words per minute, wpm) in different ways. Note that 0 wpm is equivalent to rest. rCBF = regional cerebral blood flow (from PET).

Adapted from Price *et al.*, 1992, and Friston, 1997.

distinguishes it from the responsiveness of other neighboring regions. It is not strictly the same as *localization*, in that it is not necessary to assume that the region is solely responsible for performance on a given task or to assume that other regions may not also respond to the same stimuli/conditions (Phillips *et al.*, 1984). **Functional integration**, on the other hand, refers to the way in which different regions communicate with each other. This is likely to be essential for a full understanding of how cognition is linked to the brain, and also for dismissing claims that functional imaging is a new phrenology (Friston, 2002; Horwitz *et al.*, 1999).

The basic approach of functional integration is to model how activity in different regions is interdependent. This is used to infer the *effective connectivity* or *functional connectivity* between regions when performing a task (these methods use techniques such as structural equation modeling and principal components analysis, which are beyond the scope of the present discussion). If parametric designs correlate brain activity with some cognitive/behavioral measure, then designs employing functional integration correlate different regions of brain activity with each other. To give a concrete example, Friston and Frith (1995) conducted an imaging study with a 2×2 factorial design with task instruction as one factor (generate words beginning with “A” versus repeating letters) and subject group as the other factor (participants

KEY TERM

Functional integration

The way in which different regions communicate with each other.

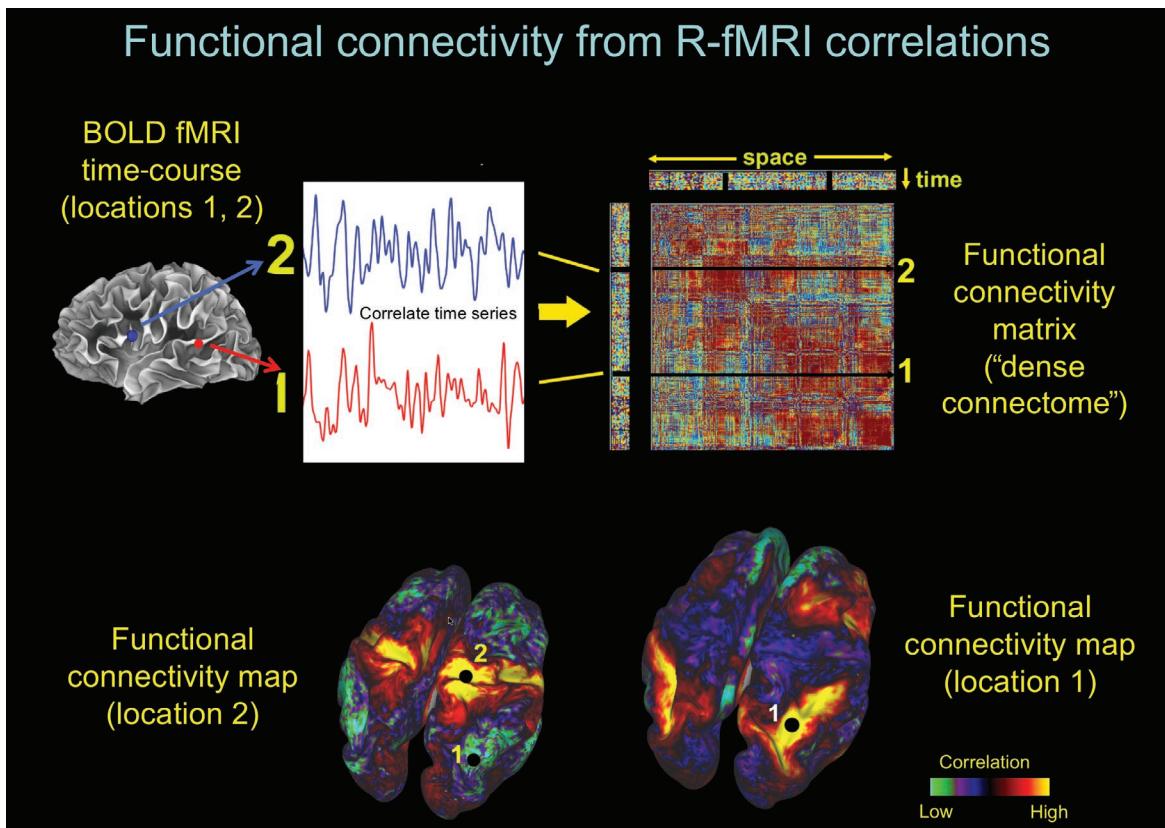


FIGURE 4.13: Every region of the brain shows fluctuations in the BOLD response over time (shown here in detail for two regions, 1 and 2). If different regions show a very similar profile of fluctuations, then this is likely to reflect the fact that they are communicating. In resting state paradigms, fluctuations in the BOLD response from all brain regions are entered into a correlation matrix and, from the pattern of correlations, sets of regions that habitually correlate together (i.e., networks) are identified.

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KEY TERMS

Resting state paradigm

A technique for measuring functional connectivity in which correlations between several regions (networks) are assessed while the participant is not performing any tasks.

Default mode network

A set of brain regions that is more hemodynamically active during rest than during tasks.

either had or had not been diagnosed as schizophrenic). Although both groups showed a number of similar frontal and temporal lobe activities, there was a strong correlation between activity in these regions in controls and a striking absence of correlation in the schizophrenics. Friston and Frith (1995) argued that schizophrenia is best characterized in terms of a failure of communication between distant brain regions (i.e., a functional disconnection).

One commonly used procedure for measuring functional integration does not use any task at all. These are known as **resting state paradigms**. Participants are merely asked to lie back and rest. In the absence of a task, the fluctuations in brain activity are little more than noise. However, in brain regions that are functionally connected the noise levels tend to correlate together. This has enabled researchers to identify sets of networks in the brain, consisting of spatially separated regions, for which fluctuations in activity tend to be shared (Damoiseaux *et al.*, 2006). For instance, one commonly studied network is called the **default mode network** of the brain and is implicated in internalized thoughts: it tends to be more active when *not* engaged in an experimental task (Raichle *et al.*, 2001). Differences in the

way that these networks operate and are constructed are found in various conditions such as schizophrenia and autism (Buckner *et al.*, 2008).

The basic principles behind resting state approaches are illustrated in Figure 4.13. Each region of the brain shows spontaneous fluctuations in the BOLD response over time. In the figure, this is shown for two brain regions (1 and 2). The time-varying activity in each brain region is then correlated with every other brain region, producing a very large correlation matrix (as shown on the right-hand side, with different colors representing different magnitudes of correlation). Through a statistical analysis of the pattern of correlations it is then possible to identify sets of regions that show a similar profile of correlations to each other, presumably because they are communicating. These sets of regions are inferred to constitute a “network.”



ONLINE RESOURCES

To watch a TEDx talk by Professor David van Essen, visit the companion website (www.routledge.com/cw/ward).

SAFETY AND ETHICAL ISSUES IN FUNCTIONAL IMAGING RESEARCH

It is essential to be aware of the local regulations that apply in your own institution but the following points generally apply:

What are the risks of taking part in functional imaging experiments?

fMRI does not use radiation and the same participants can take part in multiple experiments without any harm. Participants wear ear protectors, given that the scanner noise is very loud. Larger magnets (> 3 T) can be associated with dizziness and nausea (caused by stimulating the balance organs rather than the brain), and participants need to enter the field gradually to prevent this.

Are some people excluded from taking part in functional imaging experiments?

Before entering the scanner, all participants should be given a checklist that asks them about their current and past health. People with metal body parts, cochlear implants, embedded shrapnel or pacemakers will not be allowed to take part in fMRI experiments. In larger magnets, eye make-up should not be worn (it can heat up, causing symptoms similar to sunburn) and women wearing contraceptive coils should not be tested. Before going into the scanner both the researcher and participant should put to one side all metal objects such as keys, jewelry and coins, as well as credit cards, which would be wiped by the magnet. Zips and metal buttons are generally okay, but metal spectacle frames should be avoided. It is important to check that participants do not suffer from claustrophobia as they will be in a confined space for some time. Participants have a rubber ball that can be squeezed to signal an alarm to the experimenter, who can terminate the experiment if necessary.

What happens if a brain abnormality is detected during scanning?

There is always a very small possibility that a brain tumor or some other unsuspected abnormality could be detected during the course of the study. In such instances, the researcher has a duty to double-check this by inviting the participant back for a subsequent scan. Potential abnormalities are followed up by a neurologist (or a clinically qualified member of staff), who would inform the participant and their doctor, if need be. Wolf *et al.* (2008) provide a set of ethics concerning the incidental discovery of abnormalities during non-clinical scanning.

How can I find up-to-date details about safety in fMRI experiments?

The standard safety reference is by Shellock (2014), and updates can be found at: www.magneticresonancesafetytesting.com.

KEY TERMS**Stereotactic normalization**

The mapping of individual differences in brain anatomy onto a standard template.

Smoothing

Redistributing brain activity from neighboring voxels to enhance the signal-to-noise ratio.

ANALYZING DATA FROM FUNCTIONAL IMAGING

The images of brains with superimposed colored blobs are the outcome of several stages of data processing and statistical analysis. In fact, these images are not literal pictures of the workings of the brain at all. What these images depict are the regions of the brain that are computed to be statistically significant given the type of design used. Functional imaging is a statistical science and, as such, is susceptible to error. Although different laboratories use different packages to analyze their data, the challenges faced in analyzing and interpreting functional imaging data are common to them all (for a detailed discussion, see Petersson *et al.*, 1999a, 1999b).

A central problem faced in the analysis of functional imaging data is how to deal with individual differences. Although the gross brain structure does not differ considerably from one person to the next, there are nevertheless significant individual differences in the size of gyri and the location of folds in the brain. For example, the location of sulci can vary between people by a centimeter or more (Thompson *et al.*, 1996).

The most common way of dealing with individual differences is effectively to assume that they do not exist. Or, more properly put, individual differences needn't get in the way of making claims about general brain function. Individual differences are minimized by averaging data over many participants, and one is left with regions of activity that are common to most of us. Before this averaging process can occur, the data from each individual need to be modified in a number of ways. First, each brain is mapped onto a standard reference brain (called **stereotactic normalization**). This is followed by a process called **smoothing**, which can enhance the signal-to-noise ratio and facilitates detection of common regions of activity across individuals. Figure 4.14 summarizes the sequence from initial hypothesis to data interpretation that typically occurs in a functional imaging experiment. These main stages will be considered in turn.

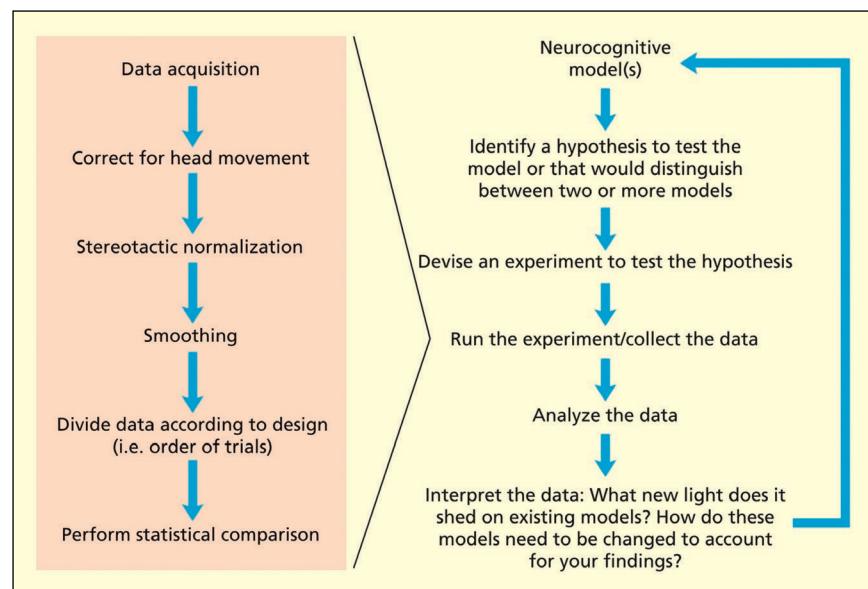


FIGURE 4.14: The main stages of analyzing data in a functional imaging experiment.

Correction for head movement

Perhaps the biggest advantage of the fMRI technique over others is its good spatial resolution. It is able to identify differences in activity over millimeter distances (although this resolution still entails millions of neurons). However, there is a downside to this; namely, that small spatial differences can produce spurious results. One key problem that has already been noted is that every brain differs spatially in terms of size and shape. The process of stereotactic normalization attempts to correct for this. A different problem is that each person's head might be aligned slightly differently in the scanner over time. If a person wriggles or moves their head in the scanner, then the position of any active region will also move around. This could either result in the region being harder to detect (because the activity is being spread around) or a false-positive result could be obtained (because head movements may appear to shift an active region between consecutive conditions). It is for this reason that the collected data are corrected for head movement (Brammer, 2001), which is minimized in the first place by physically restraining the head in position, and instructing participants to keep as still as possible.

Stereotactic normalization

The process of stereotactic normalization involves mapping regions of each individual brain onto a standard brain. Each brain is divided up into thousands of small volumes, called voxels (volume elements). Each voxel can be given three-dimensional spatial coordinates (x, y, z). This enables every x, y, z coordinate on a brain to be mapped onto the corresponding x, y, z coordinate on any other brain. Basically, the template of each brain is squashed or stretched (by applying mathematical transformations that entail an optimal solution) to fit into the standard space. The standard space that is used to report functional imaging data across most laboratories in the world is provided by the brain atlas of Talairach and Tournoux (1988). Each point in the brain is assigned a three-dimensional x, y, z coordinate (commonly referred to as the **Talairach coordinates**) with the origin lying at a region called the anterior commissure (small and easily seen in most scans). The x-coordinate refers to left and right (left is negative and right is positive). The y-coordinate refers to front and back (front/anterior is positive and back/posterior is negative) and the z-coordinate refers to top and bottom (top is positive and bottom is negative). This atlas is based on anatomical data from a single post-mortem brain. However, rather than relying on comparisons to this single brain, many contemporary studies use a template based on an average of 305 brains provided by the Montreal Neurological Institute (Collins *et al.*, 1994). This averaged template is then put into Talairach coordinates and used in favor of the single brain originally described in that atlas.

KEY TERM

Talairach coordinates

Locations in the brain defined relative to the atlas of Talairach and Tournoux.

Smoothing

After each brain has been transformed into this standard space, further stages of preprocessing *may* take place before a statistical analysis. The process of “smoothing” sounds like it could waste important information, but it is an important part of data manipulation. Smoothing spreads some

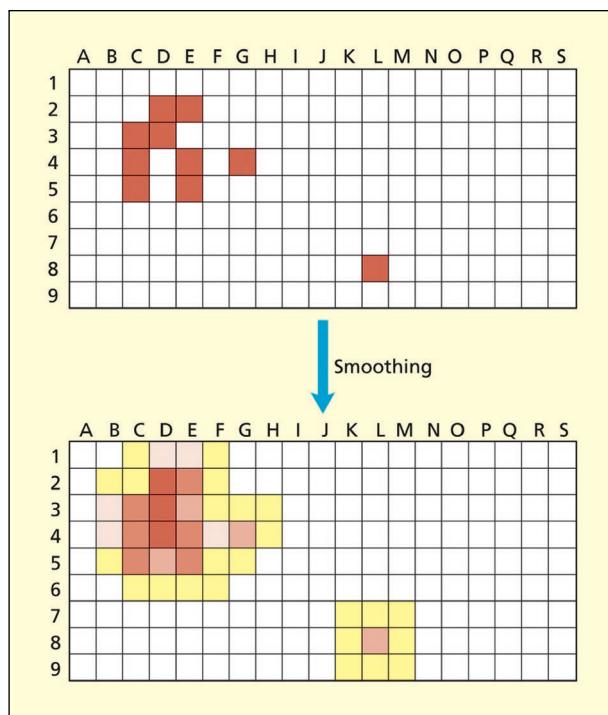


FIGURE 4.15: Smoothing spreads the activity across voxels—some voxels (e.g., D4) may be enhanced whereas others (e.g., L8) may be reduced.

detecting such a system. Indeed, there are some statistical techniques (such as multi-voxel pattern analysis, MVPA) that can be used to analyze this kind of mosaic-like neural representation that do not require smoothing (Norman *et al.*, 2006). This is considered later.

As well as enhancing the signal-to-noise ratio, smoothing offers an additional advantage for analyzing groups of participants. Smoothing increases the spatial extent of active regions. As such, when averaging the activity across individuals there is a greater chance of finding common regions of activity. Of course, if individual differences are the focus of the study, then one may justifiably choose not to smooth the data at all.

Statistical comparison

After the data have been stereotactically normalized, smoothed and corrected for head movement, it is possible to perform a statistical analysis. The standard way to do this is to ask the question: “Is the mean activity at a particular voxel in the experimental condition greater than in the baseline condition?” The same types of statistical test as would be employed in any psychology experiment can be used in functional imaging (e.g., a *t*-test to compare means). But there are complications. In most psychology experiments one would typically have, at most, only a handful of means to compare. In functional imaging, each brain slice is divided up into tens of thousands of voxels and each one needs to be considered. If one uses the standard psychology significance level of $P < 0.05$, then there would be

of the raw activation level of a given voxel to neighboring voxels. The closer the neighbor is, the more activation it gets (the mathematically minded might be interested to know that the function used is a Gaussian or normal distribution centered on each voxel). In Figure 4.15, the darker the square, the more active it is. Consider voxel D4. Prior to smoothing, this voxel is inactive, but because it has many active neighbors the voxel gets “switched on” by the smoothing process. In contrast, consider voxel L8. This voxel is initially active but, because it has inactive neighbors, it gets “switched off” by the smoothing process. Smoothing thus enhances the signal-to-noise ratio. In this instance, one assumes that the signal (i.e., the thing of interest) corresponds to the larger cluster of activity and the noise is the isolated voxel. Neighboring voxels that are active mutually reinforce each other and the spatial extent (i.e., size) of the active region is increased. If the brain happened to implement cognition using a mosaic of non-adjacent voxels, then smoothing would work against

thousands of brain voxels active just by chance. (Recall that the significance level represents the probability (P) at which one is willing to say that a result is more than just a chance occurrence. The value of 0.05 represents a 1 in 20 chance level.) How could one minimize the influence of lots of brain regions being active by chance? One could have a more conservative criteria (i.e., a lower significance level), but the danger is that this will not detect regions that are important (this is termed a type II error). For instance, in a Bonferroni correction one would divide the nominal P value (0.05) by the number of tests (i.e., voxels). A difficulty with this approach is that the activity at each voxel is not independent: neighboring voxels tend to have similar activity, particularly if smoothed. This has led to the development of sophisticated mathematical models of choosing a statistical threshold, based on spatial smoothness (so-called *random field theory*). This general method of correction is termed **Family Wise Error (FWE)**. Another common approach is to generate thousands of random brain images (e.g., by permuting the data) and select a threshold (e.g., $P < 0.05$) based on random datasets. This method of correction is termed the **False Discovery Rate (FDR)**. In this method a more conservative statistical threshold would be used for datasets in which lots of voxels are active than in a dataset in which only few voxels are active.

When reading papers that have used functional imaging methods, one sometimes observes that they report different significance levels that are “corrected” or “uncorrected.” Why is this done and is it acceptable? A corrected level implies that a more conservative criterion has been used to prevent detecting lots of regions just by chance. However, if the interest is in *one* particular voxel, then it is possible to use an uncorrected significance level (e.g., the standard $P < 0.05$) because in this instance there are not multiple comparisons over lots of brain regions. Other procedures are used when investigating effects in a predetermined region covering several voxels (a so-called *small volume correction*).

INTERPRETING DATA FROM FUNCTIONAL IMAGING

What does it mean to say that a brain region is active in a functional imaging experiment? Literally speaking, what this means is that the signal from that region (the BOLD signal in fMRI) is greater in one condition than in other conditions that are being compared (whether in a categorical design, parametric design or whatever). There are several reasons why a region may be active and not all of them are theoretically interesting. Importantly, it need not imply that the particular region is essential for the task. Alternative accounts include: an increase in signal could reflect the strategy that the participants happen to adopt, it could reflect use of some general mechanism (e.g., increased attention) that is not specific to the task or it could reflect the fact that a region is receiving input but is not responding to the input (i.e., **inhibition**). These competing scenarios can only be ruled out with more rigorous experimentation. Chance occurrences can be ruled out by replicating the results and the necessity of a region for a task can be determined using lesion methods. This is discussed in more detail below.

KEY TERMS

Family Wise Error (FWE)

An approach for correcting for many statistical comparisons based on the number of tests being conducted.

False Discovery Rate (FDR)

An approach for correcting for many statistical comparisons based on the number of positive results obtained.

Inhibition

A reduction/suppression of the activity of a brain region (or a cognitive process), triggered by activity in another region/process.

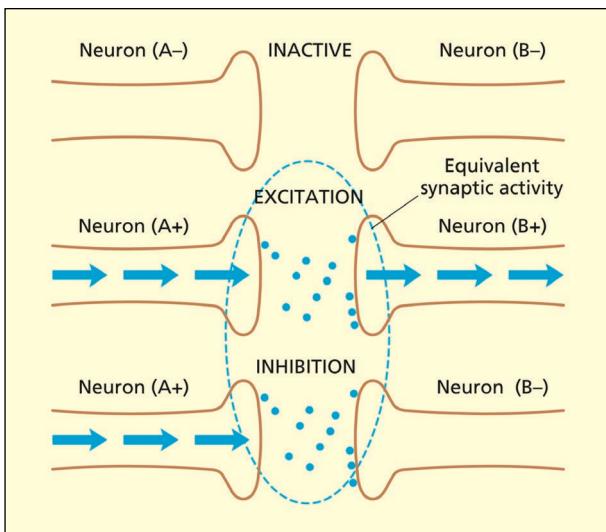


FIGURE 4.16: Excitatory and inhibitory synaptic connections both involve metabolic activity and thus an inhibited region could be mistakenly interpreted as a region of activity.

KEY TERMS

Excitation

An increase of the activity of a brain region (or a cognitive process), triggered by activity in another region/process.

Activation

An increase in physiological processing in one condition relative to some other condition(s).

Deactivation

A decrease in physiological processing in one condition relative to some other condition(s).

Inhibition versus excitation

Functional imaging signals are assumed to be correlated with the metabolic activity of neurons, and synapses in particular (see Jueptner & Weiller, 1995). However, neurons can be metabolically active by virtue of both inhibitory interactions (when the presynaptic neurons are active, the postsynaptic neuron is switched off) and **excitations** (when the presynaptic neurons are active, the postsynaptic neuron is switched on)—see Figure 4.16. Most connections are excitatory in nature. Logothetis *et al.* (2001) demonstrated that the BOLD signal used in fMRI is more sensitive to the neuronal input into a region rather than the output from the region. Thus, regions that “listen” to other active regions but do not themselves respond to it could appear as areas of activation.

It is unclear whether functional imaging can distinguish between these two types of neural function since both are assumed to be associated with similar physiological changes.

Activation versus deactivation

Activation and deactivation simply refer to the sign (positive or negative) of the difference in signal between two conditions. This is not to be confused with excitation/inhibition which refers to the nature of the mechanism by which neurons communicate. If the subtraction (Task A) – (Task B) is performed, there could be a set of regions that show a significant positive effect (i.e., “**activation**”) because they are used more in Task A than in Task B, and there could also be a set of regions that show a significant negative effect (i.e., “**deactivation**”) because they are more active in Task B than in Task A. Of course, if one had done the subtraction (Task B) – (Task A), then the same regions would be identified, but the positive and negative signs would merely swap. Thus, the terms activation and deactivation merely refer to whether there is a difference in signal between conditions and the direction of that difference. The question of *why* there is a difference is open to theoretical interpretation. If the baseline task is very different from the experimental conditions, the activations and deactivations may be very hard to interpret.

Necessity versus sufficiency

In an intriguingly titled paper, “If neuroimaging is the answer, what is the question?”, Kosslyn (1999) sets out some of the reasons why functional imaging has its limitations. One particular point that will be picked up on here is the notion that some of the regions that appear active may indeed be used during performance of the task but might not be critical to the task. For example, a region may appear to be active because of a particular strategy that the participants adopted, even though other strategies might be available.

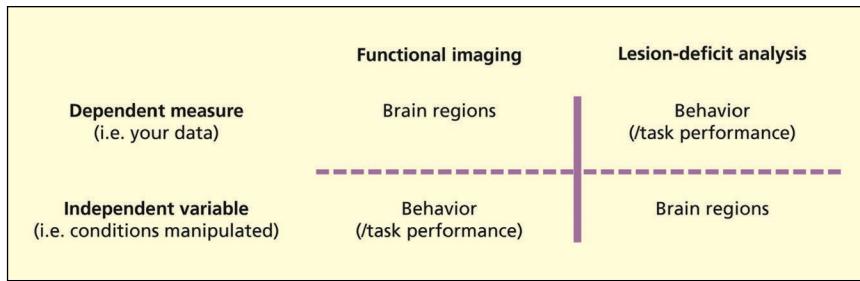


FIGURE 4.17: Functional brain imaging and lesion-deficit analysis of patients (or TMS, see Chapter 5) are logically different types of methodology. It is unlikely that one will supplant the other.

It could also be the case that the tasks being compared differ in some other, more general, way. For example, if one task is harder than the other, it could demand more attention, and this demanding of attention would have its own neural correlate. Although paying more attention could certainly help with the performing of the task, it may not in and of itself be crucial for performing the task. As such, it has been claimed that functional imaging gives us a better idea of which regions may be sufficient for performing a particular task but not always which regions are crucial and necessary for performing a task.

The value of functional imaging data is likely to be enhanced when it is used in conjunction with other methods. One early benefit of functional imaging was mooted to be that it could replace lesion-based neuropsychology. However, this is unlikely to happen because the logic of inference is different in these two methods, as illustrated in Figure 4.17. In lesion-based neuropsychology, the location of the lesion is manipulated (or selected for in a patient sample) and the resulting behavior is observed. In doing this, a causal connection is assumed between the lesion and the ensuing behavior. In functional imaging the reverse is true. In this instance, the task given to participants in the scanner is manipulated and changes in brain regions are observed. Although some of these changes are likely to be critically related to the performance of the task, other changes may be incidental to it. It is for this reason that functional imaging is unlikely to supplant the traditional lesion-based approach. The next section discusses in more detail how divergent results between imaging and neuropsychology could be reconciled.

WHY DO FUNCTIONAL IMAGING DATA SOMETIMES DISAGREE WITH LESION DATA?

There are two broad scenarios in which functional imaging data and lesion-deficit data can disagree. These are listed below, together with possible ways of resolving the disagreement, as described in the following box.

This box highlights the fact that disagreements between results from functional imaging and results from lesion data could lie with imaging results, with the lesion results, or with both. There is no magic solution for resolving the disagreements except through more rigorous experimentation. Each method has some relative merit. As such, disagreements should be viewed as something that is potentially of theoretical interest rather than dismissed as a failure of one or other method (Henson, 2005). To provide a feel for how this might be achieved, the next section considers a concrete example from the literature.

Disagreement 1: Imaging data imply that a brain region is used in a given task, but lesion data suggest that this region is not essential to the task (imaging +, lesion –)

Possible reasons for disagreement:

- The activated region reflects a particular strategy adopted by the participants that is not essential to performing the task.
- The activated region reflects the recruitment of some general cognitive resource (e.g., due to increased task difficulty, attention or arousal) that is not specific to the task.
- The activated region is being inhibited (i.e., switched off) rather than excited (i.e., switched on).
- The lesion studies have not been powerful enough to detect the importance of the region (e.g., too few patients, lesion not in the correct location, tasks used with patients not the same as those used in imaging).

Disagreement 2: Imaging data imply that a brain region is not used in a given task, but lesion data suggest that this region is critical to the task (imaging –, lesion +)

Possible reasons for disagreement:

- If the experimental task and baseline task both depend critically on this region, then a comparison between them might produce an artifactual null result.
- It might be intrinsically hard to detect activity in this region of the brain (e.g., it is a very small region, it is in different places in different individuals or genuine activity produces a small signal change).
- The impaired performance after lesion reflects damage to tracts passing through the region rather than the synaptic activity in the gray matter of the region itself.

Having your cake and eating it

A small proportion of unfortunate people in later life start to lose the meanings of words and objects that they previously understood. This deterioration can spare, at least in the early stages, memory for events, calculation abilities and syntax, among other things (e.g., Hodges *et al.*, 1992). These patients would probably be given a diagnosis of **semantic dementia**, because their functional lesion is primarily in the **semantic memory** system that stores the meaning of words and objects. Where are the anatomical lesions in these patients? Lesion studies based on voxel-based morphometry (VBM) have shown that the degree of semantic memory impairment is correlated with the amount of atrophy in the left anterior temporal lobe (Mummery *et al.*, 2000), as shown in Figure 4.18. Given this finding, it would be encouraging if functional imaging studies also activated this particular region when healthy (non-brain-damaged) people are given semantic memory tasks. However, this has not always been the case and a number of studies have reliably shown activation in a different region—the left inferior frontal gyrus (also referred to as the ventrolateral prefrontal cortex). How can these divergent results be explained? It will be argued that a more careful comparison of the tasks used can account for this divergence and reveals, in turn, more about how the brain supports semantic memory.

KEY TERMS

Semantic dementia

A progressive loss of information from semantic memory.

Semantic memory

Conceptually based knowledge about the world, including knowledge of people, places, the meaning of objects and words.

One of the first ever functional imaging studies of cognition tried to address the question of where semantic memories are stored. As already discussed, Petersen *et al.* (1988) compared brain activation in two tasks: verb generation (e.g., the participant sees CAKE and says “eat”) and reading aloud (e.g., the participant sees CAKE and says “cake”). The verb-generation task is assumed to tap semantic memory more than the reading task. However, a comparison of the two tasks shows activity in regions of the left inferior frontal gyrus, but not in the same regions that are associated with semantic memory loss. Is the imaging data or the lesion data to be believed? Could it be the case that the left inferior frontal gyrus is really involved in semantic memory? To test this hypothesis, instead of taking a group of patients with semantic memory difficulties and asking where the lesion is, one would need to take a group of patients with selective lesions to the left inferior frontal gyrus and give them the same verb-generation task that the healthy people were given when they were scanned. As it turns out, such patients do have subtle but real difficulties with these tasks. Thompson-Schill *et al.* (1998) asked these patients to generate verbs that had either a low selection demand (e.g., scissors), in which most people agree upon a verb (i.e., cut), and words with a high selection demand (e.g., cat), which do not suggest an obvious single answer. The patients are impaired on the latter but not the former. More extensive imaging data on controls show that the region is responsive to the difficulty of semantic memory retrieval (Thompson-Schill *et al.*, 1997, 1999). Thus, this disagreement is perhaps more apparent than real. The reason why patients with damage to the left inferior frontal gyrus do not show clinical symptoms of semantic memory impairment is because the region is involved in strategic retrieval operations from semantic memory when no obvious answer comes to mind. By contrast, the temporal regions may be the *store* of semantic information and lesions here can produce more devastating impairments of semantic knowledge. So why didn’t these particular imaging studies activate regions that are putatively the store of semantic knowledge? One possibility could be the baseline that was used. Petersen *et al.* (1988) compared verb generation (their semantic task) with reading (their putatively non-semantic task). However, if word reading does depend on the semantic store, and there is, in fact, good evidence that it might (Woollams *et al.*, 2007), then the two conditions would cancel each other out when subtracted away.

In this instance, an initial discrepancy between functional imaging and lesion data has resulted in a more complete understanding of how semantic memory is both stored and retrieved. This is a nice example of how the strengths of different methodologies can be combined in cognitive neuroscience.

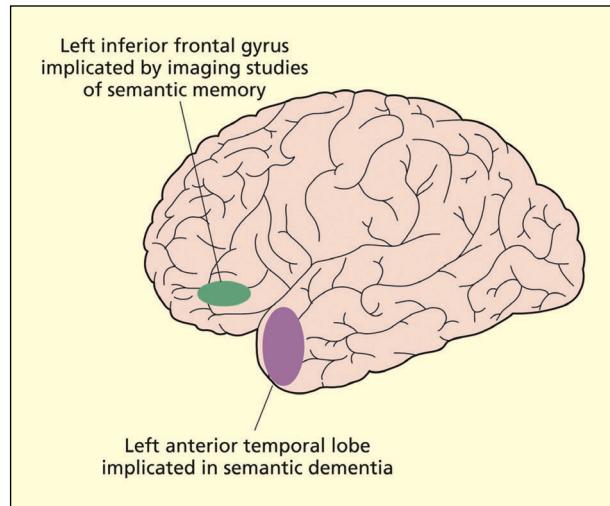


FIGURE 4.18: Studies of brain-damaged patients with semantic memory and imaging studies of semantic memory have not always highlighted the importance of the same regions.

BRAIN-READING: IS “BIG BROTHER” ROUND THE CORNER?

This chapter started with the specter of functional imaging being used to reveal one’s innermost thoughts to the outside world. It therefore seems appropriate to return to this interesting theme in light of the various points raised so far. It should by now be clear that the process of analyzing and interpreting data produced by functional imaging is not straightforward. It entails a number of stages, each with its own assumptions, rather than a literal reading of the MR signal. Nonetheless, the technology is still relatively new and the amount of progress that has already been made is substantial. Even at this early stage, there are serious studies exploring how functional imaging could be used as a lie detector and studies that try to predict the content of another person’s thoughts at some basic level (for a review, see Haynes & Rees, 2006).

It is generally believed that different classes of objects (e.g., faces, places, words, tools) activate somewhat different regions of the brain. So is it possible to infer what someone is looking at from brain activity alone? A number of studies have attempted to guess, in a third-person way, what a person is observing (Haxby *et al.*, 2001) or imagining (O’Craven & Kanwisher, 2000) on a particular trial using only the concomitant neural activity (see Figure 4.20). To achieve this, each person requires pretesting on a whole range of objects to determine the average response to that class of objects relative to some baseline (e.g., all the other objects). Rather than locating the peak area of activity (as in regular fMRI analysis), one can examine the *pattern* of activation over a distributed set of voxels to enable a more fine-grained approach. This method is called MVPA or **multi-voxel pattern analysis** (for a review see Tong & Pratte, 2012). For example, Haxby *et al.* (2001) gave participants pictures from eight different types of category, including cats, houses, faces and shoes. The neural activity from an individual trial was then compared to the previous known patterns of activity to determine the most probable category that was being viewed. This procedure could predict, given pairwise comparisons, what the person was seeing with 96 percent accuracy. The same regions of the brain are used, to some extent, when thinking about objects even when they are not physically seen. O’Craven and Kanwisher (2000) obtained comparable results on individual imagery trials. Other research has shown that activity in these regions can be used to accurately predict semantic categories when reading words (Mitchell *et al.*, 2008) or when recalling previously seen images from memory (Polyn *et al.*, 2005).

KEY TERM

Multi-voxel pattern analysis (MVPA)

An fMRI analysis method in which distributed patterns of activity are linked to cognitive processes.

COULD FUNCTIONAL IMAGING BE USED AS A LIE DETECTOR?

Lying appears to be a normal component of human social interaction. It is likely to be composed of several cognitive components. For example, it requires an understanding that other people can have states of mind that are different from one’s own (so-called theory of mind). Lying also requires an ability to inhibit a truthful response and generate a plausible alternative response. Given this complexity, there will probably be no single “deception module” in the brain dedicated

specifically to lying (Figure 4.19). Nevertheless, there is every reason to believe that studying the brain during deception might lead to more reliable indices of lying than the traditional lie detector (or “polygraph”), given that the brain is the organ that produces the lie in the first place.

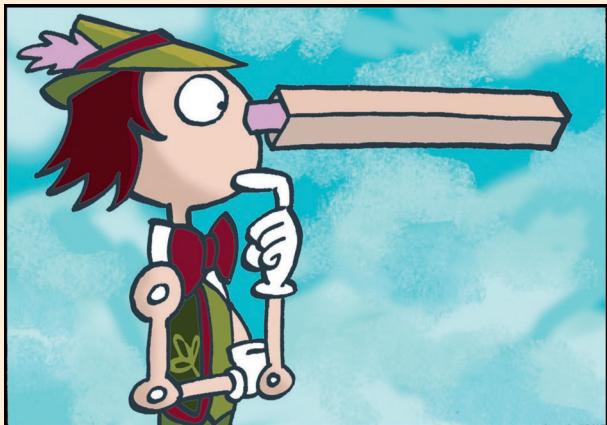


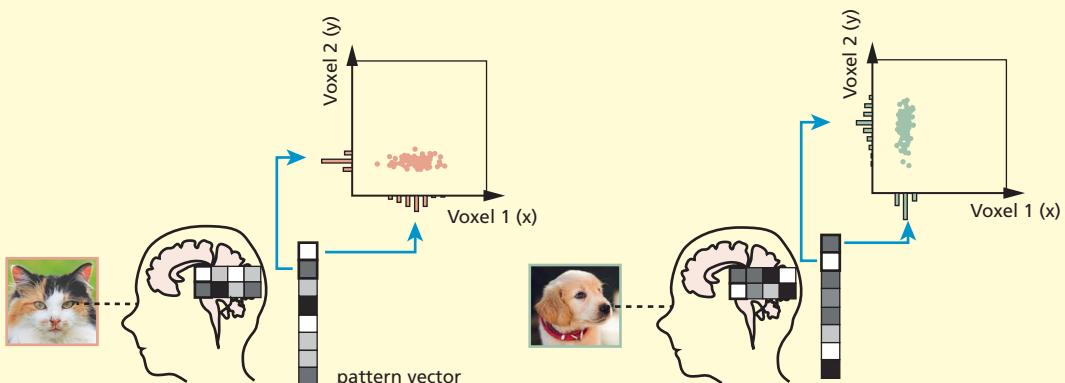
FIGURE 4.19: Not all lies are as easy to detect.

The traditional polygraph monitors a number of bodily responses, including sweating, respiration and heart rate, which are considerably downstream from the thought process that creates the lie. As these measures are associated with increased arousal generally (e.g., anxiety), they cannot exclusively detect guilt and their usage is highly questionable. Also, if a liar does not feel guilty there may be no strong arousal response.

Many studies have used fMRI to measure the neural correlates of deception and, studies have reported accuracies between 69 percent and 100 percent in separating simple deceitful versus truthful responses (Farah et al., 2014). When participants are asked to generate a lie to a question (e.g., “Who did you visit during your vacation?”, “Was that the card you were shown before?”), a number of regions are activated, including the anterior cingulate cortex. This region is of particular interest in this context, because it has been implicated in monitoring conflicts and errors (Carter et al., 1998) and also in generating the kinds of bodily response that form the basis of the traditional polygraph (Critchley et al., 2003). However, not all types of deception may recruit this region. Ganis et al. (2003) found that, if participants memorized a lie in advance of being interviewed in the scanner, then this region was not involved, but regions involved in memory retrieval were involved. Thus, to conclude, although fMRI might have some use in lie detection, it is unlikely to offer a simple solution to this complex and important real-world problem.

The studies described thus far are limited in that they generate answers from a closed set of options (e.g., cat compared with dog). However, other studies have used this approach to generate an open-ended set of responses. The primary visual cortex (also termed V1) has a particular functional layout such that it is a mosaic of small regions that are specialized for detecting lines of certain orientations and also for detecting light in particular locations. The grid of voxels used in fMRI may capture some of this patterning,

Phase 1: Record patterns of activity from a training set (e.g. cats v. dogs)



Phase 2: Create a decision boundary and test it on new examples

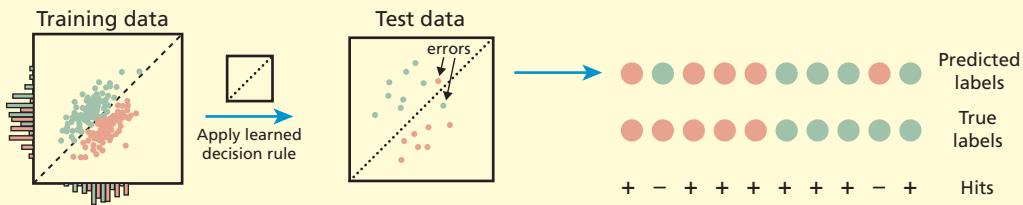


FIGURE 4.20: Multi-voxel pattern analysis (MVPA) has two main phases. Initially, participants are given certain tasks or stimuli—in this example seeing cats or dogs—and fMRI data are collected in the normal way. Different voxels might respond more or less strongly to different stimuli (this can easily be missed by traditional univariate analyses that average together activity over multiple “smoothed” voxels). A mathematical algorithm (a “classifier”) is trained to optimally discriminate the categories (e.g., cat v. dog) based on the activity across multiple voxels (note: the actual spatial arrangement of voxels isn’t crucial). In the next phase (testing), the participant is then given more tasks or stimuli (e.g., new images of cats and dogs) and the algorithm must classify them. In this phase the participant’s mind/brain is effectively being “read.”

Adapted from Haynes (2015).

and attempts have been made to reconstruct visual images (presented to a participant) based on the pattern of activity in this region. For instance, Miyawaki *et al.* (2008) used a 10×10 grid of pixels to train a classifier. Just as the classifier can search for voxels that “prefer” cats over dogs, one can do the same for voxels that prefer brightness in, say, the top left of the grid as opposed to bottom right or for voxels that prefer horizontal over vertical orientations. From this simple training, it was possible to reconstruct letters and words that were presented to the participants as shown in Figure 4.21 (top). Again, it is worth reiterating that the experimenter is not literally seeing words spelled out in a participant’s brain in the scanner. Instead, a computer algorithm is taking fluctuations in brain activity and making a best guess about whether each voxel is being activated in response to a visual stimulus or not (and from that an image is reconstructed). Attempts at generating more complex images using this method have more limited success but are good at

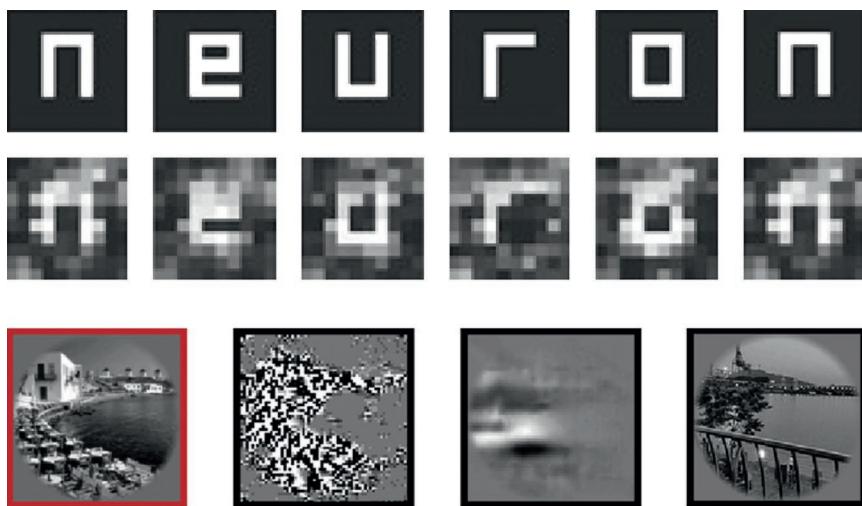


FIGURE 4.21: Can activity in the brain be used to reconstruct what image is being seen? In the top example, letters displayed in a 10×10 grid to the participants can clearly be read out from the pattern of brain activity. In the bottom example, the target image is shown on the left (red outline) and, to the right, are shown three attempts at image reconstruction from the pattern of activity (black outline). The first reconstruction uses an algorithm based on detecting local contrast. The second reconstruction uses the global (blurred) image characteristics. The final attempt involves finding a best match from a database of 6 million images (not including the target image).

Top, from Miyawaki *et al.*, 2008. Bottom, from Naselaris *et al.*, 2009.

finding a close match to a novel image from within a large database, as shown in the bottom panel of Figure 4.21 (Naselaris *et al.*, 2009).

Much of the discussion has focused on brain decoding of external inputs. What about intentions and decisions that are, by their nature, internally driven? Patterns of activity in the prefrontal cortex can be used to predict (even before the person made their response) which of two tasks will be performed—in this study the decision was whether to add or subtract digits (Haynes *et al.*, 2007). Brain activity when shown a series of goods predicts, above chance, subsequent purchasing decisions (Knutson *et al.*, 2007). Finally, a remarkable set of studies have been performed on patients in a **vegetative state** who, because of their injury, are unable to produce verbal or motor responses (Monti *et al.*, 2010; Owen *et al.*, 2006). Some of these patients are able to understand sentences by complying with instructions such as “imagine navigating around your house” or “imagine playing tennis”: these tasks have very different neural substrates related to spatial and motor imagery, respectively. In this case, the brain regions are sufficiently far apart that they do not require an MVPA-type approach. Importantly, these different neural signatures can be used as a simple substitute for communication to answer questions such as “Is your father’s name Alexander? (yes = imagine tennis, no = imagine your house).” As such, brain-reading may ultimately have real clinical significance rather than being an instrument of a “Big Brother” state.



ONLINE RESOURCES

Watch a TEDx talk by Jack Gallant on brain decoding.

KEY TERM

Vegetative state

A disorder of consciousness in which patients with severe brain damage are in a state of partial arousal.

Evaluation

In summary, brain imaging can be used to infer the *type* of stimulus that is being processed and simple cognitive decisions (e.g., add or subtract). However, it is unclear whether fMRI will ever be able to infer the *specific content* of thought. To infer, for example, whether someone in a scanner is thinking about his or her own cat or next-door's cat would require knowledge of how and where an individual stimulus is represented in the brain. We have all been exposed to different cats, houses and so on during the course of our life. Moreover, all our brains differ in subtle ways. This presents a natural boundary on the imaging enterprise that technological developments alone are unlikely to resolve.

SUMMARY AND KEY POINTS OF THE CHAPTER

- Structural imaging reveals the static physical characteristics of the brain (useful in diagnosing disease), whereas functional imaging reveals dynamic changes in brain physiology (that might correlate with cognitive function).
- Neural activity consumes oxygen from the blood. This triggers an increase in blood flow to that region (measured by PET) and a change in the amount of deoxyhemoglobin in that region (measured by fMRI).
- As the brain is always physiologically active, functional imaging needs to measure *relative* changes in physiological activity. The most basic experimental design in functional imaging research is to subtract the activity in each part of the brain while doing one task away from the activity in the same parts of the brain while doing a slightly different task. This is called cognitive subtraction.
- Other methods, including parametric and factorial designs, can minimize many of the problems associated with cognitive subtraction.
- There is no foolproof way of mapping a point on one brain onto the putatively same point on another brain because of individual differences in structural and functional anatomy. Current imaging methods cope with this problem by mapping individual data onto a common standard brain (stereotactic normalization) and by diffusing regions of significance (smoothing).
- A region of “activity” refers to a local increase in metabolism in the experimental task compared with the baseline, but it does not necessarily mean that the region is essential for performing the task. Lesion studies might provide evidence concerning the necessity of a region for a task.
- Functional imaging can be used to make crude discriminations about what someone is thinking and feeling and could potentially outperform traditional lie detectors. However, it is highly unlikely that they will ever be able to produce detailed accounts of another person’s thoughts or memories.

EXAMPLE ESSAY QUESTIONS

- What are the physiological processes that underpin fMRI? What determines the temporal and spatial resolution of this method?
- What is meant by the method of “cognitive subtraction” in functional imaging research? What problems does this method face?
- Is functional imaging ever likely to completely replace lesion methods for informing theories of cognition?
- If a brain region is shown to be “active” in a given task, does it mean that this region is critical for performing the task? If not, why not?
- Could functional imaging be used in lie detection? Could it be used to read someone else’s thoughts and feelings?



ONLINE RESOURCES

Visit the companion website at www.routledge.com/cw/ward for:

- References to key papers and readings
- Video lectures and interviews on key topics with leading psychologists Geoffrey Aguirre, Thomas Insel and author Jamie Ward
- Multiple-choice questions and interactive flashcards to test your knowledge
- Downloadable glossary

RECOMMENDED FURTHER READING

- Ferrari, M., & Quaresima, V. (2012). A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. *NeuroImage*, 63(2), 921–935. An overview of the fNIRS method.
- Huettel, S. A., Song, A. W., & McCarthy, G. (2014). *Functional magnetic resonance imaging* (3rd edition). Sunderland, MA: Sinauer Associates. Thorough but generally accessible. This is recommended for the general reader.
- Poldrack, R. A., Mumford, J. A., & Nichols, T. E. (2011). *Handbook of functional MRI data analysis*. Cambridge, UK: Cambridge University Press. For those getting hands-on experience of fMRI research.



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CHAPTER 5

The lesioned brain and stimulated brain

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Studies of humans who have been unfortunate enough to acquire brain damage have provided a rich source of information for cognitive neuroscientists. The basic premise behind the approach is that, by studying the abnormal, it is possible to gain insights into normal function. This is a form of “reverse engineering,” in which one attempts to infer the function of a component (or region) by observing what the rest of the cognitive system can and can’t do when that component (or region) is removed. Following brain damage, it may be possible to write but not speak, or recognize objects but not faces. In this way, lesions “carve cognition at its seams” (McCarthy & Warrington, 1990).

From a contemporary perspective, studies of the effects of brain lesions on cognition can be regarded as one example of a wider class of approaches in which brain functioning is disrupted or stimulated in some way—either in humans or animals. This stands in contrast to other methods, such as EEG and fMRI, where some aspect of brain activity is recorded and for which the relationship between brain and behavior is correlational. Figure 5.1 gives an overview of these brain manipulation methods summarized according